Cyclic Guanidines; III.[1] Synthesis of Novel 8,13,15-Triazasteroids and Related Heterocycles

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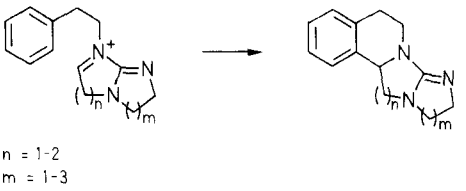
The Pictet–Spengler reaction is utilized for the generation of 8,13,15-triazasteroids and related multicyclic compounds. The constitution of **7a** is elucidated by NMR- and X-ray analysis. A second route to the triazasteroid ring system by Bischler–Napieralski type cyclization is disclosed. Synthetic alternatives as well as the variability in size and nature of rings A, B, C and D of the steroid-like skeletons are demonstrated. Synthesis covers 14 new tetra- and pentacyclic compounds on the basis of 9 novel ring systems.

Annulated heterocyclic systems have frequently been prepared by Pictet–Spengler cyclization via suitable *N*-acyliminium intermediates.[2,3] More specifically, imidazo- and pyrimidoisoquinolines were synthesized by this method (Scheme **A**).[4–10]

Scheme **A**

We report herein a mechanistically equivalent access via amidinyl-iminium ions to fused isoquinolines, and related new ring systems, which represent cyclic guanidines (Scheme **B**).

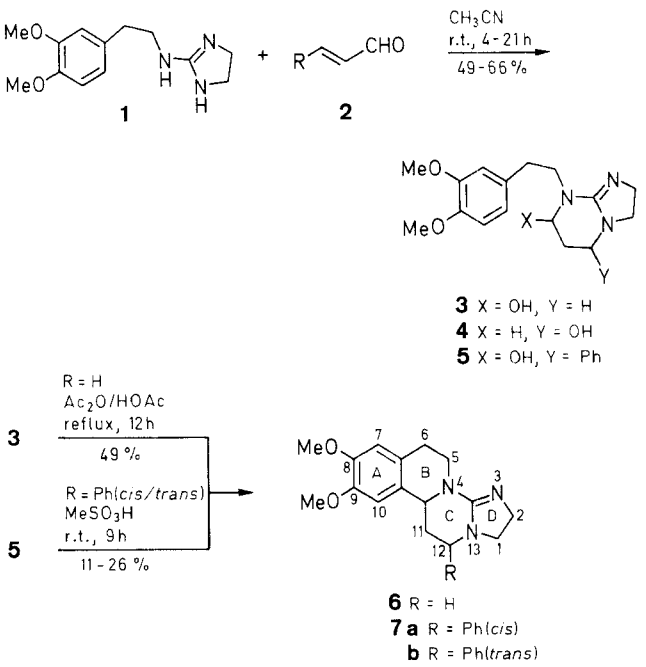


Scheme **B**

The synthesis is achieved by reacting 2-[2-(3,4-dimethoxyphenyl)ethylamino]-4,5-dihydroimidazole **(1)** with acrolein **(2a)**. The two resulting 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*] pyrimidines **3** and **4** are separated, and treatment of **3** with acetic acid in acetic anhydride results in the formation of **6** as a racemate (Scheme **C**).

Compound **6** constitutes a new ring system, named imidazo[1′,2′:1,2]pyrimido[4,3-*a*]isoquinoline, which, if the steroid numbering is applied, may be called an 8,13,15-triazasteroid.

If **1** is reacted with cinnamic aldehyde **(2b)**, the corresponding carbinolamine **5** is obtained. Treatment of **5** with methanesulfonic acid[11] (Table) yields a mixture of diastereoisomers, which can be separated into *cis*-**7a** and *trans*-**7b** (Scheme **C**). This *cis*-configuration of **7a** is deduced from the ^{1}H-NMR spectrum. The $CHCH_2CH$



Scheme C

moiety, constituting an ABXY system, displays completely analogous X and Y signals, as expected for the *cis*-orientation of the methine protons. In addition the structure of **7a** is unambiguously determined by X-ray analysis (Figure).[12]

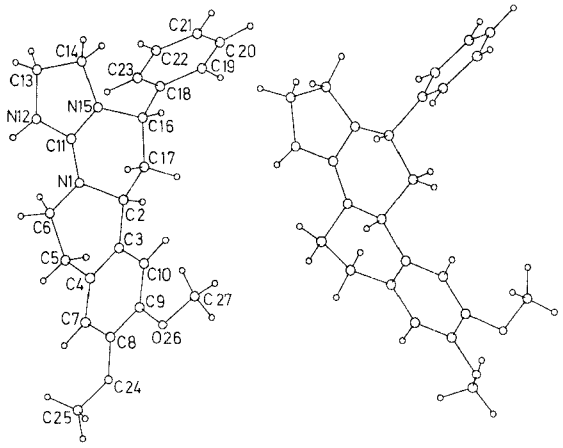
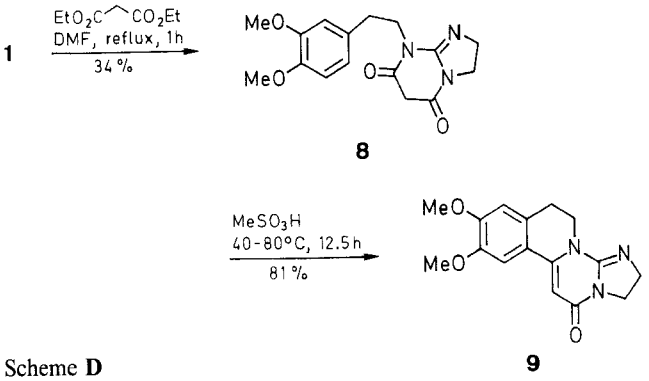


