STUDIES OF DINUCLEAR AND MONONUCLEAR COMPLEXES OF INDOMETHACIN: NEW ANTI-INFLAMMATORY DRUGS

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by

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The work presented in this thesis is my own, unless otherwise stated.

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Publications

Journal Papers

Syntheses and Characterization of Anti-Inflammatory Dinuclear and Mononuclear Zinc Indomethacin Complexes. Crystal Structures of $[Zn_2(Indomethacin)_4(L)_2]$ (L = *N,N*-Dimethylacetamide, Pyridine, 1-Methyl-2-pyrrolidinone) and $[Zn(Indomethacin)_2(L_1)_2]$ (L_1 = Ethanol, Methanol)

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List of Symbols and Abbreviations

AAS	atomic absorption spectroscopy
BM	Bohr Magneton
BVR	Biochemical Veterinary Research
CMC	carboxymethylcellulose
COX	cyclooxygenase
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EPR	electron paramagnetic resonance
e.s.d.	estimated standard deviation
eV	electron Volts
FT	Fourier transform
h	hour(s)
Im	imidazole
IndoH	indomethacin
min	minute(s)
MS	multiple scattering
n	number of rats used in the *in vivo* assays
N_i	number of independent data points in the XAFS data set
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
N_p	number of refinement parameters in the XAFS model
NPBCA	*N*-pyrimidinobenzamide-2-carboxylic acid
NSAID	non-steroidal anti-inflammatory drug

PBDA	*N*-phenylbenzamide-2,2'-dicarboxylic acid
PG	prostaglandin
PPD	prescribed daily doses per 1000 of the population
Py	pyridine
R_{as}	distance of the metal absorber atom from the scattering atom
R_{eff}	total distance travelled by the photoelectron; being twice the value of R_{as}
r.m.s	root mean square
R_{xaf}	XAFS model's goodness-of-fit parameter
σ^2	mean square deviation in the distance of the metal absorber atom from the scattering atom
s	second(s)
S_0^2/S	XAFS inelastic loss term/XAFS scale factor
SD	standard deviation
SEM	standard error of mean
SOD	superoxide dismutase
SS	single scattering
μ_{eff}	effective magnetic moment
χ_M	molar magnetic susceptibility
XAS	X-ray absorption spectroscopy
XAFS	X-ray absorption fine structure
XRD	X-ray diffraction

Abstract

Cu(II) complexes of indomethacin (IndoH) have greater efficiency and less GI toxicity in comparison with their parent drug IndoH. This drug was patented in 1994 by Biochemical Veterinary Research (BVR) and is available in Australia in a number of pharmaceutical formulations. Here, the Zn(II), Ni(II) and Co(II) complexes, that have also been patented by BVR, were studied for the chemical and physical properties, efficiencies and GI toxicities.

A number of Zn(II), Ni(II) and Co(II) complexes of Indo were prepared and characterised by various techniques, including single crystal X-ray diffraction and X-ray absorption spectroscopes (XAS). In addition, the superoxide dismutase (SOD) activity, anti-inflammatory property and GI toxicity of the prepared complexes were investigated.

The complexes are unusual in that both monomeric and dimeric complexes are formed and this is the first example of the same carboxylato ligand binding via both carboxylate oxygen atoms in monomeric and dimeric Zn(II) and Ni(II) complexes. The crystal structures of Zn-Indo complexes with *N*,*N*-dimethylacetamide (DMA), pyridine (Py), 1-methyl-2-pyrrolidinone (NMP), EtOH and MeOH as solvent ligands, $[Zn_2(Indo)_4L_2]$ (L = DMA, Py, NMP), *cis*-$[Zn(Indo)_2L_2]$ (L = EtOH, MeOH), were determined. The three dimeric complexes exhibit dinuclear paddle-wheel structures, as found in the Cu(II) acetate and $[Cu_2(Indo)_4L_2]$ (L = DMF, DMSO, DMA, EtOH, CH_3CN, Py). In these cases, the zinc ions are offset along the *z* direction, such that the L-Zn…Zn-L moiety is non-linear, unlike the Cu analogues. Each Zn has a square-pyramidal geometry bridged by four carboxylato ligands in the basal plane with the solvent ligands containing an *O*- or *N*-donor atom at the apex. The two monomeric complexes are isostructural and similar in structure to Zn acetate dihydrate. The Zn resides on a two-fold axis and the complexes have a distorted *cis*-octahedral configuration.

The structures of the dimeric and monomeric Ni(II) and Co(II) complexes were confirmed by IR, magnetic properties and X-ray absorption fine structure (XAFS). The dimeric $[Ni_2(Indo)_4(EtOH)_2]$ complex has a similar structure to that of $[Zn_2(Indo)_4L_2]$, whilst the monomeric $[Ni(Indo)_2(OH_2)_2]$ and $[Co(Indo)_2L_2]$ (L = EtOH, OH_2) have a similar *cis*-octahedral geometry as that of $[Zn(Indo)_2L_2]$.

The Ni(II) and Co(II) complexes of Indo exhibited significant SOD activities compared with the IndoH in the nitroblue tetrazolium assay. In the acute anti-inflammatory test, the Co(II) chelate was most active followed by the Zn-Indo dimer, Ni(II)-Indo dimer and monomer, and Zn-Indo monomers. Gastric irritancy was markedly reduced by Ni(II) monomer, followed in order by dimeric Ni(II) and Zn(II) complexes. Intestinal damage of the Zn(II), Ni(II) and Co(II) complexes were much less than their parent drug IndoH.

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