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(71) Applicant and

(72) Inventor: **CHAROUS, Lauren** [US/US]; 7830 North Regent Road, Fox Point, WI 53217 (US).

(74) Agent: **GROLZ, Edward, W.**; Scully, Scott, Murphy & Presser, 400 Garden City Plaza, Garden City, NY 11530 (US).

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(54) Title: A METHOD FOR TREATING INFLAMMATORY BOWEL DISEASE

(57) Abstract: The present invention is directed to a method for treating inflammatory bowel disease in a patient comprising administering to said patient a pharmaceutical compositions comprising a pharmaceutically effective amount of an anti-malarial compound in association with a pharmaceutically acceptable carrier and/or excipient that delays and targets the release of the anti-malarial compound in the gastrointestinal tract of the patient. It is also directed to the pharmaceutical composition comprising a pharmaceutically effective amount of the anti-malarial compound in association with a pharmaceutically acceptable carrier or excipient that delays and target the release of the anti-malarial compound in the gastrointestinal tract.



WO 03/039488 A2

A METHOD FOR TREATING INFLAMMATORY BOWEL DISEASE**FIELD OF THE INVENTION**

The present invention relates to a method for
10 treating inflammatory bowel disease with a novel oral
preparation of anti-malarial agents.

BACKGROUND OF INVENTION

Inflammatory bowel is an idiopathic illness
15 characterized by a constellation of historical and physical
findings as well as pathological lesions of the intestinal
mucosa in which the sustained activation of mucosal immune
responses play a major role. The major forms of
inflammatory bowel disease include: Crohn's disease (CD)
20 and Ulcerative colitis (UC). Another form of IBD is
eosinophilic gastroenteritis (EG) which is much more rare.
The prevalence of Crohn's disease is 20-100 and UC 40-100
per 100,000. Eosinophilic gastroenteritis is more rare.
The cause of all of these illnesses remains unknown despite
25 much research. Although genetic factors may predispose
individuals, and allergic disease appears frequently in
individuals with EG, the frequency of disease in first-
degree relatives argues against a simple "recessive"
inheritance patterns for any of these illnesses.
30 Crohn's disease is predominantly a small-bowel

disease with 30% of individuals having ileo-cecal disease; 40% with disease restricted to the small bowel and 30% with involvement of the colon. Complications of CD include severe diarrhea, abdominal pain, weight loss,
5 malabsorption, intra-abdominal abscesses, intestinal fistulae and obstruction, gall stones, kidney stones and an increased incidence of colon cancer. The inflammation in CD chiefly involves macrophages, and activated T cells, although eosinophilic infiltrations are noted in many
10 patients. Granulomatous changes are also seen in a minority of patients. While the inflammatory pathways of this illness remain to be fully elucidated, it is clear that pro-inflammatory mediators such as TNF- α , IL-1, IL-6 and interferon- γ play a major role in the pathogenesis of
15 this illness.

Ulcerative colitis affects the colon and rectal mucosa and superficial submucosa. The inflammatory process involves neutrophilic infiltration of the lamina propria and intestinal crypts with frequent micro-abscess
20 formation. A mixed-cell inflammatory change is commonly seen, with involvement of lymphocytes and other leukocytes, including at times prominent eosinophilic involvement with more extensive inflammation. Manifestations of UC include bloody diarrhea, abdominal and rectal pain, fever, weight
25 loss and malaise. Complications of UC include colonic perforation, toxic megacolon, arthritis, and a marked increase in the risk of colon cancer and sclerosing cholangitis.

EG may affect any portion of the gastrointestinal
30 tract, but most commonly involves the esophagus, stomach

and small bowel. The illness is characterized by blood eosinophilia and eosinophilic infiltration of the gastrointestinal mucosa and underlying tissue. Activated eosinophils are capable of releasing a variety of cellular toxins, including eosinophil cationic proteins, superoxides, and eosinophil derived neurotoxin. and eosinophil major basic protein. Eosinophils may also play a role in antigen presentation and ICAM-bearing eosinophils may have increased adhesion capacity for antologous T cells (Hansel TT, "Induction and function of eosinophil intercellular adhesion molecule-1 and HLA-DR", J Immunol 1992; 149: 2130-6). Symptoms of EG may include pain, nausea, vomiting, diarrhea, but also intestinal obstruction and perforation.

In addition to leukocyte-mediated inflammation, increasing evidence mounts for the active participation of intestinal epithelial cells in the inflammatory process. Elaboration of pro-inflammatory chemokines, such as IP-10, by these cells appears to play a prominent role in the maintenance of an inflammatory response by aiding in the recruitment of granulocytes and mononuclear cells (Uguccioni, M, et al. "Increased expression of IP-10, IL-8, MCP-1 and MCP-3 in ulcerative colitis", Am J Pathol, 1999;155:231-6; Dwinell, MB et al., "Regulated production of interferon-inducible T-cell chemoattractants by human intestinal epithelial cells", Gastroenterology, 2001; 120: 291-4).

Treatment of IBD commonly utilizes a variety of oral systemic anti-inflammatory agents designed to reduce the inflammatory response. First line therapy commonly

employs one of the 5-aminosalicylates, such as sulfasalazine, olsalazine or mesalamine.

Alternate anti-inflammatory agents given for treatment of IBD, include corticosteroids, azathioprine, cyclosporine, tacrolimus, and hydroxychloroquine (HCQ). In addition, methotrexate, the TNF- α blocker infliximab (Remicade®), and corticosteroids have been given parenterally via injection or intravenous infusion. Despite their considerable toxicity, oral and parenteral corticosteroids are considered the only proven treatment for the treatment of EG. All of these therapeutic approaches rely on the administration of these drugs systemically and derive their benefit from the general anti-inflammatory effects which result.

Only two clinical trials of the anti-malarial agent Hydroxychloroquine (HCQ) given at conventional oral doses of from 4-6 mg/kg/day (typically 400 mg/day for an average-sized person) are reported (Goenka, MK et al. Am J Gastroenterol 1996;91:917-21; Mayer, L, "The role of the epithelial cell in immunoregulation: pathogenetic and therapeutic implications", Mt. Sinai J Med, 1990; 57: 179-82); in neither was a consistent therapeutic benefit evident after 3 months therapy. For this reason, current therapeutic recommendations for IBD do not include use of HCQ or other anti-malarial agents (Podolsky, DK, "Inflammatory bowel disease", NEJM, 2002; 347: 417-29; Scholmerich, J, "Immunosuppressive treatment for refractory ulcerative colitis—where do we stand and where are we going?", Eur J Gastroenterol Hepatol 1997; 9: 842-9).

The reason for an apparent lack of rapid,

consistent effects of standard oral dosing with HCQ and other anti-malarial agents is not immediately clear. HCQ is known to have anti-inflammatory effects on many of the cells and pro-inflammatory chemokines involved in IBD.

5 Furthermore, in a variety of ex vivo and in vitro experiments, HCQ does exert a very immediate effect on leukocytes, usually in less than 1 hour of incubation.

Despite this, HCQ and other anti-malarial agents are universally considered slow acting drugs. In the
10 treatment of rheumatic diseases, such as lupus erythematosus and rheumatoid arthritis, onset of action is characteristically 3-4 months. Charous presented convincing evidence (Charous, BL et al., J Allerg Clin Immunol, 1998; 102: 198-203) that therapeutic effect in
15 asthma with oral HCQ begins only after 22 weeks of treatment.

This delay in onset appears due to the requirement for active drug concentration in target organs for the onset of therapeutic effect. Hence, one
20 requirement for drug action is time. The second requirement for onset of drug effect is that HCQ achieve therapeutic concentration in the target organs. Inasmuch as HCQ has a notable selective distribution throughout body organs (McChesney, EW, "Animal toxicity and
25 pharmacokinetics of hydroxchloroquine sulfate", Amer J Med, 1983; July: 11-18), administration by HCQ per ora does not imply that the sufficient drug concentrations will reach the inflamed interstitial mucosa. The fact that HCQ actively concentrates in organs other than bowel wall
30 serves as a likely explanation for its lack of consistent

and proven efficacy. It is noted that when given in conventional oral caplets, HCQ is virtually completely absorbed in the proximal bowel and for this reason, it cannot exert any direct effect from the bowel lumen on
5 inflammatory disease involving the jejunal, ileal, cecal, colonic or rectal mucosa.

SUMMARY OF THE INVENTION

It is therefore an object of the present
10 invention to provide a novel method for the administration of an anti-malarial agent as a localized enteric agent for treatment of diseased areas of the intestine. Specifically, the present invention is directed to the treatment of IBD, especially, Crohn's disease and
15 Ulcerative colitis, eosinophilic gastroenteritis indeterminate colitis and infections colitis comprising administering a controlled, targeted release pharmaceutical composition comprising an anti-inflammatory effective amount of an anti-malarial compound to specific
20 areas in the gastrointestinal tract (including small intestines, colon, rectum, and the like) involved in the inflammatory process. For example, the anti-malarial compound is associated with an excipient and/or carrier which controls and targets the release of the anti-malarial
25 compounds at a targeted site of the gastrointestinal tract, e.g., small intestine, colon, small bowel and the like or a portion thereof. This release is controlled in that the anti-malarial compound is not released until it reaches a particular organ or portion thereof. Once the anti-
30 malarial compound reaches the targeted site, the release

thereof may be immediate, pulsed or it may be a sustained release, i.e., released over a prolonged period of time. Thus, the pharmaceutical composition may also comprise a sustained release carrier, such as a sustained release polymer known in the pharmaceutical arts. In particular, achievable drug concentrations in the intestinal lumen by use of targeted release can be shown to be of a magnitude previously shown to block eosinophil, neutrophil, macrophage and epithelial cell inflammatory responses.

This method has the advantage providing virtually immediate therapeutic drug concentrations to areas of inflammation in the intestines which will reduce the onset of action from months to days and decrease dosage requirements to 25% of conventional oral dosing.

