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Synthesis and Structure Elucidation of Pyrimidobenzimidazoles and Fused Derivatives II [1]. Dodecahydrobenzimidazo-[2,1-*b*]quinazolines and Decahydrobenzimidazo-[2,1-*b*]benzo[*h*]quinazolines [2]

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Summary. The cyclization reactions of *trans*-3a-hexahydro-2-benzimidazolamine with 2-alkylidene- and 2-benzylidenecyclohexanones and α-tetralones, respectively, yield mixtures of two isomeric condensates each. Thorough high resolution NMR analyses (^{1}H and ^{13}C NMR, HH-COSY, *gs*-HSQC, *gs*-HMBC, 1D TOCSY, and 1D NOE difference spectra) revealed that the corresponding isomers are in all cases linearly fused diastereomeric 12α- and 12β-substituted *trans*-6aα-dodecahydrobenzimidazo[2,1-*b*]quinazolines and 7α-substituted *trans*-8aβ- and *trans*-8aα-decahydrobenzimidazo[2,1-*b*]benzo[*h*]quinazolines, respectively. The formation of corresponding angularly fused regioisomers was not observed so far. The stereochemistry and the tautomerism of some bases and their hydrochlorides as well as the regiospecific course of the cyclization reactions are discussed. Biological tests showed that the novel compounds don't exert remarkable antibacterial and antimycotic effects.

Keywords. Benzimidazo[2,1-*b*]benzo[*h*]quinazolines, *trans*-8a-decahydro; Benzimidazo[2,1-*b*]quinazolines, *trans*-6a-dodecahydro; Conformational analysis; Cyclizations, regiospecific; NMR Spectroscopy.

Introduction

In the course of investigations on dihydropyrimidines and their fused derivatives, *Wendelin et al.* [3–10] have prepared, among others, N^2-cyclohexylhexahydro-2-quinazolinamines **1**, decahydroquinazolino[2,3-*b*]quinazolines **2**, and benzo[*h*]-fused derivatives **3** with remarkable antifungal and other pharmacological activities [7–10]. In order to improve these effects, we have designed and synthesized various compounds with near structural relationship to the above mentioned bases [1, 10]. In this paper we report on dodecahydrobenzimidazo[2,1-*b*]quinazolines **4**

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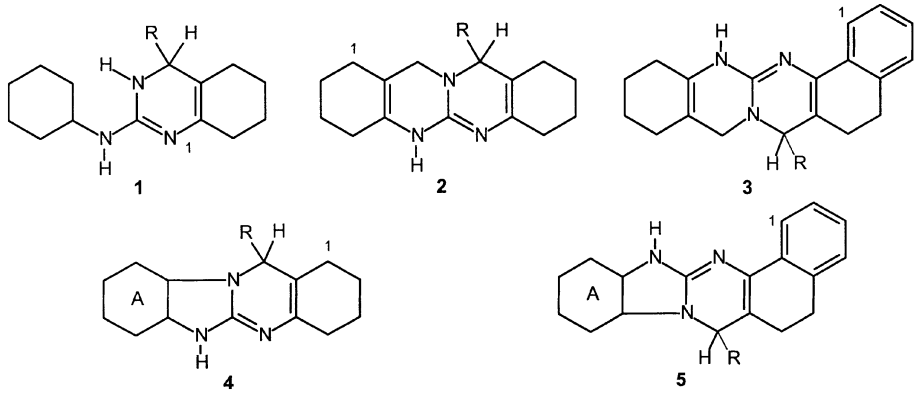
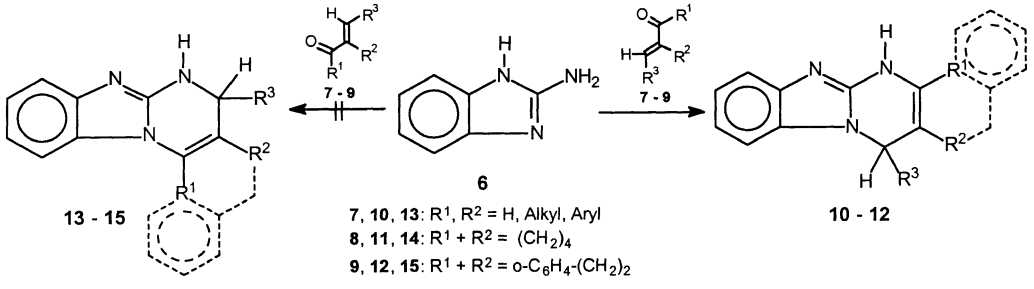
and decahydrobenzimidazo[2,1-*b*]benzo[*h*]quinazolines **5** which represent bridged and five-ring analogues of **1**, **2**, and **3** (Scheme 1).



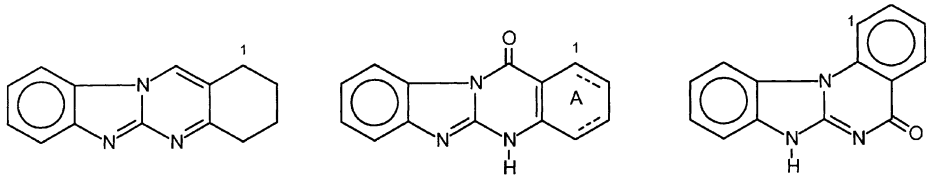
Scheme 1

A literature search revealed that compounds of type **4** and **5** are so far unknown. The more unsaturated analogues **11**, **12**, and the pyrimidobenzimidazoles **10** have been prepared by reaction of benzimidazolamine **6** and enones **8**, **9**, and **7**, respectively [1, 11–13]. As has been recently reported [1, 10, 11], these annelation reactions proceed regiospecifically under addition of the ring- and amine-N of **6** to β- and carbonyl-C of enones **7–9**, and afforded, after elimination of water, exclusively the bases **10–12**. The common feature of these condensates is the enamino group in the 1,2,3-position of the pyrimidobenzimidazole unit. Regioisomers **13** with enamino groups in the 5,4,3-position and fused derivatives **14** and **15**, respectively, have not been generated (Scheme 2). At this point it should be mentioned that 2-imidazolin- as well as di- and tetrahydro-2-pyrimidinamines have been shown to react with enones in an analogous regiospecific way [4, 7–10].



Scheme 2

In the course of the literature search we also found reports on more unsaturated benzimidazo[2,1-*b*]quinazolines **16** and isomeric benzimidazoquinazolinones **17–19** which have been synthesized by annelation reactions of **6** with 2-hydroxymethylenecyclohexanone [14], 2-oxocyclohexanecarboxamide [15], and 2-aminobenzoyl chloride [16].



16 **17** (ring A = cyclohexene)
18 (ring A = benzene) **19**

Scheme 3

Reports on pharmacological properties exist so far only in the case of substituted pyrimidobenzimidazoles of type **13** which exert neuroleptic effects [17] and PAF antagonism [18].

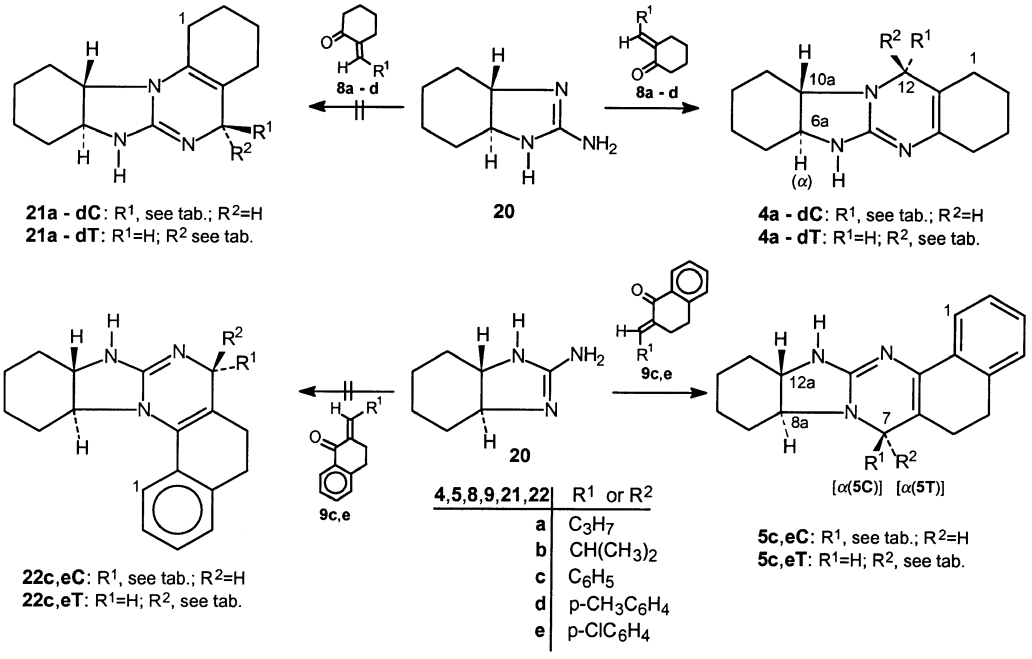
Results and Discussion

Synthesis of the target compounds **4** *and* **5**

Target compounds **4** and **5** should be synthesized (in analogy to **11** and **12**) by reaction of (racemic) *trans*-3a-hexahydro-2-benzimidazolamine **20** with 2-benzylidene- and alkylidenecyclohexanones **8a–d** [19, 20] and α-tetralones **9c,e** [21]. **20**, first mentioned in Ref. [22] as a by-product of the synthesis of 1,2-cyclohexylenediguanidine, was prepared from *trans*-1,2-cyclohexanediamine and cyanogen bromide.

After annelation of **20** with enones **8** and **9**, the generated bases were isolated in the usual way. According to TLC, all bases and hydrochlorides seemed first to be homogenous, but NMR analyses revealed that in all cases mixtures of two (racemic) diastereomers had been generated. Thus, the products were mixtures of 12α- and 12β-substituted *trans*-6aα-1,2,3,4,6,6a,7,8,9,10,10a,12-dodecahydrobenzimidazo[2,1-*b*]quinazolines **4a–dC** and **T**, and of 7α-substituted *trans*-8aβ- and *trans*-8aα-5,6,7,8a,9,10,11,12,12a,13-decahydrobenzimidazo[2,1-*b*]benzo-[*h*]quinazolines **5c,eC** and **T**.

C and **T** in the compound numbers point to the *cis*- or *trans*-position of H-10a and H-12, characteristic of diastereomers **4C** and **T**, and of H-8a and H-7, significant for the benzo-fused diastereomers **5C** and **T**, respectively. Regioisomers of type **21C** and/or **T** and **22C** and/or **T** have so far neither been detected as components of the crystalline products nor in the evaporated filtrates (Scheme 4). As for the use of the designations α and β, and to the formulae in Schemes and Figures, cf. Refs. [23–25].



Scheme 4 [23, 24]

Treatment of the crude mixture of the 7α-(4-chlorophenyl) compounds **5eC** and **5eT** with hydrochloric acid yielded a mixture of 7-(4-chlorophenyl)-5,6,8a,9,10,11,12,12a-octahydrobenzimidazobenzoquinazoline hydrochloride **23e** · HCl and salt **5eT** · HCl (Scheme 6).

Elucidation of structure and stereochemistry of condensates **4C,T** *and* **5C,T** *by NMR spectroscopy*

The structures and (partly) conformations of bases **4a–d** as well as **5c,eC** and **T** and their hydrochlorides, respectively, were established by high resolution NMR analyses based upon ^{1}H and ^{13}C NMR, HH-COSY [26], *gs*-HSQC [27], *gs*-HMBC [28], NOE difference [29], and 1D TOCSY [30] experiments. The procedure employed for the structure elucidations is lined out in the following on the example of the two-component mixture of the hydrochlorides of bases **4cC** and **4cT**. The numbering of H- and C-atoms in the following paragraphs refers to the (continuous) numbering of the respective bases and hydrochlorides as applied in Tables 1,2 and Figs. 1–3.

Assignment of C and H signals, gross constitution of the dodecahydrobenzimidazoquinazoline skeleton of **4cC** · HCl *and* **4cT** · HCl

The ^{1}H NMR spectrum of products **4cC** · HCl and **4cT** · HCl showed in scarcely occupied regions (NH-protons, *o*-protons of the phenyl substituents, methine protons in 6a, 10a, and 12-position) two sets of signals with an intensity ratio of 2:1

for the two (1:1)-condensates. In accordance with that fact, but more distinctly, two signal sets appear in the ^{13}C NMR spectrum (Table 1).

