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Recent advances on the enantioselective synthesis of C-nucleosides inhibitors of inosine monophosphate dehydrogenase (IMPDH)

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Abstract

This review will describe the recent advances in the synthesis of C-nucleosides with inhibitory activity of inosine monophosphate dehydrogenase (IMPDH), a key enzyme in the biosynthesis of guanine nucleotides. The review will cover synthetic approaches of structural analogues showing modifications in the furanose ring as well as in the heterocyclic base. Heterocyclic sugar nucleoside analogues in which the furanose ring has been replaced by a different heterocyclic ring including aza analogues, thioanalogues as well as dioxolanyl and isoxazolidinyl analogues are also considered.

Keywords

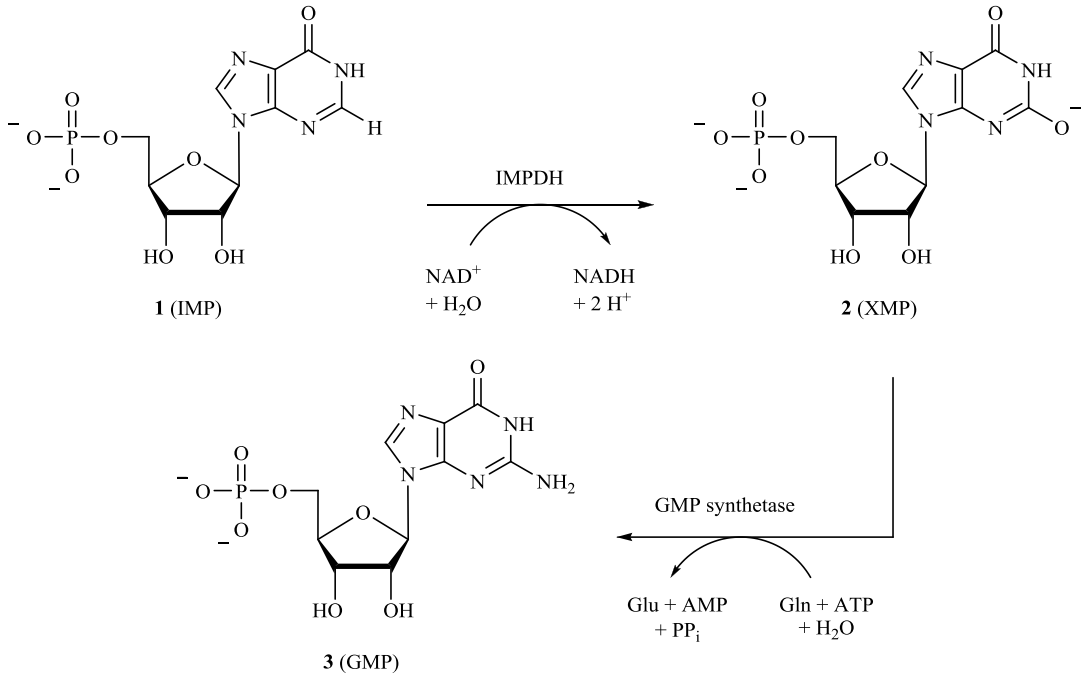
C-Nucleosides / Enzyme inhibitors / Tiazofurin / Thiazole / IMPDH / Heterocyclic nucleosides

Short Running Title

C-Nucleosides inhibitors of IMPDH

Introduction

Inosine monophosphate dehydrogenase (IMPDH) is a key enzyme in the biosynthesis of guanine nucleotides and, thus, pivotal for cell growth. In particular, it is the responsible of transforming inosine monophosphate (IMP) **1** into xanthosine monophosphate (XMP) **2**, which is subsequently transformed into guanosine monophosphate (GMP) **3** by the action of GMP-synthetase (Scheme 1).

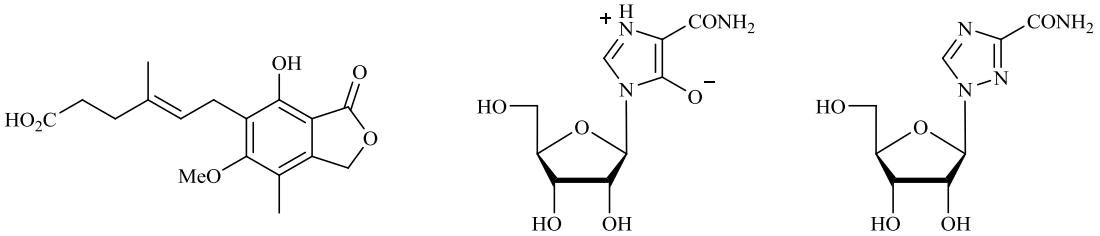


1 (IMP) **2** (XMP) **3** (GMP)

Scheme 1. Biosynthesis of guanine nucleotides

IMPDH was first suggested as a potential target for cancer chemotherapy by Weber and co-workers[1] after it was shown that the activity of IMPDH was amplified in a variety of tumors and rapidly proliferating tissues. The Biology of IMPDH including structure, mechanism and inhibition has been studied in detail [2] and several reviews have been focused on IMPDH as a drug target[3] in cancer, [4] antiviral,[5] immunosuppressive[6] and antimicrobial chemotherapy. [7]

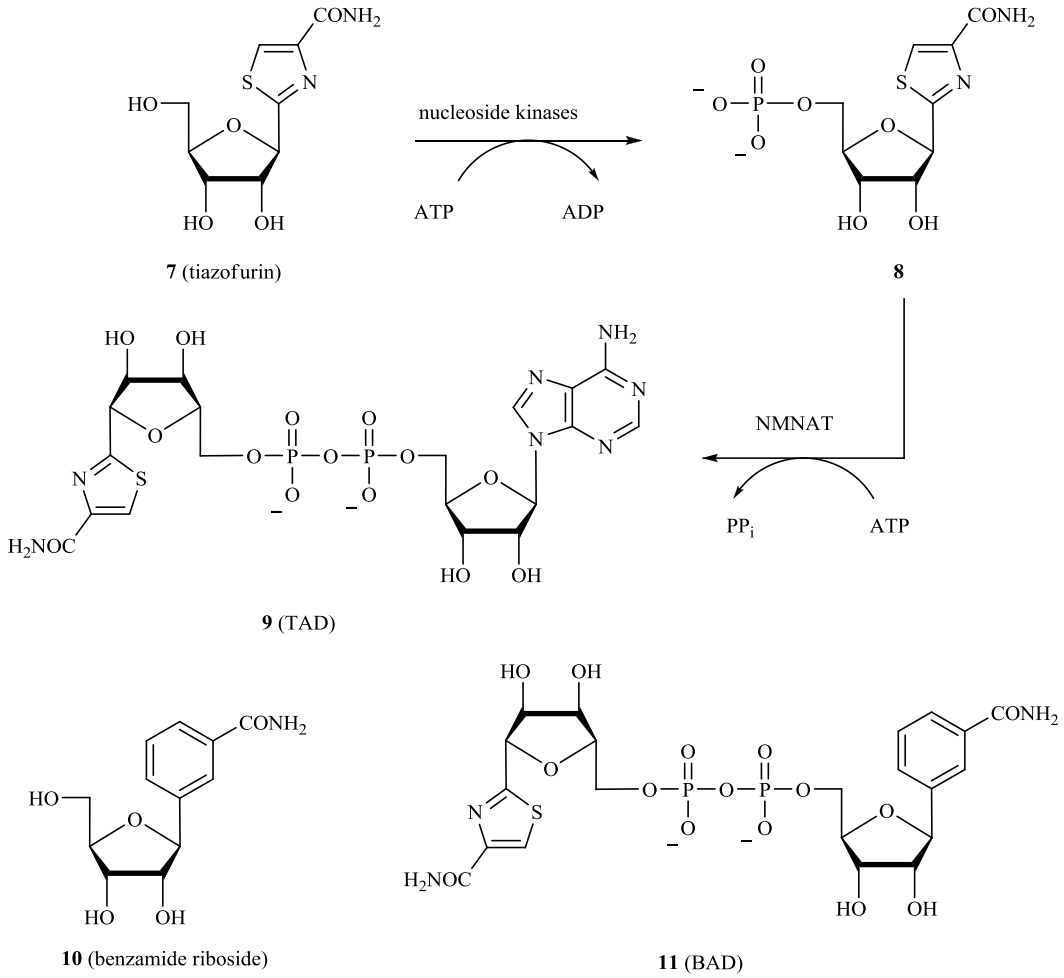
Typically, there are two classes of IMPDH inhibitors,[8] i.e. non-nucleoside inhibitors such as mycophenolic acid (MPA) **4** and nucleoside inhibitors. Among the latter are mizoribine **5** and ribavirin **6**. These nucleoside inhibitors produce IMPDH inhibition via their anabolite 5'-monophosphates. Whereas non-nucleoside inhibitors bind at the NAD site of the enzyme, the nucleoside analogues bind at the substrate site.[9] Nuclear magnetic resonance and molecular modeling studies on **4**[10] indicated that MPA is capable of binding to the nicotinamide site of the enzyme mimicking the NAD^+ inverse regulation.[11] The mechanism of action of ribavirin has been studied in combination with interferon-α (IFNα).[12] Crystal structure of IMPDH in complex with ribavirin demonstrates that **6** targets the substrate binding site.[13]



4 (mycophenolic acid) **5** (mizoribine) **6** (ribavirin)