It is another object of the present invention to provide a pharmaceutical composition comprising an anti-malarial compound in effective amounts in association with a sustained release carrier which releases the anti-malarial compound in the colon or small bowel.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 graphically depicts the effect of HCQ on eosinophil total superoxide production. In Figure 1, PMA refers to phorbol myristic acetate, IL-5 refers to interleukin 5, and PAF refers to platelet activating factor, Nil refers to the control, i.e., no HCQ and SE refers to the standard error of the mean. The data are presented as mean ISE; n=3. The * indicates $p < 0.05$; ** indicates $p < 0.01$.

Figure 2 graphically depicts the effect of HCQ on

IL-5 stimulated eosinophil survival. In the Figure, Dex refers to dexamethasone, and nil refers to IL-5 alone. The data are presented as average of duplicates from one or two experiments for each inhibitor/stimulus. Actual percentage survival at four days are given above each bar.

Figure 3 graphically depicts the mean whole blood concentration of HCQ following single day intravenous doses to male and female rats.

Figure 4 graphically depicts the mean whole blood concentration of HCQ following single day intravenous doses to male and female dogs.

Figure 5 graphically depicts the effect of 50 μ m HCQ on the elaboration of IP-10 and RANTES in primary human epithelial cells with exposure to human rhinovirus HRV_16.

Figure 6 depicts graphically the effect of varying concentrations of HCQ preincubation on the elaboration of IP-1 and RANTES in BEAS-2B epithelial cells exposed to HRV-16.

DETAILED DESCRIPTION OF THE INVENTION

The present inventor has discovered that an anti-malarial agent administered in a local or targeted fashion in a sustained release formulation, directly to the diseased organ or area of inflammation of a patient, is much more effective than when administered orally in a non-directed fashion, with the result that the drug has therapeutic utility at surprisingly low doses and with surprising rapidity in the targeted tissues or organs, while at the same time minimizing the risk of undesirable side-effects. Accordingly, the present inventor has

discovered that an anti-malarial agent administered in a local or targeted fashion, directly to the diseased organ or area of inflammation of a mammal, e.g., patient, is much more effective and efficacious than when administered in a conventional oral dosage with the result that the agent reaches a therapeutic level with surprising rapidity, in the targeted tissue organ, while the undesirable side effects are minimized.

The present invention is illustrated by comparing the effects of targeted delivery as opposed to systemic delivery of a representative anti-malarial compound, HCQ, for treatment of EG. As seen in fig. 1, IL-5 or PAF induced eosinophil superoxide is inhibited by HCQ but only at concentrations of at least 0.5 mM, or about 200 mcg/ml. Furthermore, as seen in fig 2, HCQ actively shortens eosinophil survival, to a much greater extent than a comparative dose of dexamethasone, a corticosteroid. These effects are nearly immediate and require only 1 hour pre-incubation.

On the other hand, oral or systemic administration of HCQ cannot provide adequate plasma levels of HCQ to achieve these effects. Even at doses nearly twice that used in humans, peak serum concentrations following intravenous administration of 10 mg/kg HCQ in rats was only 2 mcg/ml. See Figure 3; in dogs, peak whole blood concentrations were less than 3 mcg/ml. See Figure 4. These concentrations are approximately 1/100 of those required.

In contrast, targeted treatment of a section of the intestine with HCQ can easily reach therapeutic

concentrations. For example, a 100 mg dose (25% of the conventional dose) delivered to the small bowel at a capacity is estimated generously at 500 ml, provides a drug lumen concentration in the desired range.

5 As shown in the literature, neutrophil and macrophage superoxide release as well as macrophage release of potent chemokines such as TNF-alpha, IL-6, Interferon-gamma and T cell activation are also inhibited by HCQ at concentrations in this same range that were obtained by a
10 targeted method of the present invention, see (NP Hurst Biochem Pharm 1986; 35: 3083-89; NP Hurst Annals Rheum Dis 1987; 46: 750-56, BEEM van den Borne J Rheumatol 1997; 24: 55-60; F Goldman Blood 2000; 95: 3460-66; Sperber K et al., "Selective regulation of cytokine secretion by
15 hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1 alpha) and IL-6 in human monocytes and T cells", J Rheumatol 1993; 20: 803-08). Furthermore, at achievable concentrations of .5 to 25 mcg (1 micro-M to 50 microM) epithelial cell production of pro-inflammatory cytokines
20 such as IP-10 and RANTES is also inhibited (Tables 1, 2, Figure 2, 3). In summary, targeted delivery of HCQ can provide a high and therapeutic luminal drug concentration which cannot be matched by oral or parenteral drug administration.

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Table 1: Effect of HCQ on IP-10/RANTES Production in Primary Human Epithelial Cells in pg/ml with exposure to HRV-16

Experiment	IP-10: hrs of preincubation		Experiment	RANTES: hrs of preincubation	
	24	48		24	48
Control	31	31	Control	86	104
HRV-16	1075	1400	HRV-16	425	854
HRV-16 + 50 microM HCQ	31	112	HRV-16 + HCQ	ND	509

5

Table 2: Effect of varying concentrations of HCQ preincubation on BEAS-2B epithelial cells in pg/ml exposed to HRV-16 and assayed for IP-10 and RANTES

	IP-10: 6 hrs preincubation	IP-10: 24 hrs preincubation	RANTES: 6 hrs preincubation
Control	31	31	0
HRV-16	3123	2478	3388
HRV-16 + 0.01 μ M HCQ	3084	2506	3326
HRV-16 + 0.1 μ M HCQ	2914	1814	3128
HRV-16 + 1 μ M HCQ	3045	2098	1994
HRV-16 + 50 μ M HCQ	31	31	0

10

Accordingly, the present inventor has discovered that an anti-malarial agent administered in a local or targeted fashion, directly to the diseased organ or area of inflammation of a mammal, e.g., patient, is much more effective and efficacious than when administered orally with the result that the agent reaches a therapeutic level with surprising rapidity, in the targeted tissue or organ,

15

while undesirable side effects are minimized. By anti-malarial, as used herein, it is meant that the drug has been historically belonged to the class of drugs known as anti-malarials. Preferred anti-malarials include
5 quinolines, especially 8 and 4 aminoquinolines, acridines, e.g., 9-amino acridines and quinoline methanols, e.g., 4-quinolinemethanols.

By mammal, it is meant a member of the class mammalia of higher vertebrate that have mammary glands and
10 the females thereof have the ability to nourish their young with milk secreted by mammary glands. Examples of mammals includes cat, dog, horse, monkey, sheep, goat, cow, human and the like. The preferred mammal is human. As used herein, the term patient is synonymous with mammal. The
15 preferred patient is human.

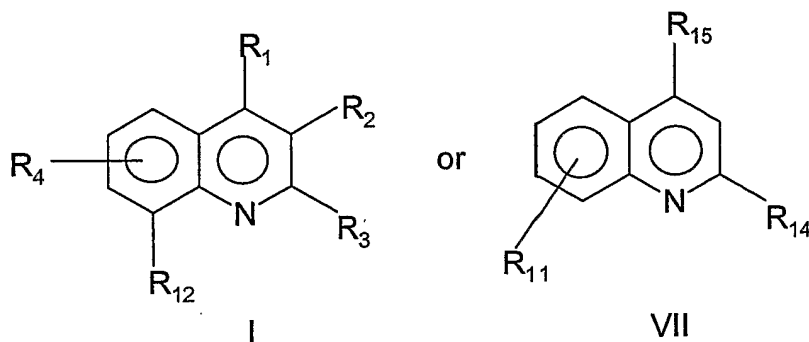
Compounds suitable for the present invention are anti-malarial agents that have immunomodulatory and anti-inflammatory effects. Anti-malarial agents are well known in the art. Examples of anti-malarial agents can be found,
20 for example, in GOODMAN AND GILMAN'S: THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, chapters 45-47, pages 1029-65 (MacMillan Publishing Co. 1985), hereby incorporated by reference.

The preferred anti-malarial compounds are
25 quinolines and more preferably aminoquinolines, especially 4- and 8-amino quinolines. An especially preferred class of antimalarials has a core quinoline structure (examples are mefloquine and quinine) which is usually substituted at one or more positions, typically at least at the 4- and/or
30 8-positions. One skilled in the art would understand that

such agents could be administered in derivatized forms, such as pharmaceutically acceptable salts, or in a form that improves their pharmacodynamic profiles, such as esterification of acid or alcohol substituents with lower alkyls (e.g., C₁₋₆) or lower alkanoyloxy

$$\begin{array}{c} \text{O} \\ || \\ (\text{OC}-\text{R}_{20}), \end{array}$$
 respectively, wherein R₂₀ is lower alkyl. Another class of antimalarials, exemplified by quinacrine, is based on an acridine ring structure, and may be substituted in the manner described above.

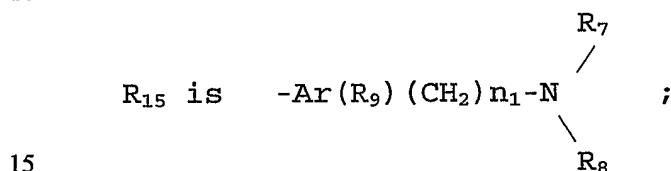
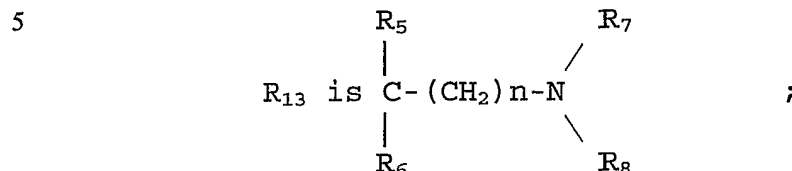
Especially preferred compounds for use in the present invention are aminoquinolines, including 4-amino and 8-aminoquinolines and their derivatives (collectively, "aminoquinoline derivatives") and aminoacridines, especially 9-amino acridines. The preferred 4- and 8-aminoquinolines and 9-amino acridines are described by the following formula:



or pharmaceutically acceptable salts thereof, wherein

R₂ and R₃ are independently hydrogen, or lower alkyl or R₂ and R₃ taken together with the carbon atoms to which they are attached form an aryl ring, which ring may

be unsubstituted or substituted with an electron withdrawing group or an electron donating group,
one of R_1 and R_{12} is NHR_{13} while the other is hydrogen;



R_4 , R_{10} , R_{11} and R_{14} are independently hydrogen or an electron donating group or electron withdrawing group;

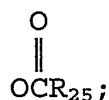
R_5 and R_6 , are independently hydrogen or lower alkyl which may be unsubstituted or substituted with an electron withdrawing or electron donating group;

20

R_7 and R_8 are independently hydrogen or lower alkyl, which may be unsubstituted or substituted with an electron withdrawing or electron donating group;

Ar is aryl having 6-18 ring carbon atoms;

25 R_9 is hydrogen or hydroxy or lower alkoxy or



R_{25} is lower alkyl or hydrogen; and

30 n and n_1 are independently 1-6.

