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Orazipone

Prop INN

OR-1384

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

C₁₃H₁₄O₄S  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 SOCl₂ 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 budesonide 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.

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.

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

### 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.
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 hemo-
tactic peptide or PMA. Neutrophil degranulation was evaluated by measuring elastase production after treat-
ment 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 IC50 values of 7.2,
7.5 and 8.1 μM. IL-2 secretion by Jurkat T-cells was also
inhibited with an IC50 value of 6.0 μM. Superoxide release
from human neutrophils elicited by chemotactic peptide or
PMA was inhibited, with respective IC50s of 4.7 and 16.8
μM. Elastase release from neutrophils treated with IL-8
decreased by 50% (IC50 = 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 admin-
istration. 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 dex-
tran sulfate model of mouse colitis. Acute colitis was
induced by administrating 4% dextran sulfate for 5 days
followed by 8 days of plain water. Chronic colitis was
induced by administrating 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, qual-
rative and quantitative histology and by measuring plas-
ma 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 candi-
date for the treatment of human inflammatory bowel dis-
 ease 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 intra-
colonic administration of orazipone in TNBS-induced col-

tis in rats and mice and immune complex colitis in rab-
bits. 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 sac-
rificed 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, col-
itis 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 for-
malin administration. Doses of 3-10 mg/kg of hydrocorti-
sone were used for comparison in the immune complex
model. Samples from all the animals underwent macro-
scopic and histological examinations together with mea-
surements 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 sam-

dles from rats and mice (10).

Local administration of orazipone reduced the num-
er 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 inflam-
mation were reduced by 80% with orazipone treatment,
while hydrocortisone treatment resulted in only a 44% re-
duction (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 inflamma-
tory 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 extract-
ed 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 macro-
scopic 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