Figure 1. IMPDH inhibitors

C-nucleosides, like tiazofurin **7** or benzamide riboside **10**, also inhibit IMPDH but through a different mechanism of action to that observed for *N*-nucleosides **5** and **6**. Tiazofurin **7** inhibits IMPDH after its previous activation through phosphorylation and adenylation to form the corresponding dinucleotide TAD, **9** an analogue of NAD (Scheme 2). Similarly, benzamide riboside **10** is converted into the active metabolite BAD **11**. [14] In fact, the identification of the active site of the enzyme [15] and selectivity studies with enzymes from different species,[16] confirmed that nicotinamide adenine dinucleotide (NAD) analogues containing *C*-nucleosides bind at the NAD site of IMPDH and, thus, they can act as competitive inhibitors of the enzyme.[17] In this respect the action of nicotinamide mononucleotide adenylyltransferase (NMNAT) is crucial since this enzyme is the responsible of catalyzing the metabolic conversion of tiazofurin (and its analogues) into its active form tiazofurin adenine dinucleotide (TAD). [18] Notably, pyridine *C*-nucleosides such as *C*-nicotinamide riboside are not metabolized into the adenylated derivatives and thus, they do not exhibit any inhibitory activity.[19]



7 (tiazofurin) **8** **9** (TAD) **10** (benzamide riboside) **11** (BAD)

Scheme 2. Activation of tiazofurin as IMPDH inhibitor

Due to the possibility of targeting both NAD- and substrate-binding sites there is a wide range of scaffolds suitable to be considered IMPDH inhibitors. [20] In particular, *C*-nucleosides have enormous potential in the development of novel IMPDH inhibitors and, consequently, a number of synthetic approaches have been developed towards their preparation. In this review, we focus our attention on *C*-nucleosides with different heterocyclic units linked to the ribose moiety. The members of this family of compounds are considered analogues of tiazofurin **7** and in addition to such product include: i) two-heteroatom containing heterocyclic analogues (selenazofurin **12**, oxazofurin **13** and imidazofurin **14**), and ii) one-heteroatom containing heterocyclic analogues (thiophenfurin **15**, selenophenfurin **16** and furanfurin **17**). Also, *C*-nucleosides in which the ribose moiety has been replaced by a different heterocyclic ring – the so-called heterocyclic-sugar nucleoside analogues-[21] will be discussed. Among these compounds are aza-tiazofurin **18**, thionucleosides **19**-**21**, dioxolanyl tiazofurin **22** and isoxazolidinyl nucleosides **23** and **24** (Figure 2).

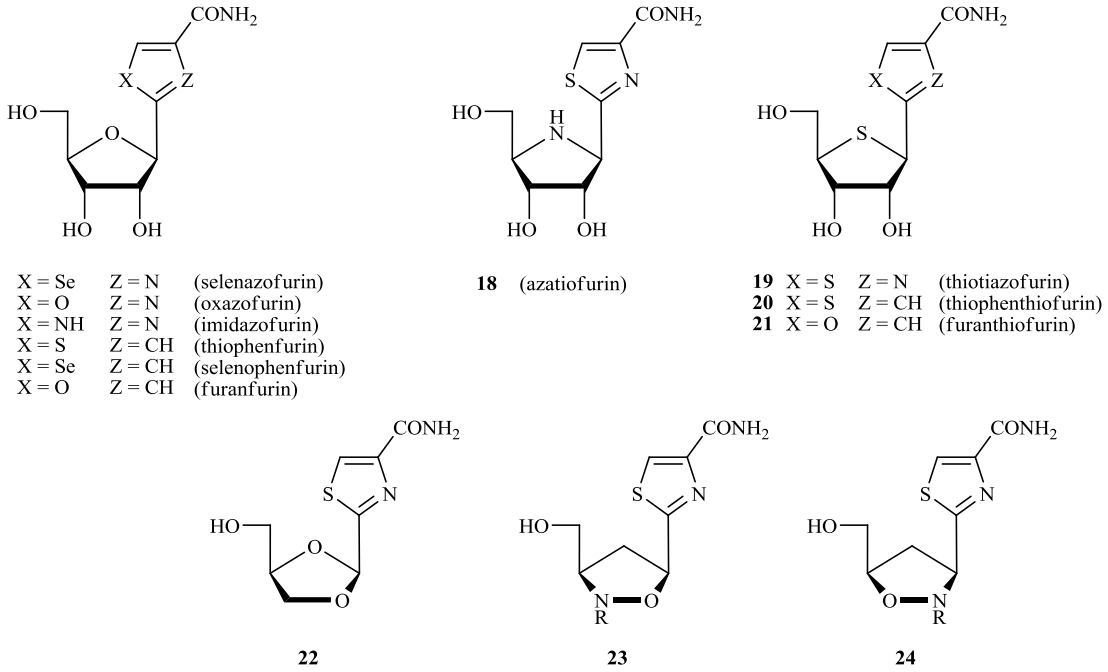
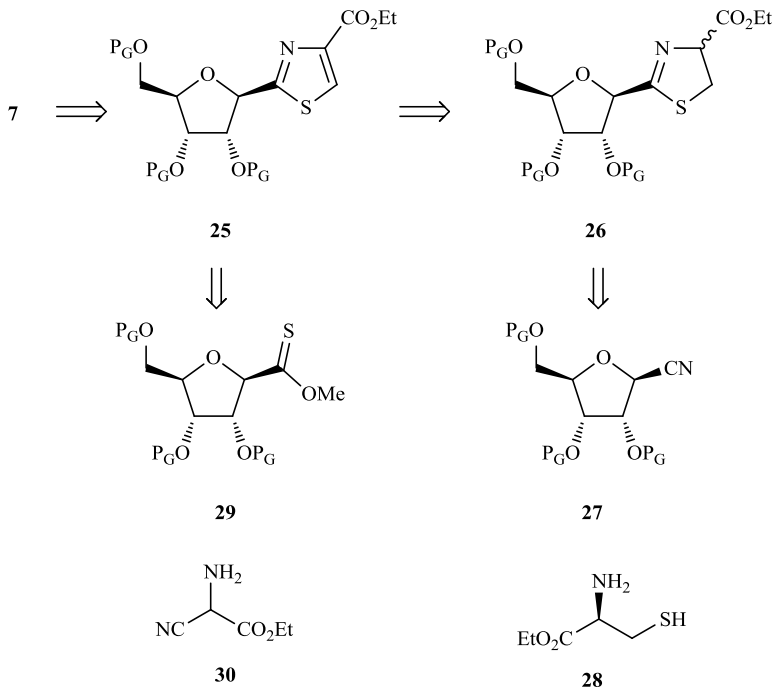


Figure 2. Tiazofurin analogues

The chemical synthesis of nucleoside analogues is a subject of interest in the framework of medicinal chemistry. [22] Although several reviews have been reported elsewhere regarding the biological activity of compounds **7** and **12**-**23**, [7-8,23] chemical synthesis is only discussed partially.[17,24] This review provides the reader with an overview of the chemical synthesis of those *C*-nucleosides. In the case of tiazofurin and their pentose-containing analogues only methodologies developed during the last decade will be considered.

2. Tiazofurin and sugar-containing analogues

Tiazofurin was first synthesized by Robins and co-workers in 1977. [25] Since then, several synthetic approaches have been reported, [26] most of them based on construction of the thiazole ring by cyclocondensation of cysteine ethyl ester **28** with a sugar-derived nitrile **27**, further oxidation of the resulting Δ^2-thiazoline **26**, deprotection and transformation of the ester **25** into the amide moiety as illustrated in the retrosynthetic analysis depicted in Scheme 3.

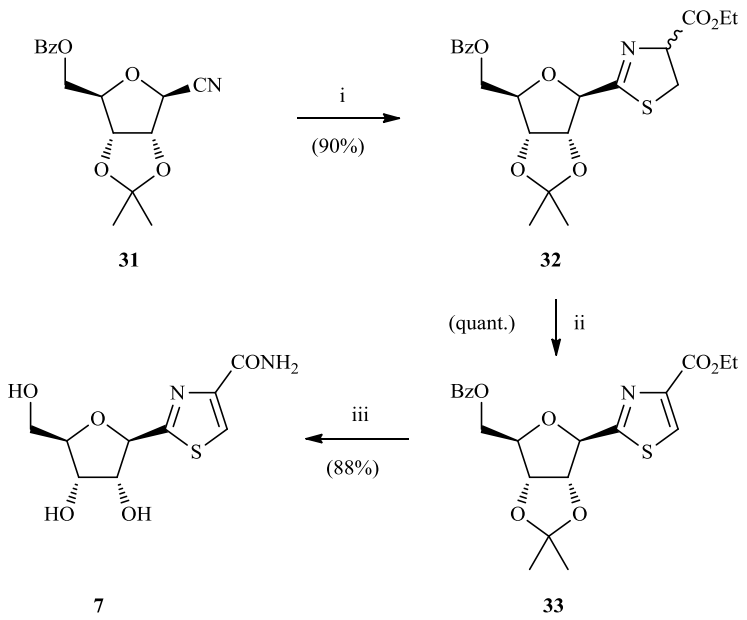


Scheme 3. Retrosynthetic analysis of tiazofurin

An inherent problem to this general approach is the oxidation step of intermediate **26**, which depending on the oxidation conditions can lead to undesired furan-derived byproducts. Also, in this approach the use of toxic oxidants like mercury salts should be avoided.