As used herein, the terms "electron donating groups" and "electron withdrawing groups" refer to the

ability of a substituent to donate or withdraw an electron relative to that of hydrogen if the hydrogen atom occupied the same position in the molecule. These terms are well understood by one skilled in the art and are discussed in
5 Advanced Organic Chemistry, by J. March, John Wiley & Sons, New York, NY, pp. 16-18 (1985) and the discussion therein is incorporated herein by reference. Electron withdrawing groups include halo, including bromo, fluoro, chloro, iodo and the like; nitro; carboxy; carbalkoxy; lower alkenyl;
10 lower alkynyl; formyl; carboamido; aryl; quaternary ammonium compounds, and the like. Electron donating groups include such groups as hydroxy; lower alkoxy; including methoxy; ethoxy and the like; lower alkyl, such as methyl; ethyl, and the like; amino; lower alkylamino;
15 diloweralkylamino; aryloxy, such as phenoxy and the like; arylalkoxy, such as benzyl and the like; mercapto, alkylthio, and the like. One skilled in the art will appreciate that the aforesaid substituent may have electron donating or electron withdrawing properties under different
20 chemical conditions. The term lower alkyl, when used alone or in conjunction with other groups, refers to an alkyl group containing one to six carbon atoms. It may be straight-chained or branched. Examples include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-
25 butyl, pentyl, neopentyl, hexyl and the like.

Lower alkoxy refers to an alkyl group which is attached to the main chain by an oxygen bridging atom. Examples include methoxy, ethoxy, and the like.

Lower alkenyl is an alkenyl group containing from 2 to 6 carbon atoms and at least one double bond. These groups may be straight chained or branched and may be in the Z or E form. Such groups include vinyl, propenyl, 1-butenyl, isobutenyl, 2-butenyl, 1-pentenyl, (Z)-2-pentenyl, (E)-2-pentyl, (Z)-4-methyl-2-pentenyl, (E)-4-methyl-2-pentenyl, allyl, pentadienyl, e.g., 1,3 or 2,4-pentadienyl, and the like. It is preferred that the alkenyl group contains at most two carbon-carbon double bonds; and most preferably one carbon-carbon double bond.

The term alkynyl include alkynyls containing 2 to 6 carbon atoms. They may be straight chain as well as branched. It includes such groups as ethynyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 3-methyl-1-pentyne, 3-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, and the like.

The term aryl refers to an aromatic group containing only carbon ring atoms which contains up to 18 ring carbon atoms and up to a total of 25 carbon atoms and includes the polynuclear aromatic rings. These aryl groups may be monocyclic, bicyclic, tricyclic, or polycyclic, and contain fused rings. The group includes phenyl, naphthyl, anthracenyl, phenanthrenyl, xylyl, tolyl and the like.

The aryl lower alkyl groups include, for example, benzyl, phenethyl, phenpropyl, phenisopropyl, phenbutyl, diphenylmethyl, 1,1-diphenylethyl, 1,2-diphenylethyl and the like.

The term halo include fluoro, chloro, bromo, iodo and the like.

The preferred values of R_2 and R_3 are independently hydrogen or alkyl containing 1-3 carbon atoms. It is most preferred that R_3 is hydrogen. It is most preferred that R_2 is hydrogen or alkyl containing 1-3 carbon atoms, especially methyl or ethyl. It is most preferred that R_2 is hydrogen or alkyl containing 1-3 carbon atoms or hydrogen and R_3 is hydrogen.

Alternatively, if R_2 and R_3 are taken together with the carbon atoms to which they are attached, it is most preferred that they form a phenyl ring. The phenyl ring is preferably unsubstituted or substituted with lower alkoxy, hydroxy, lower alkyl or halo.

It is preferred that R_4 is an electron withdrawing group, more specifically, halo, especially chloro, or is hydroxy or lower alkoxy. It is even more preferred that when R_1 is NHR_{13} , R_4 is substituted on the 7-position of the quinoline ring. It is most preferred that when R_1 is NHR_{13} , R_4 is halo.

However, when R_{12} is NHR_{13} , it is preferred that R_4 is an electron donating group, such as hydroxy or alkoxy. More specifically, it is preferred that R_4 is methoxy or ethoxy when R_{12} is NHR_{13} . It is even more preferred that R_4 is on the 6-position of the quinoline ring when R_{12} is NHR_{13} .

It is preferred that one of R_5 and R_6 is hydrogen and the other is lower alkyl. It is even more preferred

that R₅ is hydrogen and R₆ is lower alkyl, especially alkyl containing 1-3 carbon atoms and most preferably methyl.

The preferred value of R₇ is lower alkyl, especially alkyl containing 1-3 carbon atoms and most
5 preferably methyl and ethyl.

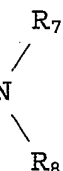
Preferred values of R₈ is lower alkyl containing 1-3 carbon atoms, and most preferably methyl and ethyl. However, it is preferred that the alkyl group is unsubstituted or if substituted, is substituted on the
10 omega (last) carbon in the alkyl substituent. The preferred substituent is lower alkoxy and especially hydroxy.

The preferred R₉ is lower alkoxy and especially hydroxy.

15 R₁₁ is preferably an electron withdrawing group, especially trifluoromethyl. It is preferably located on the 8-position of the quinoline ring.

R_{14} is preferably an electron withdrawing group, and more preferably trifluoromethyl. It is preferably present on the 2-position of the quinoline ring.

5

It is preferred that R_{15} is $\text{Ar}(\text{OH})\text{CH}_2\text{N}$ 

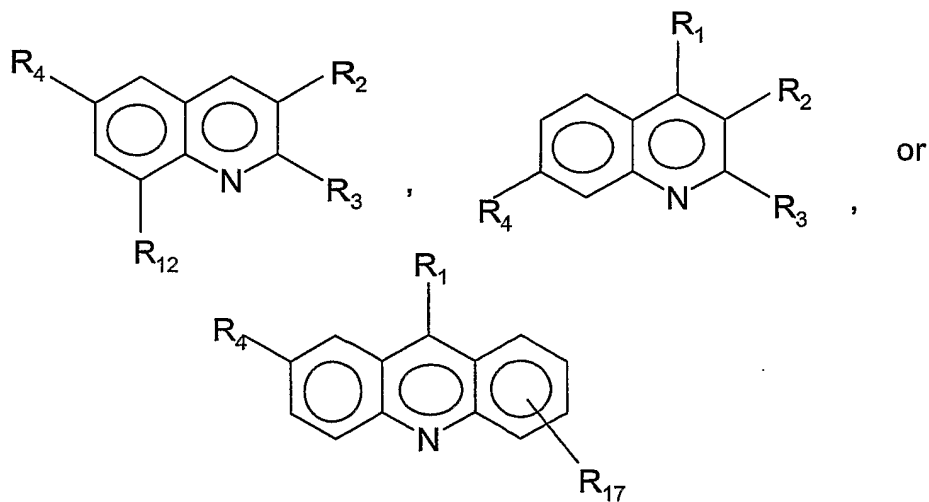
10 wherein R_7 and R_8 are independently alkyl containing 1-3 carbon atoms and Ar is phenyl.

In both R_{13} and R_{15} , it is preferred that R_7 and R_8 contain the same number of carbon atoms, although one may be unsubstituted while the other is substituted. It is also preferred that R_7 and R_8 are the same.

15

The preferred value of n is 3 or 4 while the preferred value of n_1 is 1.

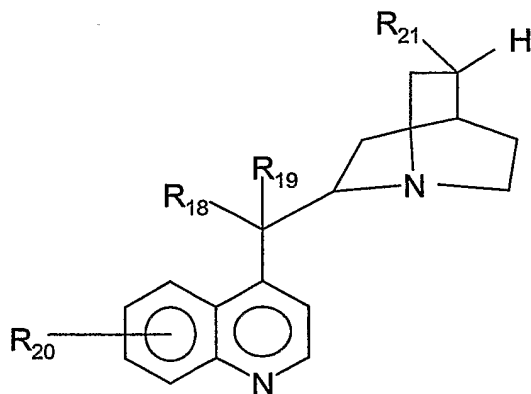
Preferred anti-malarials have the structure:



20 wherein R_{12} , R_4 , R_2 , R_3 and R_1 are as defined hereinabove and R_{17} is hydrogen, halo, lower alkyl, lower alkoxy.

Preferred anti-malarials include the 8-aminoquinolines, 9-aminocridines and the 7-chloro-4-aminoquinolines. Examples include pamaquine, primaquine, pentaquine, isopentaquine, quinacrine salts, 7-chloro-4-aminoquinolines, such as the chloroquines, hydroxychloroquines, sontoquine, amodiaquine and the like.

