Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 15 (2007) 7647–7660
Bioorganic & Medicinal Chemistry

Preparation of tetrahydroimidazo[2,1-*a*]isoquinolines and their use as inhibitors of gastric acid secretion☆

Andreas Marc Palmer,* Burkhard Grobbel, Christof Brehm, Peter Jan Zimmermann, Wilm Buhr, Martin Philipp Feth, Hans Christof Holst and Wolfgang Alexander Simon

NYCOMED GmbH, Byk-Gulden-Str. 2, D-78467 Konstanz, Germany

Received 26 June 2007; revised 8 August 2007; accepted 31 August 2007
Available online 5 September 2007

Abstract—A series of novel tetrahydroimidazo[2,1-*a*]isoquinolines was prepared based on a hetero Diels–Alder reaction between an enamine and 1,2,4-triazine as key step. A structure–activity relationship was established focussing on the influence of the substitution pattern in position 3 and 6 of the heterocycle on antisecretory activity, lipophilicity, and pK_a value. Potent inhibitors of the gastric acid pump were identified.

1. Introduction

Gastroesophageal reflux disease (GERD), the backward flow of the stomach's contents into the esophagus, is a digestive condition that affects 20% of the American population and is often manifested by heartburn, which is characterized by burning pain that radiates through chest, neck, and throat.[1,2] Peptic ulcer disease, estimated to affect 14.5 million people in the United States, is a chronic inflammation of the stomach and duodenum and is responsible for a large economic burden. The formation of peptic ulcers is favored by two factors: the hypersecretion of acid and a weakened resistance of the protective mucous coating of the stomach and duodenum.[3,4] The inhibition of acid secretion and the neutralization of formed acid constitute effective approaches for the treatment of both diseases.[1,3] A whole series of compounds, which inhibit gastric acid secretion by blockade of the gastric proton pump enzyme (H^+/K^+-ATPase), are known. Compounds designated as proton pump inhibitors (PPIs), for example, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, or tenatoprazole bind irreversibly to the H^+/K^+-ATPase and have long been available as therapeutics. A new class of compounds designated as acid pump antagonists (APAs) or as potassium competitive acid blockers (P-CABs) bind reversibly to the H^+/K^+-ATPase. Although PPIs are considered as the gold standard for the treatment of acid-related diseases, P-CABs might offer some therapeutic advantages such as better symptom control and faster healing.[5,6]

In the past two decades, one important approach for the identification of potent P-CABs relied on the structural class of substituted imidazo[1,2-*a*]pyridines. The inhibitor SCH 28080 (**1**) represents the clinical prototype of this series. SCH 28080 (**1**) inhibits the gastric proton pump enzyme (H^+/K^+-ATPase) by a kinetically competitive and reversible inhibition mechanism with respect to the potassium ion and shows excellent antisecretory and cytoprotective properties.[7–9] However, the clinical development of SCH 28080 (**1**) was stopped due to extensive metabolism and associated liver toxicity[8] (Fig. 1).

One approach to synthesize advanced chemical analogues of SCH 28080 was based on molecular modeling results, which suggested that in the gas phase, SCH 28080 could adopt various 'folded' conformations close to the global minimum of energy.[9,10] On the other hand, single-crystal X-ray analysis revealed that solid SCH 28080 existed in an 'extended' conformation.[7,10] The synthesis of simple analogues, which imitated these conformations, demonstrated that an 'extended' relationship between the phenyl group and the heterocy-

Keywords: Hetero Diels–Alder reaction; Tetrahydroimidazo[2,1-*a*]isoquinolines; Antisecretory activity; Gastric acid pump; H^+/K^+-ATPase.
☆ Design of novel P-CABs, II.—Part I: Zimmermann, P. J.; Buhr, W.; Brehm, C.; Palmer, A. M.; Feth, M. P.; Senn-Bilfinger, J.; Simon, W.-A. *Bioorg. Med. Chem. Lett.* 2007, doi:10.1016/j.bmcl.2007.08.003.
* Corresponding author. Tel.: +49 7531 84 4783; fax: +49 7531 849 2087; e-mail: andreas.palmer@nycomed.com

0968-0896/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2007.08.065

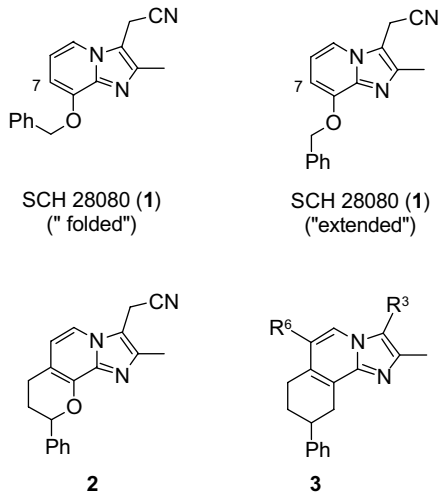


Figure 1.

clic nucleus was required for effective binding to H^+/K^+-ATPase.[9] Subsequently, the 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **2** was synthesized in which the pyrano ring was considered to enforce this requisite 'extended' relationship and to mimic a 7-methyl substituent which would be effective in overcoming the toxic properties of **1** while retaining its desirable antisecretory effects.[9,11]

In the course of our efforts to identify novel P-CABs, we were interested in the synthesis of tetrahydroimidazo[2,1-*a*]isoquinolines of the general formula **3**, which represent carbocyclic analogues of the 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **2**.[12] As the oxidative decyanation of **1** was identified as the major metabolic pathway of SCH 28080 (**1**), one important goal was to identify potent inhibitors that are devoid of the 3-cyanomethyl moiety.[8]

A second goal was the modulation of the pK_a value by introduction of different substituents R^6. The pK_a value of a potassium competitive acid blocker is an important parameter for two reasons: first, it determines the concentration of the protonated species, which is the active form for inhibiting H^+/K^+-ATPase in the parietal cell.[6,13] Second, the parietal cell is distinguished from other compartments by its low pH value of approximately 3. Hence, P-CABs with low pK_a values are accumulated in a selective manner and possible interactions with enzymes that are expressed in other cells are prevented, which should translate in an improved safety profile.

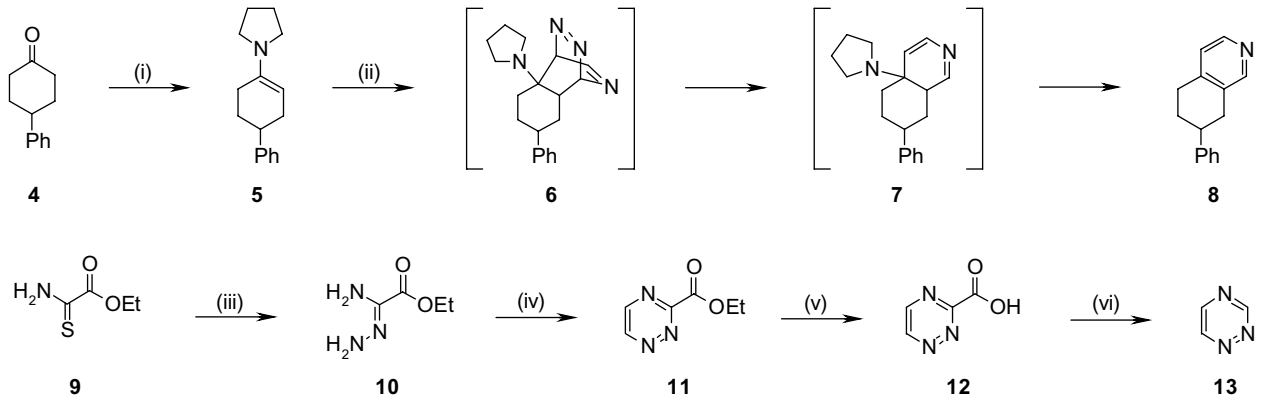
2. Results and discussion

2.1. Synthesis of tetrahydroimidazo[2,1-*a*]isoquinolines

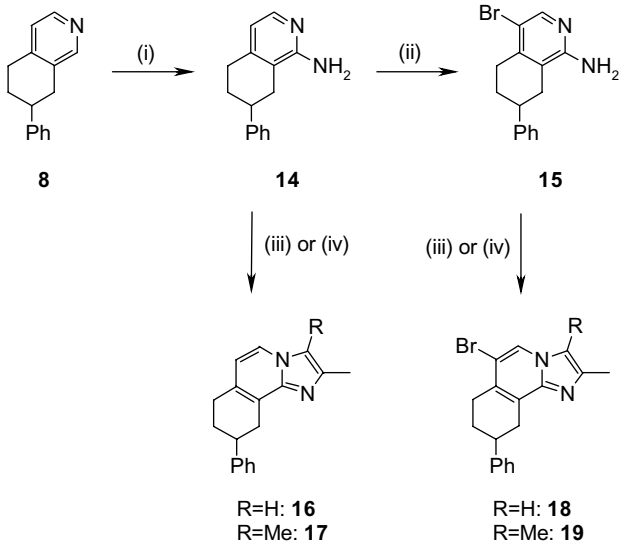
The synthesis of the target compounds was based on 7-phenyl-5,6,7,8-tetrahydroisoquinoline (**8**) as key intermediate, which in turn was obtained by hetero Diels–Alder reaction of 1-(4-phenylcyclohex-1-en-1-yl)pyrrolidine (**5**) with 1,2,4-triazine (**13**).[11,12,14] This transformation is believed to proceed via the intermediates **6** and **7**, which are formed by [4+2] cycloaddition and extrusion of nitrogen, respectively (Scheme 1).[14] The reaction sequence is completed by the elimination of pyrrolidine affording 7-phenyl-5,6,7,8-tetrahydroisoquinoline (**8**). Enamine **5** was synthesized by a titanium tetrachloride mediated condensation of 4-phenylcyclohexanone (**4**) and pyrrolidine.[15] 1,2,4-Triazine (**13**) was prepared in four steps (Scheme 1) beginning with the treatment of commercially available ethyl amino(thioxo)acetate (**9**) with hydrazine to afford ethyl amino(hydrazono)acetate (**10**).[16,17] Ethyl 1,2,4-triazine-3-carboxylate (**11**) was then secured by condensation of **10** with freshly prepared glyoxal.[18] Finally, saponification of the ester moiety and decarboxylation of the intermediate carboxylic acid **12** afforded 1,2,4-triazine (**13**) in 26% overall yield. 7-Phenyl-5,6,7,8-tetrahydroisoquinoline (**8**) was obtained in 84% yield by refluxing a solution of enamine **5** and 1,2,4-triazine (**13**) in chloroform for 18 h. This transformation was also feasible in larger scale using up to 20 g of starting material.