Typical triplet-doublet signals for the axial protons H-6aα and H-10aβ, respectively, between 2.6 and 3.3 ppm can serve as a starting point for tracing the H-7*ax,eq* and H-10*ax*,*eq* coupling chains of the cyclohexane ring in the HH-COSY spectra. Further evalution of the homonuclear ^1H shift correlation and the 1D TOCSY spectra with the assignment of H-8*ax*,*eq* and H-9*ax*,*eq* complete the skeleton of the cyclohexane moiety. The observed homoallylic long-range coupling and the ^4J-coupling between methine protons H-12 and the nearly equivalent methylene protons at C-4 on the one hand and the aromatic *o*-protons H-14,18 on the other afford the entrance into the cyclohexene moiety and the phenyl ring of **4cC** · HCl and **4cT** · HCl. Two sets of two signals each for NH-protons H-5 and H-6 argue for N,N,N′,N″-tetrasubstituted guanidine moieties as links of the cyclohexane and benzylcyclohexene substructures.

Inspection of the *gs*-HSQC spectra enables the assignment of H-bearing carbon atoms. Additionally, the *gs*-HMBC spectra reveal long-range connectivities, among others, between the centrally situated methine proton H-12 and C-5a of the benzimidazol unit, C-12a, C-4a, C-1 and C-4 of the cyclohexene ring, and C-13 as well as C-14,18 of the phenyl substituent. Corresponding long range connectivities of the methylene protons at C-1 and C-4 and of the aromatic *o*-protons H-14,18 with C-12 are also visible.

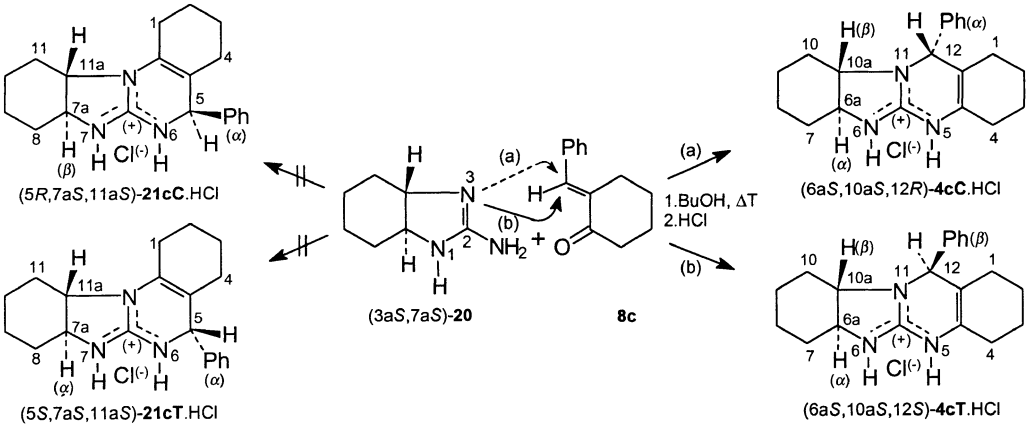
Combination of the above informations afforded the chemical shifts of all hydrogen and carbon atoms of **4cC** · HCl and also of **4cT** · HCl with only few insecurities (the signals for C^8H_2- and, partly, C^1H_2- and C^2H_2-protons of the minor product **4cT** · HCl coincided with the signals of the main product **4cC** · HCl, see Table 1). However, the data showed only that both products possess the skeleton of a dodecahydrobenzimidazoquinazoline.

Orientation of the annelation reaction: both products are regioisomers of type **4** *and represent diastereomeric trans-6aα-12α- and 12β-phenyldodecahydrobenzimidazo[2,1-b]quinazolines* **4cC** *and* **4cT**

Depending on the (*i*) regio- and (*ii*) stereocontrol of the annelation reaction of *trans*-hexahydrobenzimidazolamine **20** with benzylidenecyclohexanone **8c**, the two condensates and their hydrochlorides could *a priori* be (*i*) regioisomers of type **4c** and/or **21c**, and (*ii*) moreover, in case of each regioisomer, again two (racemic) diastereomers each, *i.e. trans*-6aα-12α- and 12β-phenyldodecahydrobenzimidazo[2,1-*b*]quinazolines **4cC** and **4cT**, and 5α-phenyl-*trans*-7aβ-and *trans*-7aα-phenyldodecahydrobenzimidazo[1,2-*a*]quinazolines **21cC** and **21cT** [23, 24], or tautomers thereof (Scheme 5).

Careful weighing and comparison of the chemical shifts of the corresponding protons in 6a,7,8- and 10a,10,9-position of the cyclohexane rings gave unequivocal hints that both components of the mixture, **4cC** · HCl and **4cT** · HCl, are regioisomers of type **4**.

In particular, the quartet-doublet signal at 0.78 ppm (**4cC** · HCl) and the triplet-doublet at 2.61 ppm (**4cT** · HCl) are distinctly highfield shifted by approximately



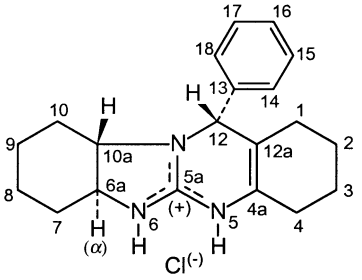
Scheme 5 [24]

0.7 ppm and 0.6 ppm. In case of **4cC** · HCl, the characteristic quartet-doublet at 0.78 ppm is obviously generated by coupling with one geminal, two *anti*-periplanar, and only one equatorial coupling partners ($^2J_{gem} = {}^3J_{ax,ax} = 12.3$ Hz, $^3J_{ax,eq} = 3.2$ Hz) and must hence belong to proton H-7*ax* or H-10*ax* of **4cC** or **4cT** · HCl, or H-8*ax* or H-11*ax* of regioisomer **21cC** or **21cT** · HCl. In case of **4cT** · HCl, the triplet-doublet at 2.61 ppm ($^3J_{ax,ax} = 12.2$ Hz, $^3J_{ax,eq} = 3.2$ Hz) belongs unambiguously to an axially oriented proton at a bridgehead (H-6a or H-10a, H-7a, H-11a) of one of the four isomers.

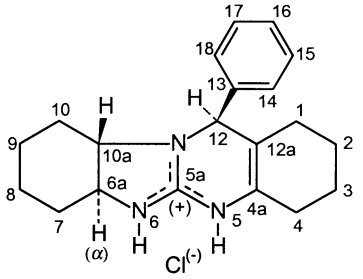
In case of both compounds, **4cC** · HCl and **4cT** · HCl, the highfield shifts of the mentioned protons point towards anisotropic shielding effects of facing phenyl rings. A glance at the formulae of the four possible isomers showed that the observed anisotropy effects are only present in case of the linearly fused regioisomers **4cC** · HCl and **4cT** · HCl with near spatial vicinity of the phenyl ring in position 12 and protons H-10*ax* and H-10a, respectively, but not in case of their regioisomers **21cC** · HCl and **21cT** · HCl. Further studies revealed that the anisotropy effect of the phenyl ring in **4cC** · HCl influences not only H-10*ax*, but to a similar extent (−0.6 ppm) also the geminal proton H-10*eq* (1.45 ppm). The linear structures of **4cC** · HCl and **4cT** · HCl were independently also proved by the HH-COSY spectra of the mixture, which showed in case of both compounds long-range couplings between H-12 and H-10a.

Additional considerations using *Dreiding* models revealed that the anisotropy effect of the phenyl ring at C-12 towards H-10*ax*α, observed in case of **4cC** · HCl, can only be expected if these groups are arranged *cis* and at the α-face (compare Fig. 1 and Ref. [23]). Consequently, as a characteristic of this diastereomer, H-12 and H-10aβ are also oriented *cis*, but situated at the β-face. These conditions are fulfilled only in case of *trans*-6aα-12α-phenyldodecahydrobenzimidazo[2,1-*b*]quinazoline **4cC** · HCl. *Vice versa*, the anisotropy effect of the phenyl ring towards H-10aβ of **4cT** · HCl can only emerge in case of a *cis*-arrangement of the phenyl substituent at C-12 and H-10aβ at the β-face, resulting in a *trans*-position of

Table 1. NMR data of 12α- and 12β-phenyl-1,2,3,4,5,6a,7,8,9,10,10a,12-dodecahydro-*trans*-6aα-benzimidazo[2,1-*b*]quinazoline hydrochlorides **4cC** · HCl and **4cT** · HCl (400 MHz ^{1}H / 100 MHz ^{13}C, *DMSO*-d_6, 300 K) [23]



4cC · HCl [24]



4cT · HCl [24]

		^{13}C	^{1}H$^{\text{multiplicity}}$($^3J_{HH}$/Hz)	^{13}C	^{1}H$^{\text{multiplicity}}$($^3J_{HH}$/Hz)
1	CH_2	24.57	*a*:1.39^{m}	24.93	*a*: 1.35^{m}
			b: 1.64^{m}		*b*: 1.55^{m}
2	CH_2	21.36	*c*: 1.50 concealed	21.52	*c*: 1.52 concealed
			d: 1.68 concealed		*d*: 1.70 concealed
3	CH_2	21.82	1.52$^{m,\ broad}$	21.77	1.67$^{m,\ broad}$
4	CH_2	25.50	2.26^{m}	25.29	2.33^{m}
4a	C	125.44	–	126.95	–
5	NH	–	10.89^{s}	–	11.05^{s}
5a	C	154.77	–	155.60	–
6	NH	–	8.66^{s}	–	8.55^{s}
6a	CH	61.91	3.25$^{t\ d}$ (12.3/3.2)	61.43	3.24$^{t\ d}$ (12.2/3.2)
7	CH_2	28.77	*ax*: 1.48$^{qua/d}$ (13.0/3.2)	28.81	*ax*:1.47$^{qua/d}$ (12.4/3.2)
			eq: 2.19^{dd} (13.0/3.2)		*eq*: 2.18^{dm} (12.4)
8	CH_2	23.36	*f*: 1.22$^{m,\ broad}$	23.36	*f*: 1.24 (?)
			g: 1.77^{dm} (12/3.2)		*g*: 1.71 (?)
9	CH_2	23.68	*ax*: 1.19$^{qua/t}$ (12.4/3.3)	23.56	*ax*: 1.05$^{qua/t}$ (12.8/3.2)
			eq: 1.64$^{d\ m}$ (12.4)		*eq*:1.80$^{d\ m}$ (12.8)
10	CH_2	28.67	*ax*: 0.78$^{qua/d}$ (12.3/3.2)	26.38	*ax*: 1.37$^{qua/d}$ (12.6/3.4)
			eq: 1.45$^{d\ m}$ (12.3)		*eq*: 2.04$^{d\ m}$ (12.6)
10a	CH	67.68	3.20$^{t\ d}$ (12.3/3.2)	63.49	2.61$^{t\ d}$ (12.2/3.2)
12	CH	62.42	4.82^{s}	60.04	4.73^{s}
12a	C	108.37	–	109.80	–
13	C	140.52	–	136.90	–
14/18	CH	127.55	7.31$^{d\ d}$ (8.0/1.4)	127.35	7.22$^{d\ d}$ (7.8/1/2)
15/17	CH	128.76	7.34–7.42	129.28	7.39$^{t\ d}$ (7.2/2)
16	CH	128.67	7.34–7.42	129.24	7.37$^{t\ m}$ (12.3)

H-10aβ and proton H-12 at the opposite α-face - steric relations which exist in case of the 12β-phenyl diastereomer **4cT** · HCl.

Analogous NMR analyses of the originally prepared (1.2:1)-mixture of bases showed that the components represented, as expected, corresponding diastereomeric bases **4cC** and **4cT**, respectively.

Stereochemistry of bases **4cC** *and* **4cT** *and their hydrochlorides*

The stereochemistry of **4cC** and **4cT** and their hydrochlorides could partly already be deduced by interpretation of the above cited chemical shifts and signal patterns of the various protons. Succeeding $^1H\{^1H\}$ 1D NOE difference measurements afforded valuable complementary informations. They proved again and independently the postulated structures of bases **4cC** and **4cT** and their salts, allowed to ensure the ^1H assignments especially of those signals which are concealed among the non-first-order aliphatic region, and provided substantial informations for the establishment of provisonal stereo formulae. Table 1 shows the complete signal sets, Fig. 1 possible stereoformulae of salts **4cC** · HCl and **4cT** · HCl with arrows symbolizing NOEs of diagnostic value.