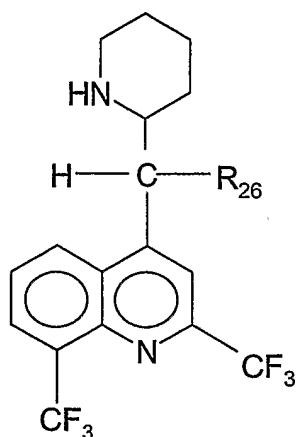
Another class of preferred anti-malarial are cinchono alkaloids and 4-quinoline methanols, such as those having the formula:



wherein one of R₁₈ and R₁₉ is hydroxy or loweralkylcarbonyloxy or hydrogen, and the other is H, and R₂₀ is hydrogen or loweralkoxy and R₂₁ is hydrogen or CH=CH₂.

Examples include rubane, quinine, quinidine, cinchoidine, epiquinine, epiquinidine, cinchonine, and the like.

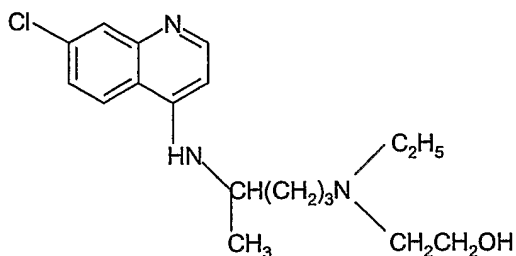
Another preferred anti-malarial methanol is mefloquine or derivative thereof of the formula:



wherein R_{26} is lower alkoxy, $\overset{\text{O}}{\parallel}\text{C}-R_{27}$ or hydroxy and
 5 R_{27} is lower alkyl.

The most preferred anti-malarials include mefloquine, and chloroquine and its congeners, such as hydroxychloroquine (HCQ), amodiaquine, pamaquine and pentaquine and pharmaceutically acceptable salts thereof.

10 The most preferred anti-malarial agent for the invention is hydroxychloroquine, shown below, or a pharmaceutically suitable salt thereof, such as hydroxychloroquine sulfate:

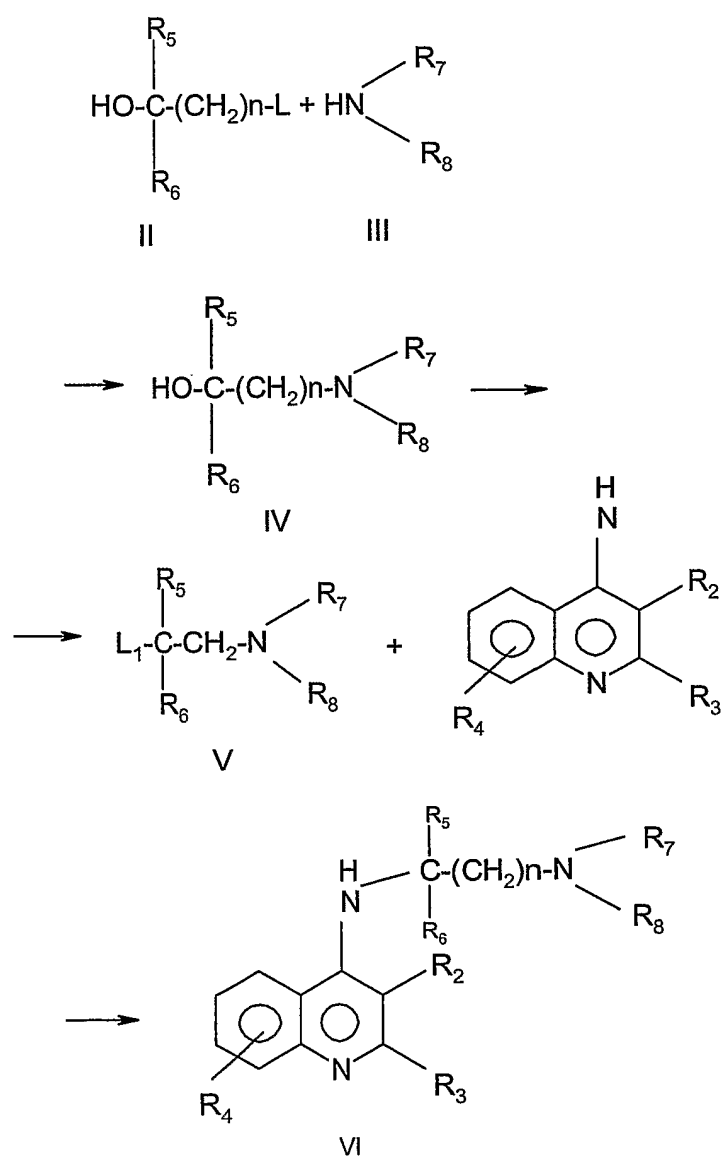


15 hydroxychloroquine

The anti-malarials are commercially available or are prepared by art recognized techniques known in the art.

For example, the 4-aminoquinolines can be prepared as follows:

5

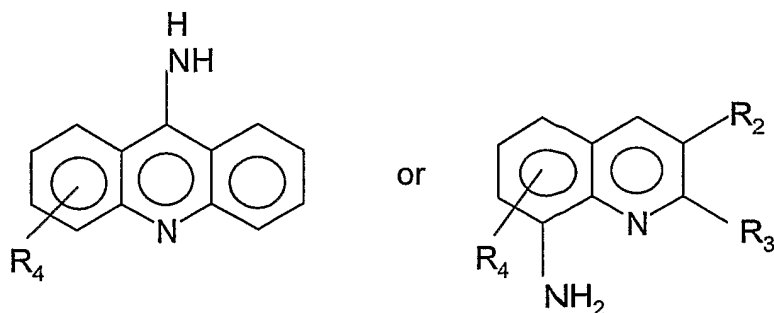


In the above scheme, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , and n are as defined hereinabove, and L and L_1 are good leaving groups, such as halides or sulfonates, e.g., mesylates or aryl sulfonates, e.g., tosylates, brosylates, and the like.

5 The compound of Formula II containing a leaving group, L , is reacted with the amine of Formula III under amine alkylation conditions. The alcohol group in the product of Formula IV (OH group) is converted to a leaving group by reactions known in the art. For example, sulfonic
10 esters, such as tosylates, mesylates or brosylates are prepared by treatment of sulfonic halides of the formula $R_{23}SO_2X_1$ wherein X_1 is halide and R_{23} is lower alkyl, such as methyl, aryl or substituted aryl, such as p-bromophenyl, p-tolyl with the alcohol of Compound IV. The reaction is
15 usually effected in the presence of a weak base, such as pyridine. Alternatively, the alcohol can be converted to the corresponding halide by reaction of the alcohol of IV with HCl, HBr, thienyl chloride, PCl_3 , PCl_5 or $POCl_3$. The product of V is then reacted under amine alkylation
20 conditions with the quinoline amine to provide the 4-amino quinoline product.

 The 9-aminoacridines and the 8-aminoquinoline are prepared similarly. More specifically, the product of V is reacted with

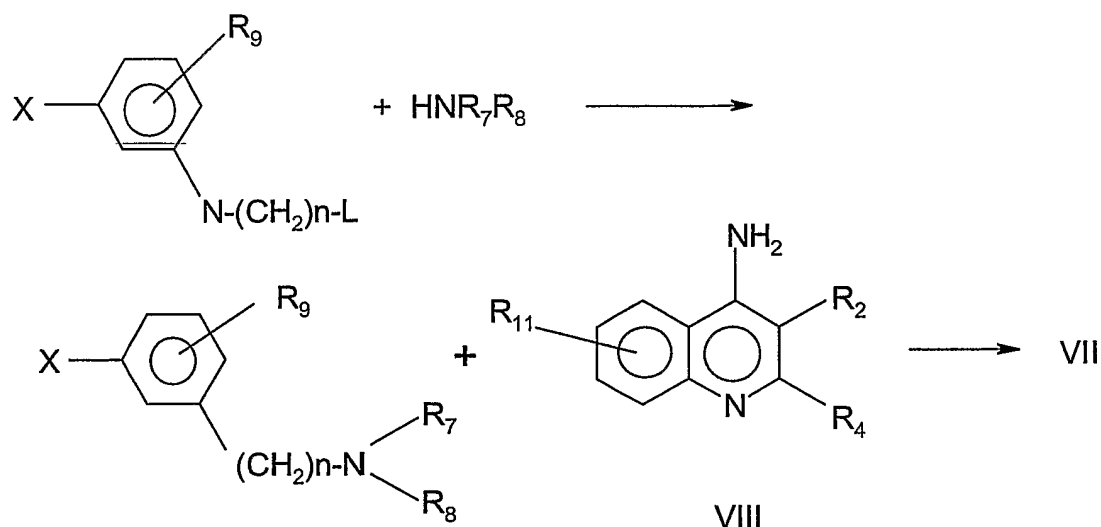
25



under amine alkylation reaction conditions.

The reactions described hereinabove are preferably conducted in solvents which are inert to the reactants and products and in which the reactants, are
5 soluble, such as tetrahydrofuran, ethers, acetones, and the like. It is preferred that the solvents are volatile. The reactions are conducted at effective reaction conditions and are conducted at temperatures ranging from room
10 temperature up to and including the reflux temperatures of the solvent.

An exemplary procedure for the preparation of compounds of Formula VII is as follows:



The first reaction is a simple amino alkylation reaction as described hereinabove. The product thereof is
 5 reacted with the amine of Formula III in the presence of a strong base such as amide to form the product of Formula VII.

Many of the compounds described hereinabove, especially the 4-quinoline methanols, can be converted to
 10 ethers by reacting the salt of the alcohols with an alkyl halide or arylalkyl halide or aryl halide to form the corresponding ether. Moreover, the esters can be formed from the hydroxy group by reacting the alcohol, such as the 4-quinoline methanol, with an alkanoic acid, arylalkonic
 15 acid or aryloic acid or acylating derivatives thereof in the presence of acid, for example, HCl, H₂SO₄ or p-toluene sulfonic acid under esterification conditions.

If any of the groups on R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ are reactive with any of the reagents used or with any

of the reactants or products, then they would be protected by protecting groups known in the art to avoid unwanted side reactions. This protecting groups normally used in synthetic organic chemistry are well known in the art.