7-Phenyl-5,6,7,8-tetrahydroisoquinolin-1-amine (**14**) was prepared by Chichibabin reaction involving the heating of 7-phenyl-5,6,7,8-tetrahydroisoquinoline (**8**) with sodium amide (Scheme 2) in a high boiling solvent, for example, degassed *N*,*N*-dimethylaniline or tetralin (220 °C, 18 h), to provide **14** in 41–48% yield.[19] We also examined the possibility to perform the Chichibabin reaction under microwave-assisted conditions. However, at a temperature of 210 °C, a mixture of **14** with its aromatic analogue (7-phenylisoquinolin-1-amine) was isolated. Whereas the amination of **8** proceeded smoothly at a temperature of 180 °C (59% yield), the reaction time (12 h) could not be significantly reduced with respect to the thermal variant. The activating and para-directing properties of the newly installed amino group were used to prepare 4-bromo-7-phenyl-5,6,7,8-tetrahydroisoquinolin-1-amine (**15**) by electrophilic substitution of **14** with *N*-bromosuccinimide. The construction of the tetrahydroimidazo[2,1-*a*]isoquinoline framework was completed by transformation of the intermediates **14** and **15** either with chloroacetone or 3-bromobutanone (Scheme 2) affording the products **16**–**19** in 46–81% yield.[20]

In order to obtain target compounds **3**, which are substituted by a carboxamide residue, we examined the alkoxycarbonylation of 6-bromo-tetrahydroimidazo[2,1-*a*]isoquinoline **19** (Scheme 3).[21] Heating a mixture of bromide **19**, palladium acetate (10 mol %), triphenylphosphine, triethylamine, and ethanol under a pressure of 6 bar carbon monoxide for 18 h at 115 °C afforded ethyl carboxylate **20** in 90% yield. After saponification of the ester function, carboxamides **22**–**28** were obtained in good yields by the reaction of carboxylic acid **21** with the respective amine and TBTU as coupling agent.[22] Ethyl carboxylate **20** also served as a starting material for the synthesis of the 6-methoxymethyl derivative **31**: after reducing the ester group with lithium aluminium hydride, the newly formed hydroxy group was converted with thionyl chloride to furnish chloride **30**. Finally,



Scheme 1. Reagents and conditions: (i) pyrrolidine, $TiCl_4$, rt, 3 h, 86%; (ii) **13**, $CHCl_3$, 60 °C, 18 h, 84%; (iii) N_2H_4, THF, EtOH, rt, 3 h, 86%; (iv) glyoxal, HOAc, THF, −75 °C, 0.25 h, then NEt_3, rt, 3 h, 51%; (v) KOH, EtOH, rt, 0.25 h, 89%; 1 N HCl, 77%; (vi) Δ, 125 °C, 1.25 h, distillation, 88%.



Scheme 2. Reagents and conditions: (i) variant 1: $NaNH_2$, tetralin, argon-filled autoclave, 220 °C, 18 h, 48%; variant 2: $NaNH_2$, *N*,*N*-dimethylaniline, argon-filled autoclave, 220 °C, 18 h, 41%; variant 3: $NaNH_2$, *N*,*N*-dimethylaniline, argon-filled microwave vial, 180 °C (MW), 12 h, 59%; (ii) NBS, CH_3CN, rt, 0.75 h, 88%; (iii) chloroacetone, THF, 2.5–4.5 d, **16**: 46%, **18**: 81%; (iv) 3-bromobutanone, THF, 70 °C, 1–7 d, **17**: 75%, **19**: 66%.

methyl ether **31** was obtained by nucleophilic substitution of **30** with sodium methylate.

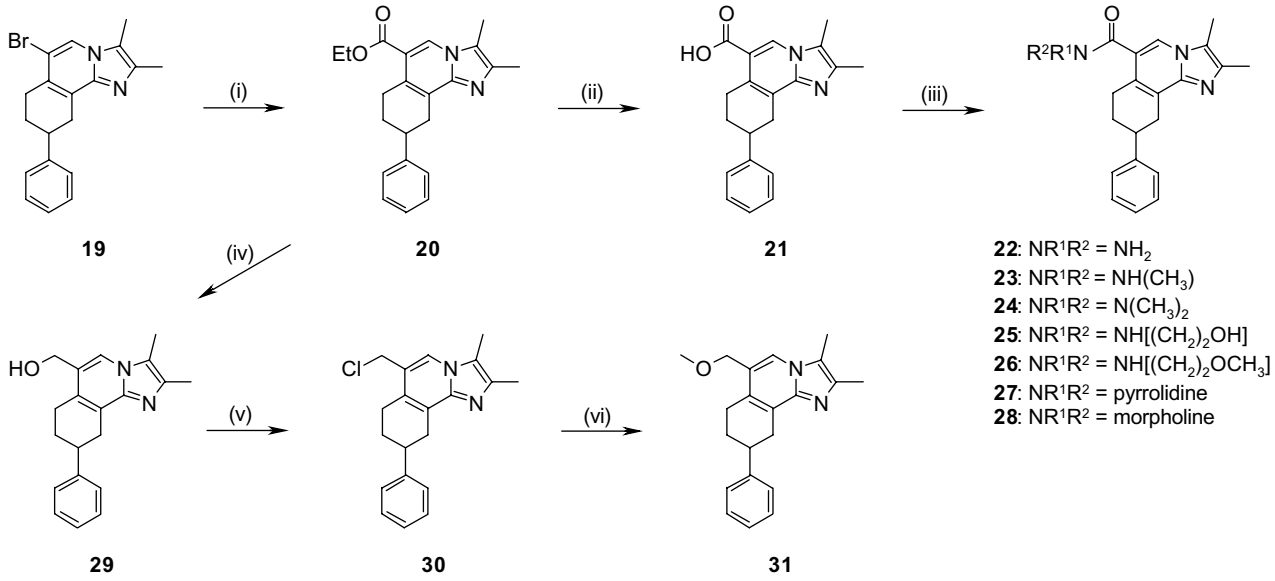
Carboxamide **32** was synthesized in an analogous manner as described for carboxylic ester **19**: aminocarbonylation of the 6-bromo intermediate **18** was accomplished in the presence of palladium acetate and triphenylphosphine using dimethylamine in tetrahydrofuran instead of ethanol.[21] Tetrahydroimidazo[2,1-*a*]isoquinoline **32** was then functionalized in the 3-position either by bromination with *N*-bromosuccinimide or by Vilsmeier formylation to furnish compounds **33** and **34**. Reduction of aldehyde **34** with sodium borohydride afforded the corresponding alcohol **35** (Scheme 4).

2.2. Inhibitory activity and physicochemical properties of tetrahydroimidazo[2,1-*a*]isoquinolines

The inhibitory and cellular activity of the tetrahydroimidazo[2,1-*a*]isoquinolines **16**, **17**, **22**–**28**, **31**–**33**, and **35** was evaluated in a competitive binding assay against H^+/K^+-ATPase from hog gastric mucosa and by determination of acid formation in gastric glands. Additionally, the lipophilicity and pK_a values of selected target compounds were determined. The data reported for 7*H*-8,9-dihydrohydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **2** was obtained from the literature.[13] The results are summarized in Table 1.

Although the inhibitory activity of 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine **2** remained unequaled, it was demonstrated that the problematic cyanomethyl group could be replaced by a methyl residue without a significant loss of affinity toward the gastric proton pump enzyme. On the other hand, this replacement caused an unfavorable alteration of the dissociation constant (**17** vs **2**). A substantial decrease of both the pK_a value and the lipophilicity with respect to compound **17** can be accomplished by introduction of a carboxamide residue. Whereas the carboxamide function in general exerts a beneficial influence on the pK_a value and the lipophilicity of the target compounds, the strength of inhibition clearly depends on the nature of the amide residue. The IC_{50} values determined for carboxamides **22**–**25** and **27** are comparable with the IC_{50} value of the 6-unsubstituted derivative **17**. Carboxamides **26** (methoxyethyl) and **28** (morpholin-4-yl) represent examples for weak inhibitors. The presence of a methoxymethyl moiety in 6-position also resulted in strong enzyme inhibition (compound **31**). However, the primary goal to improve the physicochemical properties with respect to inhibitor **2** was not accomplished with this substituent.

As expected, the nature of the 3-substituent also exerts a strong influence on the pK_a value. The comparison of the analogues **24** (3-methyl), **32** (3-unsubstituted), **33** (3-bromo), and **35** (3-hydroxymethyl) reveals that the nature of the 3-substituent also plays a crucial role for



Scheme 3. Reagents and conditions: (i) $Pd(OAc)_2$, PPh_3, Et_3N, EtOH, 6 bar CO, 115 °C, 18 h, 90%; (ii) KOH, MeOH/H_2O, 60 °C, 3 h, 93%; (iii) TBTU, CH_2Cl_2, 40 °C, 1 h, **22**: $NH_{3(g)}$, rt, 1 h, 65%, **23**: $MeNH_2$ (2 M solution in THF), rt, 1 h, 56%, **24**: $HNMe_2$ (2 M solution in THF), rt, 3 h, 72%, **25**: 2-aminoethanol, rt, 2 h, 57%, **26**: 2-methoxyethylamine, rt, 2 h, 74%, **27**: pyrrolidine, rt, 1 h, 86%, **28**: morpholine, rt, 1 h, 81%; (iv) $LiAlH_4$, THF, rt, 1 h, 44%; (v) $SOCl_2$, CH_2Cl_2, rt, 1 h, 87%; (vi) NaOMe, MeOH, 60 °C, 1.5 h, 87%.

the strength of enzyme inhibition. The fact that a 3-methyl group is required for potent enzyme inhibition is also evident from the comparison of the 6-unsubstituted tetrahydroimidazo[2,1-*a*]isoquinolines **16** and **17** where a difference in activity of more than factor 10 was observed. In all cases, potent enzyme inhibition translates into a good reduction of acid secretion in gastric glands.

3. Conclusion

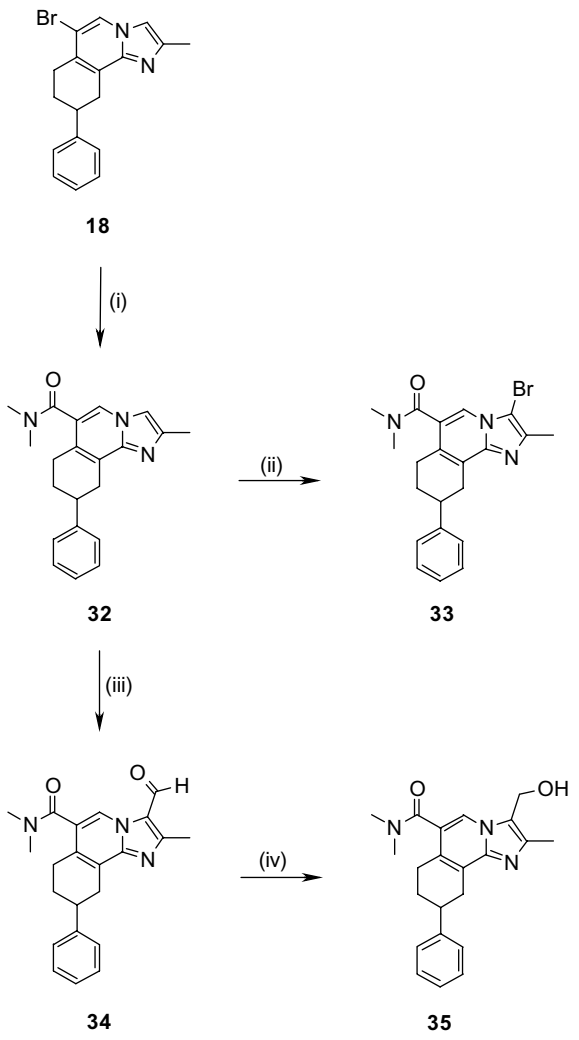
In summary, we report a general route for the preparation of 6-substituted tetrahydroimidazo[2,1-*a*]isoquinolines. The metabolically labile cyanomethyl group that constitutes a key structural element in SCH 28080 was replaced by a methyl residue without significant loss of affinity toward the gastric proton pump enzyme. The incorporation of an amide moiety resulted in derivatives with significantly reduced pK_a and $\log D$ values. Although the carbocyclic analogue of reference compound **2** was not prepared, it seems that the ring oxygen atom can be substituted with a carbon atom without considerable loss of affinity toward H^+/K^+-ATPase.