In particular, irradiation of the singlet of H-12 (4.82 ppm, Fig. 1) of **4cC** · HCl caused a distinct enhancement of the triplet-doublet for H-10aβ at 3.20 ppm; the C^4H_2-protons (2.26 ppm) gave NOEs with the N^5H-protons (10.89 ppm). These interactions prove again the linearly fused structure of a benzimidazo[2,1-*b*]quinazoline and, moreover, the *cis*-arrangements of H-12 and H-10aβ, significant for diastereomer **4cC** · HCl. In accordance with that, NOEs between H-10*ax*α (0.78 ppm) and the *o*-protons H-14,18 (7.31 ppm) indicated the *cis*-arrangement of H-10*ax* and the phenyl group at the α-face [23].

In case of diastereomer **4cT** · HCl, the linear structure could similarly be deduced from NOEs between H-12 (4.73 ppm) and H-10*eq* (2.04 ppm), and N^5H and C^4H_2 (11.05 and 2.33 ppm), respectively. Strong NOEs between H-10aβ (2.61 ppm) and the *o*-protons H-14,18 (7.22 ppm) corroborated the *cis*-arrangement of H-10a and the phenyl ring at the β-face, and accordingly the *trans*-position of H-10aβ and H-12 at the opposite α-face, which is characteristic of the diastereomer **4cT** · HCl.

Further NOEs recorded for **4cC** · HCl and **4cT** · HCl enabled the assignment of proton signals hidden in the strongly overlapped region between 1.3 and 2.2 ppm and the determination of their position. In particular, NOEs could be observed between the axially upward directed protons H-6aα, H-8*ax*, and H-10*ax*, and the downward directed protons H-10aβ, H-7*ax*, and H-9*ax*, respectively. The observed interactions reveal, just as the interpretation of the characteristic ^1H signal multiplicity of the respective protons (Table 1), the chair forms of the fused cyclohexane rings of **4cC** · HCl and **4cT** · HCl. The same chair conformation was found in case of the cyclohexylene moiety of *trans*-hexahydrobenzimidazolamine hydrobromide **20** · HBr (see Experimental).

The signals of the four pairs of methylene protons of the cyclohexene ring of **4cC** · HCl and **4cT** · HCl appeared in the range of 1.38/1.59 ppm (H_a and H_b of C^1H_2) and 2.29 ppm (C^4H_2). Distinctly differentiated signals for the geminal proton pairs with patterns characteristic of axially and equatorially directed protons, as observed in case of the cyclohexane rings and expected for stable half-chair or boat conformations [1], didn't emerge. These findings argue for conformational flexibility of the cyclohexene rings.

On the other hand, NOEs between protons H_b and H-12 reveal that these protons are located in close spatial proximity in both diastereomers. Studies of *Dreiding* models showed that this could be realized in case of half-chair as well as

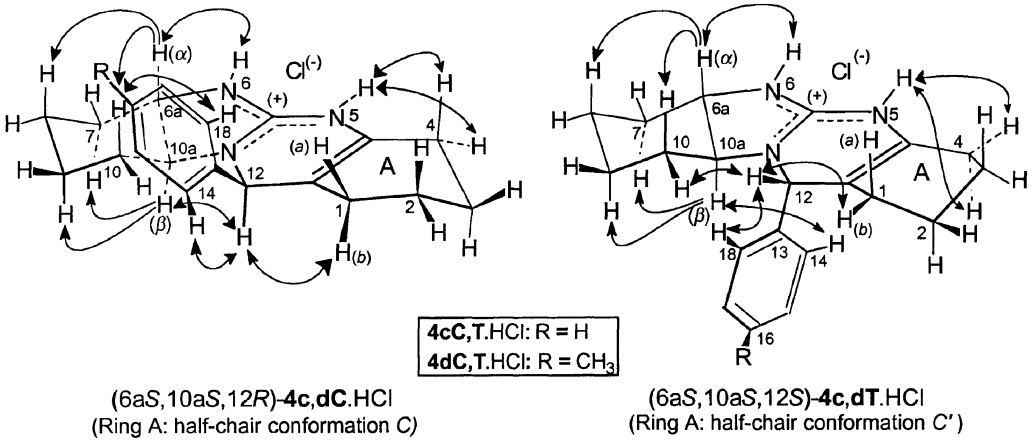


Fig. 1. Stereoformulae of diastereomers **4c**,**dC** · HCl and **4c**,**dT** · HCl [23,24] (arrows indicate observed NOEs)

of boat conformations of the cyclohexene ring. Figure 1 shows exemplarily stereoformulae for **4cC** · HCl and **4cT** · HCl with half-chair conformations *C* and *C′* of the cyclohexene moiety. In case of conformers *C*, protons H_b and H-12 are at one face, and protons H_a and the phenyl substituent are at the opposite face of the ring systems. In case of conformers *C′*, protons H_b and H-12 are also in spatial vicinity, but *trans*-arranged. H_a and phenyl group are in this case located at opposite faces of the ring system. Analogous stereo formulae with boat conformations *D* and *D′* of the cyclohexene ring could also be formulated (Fig. 2).

The observed highfield shift of the signals for protons H_a could be caused either by the shielding of H_a by facing phenyl rings in *cis*-position, as *e.g.* shown in Fig. 1 for **4cC** · HCl, or by the preferably axial position of protons H_a as pointed out for **4cT** · HCl. Both types of conformers are consistent with the so far available data and represent flexible conformations. However, further NMR investigations will be necessary to clarify whether the protons H-12 and H_b of the two diastereomers are *cis*- or *trans*-arranged in *DMSO*-d_6 solution.

Finally, the observed strong NOEs between the methine protons H-12 and the *o*-protons (H-14,18) of the phenyl substituent should be mentioned. They point, together with the above described (phenyl ring caused) highfield shifts of the flanking protons (H-10*ax* and *eq* in case of **4cC** · HCl, H-10a in case of **4cT** · HCl) and studies of *Dreiding* models, towards the existence of rotationally hindered phenyl substituents and an approximately perpendicular arrangement of phenyl and dihydropyrimidine ring in both diastereomers.

Peculiarities concerning the structure elucidation of condensates **4a,b,dC** *and* **T**

Analogous NMR investigations were accomplished with products **4a,b** and **d** generated by the reactions of *trans*-hexahydrobenzimidazolamine **20** with 2-alkylidenecyclohexanones **8a,b** and the 2-(*p*-methylbenzylidene) derivative **8d**, and with salts **4a,d** · HCl. As anticipated above, all products turned out as mixtures of two (racemic) diastereomers, *i.e.* of 12α- and 12β-substituted *trans*-6aα-dodeca-

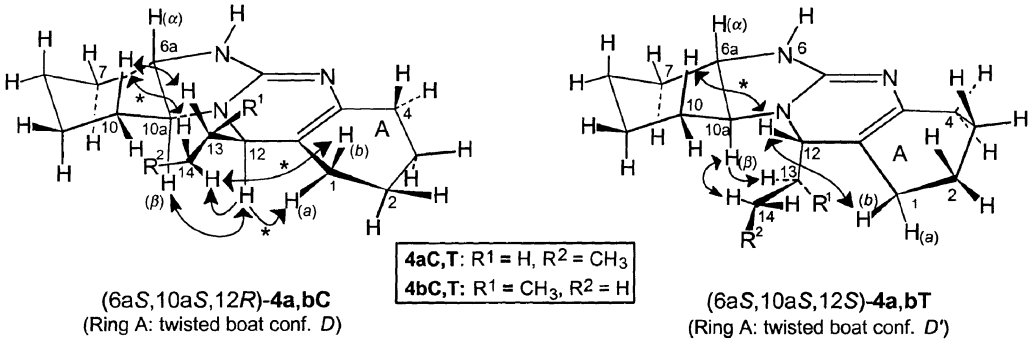


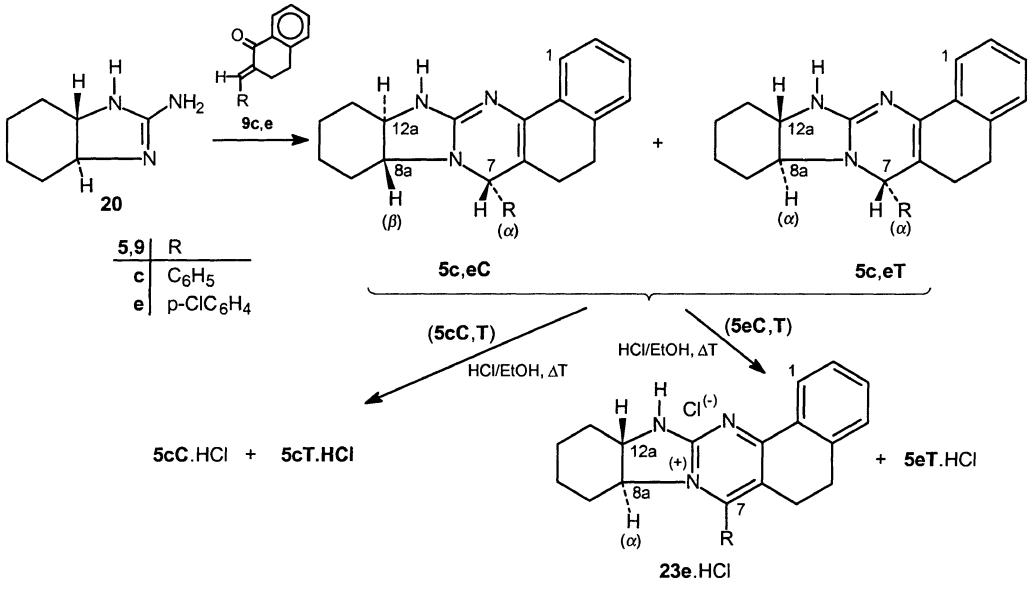
Fig. 2. Stereoformulae of diastereomers **4a**,**bC** and **4a**,**bT** (arrows indicate observed NOEs; if marked with an asterisk, they were found only in case of **4bC** or **4aT**)

hydrobenzimidazoquinazolines **4a,b,dC** and **T** (Scheme 4). Regiospecifity and diastereoselectivity of the ring closure reactions correspond to the above deduced findings for the 12-phenyl analogues **4cC** and **4cT**.

In addition, it should be noted that in case of the 12-propyl and 12-isopropyl compounds **4a** and **bC** the *cis*-position of protons H-12 and H-10aβ could again be ascertained due to mutual NOEs (Fig. 2). In accordance with these findings, complementary NOEs between H-10*ax*α and methine and methyl protons of the isopropyl group (H-13 and H-14), observed in case of **4bC**, indicate the *cis*-arrangement of these substituents at the α-face. In case of diastereomers **4a,bT** the *trans*-position of H-12 and H-10aβ follows from the NOEs between H-10aβ and protons H-13 and H-14 of the propyl and isopropyl substituent, respectively. Complementary, the *trans*-position of H-12 and H-10aβ in **4aT** can be deduced from NOEs between H-12 and H-10*ax*α, which show the *cis*-position of these protons at the α-face. In case of the isopropyl compound **4bC** the observed NOEs between methyl protons of the isopropyl group (H-14) and protons H_b at C-1, as well as between protons H-12 and H_a at C-1, indicate *cis*-arrangement of these proton pairs. Figure 2 shows possible stereoformulae of **4a,bC** and **T**, whereby the cyclohexene moieties are now exemplarily presented in slightly twisted boat conformations *D* and *D*′.

Structure elucidation of decahydrobenzimidazo[2,1-b]benzo[h]quinazolines **5c,eC** *and* **T**; *7-(4-chlorophenyl)octahydrobenzimidazo[2,1-b]benzo[h]quinazoline* **23eC**

The annelation reactions of hexahydrobenzimidazolamine **20** with the 2-benzylidene-α-tetralones **9c** and **e** afforded again mixtures of (racemic) diastereomers which represent the 7α-aryl-*trans*-8aβ- and *trans*-8aα-5,6,7,8a,9,10,11,12,12a,13-decahydrobenzimidazo[2,1-*b*]benzo[*h*]quinazolines **5c,eC** and **T**, respectively. The transformation of the (0.7:1)-mixture of **5cC** and **5cT** into the hydrochlorides yielded a (0.8:1)-mixture of **5cC** · HCl and **5cT** · HCl. In contrast, treatment of the crude (1.5:2)-mixture of 7α-(4-chlorophenyl) compounds **5eC** and **5eT** with ethanolic hydrochloric acid, evaporation of the solvent, and recrystallization of the residue generated a mixture of 7-(4-chlorophenyl)-*trans*-8aα-5,6,8a,9,10,11,12,12a-octahydrobenzimidazo[2,1-*b*]benzo[*h*]quinazoline hydrochloride (**23e** · HCl) and **5eT** · HCl.