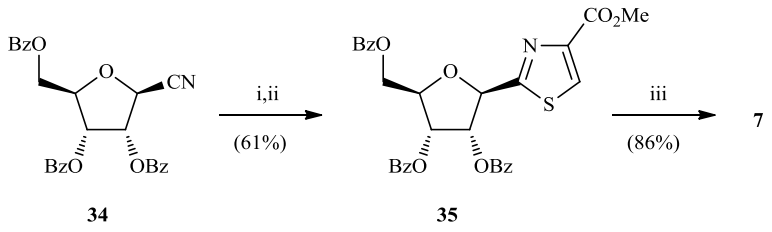
Alternatively, the thiazole ring can also be constructed from the corresponding thioester **29** by condensation with ethyl-2-amino-2-cyanoacetate (**30**) with subsequent elimination of the resulting amino group at C-5 of the thiazole ring. [27] However, this approach involves the use of hydrogen sulfide which is environmentally unsafe when used on large-scale production.

Ramasamy and co-workers reported [26,28] the synthesis of tiazofurin **7** starting from 1-cyano protected D-ribose (**31**) (Scheme 4). Condensation with **28** afforded thiazole **32** which was successfully oxidized with manganese (IV) oxide to give **33**. Further deprotection of the hydroxyl group and treatment with methanolic ammonia afforded tiazofurin **7** in 79% overall yield from **31**. The methodology did not required chromatographic purification therefore being highly suitable for large scale preparation.



Scheme 4. *Reagents and conditions:* (i) **28**·HCl, Et_3N. (ii) MnO_2, benzene, reflux. (iii) 90% TFA, then MeOH, NH_3.

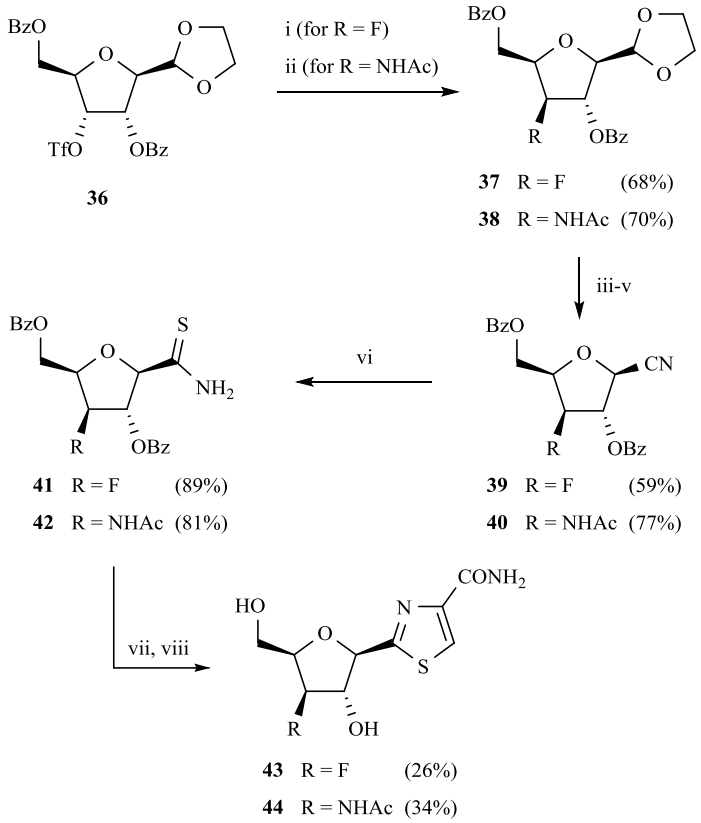
The same approach was employed by Dowden and co-workers [29] who started from the tri-*O*-benzoylateD-1-cyano-D-ribose **34** thus avoiding the final deprotection step since benzoyl groups are eliminated simultaneously during the conversion of the ester moiety into the amide function (Scheme 5). The oxidation step was carried out with bromotrichloromethane in the presence of DBU.



Scheme 5. *Reagents and conditions:* (i) **28**·HCl, Et_3N. (ii) $BrCCl_3$, DBU, CH_2Cl_2, 0 ºC. (iii) MeOH, NH_3, rt, 20 h.

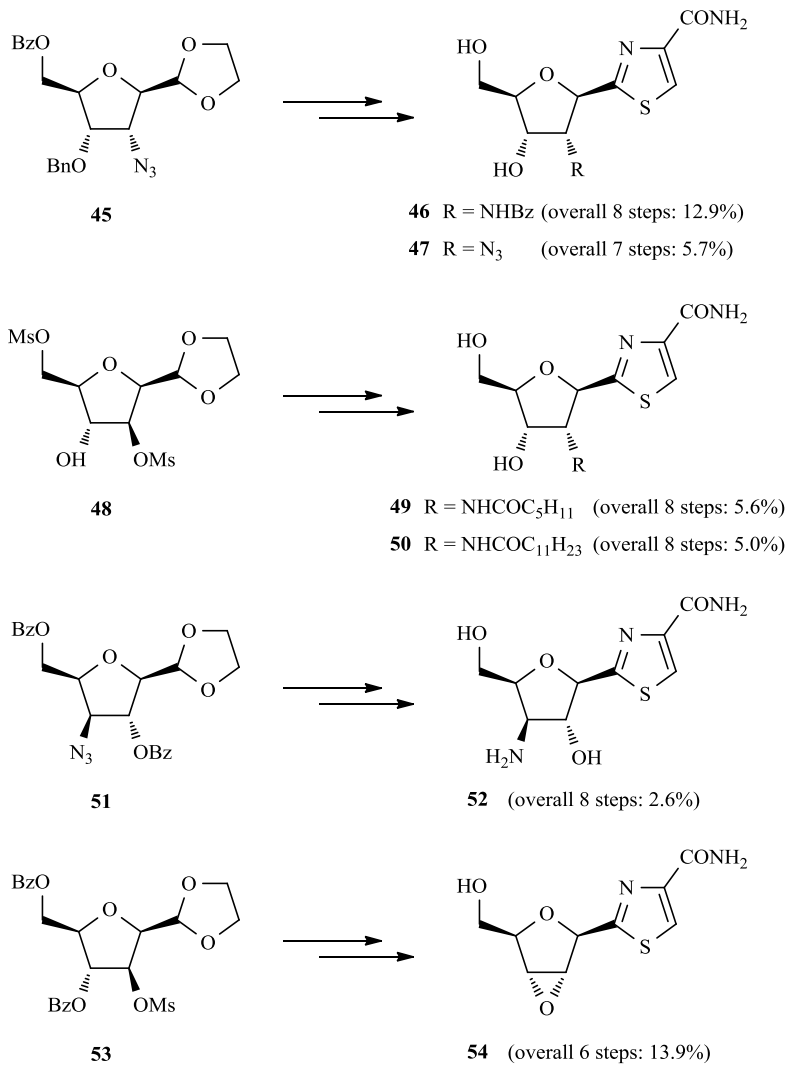
The lack of specifity and cytoxycity found for tiazofurin during phase II and III clinical trials [30] prompted the search of structural analogues, especially those with variations in the furanose ring. In this context, analogues with xylo [31] and arabino configurations have been prepared [32] and their structural features studied. [33]

Also 5'-, [25,34] 3'- [35] and 2'-substituted [36] derivatives have been reported but none showed significant biological activity. On the other hand, Popsavin and co-workers reported [37] a divergent synthesis of 3'-fluoro and 3'-acetamido analogues **43** and **44** from intermediate **36** -easily available from D-glucose-, [38] which showed potent cytotoxic activity against leukemia and colon adenocarcinoma. The synthetic approach illustrated in Scheme 6 is based on the formation of the corresponding anomeric cyanides **39** and **40**. The construction of the thiazole ring was made through the Hantzsch's condensation of thioamides **41** and **42** with ethyl bromopyruvate.



