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Pyrrolo[2,3-d]pyrimidines as a privileged framework in the search for diuretics

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Introduction. Progress in the development of purine-based drugs and research into their mechanisms of action has stimulated the parallel and rapid development of the chemistry and biology of bioisostere compounds. Purine derivatives (rolofilin, tonapofilin, naxifilin) and pyrrolopyrimidine derivatives (derenofilin) were developed for the treatment of congestive heart failure with concomitant renal failure and act as adenosine receptor (A_1AR) antagonists. However, Phase II–III clinical trials of derenofilin and rolofilin revealed a lack of therapeutic efficacy and persistent side effects (an increased incidence of seizures and neurological complications). This highlights the need for further research and the development of new purine bioisosteric agents that would retain high affinity for biological targets and have an acceptable safety profile to ensure a diuretic effect.

Materials and methods. The resynthesised 1-R-5,5-diphenyl-5,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidines were docked using AutoDock Vina into the A1AR structure (code 5UEN [1]), which contained an inhibitor (Derenofylline); with reference ligands (caffeine, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), rolo–fylline, naxifylline) used as benchmarks. Visualisation of the results and analysis were carried out using Discovery Studio v25.1.0.24284. Physico-chemical properties, drug-likeness and toxicity profiles were assessed using the SwissADME and ProTox-3.0 services. The effect of the compounds on renal excretory function in rats was determined using the method of E.B. Berkhine. The compounds, Triampur, Hydrochlorothiazide (dose 2.6 mg/kg), furosemide (4.1 mg/kg) and diacarb (25.8 mg/kg) were administered to rats as a single intragastric dose simultaneously with a water load. Biochemical parameters of plasma and urine were assessed using standard test kits, whilst the sensitivity index (SI), saluretic index, sum of Na^+ and Cl^- concentrations, and the Na^+/K^+ and $Cl^-/(Na^+ + K^+)$ ratios were determined based on the magnitude of the diuretic effect. Gloucrular filtration rate (GFR) was determined using the creatinine clearance method.

Results and discussion. According to in silico data, pyrrolopyrimidines exhibit a higher affinity for the A_1AR receptor (-10.8 − -11.2 kcal/mol) than the comparator drug, derenofilin (-9.8 kcal/mol), whilst demonstrating similar pharmacokinetic parameters and a satisfactory toxicological profile. It has been established that they increase GFR by 6–12-fold (from 146 to 944–1,716 ml/day/100 g), whilst maintaining low saluretic indices (0.10–0.20) and moderate rates of sodium and potassium excretion (the Na^+/K^+ ratio decreases to 1.4–3.7). These compounds exert their diuretic effect via haemodynamic mechanisms, by blocking adenosine-induced vasoconstriction of the afferent glomerular arterioles and increasing the glomerular filtration rate.

Conclusions. The results of in vivo experiments and computer modelling have confirmed that 5,5-diphenyl-5,7-dihydro-1H-pyrrolo[2,3-d]pyrimidines are promising A_1AR antagonists; they increase GFR without significant electrolyte loss. This suggests their potential safety for the treatment of cardiorenal syndrome and sets them apart from existing loop diuretics..

References

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