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Synthesis and SAR of a novel, potent and structurally simple LTD4 antagonist of the quinoline class

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Abstract

The two geminal ethyl groups in the succinic acid moiety of CGP57698 (4-[3-(7-fluoro-2-quinolinyl-methoxy)phenyl-amino]-2,2-diethyl-4-oxo-butanoic acid) are responsible for the high *in vitro* and *in vivo* potency of this peptidoleukotriene antagonist of the quinoline type. The synthesis and structure activity relationships of CGP57698 and its analogs are described.

Keywords: Leukotrienes; Antagonists

Clinical trials with peptidoleukotriene (pLT) antagonists have supported the concept that pLT's (LTC_4, LTD_4 and LTE_4) are important mediators of human bronchial asthma [1]. These compounds have been tested against LTD_4-induced bronchoconstriction in either normal or asthmatic subjects. Antagonists producing greater than 20 fold shifts in the LTD_4 dose response curves can be expected to inhibit both the early and late phase antigen-induced bronchoconstriction as well as the subsequent antigen-induced airway hyperresponsiveness in sensitive subjects [1]. These compounds also act against exercise- and dry cold air-induced bronchoconstriction and bronchoconstriction induced by aspirin in patients sensitive to non-steroidal antiinflammatory drugs [1]. Such pLT antagonists are bronchodilators in moderate to severe asthmatics and this effect is additive with β-agonists [1]. Thus they improve lung function values (FEV1 and PEFR), reduce the need for rescue medication and improve daytime and night-time symptoms [1]. pLT antagonists are also effective in steroid treated patients (e.g. bronchodilation) [1]. pLT antagonists appear to be safe and no mechanism-based side effects have been reported so far. Where exactly pLT antagonists will fit into the treatment of asthma

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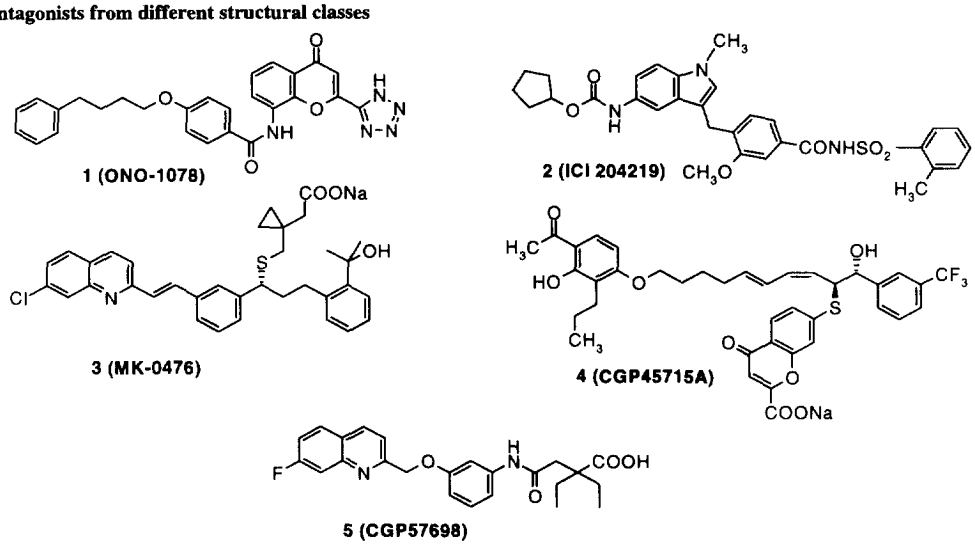
is subject of further clinical trials and has not yet been fully determined. Compounds sharing the above clinical profile come from different structural classes [2,3,4] and include ONO 1078 (pranlukast, Onon™) (**1**) [5], ICI 204219 (zafirlukast, Accolate™) (**2**) [6], MK-0476 (montelukast sodium, Singulair™) (**3**) [7] and CGP45715A (iralukast sodium) (**4**) [8]. Iralukast (**4**) is a highly potent pLT antagonist which was in advanced clinical evaluation as an aerosol formulation. As a structural analog of LTD_4, Iralukast requires a demanding synthesis and has limited oral bioavailability. Our objectives for a follow-up compound of iralukast called for structural simplicity combined with high oral potency. pLT antagonists of the quinoline type were considered to be the right target, as the design of quinoline antagonists is relatively simple and such compounds have in general good oral activity [9,10]. Quinoline antagonists are characterized by a quinoline residue substituted in position 2 by a spacer consisting of two atoms and by a second aromatic unit attached to this spacer and carrying an acidic residue. Using this approach assembling of the appropriate structural elements led to the design and the synthesis of CGP57698 (**5**).

