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Synthesis and pharmacological evaluation of 5-carboxamide-substituted tetrahydrochromeno[7,8-*d*]imidazoles

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ABSTRACT

A fast access to novel 5-carboxamide-substituted tetrahydrochromeno[7,8-*d*]imidazoles **4** was developed using the readily available preclinical candidate BYK 405879 (**1**) as starting material. The 5-amino function was installed by the Curtius rearrangement of carboxylic acid **2** or by the Hofmann rearrangement of carboxamide **8** furnishing benzimidazole **3** as key intermediate. In the Ghosh Schild rat, some of the target compounds **10**–**14** showed noteworthy activity as potassium-competitive acid blockers.

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications, such as heartburn, regurgitation, or dysphagia.[1] GERD is one of the most common gastrointestinal disorders with an annual prevalence between 10% and 23%.[2] The introduction of irreversible proton pump inhibitors (PPIs) to the market made evident that the inhibition of the gastric proton pump (H^+/K^+-ATPase) constitutes a powerful approach for the treatment of GERD.[3] PPIs, such as pantoprazole, are able to provide symptom relief, heal erosive esophagitis, and prevent further complications. The goal of the present work was the synthesis and evaluation of potassium-competitive acid blockers (P-CABs) that inhibit the H^+/K^+-ATPase in a reversible manner and might be able to overcome some limitations that are encountered during the treatment with PPIs.[4]

Recently, we reported the asymmetric synthesis of a series of tetrahydrochromeno[7,8-*d*]imidazoles by asymmetric ketone hydrogenation in the presence of the Noyori-type catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] and presented the large-scale synthesis of the P-CAB BYK 405879 (**1**).[5] In order to expand the structure–activity relationship in the field of this structural class we were interested in the synthesis of 5-amide-substituted derivatives **4** in which the amide moiety is attached to the heterocyclic core via the amino group.[6]

The hydrolysis of the carboxamide BYK 405879 (**1**) was a challenging task (Scheme 1). No transformation was observed applying a variety of conditions that are generally suitable for the cleavage of carboxamides. For instance, no reaction took place after prolonged treatment of BYK 405879 (**1**) with an excess of sodium hydroxide (ethanol/water, 80 °C), potassium hydroxide (ethylene glycol, 50–180 °C), potassium *tert*-butylate (*tert*-butanol, 2-propanol or water, 60–100 °C), hydrochloric acid (pH 1, 80 °C), or trifluoroacetic acid (neat or aqueous solution, 100 °C). In 50% sulfuric acid, BYK 405879 (**1**) was stable up to a temperature of 120 °C. At 150 °C, unspecific decomposition reactions occurred. When a solution of BYK 405879 (**1**) in hydrobromic acid/acetic acid was stirred for 18 h at room temperature, cleavage of the pyran ring took place. Heating of a solution of BYK 405879 (**1**) and potassium hydroxide in ethylene glycol and water at 205 °C afforded a product of high molecular weight (m/z = 728) along with untransformed starting material. More encouraging results were obtained when triethyloxonium tetrafluoroborate was employed (1,2-dichloroethane, 90 °C): After a reaction time of 1 d, 30% conversion was achieved and 18% of carboxylic acid **2** was detected by HPLC/MS. Finally, it was found that the hydrolysis of BYK 405879 (**1**) could be accomplished in a convenient manner under anhydrous conditions if a solution of **1** and sodium hydroxide in ethylene glycol was heated to 190 °C and the water present in the reaction mixture was removed by distillation. This afforded the carboxylic acid **2** in 80% yield on 90 g scale.

The primary product of the Curtius rearrangement of acyl azides is an isocyanate which might be isolated or trapped by a

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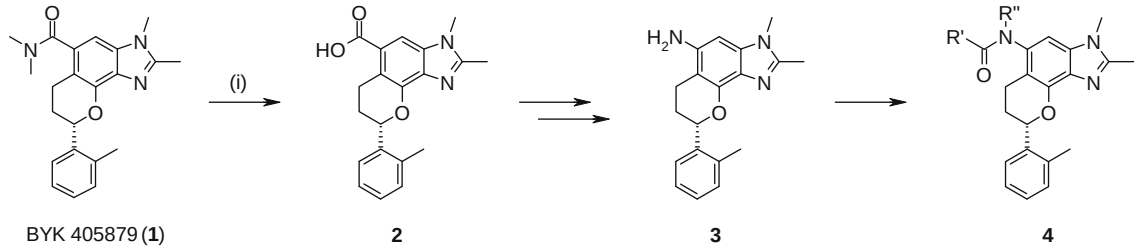


