Synthesis and evaluation of sulphonamide clubbed thiophenes as dihydrogen pteroate synthase inhibitors

Pooja Chawla*, Rupinder Kaur

ISF College of Pharmacy, GT Road, Ghal Kalan, Punjab 142001, India

Abstract

Background. Derivatives of thiophene and sulphonamide showed various pharmacological activities including antimicrobial and dihydrofolate reductase (DHFR) inhibition activity. Dihydrofolate reductase and dihydropteroate synthetase enzymes are responsible for bacterial growth and cell proliferation of cancer cells.

Method: In the first step, thiophene was synthesized from cyclohexanone, sulphur and ethyl cyanoacetate by Gewald reaction. Second step involved cyclization of ethyl 2-aminothiophene-3-carboxylate conducted using formamide. In the third step, the carbonyl group was replaced by chlorine in the presence of $POCl_3$. Then the chlorine group was removed by substituted sulphonamide. A series of derivatives were synthesized and evaluated for antimicrobial, anti-oxidant and DHFR inhibition activity. Newly synthesized derivatives of sulphonamide clubbed thiophene showed moderate to excellent antimicrobial and DHFR inhibition activity.

Results. A series of thiophene clubbed sulphonamide conjugates were designed, synthesized and their structures were characterized using ^{1}H NMR, ^{13}C NMR, IR and HR-MS spectral analysis. The antioxidant activity was performed by DPPH and hydrogen peroxide method. Among these derivatives, the compounds **a** and **b** showed comparable anti-oxidant activity 76.29% and 73.25% respectively against DPPH as compared to standard drug ascorbic acid (82.68%). Remaining conjugates displayed significant anti-oxidant activity. The docking study was performed using Molegro virtual docker (MVD) molecular docking suggested a remarkable binding pose for all the thiophene linked sulphonamide derivatives.

Conclusion. Compounds with electron donating groups showed potential activity. The binding affinity of these derivatives against dihydropteroate synthetase (DHTS) and dihydrofolate reductase (DHFR) enzymes were confirmed by molecular docking studies. The ADME and toxicity profile was studied. The compounds can serve as potential DHFR and DHTS inhibitors.