5 Examples are found in PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, by T.W. Greene, John Wiley & Sons, Inc., NY 1981 ("Greene"), the contents of which are incorporated by reference.

10 THERAPEUTICAL COMPOSITIONS OF THE INVENTION

A therapeutic composition within the present invention is formulated for controlled directed enteric delivery and includes at least one anti-malarial agent, as described above. As previously emphasized, the present
15 invention contemplates topical administration of the anti-malarial compounds to the intra-luminal bowel wall where they may be absorbed with direct local therapeutic effect. "Directed enteric delivery" and "topical administration" are used in this description to denote direct delivery to the
20 affected tissues or areas of diseased bowel. Controlled and "Targeted delivery" when used together denotes the formulation of drug with excipient and/or carrier in such a way as to facilitate drug delivery to a specific organ of the gastrointestinal tract or e.g., colon, small bowel, and
25 the like or portion thereof. "Sustained release" or synonym thereto connotes the release of the drug over a prolonged period of time. "Controlled delivery" denotes formulation of drug with carrier in such a way as to block

absorption of drug in the proximal small bowel and facilitate drug delivery to inflamed areas of the more distal small bowel and/or colon. Carrier formulations which use controlled release technologies designed to delay
5 drug release dependent on pH, transit time, or amount of hydration, or on the absence or presence of other physicochemical variables including biochemical markers of active inflammatory processes are included in this definition.

10 The anti-malarial compounds used in the present invention are administered in anti-inflammatory amounts. The anti-malarial compounds used in the present invention are administered in an amount which depends upon the condition of the subject, the type of inflammatory
15 condition of which the subject suffers, the timing of the administration of the subject, the route of administration, the particular formulation and the like. However, unlike oral dosing, which takes three to six months for therapeutic effects, controlled directed enteric therapy
20 will provide observable onset of action within two weeks. Significantly less amount of the active therapeutic moiety is needed to achieve these more rapidly achieved therapeutic benefits. It is preferred that the drug be administered at a total dose of about 2 to about 40 mg/day
25 in one or more divided doses (0.05-10% conventional dosing).

While it is possible for the anti-malarial compound to be administered alone, it is preferable to

present in a pharmaceutical formulation. The formulations used in the present invention comprise at least one anti-malarial compound according to the present invention together with one or more acceptable carriers thereof and optionally other therapeutic agents. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules. Oral formulations may further include other agents conventional in the art, such as sweeteners, flavoring agents and thickeners.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the anti-malarials in a free-flowing form

such as a powder or granules, optionally incorporating a binder (e.g., povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compounds moistened with an inert liquid diluent.

The oral formulations are prepared so as to provide a targeted and controlled release of the anti-malarials in the colon and rectum with minimal or no release in the stomach. Preferably, the anti-malarial is associated in a slow release formulation, such as e.g., tablet, so as to provide delayed or controlled release of the anti-malarials in the region having a pH relatively near the neutral range, with the additional property that it would transit into the more distal colon or small bowel.

For example, the drug is formulated with a delayed drug release dependent on transit time, amount of hydration or the presence or absence of other physiochemical variables including biochemical markers of active inflammatory processes.

The pharmaceutical compositions of the present invention comprise one or more excipients and/or carriers known in the pharmaceutical arts which delay the release of the anti-malarial drug at the desired target in the gastrointestinal tract. The identity of the specific excipient or carrier is dependent upon several factors

including the disease or condition of the patient being treated, the specific area in the gastrointestinal tract where the drug is targeted, to name just a few. The specific excipient or carrier to be used for the purpose of
5 delaying the release at a specific targeted site is well within the knowledge of the skilled artisan.

In addition, the release of the anti-malarial compound may be immediate, i.e., the release may be delayed until the drug reaches the targeted site, but than the
10 release is immediate. On the other hand, the present invention contemplates sustained release formulation, wherein the pharmaceutical composition, besides comprising the anti-malarial compound, and carrier or excipient targeted for a specific site in the body, may also contain
15 a sustained release carrier or excipient, e.g., sustained release polymer, to prolong the release thereof over a period of time. The pharmaceutical composition may comprise one or more sustained or controlled release excipients or carriers, such that a slow or sustained
20 release of the anti-malarial compound is achieved. A wide variety of suitable excipients are known in the art. Such sustained/controlled release excipients, and systems are described for example, in U.S. Patent Nos. 5,612,053, 5,554,387, 5,512,297, 5,478,574 and 5,472,271, the contents
25 of each of which is incorporated by reference. The anti-malarial compound of the present invention may be administered to a patient suffering from BD in the drug delivery device described in U.S. Patent No. 4,904,474 to

Theeves, the contents of which are incorporated by reference.

The anti-malarial compounds disclosed in the present application may be associated with a drug delivery system commercially marketed as OROS®, by ALZA corporation, for example, OROS®; Push-Pull™ System, or OROS® multi-layer, push Pull System, or OROS®, Push Stick System. Alternatively, the anti-malarial described herein may be associated with a sustained release formulation marketed as GEOMATRIX® which contains a combination of layers, each with different rates of swelling, gelling and erosion.

For instance, the anti-malarial compounds may be associated with a male piece and a female piece, with the pieces fitting together to enclose the anti-malarial therein, wherein the male piece is comprised of a material that gels in the intestinal juice, such as ethyl-acrylate-methyl methacrylate-trimethyl-ammonioethyl methacrylate chloride copolymer and a methacrylic acid-ethyl acrylate copolymer, while the female piece is made from a water insoluble polymer, as described in U.S. Patent No. 6,303,144 to Omura, the contents of which are incorporated by reference.

Other Drug delivery technologies include a coated bead system using MODAS: multiporous oral drug absorption system.

MODAS is a single unit, immediate release tablet formulation surrounded by a non-disintegrating, timed

release coating. Within the gastro-intestinal tract this coating is transformed into a semi-permeable membrane through which drug diffuses in a rate-limiting manner. The diffusion process essentially dictates the rate of presentation of drug to the gastrointestinal fluids so that uptake into the body is controlled. Each MODAS tablet initially begins as a core containing active drug plus excipients. This is then coated with a solution of insoluble polymers and soluble excipients. Once the tablet is ingested the fluid of the gastrointestinal tract dissolves the soluble excipients in the outer coating leaving just the insoluble polymer. What results is a network of tiny, narrow channels connecting fluid from the GI tract to the inner drug core of water soluble drug. This fluid passes through these channels, into the core, dissolves the drug and a resultant solution of drug diffuses out in a controlled manner to the outside. This allows for controlled dissolution and absorption. The fact that the drug releasing pores in the tablet are distributed over the entire surface of the tablet facilitates uniform drug absorption and ensures that aggressive unidirectional drug delivery with its attendant hazards cannot occur.

MODAS represents a very flexible dosage form in that both the inner core and the outer semi-permeable membrane can be altered to suit the individual drug delivery requirements of a drug. In particular, the addition of excipients to the inner core such as buffers, etc., can help produce a micro-environment within the tablet that facilitates more predictable release rates and

absorption.

The benefits of MODAS include:

- (1) Ability to reduce the dosage frequency of
5 highly water soluble drugs
- (2) Smooth plasma profiles devoid of
exaggerated peak to trough ratios
- (3) Small size dosage forms due to minimal use
of excipients.

10 Another drug delivery technology includes:
PRODAS -- Programmable Oral Drug Absorption System, based
on the encapsulation of controlled release minitablets in
the size range 1.5 to 4mm in diameter. This consists of a
hybrid of Multiparticulate and hydrophilic matrix tablet
15 technologies and incorporates into one dosage form the
benefits of both these drug delivery systems. The value of
lies in the inherent flexibility of the formulation whereby
combinations of minitablets, each with different release
rates, are incorporated into a single dosage form.

20 These combinations may include immediate release,
delayed release and/or controlled release minitablets. For
each individual compound therefore, the technology enables
the construction of a customized release profile based on
the use of different populations of mini- tablets each with
25 different release rates.

 As well as allowing for controlled absorption
over a specified period, PRODAS also
enables targeted delivery of drug to specified sites of
absorption throughout the gastrointestinal tract.
30 Combination products are also possible by using minitablets

formulated with different active ingredients.

Another drug delivery technology includes SODAS - Spheroidal Oral Drug Absorption System, another multi-particulate drug delivery technology platform on which the company was initially founded.

Based on the production of controlled release beads, it is characterized by its inherent flexibility, enabling the production of dosage forms with customized release rates that respond directly to individual drug candidate needs.

The controlled release beads produced by the SODAS technology range from 1 to 2mm in diameter. Each begins as a non-pareil core on to which a solution of active ingredient is applied. A series of subsequent coatings with timing solutions (containing both soluble and insoluble polymers) and other excipients combine to produce the outer rate controlling membrane that ultimately controls release of drug from the beads. Once produced, the controlled release beads can be packaged into a capsule or compressed into a tablet to produce the final dosage form.

Drug release from SODAS beads is by a diffusion process. Within the GI tract the soluble polymers dissolve leaving pores within the outer membrane. Fluid then enters the core of the beads and dissolves the drug. The resultant solution then diffuses out in a controlled, pre-determined manner allowing for prolongation of the in-vivo dissolution and absorption phases. As each candidate drug presents itself with different physicochemical properties the composition of the semi-permeable membrane will differ

for each individual SODAS formulation.

In addition, the immediate environment of the drug within the seed core can be manipulated through use of excipients to ensure optimal stability and solubility.

5 The unique nature of the SODAS technology gives rise to a number of attributes that directly benefit individual drugs:

(1) Controlled absorption with resultant reduction in peak
10 to trough ratios

(2) Targeted release of the drug to specific areas within the gastrointestinal tract

15 (3) Absorption irrespective of the feeding state

(4) Minimal potential for dose dumping

Another drug delivery technology is based on an
20 agglomerated hydrophilic matrix. The matrix consists of two pharmaceutically accepted polysaccharides, locust bean gum and xanthan gum. Interactions between these components in an aqueous environment form a tight gel with slowly eroding core. This system controls the rate
25 of water ingress into the matrix and the subsequent diffusion and release of the drug from the dosage form.