4. Experimental

4.1. Chemistry

4.1.1. General. All chemicals were purchased from the major chemical suppliers as highest purity grade and used without any further purification. The progress of the reaction was monitored on Macherey-Nagel HPTLC plates Nano-SIL 20 UV_{254} (0.20 mm layer, nano silica gel 60 with fluorescence indicator UV_{254}) using dichloromethane/methanol as solvent system. Column chromatography was performed with Merck silica gel 60 (70–230 mesh ASTM) with the solvent mixtures specified in the corresponding experiment. Spots were visualized by iodine vapour or by irradiation with ultraviolet light (254 nm). Melting points (mp) were taken in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. ^1H NMR spectra were recorded with a Bruker DRX 200 FT-NMR spectrometer at a frequency of 200.1 MHz, a Bruker AV 400 FT-NMR spectrometer at a frequency of 400.1 MHz, or a Bruker AV 600 FT-NMR spectrometer at a frequency of 600.1 MHz. ^{13}C NMR spectra were acquired with a Bruker AV 400 FT-NMR spectrometer at a frequency of 100.7 MHz or a Bruker AV 600 FT-NMR spectrometer at a frequency of 150.9 MHz. $CDCl_3$ or DMSO-d_6 was used as solvent. The chemical shifts were reported as parts per million (δ ppm) with tetramethylsilane (TMS) as an internal standard. High resolution mass spectra were obtained on a Bruker Daltonics MicroTOF Focus instrument using electrospray ionization (ESI positive). Elemental analysis was performed on a Carlo Erba 1106 C, H, N analyzer.

4.1.2. 1-(4-Phenyl-cyclohex-1-enyl)-pyrrolidine (5). In a flame-dried flask filled with argon, 4-phenylcyclohexanone (**4**) (12.5 g, 72 mmol) was suspended in dry hexane (250 ml) and a solution of pyrrolidine (25.0 g, 350 mmol) in hexane (30 ml) was added. The clear solution was cooled to 0 °C and a solution of titanium tetrachloride (6.8 g, 36 mmol) in hexane (50 ml) was added dropwise over a period of 1 h during which a green-white precipitate was formed. The reaction mixture was allowed to come to room temperature and stirring was continued for 3 h. The precipitate was removed by filtration and was washed with hexane (2× 20 ml). The filtrates were concentrated under reduced pressure. An oily residue (13.5 g) was isolated which was characterized by ^1H



Scheme 4. Reagents and conditions: (i) $Pd(OAc)_2$, PPh_3, $HNMe_2$, NEt_3, THF, 6 bar CO, 120 °C, 19 h, 69%; (ii) NBS, CH_2Cl_2, −75 °C, 1 h, 89%; (iii) $POCl_3$, DMF, rt, 1.5 h, then addition of **32**, DMF, 60 °C, 3 h, 78%; (iv) $NaBH_4$, MeOH, rt, 0.5 h, 63%.

NMR-spectroscopy. The sample contained 81 wt% of 1-(4-phenyl-cyclohex-1-enyl)-pyrrolidine (10.9 g, 68% yield), 15 wt% of 4-phenylcyclohexanone, and 4 wt% of pyrrolidine: ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.78, 2.25, 2.95 (3 m_c), 4.18 (m_c, 1H), 7.25 (m_c).

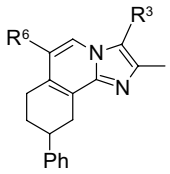
4.1.3. 7-Phenyl-5,6,7,8-tetrahydro-isoquinoline (8). In a flame-dried flask filled with argon, 1,2,4-triazine (**13**) (20.0 g, 0.25 mol) was dissolved in dry chloroform (200 ml). A solution of 1-(4-phenyl-cyclohex-1-enyl)-pyrrolidine (**5**) (92.0 g, 75 wt%, 0.30 mol) in chloroform (180 ml) was added slowly. The red solution was heated to 60 °C for 18 h. The reaction mixture was cooled to 0 °C and poured onto saturated ammonium chloride solution (300 ml). Stirring was continued for several minutes and the phases were separated. The aqueous phase was extracted with chloroform (2× 50 ml). The combined organic phases were washed with saturated ammonium chloride solution (2× 80 ml) and water (2× 80 ml), dried over sodium sulfate and evaporated to dryness. The residue (130 g of a brown oil) was purified by column chromatography [500 g of silica gel, eluant: ethyl acetate/petrol ether = 1:1 (v/v)]. A brownish oil (44.0 g, 84% yield) was isolated which was characterized as the pure title compound: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.92 (m_c, 1H), 2.15 (m_c, 1H), 2.93 (m_c, 5H), 7.02 (d, 1H), 7.28 (m_c), 8.31 (d, 1H), 8.33 (s, 1H); HRMS (ESI) *m/z* $C_{15}H_{16}N$ $[M+H]^+$ Calcd: 210.1277. Found: 210.1269.

4.1.4. Ethyl amino(hydrazono)acetate (10). In a flame-dried flask filled with argon, amino(thioxo)acetate (**9**) (13.3 g, 0.1 mol) was dissolved in ethanol (300 ml), which had been degassed with argon. The red solution was stirred at room temperature and a 1 M solution of hydrazine in THF (100 ml, 0.1 mol) was added over a period of 30 min during which hydrogen sulfide was liberated. The reaction was further stirred for 2.5 h at room temperature. After concentration of the yellow solution under reduced pressure, a yellow-red residue (22 g) was obtained which was recrystallized from petrol ether/dichloromethane [420 ml, 3:1 (v/v)]. The solution was filtered and the red, oily residue was discarded. From the filtrate a yellowish solid separated, which was collected by filtration and washed with petrol ether. Ethyl amino(hydrazono)acetate (**10**) was obtained in 54% yield (7.1 g): mp 92–94 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.38 (t, 3H), 4.35 (q, 2H), 4.52 (br s, 4H).

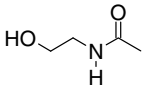
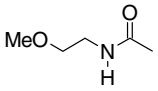
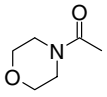
4.1.5. Ethyl 1,2,4-triazine-3-carboxylate (11). Monomeric glyoxal was prepared by heating the trimer (45 g) to 160 °C in the presence of phosphorus pentoxide (110 g).[18] The glyoxal formed was condensed into a trap cooled with liquid nitrogen and dissolved in dry THF. The monomer obtained (14 g) was pure by means of ^{1}H NMR spectroscopy: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.30 (s, CHO). A solution of monomeric glyoxal (5 g) in THF (50 ml) was transferred into a flame-dried flask filled with argon and cooled to −78 °C. A pre-cooled solution (−78 °C) of hydrazono ester **10** (11.0 g, 84 mmol) and glacial acetic acid (13 ml) in absolute ethanol (260 ml) was added over a period of 2 min. The red-yellow reaction mixture was stirred for 15 min at −75 °C. After addition of triethylamine (13 ml), the cooling bath was removed and the solution was stirred for 3 h at room temperature. It was then poured onto a mixture of saturated sodium bicarbonate solution (100 ml), ice water (200 ml), and dichloromethane (300 ml) and stirred for several more minutes. The phases were separated and the aqueous phase was extracted with dichloromethane (3× 100 ml). The combined organic phases were washed with water (3× 100 ml), dried over sodium sulfate, and concentrated under reduced pressure. The remaining yellow solid (20 g) was purified by column chromatography (500 g of silica gel, solvent: dichloromethane). Ethyl 1,2,4-triazine-3-carboxylate (**11**) was obtained as a yellow-brown oil (6.6 g, 51%) that solidified within a few hours: mp 70 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.51 (t, 3H), 4.62 (q, 2H), 8.85 (d, 1H), 9.44 (d, 1H).

4.1.6. 1,2,4-Triazine-3-carboxylic acid (12). Ethyl carboxylate **11** (5.8 g, 38 mmol) was dissolved in dry ethanol (80 ml). A filtered solution of potassium hydroxide

Table 1. Inhibitory activity and physicochemical properties of compounds **2**, **16**, **17**, **22**–**28**, **31**–**33**, **35**



3

Compound	R^3	R^6	H^+/K^+-ATPase $-\log IC_{50}$	Gastric glands $-\log IC_{50}$	pK_a	log *D* (pH 7.4)
2 (lit.[13])			7.0	7.2	6.0	
16	H	H	5.1	5.1	7.63	3.81
17	CH_3	H	6.6	6.1	8.05	3.90
22	CH_3		5.9	5.7	7.26	3.21
23	CH_3		6.2	6.0		
24	CH_3		6.0	6.4	7.16	2.90
25	CH_3		5.9	5	7.22	2.81
26	CH_3		4.9	5.9	7.22	3.31
27	CH_3		5.9	6.5	7.20	3.37
28	CH_3		5	5.2	7.05	2.76
31	CH_3		6.3	5.7	7.79	3.93
32	H		4.8	5.1	6.67	2.77
33	Br		4.9	5.0	5.11	3.80
35	CH_2OH		5.5	5.0	6.32	2.23

(2.3 g, 41 mmol) in dry ethanol (60 ml) was then added over a period of 40 min at room temperature. The resulting light-brown suspension was stirred for additional 15 min at room temperature. The precipitate was isolated by filtration, washed with ethanol (10 ml), and dried in vacuo. The potassium salt of **12** was obtained in 89% yield (5.5 g): ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 8.66 (d, 1H), 9.19 (d, 1H). 1,2,4-Triazine-3-carbox-

ylic acid (**12**) was obtained by dissolving the potassium salt of **12** (5.4 g, 33 mmol) in 34 ml of 1 N hydrochloric acid. The yellow-brown solution was freeze-dried overnight. The obtained mixture of potassium chloride and 1,2,4-triazine carboxylic acid was treated with water (7 ml). The resulting suspension was stirred for 40 min and was then filtered. The residue was washed with water (3 ml) and dried under reduced pressure (desiccating agent: phosphorus pentoxide). 1,2,4-Triazine-3-carboxylic acid (**12**) was obtained in 91% yield (3.2 g): ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 9.03 (d, 1H), 9.60 (d, 1H, 6-H). If the sample contained traces of water, a second set of signals was visible in the ^{1}H NMR spectrum.

