Poster Session 3 – Medicinal Chemistry

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Synthesis and anti-HIV activity of some new 1-[2-(alkylthio-1-benzyl-5-imidazolyl) carbonyl]-4-[3-(isopropylamino)-2-pydridyl] piperazines

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A few analogues of atevirdine (Romero *et al* 1994) or 1-[(5-methoxyindol-2-yl) carbonyl]-4-[3-(ethylamino)-2-pyridyl] piperazine — an anti-HIV belonging to non-nucleoside reverse transcriptase inhibitors, were synthesized and evaluated for anti-HIV activity. Replacement of indolyl moiety with 2-alkylthio-1-benzyl-5-imidazolyl substituent afforded 1-[2-(alkylthio-1-benzyl-5-imidazolyl) carbonyl]-4-[3-(isopropylamino)-2-pydridyl] piperazines. First 2-alkylthio-1-benzyl-5-imidazolecarboxylic acid (Hadizadeh & Tafti 2002) and 3-isopropyl amino-2-chloropyridine (New *et al* 1988) were synthesized according to published procedures through multiple steps. Then the compounds were reacted with each other in the presence of 1,1'-sulfinyldiimidazole to give the title compounds. The purity of all the compounds was confirmed using ^{1}H NMR and infrared spectroscopy methods.

Agents were dissolved in dimeythyl sulfoxide and in vitro anti-HIV tests were performed on them. The assay basically involved the killing of T4 lymphocytes by HIV. Small amounts of HIV were added to cells. After two cycles of virus production, the required cell killing was obtained. Then the test agents were added to culture (from 6.36×10^{-8} to 2.00×10^{-4} M) and the percent of protection was calculated against the control. The maximum percent of protection (14.60%) was observed at the concentration of 2.00×10^{-5} M. By increasing the concentration further the protection was reduced and so the EC50 could not be determined.

Hadizadeh, F., Tafti, F. I. (2002) *J. Heterocyclic Chem.* **39**: 841–844
New, J. S., *et al*. (1988) *J. Med. Chem.* **31**: 618–624
Romero, D. L., *et al*. (1994) *J. Med Chem.* **37**: 999–1014

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Prodrugs for the treatment of cystinosis

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Cystinosis is a rare clinical condition in which the cell removal mechanism for cystine is impaired, resulting in cystine accumulation within the lysosomes of various cells. It is symptomised by the onset of Fanconi's syndrome before the age of 1 year, failure to thrive, dehydration and acidosis. Unless dialysis or renal transplant are performed, renal tubular failure results in death at about 9 or 10 years of age.

After evaluation of a number of thiols, it was shown that cysteamine (β-mercaptoethylamine, $NH_2CH_2CH_2SH$) was most effective at cystine depletion. Cysteamine acts at the cellular level by undergoing thiol exchange with cystine in the lysosome to give cysteine and a cysteamine-cysteine dimer, both of which are readily transported out of the cell (for a review of cystinosis, its clinical presentations and current treatment, see Gahl *et al* (2002)).

Cysteamine incorporates both a primary amine and a thiol, giving it a pungent, offensive smell and taste, leading to problems with compliance. Furthermore, cysteamine is rapidly cleared and requires 3 or 4 daily doses, leading to high peak plasma concentrations and the incidence of more serious side effects (neutropenia, seizures, lethargy, and somnolence). Currently, cysteamine is admimistered as the bitartrate salt (Cystagon) or as an enteric coated formulation, which doesn't release cysteamine until lower in the gastrointestinal tract, both of which lead to some, if not all, of the side effects.

We have synthesized a number of amino acid derivatives of cysteamine designed to enter the systemic circulation, where the action of specific peptidases will release cysteamine for absorption into afflicted cells. This will reduce the side effects suffered after oral administration of cysteamine and may also reduce the problem due to the rapid clearance of cysteamine.

We have refined our prodrug approach to target cysteamine directly to the cells in which it is required to reduce the problem of rapid clearance, along with the majority of the side effects. This prodrug form will undergo little, if any, hydrolysis in the circulation and will be taken up into afflicted cells by a natural internalisation process and the cysteamine released by specific cellular enzymes.

We report here the synthesis of the cysteamine prodrugs and the initial in-vitro results of their biological screening against cultured skin fibroblasts. Both approaches yielded cysteamine prodrugs that were non-toxic in-vitro to CHO cells at concentrations up to 1 mM (Cardwell *et al* 1997) and were successful in depleting cystine levels to 9–15% (of the original concentration) over a 24-h period and compared favourably with cysteamine, which depleted the cystine levels to 10%.

Cardwell, W. A., Cairns, D., Anderson, R. J. (1997) *J. Pharm. Pharmacol.* **49**: 99
Gahl, W. A., Thoene, J. G., Schneider, J. A. (2002) *N. Engl. J. Med.* **347**: 111–121