Figure. X-Ray crystal structure of **7a** · HCl · H_2O

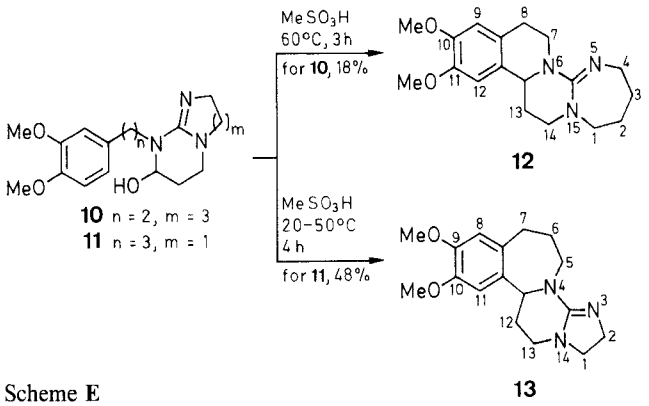
Access to this triazasteroid skeleton can also be gained by Bischler–Napieralski type cyclization. Compound **8**, which is synthesized from **1** and diethyl malonate, can under mild conditions be cyclodehydrated to give **9** in very good yield (Scheme **D**).

The synthetic approach of Scheme **C** can be further modified in order to vary the size of ring B and/or ring D. Ring B has the scope of becoming a 7-instead of a 6-membered ring and for ring D, the ring sizes are varied between 5, 6 and 7; two examples are shown in Scheme **E**. If **10**, obtained in an analogous way to **3** (Scheme **C**) from the corresponding diazepine, is cyclodehydrated, **12** is obtained, the ring system of which is named [1,3]diazepino[1′,2′: 1,2]pyrimido[4,3-*a*]isoquinoline.



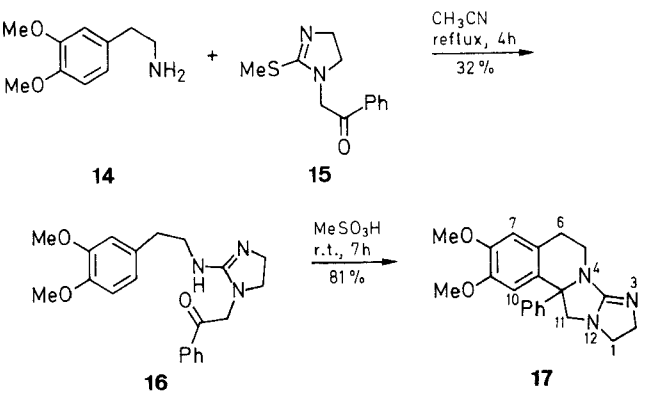
Scheme **D**

The same procedure applied to **11** leads to **13**, an imidazo[1′,2′: 1,2]pyrimido[4,3-*a*]2-benzazepine. Formation of 7-membered fused heterocycles by Pictet–Spengler cyclization have repeatedly been reported.[2,4–6]



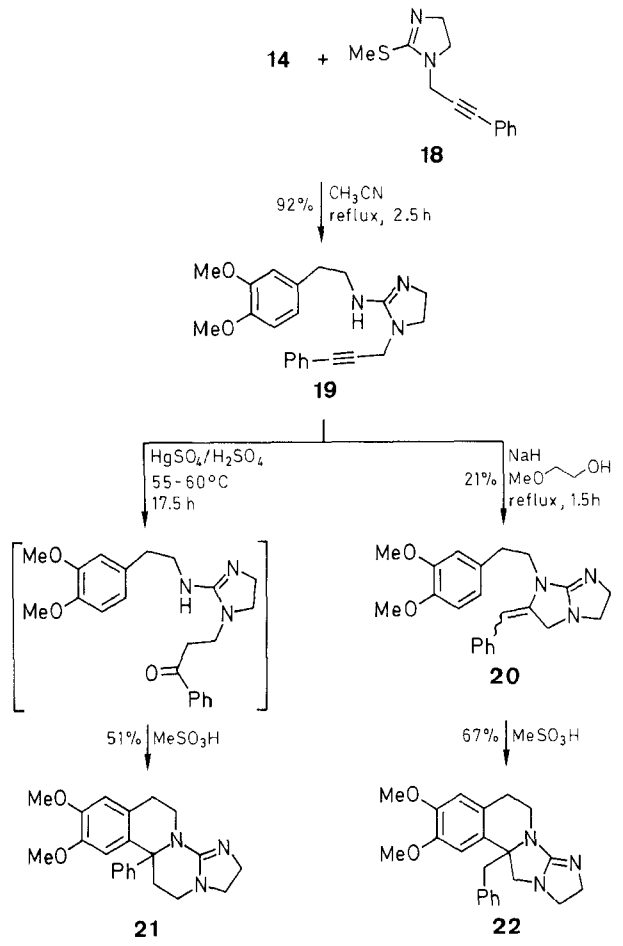
Scheme **E**

The approach according to Scheme **C** suffers from poor regioselectivity, the cogenerated **4** constituting a useless by-product. Therefore we devised a route, by which the carbonyl containing side chain becomes specifically attached to N-1, as achieved in **16** rendering it capable of performing double cyclization (Scheme **F**). The generated new ring system **17** represents an imidazo[1′,2′: 1,2]imidazo[4,3-*a*]isoquinoline. This example demonstrates the synthesis to be variable, changing ring C of the steroid skeleton to a 5-membered cycle.