4.1.7. 1,2,4-Triazine (13). A flask containing the dry carboxylic acid **12** (7.4 g, 59 mmol) was placed in a preheated oil bath (T = 120 °C). 1,2,4-Triazine (**13**) formed by decarboxylation of **12** was collected in a recipient cooled to −75 °C (acetone/dry ice bath). The destillation of **13** was facilitated by application of reduced pressure (p = 30 mbar). Within 40 min, a total amount of 2.0 g (42% yield) of 1,2,4-triazine (**13**) was collected in the recipient. Rinsing of the destillation apparatus with dichloromethane yielded further 0.58 g (12% yield) of **13**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.67 (d, 1H), 9.32 (t, 1H), 9.75 (d, 1H).

4.1.8. 7-Phenyl-5,6,7,8-tetrahydro-isoquinolin-1-yl-amine (14). (a) *Microwave synthesis*: In an argon-filled microwave reaction vessel, 7-phenyl-5,6,7,8-tetrahydro-isoquinoline (**8**) (0.25 g, 1.2 mmol) was dissolved in dimethylaniline (6.3 ml). Under an argon atmosphere, sodium amide pellets (0.16 g, 4.1 mmol) were crushed and added to the reaction mixture. The vessel was closed and heated to 180 °C in a microwave oven (Emry's optimiser, Personal Chemistry, power input: 20–25 W, pressure: 7.1–8.5 bar) for 12 h. The reaction mixture was poured onto a cold mixture of saturated ammonium chloride solution (30 ml) and ethyl acetate (30 ml). Stirring was continued for several minutes. The phases were separated and the aqueous phase was extracted with ethyl acetate (2× 15 ml). The combined organic phases were washed with saturated ammonium chloride solution (2× 15 ml) and water (2× 20 ml), dried over sodium sulfate, and evaporated to dryness. The obtained brown liquid was purified by column chromatography (15 g of silica gel 15–25 μm, eluant: dichloromethane) to give 160 mg (59% yield) of the title compound **14**. (b) *Thermal synthesis*: In a steel-autoclave filled with argon, 7-phenyl-5,6,7,8-tetrahydro-isoquinoline (**8**) (5.00 g, 23.9 mmol) was dissolved in degassed tetralin (50 ml). Crushed sodium amide pellets (2.8 g, 72 mmol) were added and the resulting suspension was heated for 18 h to 220 °C. The dark-brown reaction mixture was cooled to room temperature and poured onto a mixture of saturated ammonium chloride solution (50 ml) and dichloromethane (80 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 20 ml). The combined organic phases were washed with saturated ammonium chloride solution (50 ml) and water (2× 30 ml), dried over sodium sulfate, and concentrated under reduced pressure. The obtained dark-brown residue (60 g) contained tetralin, which was removed by column chromatography (700 g of silica gel, eluant: dichloromethane). After exchange of the eluant [diethyl ether/triethylamine = 20:1 (v/v)], 2.6 g of the title compound **14** (48% yield, yellow-brown solid) and 0.85 g of its regioisomer (7-phenyl-5,6,7,8-tetrahydro-isoquinolin-3-yl-amine, 16% yield, brown solid containing impurities) were eluted: mp 124–125 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.91 (m_c, 1H), 2.12 (m_c, 1H), 2.45 (m_c, 1H), 2.75 (m_c, 3H), 3.02 (m_c, 1H), 4.32 (br s, 2H), 6.50 (d, 1H), 7.31 (m_c), 7.85 (d, 1H). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.26; H, 7.19; N, 12.32.

4.1.9. 4-Bromo-7-phenyl-5,6,7,8-tetrahydro-isoquinolin-1-yl-amine (15). In a flask filled with argon, 7-phenyl-5,6,7,8-tetrahydro-isoquinolin-1-yl-amine (**14**) (4.20 g, 18.7 mmol) was dissolved in dry acetonitrile (60 ml). *N*-Bromosuccinimide (3.50 g, 19.7 mmol) was added in small portions over a period of 20 min. The slightly red-colored reaction mixture was stirred for 30 min at room temperature. The obtained suspension was poured onto a mixture of ice (80 g), saturated ammonium chloride solution (50 ml), and ethyl acetate (120 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (50 ml). The combined organic phases were washed with water (80 ml), dried over sodium sulfate, and concentrated under reduced pressure. Thus, 5.50 g of the title compound **15** (97% yield) was isolated. Traces of impurities (succinimide) were visible in the ^{1}H NMR spectrum of the brown solid: mp 122–125 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.92 (m_c, 1H), 2.19 (m_c, 1H), 2.47 (m_c, 1H), 2.71 (m_c, overlay with succinimide: 2.75), 2.98 (m_c, 2H), 4.50 (br s, 2H), 7.33 (m_c), 8.02 (s, 1H); HRMS (ESI) m/z $C_{15}H_{16}BrN_2$ $[M+H]^+$ Calcd: 303.0491. Found: 303.0490.

4.1.10. 2-Methyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline (16). 7-Phenyl-5,6,7,8-tetrahydro-isoquinolin-1-yl-amine (**14**) (500 mg, 2.23 mmol) was dissolved in dry THF (10 ml). Chloroacetone (0.37 g, 0.32 ml, 4.0 mmol) was added and the solution was heated to reflux. After a reaction time of 2.5 d, the red suspension was cooled to room temperature. Dichloromethane (20 ml) and water (10 ml) were added and the reaction mixture was neutralized by addition of 25% aqueous ammonia solution. The phases were separated and the aqueous phase was extracted with dichloromethane (2× 5 ml). The combined organic phases were washed with water (10 ml), dried over sodium sulfate, and concentrated under reduced pressure. The crude product (600 mg) was purified by column chromatography (25 g of silica gel, solvent: diethyl ether) and washing with diethyl ether (5 ml). Tetrahydro-imidazo[2,1-*a*]isoquinoline **16** was isolated in 46% yield (270 mg of a colorless solid): mp 113–115 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.90 (m_c, 1H, 8-H_a), 2.05 (m_c, 1H, 8-H_b), 2.29 (s, 3H, 2-CH_3), 2.81 (m_c, 3H, 7-H, 10-H_a), 2.99 (m_c, 1H, 9-H), 3.25 (m_c, 1H, 10-H_b), 6.57 (d, J = 6.9 Hz, 1H, 6-H), 7.24 (m_c, 1H, Ph), 7.35 (m_c, 4H, Ph), 7.55 (s, 1H, 3-H), 8.19 (d, J = 6.9 Hz, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 14.2 (2-CH_3), 28.3 (C-7), 29.3 (C-8), 31.4 (C-10), 38.7 (C-9), 109.6 (C-3), 113.1 (C-6), 122.6 (C-10a), 123.1 (C-5),

126.1 (Ph), 126.7 (Ph), 128.3 (Ph), 130.8 (C-6a), 141.1 (C-2), 144.0 (C-10b), 146.0 (Ph). Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.33; H, 6.89; N, 10.71.

4.1.11. 2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline (17). 7-Phenyl-5,6,7,8-tetrahydro-isoquinolin-1-yl-amine (**14**) (600 mg, 2.60 mmol) was dissolved in dry THF (8 ml). 3-Bromobutanone (0.72 g, 0.50 ml, 4.8 mmol) was added and the solution was heated to reflux. After a reaction time of 24 h, the suspension was cooled to 0 °C and stirred at this temperature for 45 min. The precipitate formed was isolated by filtration, washed with THF (5 ml) and diethyl ether (5 ml), and dried in vacuo. The hydrobromide salt of **17** (860 mg, 93%) showed a mp of 223–225 °C (decomp.). A solution of the hydrobromide salt of **17** (800 mg, 2.24 mmol) in dichloromethane (5 ml) and water (5 ml) was treated with an aqueous ammonia solution (25%) until a pH value of 8 was obtained. The phases were separated and the aqueous phase was extracted with dichloromethane (2× 3 ml). The combined organic phases were washed with water (5 ml), dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by crystallization from diethyl ether (5 ml). Tetrahydro-imidazo[2,1-*a*]isoquinoline **17** was obtained in 75% overall yield (500 mg of a colorless solid): mp 160–161 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.90 (m_c, 1H, 8-H_a), 2.06 (m_c, 1H, 8-H_b), 2.26 (s, 3H, 2-CH_3), 2.34 (s, 3H, 3-CH_3), 2.82 (m_c, 3H, 7-H, 10-H_a), 2.99 (m_c, 1H, 9-H), 3.25 (m_c, 1H, 10-H_b), 6.62 (d, J = 6.9 Hz, 1H, 6-H), 7.24 (m_c, 1H, Ph), 7.34 (m_c, 4H, Ph), 7.91 (d, J = 6.9 Hz, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.8 (3-CH_3), 13.0 (2-CH_3), 28.2 (C-7), 29.4 (C-8), 31.3 (C-10), 38.7 (C-9), 112.9 (C-6), 120.7 (C-5), 126.0 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 115.2, 122.5, 129.7, 137.3, 142.7, 146.1; Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.53; H, 7.30; N, 10.10.

4.1.12. 6-Bromo-2-methyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline, hydrochloride salt (18). In a flask filled with argon, 4-bromo-7-phenyl-5,6,7,8-tetrahydro-isoquinolin-1-yl-amine (**15**) (2.90 g, 9.6 mmol) was dissolved in dry THF (25 ml). Chloroacetone (1.30 ml, 1.51 g, 16.3 mmol) was added and the reaction mixture was heated to reflux for 2.5 d. The red-brown suspension was cooled to room temperature. The precipitate was isolated by filtration and washed with THF (10 ml) and diethyl ether (10 ml). Thus, the pure title compound **18** (2.55 g, 70% yield) was obtained as a colorless solid. The mother liquor was treated with another portion of chloroacetone (0.60 ml, 0.70 g, 7.5 mmol) and refluxed for 50 h. The precipitate formed was isolated by filtration and purified as described above. Another portion (0.40 g, 1.1 mmol, 11% yield) of the pure title compound **18** was isolated (overall yield: 81%): mp 273–275 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.02 (m_c, 1H, 8-H_a), 2.22 (m_c, 1H, 8-H_b), 2.48 (s, 2-CH_3), 3.03 (m_c, 4H, 7-H, 9-H, 10-H_a), 3.36 (m_c, 10-H_b), 7.28 (m_c, 1H, Ph), 7.37 (m_c, 4H, Ph), 7.99 (s, 1H, 3-H), 9.19 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 10.2 (2-CH_3), 28.5 (C-8), 29.8 (C-7), 31.2 (C-10), 37.3 (C-9), 111.8 (C-3), 126.1 (C-5), 126.5 (Ph), 126.8 (Ph), 128.5 (Ph), quarternary carbon atoms: 114.1, 121.7, 133.7, 137.8, 139.6, 144.5; HRMS (ESI) m/z $C_{18}H_{18}BrN_2$ $[M+H]^+$ Calcd: 341.0648. Found: 341.0628.