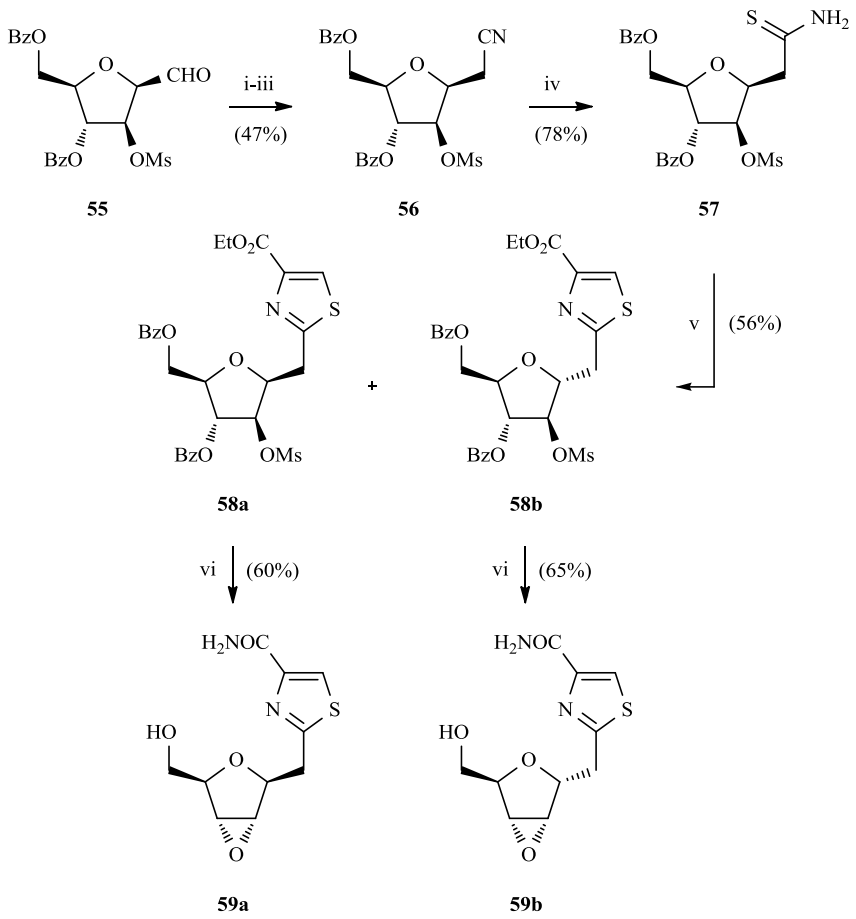
Scheme 6. *Reagents and conditions:* (i) Bu_4NF, THF, -18 ºC, 22 h. (ii) NaN_3, DMSO, THF, rt, 24 h then PtO_2, Ac_2O, AcOH, rt, 21 h. (iii) 9:1 TFA-6M HCl, 4 ºC, 6 days. (iv) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, rt, 2 h. (v) MsCl, Py, -15 ºC, 1.5 h. (vi) H_2S, DMAP, EtOH, rt, 4 h. (vii) $BrCH_2COCO_2Et$, EtOH, 80 ºC, 50 min. (viii) NH_3, MeOH, rt, 8 days.

The same authors reported [39] the synthesis of analogues **46** and **47** by using the same methodology and starting from 2-azido derivative **45** (Scheme 7). Structural analogues **49** and **50** with hexan- and dodecanamido fuctionalities at C2' have also been synthesized from **48** [40] and 3'-amino xylo derivative **52** from **51**. [41]



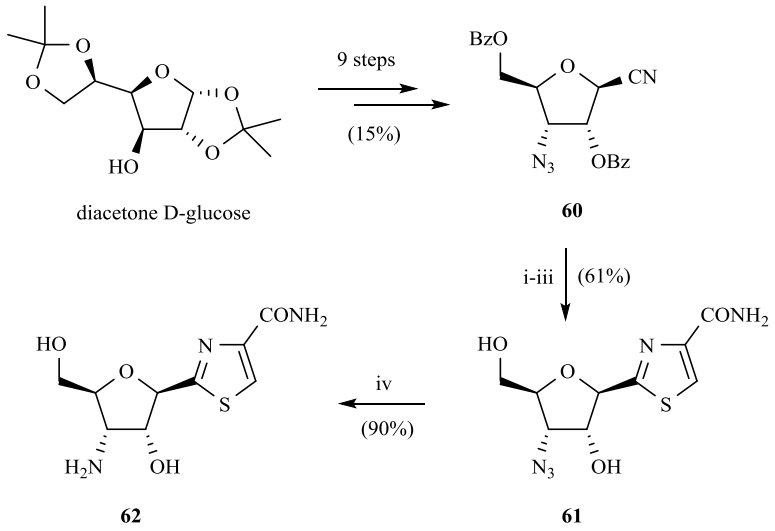
Scheme 7. Synthesis of tiazofurin analogues

2',3'-Anhidro tiazofurin **54** was synthesized from **53** in 6 steps and 13.9 overall yield. [42] Starting from aldehyde **55** -easily available from **53** by acidic hydrolysis- the homologated cyanide **56** was prepared in three steps and 47% overall yield. After formation of thioamide **57** the condensation with ethyl bromo pyruvate afforded a 3:2 mixture of anomers **58**, Methanolic ammoniolysis of these isomers furnished in one step the homologated anhydro analogues **59** (Scheme 8). [43]



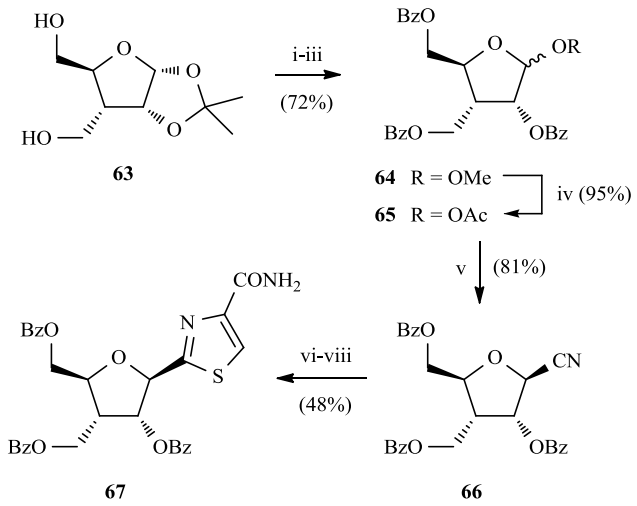
Scheme 8. *Reagents and conditions:* (i) $NaBH_4$, MeOH, 0 ºC, 40 min, then rt, 40 min. (ii) Tf_2O, Py, CH_2Cl_2, -10 ºC, 0.5 h, then rt, 0.5 h. (iii) NaCN, DMF, rt, 1.5 h. (iv) H_2S, Py, rt, 14 days. (v) $BrCH_2COCO_2Et$, EtOH, 80 ºC, 50 min. (vi) NH_3, MeOH, rt, 8 days.

Starting from diacetone-D-glucose, Chun and co-workers reported [44] the synthesis of key intermediate **60** in 9 steps and 15% overall yield (Scheme 9). Further construction of the thiazole ring was carried out through condensation with L-cysteine ethyl ester hydrochloride followed by oxidation with bromotrichloromethane in DBU. Concomitant ammoniolysis of benzoyl esters and formation of the amide group furnished azido analogue **61** which upon hydrogenation at atmospheric pressure provided the 3'-amino derivative **62** (Scheme 9).



Scheme 9. *Reagents and conditions:* (i) **28**·HCl, Et_3N, MeOH, rt, 2 h. (ii) $BrCCl_3$, DBU, CH_2Cl_2, 0 ºC, 16 h. (iii) MeOH, NH_3, rt, 24 h. (iv) H_2, PD-C, EtOH, rt, 14 h.

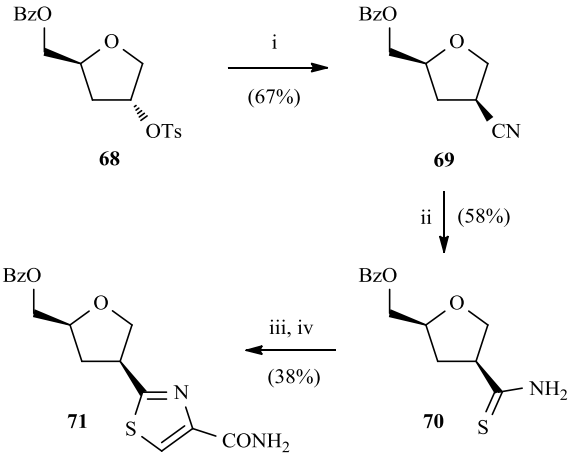
The 3'-deoxy-3'-hydroxymethyl branched derivative **67** was prepared by Chu and co-workers [45] from hydroxymethyl sugar **63**, easily available from D-xylose. [46] After obtention of tri-*O*-benzoyl derivative **64** through conventional carbohydrate chemistry the cyano group was installed at the anomeric position by reaction of trimethylsilyl cyanide with the corresponding 1-acetoxy derivative **65**. The construction of the thiazole ring was achieved as usual by reaction with L-cysteine and using bromotrichloromethane in DBU as oxidizing system of the intermediate oxazoline (Scheme 10). [45]



Scheme 10. *Reagents and conditions:* (i) BzCl, pyridine, rt, 16 h. (ii) 1% HCl in MeOH, rt, 3 h. (iii) BzCl, pyridine, rt, 16 h. (iv) $AcOH/Ac_2O/H_2SO_4$, 0 ºC, 0.5 h. (v) TMSCN, $SnCl_4$, CH_2Cl_2, reflux, 3 h. (vi) L-cysteine ethyl ester hydrochloride, Et_3N, MeOH, 2 h. (vii) DBU, $BrCCl_3$, CH_2Cl_2, 0ºC, 16 h. (viii) NH_3/MeOH, RT, 18 h.

The isodedoxy analogue of tiazofurin has been prepared from dideoxyribose **68** (Scheme 11). [47] Reaction of **68** with potassium cyanide afforded nitrile **69** which was transformed into thioamide **70** by

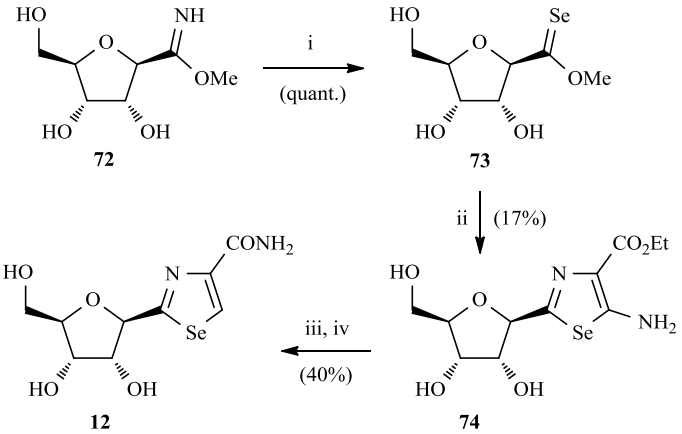
the action of hydrogen sulfide. Condensation of **70** with ethyl bromopyruvate and treatment with methanolic ammonia afforded the analogue **71**.