A further example is Microtrol™, a proven family of multiparticulate delivery technologies which improve solubility and deliver a variety of modified release
30 profiles. Microtrol is based on the use of beadlets that

can be filled into capsules or compressed into tablets. The beadlets can be coated (with an array of controlled release polymers) or uncoated. Different combinations of beadlets can be used to achieve customized release profiles.

5 These include: extended delivery Mictrol XR; pulsed delivery Microtrol PR; and delayed delivery.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and
10 absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated.

15 More than one anti-malarial compound can also be incorporated into the pharmaceutical compositions.

It is especially advantageous to formulate compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein
20 refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of anti-malarial compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical
25 carrier.

The above preferred embodiments are given to illustrate the scope and spirit of the present invention. The embodiments described herein will make apparent to those skilled in the art other embodiments. These other
30 embodiments are within the contemplation of the present

invention. Therefore, the present invention should be limited only by the appended claims.

WHAT IS CLAIMED IS:

1. A method for treating inflammatory bowel disease in a patient comprising administering to said patient a sustained release pharmaceutical composition comprising a pharmaceutically effective amount of an anti-malarial compound in association with a pharmaceutically acceptable excipient which delays and targets the release of said anti-malarial compound in the gastrointestinal tract of the patient.

2. The method according to Claim 1 wherein the inflammatory bowel disease is Crohn's disease.

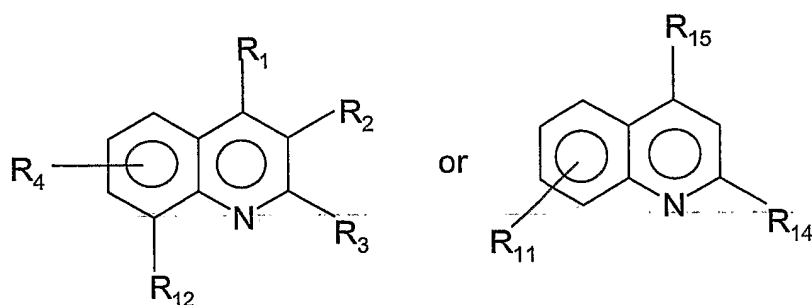
3. The method according to Claim 1 wherein the inflammatory bowel disease is ulcerates colitis.

4. The method according to Claim 1 wherein the inflammatory bowel disease is indeterminate colitis.

5. The method according to Claim 1 wherein the inflammatory bowel disease is infectious colitis.

6. The method according to Claim 1 wherein the anti-malarial compound is aminoquinoline or hydroxyquinoline.

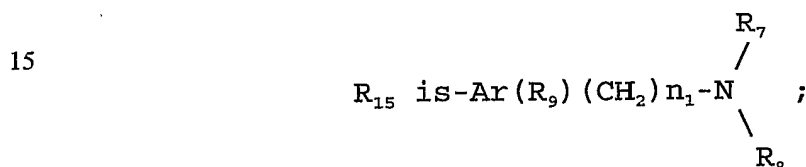
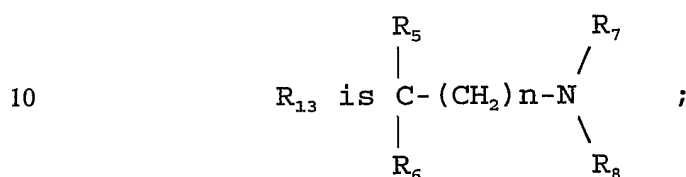
7. The method according to Claim 6 wherein said aminoquinoline has the formula:



or pharmaceutically acceptable salts thereof,

wherein

R_2 and R_3 are independently hydrogen, or lower alkyl or R_2 and R_3 taken together with the carbon atoms to which they are attached form an aryl ring, which aryl ring is unsubstituted or substituted with an electron withdrawing group or an electron donating group,
 5 one of R_1 and R_{12} is NHR_{13} while the other is hydrogen;



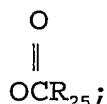
R_4 , R_{10} , R_{11} and R_{14} are independently hydrogen or
 20 an electron donating group or electron withdrawing group;

R_5 and R_6 , are independently hydrogen or lower alkyl which may be unsubstituted or substituted with an electron withdrawing or electron donating group;

R_7 and R_8 are independently hydrogen or lower
 25 alkyl, which may be unsubstituted or substituted with an electron withdrawing or electron donating group;

Ar is aryl having 6-18 ring carbon atoms which may be unsubstituted or substituted with an electron donating or electron withdrawing group;

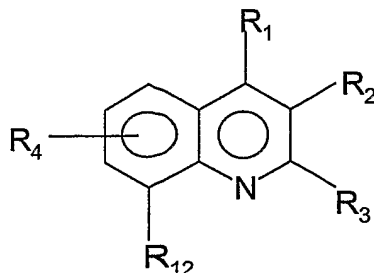
30 R_9 is hydrogen or hydroxy or lower alkoxy or



R_{25} is lower alkyl or hydrogen; and

n and n_1 are independently 1-6.

8. The method according to Claim 7 wherein the aminoquinoline is of the formula:



5 9. The method according to Claim 8 wherein R_1 is NHR_{13} and R_{12} is hydrogen.

10 10. The method according to Claim 9 wherein R_5 is hydrogen and R_6 is lower alkyl.

11. The method according to Claim 9 wherein R_5 is hydrogen and R_6 is methyl.

12. The method according to Claim 9 wherein n is 3.

13. The method according to Claim 9 wherein R_3 is hydrogen.

15 14. The method according to Claim 9 wherein R_4 is substituted in the 7-position of the quinoline ring.

15. The method according to Claim 11 wherein R_4 is 7-halo.

16. The method according to Claim 15 wherein halo is chloro.

17. The method according to Claim 9 wherein R_7 is ethyl and R_8 is ethyl or 2-hydroxy ethyl.

18. The method according to Claim 8 wherein R_{12} is NHR_{13} and R_1 is hydrogen.

25 19. The method according to Claim 18 wherein R_5

is hydrogen and R_6 is lower alkyl.

20. The method according to Claim 19 wherein R_5 is hydrogen and R_6 is methyl.

21. The method according to Claim 18 wherein n
5 is 3.

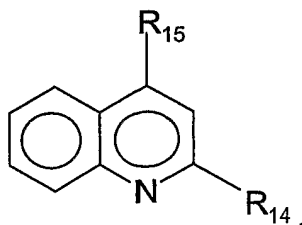
22. The method according to Claim 19 wherein R_7 is hydrogen, methyl or ethyl and R_8 is hydrogen, methyl, ethyl, propyl or isopropyl.

23. The method according to Claim 18 wherein R_4
10 is substituted on the 6-position of the quinoline ring.

24. The method according to Claim 23 wherein R_4 is 6-lower alkoxy.

25. The method according to Claim 24 wherein R_4 is 6-methoxy.

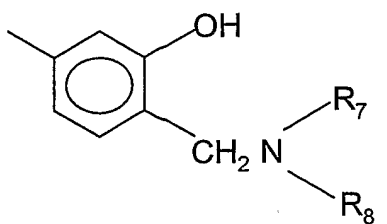
15 26. The method according to Claim 7 wherein the amino quinoline has the formula:



27. The method according to Claim 26 wherein Ar
20 is phenyl.

28. The method according to Claim 26 wherein R_9 is hydroxy.

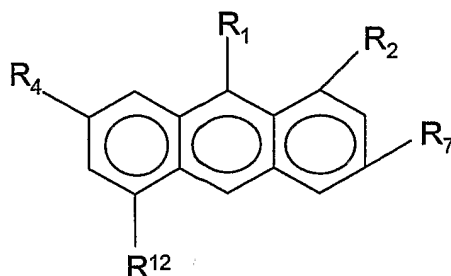
29. The method according to Claim 26 wherein
 R_{15} is



30. The method according to Claim 26 wherein R_7 and R_8 are independently lower alkyl.

31. The method according to Claim 30 wherein R_7 and R_8 are both ethyl

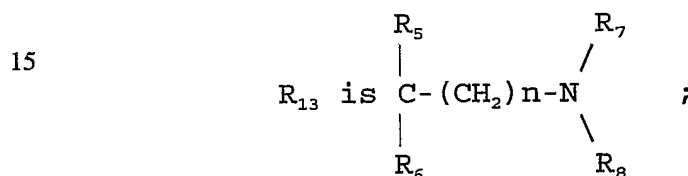
32. The method according to Claim 1 wherein the anti-malarial compound has the formula:



wherein

R_2 is hydrogen or lower alkyl;

one of R_1 and R_{12} is NHR_{13} while the other is hydrogen;



20 R_4 is hydrogen or an electron donating group or electron withdrawing group;

R_5 and R_6 , are independently hydrogen or lower alkyl which may be unsubstituted or substituted with an

electron withdrawing or electron donating group;

R_7 and R_8 are independently hydrogen or lower alkyl, which may be unsubstituted or substituted with an electron withdrawing or electron donating group; and

5 n is independently 1-6.

33. The method according to Claim 1 wherein the anti-malarial agent is pomaquine, primaquine, pentaquinine, isopentaquine, quinacrine salt, chloroquine, hydroxychloroquine, sontoquine, amodiaquine, mefloquine, or
10 mepacrine or pharmaceutically acceptable salts thereof.

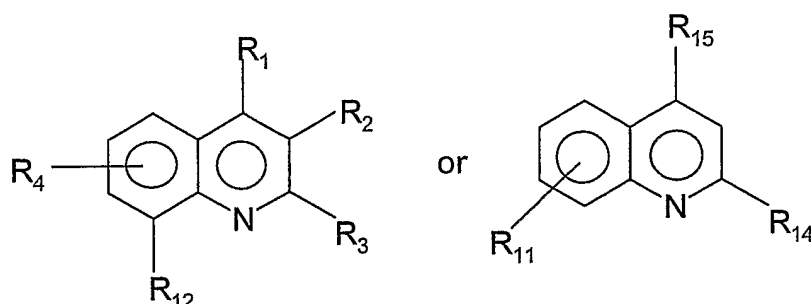
34. The method according to Claim 1 wherein the anti-malarial compound is hydroxychloroquine, chloroquine, mepacrine, mefloquinine, or pharmaceutically acceptable salts thereof.

