4,5-Functionalized-6-phenyl-3(2H)-pyridazinones as antinociceptive agents

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ANALGESIC ACTION OF KETOPROFEN ENANTIOMERS IN ANIMAL MODELS

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The analgesic activity of racemic ketoprofen (2-(3-benzoylphenyl) propionic acid) (rac-KP) and its S-(+) and R-(-) enantiomers (S-(+)-KP and R-(-)-KP) have been compared in the writhing test. Phenylbenzoquinone and etacrinic acid were used as pain inducers in mouse and rat respectively. Compounds (tromethamine salts) were administered i.v. and p.o. as aqueous solutions. Inhibitions of abdominal constrictions (mean±SEM, number of animals in parentheses) are indicated in the table:

species	route	dose (mg/kg)	S-(+)-KP	rac-KP	R-(-)-KP
rat	p.o.	2	---	56.0±10.9(11)	---
		1	60.5±4.7(12)	---	34.9±9.6(8)
	i.v.	0.3	---	78.6±4.9(21)	---
		0.15	81.7±5.8(6)	---	27.2±14.4(7)
mouse	p.o.	3	---	97.0±2.1(6)	---
		1.5	86.3±4.3(7)	---	53.9±7.1(6)
	i.v.	1	---	93.7±3.4(17)	---
		0.5	92.1±2.2(16)	---	29.2±7.2(18)

In all cases the analgesic activity of S-(+)-KP did not differ significantly from that of the rac-KP administered at double dose ($p>0,05$). On the other hand, the R-(-)-KP was significantly less active than the S-(+)-KP ($p<0,05$ p.o. and $p<0,01$ i.v., in rat; $p<0,01$ p.o. and $p<0,001$ i.v., in mouse). These results indicate that the analgesic effect shown by ketoprofen in these *in vivo* models is mainly due to the S-(+)-KP, which inhibits cyclooxygenase activity *in vitro*. The significant minor activity observed for R-(-)KP can be attributed to its enantiomeric bioinversion in both species, a metabolic process which is known to be especially relevant after oral administration.

4,5-FUNCTIONALIZED-6-PHENYL-3(2H)-PYRIDAZINONES AS ANTINOCICEPTIVE AGENTS

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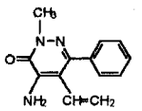
Previous studies in our laboratories examined the correlation between structure and activity in a series of 3(2H)-pyridazinone derivatives (1,2). The purpose of the present study was to determine the structure-activity relationships (SAR) in a series of compounds structurally related to the non-steroidal analgesic-antiinflammatory agent, Emorfazone [4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone] (3). Among the novel derivatives evaluated, **1** emerged as a compound of particular interest having an antinociceptive potency in the *p*-phenylquinone-induced mouse abdominal constriction model of 14.9 mg/kg s.c.: at 100 mg/kg all animals were completely protected from the irritant effects of the noxious chemical stimulus. In this model, aspirin has an ED_{50} of 316 mg/kg s.c..



1

Compound **1** was chosen, therefore, as a lead for further SAR studies and these will be reported at the meeting.

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2) V. Dal Piaz et al., *Pharmacol. Research*, **29**, 367 (1994)
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STRESS-INDUCED ANALGESIA IS CONNECTED WITH ACTIVATION OF GASTRIC AFFERENTS BY MEANS OF STRESS MEDIATORS

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In the experiments on rats and mice, the pain sensitivity provoked by four types of an acute stress is abolished by preliminary anaesthesia of gastric mucose with lidocaine or subdiaphragmal vagotomy. The ED50s of stress mediators (adenosine, adrenaline, serotonin, acetylcholine), assessed in tail-flick test as producing analgetic effect equal to 50 per cent of maximal one, were 40-60-fold less under intragastric administration compared to systemic (intraperitoneal and intramuscular) injection. Such analgesia was prevented by intragastric administration of lidocaine or subdiaphragmal vagotomy as well. Therefore, stress-induced analgesia is connected with local action of stress mediators on chemoceptors of gastric vagal afferents and has reflex nature. Moreover, both stress-induced analgesia and intragastric administration of stress mediators were prevented with intragastric administration of cholino- and adenosine blockers (hexamethonium and 1,3-dipropyl-8-phenylxanthine). It is suggested that both types of receptors participate in stress-induced analgesia.

LOCAL ANESTHETICS AND TRICYCLIC ANTIDEPRESSANTS ATTENUATE MECHANICAL HYPERALGESIA AND ALLODYNIA IN EXPERIMENTAL MODELS OF CHRONIC NEUROPATHIC PAIN

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In experimental animal models of chronic neuropathic pain, either chronic constriction of the sciatic nerve (CCI) or ligation of spinal L5/L6 nerves (SNL) produces mechanical hyperalgesia and allodynia, two prominent clinical symptoms of traumatic nerve injury. Local anesthetics (mexiletine, MEX; lidocaine, LIDO) and tricyclic anti-depressants (amitriptyline, AMI; desipramine, DES) represent current therapies that have been found to produce adequate pain relief in several clinical neuropathic pain syndromes. The present study therefore examined the antinociceptive potential of each drug class against experimental mechanical hyperalgesia (pin-prick) and allodynia (von Frey filament). Each drug was evaluated 60min post-dose following s.c. administration. MEX (10-100mg/kg), LIDO (10-100mg/kg), AMI (1-30mg/kg) and DES (1-30mg/kg) all produced similar dose-dependent reductions in mechanical hyperalgesia and allodynia observed 10-21 days after either CCI and/or SNL surgery. The rank order of potency, with the range of minimum effective doses in parentheses, was DES (3-10) ≥ AMI (10-30) > MEX (30-60) ≥ LIDO (60-100). In contrast, fluoxetine (>30mg,kg), a non-tricyclic antidepressant that appears to be clinically ineffective was inactive. Carbamazepine (>300mg/kg, p.o.) and phenytoin (>100 mg/kg) which are generally ineffective in the clinic, with the exception of trigeminal neuralgia, were also inactive in these models. Thus the pharmacological profile of the pinprick and von Frey filament-induced mechanical hyperalgesia and allodynia models, respectively, following either CCI or SNL, appears to parallel the clinical effectiveness of these drugs in the treatment of chronic painful peripheral neuropathies.