Scheme 11. *Reagents and conditions:* (i) KCN, [18]-crown-6, DMF, 24 h, 95º. (ii) H_2S, EtOH, Et_3N, 8 h. (iii) $BrCH_2COCO_2Et$, EtOH, reflux. (iv) NH_3, MeOH.

Other sugar-analogues of tiazofurin including acyclic, [48] oxetane [49] and pyranosyl [50] derivatives have also been reported in the past but either low chemical yields were obtained in their synthesis or no significant biological activity was found.

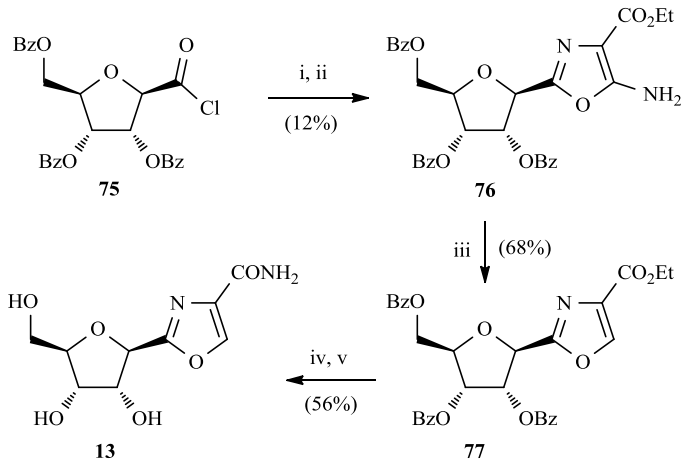
A similar approach to that employed for preparing tiazofurin and analogues with structural modifications in the furanose ring can be employed in the synthesis of analogues with heteroatoms different from sulfur in the heterocyclic base. As an example, the reaction of known imidate **72** with hydrogen selenide furnished methyl selenoate **73**. Condensation of **73** with ethyl 2-amino-2-cyanoacetate **30** afforded intermediate **74**, which was further converted into selenazofurin **12** through elimination of the amino group and formation of the amide functionality (Scheme 12). [51]



Scheme 12. *Reagents and conditions:* (i) H_2Se, MeOH, Dowex-50W-X8, -22ºC. (ii) **30**, MeOH, rt, 30 min. (iii) 18:12:31 HCl-H_2O-50% H_3PO_4, $NaNO_2$, 0ºC to rt, 1h. (iv) NH_3, MeOH, 22ºC, 24 h.

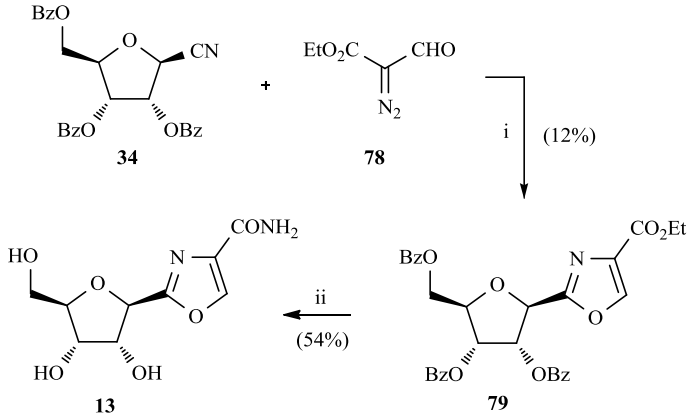
Oxazofurin **13** was prepared by condensation of **30** with acyl chloride **75** in pyridine and further aciD-induced cyclization to provide intermediate **76**. Compound **76** was obtained in only 12% yield due to the formation of undesired elimination products in both condensation and cyclization steps.

Elimination of the amino group of the oxazole ring was carried out over protected **76** to give **77**. Finally, deprotection of the benzoyl groups and formation of the amide furnished the target analogue **13** in 5 steps and 4.6% overall yield (Scheme 13). [52]



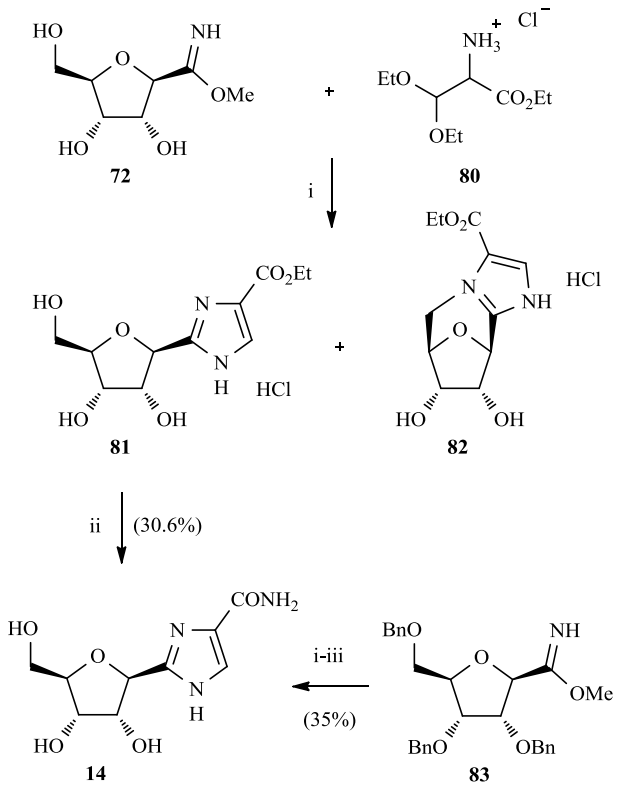
Scheme 13. *Reagents and conditions:* (i) **30**, pyridine, rt, 3 h. (ii) HCl (g), dry acetone, 4ºC, 22 h (iii) HCl-H_2O-50% H_3PO_4, $NaNO_2$, -20ºC, 4 h. (iv) 10% NH_4OH, rt, 6.5 h.

A more expeditious synthesis of **13** was achieved through the reaction of nitrile **34** with ethyl α-formyldiazoacetate **78** in the presence of rhodium (II) acetate. However, also in this case, the yield of the reaction was considerably low and other reaction conditions did not improve the result. Concomitant amide formation and deprotection in **79** provided oxazofurin **13** in 2 steps but 6.5% overall yield (Scheme 14). [53]



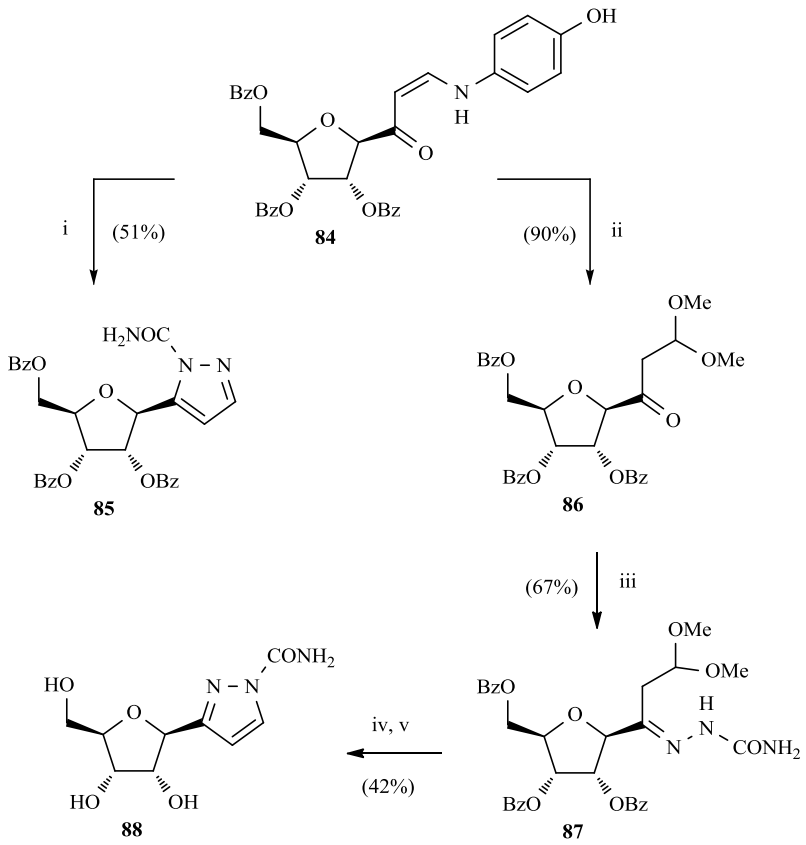
Scheme 14. *Reagents and conditions:* (i) $Rh(OAc)_2$, 85ºC, 15 h. (ii) NH_3, EtOH, rt, 35 h.

Imidazofurin **14** was obtained in two steps from imidate **72**. [54] Condensation of **72** with 2-amino-3,3-diethoxypropionate hydrochloride **80** gave a mixture of the desired product **81** and byproduct **82** (Scheme 15). Treatment of this mixture with methanolic ammonia and further chromatographic separation furnished **14** in 30.6% overall yield (2 steps). The obtention of byproducts could be avoided by working with protected (*O*-benzylated) products. Under such conditions imidazofurin **14** was obtained in 35% overall yield.



