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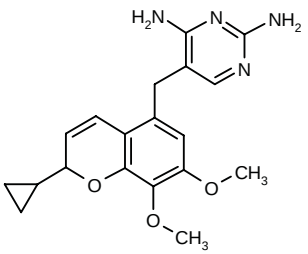
Iclaprim

Prop INN

Antibacterial
Dihydrofolate Reductase Inhibitor

AR-100
Ro-48-2622

5-(2-Cyclopropyl-7,8-dimethoxy-2*H*-1-benzopyran-5-ylmethyl)pyrimidine-2,4-diamine



$C_{19}H_{22}N_4O_3$

Mol wt: 354.4078

CAS: 192314-93-5

CAS: 474793-41-4 (as mesylate salt)

EN: 253560

Abstract

The need for potent antibacterial agents with novel mechanisms of action remains a research priority. Dihydrofolate reductase (DHFR) is an enzyme essential for bacterial survival that is an excellent target for antibacterial drug development. Diaminopyrimidines such as trimethoprim (TMP) are inhibitors of DHFR which have been used clinically as monotherapy and in combination with other agents with relative success. However, TMP is weakly bactericidal and resistance has emerged due to frequent use. Researchers have therefore focused on the discovery of synthetic derivatives of benzyldiaminopyrimidines which exhibit improved potency and selectivity and can overcome resistance. Iclaprim is a novel diaminopyrimidine that has shown potent, expanded-spectrum activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate and vancomycin-resistant *S. aureus* and macrolide-, quinolone- and TMP-resistant strains. Activity was also observed against Gram-positive and Gram-negative pathogens involved in respiratory tract infections and it proved effective in animal models of infection. Moreover, in a phase II trial, iclaprim was shown to be safe and effective as a treatment for complicated skin and soft tissue infections.

Synthesis

Iclaprim can be prepared in two related ways:

1) Reaction of cyclopropanecarbonyl chloride (I) with bis(trimethylsilyl)acetylene (II) by means of $AlCl_3$ in dichloromethane gives 1-cyclopropyl-3-(trimethylsilyl)-2-propyn-1-one (III), which is reduced with $NaBH_4$ and $CeCl_3$ in methanol to the corresponding propynol (IV). Condensation of alcohol (IV) with 3-hydroxy-4,5-dimethoxybenzaldehyde (V) by means of triphenylphosphine and diethyl azodicarboxylate in toluene yields the expected propynyl ether (VI), which is cyclized in *N,N*-diethylaniline at 200 °C to afford 2-cyclopropyl-7,8-dimethoxy-2*H*-1-benzopyran-5-carbaldehyde (VII). The condensation of aldehyde (VII) with 3-anilinopropionitrile (VIII) by means of potassium *tert*-butoxide in DMSO provides the acrylonitrile (IX), which is finally cyclized with guanidine (X) by means of potassium *tert*-butoxide in ethanol (1). Scheme 1.

2) Condensation of propynol (IV) with 3-hydroxy-4,5-dimethoxybenzoic acid methyl ester (XI) by means of triphenylphosphine and diethyl azodicarboxylate in toluene yields the expected propynyl ether (XII), which is cyclized in *N,N*-diethylaniline at 200 °C to provide 2-cyclopropyl-7,8-dimethoxy-2*H*-1-benzopyran-5-carboxylic acid methyl ester (XIII). Finally, this compound is reduced with sodium dihydridobis(2-methoxyethoxy)aluminate and morpholine in toluene to give the previously described intermediate 2-cyclopropyl-7,8-dimethoxy-2*H*-1-benzopyran-5-carbaldehyde (VII) (1). Scheme 1.

