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Novel indanyl-substituted imidazo[1,2-*a*]pyridines as potent reversible inhibitors of the gastric H^+/K^+-ATPase☆

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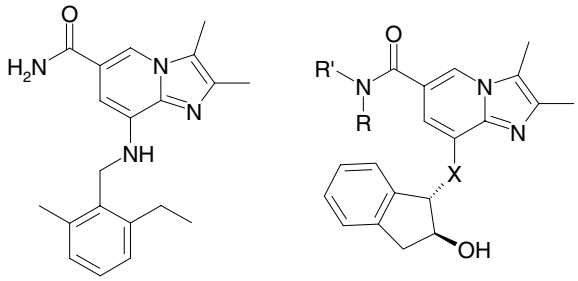
Abstract—A series of novel 8-indanylamino- and 8-indanyloxy-substituted imidazo[1,2-*a*]pyridines with reduced lipophilicity was synthesized from easily accessible starting compounds. The anti-secretory activity of these compounds has been assessed in a competitive binding assay against H^+/K^+-ATPase from hog gastric mucosa. Some of the compounds proved to be potent inhibitors of the gastric acid pump.

The gastric H^+/K^+-ATPase located in the parietal cells is responsible for the final step of acid secretion in the stomach and is the main target in the pharmacological treatment of acid related diseases. Since their introduction into the market, irreversible inhibitors of the H^+/K^+-ATPase (proton pump inhibitors, PPIs) have revolutionized the treatment of gastro-oesophageal reflux disease (GERD).[1] Despite of the clear success of these agents, there are still limitations of current GERD therapy with PPIs.[2] The new reversible potassium competitive acid blockers (P-CABs) may offer therapeutic advantages over PPI therapy, and may have the potential to achieve faster inhibition of acid secretion and longer duration of action compared to PPIs, resulting in quicker symptom relief and healing.[3]

Most of the P-CABs disclosed so far belong to the structural class of imidazo[1,2-*a*]pyridines.[4–6] More recently, a series of 8-(2,6-dialkylbenzylamino)-substituted imidazo[1,2-*a*]pyridines has been reported that effectively inhibit gastric acid secretion by reversible binding to the H^+/K^+-ATPase.[7–10] However, many compounds of this series, such as the known inhibitor AR-HO47108 (**1**)[8] (Fig. 1), suffer from high lipophilicity and are therefore susceptible to extensive metabolism.[9] As part of our studies on the development of new P-CABs, we herein report the synthesis and biological evaluation of some related 8-indanylamino- and 8-indanyloxy-substituted imidazo[1,2-*a*]pyridines **2** as well as certain derivatives thereof with significantly reduced lipophilicity (Fig. 1).[11]

Recent experiments conducted in our laboratory have demonstrated that various 8-amino- and 8-hydroxyimidazo[1,2-*a*]pyridines react with a wide range of substituted 1,2-epoxyindanes under weakly basic conditions to give the respective indanyl-substituted imidazo[1,2-*a*]pyridines.[12] In order to employ this approach for the synthesis of the target compounds **2** of both N- and O-series, the appropriate precursor imidazo[1,2-*a*]pyridines had to be prepared. The known



AR-HO47108 (**1**) **2**, X = NH, O

Figure 1. Structure of P-CAB AR-HO47108 (1) and target compound **2**.

Keywords: H^+/K^+-ATPase; Imidazo[1,2-*a*]pyridine; Anti-ulcer; Gastric acid inhibitor.
☆ Design of novel P-CABs, I.
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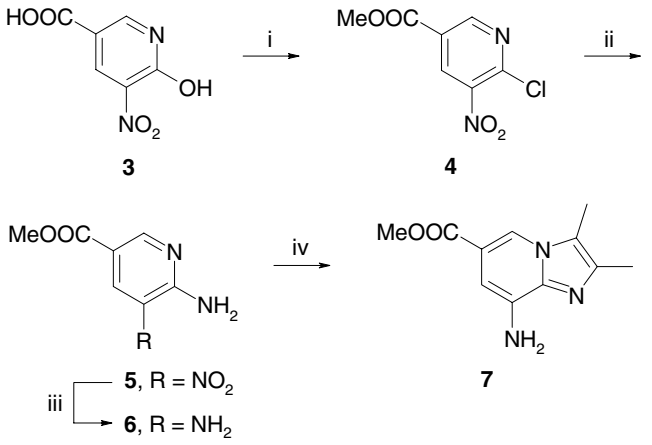
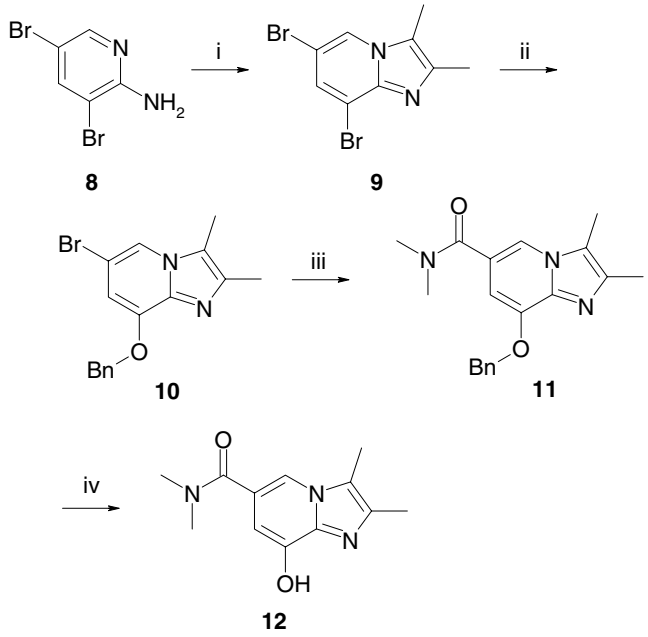