Scheme 1. Reagents and conditions: (i) NaOH, ethylene glycol, removal of water, 190 °C, 17 h, 80%.

nucleophilic solvent. The reaction typically proceeds at 100 °C and is considered as a concerted process that is accompanied by the loss of nitrogen.[7] The acyl azide starting material can be obtained in a convenient manner by treatment of the carboxylic acid with diphenylphosphoryl azide (DPPA).[8] In order to convert the intermediate isocyanate **6** directly into the corresponding *tert*-butylcarbamate **7**, the Curtius rearrangement of the acyl azide **5** was performed in *tert*-butanol (Scheme 2).

The acyl azide **5** was prepared in situ from carboxylic acid **2** and DPPA. As can be seen from Table 1, the Curtius reaction of **2** was studied in detail modifying the temperature, the reaction time, and the stoichiometry of DPPA. Despite these efforts, the yield of carbamate **7** never exceeded 33%. The best results were achieved when the reaction was conducted in refluxing *tert*-butanol (cf. entries 1–3 vs entry 4) using an excess of DPPA (3.0 equiv, cf. entries 1–3 vs entry 5). The reaction time had little influence on the isolated yield of **7** (cf. entries 1–3). It was also attempted to conduct the Curtius rearrangement in the absence of DPPA. However, attempts to prepare the acyl azide **5** via activation of the carboxylic acid **2** with thionyl chloride or TBTU and subsequent treatment of the resulting intermediate with sodium azide were not successful.

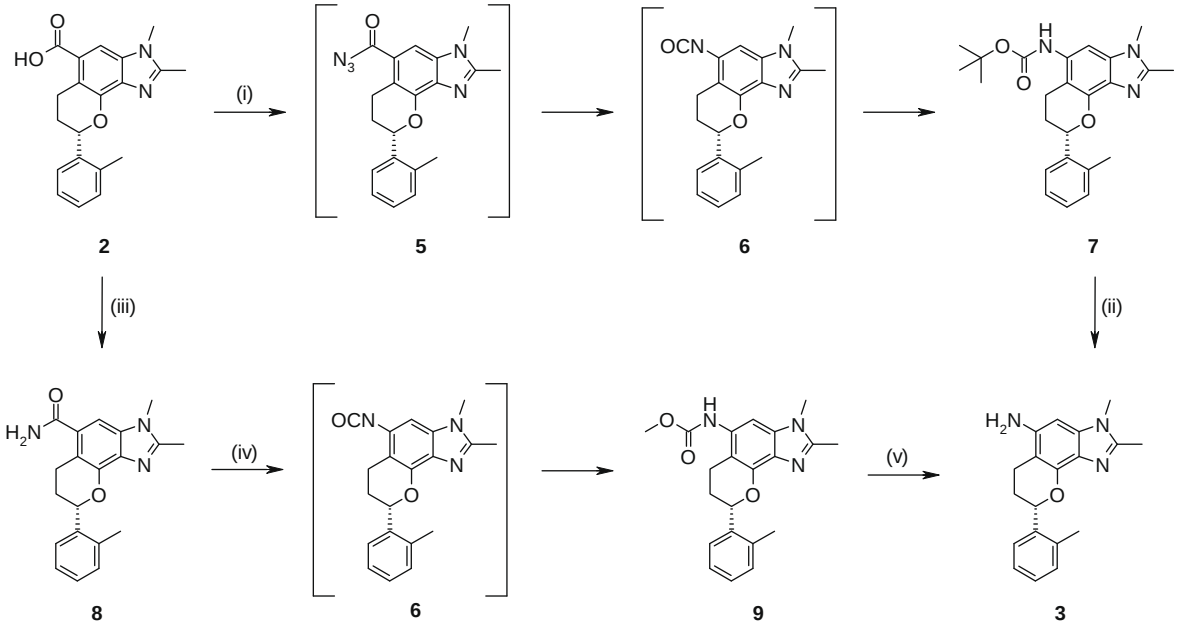
Alternatively, the Hofmann rearrangement was investigated using the unsubstituted carboxamide **8** as starting material (Scheme 2). The latter compound was obtained in excellent yield by TBTU-mediated coupling of carboxylic acid **2** with ammonia. Under classical Hofmann conditions, the respective carboxamide is treated with sodium hypobromite. Concerted rearrangement of the resulting *N*-bromoamide intermediate furnishes an isocyanate that is cleaved under the prevailing aqueous conditions to the target amine that has one carbon atom less than the starting amide.[9] Since the beginning of the 1990s the stable and commercially available diacetoxyiodobenzene (DAIB) has been applied as reagent in the modified Hofmann rearrangement.[10]