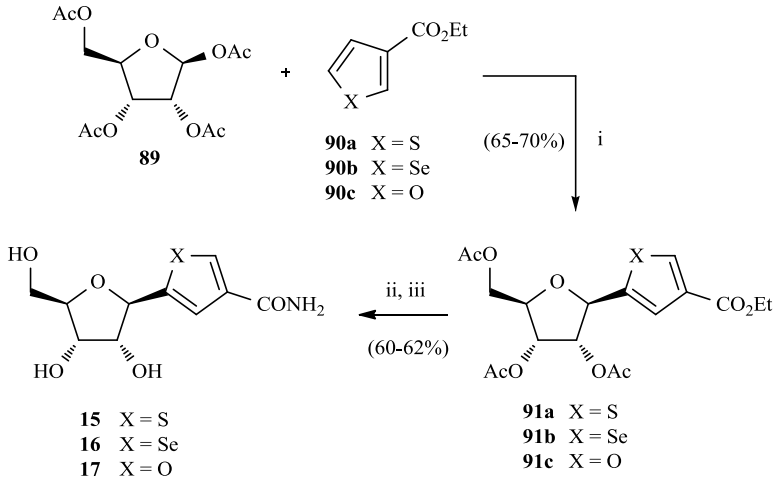
Scheme 15. *Reagents and conditions:* (i) anh. MeOH, rt, 27 h. (ii) NH_3, MeOH, rt, 6.5 h. (iii) PD-C, $HCOONH_4$, MeOH, reflux, 1.5.

The synthesis of pyrazole-containing derivatives have also been described. Treatment of glycosyl enaminone **84**, easily available from D-ribose, [55] with semicarbazide hydrochloride afforded β-D-ribofuranosyl pyrazole **85** in 51% chemical yield. Any attempt of deprotecting benzoyl groups in **85** also led to decarbamoylation of the pyrazole ring and thus, the deprotected pyrazole analogue could not be obtained. On the other hand, acidic hydrolysis of **84** furnished **86** which upon reaction with semicarbazide hydrochloride led to **87**. Cyclization of this compound in TFA and further deprotection with 10% aqueous ammonia furnished the analogue **88** in 25% overall yield (4 steps from **84**) (Scheme 16). [56]



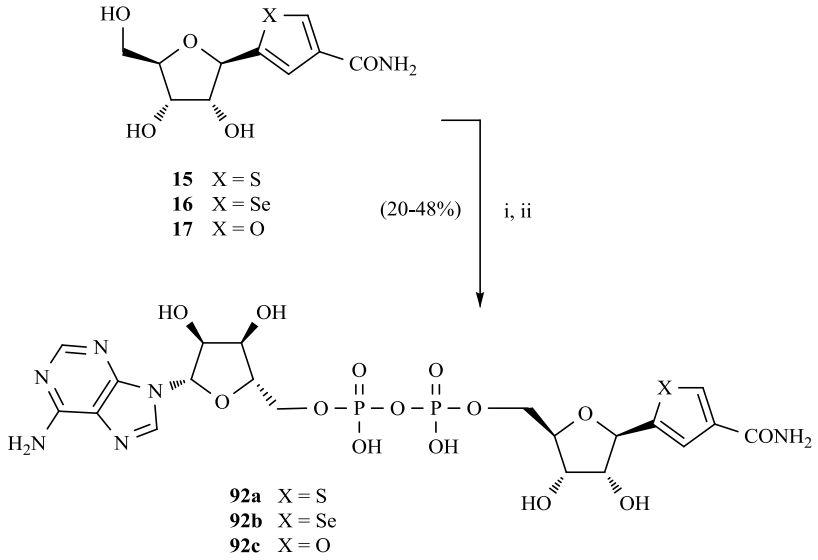
Scheme 16. *Reagents and conditions:* (i) dioxane, $NH_2NHCONH_2$·HCl, r.t., 4 days. (ii) MeOH, HCl, r.t., 15 h. (iii) EtOH, $NH_2NHCONH_2$·HCl, r.t., 5 h. (iv) TFA, r.t., 30 min. (v) aq NH_4OH, refrigerator, 3 days.

Tiazofurin analogues containing one heteroatom in the base moiety, i.e. thiophenfurin **15**, selenophenfurin **16** and furanfurin **17** can be accessed following the same approach. Franchetti and co-workers reported [57] the condensation of the corresponding 3-(ethoxycarbonyl) heterocycle with tetra-*O*-acetyl-β-D-ribofuranose in the presence of tin (IV) chloride. The reaction afforded 2- and 5-regioisomers as mixture of α and β anomers. [58] After chromatographic separation of the desired isomer the benzoyl groups were removed with sodium ethoxide in ethanol and the ester functionality transformed into the amide by treatment with 30% aqueous ammonium hydroxide (Scheme 17).



Scheme 17. *Reagents and conditions:* (i) $SnCl_4$, 1,2-dichloroethane. (ii) NaOEt, EtOH. (iii) 30% NH_4OH.

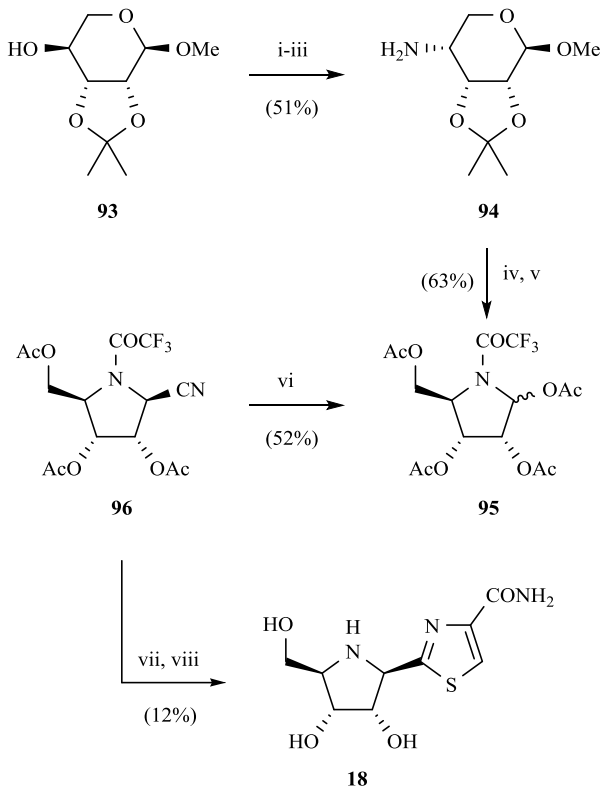
Other analogues containing disubstituted amides at the heterocyclic ring have been prepared in the case of furanfurin. [59] Analogues **15-17** have also been employed for preparing the corresponding dinucleotides, isosteric NAD analogues. [60] The synthesis was carried out by imidazole-catalyzed coupling of the corresponding monophosphates with AMP (Scheme 18)



Scheme 18. *Reagents and conditions:* (i) $POCl_3$, $(MeO)_3PO$, H_2O, 10ºC, 14 h then 2 M TEAB. (ii) AMP, carbonyldiimidazole, Bu_3N, DMF, rt, 3 days.

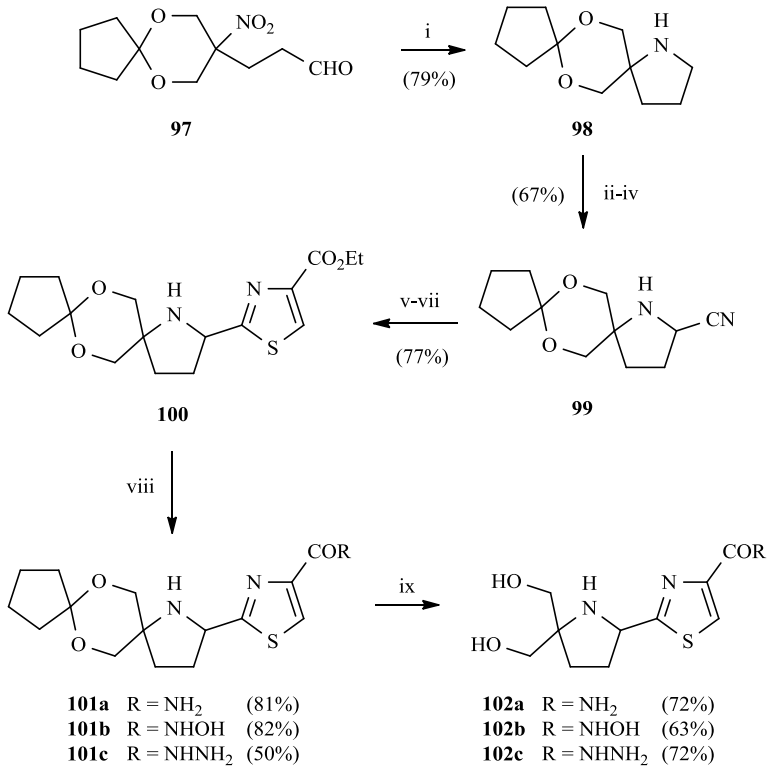
3. Heterocyclic sugar analogues

The synthesis of azatiazofurin **18** started from α-L-lyxopyranoside **93**. Activation of the free hydroxyl group with trimethylsilyl triflate, displacement with sodium azide and further catalytic hydrogenation resulted in aminosugar **94**. Acid hydrolysis, followed by rearrangement and acetylation provided key intermediate **95**, which was cyanylated to give nitrile **96**. Treatment of this compound with hydrogen sulfide and ethylbromopyruvate followed by simultaneous deprotection and amide formation furnished **18** in 8 steps and 2% overall yield from **93** (Scheme 19). [61]



