Tetrahedron Letters 50 (2009) 3917–3919

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and pharmacological evaluation of potential metabolites of the potassium-competitive acid blocker BYK 405879

Andreas Marc Palmer [a,*], Gabriela Münch [a], Burkhard Grobbel [a], Wolfgang Kromer [b]

[a] NYCOMED GmbH, Department of Medicinal Chemistry, Byk-Gulden-Str. 2, D-78467 Konstanz, Germany
[b] NYCOMED GmbH, Department of Pharmacology, Byk-Gulden-Str. 2, D-78467 Konstanz, Germany

ARTICLE INFO

Article history:
Received 3 March 2009
Revised 14 April 2009
Accepted 17 April 2009
Available online 23 April 2009

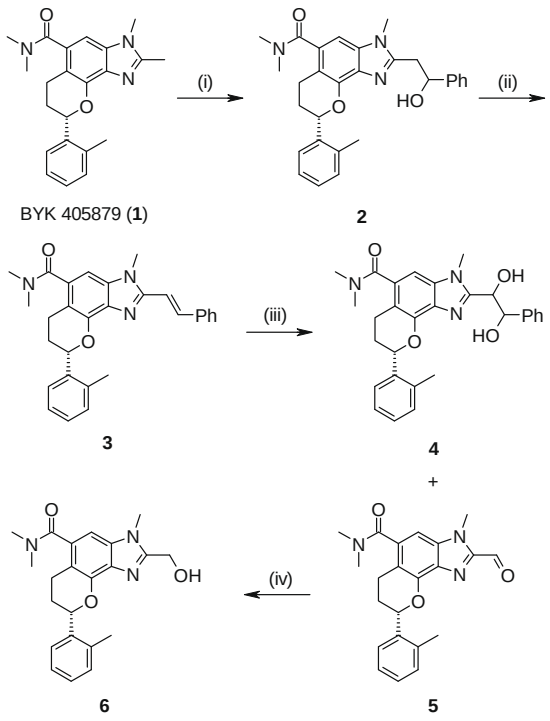
Keywords:
Phase I metabolism
Potassium-competitive acid blocker
Pharmacological activity
Synthesis of potential metabolites

ABSTRACT

Four potential metabolites of the potassium-competitive acid blocker BYK 405879 (**1**) were synthesized which might be formed in vivo by enzymatic oxidation of the pyran moiety or the methyl groups attached to the (hetero) aromatic system. In all cases, the oxidation of the parent compound **1** was accompanied by a significant loss of pharmacological activity and by a decrease in lipophilicity. The target compounds **6**, **14**, **20,** and **21** constitute valuable tool substances for the investigation of the metabolic fate of BYK 405879 (**1**).

A drug has to face several stability challenges after oral administration until it finally reaches systemic circulation.[1] During its movement through the gut and the gut wall, it might undergo intestinal decomposition and metabolism. In the liver, the molecule might be transformed by monooxygenases (hepatic metabolism). Once it has reached the blood stream, the substance might be degraded by hydrolytic enzymes present in the plasma. Drug metabolism, that is, the biotransformation of a drug, comprises two phases. Whereas in phase I the molecular structure itself is modified, in phase II polar groups are added to the molecular structure. The ultimate goal of drug metabolism is the production of more polar products that possess higher aqueous solubility and are more readily excreted from the body via bile and urine.

Recently, we wrote on the large-scale synthesis of the benzimidazole BYK 405879 (**1**) that constitutes a promising candidate for further development as potassium-competitive acid blocker (P-CAB).[2] P-CABs might be an excellent option for the treatment of a variety of gastrointestinal diseases, such as, for example, gastroesophageal reflux disease and gastric ulcer, and might be able to overcome some of the limitations encountered during the therapy with proton pump inhibitors (PPIs, current gold standard).[3] In this Letter, we describe the preparation and pharmacological activity of several potential metabolites of BYK 405879 (**1**) that might be formed during oxidative phase I metabolism. The test model (inhibition of the pentagastrin-stimulated acid secretion in the Ghosh Schild rat) was described previously.[4]



Scheme 1. Reagents and conditions: (i) *t*-BuOK, PhCHO, THF, rt, 17 h, 67%; (ii) MsOH, HOAc, rt, 3 d, 88%; (iii) $K_2OsO_4 \cdot 2H_2O$, NMO, citric acid, *t*-BuOH, H_2O, rt, 17 h, then Na_2SO_3, 32% **4**, 39% **5**; (iv) $NaBH_4$, MeOH, rt, 1 h, 55%.

