Abstract

This thesis reports the syntheses and biological activities of benzo- and thieno-fused 7-deazapurine ribonucleosides, which were designed as extended analogues of potent cytostatic 6-hetaryl-7-deazapurine or 6-amino-7-hetaryl-7-deazapurine ribonucleosides. First of all, multigram syntheses of (di)chloro-9*H*-pyrimido[4,5-*b*]indoles from simple chloro-nitrobenzenes were developed. Pyrimidoindoles were successfully glycosylated and used for the synthesis of 4-hetaryl-6-chloro-, 4,6-bis(hetaryl)-, 4-amino-6-hetaryl-, 4-amino-5-hetaryl- and 4-susbtituted pyrimido[4,5-*b*]indole ribonucleosides. Hetaryl groups were introduced by Suzuki or Stille cross-coupling reaction. Standard catalysts and conditions were used for reaction in position 4. To observe some reactivity of unreactive chlorine in position 6, modification of standard protocol was necessary. Screening of several ligands had been done and Buchwald ligand X-Phos was found to be optimal. As chlorine in position 4 is activated for nucleophilic substitution, amino and dimethylamino derivatives were prepared by reaction with aqueous ammonia and dimethylamine, respectively. 4-Alkyl derivatives were synthesized by palladium-catalyzed alkylation with trialkylaluminium or by Negishi coupling in case of cyclopropyl derivative. Desired free nucleosides were obtained directly from reaction with nucleophiles or by Zemplén deprotection. The whole series of new ribonucleosides were screened for cytotoxic and antiviral (HCV and dengue) activity. 4-Amino-5(6)-hetaryl- as well as 4,6-disubstituted nucleosides were completely inactive, whereas several compounds from 4-hetaryl-6-chloro series showed interesting anti-dengue activities and 4-methylpyrimidoindole nucleoside displayed sub-micromolar activity against HCV.

The syntheses of two series of thienopyrrolopyrimidine ribonuclesides were developed. Tricyclic bases were synthesized from simple dichloropyrimidine and iodothiophene by three-step methodology involving thermally or photochemically induced cyclization of tetrazoles. Target nucleosides bearing hetaryl, amino, dimethylamino, methyl, methoxy and methylsulfanyl groups in position 4 were synthesized by the same methodology as pyrimidoindole derivatives. Thieno-fused nucleosides are also completely new, so they are screened for cytotoxic, antiviral (HCV, dengue, influenza, coxsackie, herpes simplex virus) and antimicrobial activity. Methyl, methoxy and methylsulfanyl derivatives from both series showed submicromolar activities accompanied by cytotoxicity in micromolar range.