Scheme 1. Reagents and conditions: (i) (1) $SOCl_2$, cat. DMF, 80 °C, 16 h; (2) CH_3OH, 0 °C, 30 min, 63%; (ii) $NH_{3(g)}$, CH_3OH, 0 °C, 2 h, 89%; (iii) Raney–Ni, $N_2H_4{\cdot}H_2O$, CH_3OH, reflux, 15 min, 83%; (iv) 3-bromo-2-butanone, CH_3CN, 100 °C, 3 h, 49%.



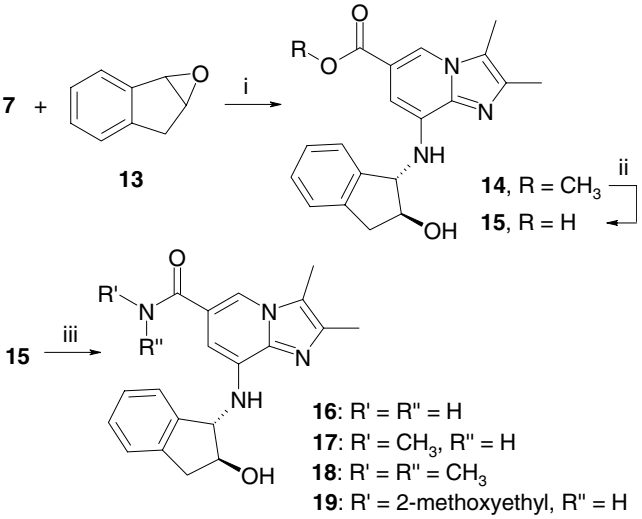
Scheme 2. Reagents and conditions: (i) 3-bromo-2-butanone, THF, 90 °C, 10 d, 65%; (ii) NaH, BnOH, DMF, rt, 20 h, 79%; (iii) $Pd(OAc)_2$, PPh_3, THF, Et_3N, 2 M Me_2NH in THF, 10 bar CO, 120 °C, 16 h, 81%; (iv) Pd/C (10%), EtOH, 1,4-cyclohexadiene, reflux, 3 h, 85%, Bn: benzyl.

imidazo[1,2-*a*]pyridine building block **7** (Scheme 1) was synthesized with only minor modifications to the published procedure.[7b] Starting from known 6-hydroxy-5-nitronicotinic acid **3**,[13] chlorination and subsequent careful treatment of the intermediate acid chloride with methanol led to the carboxylic ester **4**, which in turn was reacted with gaseous ammonia to give the 2-aminopyridine **5**. On the other hand, when aqueous ammonia was applied for the reaction, substantial amounts of the corresponding carboxamide were obtained as by-product. Subsequent reduction of the nitro group of **5** led to the diaminopyridine **6** which, upon treatment with 3-bromo-2-butanone, yielded the 8-aminoimidazo[1,2-*a*]pyridine **7**, required to access the N-series of the target compounds **2** (Scheme 1).[14]

The synthesis of the unknown 8-hydroxy-imidazo[1,2-*a*]pyridine **12** (Scheme 2) started from commercially available 2-amino-3,5-dibromopyridine (**8**), which was reacted with 3-bromo-2-butanone to give the imidazo[1,2-*a*]pyridine **9**. Reaction of dibromo compound **9** with benzyl alkoxide provided regioselectively the 8-benzyloxy-substituted bromoimidazo[1,2-*a*]pyridine **10**.[15] The introduction of the carbonyl group in 6-position of **10** was then effected by palladium-catalyzed aminocarbonylation[16]: Heating a mixture of bromide **10**, palladium acetate (15 mol %), triphenylphosphine and dimethylamine (2 M solution in tetrahydrofuran) under a pressure of 10 bar carbon monoxide furnished directly the *N*,*N*-dimethylcarboxamide **11** in 81% yield. Finally, cleavage of the benzyl ether by hydrogenation of **11** provided the 8-hydroxy-imidazo[1,2-*a*]pyridine **12**, which served as an entry to the O-series of the target compounds **2** (Scheme 2).