4.1.13. 6-Bromo-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline, hydrobromide salt (19). In a flask filled with argon, 4-bromo-7-phenyl-5,6,7,8-tetrahydro-isoquinolin-1-yl-amine (**15**) (6.40 g, 21.1 mmol) was dissolved in dry THF (120 ml). 3-Bromobutanone (4.2 ml, 6.0 g, 40 mmol) was added and the reaction mixture was heated to reflux for 90 h. A precipitate was formed which was isolated by filtration, washed with THF, and dried in vacuo (3.0 g of pure **19**, colorless solid). The mother liquor was treated with another portion of 3-bromobutanone (3.0 ml, 4.3 g, 29 mmol) and was refluxed for another 75 h. A second crop of crystals was obtained, which was isolated and purified as described above (3.0 g of pure **19**, colorless solid). Thus, a total amount of 6.0 g (66% yield) of the title compound **19** was obtained: mp 263–265 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.00 (m_c, 1H, 8-H_a), 2.20 (m_c, 1H, 8-H_b), 2.43 (s, 3H, 2-CH_3), 2.50 (s, 3-CH_3), 3.00 (m_c, 4H, 7-H, 9-H, 10-H_a), 3.24 (m_c, 10-H_b), 7.29 (m_c, 1H, Ph), 7.38 (m_c, 4H, Ph), 8.96 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.4 (3-CH_3), 9.3 (2-CH_3), 28.4 (C-8), 29.8 (C-7), 31.2 (C-10), 37.3 (C-9), 124.2 (C-5), 126.6 (Ph), 126.8 (Ph), 128.5 (Ph), quarternary carbon atoms: 114.3, 119.1, 121.3, 129.0, 136.8, 139.2, 144.5; HRMS (ESI) m/z $C_{19}H_{20}BrN_2$ $[M+H]^+$ Calcd: 355.0804. Found: 355.0793.

4.1.14. 2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid ethyl ester (20).[21] In a steel autoclave filled with argon, bromo derivative **19** (5.00 g, 11.5 mmol) was dissolved in dry ethanol (100 ml). After addition of triethylamine (7.5 ml, 53 mmol) a brown solution was obtained, which was treated with palladium acetate (0.27 g, 1.2 mmol) and triphenylphosphine (0.40 g, 1.5 mmol). The autoclave was pressurized with carbon monoxide (6 bar) and heated to 115 °C. The reaction mixture was kept for 18 h at this temperature, cooled to room temperature, and poured onto a mixture of ice water (300 ml) and dichloromethane (300 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 50 ml). The combined organic phases were washed with water (100 ml), dried over sodium sulfate, and concentrated under reduced pressure. A brown solid (4.5 g) was obtained, which was purified by column chromatography [120 g of silica gel, eluant: petrol ether/ethyl acetate = 6:4 (v/v)]. An almost colorless solid was isolated (3.6 g, 90% yield) which was characterized as the pure title compound **20**: mp 165–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.35 (t, J = 7.1 Hz, 3H, COOEt), 1.87 (m_c, 1H, 8-H_a), 2.11 (m_c, 1H, 8-H_b), 2.29 (s, 3H, 2-CH_3), 2.41 (s, 3H, 3-CH_3), 2.85 (m_c, 1H, 10-H_a), 3.02 (m_c, 2H, 7-H_a, 9-H), 3.14 (m_c, 1H, 7-H_b), 3.31 (br s, H_2O, 10-H_b), 4.32 (q, J = 7.1 Hz, 2H, COO-Et), 7.24 (m_c, 1H, Ph), 7.35 (m_c, 4H, Ph), 8.50 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.7 (3-

CH_3), 13.1 (2-CH_3), 14.1 (COOEt), 27.1 (C-7), 29.4 (C-8), 31.8 (C-10), 37.8 (C-9), 60.7 (COOEt), 125.3 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 115.5, 116.6, 123.5, 129.1, 139.4, 142.9, 145.9, 165.5 (COOEt). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.67; H, 6.91; N, 7.95.

4.1.15. 2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid (21). A solution of ethyl carboxylate **20** (4.10 g, 11.7 mmol) in methanol (80 ml) was treated with an aqueous solution of potassium hydroxide (1.40 g, 25.0 mmol in 8 ml of water). The slightly yellow solution was heated to 60 °C for 3 h. After the methanol was removed under reduced pressure, the reaction mixture was diluted with water (30 ml) and extracted with ethyl acetate (2× 20 ml). The organic phases were discarded and the aqueous phase (initial pH value: 11) was acidified by addition of hydrochloric acid (6 N, final pH value: 3). A suspension was obtained which was stirred for 2 h at room temperature. A colorless solid was isolated by filtration, which was washed with portions of water (30 ml) and acetone (10 ml), and then dried in vacuo. The pure title compound **21** (3.5 g) was obtained in 93% yield: mp 343–345 °C (decomp.); ^{1}H NMR (400 MHz, D_2O + NaOD): δ = 1.61 (m_c, 1H, 8-H_a), 2.04 (m_c, 1H, 8-H_b), 2.21 (s, 3H, 2-CH_3), 2.22 (s, 3H, 3-CH_3), 2.62 (dd, 1H, 10-H_a), 2.84 (m_c, 1H, 9-H), 2.94 (m_c, 2H, 7-H), 3.08 (dd, 1H, 10-H_b), 7.27 (m_c, 3H), 7.37 (m_c, 2H), 8.00 (s, 1H); ^{13}C NMR (100.7 MHz, D_2O + NaOD): δ = 7.0 (3-CH_3), 11.6 (2-CH_3), 27.3 (C-7), 29.2 (C-8), 31.4 (C-10), 38.1 (C-9), 120.7 (C-5), 126.5 (Ph), 126.8 (Ph), 128.8 (Ph), quarternary carbon atoms: 117.1, 122.2, 125.7, 131.0, 137.5, 143.1, 146.4, 174.8 (COOEt); HRMS (ESI) *m/z* $C_{20}H_{21}N_2O_2$ $[M+H]^+$ Calcd: 321.1598. Found: 321.1591.

4.1.16. 2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid amide (22).[22] Under an argon atmosphere, a suspension of carboxylic acid **21** (450 mg, 1.40 mmol) in dry dichloromethane (18 ml) was treated with TBTU (500 mg, 1.56 mmol). The reaction mixture was heated to reflux for 1 h. The well-stirred suspension was cooled to room temperature and was saturated with ammonia gas for 1 h. The colorless suspension was poured onto a mixture of saturated ammonium chloride solution (20 ml) and dichloromethane (30 ml). The mixture was stirred for several minutes and the pH (initial value: 10) was adjusted to 6 by addition of 6 N hydrochloric acid. The phases were separated and the aqueous phase was extracted with dichloromethane (20 ml). The combined organic phases were concentrated under reduced pressure. The oily residue was treated with acetone (10 ml) at which point crystallization occurred. The solid was isolated by filtration and washed with acetone (8 ml) and diethyl ether (10 ml). After drying in vacuo, the title compound **22** was obtained in form of a colorless solid (290 mg, 65% yield): mp 298–300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.94 (m_c, 1H, 8-H_a), 2.17 (m_c, 1H, 8-H_b), 2.44 (s, 3H, 2-CH_3), 2.49 (s, 3-CH_3), 2.98 (m_c, 1H, 10-H_a), 3.11 (m_c, 3H, 7-H, 9-H), 3.36 (m_c, 10-H_b), 7.32 (m_c, 5H, Ph), 7.78 (s, 1H, $CONH_2$), 8.20 (s, 1H, $CONH_2$), 8.67 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.3 (3-CH_3), 9.8 (2-CH_3), 26.8 (C-7), 28.5 (C-8), 31.2 (C-10), 37.5 (C-9), 122.4 (C-5), 126.4 (Ph), 126.8 (Ph), 128.4 (Ph), quarternary carbon atoms: 118.8, 120.7, 125.6, 130.3, 138.0, 145.1, 166.6 ($CONH_2$); HRMS (ESI) *m/z* $C_{20}H_{22}N_3O$ $[M+H]^+$ Calcd: 320.1757. Found: 320.1751.

4.1.17. General procedure for the conversion of 2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid (21) into carboxamides.[22] Under an argon atmosphere, a suspension of carboxylic acid **21** (450–500 mg) in dry dichloromethane (8–15 ml) was treated with TBTU (1.1 equiv). The reaction mixture was heated to reflux for 1 h. The suspension was cooled to room temperature and the respective amine (1.0–1.1 equiv) was added slowly. Stirring was continued for 1–3 h at room temperature and the reaction was quenched by addition of saturated ammonium chloride solution (5–15 ml) and dichloromethane. The biphasic mixture was stirred for several minutes. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with saturated sodium bicarbonate solution and water, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography and/or by washing with diethyl ether. The respective title compound was isolated as a colorless solid.

4.1.17.1. 2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid methylamide (23). Preparation by condensation of carboxylic acid **21** (450 mg, 1.40 mmol) with methylamine (750 µl of a 2 M solution in THF, 1.50 mmol) as described in the general procedure, purification of crude **23** was achieved by washing with diethyl ether (15 ml): 260 mg; 56% yield; mp 266–268 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.86 (m_c, 1H, 8-H_a), 2.08 (m_c, 1H, 8-H_b), 2.27 (s, 3H, 2-CH_3), 2.38 (s, 3H, 3-CH_3), 2.78, 2.80 (d, m_c, 4H, CONHMe, 10-H_a), 2.89 (m_c, 2H, 7-H), 2.99 (m_c, 1H, 9-H), 3.30 (m_c, 10-H_b), 7.24 (m_c, 1H, Ph), 7.34 (m_c, 4H, Ph), 8.11 (s, 1H, 5-H), 8.30 (q, 1H, NH); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.8 (3-CH_3), 13.0 (2-CH_3), 25.9 (CONHMe), 26.2 (C-7), 29.3 (C-8), 31.6 (C-10), 38.2 (C-9), 120.6 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 115.9, 122.1, 123.0, 128.2, 138.2, 142.3, 145.9, 166.9 (CONHMe); HRMS (ESI) *m/z* $C_{21}H_{24}N_3O$ $[M+H]^+$ Calcd: 334.1914. Found: 334.1890.