* Corresponding author. Tel.: +49 7531 844783; fax: +49 7531 8492087.
E-mail address: andreas.palmer@nycomed.com (A.M. Palmer).

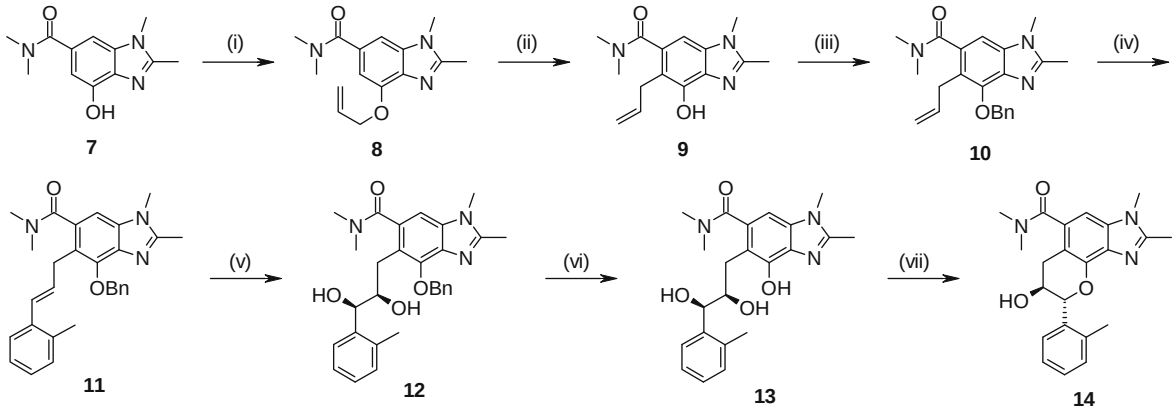
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.04.070

For the preparation of the 2-hydroxymethyl metabolite **6**, the advantage of the acidic properties of the 2-methyl group of BYK 405879 was taken into consideration. (Scheme 1).

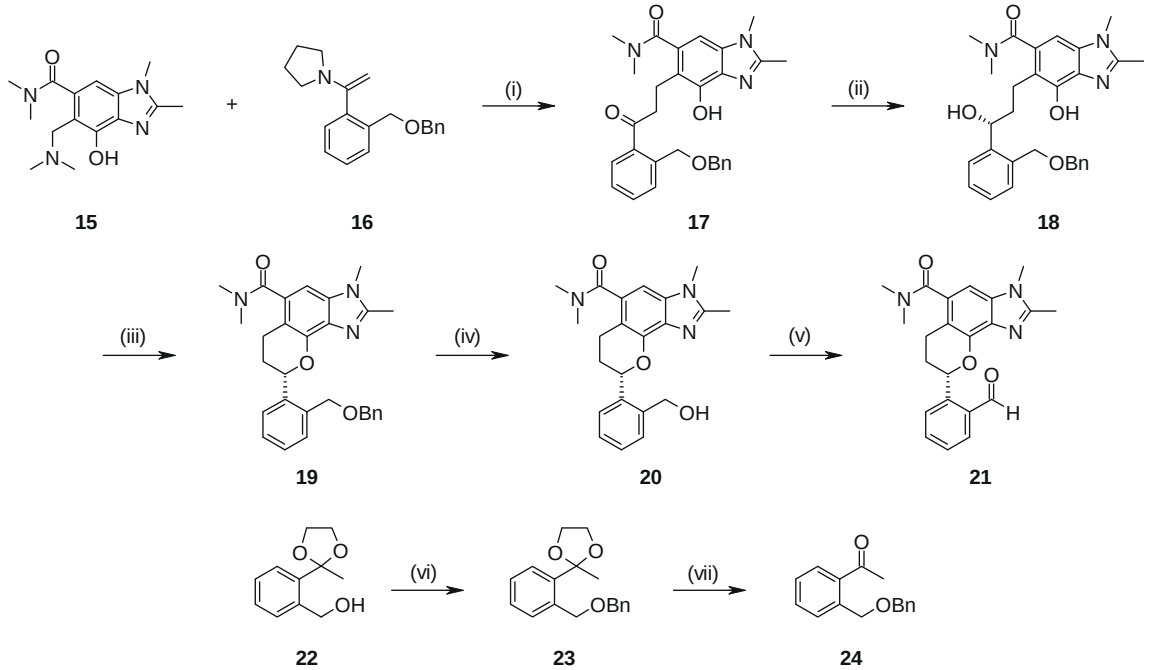
Selective deprotonation of BYK 405879 (**1**) with potassium *tert*-butylate and addition of the resulting anion to benzaldehyde afforded the alcohol **2**. The olefin **3** was secured by acid-catalyzed elimination of water from intermediate **2**. Oxidation of the double bond with potassium osmate(VI) dihydrate/*N*-methyl-morpholine-N-oxide yielded a mixture of diol **4** and aldehyde **5** which could be separated by column chromatography. Finally, the 2-hydroxymethyl derivative **6** of BYK 405879 (**1**) was obtained by sodium-borohydride-mediated reduction of aldehyde **5**. Alcohol **6** (ED_{50} = 1.0 μmol/kg) was found to be significantly less active than the parent compound BYK 405879 (ED_{50} = 0.23 μmol/kg).