Scheme 6 [24]

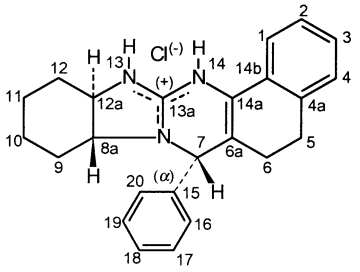
Detailed NMR studies as in the case of **4cC** and **4cT** showed that the benzimidazopyrimidine substructures of **5c,eC** and **T**, with cyclohexane rings in chair conformation and perpendicularly arranged aryl substituents at C-7, are nearly identical with the corresponding substructures of **4cC** and **4cT**. The assignment of the protons of the fused benzene ring of salts **5c,eC** and **T** · HCl was successful starting from the downfield shifted signals for the aromatic proton H-1 which gave NOEs to $N^{14}H$.

Two pairs of signals with a rather similar signal pattern in the range of 1.8–2.2 and 2.5–2.8 ppm were characteristic of the ethano bridges between the pyrimidine and benzene rings. On account of *gs*-HSQC and *gs*-HMBC experiments, the signals at higher field could be assigned to the methylene protons H_a and H_b at C-6, neighbouring the chiral center C-4, and the signals at lower field to the benzyl protons H_c and H_d at C-5 (Table 2).

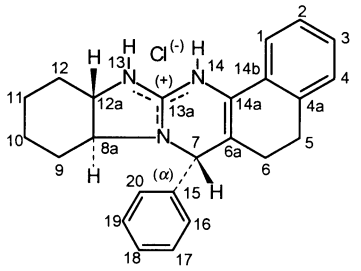
NOEs between methine protons H-7 and H_b at C-6 of **5c,eC** and **T** · HCl, respectively (Fig. 3), indicated that these protons are in spatial vicinity and could be *cis*-arranged. The signals for protons H_a are slightly highfield shifted in comparison with the signals for H_b which points towards anisotropic effects of the facing phenyl rings at C-7. Figure 3 shows a stereoformula with puckered (half-chair-like) conformation of the cyclohexadiene moiety for diastereomer **5cC** · HCl which is consistent with these findings. On the other hand, protons H_a and phenyl group could also be arranged *trans* and at opposite faces of the ring systems. The highfield shift of H_a could in this case result from the axial position. The conformational formula for diastereomer **5cT** · HCl in Fig. 3 is consistent with this second, alternative model.

Additional informations about the conformation of the cyclohexadiene moiety followed from the detailed analyses of the typical signal patterns for protons

Table 2. NMR data of 7α-phenyl-5,6,7,8a,9,10,11,12,12a,13-decahydro-*trans*-8aβ- and *trans*-8aα-benzimidazo[2,1-*b*]benzo[*h*]quinazoline hydrochlorides **5cC** · HCl and **5cT** · HCl (400 MHz ^{1}H / 100 MHz ^{13}C, $CDCl_3$, 300 K) [23]



5cC · HCl [23, 24]



5cT · HCl [23, 24]

		^{13}C	^{1}H$^{\text{multiplicity}}$ ($^{3}J_{HH}$/Hz)	^{13}C	^{1}H$^{\text{multiplicity}}$ ($^{3}J_{HH}$/Hz)
1	CH	122.19	7.88^{d} (7.6)	122.29	7.93^{d} (7.6)
2	CH	127.43	7.37^{t} (7.8)	127.51	7.38 (concealed)
3	CH	128.73	7.23^{t} (7.6)	128.78	7.22^{t} (7.6)
4	CH	127.54	7.08^{d} (7.4)	127.63	7.11^{d} (7.8)
4a	C	127.01	–	126.85	–
5	CH_2	27.60	*c*: 2.61$^{d\ t}$ (15.0/7.4)	27.69	*c*: 2.66$^{d\ t}$ (15.6/7.8)
			d: 2.75$^{d\ t}$ (15.2/7.6)		*d*: 2.79$^{d\ t}$ (14.6/7.3)
6	CH_2	23.51	*a*: 1.73^{m}, partly concealed	24.17	*a*: 1.97$^{d\ t}$ (15.0/7.6)
			b: 1.94 (13.3/6.8)		*b*: 2.24$^{d\ d\ d}$ (16.2/9.1/7.2)
6a	C	110.11	–	111.18	–
7	CH	62.14	5.13^{s}	60.11	4.99^{s}
8a	CH	67.87	3.28$^{t\ d}$ (12.0/3.2)	63.74	2.68$^{t\ d}$ (12.2/23.2)
9	CH_2	28.75	*ax*: 0.80$^{qua/d}$ (12.6/3.2)	26.56	*ax*: 1.45$^{qua/d}$ (12.0/3.6)
			eq: 1.49^{d} (12.2)		*eq*: 2.08$^{d\ m}$ (12.2)
10	CH_2	23.83	*ax*: 1.19$^{m,\ broad}$	23.51	*ax*: 1.07$^{qua/t}$ (12.8/3.6)
			eq: 1.66$^{d\ m}$ (11.2)		*eq*: 1.80^{d} (12.8)
11	CH_2	23.69	*ax*: 1.38$^{qua/m}$ (13.0)	23.69	*ax*: 1.42$^{qua/m}$ (12.8)
			eq: 1.82^{d} (12.4)		*eq*: 1.77^{d} (12.4)
12	CH_2	28.85	*ax*: 1.28$^{qua\ m}$ (12.6)	28.85	*ax*: 1.32$^{qua/m}$ (13.0/3.2)
			eq: 2.17^{d} (12.6)		*eq*: 2.18^{d} (12.4)
12a	CH	62.09	3.32$^{t\ d}$ (12.0/3.2)	61.62	3.31$^{t\ d}$ (12.0/3.2)
13/14	2NH	–	9.05^{s}/11.63^{s}	–	9.01^{s}/11.81^{s}
13a	C	155.97	–	156.73	–
14a	C	125.18	–	125.62	–
14b	C	134.00	–	134.98	–
15	C	140.05	–	136.47	–
16/20	CH	127.96	7.37^{b}	127.68	7.28^{m}
17/19	CH	128.96	7.38^{b}	129.51	7.41$^{t\ d}$ (7.2/2)
18	CH	129.07	7.38^{b}	129.66	7.39^{m}

H_a–H_d. These signals (each approximately a five line system, line distance about 7.4 Hz, intensity ratio 1:2:2:2:1) resulted from the partial overlap of the six lines of doublet-triplets, generated each by one geminal (~14.7 Hz) and two vicinal couplings (~7.3 Hz) with neighbouring protons of the ethano bridges. These

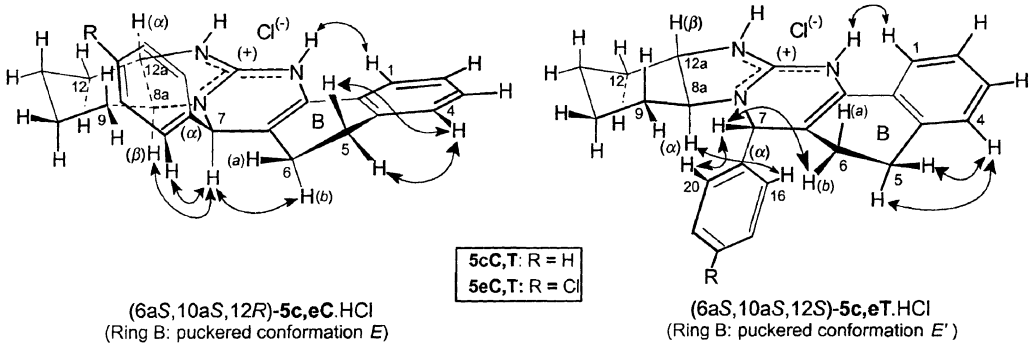


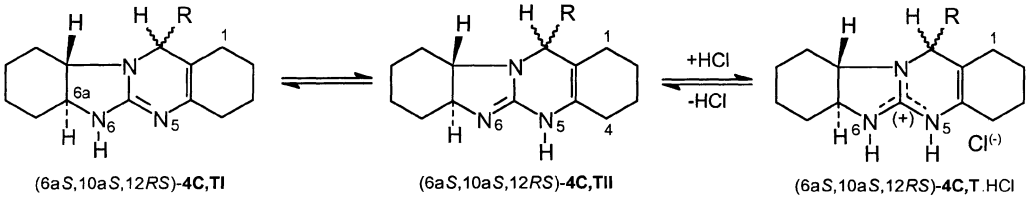
Fig. 3. Stereoformulae of diastereomers **5c**,**eC** · HCl and **5c**,**eT** · HCl [23,24] (arrows indicate observed NOEs)

findings argue against stable conformations with axially and equatorially directed protons, and point towards the existance of flexible conformations of ethano bridges and the whole cyclohexadiene moieties of **5c,eC** and **T** in solution. Nevertheless, it is so far not clear whether protons H-7 and H_b are *cis*- or *trans*-arranged and, accordingly, if the molecules exist (in the average) as conformers of type *E* or *E*′.

For the NMR analysis of 7-(4-chlorophenyl)octahydrobenzimidazobenzoquinazoline hydrochloride **23eC** · HCl with aromatic pyrimidine ring see Experimental.

Tautomerism of bases **4C** *and* **T, 5C** *and* **T**, *and their hydrochlorides*

The appearence of two sharp singlets each for the NH-protons H-5 and H-6 of salts **4a,c,dC** and **T** · HCl, and H-13 and H-14 of salts **5c,eC** and **T** · HCl, respectively, showed that these salts contained stable guanidinium ions with 2 substituents at each of the three nitrogen atoms as substructures. In contrast, no definite signals for NH-protons could be observed in the ^{1}H NMR spectra of solutions of the bases **4,5C** and **T** in *DMSO*-d_6. These findings pointed towards a rapid exchange of NH-protons between N-5 and N-6 (N-13 and N-14) and the existance of an equilibrium between the possible tautomeric forms **4C,TI** and **II** and **5C,TI** and **II**, respectively, in *DMSO*-d_6 solutions (Scheme 7).



Scheme 7 [24]

However, in case of the mixture of *trans*-6aα-12α- and 12β-propyldodecahydrobenzimidazoquinazoline **4aC** and **4aT**, the ^{1}H NMR spectrum in $CDCl_3$ showed a broad signal for NH-protons at 4.68 ppm, which on irradiation gave scalar enhancements of the vicinal hydrogen atoms H-6a of **4aC** (3.01 ppm) and **4aT** (2.91 ppm), but no NOE with the methylene protons at C-4. This finding pointed towards a preferred existence of **4aC** and **4aT** as tautomers **I** in $CDCl_3$.

For reasons of simplification, the bases **4** and **5** in this paper are formulated, vicariously for the actual mixture of tautomers, as tautomers **I** with the mobile NH-proton attached to the (more basic) nitrogen atoms N-6 and N-13 of the imidazol moieties of **4** and **5**, respectively.

Mechanism of the regiospecific annelation reactions and a note concerning their diastereoselectivity

The following discussion is carried out on hand of the annelation reaction of hexahydrobenzimidazolamine (3a*S*,7a*S*)-**20** (as a substitute for racemic *trans*-3a-**20**) with benzylidenecyclohexanone **8c** and refers to Scheme 5.