Introduction

According to the Centers for Disease Control and Prevention, approximately 2 million Americans per year acquire infections during hospitalization for other conditions and about 88,000 of these die from their infections. The FDA has estimated that 70% of the Gram-positive bacteria responsible for these infections are resistant

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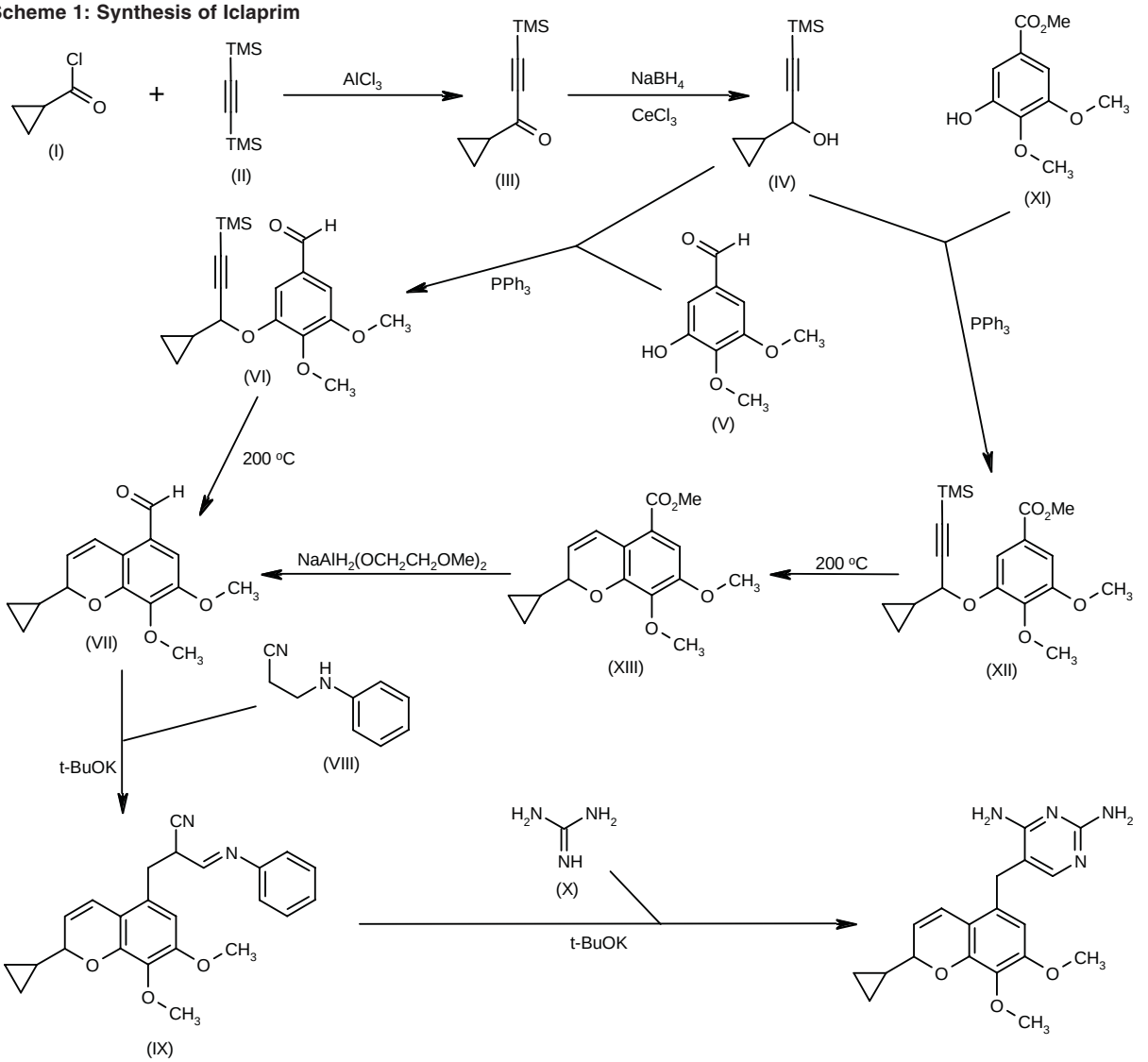
Scheme 1: Synthesis of Iclaprim



to at least 1 commonly used antibacterial agent. The need for potent antibacterial agents with novel mechanisms of action therefore remains a research priority.