Figure 1
pLT antagonists from different structural classes

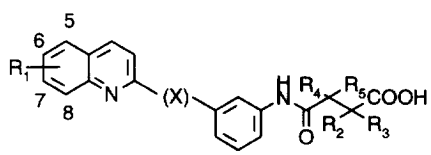


A number of analogs of CGP57698 (**5**) have been synthesized in order to determine the SAR in this series of quinoline pLT antagonists. Compounds **5** to **23** in Table 1 illustrate the influence of the substitution in the quinoline moiety on the biological activity. The 7-fluorine substitution in the quinoline residue of CGP57698 (**5**) is optimal in terms of the LTD_4 antagonist activity *in vitro* (Table 1) as well as *in vivo* (Table 2). Compounds **6** to **8** with fluorine in the positions 5,6 and 8 of the quinoline system and the di-fluoro compound **9** have somewhat reduced *in vitro* activities in the subnanomolar to nanomolar range. The 7-chloro

derivative **10** and the unsubstituted compound **12** showed high *in vitro* and *in vivo* potency, whereas the 7-bromo derivative **11** was already *in vitro* 20 times less active than CGP57698 (**5**). With an IC_{50} value of 3 nM *in vitro* the trifluoromethyl derivative **13** had surprisingly no oral activity *in vivo* up to a dose of 10 mg/kg. Compounds **14** to **23** with a variety of other quinoline substituents were considerably (45 times to more than 3 orders of magnitude) less potent than CGP57698 (**5**) *in vitro*. Polar groups like hydroxy or bulky groups like benzyl appear to be detrimental to the antagonist activity. The structure of the acidic residue is of great importance for the pLT antagonist potency of quinoline type antagonists as shown by compounds **24** to **31** in table 1. In CGP57698 (**5**) the acidic group is derived from succinic acid with two geminal ethyl groups in position 2, which are essential for the high potency of CGP57698 (**5**). The unsubstituted succinic acid derivative **24** was 3 orders of magnitude less potent *in vitro*. The activity is back in the nanomolar range with a selection of alkyl groups in position 2 of the succinic acid. An almost complete loss of activity occured with a shift of the two geminal groups from position 2 to position 3 in the succinic acid residue (compound **31**). With compounds **32** to **34** in table 1 the influence of different two atom spacers on the antagonist activity has been explored. Inversion of the atom sequence in the spacer from -CH_2O- to -OCH_2- (compound **32**) practically abolished the *in vitro* activity. Replacement of oxygen by sulfur, while maintaining the normal atom sequence in the spacer (compound **33**) decreased the *in vitro* potency 20 times, whereas compound **34** with a double bond as spacer was equipotent to CGP57698 (**5**) *in vitro*.

Table 2 demonstrates the excellent potency of CGP57698 (**5**) in comparison with ICI 204219 *in vitro* as well as *in vivo*. The complete pharmacological profile of **5** will be published elsewhere [11]. Compounds **10** and **12** with subnanomolar activity *in vitro* in the guinea-pig ileum test had also *in vivo* comparable activity to CGP57698 (**5**) (table 2).