Scheme **F**

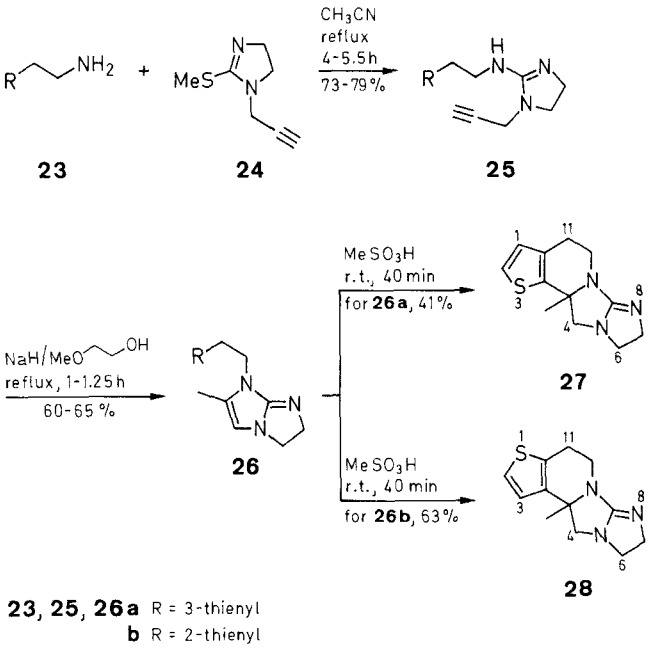
A more versatile synthetic strategy is shown in Scheme **G**. Building block **19** offers access to two different heterocycles. If the triple bond in **19** is first hydrated with the aid of mercuric sulfate and the intermediate subjected to cyclocondensation, compound **21** containing a triazasteroid framework, is obtained.



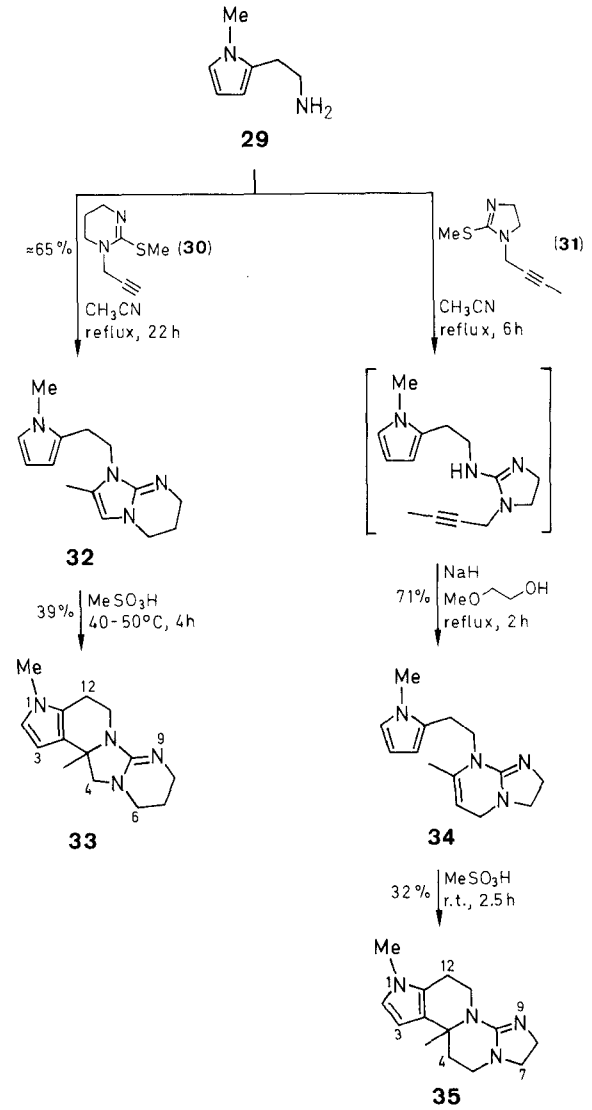
Scheme **G**

If, on the other hand, **19** performs a base induced intramolecular addition to its triple bond,[13] the resulting enamine **20** easily undergoes the acid catalyzed ring closure to yield **22** constituting a heterocycle of ring sequence 6,6,5,5 (A, B, C, D), like compound **17** as illustrated in Scheme **F**.

The synthetic principle can be extended to different heteroaromatic rings acting as π-nucleophiles, thereby illustrating the variability in ring A. Thus aminoethylthiophenes **23a,b** are reacted with 2-methylthio-1-(2-propynyl)-4,5-dihydroimidazole **(24)** to give compounds **25a,b**, which in basic medium undergo intramolecular addition yielding intermediates **26a,b**. Cyclizations of this type are well documented in the literature.[14] Acid catalyzed ring closure furnishes the imidazo[1′,2′:1,2]imidazo[3,4-*a*]thieno[2,3-*c*]pyridine **27** and the imidazo[1′,2′:1,2]imidazo[3,4-*a*]thieno[3,2-*c*]pyridine **28** (Scheme **H**). Numerous examples exist of thiophene being used as π-nucleophile in Pictet–Spengler reactions on the route to diverse heterocycles.[2,6,7]



Scheme **H**

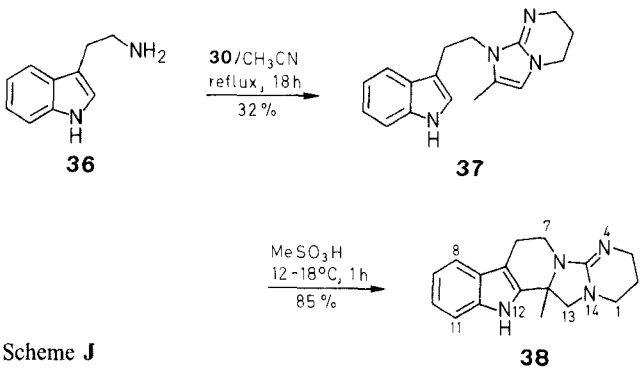


Scheme **I**

Similarly the pyrrole ring may be used as a π-nucleophile. When 2-aminoethyl-1-methyl pyrrole **29** is reacted with **30** substitution of the methylthio group, intramolecular amination of the triple bond,[13] and 1,3-H shift occur in one step, yielding **32**. (Scheme **I**). Methanesulfonic acid induces formation of the tetracyclic compound **33**, a pyrimido[1′,2′:1,2]imidazo[3,4-*a*]-pyrrolo[3,2-*c*]pyridine.