4.1.17.2. 2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid dimethylamide (24). Preparation by condensation of carboxylic acid **21** (500 mg, 1.56 mmol) with dimethylamine (0.80 ml of a 2 M solution in THF, 1.6 mmol) as described in the general procedure, purification of crude **24** was achieved by column chromatography [30 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)] and subsequent washing with diethyl ether (8 ml): 390 mg, 72% yield; mp 239–241 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.92 (m_c, 1H, 8-H_a), 2.08

(m_c, 1H, 8-H_b), 2.27 (s, 3H, 2-CH_3), 2.36 (s, 3H, 3-CH_3), 2.66 (m_c, 2H, 7-H), 2.86 (s, m_c, 4H, $CONMe_2$, 10-H_a), 3.03 (s, br s, 4H, $CONMe_2$, 9-H), 3.32 (dd, 10-H_b), 7.24 (m_c, 1H, Ph), 7.34 (m_c, 4H, Ph), 8.03 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.8 (3-CH_3), 13.0 (2-CH_3), 25.4 (C-7), 29.1 (C-8), 31.5 (C-10), 34.1, 38.2 ($CONMe_2$), 38.3 (C-9), 118.4 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 116.1, 122.0, 123.4, 126.6, 138.2, 142.1, 145.8, 167.3 ($CONMe_2$). Anal. Calcd for $C_{22}H_{25}N_3O$: C, 76.05; H, 7.25; N, 12.09. Found: C, 75.60; H, 7.22; N, 12.02.

4.1.17.3. 2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid (2-hydroxy-ethyl)-amide (25). Preparation by condensation of carboxylic acid **21** (450 mg, 1.40 mmol) with 2-amino-ethanol (101 mg, 100 μl, 1.66 mmol) as described in the general procedure, purification of crude **25** was achieved by washing with diethyl ether (15 ml): 290 mg, 57% yield; mp 265–267 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.86 (m_c, 1H, 8-H_a), 2.08 (m_c, 1H, 8-H_b), 2.27 (s, 3H, 2-CH_3), 2.39 (s, 3H, 3-CH_3), 2.85 (m_c, 3H, 7-H, 10-H_a), 3.00 (m_c, 1H, 9-H), 3.25 (m_c, 10-H_b, CONH$(CH_2)_2$OH), 3.54 (m_c, 2H, CONH$(CH_2)_2$OH), 4.72 (br s, 1H, OH), 7.24 (m_c, 1H, Ph), 7.33 (m_c, 4H, Ph), 8.12 (s, 1H, 5-H), 8.35 (t, 1H, NH); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.8 (3-CH_3), 13.1 (2-CH_3), 26.2 (C-7), 29.4 (C-8), 31.6 (C-10), 37.9 (C-9), 42.0, 59.7 (CONH$(CH_2)_2$OH), 120.7 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 115.9, 122.1, 123.0, 128.1, 138.3, 142.4, 146.0, 166.7 (CONH$(CH_2)_2$OH); HRMS (ESI) *m/z* $C_{22}H_{26}N_3O_2$ $[M+H]^+$ Calcd: 364.2020. Found: 364.2006.

4.1.17.4. 2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid (2-methoxy-ethyl)-amide (26). Preparation by condensation of carboxylic acid **21** (450 mg, 1.40 mmol) with 2-methoxy-ethylamine (112 mg, 130 μl, 1.50 mmol) as described in the general procedure, purification of crude **26** was achieved by washing with diethyl ether (15 ml): 390 mg, 74% yield; mp 208–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.87 (m_c, 1H, 8-H_a), 2.09 (m_c, 1H, 8-H_b), 2.27 (s, 3H, 2-CH_3), 2.38 (s, 3H, 3-CH_3), 2.85 (m_c, 3H, 7-H, 10-H_a), 2.99 (m_c, 1H, 9-H), 3.27 (m_c, 10-H_b, CONH$(CH_2)_2$OMe), 3.40 (m_c, 2H, CONH$(CH_2)_2$OMe), 3.46 (m_c, 2H, CONH$(CH_2)_2$OMe), 7.24 (m_c, 1H, Ph), 7.33 (m_c, 4 H, Ph), 8.07 (s, 1H, 5-H), 8.43 (t, 1H, NH); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.8 (3-CH_3), 13.1 (2-CH_3), 26.2 (C-7), 29.4 (C-8), 31.7 (C-10), 38.2 (C-9, CONH$(CH_2)_2$OMe), 57.9, 70.4 (CONH$(CH_2)_2$OMe), 120.6 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 115.9, 121.9, 123.0, 128.0, 138.3, 142.4, 146.0, 166.6 (CONH$(CH_2)_2$OMe); HRMS (ESI) *m/z* $C_{23}H_{28}N_3O_2$ $[M+H]^+$ Calcd: 378.2176. Found: 378.2164.

4.1.17.5. (2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinolin-6-yl)-pyrrolidin-1-yl-methanone (27). Preparation by condensation of carboxylic acid **21** (450 mg, 1.40 mmol) with pyrrolidine (107 mg, 126 μl, 1.50 mmol) as described in the general procedure, purification of crude **27** was achieved by washing with diethyl ether (10 ml): 450 mg, 86% yield; mp 239–241 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.88 (m_c, 5H, CO-pyrrolidine, 8-H_a), 2.08 (m_c, 1H, 8-H_b), 2.27 (s, 3H, 2-CH_3), 2.37 (s, 3H, 3-CH_3), 2.69 (m_c, 2H, 7-H), 2.86 (m_c, 1H, 10-H_a), 3.03 (m_c, 1H, 9-H), 3.22 (m_c, 3H, CO-pyrrolidine, 10-H_b), 3.47 (m_c, 2H, CO-pyrrolidine), 7.24 (m_c, 1H, Ph), 7.34 (m_c, 4H, Ph), 8.08 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.8 (3-CH_3), 13.0 (2-CH_3), 24.1, 25.5 (CO-pyrrolidine), 25.6 (C-7), 29.1 (C-8), 31.5 (C-10), 38.3 (C-9), 45.2, 48.2 (CO-pyrrolidine), 118.5 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 116.1, 123.1, 123.5, 126.5, 138.1, 142.1, 145.9, 165.6 (CO-pyrrolidine); Anal. Calcd for $C_{24}H_{27}N_3O$: C, 77.18; H, 7.29; N, 11.25. Found: C, 76.77; H, 7.27; N, 11.38.

4.1.17.6. (2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinolin-6-yl)-morpholin-4-yl-methanone (28). Preparation by condensation of carboxylic acid **21** (450 mg, 1.40 mmol) with morpholine (130 mg, 130 μl, 1.49 mmol) as described in the general procedure, purification of crude **28** was achieved by washing with diethyl ether (10 ml): 440 mg, 81% yield; mp 184–186 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K): δ = 1.92 (m_c, 1H, 8-H_a), 2.12 (m_c, 1H, 8-H_b), 2.28 (s, 3H, 2-CH_3), 2.36 (s, 3H, 3-CH_3), 2.70 (m_c, 2H, 7-H), 2.92 (dd, 10-H_a), 3.06 (m_c, 1H, 9-H), 3.35 (dd, 1H, 10-H_b), 3.47 (br s, 4H, CO-morpholine), 3.60 (br s, CO-morpholine), 7.21 (m_c, 1H, Ph), 7.32 (m_c, 4H, Ph), 7.93 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6, 273 K): δ = 7.9 (3-CH_3), 13.0 (2-CH_3), 25.6 (C-7), 29.1 (C-8), 31.4 (C-10), 38.2 (C-9), 41.7, 47.1, 65.9, 66.1 (CO-morpholine), 118.8 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 116.1, 121.0, 123.5, 138.3, 142.1, 145.8, 166.0 (CO-morpholine). Anal. Calcd for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.79. Found: C, 73.92; H, 7.02; N, 10.86.

4.1.18. (2,3-Dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinolin-6-yl)-methanol (29). In a flame-dried flask filled with argon, ethyl carboxylate **20** (2.50 g, 7.2 mmol) was dissolved in dry THF (30 ml). At room temperature, lithium aluminium hydride (0.40 g, 10.5 mmol) was added in small portions. Stirring was continued for 1 h at room temperature and the reaction mixture was quenched by addition of water (0.5 ml) and a sodium hydroxide solution (15 wt%, 0.5 ml) and diluted with more water (1.5 ml). The gray suspension was stirred for 20 min at room temperature and was filtered. The filter cake was washed with THF (3× 10 ml) and then suspended in a mixture of chloroform (30 ml) and methanol (15 ml). The resulting slurry was stirred for 1 h at room temperature. Insoluble material was removed by filtration and the filter cake was washed with chloroform (10 ml) and methanol (10 ml). The combined filtrates were evaporated to dryness. The residue, 980 mg of a colorless solid (44% yield), was dried in vacuo and characterized as the title compound **29**: mp 290–292 °C, ^{1}H NMR (600 MHz, DMSO-d_6, 353 K): δ = 1.94 (m_c, 1H, 8-H_a), 2.14 (m_c, 1H, 8-H_b), 2.27 (s, 3H, 2-CH_3), 2.36 (s, 3H, 3-CH_3), 2.87 (m_c, 3H, 7-H, 10-H_a), 2.99 (m_c, 9-H), 3.31 (dd, 1H, 10-H_b), 4.54 (s,

2H, CH_2OH), 4.91 (br s, 1H, OH), 7.22 (m_c, 1H, Ph), 7.33 (m_c, 4H, Ph), 7.88 (s, 1H, 5-H); ^{13}C NMR (150.9 MHz, DMSO-d_6, 353 K): δ = 7.3 (3-CH_3), 12.4 (2-CH_3), 24.2 (C-7), 29.0 (C-8), 31.2 (C-10), 38.0 (C-9), 58.9 (CH_2OH), 118.3 (C-5), 125.6 (Ph), 126.3 (Ph), 127.9 (Ph), quarternary carbon atoms: 114.8, 122.0, 124.5, 129.5, 136.5, 141.8, 145.7; HRMS (ESI) *m/z* $C_{20}H_{23}N_2O$ $[M+H]^+$ Calcd: 307.1805. Found: 307.1794.

4.1.19. 6-Chloromethyl-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline (30). At room temperature, thionyl chloride (0.23 ml, 0.38 g, 3.2 mmol) was added slowly to a suspension of alcohol **29** (0.95 g, 3.1 mmol) in dry dichloromethane (25 ml). The resulting solution was stirred for 1 h at room temperature, cooled to 0 °C, and treated slowly with a mixture of saturated sodium bicarbonate solution (8 ml) and water (5 ml). The cooling bath was removed and the biphasic mixture was stirred for 10 min. The phases were separated and the aqueous phase was extracted with dichloromethane (10 ml). The combined organic phases were washed with water (10 ml), dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The remaining brown solid was suspended in diethyl ether (12 ml). The title compound **30** was isolated by filtration, washed with diethyl ether (5 ml), and dried in vacuo (880 mg, 87% yield): mp 155–157 °C; ^1H NMR (200 MHz, DMSO-d_6): δ = 1.95 (m_c, 1H), 2.14 (m_c, 1H), 2.27 (s, 3H), 2.37 (s, 3H), 2.92 (m_c, 4H), 3.27 (m_c, 1H), 4.90 (m_c, 2H), 7.29 (m_c, 5 H), 8.27 (s, 1H); HRMS (ESI) *m/z* $C_{20}H_{22}ClN_2$ $[M+H]^+$ Calcd: 325.1466. Found: 325.1459.

