Drugs of the Future 1998, 23(1): 28-31

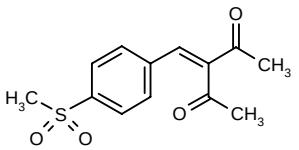
Orazipone

Prop INN

Agent for Inflammatory Bowel Disease
Cytokine Modulator

OR-1384

3-[4-(Methylsulfonyl)benzylidene]pentane-2,4-dione



$C_{13}H_{14}O_4S$ Mol wt: 266.31

CAS: 137109-78-5

EN: 251434

Synthesis

By condensation of 4-(methylsulfonyl)benzaldehyde (I) with pentane-2,4-dione (II) by means of $SOCl_2$ in isopropanol (1). Scheme 1.

Description

Crystals, m.p. 139-40 °C.

Introduction

Inflammatory bowel disease (IBD) represents a group of chronic idiopathic disorders involving either the colon exclusively (ulcerative colitis) or any part of the gastrointestinal tract (Crohn's disease). Management of IBD is based upon regimens which decrease mucosal inflammation (2). Currently used medications include aminosalicylates, glucocorticoids, antibiotics and immunomodulators (3-6) (Table I). New formulations of budenosine have recently been introduced: budesonide controlled ileal-release (CIR) capsules (Entocort®; Astra) and budesonide pH-modified-release capsules (Budenofalk; Falk).

During the past decade, research on the etiology and pathogenesis of chronic IBD has focused on immunological features. Research efforts have led to the identification of immunoinflammatory mediators which provide specific targets for pharmacological intervention. Future medical options for the treatment of IBD, together with drugs under development, are shown in Table II which has been prepared from Prous Science databases.

Scheme 1: Synthesis of Orazipone

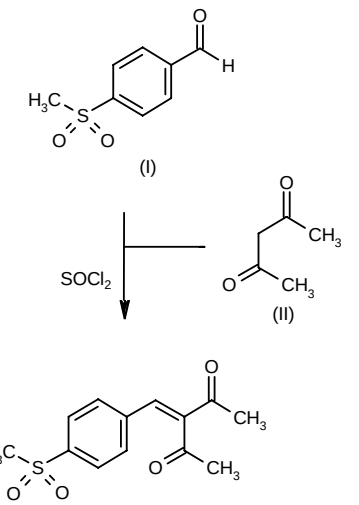


Table I: Drug therapy for IBD.

Aminosalicylates
Mesalamine
Olsalazine
Balsalazide
Sulfasalazine
Immunomodulators
Azathioprine
6-Mecaptopurine
Cyclosporine A
Methotrexate
Glucocorticoids
Budesonide
Prednisone
Antibiotics
Metronidazole

One compound in this table, orazipone (OR-1384) from Orion, has been selected as a candidate for the treatment of IBD and is described in this monograph.

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Table II: Research and development on future medical options for IBD.

	Source	Status
Targeting mediators of inflammation		
Cytokine modulators		
Antibody to IL-12	NIH	Research
CDF-571	Celltech	Phase II
Infliximab/Avakine[1]	Centocor	Preregistered
Orazipone (OR-1384)[2]	Orion	Phase I
rhIL-10	Schering-Plough	Phase II
rhIL-11	Schering-Plough	Phase I
5-Lipoxygenase inhibitors		
MK-591[3]	Merck & Co.	Phase III
Leukotriene B_4 antagonists		
VML-295	Vanguard Medica; Lilly	Phase II
Leukotriene A_4 hydrolase inhibitors		
SC-57461A	Searle	Preclinical
Thromboxane A_2 antagonists		
Ono-NT-126	Ono	Preclinical
PAF antagonists		
Lexipafant[3]	British Biotech	Clinical
WO 9709329[4]	Uriach	Biological testing
Omega-3 fatty acids[5]	----	Clinical
Tachykinin NK antagonists		
Osanetant (SR-142801)	Sanofi	Preclinical
Saredutant (SR-48968)	Sanofi	Phase I
SR-140333A	Sanofi	Preclinical
Antioxidants		
BXT-51072	Oxis	Phase I
LY-231617	Lilly	Preclinical
SI-3501[6]	Seikagaku; Kaken; Meiji Seika	Phase II
Tazofelone	Roberts licensed from Lilly	Phase II
Targeting adhesion molecules		
LDP-02[7]	LeukoSite	Preclinical
ISIS-2302[8]	Isis; Boehringer Ingelheim	Phase III
ISIS-3082[8]	Isis	Preclinical
Targeting nicotine receptors		
Transdermal nicotine	Mayo Clinic; Medeva	Phase III
Nicotine carbomer[9]	Mayo Clinic; Medeva	Clinical
Antibiotics		
Rifaximin	Wasserman; Salix	Clinical
Miscellaneous agents		
ALX-0600 (GLP-2)[10]	Allelix	Preclinical
CARN-1000/Alimisase[11]	Carrington	Phase III
DA-9601[12]	Dong-A	Preclinical
Diethylhomospermine[13]	SunPharm	Preclinical
Prezatide copper acetate (Iamin-IB Solution)	ProCyte	Phase II