If **30** is replaced by butynyl derivative **31** as reactant partner of **29**, the 6-membered ring **34** is formed, which is surprising at first glance, but according to Baldwin[15] is a favoured 6-*Endo-Dig* process. This, however, does not explain why the potentially competing 5-*Exo-Dig* process does not occur here. Intramolecular electrophilic aromatic substitution of **34** gives rise to formation of **35**, an isomer of **33**, the ring system constituting an imidazo-[1′,2′-1,2]pyrimido[3,4-*a*]pyrrolo[3,2-*c*]pyridine.

Finally we tested the feasibility of ring A being replaced by an indole moiety. Thus substrate **36** is transformed by a reaction sequence analogous to Scheme **I** (**29** → **33**) via **37** into the pentacyclic structure **38** (Scheme **J**). This fusion proceeds under mild conditions with excellent yield. The obtained β-carboline **38**, a pyrimido[1″,2″:1′,2′]imidazo[3′,4′:1,2]pyrido[3,4-*b*]indole, simultaneously represents a cyclic guanidine, and is closely related to many indole alkaloids. Therefore compounds of this type bear the potential of exhibiting useful biological properties.



36 **37** **38**

Scheme **J**

Attempts were made also to use furan and imidazole rings as π-nucleophiles in annulation reactions along the lines of Schemes **C** and **I**. These experiments, however, were unsuccessful. The results of all cyclizations performed by the Typical Procedure are summarized in the Table.

Table. Preparation of Heterocycles according to the Typical Procedure

Substrate	Reaction Conditions: Temp. (°C)/Time (h)	Product	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS m/z (%)
5	20/9	**7a** · HCl	26	239–242	see experimental section		
5	20/9	**7b** · HCl	11	249–252	see experimental section		
8	40–80/12.5	**9**	81	253–256	$C_{16}H_{17}N_3O_3$ (299.3)	2.96 (t, 2H, J = 7), 3.84–4.17 (m, 6H), 3.91 (s, 3H), 3.94 (s, 3H), 5.72 (s, 1H), 6.70, 7.07 (2s, 2H)	–
10	60/3	**12**	18	111–116	$C_{18}H_{25}N_3O_2$ (315.4)	1.32–3.52 (m, 15H), 3.87 (s, 6H), 4.48 (m, 2H), 6.62 (s, 2H)	315 (100), 300 (80)
11	20–50/3	**13**	48	85–90	$C_{17}H_{23}N_3O_2$ (301.4)	1.56–4.11 (m, 14H), 3.85 (s, 3H), 3.87 (s, 3H), 4.60 (dd, 1H, J = 4, 12), 6.61 (s, 1H), 6.62 (s, 1H)	–
16	20/7	**17**	81	214–216	$C_{21}H_{23}N_3O_2$ (349.4)	2.36–4.19 (m, 10H), 3.84 (s, 3H), 3.88 (s, 3H), 6.66 (s, 2H), 7.33 (m, 5H)	–
19	20/1	**21**	51	220–225	$C_{22}H_{25}N_3O_2$ (363.5)	2.33–4.06 (m, 12H), 3.90 (s, 3H), 3.97 (s, 3H), 6.88, 7.02 (2s, 2H), 7.16–7.34 (m, 5H)	–
20	20/1.5	**22** · HCl	67	257–259	$C_{22}H_{25}N_3O_2 \cdot HCl \cdot 0.5H_2O$ (408.9)	2.45–4.25 (m, 12H), 3.86 (s, 6H), 6.79, 6.82 (2s, 2H), 7.05–7.43 (m, 5H)[b]	–
26a	20/0.7	**27**	41	88–90	$C_{12}H_{15}N_3S$ (233.3)	1.67 (s, 3H), 2.36–4.14 (m, 10H), 6.75 (d, 1H, J = 5), 7.18 (d, 1H, J = 5)	–
26b	20/0.7	**28**	63	159–161	$C_{12}H_{15}N_3S$ (233.3)	1.60 (s, 3H), 2.42–4.19 (m, 10H), 6.81 (d, 1H, J = 5), 7.14 (d, 1H, J = 5)	–
32	20–50/22	**33**	39	136–137	$C_{14}H_{20}N_4$ (244.3)	1.52 (s, 3H), 1.76 (m, 2H), 3.48 (s, 3H), 3.21, 3.47 (2d, 2H, J = 8), 2.16–4.22 (m, 8H), 5.96 (d, 1H, J = 3), 6.53 (d, 1H, J = 3)	244 (65), 229 (100)
34	20/2.5	**35**	32	139–141	$C_{14}H_{20}N_4$ (244.3)	1.99 (s, 3H), 3.48 (s, 3H), 1.99–4.56 (m, 12H), 5.88 (d, 1H, J = 3), 6.50 (d, 1H, J = 3)	244 (80), 229 (100)
37	12–18/1	**38**	85	308 (dec)	$C_{17}H_{20}N_4$ (280.4)	1.66 (s, 3H), 1.74 (m, 2H), 2.49–4.12 (m, 8H), 3.33, 3.69 (2d, 2H, J_{AB} = 8), 7.10, 7.18, 7.39, 7.49 (m, 4H)[b]	280 (70), 265 (100)

[a] Satisfactory microanalyses obtained: C, H, Cl, N, S < ±0.4, except **12**, C −0.61.
[b] Recorded in CD_3OD.

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on Bruker instruments, usually on the WH-90 unit, if not stated otherwise, routinely using TMS as internal standard. Mass spectra were recorded on a Varian-MAT-CH7 mass spectrometer, operated on line with an Incos 2100 data system. Experimental conditions: electron energy 70 eV, ion source temperature 200 °C, emission current 300 μA; direct insertion probe with manual temperature control; scan range *m/z* 10-650 in 5 or 6 seconds.

TLC used Merck silica gel plates of type 60 F_{254} and 0.25 mm layer thickness; Schlittler's Reagent was used as indicator.

Compound **1** was prepared in analogy to 2-(β-hydroxyethylamino)-2-imidazoline[16] from 3,4-dimethoxyphenethylamine **14**.

