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ed out external validation by removing 5 compounds randomly, ... QSAR on the remaining 17 compounds and using the QSAR to ...tivity of the 5 test compounds. This procedure was carried out 4 ... mean errors found each time were: 0.181, 0.167, 0.208 and 0.190. ...lard error of the mean from equation 1 is 0.182, these errors indicate ... has good predictivity. We further carried out 100 randomisations of ...data, to check for chance correlations; the mean r^2 found was 0.186, ...um r^2 found was 0.520. Thus the risk that equation1 is due to chance

... put a precise physicochemical meaning on the descriptors selected ...but they can be interpreted as modelling molecular bulk and weak ...teractive forces. This accords with the conclusions of a previous ...n et al 2001) of P-glycoprotein-associated ATPase activity of a ... of drugs.

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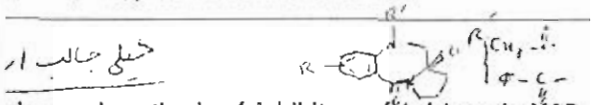

...sign and synthesis of inhibitors of *Leishmania* NAD-glycerol-3-phosphate dehydrogenase

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...ases are parasitic diseases caused by different species belonging to ...*ishmania*, a protozoa transmitted by the phlebotomine sandfly. ...therapeutic treatments for the disease have appreciable toxicity and ...mic areas, up to 40% of the parasites exhibit some degree of ...rently available therapies involve either intravenous or intramus-...and the need for an orally active agent has led to the development of ...owever, there is still a need for alternative oral treatments that are ...cacious and safe (TDR News 2000).

...id parasites are highly dependent on glycolysis as a source of ATP ...pperdoes 1987). The glycolytic enzyme glycerol-3-phosphate ... (G3PDH) is common to both parasite and host, and uses the same ... On comparison of the three-dimensional structures of human and ...*exicana* GAPDH, there are exploitable differences for rational drug ...AD binding region is well conserved around the nicotinamide moiety ..., whereas the adenosine binding region shows structural differences ...te and host enzymes, particularly in the vicinity of the adenosine ...et al 2000).

...lies have shown that the topology of the NAD binding channel in ...mpatible with the *R*-isomeric analogues of pyrrolobenzodiazepine ...benzodiazepine moiety occupies the adenine region of the binding ... fused pyrrolo ring is positioned in the ribosyl region, and a ...l group binds to the phosphate binding region of the cofactor. The ...-isomers of these antibiotics are known cytotoxic agents (Jenkins et ...*R*-stereochemistry at position 11a, coupled with the presence of a ...t position 10, is compatible with the NAD binding channel and ...g with DNA thus overcoming potential host cytotoxicity (Thurston ...tion of the *R*-isomer from D-proline, protected at the α-carboxylic ...action with the acyl chloride of the 2-nitrobenzoic acid analogue ...988). Subsequent reduction of the α-ester to the aldehyde and the ... the amine results in spontaneous intramolecular cyclisation to the ...benzodiazepine isomer (Kamal et al 1997).

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Synthesis and calcium channel antagonist activity of 2-imidazolyl-substituted dihydropyridines

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Structurally diverse groups of compounds are known to be effective as calcium antagonists (Goldmann & Stoltefuss 1991). The most potent class of antagonists comprises derivatives of 1,4-dihydropyridine. The effect of various C-4 imidazolyl substituents in conjunction with different C-3, C-5 diesters on calcium-channel antagonist activity have been previously reported (Shafiee et al 1998; Hadizadeh et al 2002). We now report synthesis (Hantzch 1882; Archibald et al 1990) and calcium-channel antagonist activity of 12 new methyl and ethyl diester analogues of nifedipine in which the o-nitrophenyl group at 4 position is replaced by 1-benzyl-2-alkylthio-5-imidazolyl substituent, and its methyl group at 2 position is replaced by 2-(1*H*-imidazol-1-yl)ethyl or 2-(dimethylamino)ethyl substituent. Guinea-pig ileum contractile response to KCl, acetylcholine (Ach) and electrical stimulations of title compounds were determined according to Bolger et al (1983) and Rovnyak et al (1992). The IC50 values were determined as concentration needed to produce 50% relaxation of contracted guinea-pig ileum in different tests. The IC50 (μM) values of the lead compound were 67.0 , 66.1 and 16.0 in acetylcholine, KCl and electrical stimulation tests. The IC50 (n.s.) for nifedipine was 14.0 in the KCl test.

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Synthesis of S-nitraso captopril

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Angiotensin converting enzyme (ACE) inhibitors are a group of drugs developed during the 1970s. They are currently used extensively in the treatment of hypertension and cardiac failure and have recently been shown to improve prognosis after myocardial infarction.

Captopril is an ACE-inhibitor that has until recently dominated clinical practice. During the last few years, other new long-acting members have become available, including perindopril, lisinopril, cilazapril, quinapril, fosinopril, ramipril, trandolapril and zofenopril. None of these possess significantly different clinical properties to captopril. This study describes the synthesis of potential analogues of captopril, and is part of a wider study, which aims to enhance the therapeutic profile of this drug, particularly with regard to specific routes of administration.