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Discovery of a novel benzyloxyisoquinoline derivative with potent anti-*Helicobacter pylori* activity

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Abstract

The synthesis and *in vitro* optimization of the anti-*Helicobacter pylori* activity of a novel series of benzyloxyisoquinoline derivatives discovered by a random screening process, are described. FR180102 (**7f**), having a 3-acetamido-2,6-dichlorobenzyl moiety, was found to have extremely potent activity against *H. pylori* and no effect against a series of common Gram-positive and Gram-negative bacteria.

Keywords; Antibacterials, Bacteria, Antimicrobial compds, Gastrointestinal activity

Introduction

Since its discovery, the relationship between infection with *Helicobacter pylori* bacteria and various benign and malignant gastric diseases has been reported by many investigators, indicating the importance of effective eradication strategies [1,2,3]. Whilst the obvious remedy of treating *H. pylori* infection with antibiotics is attractive, in practice this has often proven futile [4]. To date only a small number of double- and triple-therapy regimens have attained widespread clinical use [5,6], such as combination of broad-spectrum antibiotics, for example amoxicillin (AMPC, **1**) and clarithromycin (CAM, **2**) with inhibitors of acid secretion, for example H_2-antagonists or proton-pump inhibitors. Although eradication of *H. pylori* with triple-therapy regimens containing antibacterial agents has shown a reasonable, if somewhat variable response, there remain a number of unsolved problems such as drug resistance [7,8,9], side effects [10,11] and non-compliance [12,13]. As a result, the need for alternative and novel treatments is evident, and has stimulated the search for novel agents that are *H. pylori* specific and suitable for single-therapy treatment [14,15,16,17].

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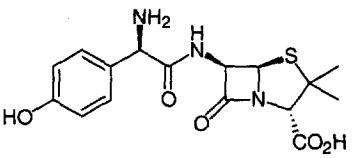
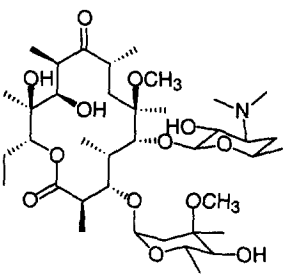
Fig. 1 Anti-*H. pylori* Agents

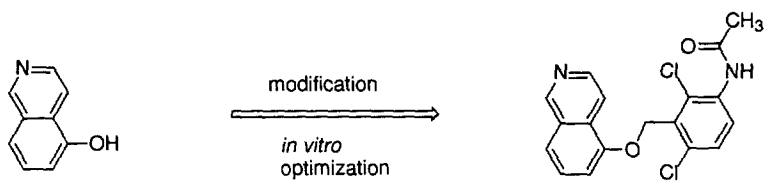


Amoxicillin (AMPC, **1**)



Clarithromycin (CAM, **2**)

As a result of a directed random screening program of various aromatic derivatives, we discovered that 5-hydroxyisoquinoline **3** possessed weak *H. pylori* specific activity. During studies to enhance the antibacterial efficacy of **3**, we investigated the preparation of a novel series of benzyloxy derivatives and have successfully optimized the *in vitro* activity leading to the discovery of FR180102 (**7f**), a novel, potent benzyloxyisoquinoline derivative, containing a 3-acetamido-2,6-dichlorobenzyl substituent, that possesses a very strong, *H. pylori* specific effect. In this paper, we report the synthesis and biological activity of this series of compounds.