Compounds **10** and **11** were prepared from 2-[2-(3,4-Dimethoxyphenyl)ethylamino]-4,5,6,7-tetrahydro-1*H*-diazepine and 2-[3-(3,4-Dimethoxyphenyl)propylamino]-4,5-dihydroimidazole, respectively, by reaction with acrolein in analogy to the procedure for **3**.

10; yield: 68%, oil; TLC: R_f = 0.54, mobile phase: 2-butanol/HCO_2H (85%)/water (15:3:2).

^{1}H-NMR (CDOD, 250 MHz): δ = 1.47–1.77 (m, 4H, $2CH_2$), 2.73–3.80 (m, 13H, $6CH_2$ + CH), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.74–6.94 (m, $3H_{arom}$).

11; yield: 57%, oil; TLC: major spot at R_f = 0.31 and minor impurity at R_f = 0.15, mobile phase: THF/MeOH/ammonia (16:4:3).

2-[2-(3,4-Dimethoxyphenyl)ethylamino]-1-phenacyl-4,5-dihydroimidazole (**16**) was obtained as its HCl salt starting from **14** and **15** similar to a literature procedure.[17] **16** · HCl; yield: 32%; cream colored crystals; mp 127–129 °C.

^{1}H-NMR (DMSO-d_6): δ = 2.75 (t, 2H, *J* = 7 Hz, CH_2Ar), 3.42 (m, 2H, NCH_2), 3.67 (s, 3H, OCH_3), 3.71 (m, 4H, CH_2CH_2), 3.76 (s, 3H, OCH_3), 5.26 (s, 2H, CH_2C=O), 6.64–7.09 (m, $3H_{arom}$), 7.45–8.14 (m, $5H_{arom}$), 8.80 (t, 1H, *J* = 6 Hz, NH), 9.13 (s, 1H, NH).

Compound **19** was prepared as its HCl salt from **14** · HCl and **18** following Ref. 17.

19 · HCl; yield: 92%; white crystals; mp 165–168 °C; TLC: R_f = 0.18, mobile phase: toluene / dioxane / EtOH / ammonia (10:8:3:1).

^{1}H-NMR (CD_3OD): δ = 2.88 (t, 2H, *J* = 7 Hz, CH_2Ar), 3.55 (t, 2H, *J* = 7 Hz, NCH_2), 3.73 (s, 3H, OCH_3), 3.76 (m, 4H, CH_2CH_2), 3.81 (s, 3H, OCH_3), 4.45 (s, 2H, $CH_2C{\equiv}C$), 6.78–6.92 (m, $3H_{arom}$), 7.39 (m, $5H_{arom}$).

8-[(2-(3,4-Dimethoxyphenyl)ethyl]-7-hydroxy-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (3) and 8-[2-(3,4-dimethoxyphenyl)ethyl]-5-hydroxy-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (4):

2-[2-(3,4-dimethoxyphenyl)ethylamino]-4,5-dihydroimidazole (**1**; 20 g, 80.2 mmol) is suspended in CH_3CN (120 mL), and while stirring at r.t., a solution of acrolein (**2a**; 5.6 mL, 83.8 mmol) in CH_3CN (10 mL) is added dropwise within 10 min. After stirring another 4 h at r.t. a precipitate is formed, which is separated by suction, washed successively with CH_3CN and Et_2O and dried affording **4** as colorless crystals; yield: 5.7 g (23%); TLC: single spot, R_f = 0.085; mobile phase: EtOAc/*i*-PrOH/ammonia (21:15:6).

^{1}H-NMR (CD_3OD): δ = 1.89 (m, 2H, CCH_2C), 2.81 (t, 2H, *J* = 7 Hz, CH_2Ar), 3.32 (t, 2H, *J* = 7 Hz, NCH_2), 3.49 (m, 6H, $3NCH_2$), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.85 (t, 1H, *J* = 3 Hz, CH), 6.67–7.00 (m, $3H_{arom}$).

After standing at r.t. for 40 h, a second solid crystallizes from the mother liquor. Recrystallization from *i*-PrOH, washing and drying gives **3** as white crystals; yield: 12 g (49%); TLC: single spot at R_f = 0.17, with minor impurity; mobile phase: EtOAc/*i*-PrOH/ammonia (21:15:6).

^{1}H-NMR (CD_3OD): δ = 1.88 (m, 2H, CCH_2C), 2.82 (t, 2H, *J* = 7 Hz, CH_2Ar), 3.16 (t, 2H, *J* = 7 Hz, NCH_2), 3.43 (m, 6H, $3NCH_2$), 3.77 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.63 (t, 1H, *J* = 3 Hz, CH), 6.69–7.10 (m, $3H_{arom}$).

8,9-Dimethoxy-1,2,5,6,11,12-hexahydro-10b*H*-imidazo[1′,2′:1,2]pyrimido[4,3-*a*]isoquinoline (6):

A mixture of **3** (3.7 g, 12.1 mmol), Ac_2O (5.7 mL, 60.6 mmol) and glacial AcOH (30 mL) is refluxed for 12 h, concentrated under reduced pressure, toluene (ca. 50 mL) is added and evaporated again. The oily residue is treated with water (50 mL), Et_2O (50 mL) and 5 N NaOH (ca. 30 mL). The precipitated crystals are separated by suction, washed with Et_2O, dissolved in CH_2Cl_2 and filtered. The filtrate is concentrated *in vacuo* and the solid residue washed with Et_2O and dried, giving **6**, as cream-colored crystals; yield: 1.7 g (49%); mp 126–129 °C.

$C_{16}H_{21}N_3O_2$	calc.	C 66.88	H 7.37	N 14.62
(287.4)	found	66.66	7.32	14.52

^{1}H-NMR ($CDCl_3$): δ = 1.73–3.91 (m, 11H, $5CH_2$ + CH), 3.87 (s, 6H, $2OCH_3$), 4.44 (t, 2H, *J* = 8 Hz, $=NCH_2$), 6.66, 6.70 (2s, $2H_{arom}$).

MS: *m/z* = 287 (M^+), 272 ($M^+ - CH_3$).