The known building block **7** was used as starting material for the synthesis of the potential 7-hydroxy metabolite **14** (Scheme 2).[2] Functionalization of the heterocycle was accomplished by O-allylation of **7** and by subsequent Claisen rearrangement of the obtained intermediate **8**. The phenolic hydroxy group was protected by transformation of **9** with benzyl bromide. The *ortho*-methylphenyl moiety was installed by cross metathesis reaction of olefin **10** with 2-methylstyrene in the presence of second generation Grubbs catalyst. A similar approach has already proven its value in the structurally related imidazo[1,2-*a*]pyridine series.[4] Bishydroxylation of the double bond present in **11** was accomplished in quantitative yield using potassium osmate(VI) dihydrate and *N*-methylmorpholine-*N*-oxide as reagents. Removal of the benzyl-protecting group by catalytic hydrogenation afforded the triol **13** that was converted under Mitsunobu conditions to the 7-hydroxy analog **14** of BYK 405879 (**1**). As in the case of the 2-hydroxymethyl derivative **6** the potential metabolite **14** inhibited the pentagastrin-stimulated acid secretion in the Ghosh Schild rat in a less effective manner (ED_{50} = 2.0 μmol/kg) than the parent compound BYK 405879 (**1**).

Further metabolites of BYK 405879 (**1**) might be formed by oxidation of the methyl group attached to the phenyl ring affording the corresponding alcohol **20** or the aldehyde **21**. Mannich base



Scheme 2. Reagents and conditions: (i) allyl bromide, K_2CO_3, DMF, rt, 16 h, 78%; (ii) melting, 220 °C, 4 h, 81%; (iii) benzyl bromide, K_2CO_3, DMF, rt, 16 h, 100%; (iv) 2-methylstyrene, 2nd generation Grubbs catalyst, CH_2Cl_2, 45 °C, 16 h, 60%; (v) $K_2OsO_4{\cdot}2H_2O$, citric acid, NMO, *t*-BuOH, H_2O, rt, 20 h, 100%; (vi) Pd/C, H_2, EtOH, rt, 2 h, 90%; (vii) PPh_3, DIAD, THF, rt, 2 h, 38%.



Scheme 3. Reagents and conditions. (i) toluene, 100 °C, 3 h, 51%; (ii) $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN], *t*-BuOK, 80 bar H_2, 2-PrOH, *t*-BuOH, 70 °C, 17 h, 89%, 94.9% ee; (iii) PPh_3, DIAD, THF, rt, 2 h, 70%; (iv) H_3PO_4, 80 °C, 1 h, 36%; (v) SO_3–pyridine, Et_3N, DMSO, rt, 20 h; (vi) NaH, TBAI, BnBr, DMF, rt, 1–2 h, 57%; (vii) HCl, THF, 50 °C, 2 h, 94%.