With the key intermediates **7** and **12** in hand, the synthesis of the final compounds **2** had to be accomplished. In the case of the N-series, simple heating of the 8-aminoimidazo[1,2-*a*]pyridine **7** with 1,2-epoxyindane **13** (Scheme 3) in a mixture of dioxane and water in the absence of a base provided the racemic 8-indanylamino-substituted imidazo[1,2-*a*]pyridine ester **14** in good yield and with high *trans*-selectivity (>95%). After saponification of the ester **14** to the carboxylic acid **15**, the carboxamides **16**–**19** were prepared by reaction of **15** with the respective amine using TBTU[17] as coupling reagent. The low yield for the carboxamides **16** and **17** was mainly due to losses during the workup procedure (Scheme 3).

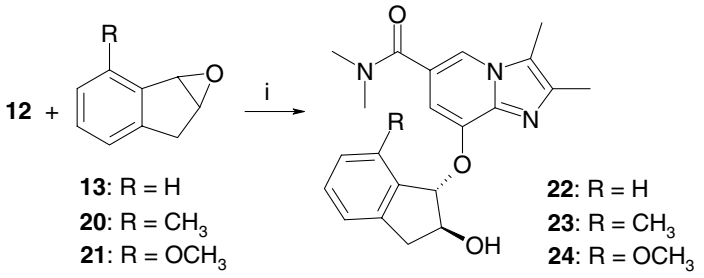
The analogous reaction of the 8-hydroxy-imidazo[1,2-*a*]pyridine **12** with 1,2-epoxyindane (**13**) only proceeded well in the presence of a base. The highest yield of the



Scheme 3. Reagents and conditions: (i) dioxane, H_2O, 100 °C, 60 h, 77%; (ii) dioxane, 2 N NaOH, reflux, 1 h, 73%; (iii) TBTU, CH_2Cl_2, rt, **16**: $NH_{3(g)}$, 1.5 h, 10%, **17**: 8 M $MeNH_2$ in EtOH, 3 d, 20%, **18**: 5.6 M Me_2NH in EtOH, 16 h, 73%, **19**: 2-methoxyethylamine, 2 h, 56%.

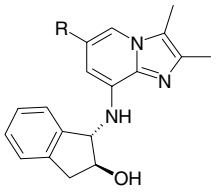
product **22** was obtained using triethylamine. As in the case of the N-series, the *trans*-product was formed in a selective manner (>95%). Additionally, we were interested in compounds carrying a substituent in 7′-position of the indane ring, since substituents such as 7′-methyl or 7′-methoxy would further restrict the possible conformations of the rotatable indanyl moiety. The required 7-methyl-1,2-epoxyindane (**20**) and 7-methoxy-1,2-epoxyindane (**21**) were prepared from the corresponding indenes by bromohydroxylation and subsequent epoxide formation under basic conditions in analogy to the known procedure for 1,2-epoxyindane (**13**).[18] The reaction of the amide **12** with the epoxides **20** and **21** proceeded sluggishly and provided the respective target compounds **23** and **24** in low yields. Apparently, the nucleophilic attack of the hydroxy group of **12** on the epoxide ring is sterically hindered by the 7-substituent adjacent to the benzylic position, thus leading to concomitant decomposition of the starting epoxides **20** and **21**, respectively (Scheme 4).

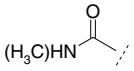
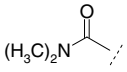
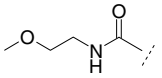
All indanyl-substituted imidazo[1,2-*a*]pyridines **16**–**19** and **22**–**24**, as well as the known P-CAB **1**,[19] were evaluated in a competitive binding assay against H^+/K^+-ATPase from hog gastric mucosa.[6b] Additionally, the lipophilicity and pK_a values of all the target compounds were determined.[20] The results are summarized in Tables 1 and 2. The replacement of the 2,6-dialkylbenzyl group of **1** by an indanyl



Scheme 4. Reagents and conditions: (i) EtOH, H_2O, Et_3N, **22**: 70 °C, 3 h, 51%, **23**: 30 °C, 5 h, 20%, **24**: 30 °C, 4 h, 19%.