8-[(2-(3,4-Dimethoxyphenyl)ethyl]-7-hydroxy-5-phenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (5):

To a stirred suspension of **1** (24.93 g, 100 mmol) in CH_3CN (320 mL), cooled to 15 °C is added a solution of *trans*-cinnamic aldehyde (**2b**; 13.23 mL, 106 mmol) in CH_3CN (40 mL) in the course of 45 min. After stirring for 3 h at r.t. the mixture becomes a clear solution and another 2 h later precipitation starts. Altogether after 21 h at r.t. the separated crystals are collected, washed with CH_3CN and EtOAc and dried to give white crystals (33.1 g). From the mother liquor another crop of crystals (2.74 g) is obtained. The two solid portions are combined and chromatographed over a short column of silica gel (300 g) using THF/MeOH/ammonia (80:20:1) as eluent. The collected fractions are combined, concentrated under reduced pressure, and the residue is washed with Et_2O and dried affording colorless crystals (21.16 g). From the Et_2O washings another crop of colorless solid (4.0 g) can be obtained; total yield: 25.16 g (66%); mp 147–148 °C; TLC: single spot R_f = 0.55; mobile phase: EtOAc/*i*-PrOH/ammonia (21:15:6).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.00 (m, 2H, CCH_2C), 2.45–3.58 (m, 8H, $4CH_2$), 3.86, 3.96 (2s, 6H, $2OCH_3$), 4.16 (m, 1H, HCO), 4.25 (dd, 1H, *J* = 10, 3 Hz, HCPh), 4.76 (s, 1H, OH), 6.89 (m, $3H_{arom}$), 7.38 (m, $5H_{arom}$).

MS: *m/z* = 381 (M^+), 363 ($M^+ - H_2O$).

(±)-*cis*- and *trans*-8,9-Dimethoxy-12-phenyl-1,2,5,6,11,12-hexahydro-10b*H*-imidazo[1′,2′:1,2]pyrimido[4,3-*a*]isoquinoline (7a and 7b); Typical Procedure:

Compound **5** (21 g, 55 mmol) and $MeSO_3H$ (55 mL) are combined resulting in a dark red solution. TLC control after 9 h stirring at r.t. shows the reaction to be complete. The mixture is poured onto crushed ice (200 g), made alkaline by addition of 5 N NaOH (250 mL) and extracted with CH_2Cl_2 (2 × 250 mL). The combined organic phases are dried ($MgSO_4$) and concentrated *in vacuo*; the residue is taken up in EtOAc and filtered. The filtrate is again concentrated under reduced pressure and dried yielding a brown solid (17.56 g), which on TLC displays mainly 2 spots at R_f = 0.53 and 0.43 [mobile phase: EtOAc/*i*-PrOH/ammonia (21:15:6)]. The solid is chromatographed over a column of silica gel (1880 g) using THF/MeOH/ammonia (16:4:3) as eluent. The fractions containing the faster moving material are combined and concentrated *in vacuo*. The residue is suspended in water and dissolved by addition of 2 N HCl until pH 2 is reached. After a short period, colorless crystals precipitate from the solution, which are separated and dried in an oven at 50 °C to give **7a** as hydrochloride salt; yield: 5.7 g (26%); mp 239–242 °C.

$C_{22}H_{25}N_3O_2 \cdot HCl$	calc.	C 66.07	H 6.55	N 10.51	Cl 8.86
(399.9)	found	66.03	6.52	10.42	8.95

^{1}H-NMR (CD_3OD): δ = 1.83–4.17 (m, 10H, $5CH_2$), 3.74 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.74 (dd, 1H, *J* = 10.6, 4.2 Hz, CHAr), 4.96 (dd, 1H, *J* = 10.6, 3 Hz, CHPh), 6.79 (s, $1H_{arom}$), 6.85 (s, $1H_{arom}$), 7.42 (s, $5H_{arom}$).

For the purpose of X-ray analysis the compound is dissolved in hot EtOH (95%), cooled and slowly evaporated, yielding **7a** · HCl in monohydrate form.

$C_{22}H_{25}N_3O_2 \cdot HCl \cdot H_2O$, M_r = 417.94, triclinic, space group PI. a = 10.378 (3), b = 13.481 (2), c = 16.511 (5) Å, α = 75.86 (2), β = 84.45 (3), γ = 81.88 (2)°, V = 2214.4 Å^3, Z = 4 (2 independent molecules), D_c = 1.25 g · cm^{-3}. μ = 17.5 cm^{-1}. 7539 unique reflections were measured (at room temperature) on a CAD-4 Enraf-Nonius automatic diffractometer using CuKα monochromatized radiation ($\bar{\lambda}$ = 1.54178 Å), $\theta/2\theta$ scan mode to a θ = 65°. 5256 reflections with $I \geq 3\sigma(I)$ were considered observed. The structure was solved by direct methods (MULTAN 80) and Fourier techniques which showed the two independent water molecules originating from the crystallization process. Block-diagonal matrix least squares were used for the refinement, anisotropic for all the non-hydrogen atoms. When necessary the hydrogen atoms were searched in ΔF synthesis, if not they were introduced in calculated positions; the ones from water were not found. The final R value was 0.093 (5256 reflections, 749 parameters).

The fractions from the column containing the slower moving material are also combined and treated as above, leading to the isolation of **7b** · HCl; yield 2.42 g (11%); mp 249–252°C.

$C_{22}H_{25}N_3O_2 \cdot HCl$ (399.9)	calc.	C 66.07	H 6.55	N 10.51	Cl 8.86
	found	65.81	7.87	10.37	8.99

^{1}H-NMR (CD_3OD): δ = 2.10–4.17 (m, 10H, 5CH_2), 3.73 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.56 (dd, 1H, J = 10, 4 Hz, CHPh), 4.77 (d, 1H, J = 4 Hz, CHAr), 6.55 (s, 1 H_{arom}), 6.79 (s, 1 H_{arom}), 7.42 (m, 5 H_{arom}).

MS: m/z (%) = 363 (M^+, 100), 348 (75), 258 (20).

