1-aryl-4-nitro-1H-imidazoles, a new promising series for the treatment of human African trypanosomiasis

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 1022791
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Year 2011
Title 1-aryl-4-nitro-1H-imidazoles, a new promising series for the treatment of human African trypanosomiasis
Journal European journal of medicinal chemistry
Volume 46
Number 5
Pages / **Article-Number** 1524-35
Keywords Nitroimidazole, Antiprotozoal activity, Sleeping sickness, Genotoxicity, Ames test, Micronucleus test

Nitroimidazoles are a well-known class of antibacterial and antiprotozoal drugs but in spite of the widespread clinical and veterinary use of these drugs, this family has been stigmatized in part due to associated genotoxicity problems. Here we report the synthesis, the anti-trypanosomal activity and a structure-activity relationship (SAR) study of a series of about fifty 1-aryl-4-nitro-1H-imidazoles, with an emphasis on selected in vivo active molecules. Compounds 4-nitro-1-{4-(trifluoromethoxy)phenyl}-1H-imidazole and 1-(3,4-dichlorophenyl)-4-nitro-1H-imidazole are curative in mouse models of both acute and chronic African trypanosomiasis when given orally at doses of 25-50 mg/kg for 4 days for the acute infection, and 50-100 mg/kg (bid) for 5 days in the chronic model. While both compounds are bacterial mutagens, activity is lost in strains lacking bacterial specific nitro-reductases. Mammalian nitro-reductases do not reduce nitroaromatic compounds with low redox potentials with same avidity as their bacterial counterparts and these compounds were shown to be devoid of genotoxicity in mammalian cells. Both compounds are promising leads for the treatment of human African trypanosomiasis (HAT or sleeping sickness), including the fatal stage 2 of the disease, for which new treatments are urgently needed

Publisher EDIFOR
ISSN/ISBN 0223-5234
edoc-URL http://edoc.unibas.ch/dok/A6002080
Full Text on edoc No;
Digital Object Identifier DOI 10.1016/j.ejmech.2011.01.071
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/21353728
ISI-Number WOS:000289655100008
Document type (ISI) Journal Article