Dihydrofolate reductase (DHFR) is an enzyme essential for bacterial survival that has been identified as a target for antibacterial drug development. This enzyme is involved in the initial production of tetrahydrofolate and in its recycling after reoxidation in the formation of thymidylate from deoxyuridylate. The amino acid sequence of this enzyme varies considerably between species and homology between bacterial and mammalian enzymes is < 30%. Moreover, the active site of bacterial and mammalian DHFRs is very different. Thus, DHFR represents an excellent target for the development of potent and selective inhibitors as potential antibacterial agents (2).

Diaminopyrimidines such as trimethoprim (TMP), launched in 1961, and brodimoprim, launched in 1993, have been recognized for years as effective antibacterial agents since they not only act as thymine substitutes but also inhibit folic acid metabolism via inhibition of DHFR. These agents have been used clinically with relative success as monotherapy and in combination with other agents such as sulfonamides (inhibitors of pteridine reductase). For example, cotrimoxazole is a combination of sulfamethoxazole and TMP that was once widely used in the clinic but is now limited to *Pneumocystis carinii* infections. TMP does not exhibit acute toxicity and has an excellent safety profile. However, it is weakly bactericidal and resistance, although not extensive, has emerged due to frequent use (3-8). The reduced susceptibility of bacteria to TMP has been identified as being due to point

mutations in DHFR, including a Phe-to-Tyr mutation in *Staphylococcus aureus* (F98Y) and *Staphylococcus epidermidis* (F99Y) and an Ile-to-Leu mutation in *Streptococcus pneumoniae* (I100L) (9, 10). Researchers have therefore focused on the discovery of synthetic derivatives of the benzyldiaminopyrimidine series with improved pharmacological and physicochemical profiles to enhance potency and selectivity and to overcome resistance.

From these intensive research efforts, iclaprim (AR-100, Ro-48-2622) has emerged. The compound has shown potent, expanded-spectrum activity against Gram-positive bacteria including methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate and vancomycin-resistant *S. aureus* (VISA, VRSA) and macrolide-, quinolone- and TMP-resistant strains. Activity was also observed against Gram-positive and Gram-negative pathogens involved in respiratory tract infections (*e.g.*, *S. pneumoniae*, *Haemophilus influenzae*, *Chlamydia* spp.). The agent is rapidly bactericidal and penetrates well into tissues. Iclaprim can be administered by both the intravenous and oral routes and was chosen for further development as an antibacterial agent (11-13).

Antibacterial Activity

Iclaprim specifically and selectively inhibited purified wild-type and mutant DHFR enzymes at low concentrations, being more potent that TMP. No significant inhibitory effect was observed against human wild-type DHFR for either agent (IC_{50} > 300 μM). In contrast, iclaprim and TMP comparably inhibited wild-type DHFR enzymes isolated from *Escherichia coli* (IC_{50} = 0.007 μM) and *S. aureus* (IC_{50} = 0.007 μM); both agents equally inhibited wild-type DHFR from *S. epidermidis* and *Pseudomonas aeruginosa*, but iclaprim was more potent than TMP against wild-type DHFR from *Mycobacteium bovis* and *Mycobacterium tuberculosis*. Iclaprim was more potent than TMP in inhibiting DHFR isolated from wild-type *P. carinii* (IC_{50} = 2.4 μM *vs.* 43 μM), wild-type *S. pneumoniae* (IC_{50} = 0.008 μM *vs*. 0.075 μM) and mutant (F98Y, I100l) *S. aureus* (IC_{50} = 0.8 μM *vs*. 15 μM and 4 μM *vs.* 300 μM from 2 different studies) and *S. pneumoniae* (IC_{50} = 0.043 μM *vs.* 3 μM and 1 μM *vs.* 100 μM from 2 different studies) (13-15).