According to earlier accomplished NMR investigations [31], enone **8c** exists in solution as (*E*)-isomer, and we assume that the enone participates in this form in the reaction. The cyclization reactions obviously start with a regiospecific (but not diastereospecific) addition of N-3 of *S*,*S*-**20** to the β-carbon atom of enone (*E*)-**8c** from the *Re*-face (backside, a) or *Si*-face (front, b) of **8c** (Scheme 5; a: dotted arrow, b: standard arrow). Subsequent addition of the amino group to the carbonyl group and elimination of water yields in case (a) the (6a*S*,10a*S*,12a*R*)-enantiomer of *trans*-6aα-12α-phenyldodecahydrobenzimidazo[2,1-*b*]quinazoline **4cC** with *cis*-arranged hydrogen atoms H-10a and H-12, and in case (b) the (6a*S*,10a*S*,12a*S*)-enantiomer of 12β-diastereomer **4cT** with H-10a and H-12 in *trans*-position. Analogous reaction of (3a*R*,7a*R*)-**20** with (*E*)-**8c** yields the mirror image isomers (6a*R*,10a*R*,12a*S*)-**4cC** and (6a*R*,10a*R*,12a*R*)-**4cT**.

As for the diastereoselectivity of the reaction, it must be stated that the total amounts and ratios of diastereomers of type **C** and **T** in the reaction mixtures were only determined in case of **4b** and **4c**. The NMR analyses of the respective crude products showed that they consisted of a (1.5:1)-mixture of **4bC** and **4bT** and of a (1:1)-mixture of **4cC** and **4cT** in total yields (**C**+**T**) of ~52% and ~66%, respectively, and some impurities each. Hints at corresponding regioisomers **21** didn't emerge. Accordingly, the annelation reactions seemed to take place, so far as investigated, regio specifically, but without distinct diastereoselectivity.

Attempts to produce mixture with distinct excess of 12α- or 12β-phenyl diastereomer, **4cC** or **4cT**, from amine **20** and enone **8c** by variation of solvent (toluene, dimethylformamide) and reaction temperature were not successful. However preliminary experiments showed that mixtures of diastereomers **4cC** and **4cT** and their salts could be separated by means of combinations of fractionated crystallization, chromatography, and auxiliary reagents, and that the preparation of the enantiomers of **4cC** or **4cT**, respectively, will also be possible. Detailed procedures for the preparation of diastereomers and enantiomers of some pharmacologically highly active mixtures will be reported in a forthcoming paper.

Results of biological tests

Compounds **4a,c** and **5c** ((**C**:**T**)-ratios 2:1, 1.2:1, and 0.7:1) were tested for antibacterial (*Staphylococcus aureus*, ATCC 6538; *Enterococcus faecalis*, ATCC 29212; *Bacillus subtilis*, ATCC 1813; *Bacillus cereus*, ATCC 11778; *Escherichia coli*, ATCC 25922; *Pseudomonas aeruginosa*, ATCC 27853) and antifungal effects (*Candida albicans*, ATCC 10231; *Trichophyton mentagrophytes*, ATCC 9533; *Aspergillus niger*, ATCC 16404). The antimicrobial tests were carried out by means of the disk diffusion method [32]. At concentrations of 0.1 mg/cm^3 (disk contents 0.02 cm^3/0.06 cm^3; disk diameter 6 mm/9 mm), none of the compounds exerted inhibitory effects to the tested microorganisms. Ciprofloxacin, chloramphenicol, amphotericin B, flucytosine, and other agents, used as standards for control, were highly active. Tests for pharmacodynamic activities are in progress. The results will be reported in due course.

Experimental

Melting points were determined on a *Kofler* melting point apparatus and are uncorrected. Thin-layer chromatograms (TLC) were run on TLC plastic sheets covered with silica gel 60 F254 (E. Merck, Darmstadt); eluation systems: toluene:methanol = 80:20 (ES 1), toluene:methanol = 80:40 (ES 2), toluene:methanol:glacial acetic acid = 80:20:5 (ES 3). The spots were detected by visual examination under UV light (254 and 356 nm). Infrared spectra were recorded with Perkin-Elmer 881 and 2000 FTIR spectrophotometers in KBr disks, frequencies are reported in cm^{-1} (s = strong, m = middle, w = weak).

NMR spectra were acquired 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 and a temperature of 300°K. 1D and 2D NMR experiments were performed using a reverse geometry 5 mm broad-band probehead and a pulsed field gradient unit. The HH-COSY [26], *gs*-HSQC [27], *gs*-HMBC [28], 1D NOE difference [29], and selective 1D TOCSY [30] experiments were performed using pulse programs supplied by the manufacturer. The *gs*-HMBC experiment was optimized for a coupling constant of 8 Hz (62.5 ms). All NOEs were measured in degassed samples. For the 1D NOE experiments, 5 s pre-irradiation times were used. FIDs were exponentially multiplied prior to *Fourier* transformation (LB = 1 Hz). Subsaturating irradiation power levels (typically −6 dB) were carefully adjusted to avoid spill-over effects to adjactent signals. Selective 1D TOCSY experiments were achieved with a series of mixing times for each of the various compounds (typically 0.04–0.12 s). 15–25 mg of the substances were dissolved in 0.5 cm^3 of deuterated solvents. All chemical shifts are reported as δ units (ppm) with *TMS* as internal standard. The assignment of atoms marked with an asterisk is not secured.

Mass spectra were taken with a Finnigan Mat 212 Spectrometer (EI, 120 ev, $R = 1000$) by *R. Saf*, Institute of Chemical Technology of Organic Materials, Technical University Graz. Elemental analyses (including all elements except oxygen) were performed by *J. Theiner*, Institute of Physical Chemistry, University of Vienna; they agreed favourably with the calculated values.

The biological tests were accomplished by Prof. Dr. *F. Reinthaler* and Mag. *U. Eibel*, Institute of Hygiene, Karl-Franzens-University Graz, Austria, according to Ref. [32]. The solutions applied for testing (0.1 mg/cm^3) were prepared by dissolving of 1 mg of **4a,c** and **5c** ((**C**:**T**)-ratios 2:1, 1.2:1, and 0.7:1) in a mixture of 1 cm^3 *DMSO* and 0.25 mg glacial acetic acid and dilution with water to 10 cm^3.

The applied enones, 2-butylidene- and 2-isobutylidenecyclohexanones **8a,b**, 2-benzylidene- and 2-(*p*-methylbenzylidene)cyclohexanones **8c,d**, and 2-benzylidene- and 2-(*p*-chlorobenzylidene)-α-tetralones **9c,e**, were prepared by base catalyzed aldol condensation as described earlier [19–21].

trans-3a-3a,4,5,6,7,7a-Hexahydro-2-benzimidazolamine hydrobromide (**20** · HBr; $C_7H_{14}BrN_3$)

To a cooled solution of 24 g (0.21 mol) of (racemic) *trans*-1,2-cyclohexanediamine in 100 cm^3 of ice-H_2O, a solution of 22 g (0.21 mol) of cyanogen bromide in a mixture of 100 cm^3 H_2O and 20 cm^3 *THF* was added dropwise with stirring at such a rate that the internal temperature did not exceed 30°C. When the addition was finished and the exothermic reaction subsided, the ice bath was removed. The reaction mixture was stirred at room temperature for 3 h, filtered, and evaporated to dryness. The residue was crystallized from ethanol.

Yield: 42.05 g (91%); m.p.: 205°C; IR (KBr): $\nu = 3450$–2800s with 3200w, 3110w, 2950s, 2860m; 1674s, 1596s, 1550s, 1443m, 1379s, 1265s, 1099s, 686s, 616s cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 400 MHz; assignment proved by HH-COSY, *gs*-HSQC, NOE): 1.27 and 1.70 (qua m?, $J = 9.6$ Hz, and d, $J = 10.5$ Hz, 2×2H, H-5*ax*,6*ax* and H-5*eq*,6*eq*, 5-CH_2 and 6-CH_2), 1.33 and 2.00 (qua d, $J = 11.2$, 2.8 Hz, and d, $J = 11.8$ Hz, 2×2H, H-4*ax*,7*ax* and H-4*eq*,7*eq*, 4-CH_2 and 7-CH_2), 3.08 (m, 2H, H-3a and H-7a), 8.01 (s, broad, 4H, H-1, H-3, and NH_2) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz): 23.28 (C-5 and C-6), 28.43 (C-4 and C-7), 62.07 (C-3a and C-7a), 161.75 (C-2) ppm.

General procedure for the preparation of the mixtures of 12α- and 12β-substituted trans-6aα-dodecahydrobenzimidazo[2,1-b]quinazolines **4a–dC** *and* **T**, *7α-substituted trans-8aβ- and trans-8aα-decahydrobenzimidazo[2,1-b]benzo[h]quinazolines* **5c,eC** *and* **T**, *and hydrochlorides of* **4a,c,d** *and* **5c,eC** *and* **T**

Hydrobromide **20** · HBr (8.80 g, 40 mmol) was added to a freshly prepared solution of sodium butylate (0.92 g (40 mmol) Na in 80 cm^3 of dry butanol) and stirred for 0.5 h. Then, 40 mmol of the α,β-unsaturated ketones **8a–d** and **9c,e**, respectively, were added. The mixture is heated to reflux for the indicated time. After cooling, the reaction mixture was diluted with $CHCl_3$ and washed with H_2O to remove NaBr. The organic layer was dried over Na_2SO_4 and evaporated to dryness. For crystallization, the residue was triturated with the indicated solvent.

If the base didn't crystallize, the residue was suspended in 5 cm^3 ethanol. Then 4 *M* ethanolic HCl was added (*pH* 3). The resulting solution was filtered and evaporated to dryness. The obtained residue was recrystallized from the indicated solvent. The same procedure was applied for the preparation of hydrochlorides from bases in general.

(2:1)-Mixture of trans-6aα-12α- and 12β-propyl-1,2,3,4,5,6a,7,8,9,10,10a,12-dodecahydrobenzimidazo[2,1-b]quinazoline (**4aC** and **4aT**; $C_{17}H_{27}N_3$) *and (5:1)-mixture of* **4aC** · HCl *and* **4aT** · HCl ($C_{17}H_{28}ClN_3$)

6.09 g Butylidenecyclohexanone **8a**; time = 2.5 h; solvent: acetone-methanol; TLC (ES 2): $R_f = 0.37$; colourless needles; m.p.: 185–187°C; yield: 4.1 g (37%); IR (KBr): $\nu = 3420/3210/3120$m/w/w (NH), 2935/2860/2820s/m/w (CH_2), 1695 w (C = C-N), 1660/1625/1568m/s/s (C = N, NH), 1448/1438s/s (CH_2), 1377s cm^{-1}.

^{1}H NMR of **4aC** ($CDCl_3$, δ, 400 MHz; the carbon atoms of the propyl substituent are continuously numbered from 13 to 15): 0.87 (t, $J = 7.2$ Hz, 3H, 15-CH_3), 1.29 and 1.45 (2m, 2×1H, 14-CH_2), 1.30 and 2.06 (qua m, $J = 10.4$, and dm, $J = 11.2$ Hz, 2×1H, H-7*ax* and H-7*eq*), 1.33 and 1.80 (qua d, $J = 11.2$, 3.4 Hz, and dm, $J = 12.8$ Hz, 2×1H, H-9*ax* and H-9*eq*), 1.40 and 1.53 (2m, 2×1H, 13-CH_2), 1.43 and 1.56 (2m, 2×1H, H_a and H_b, 1-CH_2), 1.48 and 2.02 (qua d, $J = 12.4$, 2.8 Hz, and dd, $J = 12.4$, 2.8 Hz, 2×1H, H-10*ax* and H-10*eq*), 1.60 and 1.68 (2m, 2×1H, 2-CH_2), 1.60 (m, 2H, 3-CH_2), 1.64 and 1.78 (m and dm, $J = 14.0$ Hz, 2×1H, H-8*ax** and H-8*eq*), 2.01 (m, 2H, 4-CH_2), 2.80 (td, $J = 11.3$, 3.4 Hz, 1H, H-10a), 3.01 (td, $J = 11.3$, 3.4 Hz, 1H, H-6a), 3.91 (s, broad, 1H, H-12), 4.68 (broad, 1H, H-5) ppm; ^{13}C NMR of **4aC** ($CDCl_3$, δ, 100 MHz): 14.37 (C-15), 16.15 (C-14), 23.05 (C-1*), 23.15 (C-2*), 23.93 (C-8), 24.37 (C-9), 25.72 (C-3), 29.89 (C-10), 30.16

(C-4), 30.67 (C-7), 35.13 (C-13*), 58.87 (C-12), 60.29 (C-6a), 67.37 (C-10a), 104.24 (C-12a), 137.04 (C-4a), 157.79 (C-5a) ppm.