Table 1
The Curtius rearrangement of the carboxylic acid **2** to the *tert*-butyl carbamate **7** (DPPA, 4.0 equiv of Et_3N, *t*-BuOH)

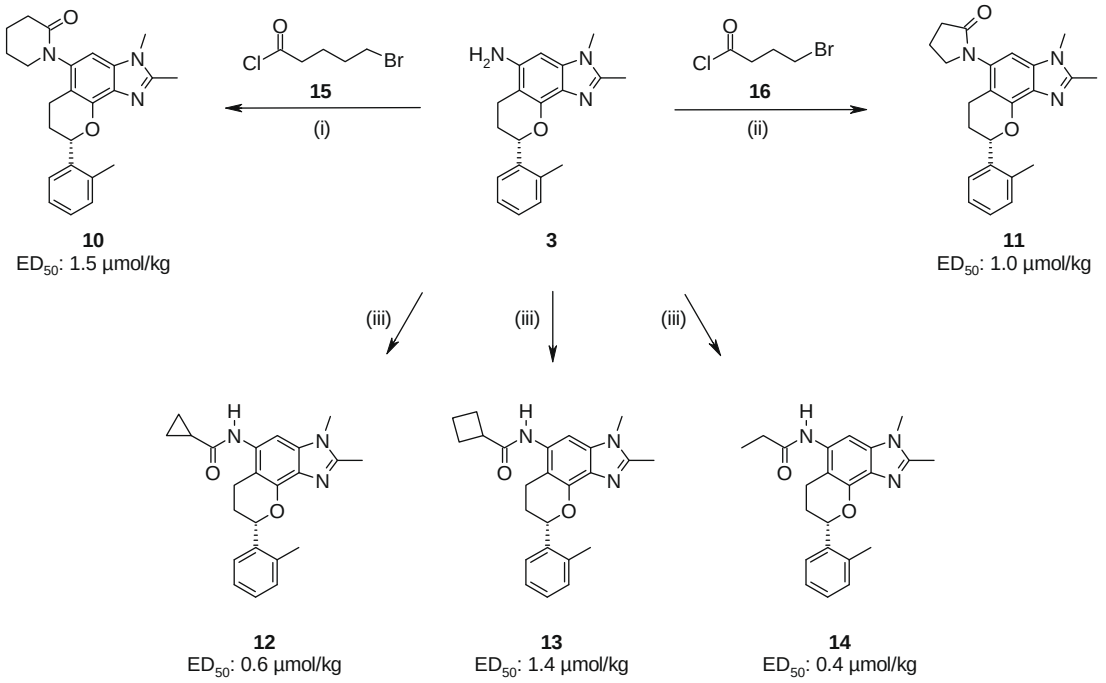
Entry	Equiv of DPPA	Temperature	Time (h)	Yield of **7**
1	3.0	Reflux	1	33%
2	3.0	Reflux	3	32%
3	3.0	Reflux	16	30%
4	3.0	50 °C	0.75	26%[a]
5	1.5	Reflux	3	—[b,c]

[a] The product **7** was obtained in 80% purity.
[b] A different batch of starting material **2** was employed for this transformation.
[c] Nonuniform and incomplete conversion.

The use of DAIB in methanolic potassium hydroxide solution at 5–10 °C generated methyl carbamates in good yields from the corresponding primary carboxamides. Indeed, when a methanolic solution of carboxamide **8**, DAIB (1.4 equiv), and potassium hydroxide (2.5 equiv) was stirred for 2 h at 0 °C or at room temperature, the carbamate **9** was obtained in 70–73% yield along with traces of an undefined by-product. On the other hand, no reaction occurred when *tert*-butanol was employed as solvent (35 °C, 4 h).