The antibacterial activity of iclaprim and related drugs is shown in Table I.

The spontaneous frequency of resistance in *S. aureus* to iclaprim and TMP was determined to be approximately 10^{-10}. Results from resistance induction experiments using TMP-sensitive and TMP-resistant *S. aureus* strains showed that in the presence of TMP, the MIC in TMP-sensitive strains increased from 2 μg/ml to > 128 μg/ml after 4 passages; the MIC remained elevated even during 5 passages in the absence of TMP. Resistance was shown to be due to a single F98Y mutation. In contrast, the MIC of iclaprim in both TMP-sensitive and TMP-resistant strains increased only 4-8-fold after 17 passages. Sensitivity was regained after further passages in the absence of iclaprim (16).

Iclaprim exhibited potent activity against Gram-positive bacteria and some isolates responsible for upper respiratory infections in several *in vitro* studies (17-33).

A study examining the activity of iclaprim against 796 recent clinical isolates showed that it was at least 16 times more potent than TMP against *S. aureus*, enterococci and streptococci. The $MIC_{50/90}$ values for iclaprim against methicillin-susceptible *S. aureus* (MSSA) and TMP-susceptible MRSA were 0.06/0.12 and 0.06/0.5 mg/l, respectively; iclaprim had higher MIC values for several strains of MRSA with reduced susceptibility to TMP. Iclaprim was very active ($MIC_{50/90}$) against group A streptococci (0.015/0.06 mg/l or less), viridans streptococci (0.06/4 mg/l) and *S. pneumoniae* (0.06/8 mg/l); activity varied against penicillin-susceptible (0.03/0.06 mg/l), -intermediate (0.06/8 mg/l) and -resistant (4/8 mg/l) strains. The $MIC_{50/90}$ values for iclaprim against *Enterococcus faecalis*, *Enterococcus faecium*, *H. influenzae* and *Moraxella catarrhalis* were 32, 0.03/32, 0.12/8 and 4/4 mg/l, respectively. The MIC_{50} and MIC_{90} values for iclaprim against Enterobacteriaceae ranged from 1 mg/l to 16 mg/l and from 8 mg/l to > 32 mg/l, respectively. The agent was less active against *S. epidermidis* ($MIC_{50/90}$ = 32/32 mg/l or greater) and *S. haemolyticus* ($MIC_{50/90}$ = 16/32 mg/l or greater) and very little activity was observed against *Acinetobacter* spp. and *Stenotrophomonas maltophilia* (17).

A study comparing the activity of iclaprim with several other antibacterial agents against 325 clinical isolates demonstrated that iclaprim was superior to TMP, ciprofloxacin, vancomycin, linezolid, erythromycin and clindamycin against staphylococci, including both MSSA and MRSA. Superior or comparable activity was noted against streptococci (including some penicillin-resistant pneumococci), enterococci and *H. influenzae*. Iclaprim was more potent than TMP but less active than the other comparators against *M. catarrhalis* (18).

The MICs and kill kinetics of several antibacterials were examined against a strain of VRSA carrying the *vanA* resistance gene that was isolated from the heel wound of a patient. The VRSA was resistant to licensed β-lactams, macrolides, tetracycline and aminoglycosides and also had alterations in *gyrA* and *grlB* conferring resistance to available quinolones. However, TMP/sulfamethoxazole and iclaprim exhibited a low MIC of 0.25 μg/ml (19, 20).

Iclaprim was shown to have good activity against *S. pneumoniae* strains including isolates resistant to penicillin, erythromycin, TMP/sulfamethoxazole and ciprofloxacin. The $MIC_{50/90}$ values for iclaprim for the 801 isolates (600 respiratory and 201 from blood) were 0.03/0.5 μg/ml. The $MIC_{50/90}$ values for iclaprim against penicillin-resistant (n=40), erythromycin-resistant (n=103), TMP/sulfamethoxazole-resistant (n=113) and ciprofloxacin-resistant (n=24) strains tested were 1/2, 0.5/2, 2/4 and 0.03/1 μg/ml, respectively (21).