15 and enamine **16** were used as starting materials for the synthesis of these target compounds (Scheme 3). The preparation of benzimidazole **15** was described previously.[2] Enamine **16** was obtained by titanium tetrachloride-mediated condensation of pyrrolidine with 2-benzyloxymethylacetophenone **24**. The latter compound could not be prepared in a direct manner by benzyl protection of 2-hydroxymethylacetophenone and was synthesized from the known acetal derivative **22** as depicted in Scheme 3.[5] The prochiral ketone **17** was isolated in 51% yield after heating a toluene solution of **15** and **16** at 100 °C for 3 h. This substrate was reduced by asymmetric hydrogenation in the presence of $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] and the corresponding chiral alcohol **18** was obtained in excellent yield (89%) and optical purity (94.9% ee). The tetrahydrochromeno[7,8-*d*]imidazole scaffold was constructed by intramolecular Mitsunobu reaction of diol **18**. In order to avoid a possible hydrogenolytic cleavage of the pyran ring present in **19**, the benzyl-protecting group was removed under acid-catalyzed conditions affording the target compound **20**. Finally, oxidation of the hydroxy function of alcohol **20** to the corresponding aldehyde **21** was accomplished under Parikh Doering conditions.[6] The pharmacological activity of alcohol **20** was evaluated in the Ghosh Schild rat (ED_{50} >3.0 μmol/kg) and it was found that the putative metabolite **20** was significantly less active than the parent compound **1**.

In conclusion, four potential metabolites of the potassium-competitive acid blocker BYK 405879 (**1**) were synthesized which might be formed in vivo by enzymatic oxidation of the pyran moiety or the methyl groups attached to the (hetero) aromatic system. In all cases, the oxidation of the parent compound **1** resulted in a significant loss of pharmacological activity. As expected, all hydroxy derivatives were found to be less lipophilic (**6**: log *D* = 2.5, **14** and **20**: log *D* = 2.2) than the parent compound **1** (log *D* = 2.8).[7] The target compounds **6**, **14**, **20,** and **21** constitute valuable tool substances for the investigation of the metabolic fate of BYK 405879 (**1**).

Acknowledgment

We are grateful to Mr. W. Prinz for the pharmacological evaluation of the target compounds in the Ghosh Schild rat.

References and notes

1. Kerns, E. H.; Di, L.. *Chapter 11 in Drug-like Properties: Concepts Structure Design and Methods—From ADME to Toxicity Optimization*; Elsevier Academic Press: Burlington, 2008.
2. Palmer, A. M.; Webel, M.; Scheufler, C.; Haag, D.; Müller, B. *Org. Process Res. Dev.* **2008**, *12*, 1170–1182.
3. (a) Schubert, M. L.; Peura, D. A. *Gastroenterology* **2008**, *134*, 1842–1860; (b) Vesper, B. J.; Altman, K. W.; Elseth, K. M.; Haines, G. K., III; Pavlova, S. I.; Tao, L.; Tarjan, G.; Radosevich, J. A. *ChemMedChem* **2008**, *3*, 552–559; (c) Scarpignato, C.; Hunt, R. H. *Curr. Opin. Pharmacol.* **2008**, *8*, 677–684; (d) Shin, J. M.; Vagin, O.; Munson, K.; Kidd, M.; Modlin, I. M.; Sachs, G. *Cell. Mol. Life Sci.* **2008**, *65*, 264–281.
4. Palmer, A. M.; Grobbel, B.; Jecke, C.; Brehm, C.; Zimmermann, P. J.; Buhr, W.; Feth, M. P.; Simon, W.-A.; Kromer, W. *J. Med. Chem.* **2007**, *50*, 6240–6264.
5. Kotali, A.; Lafazanis, I. S.; Christophidou, A. *ARKIVOC* **2003**, 56–68.
6. Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
7. The log *D* values were determined by HPLC.