^{1}H NMR of **4aT** ($CDCl_3$, δ, 400 MHz; only significant signals cited): 0.85 (t, $J = 7.2$ Hz, 3H, 15-CH_3), 1.24–1.32 (2H, 14-CH_2), 1.28 and 1.99 (2m, 2×1H, H-7*ax** and H-7*eq*), 1.40 and 1.63 (2×1H, H_a and H_b, 1-CH_2), 1.41 (m, broad, 2H, 13-CH_2), 1.44 and 1.82 (2m, 2×1H, H-9*ax** and H-9*eq*), 1.58 (m, 2H, 3-CH_2*), 1.60 and 1.71 (m and d, $J = 12.6$ Hz, 2×1H, H-8*ax** and H-8*eq*), 1.75 and 2.08 (qua d, $J = 12.0$, 3.2, and d, $J = 12.0$ Hz, 2×1H, H-10*ax* and H-10*eq*), 2.02 (m, 2H, 4-CH_2), 2.87 (m, 1H, H-10a), 2.91 (m, 1H, H-6a), 3.82 (t indicated, 1H, H-12), 4.68 (broad, 1H, H-5) ppm; ^{13}C NMR of **4aT** ($CDCl_3$, δ, 100 MHz): 14.44 (C-15), 16.53 (C-14), 23.08 (C-1), 23.31 (C-2*), 24.01 (C-8*), 24.17 (C-9*),27.02 (C-3*), 29.77 (C-10), 30.13 (C-4), 32.52 (C-13), 55.26 (C-12), 59.53 (C-6a), 62.22 (C-10a), 105.49 (C-12a), 138.45 (C-4a), 159.11 (C-5a) ppm.

(5:1)-Mixture of hydrochlorides **4aC** · HCl *and* **4aT** · HCl

Pale yellow crystals; m.p.: 179–182°C (toluene-ethanol); TLC (ES 3): $R_f = 0.44$.

^{1}H NMR of **4aC** · HCl (*DMSO*-d_6, δ, 400 MHz): 0.89 (t, $J = 7.3$ Hz, 3H, 15-CH_3), 1.19–1.36 (2H, 14-CH_2), 1.24 and 1.78 (m, concealed, and d, $J = 11.4$ Hz, 2×1H, H-9*ax* and H-9*eq*), 1.30 and 1.70 (m, concealed, and d, $J = 11.2$ Hz, 2×1H, H-8*ax** and H-8*eq*), 1.35 and 2.08 (m, concealed, and dm, $J = 12.8$ Hz, 2×1H, H-7*ax* and H-7*eq*), 1.42 and 1.61 (2m, 2×1H, H_a and H_b, 1-CH_2), 1.48 (2H, 3-CH_2), 1.52 and 2.19 (m, concealed, and dm, $J = 11.6$ Hz, 2×1H, H-10*ax* and H-10*eq*), 1.55 (m, broad, 2H, 2-CH_2*), 1.63–1.72 (2H, 13-CH_2), 2.07 (m, 2H, 4-CH_2), 3.25 (td, $J = 8.8$, 3.2 Hz, and m, overlapping, 2×1H, H-6a and H-10a), 4.17 (s, broad, 1H, H-12), 8.63 (s, 1H, 6-NH), 10.69 (s, 1H, 5-NH) ppm; ^{13}C NMR of **4aC** · HCl (*DMSO*-d_6, δ, 100 MHz): 13.92 (C-15), 15.46 (C-14), 21.31 (C-3), 21.71 (C-2), 23.06 (C-8), 23.47 (C-9), 24.13 (C-1), 24.92 (C-4), 28.34 (C-7), 28.61 (C-10), 33.87 (C-13), 56.51 (C-12), 61.03 (C-10a), 66.12 (C-6a), 107.09 (C-12a), 126.47 (C-4a), 154.29 (C-5a) ppm.

^{1}H NMR of **4aT** · HCl (*DMSO*-d_6, δ, 400 MHz): 0.88 (t, $J = 7.2$ Hz, 3H, 15-CH_3), 0.98 and 1.25 (2m, 2×1H, 14-CH_2, 1.18 and 1.72 (2m, 2×1H, 9-CH_2^*), 1.22 and 1.65 (2m, 2×1H, 8-CH_2^*), 1.35 and 2.08 (m and dm, $J = 11.8$ Hz, 2×1H, H-7*ax* and H-7*eq*), 1.38 and 1.52 (2m, 2×1H, H_a and H_b 1-CH_2), 1.48 (2H, 2-CH_2^*), 1.49 and 1.63 (2m, 2×1H, 13-CH_2), 1.51 and 2.17 (m and dm, $J = 11.6$ Hz, 2×1H, H-10*ax* and H-10*eq*), 1.54 (2H, 3-CH_2), 2.05 (m, 2H, 4-CH_2), 3.11 and 3.13 (2m, overlapping, 2×1H, H-10a and H-6a), 4.08 (s, broad, 1H, H-12), 8.45 (s, 1H, 6-NH), 10.99 (s, 1H, 5-NH) ppm; ^{13}C NMR of **4aT** · HCl (*DMSO*-d_6, δ, 100 MHz): 13.79 (C-15), 15.06 (C-14), 21.41 (C-3), 21.59 (C-2), 23.36 (C-8), 24.68 (C-9), 24.69 (C-1), 26.02 (C-4), 27.98 (C-10), 28.34 (C-7), 30.99 (C-13), 53.91 (C-12), 61.16 (C-10a), 62.37 (C-6a), 107.89 (C-12a), 126.89 (C-4a), 156.09 (C-5a) ppm.

(2.3:1)-Mixture of trans-6aα-12α- and 12β-isopropyl-1,2,3,4,5,6a,7,8,9,10,10a,12-dodecahydrobenzimidazo[2,1-b]quinazoline (**4bC** *and* **4bT**; $C_{17}H_{27}N_3$)

6.09 g 2-Isobutylidenecyclohexanone (**8b**); time = 3.5 h. According to NMR, the crude residue (after evaporation, 6.5 g) consisted of a (1.5:1)-mixture of **4bC** and **4bT** (~5.7 g, 52%) and some impurities. Treatment with acetone gave a (2.3:1)-mixture of **4bC** and **4bT**; TLC (ES2): $R_f = 0.42$; colourless crystals; m.p.: 223°C; yield: 4.8 g (44%); IR (KBr): ν = 3419s, 3109m, 2930/2859/2836s/s/s, 1655/1625s/s, 1445s, 1371s, 1171s cm^{-1}.

^{1}H NMR of **4bC** (*DMSO*-d_6, δ, 400 MHz; the carbon atoms of the isopropyl substituent are numbered, as shown in Fig. 2, with 13, 14 and 14′): 0.83, 0.90, and 1.64 (2d, $J = 7.2$ Hz, and octet, $J = 7.2$ Hz, 2×3H and 1H, 14′-CH_3, 14-CH_3 and 13-CH), 1.23 (2H, 3-CH_2^*), 1.25 and 1.73 (qua d, $J = 10.0$, 4.0 Hz, and dm, $J = 10$ Hz, 2×1H, H-9*ax* and H-9*eq*), 1.27 and 1.70 (2m, overlapping, 2×1H, H-8*ax* and H-8*eq*), 1.31 and 1.98 (qua m, $J = 11.2$ Hz, and dm, $J = 11.2$ Hz, 2×1H, H-7*ax* and H-7*eq*), 1.34 (m, broad, 2H, 2-CH_2^*), 1.42 and 1.90 (qua d, $J = 12.0$, 3.6 Hz, and d, $J =$

12.0 Hz, 2×1H, H-10*ax* and H-10*eq*), 1.57 and 1.93 (m, and d, J = 14.6 Hz, 2×1H, H_a and H_b, 1-CH_2), 1.95 (m, 2H, 4-CH_2), 2.82 (td, J = 11.2, 3.2 Hz, 1H, H-10a), 2.99 (td, J = 10.8, 3.2 Hz, 1H, H-6a), 3.59 (s, broad, 1H, H-12) ppm; ^{13}C NMR of **4bC** (*DMSO*-d_6, δ, 100 MHz): 16.12 (C-14), 19.49 (C-14′), 22.02 (C-8*), 22.10 (C-3*), 22.76 (C-9*), 23.50 (C-10*), 23.76 (C-1*), 24.50 (C-2*), 28.13 (C-4*), 29.13 (C-10*), 29.49 (C-7), 35.48 (C-13), 62.42 (C-6a), 66.51 (C-10a), 62.67 (C-12), 102.81 (C-12a), 131.34 (C-4a), 149.82 (C-5a) ppm.

^{1}H NMR of **4bT** (*DMSO*-d_6, δ, 400 MHz; only significant signals cited): 0.81, 0.83, and 1.87 (2d, J = 7.2 Hz, and m, 2×3H and 1H, 14′-CH_3, 14-CH_3), 13-CH), 1.15 and 2.03 (td, J = 12.0, 3.6 Hz, and d, J = 12.0 Hz, 2×1H, H-10*ax* and H-10*eq*), 1.21 and 1.68 (2m, 2×1H, H_a and H_b, 1-CH_2), 1.28 and 1.93 (qua m, J = 10.8 Hz, and dm, J = 10.8 Hz, 2×1H, H-7*ax* and H-7*eq*), 1.30 and 1.89 (qua m, J = 12 Hz, and d, J = 12 Hz, 2×1H, H-9*ax* and H-9*eq*), 1.36 and 2.02 (m, overlapping, and d, J = 12.8 Hz, 2×1H, H-8*ax** and H-8*eq*), 1.96 (m, 2H, 4-CH_2), 2.73 (td, J = 10.8, 3.2 Hz, 1H, H-6a), 2.94 (td, J = 10.8, 3.2 Hz, 1H, H-10a), 3.57 (s, broad, 1H, H-12) ppm; ^{13}C NMR of **4bT** (*DMSO*-d_6, δ, 100 MHz): 17.02 (C-14), 18.67 (C-14′), 22.68 (C-9), 22.97 (C-8*), 23.22 (C-3*), 23.50 (C-2*), 23.65 (C-1*), 28.40 (C-4*), 29.13 (C-10*), 29.38 (C-7*), 30.74 (C-13), 59.37 (C-6a), 60.02 (C-12), 61.66 (C-10a), 103.51 (C-12a), 133.72 (C-4a), 150.64 (C-5a) ppm.

(1.2:1)-Mixture of trans-6aα-12α- and 12β-phenyl-1,2,3,4,5,6a,7,8,9,10,10a,12-dodecahydrobenzimidazo[2,1-b]quniazoline (**4cC** *and* **4cT**; $C_{20}H_{25}N_3$) *and (4.5:1)-mixture of* **4cC** · HCl *and* **4cT** · HCl ($C_{20}H_{26}ClN_3$)

7.45 g 2-Benzylidenecyclohexanone (**8c**); time = 2 h. According to NMR, the crude residue (after evaporation, 8.9 g) consisted of a (1:1)-mixture of **4cC** and **4cT** (~8.1 g, 66%) and some impurities. Treatment with diethylether gave, according to NMR, a (1.2:1)-mixture of **4cC** and **4cT**; TLC (ES2) R_f = 0.48; colourless needles; m.p.: 225–227°C (ethanol); yield: 5.8 g (47%); MS: m/z(%) = 307 (M^+, 30), 306 (M^+-1, 12), 230 (M^+-77, 100), 216 (M^+-91, 28), 162 (21), 105 (13), 91 (4), 77 ($C_6H_5^+$, 12), 38 ($H^{37}Cl^+$, 4), 36 ($H^{35}Cl^+$, 12); IR (KBr): ν = 3430/3210/3120m/w/w (NH), 3060/3005w/w (ArH), 2920/2860/2380s/m/m (CH_2), 1660s (C = C-N), 1630s (C = N, NH), 1490/1437w/s (CH_2), 1368s, 738m (C_6H_5) cm^{-1}.