Table I: Activity of iclaprim and related antibacterial drugs (data from Prous Science Integrity®).

Microorganism	Drug	MIC_{50} (μg/ml)
Staphylococcus aureus	Cotrimoxazole	0.06-2
	Epiroprim	≤ 0.06-0.667
	Iclaprim	0.03-0.12
	Trimethoprim	≤ 0.5-2
Staphylococcus aureus (methicillin-resistant)	Cotrimoxazole	≥ 0.06
	Iclaprim	0.06
	Epiroprim	0.06
	Trimethoprim	0.31-0.5
Streptococcus pyogenes	Cotrimoxazole	≤ 0.06-2
	Epiroprim	1
	Iclaprim	≤ 0.015-0.06
	Trimethoprim	≤ 0.06
Viridans group streptococci	Cotrimoxazole	< 250
	Epiroprim	1
	Iclaprim	0.06-0.25
	Trimethoprim	0.01-8
Streptococcus pneumoniae	Cotrimoxazole	≤ 0.12-4
	Epiroprim	0.125
	Iclaprim	0.03-1
	Trimethoprim	≤ 0.05-16
Streptococcus pneumoniae (penicillin-resistant)	Cotrimoxazole	≤ 2
	Epiroprim	16
	Iclaprim	1-4
	Trimethoprim	1.25-128
Haemophilus influenzae	Cotrimoxazole	≤ 0.12-0.5
	Epiroprim	2
	Iclaprim	≤ 0.5
	Trimethoprim	0.25-1
Haemophilus influenzae (β-lactamase +)	Cotrimoxazole	0.12
	Iclaprim	0.12
	Trimethoprim	0.25

The bactericidal activity and postantibiotic effect (PAE) of iclaprim against *S. aureus* (ATCC 25923; penicillin- and TMP-resistant 101), VISA (Mu3), *S. pneumoniae* (ATCC 29212) and *E. faecalis* (E-80-8) were examined and compared to vancomycin. Rapid bactericidal activity (99.9% kill by 3-5 h) was obtained for iclaprim against AT 25923, 101 and Mu3. When concentrations of the agent were increased 2-8-fold, a rapid bactericidal action was observed that was independent of concentration. Vancomycin was slowly bactericidal (90% kill after 16 h with concentrations 16-fold higher than the MIC) against ATCC 25923 and 101. A significant PAE was observed after exposure of bacteria to iclaprim for 1-2 h. A PAE was even observed in some cases at sub-MIC concentrations (22).

An *in vitro* study using *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *E. faecalis*, *E. coli* and *H. influenzae* isolates (including penicillin-, vancomycin- and TMP-resistant isolates) showed that iclaprim had broad-spectrum activity. The MIC_{90} values obtained against staphylococci (regardless of oxacillin susceptibility), *S. pneumoniae* (including penicillin- and TMP-resistant strains) and VISA (Mu3, Mu50, 992 and 14379) were < 0.06, 0.5 and 0.06 μg/ml, respectively. Iclaprim did not show synergistic or antagonistic activity when tested in combination with vancomycin, penicillin, rifampicin, erythromycin or TMP. However, synergistic activity was observed when iclaprim was combined with sulfamethoxazole or sulfadiazine (23).

Another study examined the efficacy of iclaprim against 10 strains of *Chlamydia trachomatis*, 10 isolates of *Chlamydia pneumoniae* (including TW183, AR-39, CM-1, W6805) and 6 recent isolates from patients with community-acquired pneumonia, and compared its activity with TMP, azithromycin and levofloxacin. The activity of iclaprim was significantly more potent than TMP but comparable to azithromycin and levofloxacin. The MIC_{90} and MBC_{90} values for iclaprim against *C. pneumoniae* and *C. trachomatis* were both 0.5 μg/ml as compared to 128 μg/ml or greater obtained for TMP. The MIC_{90} and MBC_{90} values for azithromycin and levofloxacin were 0.125 and 0.2 μg/ml, respectively (24).