[1]Anti-TNF-α MAb. [2]It is expected to proceed to phase II in 1998. [3]Not associated with clinical efficacy. [4]Patent literature. [5]They reduce production of LTB_4 and TXA_2 or inhibit cytokine (IL-1β or TNF) production. [6]Lecitin-modified superoxide dismutase. [7]Humanized MAb to the α_4/β_7 integrin. [8]Murine-specific ICAM-1 antisense oligonucleotide. [9]Oral and enema formulations. [10]Glucagon-like peptide.[11]Highly acetylated, polydispersed, linear complex carbohydrate. [12]Extract from *Antemisia asiatica*. [13]Polyamine analog. Source: Prous Science databases.

Pharmacological Actions

Orazipone is a locally acting thiol modulating agent that inhibits the activation of inflammatory cells and decreases the formation of key inflammatory cytokines.

The immunomodulating effects of orazipone on human monocytes, T-cells and neutrophils were assessed in an *in vitro* study. IL-1β, IL-8 and TNF-α secretion from isolated monocytes was assayed in the presence and absence of orazipone after the cells were

challenged with lipopolysaccharide. IL-2 secretion and NADPH activity in human Jurkat T-cells were assayed after challenge with phytohemagglutinin and phorbol ester (PMA), while superoxide production was assayed in isolated human neutrophils activated by either hemotactic peptide or PMA. Neutrophil degranulation was evaluated by measuring elastase production after treatment with IL-8. In addition, the oxidative burst from rat peripheral neutrophils in whole blood was measured 1 h after intracolonic administration of 10 mg/kg of orazipone (7).

IL-1β, TNF-α and IL-8 secretion by monocytes was inhibited by orazipone, with respective IC_{50} values of 7.2, 7.5 and 8.1 μM. IL-2 secretion by Jurkat T-cells was also inhibited with an IC_{50} value of 6.0 μM. Superoxide release from human neutrophils elicited by chemotactic peptide or PMA was inhibited, with respective IC_{50}s of 4.7 and 16.8 μM. Elastase release from neutrophils treated with IL-8 decreased by 50% (IC_{50} = 18.9 μM). An analog of orazipone which does not form adducts with thiol groups had no effect on any cell type. Orazipone had no effect on NADPH oxidase from human neutrophils nor on oxidative burst in rat peripheral neutrophils after intracolonic administration. The study showed that orazipone inhibits the release of IL-1β, IL-8, TNF-α and IL-2 from monocytes and T-cells and inhibits oxygen radical production and elastase release from neutrophils. In addition, the local action of orazipone was confirmed by the drug's lack of effect on oxidative burst in rat peripheral neutrophils (7).

The effects of orazipone on inflammation and tissue damage were evaluated in an *in vivo* study using a dextran sulfate model of mouse colitis. Acute colitis was induced by administering 4% dextran sulfate for 5 days followed by 8 days of plain water. Chronic colitis was induced by administering dextran sulfate for 2 cycles of 7 days each, followed by 7 days of water. Orazipone was given intrarectally at doses of 25, 50 and 100 mg/kg/day during the water period and the results were compared to 100 mg/kg/day of 5-aminosalicylic acid (5-ASA) or vehicle given once daily during 8 days of water feeding. The mice were sacrificed at the end of treatment and the efficacy of orazipone was evaluated by disease activity index, qualitative and quantitative histology and by measuring plasma and tissue levels of IL-1β, IL-6, TNF-α and colonic myeloperoxidase (8, 9).