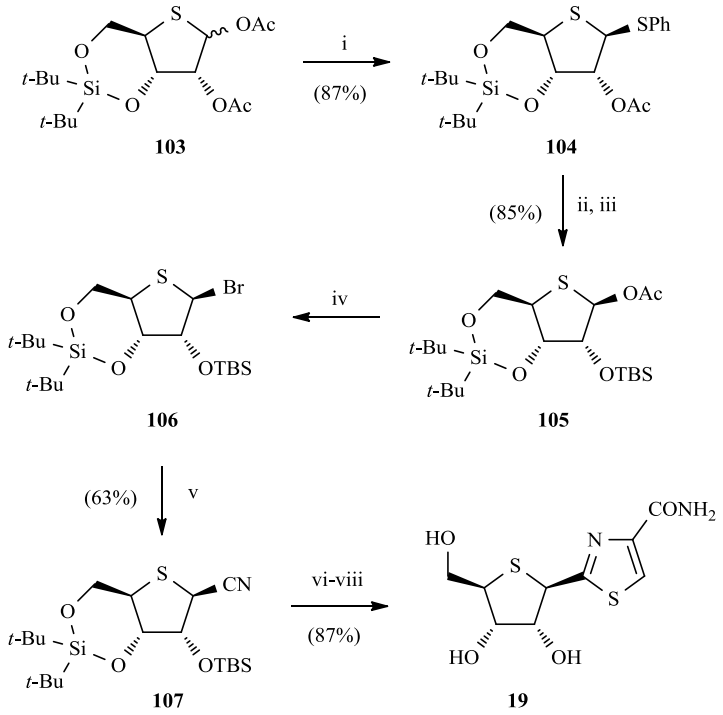
Scheme 19. *Reagents and conditions:* (i) Tf_2O, DMAP, pyridine, CH_2Cl_2. (ii) NaN_3, DMF, rt, 3 h. (iii) H_2, PD-C, EtOH, 50 psi, 16 h. (iv) AcOH, H_2O, 68ºC, 2.5 h, then Ac_2O, AcOH, H_2SO_4, 4ºC, 2 days. (v) TMSCN, $BF_3{\cdot}Et_2O$, 40ºC, 1h. (vi) H_2S, DMAP, rt, 2 days then $BrCH_2COCO_2Et$, MeCN, 0ºC, 1 h, then rt, overnight. (vii) NH_3, MeOH, 0ºC, 5 days.

Novel aza analogues of tiazofurin have been prepared for their evaluation as antiviral agents (Scheme 20). [62] The synthesis of intermediate nitrile **99** was carried out from γ-nitroaldehyde **97** which was prepared in multigram scale. Cyclization of **97** afforded pyrrolidine **98** which was transformed into **99** by treatment with *N*-chlrosuccinimide to generate an intermediate cyclic imine that was immediately cyanylated with hydrogen cyanide in the presence of Hünig's base. The cyanation step took place with 98% chemical yield. In the case of using trimethylsilyl cyanide in the presence of cesium fluoride the yield dropped to 65%. The construction of the thiazole ring was made through condensation of nitrile **99** with L-cysteine ethyl ester and subsequent oxidation with manganese (IV) oxide. Three different analogues **102a-c** were prepared by treating **100** with ethanolic ammonia, hydroxylamine and hydrazine monohydrate followed by acidic hydrolysis with hydrochloric acid in methanol.



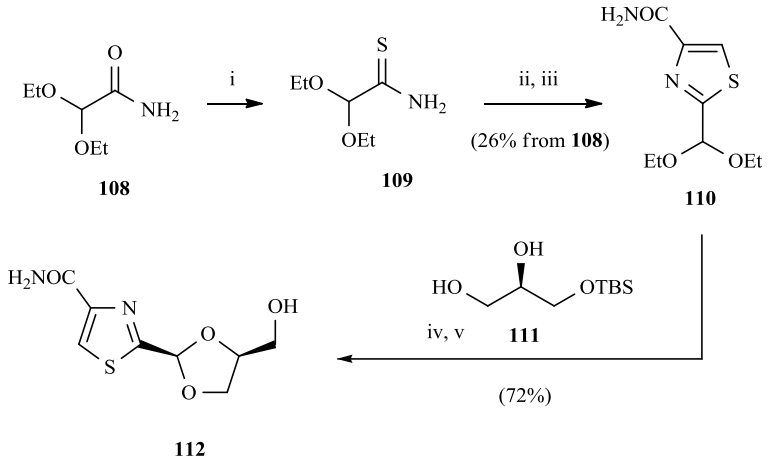
Scheme 20. *Reagents and conditions:* (i) Al–$HgCl_2$, THF–H_2O, rt, 3 hours. (ii) NCS, THF, rt, 2 hours; (iii) DBU, CH_2Cl_2, rt, 3 hours. (iv) 2M HCN in DIPE, rt, 24 hours. (v) $(CF_3CO)_2O$, Py, DMAP, 0◦C, 2 hours. (vi) L-cysteine ethyl ester · HCl, TEA, MeOH, rt, 1.5 hours. (vii) DBU, $BrCl_3$, CH_2Cl_2, 0◦C, 24 hours. (viii) for **101a**: aq NH_3, EtOH, rt, 72 hours; for **101b**: $NH_2OH{\cdot}HCl$, EtONa, EtOH, rt, 24 hours; for **101c**: $NH_2NH_2{\cdot}H_2O$, EtOH, rt, 24 hours. (ix) conc. HCl, MeOH/H_2O, rt, 1–3 days.

Thiotiazofurin **19** was prepared from 1,2-di-*O*-acetyl-4-thioribofuranose **103**. After obtention of the anomeric bromide **106** through conventional carbohydrate chemistry, nitrile **107** was obtained by treatment of **106** with mercury (ii) cyanide. The thiazole ring was formed by condensation with L-cysteine ethyl ester and oxidation with bromotrichloromethane in DBU. Deprotection and amide formation afforded **19** in 8 steps and 40.5% overall yield from **103** (Scheme 21). [63]



Scheme 21. *Reagents and conditions:* (i) (phenylthio)trimethylsilane, $SnCl_4$ CH_2Cl_2, -10ºC, 10 h. (ii) MeOH, NH_3, rt, overnight, then TBSCl, DMF, imidazole, rt, overnight. (iii) $Hg(OAc)_2$, AcOH, rt, 14 h. (iv) TMSBr, CH_2Cl_2, rt, 27 h. (v) $Hg(CN)_2$, MeCN, rt, 22 h. (vi) L-cysteine ethyl ester · HCl, *i*-$PrEt_2N$, 1,2-dichloroethane, rt, 5 days. (vii) DBU, $CBrCl_3$, CH_2Cl_2, rt, 6 h. (viii) NH_3, MeOH, rt, 9 h.

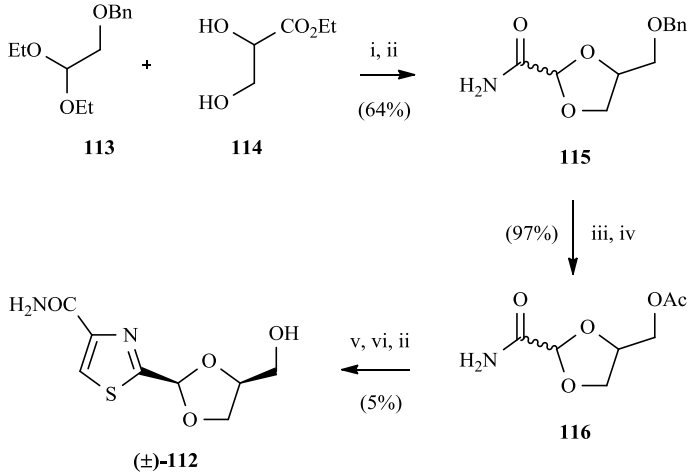
Optically active dioxolanyl analogue **112** was synthesized through condensation of thiazole **100** with chiral diol **111** in an acidic medium (Scheme 22). [64] Compound **110** was prepared in a one-pot procedure from 2,2-diethoxyacetamide **108** via reaction with P_4S_{10} and condensation with ethyl bromopyruvate.



Scheme 22. *Reagents and conditions:* (i) P_4S_{10}, dioxane, r.t., 30 min. (ii) ethyl bromopyruvate, EtOH, reflux, 5h. (iii) NH_3, MeOH, r.t., l h. (iv) benzene, TsOH, reflux, 3h. (v) n-Bu_4NF, THF, r.t., lh.