^{1}H NMR of **4cC** (*DMSO*-d_6/$CDCl_3$, δ, 400 MHz; ratio of **4cC**:**4cT** = 7.5:1; for the numbering, see Table 1): 0.67 and 1.14 (qua d, J = 12.0, 3.8 Hz, and dm, J = 12.4 Hz, 2×1H, H-10*ax* and H-10*eq*), 1.13 and 1.50 (qua d, J = 13.0, 3.6 Hz, and d, J = 12.0 Hz, 2×1H, H-9*ax* and H-9*eq*), 1.15 and 1.65 (m, and dd, J = 12.0, 3.4 Hz, 2×1H, H-8*ax* and H-8*eq*), 1.25 and 1.47 (2×dm, J = 11.5 Hz, 2×1H, H_a and H_b, 1-CH_2), 1.34 and 1.96 (qua d, J = 12.0, 3.4 Hz, and dd, J = 12.4, 3.2 Hz, 2×1H, H-7*ax* and H-7*eq*), 1.53 (m, broad, 2H, 3-CH_2^*), 1.54 (m, broad, 2H, 2-CH_2^*), 2.09 (m, 2H, 4-CH_2), 2.81 (td, J = 11.6, 2.4 Hz, 1H, H-10a), 2.99 (td, J = 11.2, 3.2 Hz, 1H, H-6a), 4.62 (s, 1H, H-12), 7.23 (t, J = 6.4 Hz, 1H, H-16, *p*-H), 7.28 (t, J = 6.8 Hz, 2H, *m*-H), 7.37 (d, J = 6.8 Hz, 2H, *o*-H) ppm; ^{13}C NMR of **4cC** (*DMSO*-d_6/$CDCl_3$, δ, 100 MHz): 22.90 (2C, C-2* and C-3*), 23.82 (C-8*), 24.16 (C-9), 25.78 (C-1), 29.36 (C-10), 29.80 (C-7), 30.23 (C-4), 59.85 (C-6a), 64.77 (C-12), 67.79 (C-10a), 106.52 (C-12a), 127.44 (C-16, *p*-C), 128.06 (C-14, 18, *o*-C), 128.20 (C-15,17, *m*-C), 136.2 (C-4a*), 144.24 (C-13, 1′-C), 157.37 (C-5a) ppm.

^{1}H NMR of **4cT** (*DMSO*-d_6/$CDCl_3$, δ, 400 MHz; ratio of **4cC**:**4cT** = 1:3): 0.99 and 1.63 (qua t, J = 13.6, 3.6 Hz, and d, J = 13.6, 2×1H, H-9*ax* and H-9*eq*), 1.15 and 1.85 (qua d, J = 12.4, 3.2 Hz, and d, J = 12.4, 2×1H, H-7*ax* and H-7*eq*), 1.16 and 1.58 (2m, 2×1H, H-8*ax* and H-8*eq*), 1.18 and 1.91 (qua d, J = 12.2, 3.2 Hz, and dd, J = 12.2, 3.2 Hz, 2×1H, H-10*ax* and H-10*eq*), 1.52 and 1.77 (2m, 2×1H, H_a and H_b, 1-CH_2), 1.53 (m, broad, 2H, 3-CH_2^*), 1.35 (m, broad, 2H, 2-CH_2^*), 2.06 (m, 2H, 4-CH_2), 2.30 (td, J = 11.2, 3.2 Hz, 1H, H-10a), 2.85 (td, J = 11.2, 3.2 Hz, 1H, H-6a), 4.48 (s, 1H, H-12), 7.13 (dd, J = 7.8, 2.2 Hz, 2H, H-14,18, *o*-H), 7.17 (td, J = 7.2, 2 Hz, 1H, H-16, *p*-H), 7.21 (td, J = 7.2, 2.4 Hz, 2H, H-15,17, *m*-H) ppm; ^{13}C NMR of **4cT** (*DMSO*-d_6/$CDCl_3$, δ, 100 MHz): 22.26 (C-2), 22.57 (C-3), 23.10 (C-9), 23.40 (C-8), 25.85 (C-1), 26.28 (C-10), 28.90

(C-7), 29.65 (C-4), 58.59 (C-6a), 60.28 (C-12), 61.67 (C-10a), 107.18 (C-12a), 127.27 (C-16, *p*-C), 127.08 (C-14,18, *o*-C), 127.93 (C-15,17, *m*-C), 136.75 (C-4a), 139.41 (C-13, 1′-C), 156.73 (C-5a) ppm.

(4.5:1)-Mixture of hydrochloride **4cC** · HCl *and* **4cT** · HCl

Colourless plates; m.p.: 160–162°C (cyclohexane-ethanol); TLC (ES 3): $R_F = 0.42$; IR (KBr): $\nu =$ 3500-2700s with 3380w, 3080m, 2920s, 2840m, 1710/1700/1630/1590/1560w/w/s/w/w cm^{-1}; ^1H (*DMSO*-d_6, δ, 400 MHz) and ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz): see Table 1.

(1.2:1)-Mixture of trans-6aα-12α- and 12β-(p-tolyl)-1,2,3.4,5,6a,7,8,9,10,10a,12-dodecahydrobenzimidazo[2,1-b]quinazoline (**4dC** *and* **4dT**; $C_{21}H_{27}N_3$) *and (0.7:1)-mixture of* **4dC** · HCl *and* **4dT** · HCl ($C_{21}H_{28}ClN_3$)

8.01 g of 2-(4-Methylbenzylidene)cyclohexanone (**8d**); time = 2.5 h; solvent: acetone; TLC (ES 1): $R_f = 0.43$; colourless crystals; m.p.: 221°C; yield: 9.9 g (77%).

^1H NMR of **4dC** (*DMSO*-d_6, δ, 400 MHz; numbering as in case of **4cC**, see Table 1; only significant signals cited): 0.62 and 1.08 (qua d, $J = 10.8$, 3.2 Hz, and dm, $J = 12.0$ Hz, 2×1H, H-10*ax* and H-10*eq*), 1.12 and 1.60 (2m, 2×1H, H-8*ax* and H-8*eq*), 1.22 and 1.45 (2m, 2×1H, H-9*ax** and H-9*eq*), 1.27 and 1.91 (2m, 2×1H, H-7*ax* and H-7*eq*), 1.41 and 1.60 (2m, 2×1H, H_a and H_b, 1-CH_2^*), 1.55 (m, broad, 2H, 3-CH_2^*), 1.94 (m, 2H, 4-CH_2), 2.27 (s, 3H, 19-CH_3, *p*-CH_3), 2.78 (td, $J =$ 11.6, 3.2 Hz, 1H, H-10a), 2.88 (td, $J = 11.6$, 3.6 Hz, 1H, H-6a), 4.68 (s, 1H, H-12), 7.07 (d, $J =$ 8.0 Hz, 2H, H-15,17, *m*-H), 7.19 (d, $J = 8.0$ Hz, 2H, H-14,18, *o*-H) ppm; ^{13}C NMR of **4dC** (*DMSO*-d_6, δ, 100 MHz): 20.59 (C-19), 29.13 (C-4), 58.20 (C-6a), 63.2 (C-12), 66.4 (C-10a), 127.49 (C-14,18, *o*-C), 128.33 (C-15,17, *m*-C), 134.72 (C-16, *p*-C), 136.1 (C-13, 1′-C) ppm.

^1H NMR of **4dT** (*DMSO*-d_6, δ, 400 MHz): 0.97 and 1.65 (qua t, $J = 13.6$, 3.4 Hz, and d, $J =$ 13.6, 2×1H, H-9*ax* and H-9*eq*), 1.13 and 1.87 (qua d, $J = 12.8$, 3.6 Hz, and dd, $J = 11.8$, 3.0 Hz, 2×1H, H-7*ax* and H-7*eq*), 1.19 and 1.60 (qua m, $J = 11.6$ Hz, and d, $J = 12.8$, 2×1H, H-8*ax* and H-8*eq*), 1.20 and 1.92 (m and d, $J = 12.8$ Hz, 2×1H, H-10*ax** and H-10*eq*), 1.38 and 1.53 (2m, 2×1H, 2-CH_2), 1.53 and 1.57 (2m, 2×1H, 3-CH_2^*), 1.53 and 1.78 (2m, 2×1H, H_a and H_b, 1-CH_2), 2.06 (m, 2H, 4-CH_2), 2.24 (td, $J = 11.2$, 3.4 Hz, 1H, H-10a), 2.28 (s, 3H, 19-CH_3, *p*-CH_3), 2.80 (td, $J = 11.6$, 3.2 Hz, 1H, H-6a), 4.48 (s, 1H, H-12), 7.04 (d, $J = 8.0$ Hz, 2H, H-15,17, *m*-H), 7.08 (d, $J = 8.0$ Hz, 2H, H-14,18, *o*-H) ppm; ^{13}C NMR of **4dT** (*DMSO*-d_6, δ, 100 MHz): 20.59 (C-19), 22.39 (C-8*), 22.55 (C-3*), 22.65 (C-2), 23.49 (C-9*), 25.83 (C-1), 28.30 (C-4), 28.34 (C-10), 29.13 (C-7), 58.56 (C-6a), 59.66 (C-12), 61.74 (C-10a), 106.93 (C-12a), 127.12 (C-14,18, *o*-C), 128.79 (C-15,17, *m*-C), 136.61 (C-13, 1′-C), 136.80 (C-16, *p*-C) ppm.

(0.7:1)-Mixture of hydrochlorides **4dC** · HCl *and* **4dT** · HCl

Colourless crystals; m.p.: 149°C (cyclohexane-ethanol); TLC (ES 3) $R_f = 0.40$; IR (KBr): $\nu =$ 3450-2750s with 2937/2861s/s, 1710/1634m/s, 1513m, 1447m, 1374m, 829/814m/m cm^{-1}.

^1H NMR of **4dC** · HCl (*DMSO*-d_6, δ, 400 MHz): 0.67 and 1.36 (qua d, $J = 8.4$, 3.2 Hz, and dm, J = 8.4 Hz, 2×1H, H-10*ax* and H-10*eq*), 1.04 and 1.54 (2m, 2×1H, H_a and H_b 1-CH_2), 1.08 and 1.41 (qua m, $J = 13.6$ Hz, and m, 2×1H, H-9*ax* and H-9*eq*), 1.25 and 1.40 (2m, 2×1H, 2-CH_2^*), 1.31 and 2.01 (2m, 2×1H, H-7*ax* and H-7*eq*), 1.20 and 1.43 (2m, broad, 2×1H, H-8*ax** and H-8*eq**), 1.50 (m, broad, 2H, 3-CH_2), 2.16 (m, 2H, 4-CH_2), 2.39 (s, 3H, 19-CH_3), 3.14 (m, 1H, H-6a), 3.29 (td, $J =$ 10.8, 3.2 Hz, 1H, H-10a), 4.99 (s, 1H, H-12), 7.20 (d, $J = 8.0$ Hz, 2H, H-15,17, *m*-H), 7.27 (d, $J =$ 8.0 Hz, 2H, H-14,18, *o*-H), 8.74 (s, 1H, 6-NH), 10.95 (s, 1H, 5-NH) ppm; ^{13}C NMR of **4dC** · HCl (*DMSO*-d_6, δ, 100 MHz): 20.70 (C-19), 21.21 (C-1), 21.43 (C-3), 23.15 (C-2), 24.20 (C-9), 24.55 (C-8), 24.68 (C-7*), 24.87 (C-4), 28.29 (C-10), 60.73 (C-12), 61.11 (C-6a), 66.43 (C-10a), 108.68

(C-12a), 124.69 (C-4a), 127.52 (C-14,18, *o*-C), 129.12 (C-15,17, *m*-C), 134.16 (C-13), 137.44 (C-16), 153.92 (C-5a) ppm.

^{1}H NMR of **4dT** · HCl (*DMSO*-d_6, δ, 400 MHz): 0.98 and 1.64 (qua m, J = 14.0 Hz, and m, 2×1H, H-9*ax* and H-9*eq*), 1.23 and 2.07 (2m, 2×1H, H-7*ax* and H-7*eq*), 1.26 and 2.04 (m, and d, J = 9.2 Hz, 2×1H H-10*ax* and H-10*eq*), 1.28 and 1.60 (2m, 2×1H, H-8*ax** and H-8*eq**), 1.39 and 1.88 (2m, 2×1H, H_a and H_b, 1-CH_2), 1.45 (m, broad, 2H, 2-CH_2), 1.70 (m, broad, 2H, 3-CH_2), 1.98 (m, 2H, 4-CH_2), 2.29 (s, 3H, 19-CH_3), 2.47 (td, J = 11.6, 2.8 Hz, 1H, H-10a), 3.20 (tm, J = 11.6 Hz, 1H, H-6a), 4.95 (s, 1H, H-12), 7.15 (d, J = 8.4 Hz, 2H, H-14,18, *o*-H), 7.23 (d, J = 8.4 Hz, 2H, H-15,17, *m*-H), 8.71 (s, 1H, 6-NH), 11.27 (s, 1H, 5-NH) ppm; ^{1}C NMR of **4dT** · HCl (*DMSO*-d_6, δ, 100 MHz): 20.75 (C-19), 21.39 (C-2), 21.94 (C-3), 23.06 (C-9), 23.24 (C-8), 24.53 (C-1), 25.88 (C-4), 28.32 (C-7), 28.43 (C-10), 58.14 (C-12), 60.68 (C-6a), 62.89 (C-10a), 110.18 (C-12a), 125.54 (C-4a), 127.39 (C-14,18, *o*-C), 129.81 (C-15,17, *m*-C), 137.98 (C-16), 138.36 (C-13), 154.78 (C-5a) ppm.