4.1.20. 6-Methoxymethyl-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline (31). Chloride **30** (500 mg, 1.54 mmol) was suspended in dry methanol (12 ml). After the addition of sodium methylate (solution: 30 wt% in methanol, 0.56 ml, 3.0 mmol), the reaction mixture was heated to 60 °C. Within a period of 90 min a yellow solution was formed, which was cooled to room temperature and poured onto a mixture of saturated ammonium chloride solution (20 ml) and dichloromethane (50 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (3× 5 ml). The combined organic phases were washed with water (15 ml), dried over sodium sulfate, and concentrated under reduced pressure. An oily residue (520 mg) was isolated, which was purified by column chromatography [20 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)]. Evaporation of the corresponding fractions afforded an oily residue (380 mg), which was crystallized from diethyl ether (3 ml). The title compound **31** was isolated by filtration, washed with diethyl ether (1 ml), and dried in vacuo (210 mg of a colorless solid, 44% yield): mp 113–114 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.90 (m_c, 1H, 8-H_a), 2.11 (m_c, 1H, 8-H_b), 2.26 (s, 3H, 2-CH_3), 2.36 (s, 3H, 3-CH_3), 2.80 (m_c, 3H, 7-H, 10-H_a), 2.96 (m_c, 1H, 9-H), 3.25 (m_c, s, 10-H_b, CH_2OCH_3), 4.44 (s, 2H, CH_2OCH_3), 7.24 (m_c, 1H, Ph), 7.33 (m_c, 4 H, Ph), 7.98 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 7.8 (3-CH_3), 13.0 (2-CH_3), 24.7 (C-7), 29.3 (C-8), 31.6 (C-10), 38.3 (C-9), 57.2, 70.0 (CH_2OMe), 120.5 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 115.3, 120.5, 122.7, 129.7, 137.5, 142.5, 146.1; HRMS (ESI) *m/z* $C_{21}H_{25}N_2O$ $[M+H]^+$ Calcd: 321.1961. Found: 321.1951.

4.1.21. 2-Methyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid dimethylamide (32).[21] In a steel autoclave filled with argon, bromide **18** (2.80 g, 7.4 mmol) was suspended in dry THF (10 ml). After the addition of dimethylamine (38.0 ml of a 2 M solution in THF, 76 mmol), palladium acetate (0.30 g, 1.3 mmol), triphenylphosphine (1.10 g, 4.2 mmol), and triethylamine (2.0 ml, 14 mmol), the autoclave was pressurized with carbon monoxide (6 bar) and heated to 120 °C. The reaction mixture was kept for 19 h at this temperature, cooled to room temperature, and poured onto a mixture of saturated ammonium chloride solution (80 ml) and ethyl acetate (80 ml). The phases were separated and the aqueous phase was extracted with ethyl acetate (3× 20 ml). The combined organic phases were washed with saturated ammonium chloride solution (2× 50 ml) and water (2× 50 ml), dried over sodium sulfate, and concentrated under reduced pressure. A brown solid (6 g) was obtained, which was purified by column chromatography [100 g of silica gel, eluant: ethyl acetate/methanol = 100:3 (v/v)] and subsequently washed with diethyl ether. This afforded the pure carboxamide **32** (1.7 g of a colorless solid, 69% yield): mp 215–217 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.91 (m_c, 1H, 8-H_a), 2.03 (m_c, 1H, 8-H_b), 2.30 (s, 3H, 2-CH_3), 2.66 (m_c, 2H, 7-H), 2.85, 2.88 (s, m_c, 4H, $CONMe_2$, 10-H_a), 3.01, 3.04 (s, m_c, 4H, $CONMe_2$, 9-H), 3.31 (m_c, 10-H_b), 7.24 (m_c, 1H, Ph), 7.34 (m_c, 4H, Ph), 7.58 (s, 1H, 3-H), 8.29 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 14.1 (2-CH_3), 25.6 (C-7), 28.9 (C-8), 31.6 (C-10), 34.1, 38.2 ($CONMe_2$), 38.3 (C-9), 110.2 (C-3), 120.8 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 122.2, 123.6, 127.8, 142.0, 143.3, 145.8, 167.0 ($CONMe_2$). Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.63; H, 6.95; N, 12.57.

4.1.22. 3-Bromo-2-methyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid dimethylamide (33). 7,8,9,10-Tetrahydro-imidazo[2,1-*a*]isoquinoline **32** (350 mg, 1.05 mmol) was dissolved in dry dichloromethane (8 ml). The solution was cooled to −75 °C and a suspension of *N*-bromosuccinimide (195 mg, 1.10 mmol) in dichloromethane (6 ml) was added over a period of 10 min. The reaction mixture was stirred for 1 h at −75 °C and was then quenched by addition of saturated sodium bicarbonate solution (8 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2× 5 ml). The combined organic phases were washed with water (10 ml), dried over sodium sulfate, and concentrated under reduced pressure. The foamy, colorless residue (500 mg) was crystallized from diethyl ether (10 ml). The pure bromo derivative **33** (385 mg, 89% yield) was isolated as a colorless solid: mp 166–168 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 1.94 (m_c, 1H, 8-H_a), 2.09 (m_c, 1H, 8-H_b), 2.32 (s, 3H, 2-CH_3), 2.69 (m_c, 2H, 7-H), 2.85, 2.89 (s, m_c, 4H, $CONMe_2$, 10-H_a), 3.03 (s, m_c, 4H, $CONMe_2$, 9-H) 3.33 (m_c, 10-H_b), 7.25 (m_c, 1H, Ph),

7.35 (m_c, 4H, Ph), 8.06 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 13.3 (2-CH_3), 25.5 (C-7), 28.8 (C-8), 31.0 (C-10), 34.2, 38.1 ($CONMe_2$), 38.1 (C-9), 118.4 (C-5), 126.2 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 123.8, 124.4, 128.8, 140.8, 143.5, 145.6, 166.4 ($CONMe_2$). Anal. Calcd for $C_{21}H_{22}BrN_3O$: C, 61.17; H, 5.38; N, 10.19; Br, 19.38. Found: C, 61.24; H, 5.38; N, 10.16; Br, 19.29.

4.1.23. 3-Formyl-2-methyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid dimethylamide (34). Under an argon atmosphere at a temperature of 0 °C, phosphorus oxychloride (0.33 ml, 0.54 g, 3.5 mmol) was added dropwise to dry DMF (3.5 ml). After stirring the pink solution for 90 min at room temperature, a solution of 7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline **32** (800 mg, 2.4 mmol) in dry DMF (11 ml) was slowly added. The resulting red solution was stirred for 1 h at room temperature and then for 3 h at 60 °C. The reaction mixture was cooled to room temperature, poured onto a mixture of ice water (20 ml) and dichloromethane (20 ml), and neutralized by addition of 25% aqueous ammonia solution. The phases were separated and the aqueous phase was extracted with dichloromethane (3× 10 ml). The combined organic phases were washed with water (4× 10 ml), dried over sodium sulfate, and concentrated under reduced pressure. The colorless residue (1.1 g) was purified by column chromatography [40 g of silica gel, eluant: ethyl acetate/methanol = 20:1 (v/v)]. The composition of the obtained slightly red solid (680 mg, 78%, mp 205–207 °C) was determined by ^{1}H NMR spectroscopy. The sample consisted of aldehyde **34** along with 9 wt% of untransformed starting material **32**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.00 (m_c, 1H), 2.25 (m_c, 1H), 2.70 (s, 3H), 2.92, 2.95, 3.00, 3.17 (m_c, s, m_c, s, 10H), 3.57 (m_c, 1H), 7.31 (m_c), 9.30 (s, 1H), 9.98 (s, 1H); HRMS (ESI) *m/z* $C_{22}H_{24}N_3O_2$ $[M+H]^+$ Calcd: 362.1863. Found: 362.1850.

4.1.24. 3-Hydroxymethyl-2-methyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[2,1-*a*]isoquinoline-6-carboxylic acid dimethylamide (35). Aldehyde **34** (300 mg containing 9 wt% of **32**, 0.83 mmol) was dissolved in dry methanol (10 ml). Sodium borohydride (40 mg, 1.06 mmol) was added in small portions. A clear solution was obtained, which was stirred for 30 min at room temperature and then poured onto a mixture of saturated ammonium chloride solution (10 ml) and dichloromethane (20 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (3× 5 ml). The combined organic phases were washed with saturated ammonium chloride solution (10 ml) and water (10 ml), dried over sodium sulfate, and concentrated under reduced pressure. The colorless residue (300 mg) was purified by column chromatography [30 g of silica gel, eluant: dichloromethane/methanol = 100:3 (v/v)]. The pure title compound (190 mg, 63% yield) was isolated as a colorless solid: mp 385–388 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.94 (m_c, 1H, 8-H_a), 2.10 (m_c, 1H, 8-H_b), 2.31 (s, 3H, 2-CH_3), 2.67 (m_c, 2H, 7-H), 2.86, 2.89 (s, m_c, 4H, $CONMe_2$, 10-H_a), 3.02 (s, 4H, $CONMe_2$, 9-H), 3.31 (m_c, 10-H_b), 4.74 (d, J = 4.8 Hz, 2H, CH_2OH), 5.05 (t, J = 5.1 Hz, 1H, CH_2OH), 7.24 (m_c, 1H, Ph), 7.34 (m_c, 4H, Ph), 8.12 (s, 1H, 5-H); ^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 13.0 (2-CH_3), 25.5 (C-7), 29.0 (C-8), 31.4 (C-10), 34.1, 38.2 ($CONMe_2$), 38.3 (C-9), 51.4 (CH_2OH), 119.2 (C-5), 126.1 (Ph), 126.7 (Ph), 128.3 (Ph), quarternary carbon atoms: 120.8, 122.1, 123.6, 127.9, 139.7, 142.7, 145.8, 167.1 ($CONMe_2$); HRMS (ESI) *m/z* $C_{22}H_{26}N_3O_2$ $[M+H]^+$ Calcd: 364.2020. Found: 364.2003.