8-[2-(3,4-Dimethoxyphenyl)ethyl]-2,3,5,6,7,8-hexahydroimidazo [1,2-*a*]pyrimidine-5,7-dione (8):

Compound **1** (7.48 g, 30 mmol), diethyl malonate (5.47 mL, 36 mmol) and DMF (75 mL) are combined and refluxed for 1 h. The mixture is concentrated *in vacuo* and the residue chromatographed on silica gel (100 g) using THF as eluent. The collected fractions containing pure material are combined, the solvent evaporated under reduced pressure, the residue washed with Et_2O and dried furnishing **8** as ivory-colored crystals; yield: 3.2 g (34%); mp 172–173°C; TLC: R_f = 0.3; mobile phase: THF/MeOH (4:1).

^{1}H-NMR (DMSO-d_6): δ = 2.64–4.12 (m, 10H, 5CH_2), 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.67–7.02 (m, 3 H_{arom}).

MS: m/z (%) = 317 (M^+, 5), 248 (10), 164 (100).

8,9-Dimethoxy-10b-phenyl-1,2,5,6,11,12-hexahydro-10b*H*-imidazo [1′,2′:1,2]pyrimido[4,3-*a*]isoquinoline (21):

A mixture of **19** (10.1 g, 27.8 mmol), $HgSO_4$ (1.52 g), water (44.7 mL) and conc. H_2SO_4 (1.78 mL) is stirred for 17.5 h at 55–60°C. TLC control (eluent: EtOAc/MeOH/AcOH [5:5:1]) shows the reaction to be complete. The solution is concentrated *in vacuo*, toluene (2 × 50 mL) is added and each time evaporated under reduced pressure. The residual raspberry-colored oil, which contains the intermediate keto compound, is subjected to cyclization according to the Typical Procedure (see above) resulting in the formation of **21** as indicated in the Table.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-2-benzylidene-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole (20):

A mixture of **19** · HCl (14 g, 35 mmol), NaH dispersion (55–60% in oil, 1.53 g, 35 mmol) and 2-methoxyethanol (140 mL) is refluxed for 1.5 h. The solvent is evaporated *in vacuo* and the residue taken up in water (150 mL) and adjusted to pH 2 by addition of 2N HCl. After extracting with Et_2O (100 mL), the aqueous layer is neutralized (pH 6–7) by addition of 2N NaOH and once more extracted with Et_2O (100 mL). The aqueous solution is treated with 2N NaOH (6 × 2 mL) portionwise, followed each time by an extraction step with Et_2O (6 × 50 mL). The first 4 extracts of the latter procedure, which according to TLC contain uniform material, are combined, filtered and concentrated *in vacuo*. The oily residue crystallizes after 1 d. Washing with Et_2O and drying yields **20** as ivory-colored crystals. Yield: 2.7 g (21%), mp 108–110°C; TLC: R_f = 0.31, mobile phase: EtOAc/*i*-PrOH/ammonia (70:30:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 2.44 (m, 2H, CH_2Ar), 3.12 (t, 2H, J = 7 Hz, NCH_2), 3.58 (m, 2H, NCH_2), 3.76 (s, 3H, OCH_3), 3.78 (s, 2H, CH_2C=C), 3.81 (s, 3H, OCH_3), 3.98 (t, 2H, J = 7 Hz, =NCH_2), 5.62 (s, 1H, HC=C), 6.24 (m, 2 H_{arom}), 6.63 (d, 1 H_{arom}, J = 8 Hz), 7.29 (m, 5 H_{arom}).

1-(2-Propynyl)-2-(2-thien-3-ylethylamino)-4,5-dihydro-1*H*-imidazole (25a):

From 3-(2-aminoethyl)thiophene (**23a**; 19.08 g, 150 mmol) and 1-(2-propynyl)-2-methylthio-4,5-dihydroimidazole hydrochloride (**24** · HCl, 28.6 g, 150 mmol) according to the procedure for **19**. **25a** · HCl; ivory-colored crystals; yield: 29.6 g (73%); mp 155–157°C.

^{1}H-NMR (CD_3OD): δ = 2.93 (t, 1H, J = 3 Hz, C≡CH), 2.95 (t, 2H, J = 7 Hz, CH_2Ar), 3.54 (t, 2H, J = 7 Hz, CH_2N), 3.70 (m, 4H, CH_2CH_2), 4.23 (d, 2H, J = 3 Hz, CH_2C≡C), 7.07 (m, 1H, H-4), 7.23 (m, 1H, H-2), 7.38 (m, 1H, H-5).

1-(2-Propynyl)-2-(2-thien-2-ylethylamino)-4,5-dihydroimidazole (25b):

Analogous to the above mentioned procedure 2-(2-aminoethyl)thiophene (**23b**, 19.08 g, 150 mmol) and **24** · HCl (28.6 g, 150 mmol) are reacted affording **25b** · HCl as cream-colored crystals; yield: 32 g (79%); mp 165–167°C.

^{1}H-NMR (CD_3OD): δ = 2.94 (t, 1H, J = 3 Hz, HC≡C), 3.17 (t, 2H, J = 7 Hz, CH_2Ar), 3.57 (t, 2H, J = 7 Hz, CH_2N), 3.74 (m, 4H, CH_2CH_2), 4.25 (d, 2H, J = 3 Hz, CH_2C≡C); 6.96 (d, 2H, J = 3.5 Hz, H-3 + H-5), 7.27 (t, 1H, J = 3.5 Hz, H-4).

1-[2-(3-Thienyl)ethyl]-2-methyl-5,6-dihydro-1*H*-imidazo[1,2-*a*] imidazole (26a):

Compound **25a** · HCl (26.36 g, 97.7 mmol) is reacted as described for **20**, and the resultant residue heated for 30 min in 2N HCl (100 mL) to 50–60°C and the mixture worked up in analogy to the preparation of **20**. The obtained base **26a** is transformed into its hydrochloride; yield: 15.18 g (65%); mp 201–206°C.