(0.7:1)-Mixture of 7α-phenyl-trans-8aβ- and trans-8aα-5,6,7,8a,9,10,11,12,12a,13-decahydrobenzimidazo[2,1-b]benzo[h]quinazoline (**5cC** *and* **5cT**; $C_{24}H_{25}N_3$) *and (0.8:1)-mixture of* **5cC** · HCl *and* **5cT** · HCl ($C_{24}H_{26}ClN_3$)

9.37 g 2-Benzylidene-α-tetralone (**9c**); time = 2.5 h; solvent: acetone; TLC (ES 2): R_f = 0.40; colourless needles; m.p.: 215–217°C (butanol); yield: 8.3 g (58%); IR (KBr): ν = 3440/3190/3150m/m/m (NH), 3062/3022w/w (ArH), 2938/2860/2830s/m/w (CH_2), 1630s (C=C–N), 1605s (C=N, NH, benzene rings), 1487/1450/1435w/m/s (CH_2), 1368s, 772/742s/s (phenyl, *o*-C_6H_4), 702s, 652m cm^{-1}.

^{1}H NMR of **5cC** ($CDCl_3$, δ, 400 MHz; only significant signals are cited; numbering in analogy to **5cC** · HCl, see Table 2): 0.72 and 1.58 (qua d, J = 12.0, 3.4 Hz, and m, 2×1H, H-9*ax* and H-9*eq*), 1.81 and 2.01 (2m, 2×1H, H_a and H_b, 6-CH_2), 2.50 (td, J = 11.8, 3.4 Hz, 1H, H-8a), 2.53 and 2.78 (2m, 2×1H, H_c and H_d, 5-CH_2), 3.03 (td, J = 11.8, 3.1 Hz, 1H, H-12a), 5.02 (s, 1H, H-7), 7.02 (t, J = 7.4 Hz, 1H, H-2), 7.07 (t, J = 7.6 Hz, 1H, H-3), 7.20 (d, J = 7.6 Hz, 1H, H-4), 7.29 (m, 3H, H-17,19, *m*-H, and H-18, *p*-H), 7.45 (d, J = 6.5 Hz, 2H, H-16,20, *o*-H), 7.80 (d, J = 7.4 Hz, 1H, H-1) ppm; ^{13}C NMR of **5cC** ($CDCl_3$, δ, 100 MHz): 24.16 (C-6), 28.34 (C-5), 29.67 (C-9), 59.86 (C-12a), 64.50 (C-7), 67.78 (C-8a), 108.50 (C-6a), 125.96 (C-1), 126.46 (C-4), 126.58 (C-2), 127.41 (C-18, *p*-C), 127.60 (C-3), 127.85 (C-16,20, *o*-C), 128.63 (C-17,19, *m*-C), 135.91 (C-15, 1′-C), 159.28 (C-13a) ppm.

^{1}H NMR of **5cT** ($CDCl_3$, δ, 400 MHz): 1.37 and 2.05 (qua d, J = 12.3, 3.6 Hz, and d, J = 12.3 Hz, 2×1H, H-9*ax* and H-9*eq*), 2.00 and 2.20 (2m, 2×1H, H_a and H_b, 6-CH_2), 2.59 and 2.70 (2m, 2×1H, H_c and H_d, 5-CH_2), 2.89 (td, J = 11.2, 3.2 Hz, 1H, H-8a), 3.08 (td, J = 11.2, 3.2 Hz, 1H, H-12a), 4.78 (s, 1H, H-7), 7.10 (t, J = 7.6 Hz, 1H, H-2), 7.15 (t, J = 7.6 Hz, 1H, H-3), 7.18 (d, J = 7.6 Hz, 1H, H-4), 7.26 (d, J = 7.8 Hz, 2H, H-16,20, *o*-H), 7.29 (m, 3H, H-17,19, *m*-H and H-18, *p*-H), 7.86 (d, J = 7.6 Hz, H-1) ppm; ^{13}C NMR of **5cT** ($CDCl_3$, δ, 100 MHz): 24.04 (C-6), 28.26 (C-9), 29.41 (C-5), 59.52 (C-12a), 61.27 (C-7), 62.32 (C-8a), 110.26 (C-6a), 122.99 (C-1), 126.09 (C-2), 126.54 (C-3), 126.78 (C-4), 127.11 (C-18, *p*-C), 128.08 (C-16,20, *o*-C), 128.45 (C-17,19, *m*-C), 135.75 (C-15, 1′-C), 159.38 (C-13a) ppm.

(0.8:1)-Mixture of hydrochlorides **5cC** · HCl *and* **5cT** · HCl

Colourless crystals, m.p.: 227–230°C (cyclohexane-ethanol); TLC (ES 2) R_f = 0.41; IR (KBr): ν = 3400-2600s with 2940s, 2840m; 1700/1633w/s, 1540m, 1495/1452/1448m/m/m, 704s cm^{-1}; ^{1}H (*DMSO*-d_6, δ, 400 MHz) and ^{13}C NMR (*DMSO*-d_6, δ, 100 MHz) of **5cC** · HCl and **5cT** · HCl: see Table 2.

Crude (1.5:2)-mixture of 7α-(4-chlorophenyl)-trans-8aα- and trans-8aβ-5,6,7,8a,9,10,11,12,12a,13-decahydrobenzimidazo[2,1-b]benzo[h]quinazoline (**5eC** *and* **5eT**; $C_{24}H_{24}ClN_3$)*, and (1:2)-mixture of 7-(4-chlorophenyl)-5,6,8a,9,10,11,12,12a-octahydrobenzimidazo[2,1-b]benzo[h]quinazoline hydrochloride* (**23e** · HCl; $C_{24}H_{24}Cl_2N_3$) *and* **5eT** · HCl ($C_{24}H_{25}Cl_2N_3$)

10.75 g 2-(4-Chlorobenzylidene)-α-tetralone (**9e**); time = 1.5 h. The crude mixture of the bases (10.5 g) consisted, according to NMR, of a (1.5: 2)-mixture of **5eC** and **5eT** (TLC, ES 2: $R_f = 0.48$) and some impurities. Treatment of the crude product with ethanolic HCl, evaporation of the solvent, and recrystallization of the residue from acetone yielded 8.54 g of a (1:2)-mixture of **23e** · HCl (∼2.84 g (16.7%)) and **5eT** · HCl (∼5.70 g (33.4%)); pale yellow crystals; m.p.: 225°C.

^{1}H NMR of **5eC** and **5eT** ($CDCl_3$, δ, 400 MHz; preliminary analysis of the crude mixture; numbering in analogy to **5cC** and **5cT** · HCl, see Table 2), signals for **5eC**: 0.94 (qua d, J = 12.4, 3.6 Hz, 1H, H-9*ax*), 2.56 (td, J = 11.4, 3.8 Hz, 1H, H-8a), 3.03 (td, J = 11.4, 3.2 Hz, 1H, H-12a), 4.98 (s, 1H, H-7) ppm; signals for **5eT**: 2.78 (td, J = 11.2, 3.6 Hz, 1H, H-8a), 3.10 (td, J = 11.8, 3.6 Hz, 1H, H-12a), 4.72 (s, 1H, H-7) ppm.

^{1}H NMR of **5eT** · HCl (*DMSO*-d_6, δ, 400 MHz): 1.04 and 1.70 (qua t, J = 12.8, 3.8 Hz, and m, 2×1H, H-10*ax* and H-10*eq*), 1.23 and 2.16 (qua d, J = 12.4, 3.6 Hz, and d, J = 12.4 Hz, 2×1H, H-12*ax* and H-12*eq*), 1.26 and 1.68 (qua m, J = 12.8 Hz, and m, 2×1H, H-11*ax* and H-11*eq*), 1.45 and 2.04 (qua d, J = 12.4, 3.6 Hz, and d, J = 12.4 Hz, 2×1H, H-9*ax* and H-9*eq*), 1.82 and 2.28 (2dt, J = 16.0, 7.6 Hz, 2×1H, H_a and H_b, 6-CH_2), 2.55 and 2.75 (2m, 2×1H, H_c and H_d, 5-CH_2), 2.61 (td, J = 11.6, 3.6 Hz, 1H, H-8a), 3.35 (td, J = 11.6, 3.6 Hz, 1H, H-12a), 5.41 (s, 1H, H-7), 7.22 (dm, J = 6.8 Hz, 1H, H-4), 7.28 (td, J = 8.4, 2.1 Hz, 1H, H-3), 7.32 (tm, J = 7.2 Hz, 1H, H-2), 7.42 (d, J = 8.4 Hz, 2H, H-16,20, *o*-H), 7.52 (d, J = 8.4 Hz, 2H, H-17,19, *m*-H), 7.75 (dd, J = 8.4, 1.2 Hz, 1H, H-1), 8.62 (s, 1H, 13-NH), 12.07 (s, 1H, 14-NH) ppm; ^{13}C NMR of **5eT** · HCl (*DMSO*-D_6, δ, 100 MHz): 23.02 (C-10), 23.27 (C-11*), 23.38 (C-6), 25.92 (C-9), 26.93 (C-5), 28.27 (C-12), 57.28 (C-7), 61.12 (C-12a), 62.99 (C-8a), 112.65 (C-6a), 121.73 (C-1), 124.97 (C-14a), 126.62 (C-3), 126.99 (C-14b), 127.98 (C-4), 128.74 (C-2), 129.48 (C-17,19, *m*-C), 129.75 (C-16,20, *o*-C), 133.89 (C-18, *p*-C), 135.45 (C-4a), 135.79 (C-15, 1′-C), 156.22 (C-13a) ppm.

^{1}H NMR of **23e** · HCl (*DMSO*-d_6, δ, 400 MHz): 0.80 and 1.64 (qua m, J = 12.4 Hz, and d, J = 12.0 Hz, 2×1H, H-10*ax* and H-10*eq**), 1.18 and 1.65 (m, concealed, and d, J = 12.0 Hz, 2×1H, H-11*ax** and H-11*eq*), 1.28 and 2.04 (m, concealed, and d, J = 9.6 Hz, 2H, H-12*ax** and H-12*eq*), 1.82 and 2.32 (2m, concealed, 2×1H, H-9*ax* and H-9*eq*), 2.08 and 2.20 (2m, concealed, 2×1H, H_a and H_b, 6-CH_2), 2.75−3.0 (m, concealed, 2H, 5-CH_2), 3.44 (td, J = 11.6, 4.4 Hz, 1H, H-8a), 4.53 (m, broad, 1H, H-12a), 7.33 (d, J = 8.6 Hz, 1H, H-4), 7.42 (concealed, 1H, H-2*), 7.50 (concealed, 2H, H-17,19, *m*-H), 7.53 (concealed, 1H, H-3*), 7.65 (m, 2H, H-16,20, *o*-H), 8.22 (dd, J = 8.4, 1.2 Hz, 1H, H-1), 8.44 (s, 1H, 13-NH) ppm; ^{13}C NMR of **23e** · HCl (*DMSO*-d_6, δ, 100 MHz): 22.92 (C-10*), 23.13 (C-9*), 23.70 (C-6*), 23.80 (C-5), 24.18 (C-11), 29.84 (C-12), 47.83 (C-12a), 63.38 (C-8a), 112.23 (C-6a), 126.42 (C-1), 127.20 (C-2), 132.71 (C-3), 128.37 (C-4), 129.34 (C-17,19, *m*-C*), 130.76 (C-16,20, *o*-C*), 130.26 (C-18, *p*-H), 130.76 (C-16), 130.89 (C-14b), 133.21 (C-4a), 134.66 (C-15, 1′-C), 154.30 (C-13a), 156.57 (C-7), 164.78 (C-14a) ppm.

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