DEGRADATION KINETICS OF AZIRIDINYL QUINOID ANTITUMOUR AGENTS

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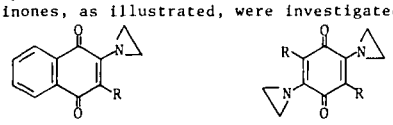
Aziridinylquinones such as triaziquon, carboquone and AZQ show pronounced antitumour activity. The mechanism of action of this class of compounds has not been unambiguously elucidated yet. Apart from a preceding (bio)reductive activation step it has also been suggested that aziridinylquinones alkylate DNA without prior reduction. This mechanism involves protonation of the aziridine function, which then becomes an attractive electrophilic centre, for an attack of nucleophilic DNA parts. If this is true, the antitumour activity should parallel, to a certain extent, the acid activated degradation following the reaction scenario: aziridine protonation and ring opening after nucleophilic water attack. The chemical stability of 32 aziridinyl substituted naphthoquinones and benzoquinones, as illustrated, were investigated,



Clear trends in the relation structure-chemical stability could be assigned, using stability indicating UV spectrophotometrical and HPLC assays. However, for both the naphthoquinones and benzoquinones it appeared that introduction of an electron donating or withdrawing R substituents stabilizes the aziridine moiety against acid-catalyzed degradation. This implies that electronic influences are less important than steric properties of the substituents. Introduction of a methyl group on the aziridine ring strongly destabilizes the compounds. Research in progress on the antitumour activity of the compounds may cast further light on the relation structure-chemical stability-biological activity.

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Protein separations on new surface-stabilized silica-based gelfiltration columns.

A. DAMS

Two columns for gelfiltration chromatography, that separate proteïns and other biological molecules by size, have been developed.
The "Zorbax" GF 250 column performs separations of biomolecules having molecular weights from 4.000 to 400.000 daltons with high resolution, outstanding reproducibility and durability over a broad pH range.
The "Zorbax" GF 450 supplements the GF 250 column and is designed for separations in the 17.500 to 900.000 daltons range.
Both "Bioseries" gelfiltration columns are able to perform separations for long periods in aqueous mobile phases having pH-values up to 8.5. Efficiency is generally ± 40.000 plates per meter, which provides resolution approximately twice that of competetive columns. Typical proteïn recovery rates are 95 percent or greater. Biological activity is generally maintained.

The silica media are stabilized with a zirconia surface treatment, which provides excellent resistance to base-catalyzed hydrolysis. The spherical particles average four microns (GF 250) or six microns (GF 450).

Pore size for particles used in the GF 250 is 150 angström, pore size in the GF 450 is 300 angström.

Both columns are 25 cm long and have an internal diameter of 9.4 mm.

Other "Bioseries" columns include the PEP RP1 for reversed phase separation of peptides and proteïns and the PTH for the isocratic analysis of pth-amino-acids.

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RP-HPLC DETERMINATION OF TIMOLOL AND PROPRANOLOL IN RAT PLASMA BY ION-PAIR CHROMATOGRAPHY AND COMBINED SOLID-PHASE/LIQUID-LIQUID EXTRACTION

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Acute poisoning caused by overdose ingestion of beta-blocking drugs is characterized by haemodynamic disturbances, which sometimes can lead to a fatal outcome. Preliminar experiments in rats have suggested that the toxicological profile of these drugs might be determined by a yet unknown pharmacological property (1). Therefore, a study was performed in rats in order to investigate the haemodynamic and respiratory effects after beta-blocker overdosage. In this study, the effects observed were related to the plasma concentrations of the drugs.
For this purpose, a method was developed for the determination of two beta-blocking drugs, timolol and propranolol in 20-80 µl of rat plasma. The beta-blocker carazolol was used as an internal standard. The drugs were extracted from plasma by solid-phase extraction using 1-ml octadecylsilane extraction columns fitted to a Baker-10 SPE extraction manifold. Further clean-up of the extracts was obtained by a micro liquid-liquid extraction of the column eluate. By using this procedure, two different separation techniques (liquid-solid and liquid-liquid extraction) are used, each with a different selectivity range. As a result, the selectivity and sensitivity obtained by using the combined procedure are superior to those obtained by using existing extraction methods.
Quantitation was performed by RP-HPLC using ion-pair chromatography on an ODS column, and UV-detection at 295 nm for timolol and 225 nm for propranolol. For propranolol concentrations below 1 mg/l fluorescence detection was used (λex = 282 nm, λem = 334 nm). The sensitivity was 50 µg/l for both timolol and propranolol.

1. D.J.de Wildt, B.Sangster, J.J.M.Langemeijer, G.de Groot, J.Toxicol.: Clin.Toxicol., 22 (1984) 115

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ENANTIOSELECTIVITY IN THE BIOTRANSFORMATION OF ORG 3770 AS DETERMINED BY ^{1}H NMR AND HPLC

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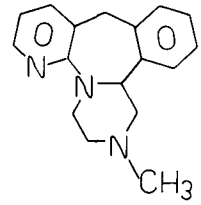
Org 3770, an antidepressant drug under development, is a racemic compound. We determined the enantiomeric ratio of the main metabolites in rat, rabbit and dog. For unconjugated metabolites in urine we used ^{1}H NMR in the presence of Pirkle's alcohol; assignment of the enantiomers was done by comparison with synthetic optically pure compounds. The enantiomeric ratio of the glucuronides could be determined directly by ^{1}H NMR or HPLC since diastereomers are formed on conjugation with glucuronic acid. There were clear enantiomeric preferences in the metabolic pathways, which were strongly dependent on sex and species. It must be emphasized that whatever the enantioselectivity is, it is the proof of efficacy and safety of the drug that matters.



Org 3770

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