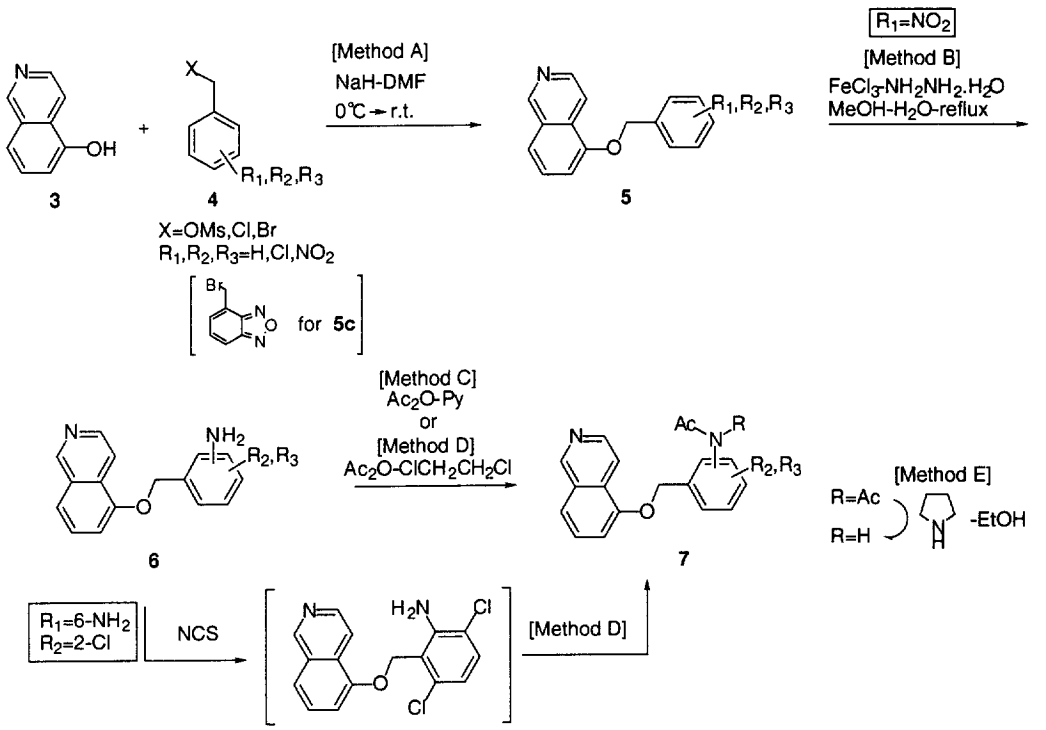


3 **FR180102 (7f)**

Synthesis

5-Hydroxyisoquinoline derivatives having various substituted benzyl moieties were synthesized by the methods(A~E) shown in Scheme 1. Treatment of commercially available **3** with sodium hydride in DMF at 0°C, followed by addition of an electrophilic benzyl derivative **4** yielded coupled compounds **5** in good yield. Compounds **6** with R_1=NH_2 were prepared by reduction of the nitro group. Since the chloro groups and possibly the isoquinoline ring were potentially labile under hydrogenolysis conditions, we opted to employ iron-catalyzed reduction with hydrazine (NH_2NH_2-$FeCl_3$). Subsequent acylation of the amino group (Ac_2O-pyridine, Method C) afforded acetamides **7**. Occasionally, acetylation under these conditions afforded substantial amounts of di-acylated compound that could be readily converted to the mono-acyl derivative by treatment with a secondary amine (pyrrolidine-ethanol, Method E). Alternatively, selective monoacylation was achieved in the absence of base (Ac_2O-$ClCH_2CH_2Cl$, Method D). The electrophilic benzyl derivatives **4** were commercially available or very readily prepared by adaptation of the methods described by Abe *et. al* [18].

Scheme 1 Synthesis of Benzyloxyisoquinolines

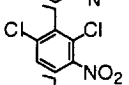
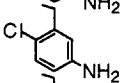
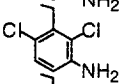
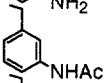
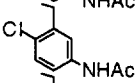
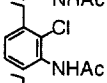
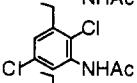
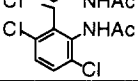
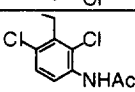


As a typical procedure, FR180102 (**7f**) was synthesized in the following way: A solution of amine **6d** (1.0 g, 3.13mmol) in $ClCH_2CH_2Cl$ (17 mL) was treated with Ac_2O (3 mL) at 70°C for 1 hour. After quenching with sat. aq. $NaHCO_3$ and stirring for 1 hour, standard extractive work-up and recrystallization from CH_2Cl_2-hexane gave FR180102 (**7f**) (1.07 g, 95%) as a white powder: mp 219-220°C; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.27 (s, 3H), 5.48 (s, 2H), 7.20-7.26 (m, 1H), 7.43 (d, 1H, J= 9 Hz), 7.51-7.63 (m, 2H), 7.72 (bs, 1H), 7.94 (d, 1H, J= 5.8 Hz), 8.42-8.50 (m, 2H), 9.22 (s, 1H); IR (KBr) *inter alia* 1697 cm^{-1}; MS *m/z* 361 (MH^+). Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_2$: C, 59.85; H, 3.91; N, 7.75. Found: C , 59.70; H, 3.63; N, 7.52.