4.2. Biochemistry

4.2.1. Determination of inhibitory activity in a competitive binding assay against H^+/K^+-ATPase from hog gastric mucosa. Given data are the mean IC_{50} values from 2 to 3 independent determinations. The malachite green assay modified from Yoda, A.; Hokin, L. E. (*Biochem. Biophys. Res. Commun.* **1970**, *40*, 880–886) was used for the determination of H^+/K^+-ATPase IC_{50}: Lanzetta, P. A.; Alvarez, L. J.; Reinach, P. S.; Candia, O. A. *Anal. Biochem*. **1979**, *100*, 95–97. Pipes [piperazine-1,4-bis(2-ethanesulfonic acid)], sucrose, nigericin, Na–ATP, and malachite green were purchased from Sigma–Aldrich; Tris [Tris(hydroxymethyl)aminomethane], KCl, and ammoniumheptamolybdate tetrahydrate from Merck; and $MgCl_2$ from Fluka. Final assay concentrations: 4 mM Pipes/8 mM Tris buffer, pH 7.4, 0.25 M sucrose, 1 mM KCl, 1 mM $MgCl_2$, 0.5–1 μg/100 μl nigericin (1:1 ratio with enzyme), 0.5–1 μg/100 μl enzyme (dependent on K^+-stimulated, specific activity), and 1 mM Na–ATP (high grade), reaction volume: 101 μl. Preparation of malachite green reagent: two parts of malachite green stock solution (1.2 M in H_2O, protected from light and used within 12 weeks) was mixed with one part of ammoniumheptamolybdate tetrahydrate stock solution (42 g/l in 4 N HCl) and kept for 30 min at room temperature prior to use. A Pipes/Tris buffer based solution with sucrose and $MgCl_2$ was prepared. Nigericin and enzyme were added to reach the final concentrations mentioned above. Eighty microliters per well of this mixture was placed into 96-well flat bottom plates (clear, polystyrol, Greiner bio-one). Ten microliters per well of KCl (1 mM final) was used for stimulation of the H^+/K^+-ATPase activity. Test substances were dissolved as 10 mM solutions in 100% DMSO. One microliter of substance solution was added in dilutions ranging from 1×10^{-4} to 1×10^{-9} M (final). The enzymatic reaction was started by the addition of 10 μl ATP (1 mM final). The assay was incubated for 30 min at room temperature. The reaction was stopped by the addition of 150 μl of malachite green reagent and incubated for another 15 min prior to photometric reading of the plate at 680 nm in a PowerWave HT Microplate spectral photometer (BioTek). The results were analyzed with GraphPad Prism software (Version 4.02) to calculate IC_{50} values by sigmoidal curve fitting. 'Enzyme' refers to H^+/K^+-ATPase-containing vesicles prepared from hog gastric mucosa as described in Rabon, E. C.; Im, W. B.; Sachs, G. *Methods Enzymol.* **1988**, *157*, 649–654.

4.2.2. ^{14}C-Dimethylaminopyridine accumulation in intact gastric glands. Gastric acid secretion is stimulated by gastrin, histamine and acetylcholine via the receptors

on the parietal or the enterochromaffin-like cell. These physiologic stimuli influence the intracellular cyclic AMP and Ca^{2+} levels, thus leading to relocation and activation of H^+/K^+-ATPase. Instead of the physiologic agonists, the membrane-permeant dibutyryl-cyclic AMP was used to stimulate receptor-independent acid secretion in isolated gastric glands. Accumulation of the weak base ^{14}C-dimethylaminopyridine (^{14}C-AP) in the acidic compartment of the canaliculi serves as an indirect measure of acid secretion and forms the basis of measurement of acid secretion in this in vitro model of the mammalian stomach. Intact gastric glands were prepared from anesthesized New Zealand rabbits (weight 2–3 kg) by high-pressure perfusion of the stomach, separation of the fundic mucosa, and subsequent collagenase digestion of fragments of the mucosa (Berglindh, T; Helander, H. F.; Obrink, K. J. *Acta Physiol. Scand.* **1976**, *97*, 401–414; Berglindh, T.; Obrink, K. J. *Acta Physiol. Scand.* **1976**, *96*, 150–159). After the gastric glands were washed several times, they were suspended in Krebs–Henseleit solution containing 2 mg/ml rabbit serum albumin and 2 mg/ml glucose. The glands were incubated for 30 min at 37 °C in a shaker bath (200 osc/min) in the presence of 0.125 μM ^{14}C-AP (113 μCi/μmol) at pH 7.4. The glands were stimulated with 1 mM dibutyryl cAMP in the absence or presence of the corresponding inhibitor (concentration range 3 nM–100 μM). The reaction was stopped by centrifugation (10 s at 20,000*g*). After centrifugation, the accumulation of ^{14}C-AP in the glands was calculated as follows: radioactivity was measured in an aliquot of the supernatant (200 μl) and in the precipitate after dissolution in 1 ml of 1 N NaOH. In order to calculate the amount of protein, the Eppendorf tubes were weighed empty, with protein (wet weight) and with freeze-dried protein (dry weight). This ratio of supernatant and pellet protein radioactivity was used to calculate the accumulation of ^{14}C-AP in the glands. The inhibitor concentration required to achieve 50% inhibition (IC_{50}) of ^{14}C-AP accumulation was determined by fitting the equation for the expected inhibition pattern to the data points.

4.3. Physical chemistry

4.3.1. General. The determination of dissociation constants (pK_a) and lipophilicity [log *P*, log *D*(pH 7.4)] was performed on a Sirius GL pK_a analyzer specifically designed for pH-metric pK_a and 1-octanol/water partition coefficient measurements (Sirius Analytical Instruments Ltd, Forest Row, UK).

4.3.2. Determination of dissociation constants. The pK_a values of the investigated compounds were determined by potentiometric co-solvent titrations in 0.15 mol/l KCl solutions in the pH range of 2.0–11.0 at 25 °C using methanol as co-solvent in varying portions and 0.5 mol/l KOH and HCl as titrants, respectively. Linear extrapolation to 0% co-solvent-content was performed by the Yasuda-Shedlovsky plot method implemented in the software RefinementPro 2 from SIRIUS (Avdeef, A.; Box, K. J.; Comer, J. E. A., Gilges, M.; Hadley, M.; Hibbert, C.; Patterson, W.; Tam, K. Y. *J. Pharm. Biomed. Anal.* **1999**, *20*, 631–641).

4.3.3. Determination of distribution coefficients. The distribution coefficients between 1-octanol and aqueous KCl solution were determined at 25 °C by potentiometric titrations in the pH range of 2.0–11.0. The titrations were performed in mixtures of 0.15 mol/l KCl solution and water saturated 1-octanol with varying 1-octanol portions using 0.5 mol/l KOH and HCl as titrants, respectively. The log *D* values in dependence of pH were obtained by least squares fitting of the experimental data to a theoretical function of the distribution coefficient *D* (RefinementPro2): Comer, J.; Tam, K.; *Lipophilicity profiles: Theory and Measurement, in Pharmakokinetic Optimization in Drug Research: Biological, Physicochemical and Computational Strategies*, Testa, B.; van de Waterbeemd, H.; Folkers, G.; Guy, R., Eds.; VHCA: Zurich, 2001, pp 275–304.

Acknowledgments

We are grateful to Ms. C. Jecke, Ms. G. Münch, Ms. M. David, Ms. I Hartig-Beecken, and Ms. B. Bössenecker for technical assistance.

Supplementary data

NMR spectra (^{1}H, ^{13}C, H,C-HMBC) of all target compounds. This material is available free of charge via the Internet at http://www.sciencedirect.com. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.08.065.

References and notes

1. NIH Publication No. 03-0882, June 2003, http://digestive.niddk.nih.gov/ddiseases/pubs/gerd/index.htm.
2. Locke, G. R., 3rd; Talley, N. J.; Fett, S. L.; Zinsmeister, A. R.; Melton, L. J., 3rd *Gastroenterology* **1997**, *112*, 1448–1456.
3. NIH Publication No. 05-4225, October 2004, http://digestive.niddk.nih.gov/ddiseases/pubs/hpylori/index.htm.
4. Lethbridge-Cejku, M.; Vickerie, J. Summary health statistics for U.S. adults: National Health Interview Survey, 2003. *National Center for Health Statistics, Vital Health Stat.* **2005**, *10*.
5. (a) Parsons, M. E.; Keeling, D. J. *Expert Opin. Investig. Drugs* **2005**, *14*, 411–421; (b) Fass, R.; Shapiro, M.; Dekel, R.; Sewell, J. *Aliment. Pharmacol. Ther.* **2005**, *22*, 79–94; (c) Vakil, N. *Aliment. Pharmacol. Ther.* **2004**, *19*, 1041–1049.
6. Andersson, K.; Carlsson, E. *Pharmacol. Ther.* **2005**, *108*, 294–307.
7. Kaminski, J. J.; Bristol, J. A.; Puchalski, C.; Lovey, R. G.; Elliott, A. J.; Guzik, H.; Solomon, D. M.; Conn, D. J.; Domalski, M. S.; Wong, S.-C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; Steinberg, M.; McPhail, A. T. *J. Med. Chem.* **1985**, *28*, 876–892.
8. Kaminski, J. J.; Hilbert, J. M.; Pramanik, B. N.; Solomon, D. M.; Conn, D. J.; Rizvi, R. K.; Elliott, A. J.; Guzik, H.; Lovey, R. G.; Domalski, M. S.; Wong, S.-C.; Puchalski, C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; McPhail, A. T. *J. Med. Chem.* **1987**, *30*, 2031–2046.

9. Kaminski, J. J.; Puchalski, C.; Solomon, D. M.; Rizvi, R. K.; Conn, D. J.; Elliott, A. J.; Lovey, R. G.; Guzik, H.; Chiu, P. J. S.; Long, J. F.; McPhail, A. T. *J. Med. Chem.* **1989**, *32*, 1686–1700.
10. Folded conformation: phenyl ring directed toward and over the imidazo[1,2-*a*]pyridine ring system; extended conformation: phenyl ring oriented out and away from the heterocyclic nucleus.
11. Gold, E. H.; Kaminski, J. J.; Puchalski, D. US 4468400.
12. Brehm, C.; Chiesa, M. V.; Zimmermann, P. J.; Buhr, W.; Simon, W. A.; Kromer, W.; Postius, S.; Palmer, A. WO 2005/090346.
13. Kaminski, J. J.; Wallmark, B.; Briving, C.; Andersson, B. M. *J. Med. Chem.* **1991**, *34*, 533–541.
14. Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179–2182.
15. White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213–214.
16. (a) Krass, D.; Paudler, W. W. *Synthesis* **1974**, 351–352; (b) Paudler, W. W.; Barton, J. M. *J. Org. Chem.* **1966**, *31*, 1720–1722.
17. (a) Boger, D. L.; Panek, J. S.; Yasuda, M. *Organic Syntheses* **1988**, *66*, 142–150; (b) Schmidt, P.; Druey, J. *Helv. Chim. Acta* **1955**, *38*, 1560–1564.
18. Glyoxal was prepared by phosphorous pentoxide-mediated cleavage of the corresponding trimer and subsequent destillation, see Wang, Y.; Arif, A. M.; Gladysz, J. A. *Organometallics* **1994**, *13*, 2164–2169, and Section 4.
19. Separation of the product from regioisomeric 7-phenyl-5,6,7,8-tetrahydroisoquinolin-3-amine (16–21%) was accomplished by column chromatography (see Section 4).
20. Best results were obtained when the formed imidazo[1,2-*a*]pyridine salt was removed by filtration and when the corresponding α-halo ketone was added in several portions (see Section 4).
21. (a) Head, R. A.; Ibbotson, A. *Tetrahedron Lett.* **1984**, *25*, 5939–5942; (b) Horino, H.; Sakaba, H.; Arai, M. *Synthesis* **1989**, 715–718.
22. TBTU = *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate, see, for example, Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852.