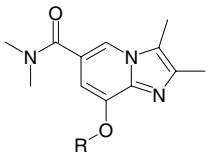
Table 1. Inhibition of H^+/K^+-ATPase by compounds **1** and **16**–**19**

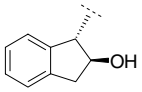
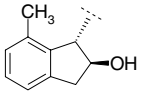
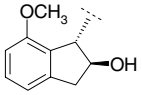


Compound	R	H^+/K^+-ATPase $-\log IC_{50}$[a]	pK_a[b]	log P[b,c] log D (pH 7.4)[d]
1	AR-HO47108	6.2	6.10 (±0.01)	4.95 (±0.08) 4.93
16		4.8	5.97 (±0.02)	3.11 (±0.05) 3.09
17		5.4	5.97 (±0.02)	3.40 (±0.04) 3.39
18		6.3	6.24 (±0.02)	2.85 (±0.05) 2.82
19		4.7	6.01 (±0.04)	3.43 (±0.05) 3.41

[a] For assay details, see Ref. 6b.
[b] See Ref. 20.
[c] 1-Octanol/water partition coefficient of the neutral species.
[d] 1-Octanol/water distribution coefficient at pH 7.4.

Table 2. Inhibition of H^+/K^+-ATPase by compounds **22**–**24**



Compound	R	H^+/K^+-ATPase $-\log IC_{50}$[a]	pK_a[b]	$\log P$[b,c] $\log D$ (pH 7.4)[d]
22		5.7	6.21 (±0.02)	2.20 (± 0.06) 2.16
23		6.9	6.22 (±0.02)	2.59 (± 0.02) 2.56
24		5.7	6.27 (±0.01)	2.30 (± 0.05) 2.27

[a] For assay details, see Ref. 6b.
[b] See Ref. 20.
[c] 1-Octanol/water partition coefficient of the neutral species.
[d] 1-Octanol/water distribution coefficient at pH 7.4.

moiety (compound **16**) led to an approximately 25-fold reduction in activity ($-\log IC_{50} = 4.8$). On the other hand, a substantial increase in potency was observed when one of the amide hydrogens of **16** was replaced by a methyl group (**17**) and was even higher when both of the amide hydrogens were substituted by methyl (**18**). When the methyl group of **17** was replaced by 2-methoxyethyl (**19**), the activity again dropped considerably. The dimethylamide analogue **22** of the O-series was less active than **18**, but introduction of a 7′-methyl group (compound **23**) increased significantly the activity ($-\log IC_{50} = 6.9$). However, the 7′-methoxy derivative **24** was found to be equipotent to **22**. The replacement of the 2,6-dialkylbenzyl group by indanyl did not change the basicity of the compounds to a large extent (pK_a values ranging from 5.97 to 6.24), but the lipophilicity was significantly reduced with the more polar 3-hydroxy-indanyl moiety (**16** vs **1**). The increase of the pK_a value as well as the decrease of the $\log P$ value of compound **18** compared to **16** and **17** is in agreement with theoretical predictions using fragmental based programs for pK_a and $\log P$ calculations, such as ACD/pK_a DB, ACD/$\log P$ DB or *c*$\log P$.[21] As shown by comparison of the dimethylamides **18** and **22**, the lipophilicity was even further decreased when the bridging nitrogen was replaced by oxygen.

In summary, we have reported a convenient synthesis of 8-indanylamino- and 8-indanyloxy-substituted imidazo[1,2-*a*]pyridines with improved physicochemical properties compared to the 2,6-dialkylbenzylamino-substituted series. The in vitro activity of compounds **18** and **23** as antagonists of the gastric H^+/K^+-ATPase is excellent: the strength of inhibition of both compounds is comparable to that of the known P-CAB AR-HO47108 (**1**).

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20. The determination of dissociation constants (pK_a) and lipophilicity [log *P*, log *D* (pH 7.4)] was performed on a Sirius GLpK_a analyzer specially designed for pH-metric pK_a and 1-octanol/water partition coefficient measurements (Sirius Analytical Instruments Ltd, Forest Row, UK). The pK_a values of the investigated compounds were determined by potentiometric co-solvent titrations in 0.15 mol/L KCl solutions in the range of pH 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 Yasuda–Shedlovsky plot method implemented in the software RefinementPro2 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). The distribution coefficients between 1-octanol and aqueous KCl solution were determined at 25°C by potentiometric titrations in the range of pH 2.0–11.0. The titrations were performed in mixtures of 0.15 mol/L KCl solutions 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 for the distribution coefficient *D* (RefinementPro2): Comer, J.; Tam, K. *Lipophilicity Profiles: Theory and Measurement, in Pharmacokinetic Optimization in Drug Research: Biological, Physicochemical and Computational Strategies*, Editors: Testa, B.; van de Waterbeemed, H.; Folkers, G.; Guy, R.; VHCA: Zurich, 2001, 275.
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