^{1}H-NMR (CD_3OD): δ = 1.96 (d, 3H, J = 1 Hz, CH_3), 3.10 (t, 2H, J = 7 Hz, CH_2Ar), 4.08 (t, 2H, J = 7 Hz, NCH_2), 4.18 (m, 4H, CH_2CH_2), 6.73 (q, 1H, J = 1 Hz, HC=C), 6.99 (m, 1H, H-4), 7.16 (m, 1H, H-2), 7.41 (m, 1H, H-5).

1-[2-(2-Thienyl)ethyl]-2-methyl-5,6-dihydro-1*H*-imidazo[1,2-*a*] imidazole (26b):

Compound **25b** · HCl (25.98 g, 96.3 mmol) is reacted as described above giving **26b** · HCl as cream-colored crystals; yield: 15.46 g (60%); mp 209–217°C (dec.)

^{1}H-NMR (CD_3OD): δ = 1.95 (d, 3H, J = 1 Hz, CH_3), 3.27 (t, 2H, J = 7 Hz, CH_2Ar), 4.10 (t, 2H, J = 7 Hz, NCH_2), 4.16 (m, 4H, CH_2CH_2), 6.74 (q, 1H, J = 1 Hz, HC=C), 6.91, 7.02, 7.30 (m, 3 H_{arom}).

1-[2-(1-Methyl-2-pyrrolyl)ethyl]2-methyl-1,5,6,7-tetrahydroimidazo [1,2-*a*]pyrimidine (32):

A mixture of 2-(2-aminoethyl)-1-methylpyrrole (**29**; 17.39 g, 140 mmol), 2-methylthio-1-(2-propynyl)-1,4,5,6-tetrahydropyrimidine hydrochloride (**30** · HCl; 28.66 g, 140 mmol) and CH_3CN (290 mL) is refluxed for 22 h. The mixture is concentrated *in vacuo*, taken up in water (180 mL) and extracted with EtOAc (100 mL). A solution of 10N NaOH (2 mL) is added to the aqueous phase, which again is extracted with EtOAc (100 mL). Then 10N NaOH (4 × 4 mL) is added portionwise to the aqueous solution, each time followed by an extraction step with EtOAc (4 × 100 mL). Finally the aqueous phase is made strongly alkaline by addition of 10N NaOH (100 mL) and again extracted with EtOAc (2 × 100 mL).

The last two extracts are united, concentrated *in vacuo*, the residue dissolved in EtOAc (200 mL), treated with charcoal and filtered. Addition of Et_2O (600 mL) to the filtrate causes a precipitate to form, from which the solution is decanted. Concentration of the solution *in vacuo* yields a dark brown oil; yield: 22.87 g (ca. 65%); TLC: main product at R_f = 0.24 with impurities at R_f = 0.28 and R_f = 0.32; mobile phase: 2-butanol/HCO_2H (85%)/water (15:3:2).

8-[2-(1-Methylpyrrol-2-yl)ethyl]-7-methyl-2,3,5,8-tetrahydroimidazo[1,2-*a*]pyrimidine (34):

A mixture of **29** (17.4 g, 140 mmol) and 2-methylthio-1-(2-butynyl)-4,5-dihydroimidazole hydrochloride (**31** · HCl, 34.4 g,

168 mmol) is reacted analogous to Ref. 16 affording 2-[2-(1-methylpyrrol-2-yl)ethylamino]-1-(2-butynyl)-4,5-dihydroimidazole hydrochloride; yield: 42.77 g (ca. 100%); TLC: R_f = 0.33 with minor impurity of **31** at R_f = 0.83; mobile phase: EtOAc/*i*-PrOH/ammonia (21:15:6).

This intermediate (28 g, 100 mmol) is combined with NaH dispersion (55–60% in oil, 4.4 g, 100 mmol) and 2-methoxyethanol (280 mL) and refluxed for 2 h. The solvent is evaporated *in vacuo*, the residue dissolved in water (200 mL) and 2 N HCl (ca. 70 mL) and the solution is extracted with Et_2O (2 × 150 mL). After neutralizing the aqueous solution by addition of 2 N NaOH, one more extraction with Et_2O is performed. To the resultant aqueous phase 5 N NaOH (5 × 5 mL) is added successively, each time followed by an extraction step with Et_2O (5 × 100 mL). After TLC control, extracts no. 2–4 are combined, dried ($MgSO_4$), and concentrated under reduced pressure leaving **34** as a light brown oil; yield: 17.31 g (71%); TLC: R_f = 0.83 with three minor impurities at R_f = 0.38, 0.48 and 0.87; mobile phase: EtOAc/*i*-PrOH/ammonia (21:15:6).

The structure of **34** is deduced from end product **35** (Table).

1-[2-(3-Indolyl)ethyl]-2-methyl-1,5,6,7-tetrahydroimidazo[1,2-*a*] pyrimidine (37):

Tryptamine hydrochloride (**36** · HCl, 20.94 g, 106.5 mmol) and **30** (21.5 g, 127.8 mmol) are reacted as described above for **32**. Compound **37** (12 g) is obtained as cream-coloured crystals.

^{1}H-NMR (DMSO-d_6): δ = 1.74 (d, 3 H, J = 1 Hz, CH_3), 1.85 (m, 2 H, CCH_2C), 3.05 (t, 2 H, J = 7 Hz, CH_2Ar), 3.46 (m, 2 H, NCH_2), 3.64 (t, 2 H, J = 7 Hz, NCH_2), 3.87 (m, 2 H, $=NCH_2$), 5.85 (m, 1 H, HC=C), 6.85–7.61 (m, 5 H_{arom}), 7.72 (s, 1 H, NH).

MS: m/z (%) = 280 (M^+, 5), 137 (100).

Using ethereal HCl, **37** (12 g) is transformed into its hydrochloride **37** · HCl (10.63 g, 32%); mp 190–192 °C. This salt is used for the cyclization according to the Typical Procedure to prepare **38** (Table).

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