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Abstract

Design and Synthesis of *S*-ribosylhomocysteine analogues

by

Christiane E. Chbib

Bacteria are known to release a large variety of small molecules known as autoinducers (AI) which effect quorum sensing (QS) initiation. The interruption of QS effects bacterial communication, growth and virulence. Three novel classes of *S*-ribosylhomocysteine (SRH) analogues as potential inhibitors of *S*-ribosylhomocysteinase (LuxS enzyme) and AI-2 modulators of QS were developed. The synthesis of 2-deoxy-2-bromo-SRH analogues was attempted by coupling of the corresponding 2-bromo-2-deoxypentafuranosyl precursors with the homocysteinate anion. The displacement of the bromide from C2 rather than the expected substitution of the mesylate from C5 was observed. The synthesis 4-C-alkyl/aryl-S-ribosylhomocysteine analogues involved: (i) conversion of the D-ribose to the ribitol-4-ulose; (ii) diastereoselective addition of various alkyl or aryl or vinyl Grignard reagents to 4-ketone intermediate; (iii) oxidation of the primary hydroxyl group at C1 followed by the intramolecular ring closure to the corresponding 4-C-alkyl/aryl-substituted ribono-1,4-lactones; (iv) displacement of the activated 5-hydroxyl group with the protected homocysteinate. Treatment of the 4-C-alkyl/aryl-substituted SRH analogues with lithium triethylborohydride effected reduction of the ribonolactone to the ribose (hemiacetal) and subsequent global deprotection with trifluoroacetic acid provided 4-C-alkyl/aryl-SRHs. The 4-[thia]-SRH were prepared from the 1-deoxy-4-thioribose through the coupling of the α-fluoro thioethers (thioribosyl fluorides) with homocysteinate anion. The 4-thia-SRH analogues showed concentration dependent effect on the growth on *las (*50% inhibitory effect at 200 µg/mL). The most active was 1-deoxy-4-[thia]-SRH analogue with sufur atom in the ring oxidized to sulfoxide decreasing *las* gene activity to approximately 35% without affecting *rhl* gene. Neither of the tested compounds had effect on bioluminescence nor on total growth of *V. harveyi*, but had however slight inhibition of the QS.

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Department: Chemistry and Biochemistry
Major Professor: Dr Stanislaw F. Wnuk