15 35. The method according to Claim 1 wherein the anti-malarial compound is hydroxychloroquine or a pharmaceutically acceptable salt thereof.

36. A pharmaceutical composition comprising a pharmaceutically effective amount of an anti-malarial
20 compound in association with a pharmaceutically acceptable excipient which delays and targets the release of said anti-malarial compound in the gastrointestinal tract.

37. The pharmaceutical composition according to Claim 36 wherein the anti-malarial compound is
25 aminoquinoline or hydroxyquinoline.

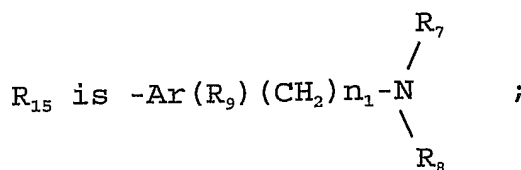
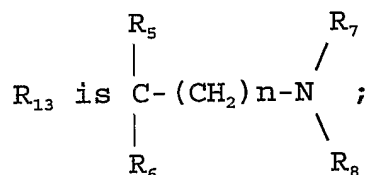
38. The pharmaceutical composition according to Claim 37 wherein said aminoquinoline has the formula:



or pharmaceutically acceptable salts thereof,
wherein

R_2 and R_3 are independently hydrogen, or lower
alkyl or R_2 and R_3 taken together with the carbon atoms to
which they are attached form an aryl ring, which aryl ring
is unsubstituted or substituted with an electron
withdrawing group or an electron donating group,

one of R_1 and R_{12} is NHR_{13} while the other is
hydrogen;



R_4 , R_{10} , R_{11} and R_{14} are independently hydrogen or
an electron donating group or electron withdrawing group;

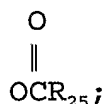
R_5 and R_6 , are independently hydrogen or lower
alkyl which may be unsubstituted or substituted with an
electron withdrawing or electron donating group;

R_7 and R_8 are independently hydrogen or lower
alkyl, which may be unsubstituted or substituted with an

electron withdrawing or electron donating group;

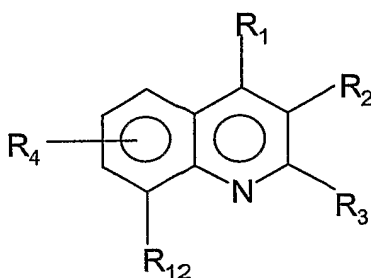
Ar is aryl having 6-18 ring carbon atoms which may be unsubstituted or substituted with an electron donating or electron withdrawing group;

5 R_9 is hydrogen or hydroxy or lower alkoxy or



10 R_{25} is lower alkyl or hydrogen; and
n and n_1 are independently 1-6.

39. The pharmaceutical composition according to Claim 38 wherein the aminoquinoline is of the formula:



15 40. The method according to Claim 39 wherein R_1 is NHR_{13} and R_{12} is hydrogen.

41. The method according to Claim 40 wherein R_5 is hydrogen and R_6 is lower alkyl.

42. The method according to Claim 40 wherein R_5 is hydrogen and R_6 is methyl.

20 43. The method according to Claim 40 wherein n is 3.

44. The method according to Claim 40 wherein R_3 is hydrogen.

25 45. The method according to Claim 40 wherein R_4 is substituted in the 7-position of the quinoline ring.

46. The method according to Claim 40 wherein R_4

is 7-halo.

47. The pharmaceutical composition according to Claim 46 wherein halo is chloro.

48. The pharmaceutical composition according to
5 Claim 40 wherein R_7 is ethyl and R_8 is ethyl or 2-hydroxy ethyl.

49. The pharmaceutical composition according to Claim 39 wherein R_{12} is NHR_{13} and R_1 is hydrogen.

50. The pharmaceutical composition according to
10 Claim 49 wherein R_5 is hydrogen and R_6 is lower alkyl.

51. The pharmaceutical composition according to Claim 50 wherein R_5 is hydrogen and R_6 is methyl.

52. The pharmaceutical composition according to Claim 49 wherein n is 3.

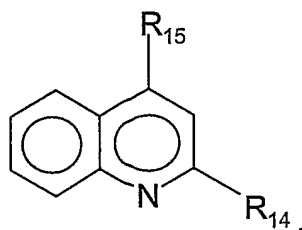
53. The pharmaceutical composition according to
15 Claim 50 wherein R_7 is hydrogen, methyl or ethyl and R_8 is hydrogen, methyl, ethyl, propyl or isopropyl.

54. The pharmaceutical composition according to Claim 49 wherein R_4 is substituted on the 6-position of the
20 quinoline ring.

55. The pharmaceutical composition according to Claim 54 wherein R_4 is 6-lower alkoxy.

56. The pharmaceutical composition according to Claim 55 wherein R_4 is 6-methoxy.

57. The pharmaceutical composition according to
25 Claim 38 wherein the amino quinoline has the formula:

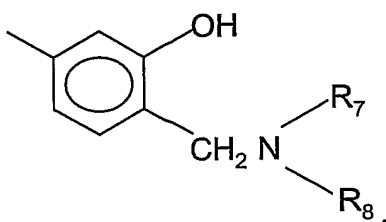


58. The pharmaceutical composition according to Claim 57 wherein Ar is phenyl.

59. The pharmaceutical composition according to Claim 57 wherein R₉ is hydroxy.

60. The pharmaceutical composition according to Claim 57 wherein

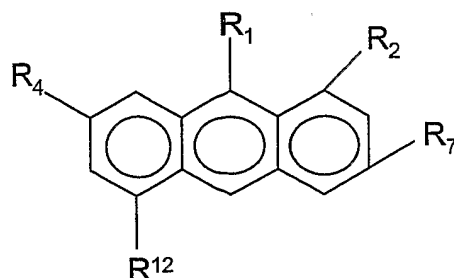
R₁₅ is



61. The pharmaceutical composition according to Claim 57 wherein R₇ and R₈ are independently lower alkyl.

62. The pharmaceutical composition according to Claim 61 wherein R₇ and R₈ are both ethyl

63. The pharmaceutical composition according to Claim 36 wherein the anti-malarial compound has the formula:

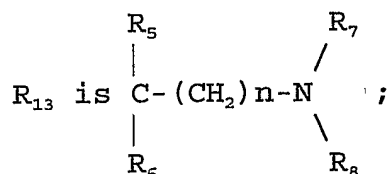


wherein

R_2 is hydrogen or lower alkyl;

one of R_1 and R_{12} is NHR_{13} , while the other is

5 hydrogen;



10

R_4 is hydrogen or an electron donating group or electron withdrawing group;

15 R_5 and R_6 , are independently hydrogen or lower alkyl which may be unsubstituted or substituted with an electron withdrawing or electron donating group;

R_7 and R_8 are independently hydrogen or lower alkyl, which may be unsubstituted or substituted with an electron withdrawing or electron donating group; and

20 n is independently 1-6.

64. The pharmaceutical composition according to Claim 36 wherein the anti-malarial agent is pomaquine, primaquine, pentaquinine, isopentaquine, quinacrine salt, chloroquine, hydroxychloroquine, sontoquine, amodiaquine, 25 mefloquine, or mepacrine or pharmaceutically acceptable salts thereof.

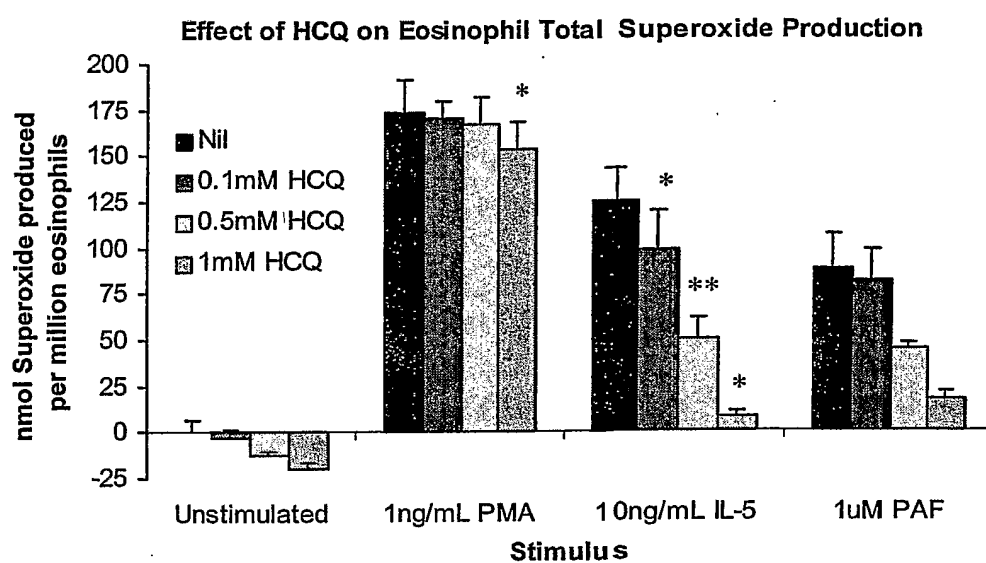
65. The pharmaceutical composition according to

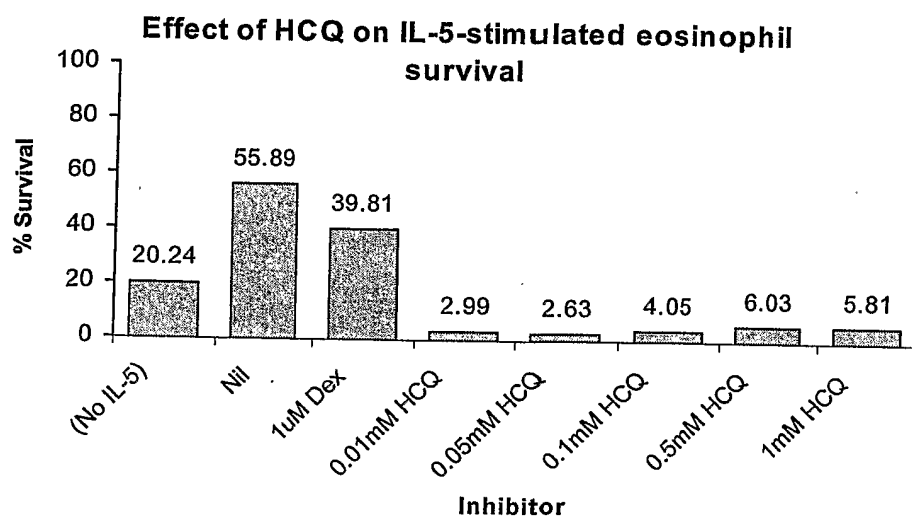
Claim 36 wherein the anti-malarial compound is hydroxychloroquine, chloroquine, mepacrine, mefloquine, or pharmaceutically acceptable salts thereof.