Table 1
SAR of CGP57698 (5) and its analogs 6-34



compound	R_1	R_2	R_3	R_4	R_5	X	IC_{50}(nM)[a]
CGP57698 (5)	7-F	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O$-	0.2
6	5-F	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O$-	0.3
7	6-F	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O$-	2
8	8-F	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O$-	6

Table 1 continued

compound	R_1	R_2	R_3	R_4	R_5	X	IC_{50}(nM)[a]
9	6,7-di-F	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	0.5
10	7-Cl	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	0.8
11	7-Br	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	4
12	-H	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	0.9
13	$7-CF_3$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	3
14	$7-CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	11
15	$6-CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	24
16	$6,7-di-CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	11
17	$6-(CH_2)_3-7$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	9
18	$7-OCH_3$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	80
19	7-OH	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	0 @ 240
20	$7-OCH_2Ph$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	0 @ 200
21	$7-OCH_3$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	80
22	$7-OCF_3$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	9
23	$7-COCH_3$	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	2500
24	7-F	-H	-H	-H	-H	$-CH_2O-$	200
25	7-F	$-CH_3$	$-CH_3$	-H	-H	$-CH_2O-$	1.4
26	7-F	$-CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2O-$	6.4
27	7-F	-n-propyl	-n-propyl	-H	-H	$-CH_2O-$	2
28	7-F	-n-butyl	-n-butyl	-H	-H	$-CH_2O-$	1
29	7-F	$-(CH_2)_4-$		-H	-H	$-CH_2O-$	10
30	7-F	$-(CH_2)_5-$		-H	-H	$-CH_2O-$	7.3
31	7-F	-H	-H	$-CH_2CH_3$	$-CH_2CH_3$	$-CH_2O-$	140
32	-H	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-OCH_2-$	3900
33	7-F	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H	$-CH_2S-$	4
34	7-F	$-CH_2CH_3$	$-CH_2CH_3$	-H	-H		0.4

[a] LTD_4 antagonism guinea-pig ileum [12] (n=3-5)

Table 2

***In vitro* and *in vivo* activity of CGP57698 (5), ICI 204219 (2) 10, 12 and 13**

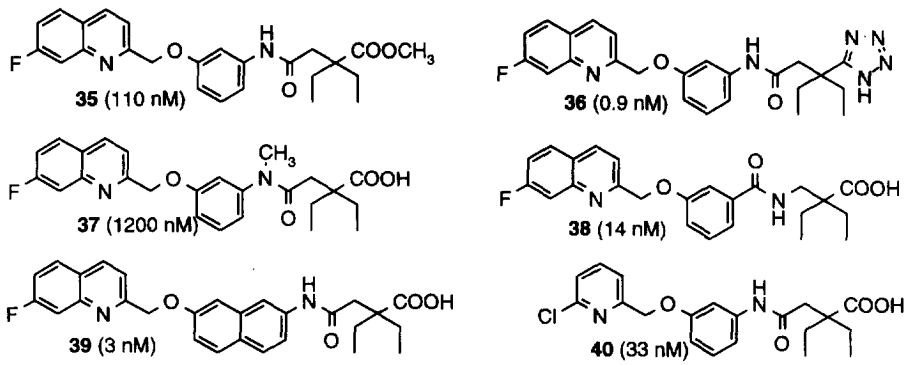
Compound	Inhib. of [^{3}H]-LTD_4 binding to guinea-pig lung membranes IC_{50} (nM) [13] (n=4)	LTD_4 antagonism guinea-pig ileum IC_{50} (nM) [12] (n=3-5)	LTD_4-induced bronchospasm guinea-pig ED_{50} (mg/kg) p.o. -2 h [14] (n=3-6)
CGP57698 (5)	6	0.2	0.07
ICI 204219 (2)[a]	44	5	0.55
10	64	0.8	0.11
12	9	0.9	0.42
13	not determined	3	inactive at 10 mg/kg p.o.