Anti-*Helicobacter pylori* Activity

In the search for novel compounds with anti-*H. pylori* activity, we initiated a random screening effort and uncovered 5-hydroxyisoquinoline **3** as a weakly active lead compound (Table 1). Interestingly, other positional isomers were devoid of activity (data not shown), leading us to speculate that modification of **3** may lead to a novel, selective inhibitor of *H. pylori* growth. It is well known that AMPC (**1**) and CAM (**2**), the antibacterial agents most commonly used in triple therapy against *H. pylori*, display more potent activity against Gram-positive bacteria than against Gram-negative bacteria [19,20], and furthermore earlier SAR of inhibitors suggests striking similarities with Gram-positive bacteria [21,22]. Accordingly, even though *H. pylori* is classified as Gram-negative on the basis of bacterial

Table 1
Anti-*H.pylori* Activity of Benzyloxyisoquinoline Derivatives

R	Compound No.	Synthetic Method	Yield (%)	MIC(μg/ml)* *Helicobacter pylori* 8007	9005	13001	FP1757
H	**3**			25	50	25	50
	**5a**	A	81	1.56	1.56	0.78	1.56
	**5b**	A	24	0.78	1.56	0.78	0.78
	**5c**	A	71	0.39	0.78	0.2	0.78
	**5d**	A	82	1.56	1.56	1.56	1.56
	**6a**	A,B	100,91	1.56	1.56	0.78	1.56
	**6b**	A,B	100,67	0.39	0.39	0.39	0.39
	**6c**	A,B	100,43	0.39	0.39	0.2	0.78
	**6d**	A,B	82,98	0.78	0.78	0.78	0.78
	**7a**	A,B,C	100,91,87	0.78	0.78	0.78	1.56
	**7b**	A,B,C	100,67,66	0.78	0.78	0.78	1.56
	**7c**	A,B,C,E	100,43,56,71	0.39	0.39	0.39	0.39
	**7d**	A,B,D	31,68,48	0.39	0.39	0.2	0.39
	**7e**	A,B,D	80,80,36	≥12.5	≥12.5	≥12.5	≥12.5
	**7f (FR180102)**	A,B,D	82,98,95	0.025	0.05	0.025	0.0125
	AMPC (1)			0.1	0.1	0.025	0.025
	CAM (2)			0.05	0.1	0.05	0.05

*; MIC(μg/ml), Brucella Agar + 7% horse blood, 37°C, 72h, 10%-CO_2, stamp method

classification, we speculated that introduction of lipophilic substituents to **3** would improve anti-*H. pylori* activity, since such stepwise increase of lipophilicity generally leads to more potent activity for antibacterial agents against Gram-positive bacteria.

Table 1 shows the results of benzylation of **3** and antibacterial activity is expressed as minimum inhibitory concentration values (MIC,μg/ml). Benzyl derivative **5a** showed about 20-fold improved activity compared to **3**. We next attempted to further increase lipophilicity by the introduction of chloro substituents. 2,6-Dichloro derivative **5b** had slightly improved activity, however benzofuroxan **5c** was even better still, indicating the benefits of nitrogen-containing substituents. While amine **6a** did not have improved activity, we found that a combination of amino and chloro groups (**6b-d**) was compatible with good activity. Whilst nitro compound **5d** was not improved, we were surprised to find that **7f**, containing a 3-acetamido-2,6-dichlorobenzyl substituent had remarkably potent *in vitro* anti-*H.pylori* activity. Meanwhile, no chloro substituents or the mono chloro derivatives (**7a-c**), or the regioisomer **7d** were not improved. Furthermore, the positional isomer **7e**, having a 2-acetamido group showed dramatically decreased activity. From this data it is clear that the activity of **7f** is highly specific in connection with the structure, moreover the anti-*H.pylori* activity was superior to AMPC or CAM. On the other hand, **7f** has no activity against other common bacteria (Table 2), so we conclude that **7f** is a novel and selective inhibitor of *H.pylori* growth. However, **7f** has so far shown no *in vivo* efficacy in mouse infection models.

Table 2
Antibacterial Activity Against Other Common Bacteria

Compound	MIC(μg/ml)*				
	S.aureus 209P JC-1	*E.faecalis* 0115	*E.coli* NIHJ JC-2	*S.marcescens* 3013	*M.(B.)catarrhalis* 6014
FR180102 (7f)	>100	>100	>100	>100	>100
AMPC (1)	0.05	0.39	3.13	>100	0.39
CAM (2)	0.1	0.2	100	100	<0.025

*; MIC(μg/ml), Mueller-hinton Agar (Difco), 37°C, 18h, stamp method

Summary

In this communication, we have reported the discovery of FR180102 (**7f**), a novel, potent benzyloxyisoquinoline anti-*H. pylori* agent, that contains a 3-acetamido-2,6-dichlorobenzyl substituent. Future publications will consider the therapeutic effect of a series of these compounds, as well as detailed *in vitro* structure activity relationships.

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