blinded placebo-controlled study. Participants received single oral tablet of DA–8159 (12.5 to 300
mg) or placebo. Adverse effects and pharmacokinetic parameters were monitored during experiments.
DA–8159 was well tolerated and the frequency of adverse events was dose-related. The most
common side effects were headache and facial flushing, which are related with inhibition of PDE5.
Mean plasma concentrations of DA–8159, maximum concentration (Cmax), and area under the
concentration–time curve from time 0 to the time of the last detectable concentration (AUC0–tldc)
increased with increasing dose, with the time to the peak concentration in plasma occurring at 1.17 to
1.92 hours postdosing. Plasma elimination half–life (t1/2) ranged from 7.3 to 12.1 hours with an
average of 10 hours. This study indicates DA–8159 is safe and well tolerated after single oral dose in
healthy males up to 300 mg without severe adverse events and warrants further clinical investigation.

[PA1–21] [ 10/18/2002 (Fri) 09:30 – 12:30 / Hall C ]

Evaluation of electroretinogram and retinal histopathology in rabbits administered
DA–8159, a selective PDE 5 inhibitor

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DA–8159, a selective inhibitor of phosphodiesterase type 5 (PDE5: IC50 5ng/ml), is being developed
as a new treatment for erectile dysfunction. Since DA–8159 has been shown to inhibit PDE6 enzyme
(IC50 53ng/ml), we evaluated the effect of DA–8159 on electroretinogram (ERG) and retinal
histopathology in rabbits. The effect of oral DA–8159 (5 to 30mg/kg) on ERG recordings was
investigated at pre–treatment, 1 and 5 hrs after administration in rabbits. Plasma and intravitreal
concentration of DA–8159 was determined at each time point, and the electromicroscopic
examination on retinal blood vessel was also performed. DA–8159 did not induce any significant
difference in either a– or b–wave amplitudes. The implicit time of the a– and b–wave also did not
show remarkable changes. In the highest dose group, however, mild and transient changes in rod and
cone response were observed 1 hr after administration, which disappeared at 5 hrs post–dosing.
Intravitreal concentration of DA–8159 was about half of the concentration of sildenafil after the same
oral dose. There was no histopathological evidence of toxicity on retinal blood vessels. These data
suggest DA–8159 has a lower risk potential of ocular side effects, but further evaluation of the effects
of DA–8159 on visual functions in human must be performed.

[PA1–22] [ 10/18/2002 (Fri) 09:30 – 12:30 / Hall C ]

Induction of penile erection in spinal cord–injured rabbits by administration of DA–
8159, a new selective PDE 5 inhibitor

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DA–8159 is a new, highly selective, potent cyclic–GMP phosphodiesterase 5 inhibitor developed by
Dong–A Pharmaceutical Company(Kyunggi, Korea) as an oral drug for the treatment of erectile
dysfunction. NO– cGMP signal transduction pathway plays a key role for relaxation of corpus
cavernosal smooth muscle. In this study, the efficacy of DA–8159 was evaluated by measuring the
length of uncovered penile mucosa in spinal cord injury(SCI) rabbits. Spinal cord injury is regarded as
one of the main risk factors for erectile dysfunction in human. In this study, SCI was induced by spinal
cord transection at the local level(L2–L4) preventing the effective release of penile neurotransmitter,
nitric oxide, from nonadrenergic–noncholinergic nerves. It was proven that penile erection was
induced in SCI-injured rabbits models after oral and IV administration of DA–8159 (0.3mg/kg–
10mg/kg). Furthermore, the efficacy was potentiated by administration of sodium nitroprusside. These
results demonstrate that DA–8159 has a reliable and reproducible effect on penile erection in spinal
cord injured rabbits.

[PA1–23] [ 10/18/2002 (Fri) 09:30 – 12:30 / Hall C ]

Pharmacology of novel vanilloid receptor antagonists

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Capsaicin and analogues are valuable analgesic agents when administered to mammals, including
humans. However, their pungency, hypothermia and the effects on the cardiovascular and respiratory
systems through their general activation of primary afferents severely limit their use. So competitive
antagonists have been pursued as a novel pharmacological agent for analgesics, rather than agonists.
We have identified a new class of potent and selective vanilloid receptor (VR) antagonists. These
antagonists exhibit highly potent antagonistic activities in both 45Ca2+-uptake and single channel
patch clamp assays as well as analgesia in capsaicin test and PBQ writhing test. Furthermore, these
compounds are devoid of the important shortcomings of capsaicin, such as hypothermia and
pungency. These results suggest that VR blockade could be a novel therapeutic approach to
analgesia.

[PA1–24] [ 10/18/2002 (Fri) 09:30 – 12:30 / Hall C ]

IN VIVO METABOLISM OF 2–METHYLAMINOETHYL–4,4′–DIMETHOXY–5,6,5′,6′–
DIMETHYLENEDIOXYBIPHENYL–2′–CARBOXY–2′–CARBOXYLATE (DDB–S) BY LC/ESI
TANDEM MASS SPECTROMETRY

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2–Methylaminoethyl–4,4′–dimethoxy–5,5′,6,5′,6′–dimethylenedioxybiphenyl–2′–carboxy–2′–carboxylate
(DDB–S) is a synthetic compound derived from DDB, which is protects liver against carbon
tetrachloride–, D–galactosamine–, thioacetamide–, and prednisolone–induced hepatic injury in
experimental animals. We assessed the use of liquid chromatography/electrospray iontrap tandem
mass spectrometry (LC/MS/MS) method to identify and quantify in vivo metabolites and to measure
excretion. DDB–S was administered intravenously to rats, and samples of urine, and feces were
collected and analyzed by LC/MS. This method identified twelve metabolites in urine and feces. The
major metabolic pathways of DDB–S in rats were identified as demethylation of the
dimethylenedioxyphenyl group and demethylation of the carboxymethyl moiety. The others were
identified as demethylation and dimethylation, and glucuronidation.

[PA1–25] [ 10/18/2002 (Fri) 09:30 – 12:30 / Hall C ]

Selectivity of the optical isomers of KR30031 on MDR reversal activity and
cardiotoxicity