A study using HeLa cells infected with *Listeria monocytogenes* demonstrated that iclaprim and TMP had similar inhibitory activity against this bacterial strain. The MIC values for iclaprim when tested in Isosensitest broth,

brain heart infusion broth and EMEM were 0.6, 0.6 and 8 μg/ml, respectively. In time-kill studies, iclaprim was shown to decrease colony counts by several log units. Iclaprim concentrations of 1-8 x MIC decreased intracellular *Listeria* load by 1-1.5 log. No membrane damage or cytotoxicity was noted with iclaprim concentrations up to 100 μg/ml (25).

Iclaprim was shown to be active against several atypical respiratory pathogens including isolates of *Mycoplasma pneumoniae* (n=20), *Mycoplasma hominis* (n=22), *Ureaplasma urealyticum* (n=22) and *Legionella pneumophila* (n=56). The $MIC_{50/90}$ values for the strains tested were 128/128, 64/128, 32/128, 0.03/0.06 μg/ml, respectively. Although comparable activity was observed for TMP/sulfamethoxazole, iclaprim was superior to the TMP/sulfamethoxazole combination against *L. pneumophila* and superior to TMP and sulfamethoxazole alone against *M. pneumoniae*, *M. hominis* and *U. urealyticum*. The activity of iclaprim against these isolates was less than that of levofloxacin or clarithromycin (26).

The efficacy of iclaprim was demonstrated *in vivo* in a murine model of staphylococcal septicemia using an MRSA strain. The activity of iclaprim administered either i.v. or p.o. once at 10 min postinfection or b.i.d. 10 min and 4 h postinfection was compared to s.c. vancomycin. Survival was significantly prolonged at 7 days postinfection in mice treated with i.v. iclaprim (ED_{50} = 1.3 mg/kg once daily and 5.1 mg/kg b.i.d.). The ED_{50} values for p.o. iclaprim and s.c. vancomycin were 17.4 mg/kg once daily, 21.7 mg/kg b.i.d. and 0.9 mg/kg, respectively (34).

Iclaprim was also proven effective in both a murine peritonitis (using an MRSA strain) and pneumonia (using a penicillin-resistant *S. pneumoniae* strain) model. The ED_{50} values for the respective models were 3.8 mg/kg and 14 mg/kg b.i.d. (35).

Pharmacokinetics

The pharmacokinetics of single-dose iclaprim (30 mg/kg i.v. or p.o. and 60 mg/kg s.c.) were determined in mice. The half-life ($t_{1/2}$) values were 10 and 13 min following i.v. and s.c. dosing, respectively. Peak plasma concentrations (C_{max}) at 15 min after p.o. and i.v. dosing were 0.5 and 1.7 μg/ml, respectively. Bioavailability was determined to be approximately 30% (35).

Clinical Studies

A randomized, double-blind, comparator-controlled (*i.e.*, standard vancomycin therapy) phase II trial conducted in 92 patients with complicated skin and soft tissue infections examined the efficacy and safety of iclaprim (1 or 2 mg/kg by i.v. infusion b.i.d. for 10 days). Iclaprim was well tolerated. Adverse events were not frequent and were similar for all treatment groups. No laboratory abnormalities were observed with treatment. The clinical cure rates for evaluable patients were 92.9% (26/28 patients) and 93.5% (29/31 patients) for iclaprim doses of 1 and 2 mg/kg, respectively, as compared to 92.9% (26/28 patients) for vancomycin. Microbiological success rates were 57.1% (16/28 patients) and 76.7% (23/30 patients), respectively, for 1 and 2 mg/kg iclaprim as compared to 50% (13/26 patients) for vancomycin (36).

Iclaprim continues in phase II development for the treatment of complicated skin and soft tissue infections (37).

Sources

Arpida Ltd. (CH); licensed from F. Hoffmann-La Roche AG (CH).

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