[a] Values determined at Novartis Pharma AG, Basel

The structures shown in figure 2 complete the SAR picture of this series of quinoline pLT antagonists. The methyl ester **35** of CGP57698 (**5**) had weak LTD_4 antagonist activity with an IC_{50} value of 110 nM *in vitro*. The corresponding tetrazole **36** showed similar *in vitro* activity as the parent compound. Interestingly the *N*-methyl derivative **37** was practically inactive. Inversion of the amide (compound **38**), replacement of the central phenyl nucleus by a naphtyl

residue or replacement of the quinoline system by a pyridyl ring (compounds **39** and **40**) had to be paid with considerable weaker activity *in vitro*.

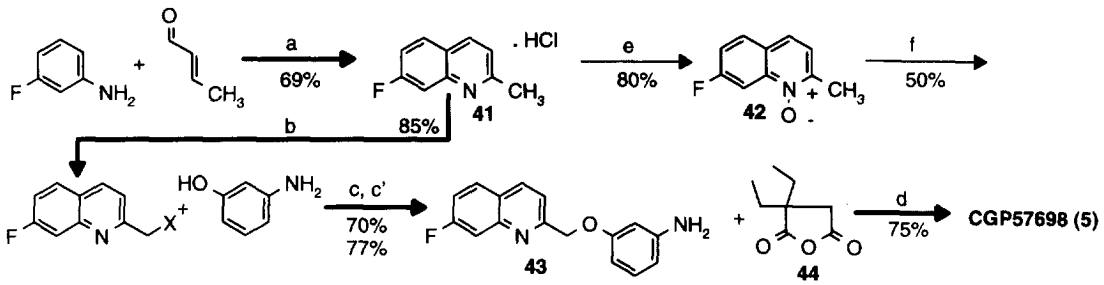
Figure 2
More detailed SAR of quinoline pLT antagonists 35-40



In parentheses: IC_{50} values for the inhibition of LTD_4-induced guinea-pig ileum contractions [12]

CGP57698 (**5**) and its analogs can be synthesized in only four steps (sequence a,b,c,d scheme 1). A modified Skraup reaction between 3-fluoroaniline, crotonaldehyde and the oxidant *p*-chloranil gave rise to 7-fluoroquinaldine (**41**) [15]. Side chain bromination under carefully controlled conditions followed by substitution with 3-aminophenol led to the aniline derivative **43**, which upon condensation with 2,2-diethylsuccinic anhydride (**44**) [16] yielded the desired product **5**. Alternatively side chain chlorination of the quinaldine **41** can be achieved *via* the *N*-oxide **42** (sequence e,f scheme 1). The four step sequence has been used to prepare CGP57698 (5) on a 10 kg scale.

Scheme1
Synthesis of CGP57698 (5)



Reagents and conditions: a) *p*-Chloranil, 2-butanol/HCl, 60°, 3 h; b) 1. NaOH, H_2O, isopropylacetate; 2. NBS, AIBN, 78°, 5 h (X=Br); c) $NaOCH_3$, MeOH, 5-10° (X=Br); c') $NaOCH_3$, MeOH, DMF, 5-10°, 15 h (X=Cl); d) MTBE, 50°, 5 h e) MCPBA, CH_2Cl_2, 5°, 16 h; f) Benzenesulfonylchloride, toluene, 50°, 8 h.

In summary CGP57698 (**5**) is a pLT antagonist of the quinoline type with equal potency against LTD_4 and LTE_4. The compound is in comparison to other pLT antagonists (e.g. ICI 204219, MK-0476) simpler to synthesize. CGP57698 (**5**) demonstrated good oral bioavailability (rats and marmosets) [11] and is biologically active in guinea-pig bronchoconstriction models *via* the oral route with high potency and long duration of action. Cardiovascular and central nervous system safety pharmacology as well as 3 month oral toxicity studies in rats and marmosets did not reveal prohibitive results for the further development of the compound [11]. The pharmacological profile indicates that CGP57698 (5) might be of value in the treatment of asthma and other pLT dependent diseases.

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