Scheme 2. Reagents and conditions: (i) DPPA, Et_3N, *t*-BuOH, see Table 1; (ii) TFA, CH_2Cl_2, rt, 1 h, 59–85%; (iii) TBTU, EtN(i-Pr)$_2$, DMF, 40 °C, 1 h, then NH_3, MeOH, rt, 16 h, 84–90%; (iv) PhI(OAc)$_2$, KOH, MeOH, 0 °C or rt, 2 h, 70–73%; (v) NaOH, dioxane, 100 °C, 18 h, 42–59%.



Scheme 3. Reagents and conditions: (i) **15**, Et_3N, THF, rt, 1 h, then *t*-BuOK, THF, 0 °C, 2 h, 39%; (ii) **16**, Et_3N, THF, rt, 1 h, then *t*-BuOK, THF, 0 °C, 2 h, 41% (containing traces of 12); (iii) RCOOH, TBTU, $EtN(i\text{-}Pr)_2$, DMF, 40-45 °C, 0.75 h, then **3**, rt, 2-22 h, R = c-Pr (**12**): 60%, R = c-Bu (**13**): 26%, R = Et (**14**): 48%.

The key intermediate **3** was obtained by cleavage of the carbamate **7** or **9** obtained by the Curtius rearrangement/Hofmann rearrangement, respectively (Scheme 2). Rapid conversion of the *tert*-butyl carbamate **7** to the amine **3** occurred in the presence of trifluoroacetic acid (room temperature, 1 h, 85% yield). The methyl carbamate **9** was resistant against acid-catalyzed cleavage (trifluoroacetic acid, dichloromethane, room temperature, 4 h, reflux, 2 h). However, smooth transformation to the amine **3** took place, when a solution of methyl carbamate **9** in 1,4-dioxane and aqueous sodium hydroxide (2 N) was heated overnight.

A two step sequence, comprising amide formation and nucleophilic substitution, was applied to complete the synthesis of target compounds **10** and **11** containing a cyclic carboxamide residue (Scheme 3). The piperidin-2-one derivative **10** was obtained in 39% yield by conversion of amine **3** with 5-bromopentanoyl chloride (**15**) and subsequent addition of potassium *tert*-butylate. In the same manner, the pyrrolidin-2-one-substituted tetrahydrochromeno[7,8-*d*]imidazole **11** was prepared from amine **3** and 4-bromobutanoyl chloride (**16**). In order to secure target compounds **12**–**14** containing an open-chain carboxamide residue, the respective carboxylic acid was activated by treatment with O-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) and was coupled with the 5-amino-substituted benzimidazole **3**.

The pharmacological activity of the target compounds **10**–**14** was assessed in the Ghosh Schild rat, that is, the reduction of the pentagastrin-stimulated acid secretion by the respective P-CAB was determined as described previously (Scheme 3).[11] The cyclopropylcarboxamide **12** and the propionamide **14** caused noteworthy inhibition with ED_{50} values of 0.6 µmol/kg and 0.4 µmol/kg, respectively. Ring expansion to the cyclobutylcarboxamide **13** was accompanied by a reduction of pharmacological activity (ED_{50} = 1.4 µmol/kg). In the same manner, the cyclic carboxamides **10** (ED_{50} = 1.5 µmol/kg) and **11** (ED_{50} = 1.0 µmol/kg) were found to be significantly less active than their open chain analogs **12** and **14**.

In conclusion, a fast access to novel 5-carboxamide-substituted tetrahydrochromeno[7,8-*d*]imidazoles **4** was developed using the readily available candidate BYK 405879 (**1**) as starting material. The 5-amino function was installed by the Curtius rearrangement of carboxylic acid **2** or by the Hofmann rearrangement of carboxamide **8** furnishing benzimidazole **3** as key intermediate. In the Ghosh Schild rat, some of the target compounds **10**–**14** showed noteworthy activity as potassium-competitive acid blockers with ED_{50} values comparable to that of BYK 405879 (ED_{50} = 0.23 µmol/kg). A more detailed investigation of the structure-activity relationship within this new class of P-CABs appears to be worthwhile.

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