Disease activity index, myeloperoxidase, acute and chronic inflammation and crypt scores were all reduced by orazipone. The same occurred with plasma and colonic tissue IL-1β and IL-6 levels. Disease activity index was effectively inhibited after 4 days of treatment with orazipone at doses of 50 and 100 mg/kg in comparison to 5-ASA administration. After 8 days of therapy, the effect of orazipone appeared to be equal to that of 5-ASA in acute colitis, while in chronic colitis, the drug's effect at 25-100 mg/kg appeared to be superior to that of 5-ASA (8, 9).

These results indicate that orazipone is a good candidate for the treatment of human inflammatory bowel disease due to its inhibitory effects on colonic inflammation and proinflammatory cytokine release and its healing effect on colonic lesions (8, 9).

Another *in vitro* study examined the effects of intracolonic administration of orazipone in TNBS-induced colitis in rats and mice and immune complex colitis in rabbits. In rats, 3-30 mg/kg of orazipone was administered once daily beginning 1 h before TNBS treatment and compared to 100 mg/kg of 5-ASA. The animals were sacrificed 96 h after TNBS administration. In the mouse model, 30 mg/kg of orazipone was administered 1 h before TNBS and the mice were sacrificed 48 and 72 h after TNBS treatment. In the immune complex model, colitis was induced using dilute formalin given intracolonically and by intravenous administration of HSA/anti-HSA complexes. A once-daily dose of 3-30 mg/kg of the drug was administered intracolonically 24 h before formalin treatment and rabbits were sacrificed 48 or 72 h after formalin administration. Doses of 3-10 mg/kg of hydrocortisone were used for comparison in the immune complex model. Samples from all the animals underwent macroscopic and histological examinations together with measurements of myeloperoxidase activity to determine the extent of inflammation and colon damage. In addition, levels of IL-1β and TNF-α were assessed in colon samples from rats and mice (10).

Local administration of orazipone reduced the number of colonic lesions in all three models. In addition, myeloperoxidase activity in rats was reduced by 70%, while 5-ASA had only a slight effect. Neutrophil infiltration was also reduced in the mouse model, and tissue levels of IL-1β and TNF-α were decreased in both rats and mice by 44-53%. In the rabbit model, lesions and inflammation were reduced by 80% with orazipone treatment, while hydrocortisone treatment resulted in only a 44% reduction (10).

The results from this study again demonstrate the therapeutic value of orazipone in the treatment of colonic lesions and inflammation due to its inhibition of inflammatory mediators *in vivo*.

The protective effects of orazipone on gastric mucosa were evaluated in an *in vivo* study in rats. Gastric injury was induced in Wistar rats by intragastric instillation of absolute ethanol or acidified 5-ASA. Prior to injury, the animals were treated with 30 mg/kg of orazipone in 1-2 ml of methylcellulose and sacrificed either 1 h (ethanol group) or 4 h (5-ASA group) postinjury. Samples extracted from the rats were scored from 0 to 3 by macroscopic and microscopic examination. The examinations showed that orazipone reduced the macroscopic lesion score from 2.5 to 0.71 (70%) and the microscopic lesion score from 2.38 to 0.86 (63%) in the ethanol group. The macroscopic lesion core in the 5-ASA group was reduced from 2.5 to 0.75 (70%) and the microscopic lesion score decreased from 2.38 to 1.00 (58%). The histological examination of the samples were in good agreement with the macroscopic analysis. The study confirmed the ability of orazipone to protect the gastric mucosa from injury induced by ethanol and 5-ASA (11).

Orazipone is in phase I and will proceed to phase II clinical trials in 1998 for inflammatory bowel disease (12).

Manufacturer

Orion Pharma (FI).

References

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