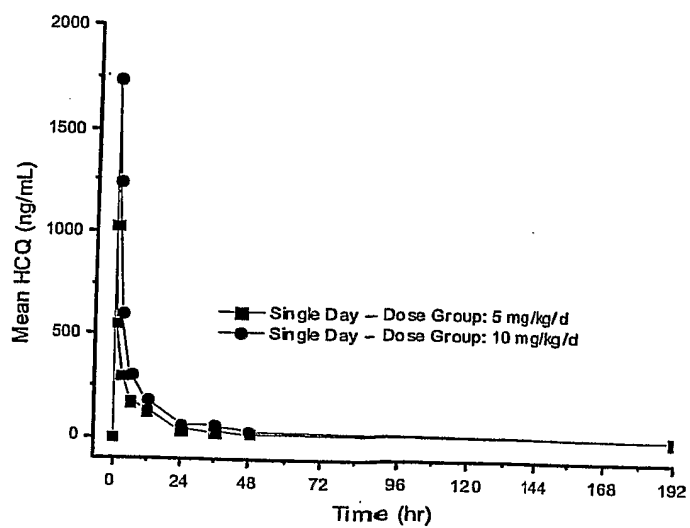
66. The pharmaceutical composition according to
5 Claim 36 wherein the anti-malarial compound is hydroxychloroquine or a pharmaceutically acceptable salt thereof.

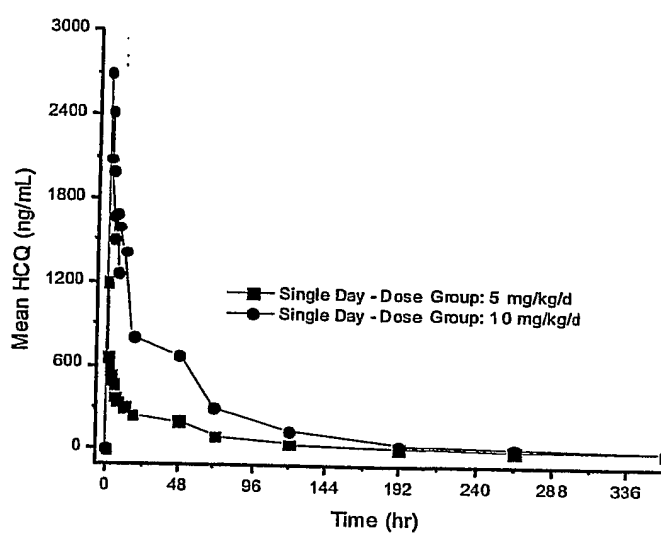
67. The method according to Claim 1 wherein the inflammatory bowel disease is eosinophilic gastroenteritis.

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**FIGURE 1**

**FIGURE 2**

**FIGURE 3**

**FIGURE 4**

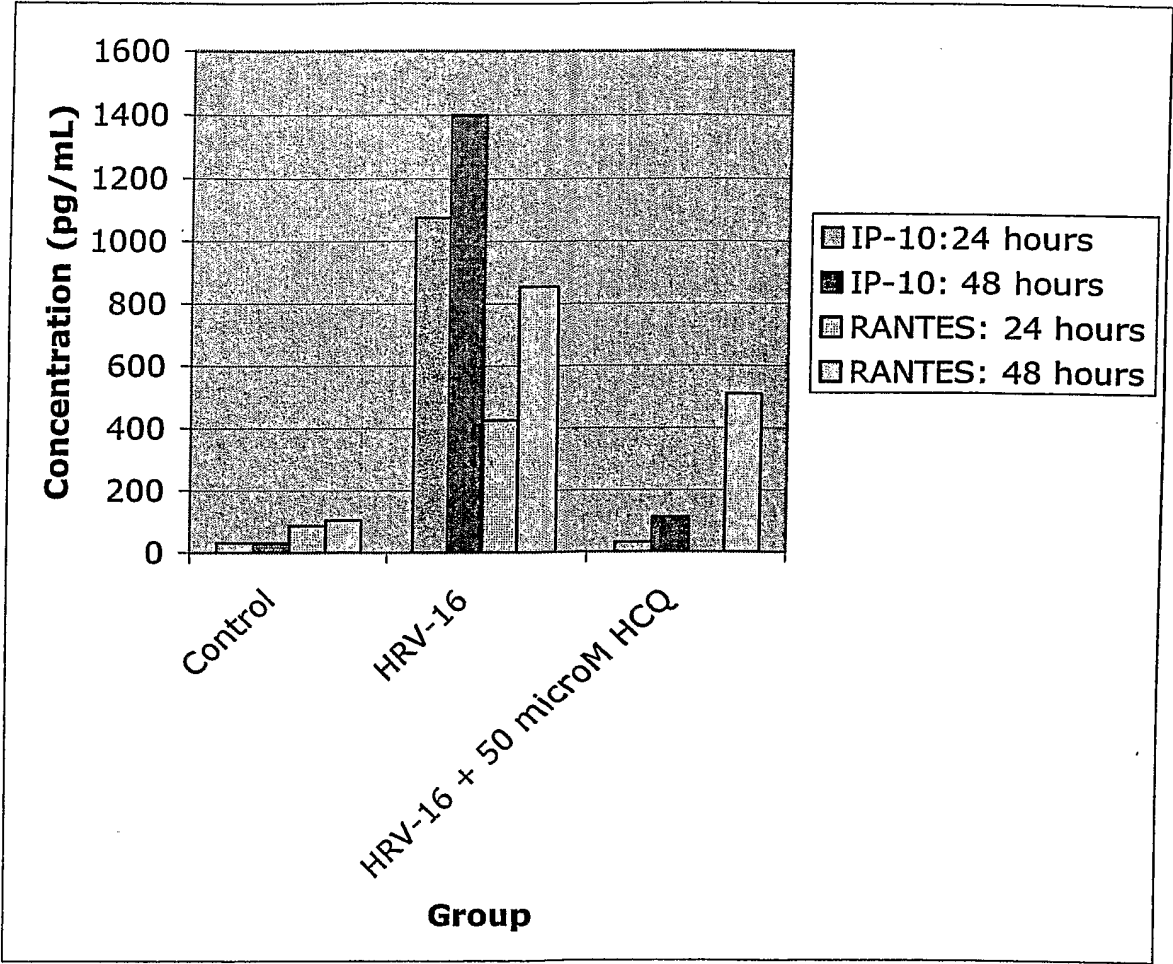


FIGURE 5

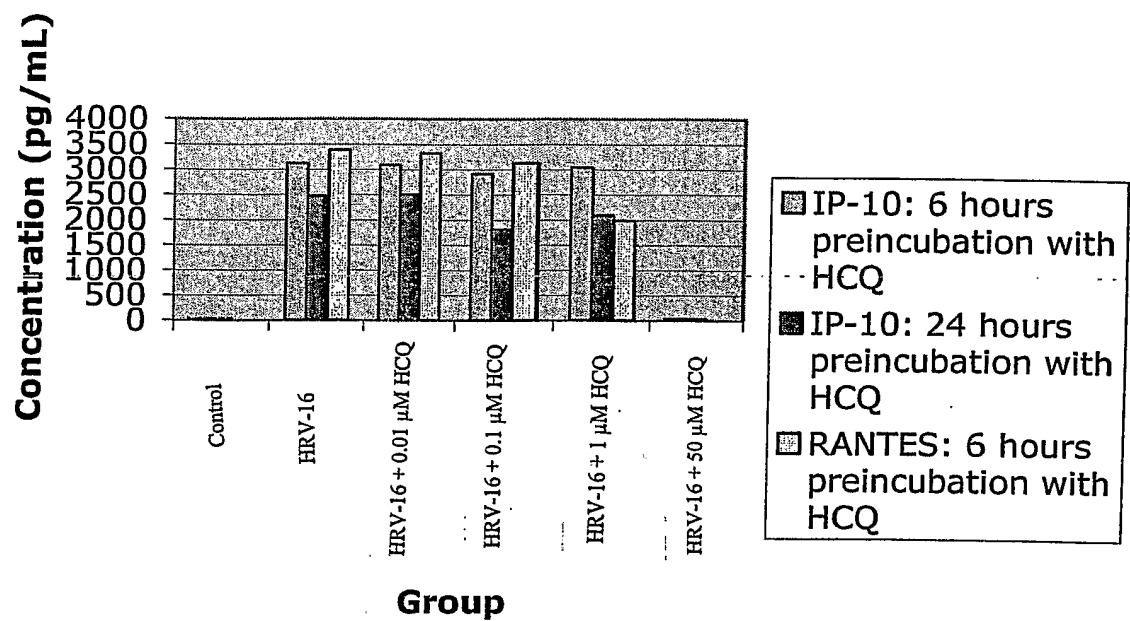


FIGURE 6