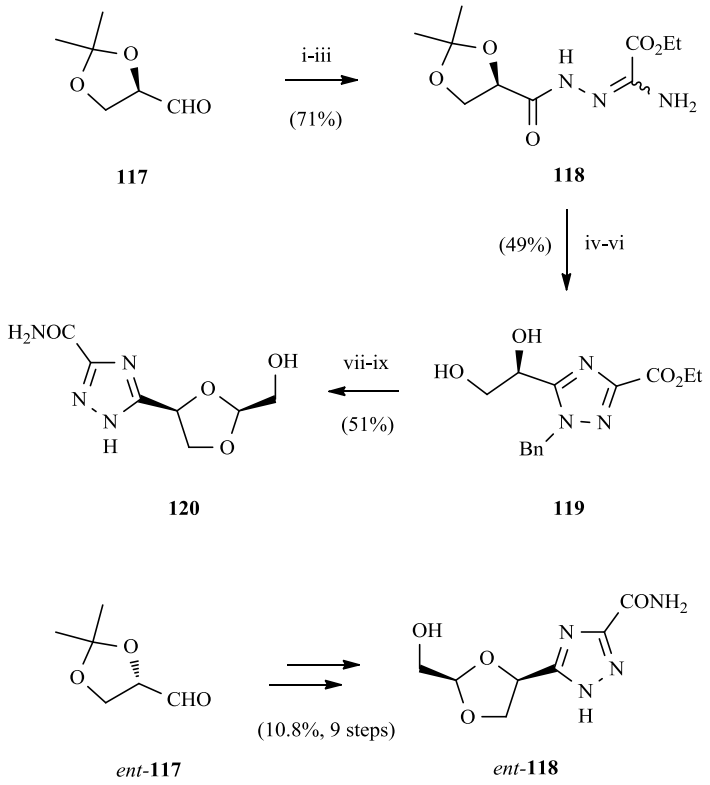
Racemic **112** was also prepared by forming first the dioxolane ring and then constructing the thiazole ring by the same methodology, i.e. condensation of a thioamide with ethyl bromomopyruvate (Scheme

23). [65] Compound **116** was preferentially obtained as the undesired trans-isomer. After formation of the thiazole ring, deprotection and amidation, the *cis*-dioxolane **112** was isolated in only 5% overall yield.



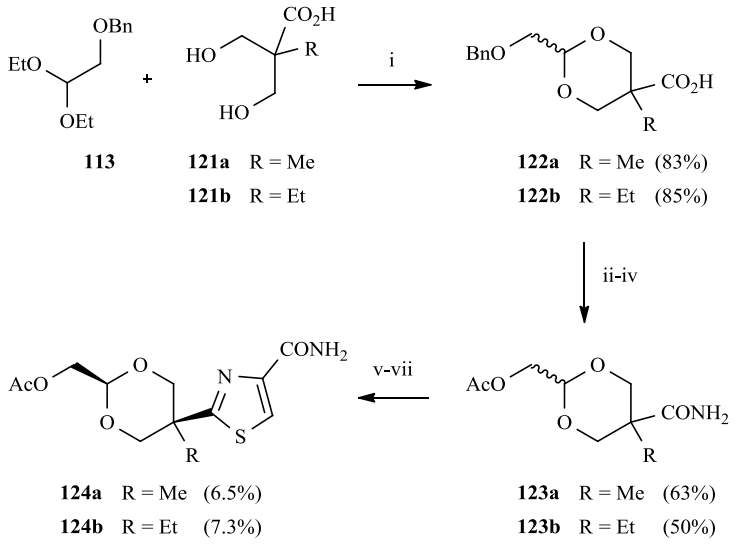
Scheme 23. *Reagents and conditions:* (i) benzene, TsOH, reflux. (ii) NH_3, MeOH, r.t. (iii) H_2, PD-C, EtOH. (iv) Ac_2O, Py, rt. (v) P_4S_{10}, dioxane, r.t. (vi) bromopyruvate, EtOH, reflux.

Dioxolanyl analogues bearing a triazole unit have been prepared by Chu and co-workers. [66] Starting from protected D-glyceraldehyde **117** the triazole ring was synthesized via the corresponding hydrazine derivative **118** obtained from the reaction of an intermediate anhydride with amidrazonate. Construction of the 1,3-dioxolane ring was carried out by condensation the free diol **119** with 2-benzoyloxyacetaldehyde dimethyl acetal (Scheme 24). Two isomers were formed in this reaction and after chromatographic separation the desired *cis* isomer **120** was obtained in 51% yield from the diol after treatment with methanolic ammonia. The overall yield from D-glyceraldehyde was 17.9% / for 9 steps. Enantiomeric *ent*-**118** was also prepared from L-glyceraldehyde *ent*-**117** in 10.8% overall yield (9 steps).



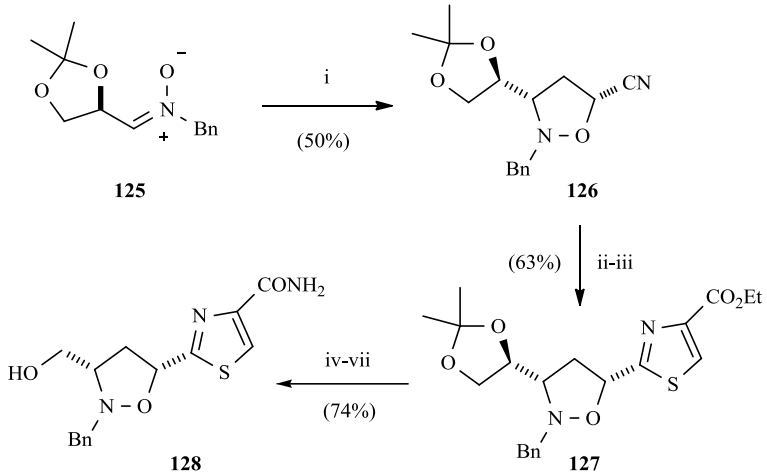
Scheme 24. *Reagents and conditions:* (i) $KMnO_4$, KOH, then 0.5 N H_2SO_4. (ii) ClCOOEt, Et_3N, then NH_4OH. (iii) amidrazonate, [H_2N-N=C(NH_2)-CO_2Et]. (iv) reflux in xylene, 4 h. (v) BnBr, NaH, DMF. (vi) CF_3CO_2H, THF/H_2O (2:1), 50 ºC, 8 h. (vii) $BzOCH_2CH(OMe)_2$, p-TsOH, benzene, reflux. (viii) H_2, $PdCl_2$, EtOH, 50 psi, 6 h. (ix) NH_3, MeOH, autoclave, 110 ºC, 24 h.

Following a similar strategy to that illustrated in Scheme 23 for the synthesis of dioxo1any1 ana1ogue **112**, You and co-workers reported [67] the synthesis of a ring-expanded 1,3-dioxane analogue (Scheme 25). Condensation of **113** with diols **121** afforded 1,3-dioxanes **122**. These compounds were transformed into **123** which were used for constructing the thiazo1e ring and obtaining, after deprotection and amide formation, the analogues **124**.



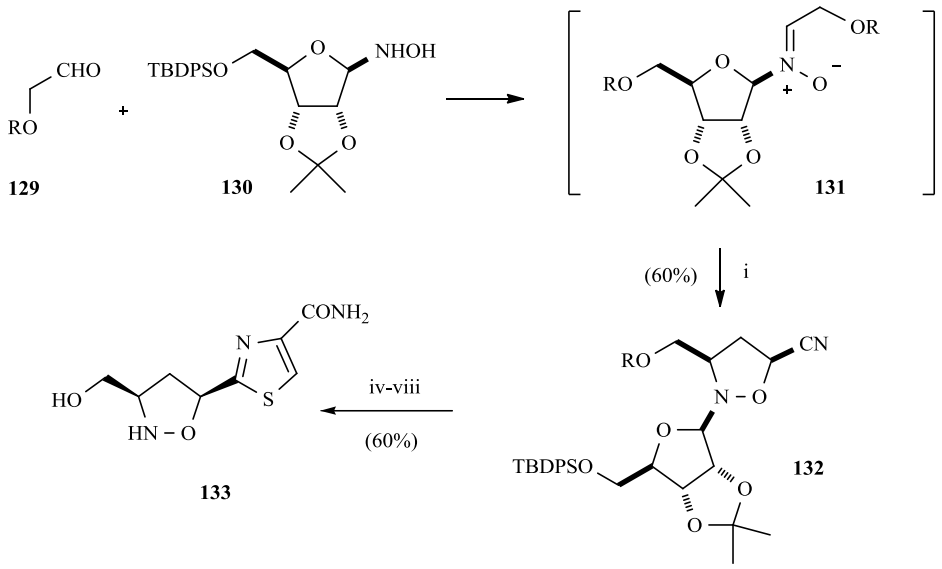
Scheme 25. *Reagents and conditions:* (i) THF, $BF_3{\cdot}Et_2O$, 24 h. (ii) ClCOOEt, THF, TEA, -20ºC to rt., 30 min, then NH_3 (g), -20ºC to rt., 20 h. (iii) PD-C, H_2, MeOH, 10 h. (iv) Ac_2O, Py, rt., 12 h. (v) P_4S_{10}, dioxane, reflux, 1 h. (vi) $BrCH_2COCO_2Et$, EtOH, reflux, 2 h. (vii) NH_3, MeOH, rt., 3 days.

Several isoxazolidinyl analogues of tiazofurin have been prepared through diverse strategies based on 1,3-dipolar chemistry of nitrones. The cycloaddition of D-glyceraldehyde-derived nitrone **125** with acrylonitrile afforded a 35:50:10:5 mixture of adducts from which the major one **126** was chromatographically separated (Scheme 26). [68] Formation of the thiazole ring was achieved by condensation with L-cysteine ethyl ester and oxidation with manganese (IV) oxide. The hydroxymethyl group was unmasked by acetonide hydrolysis and further oxidation to obtain an intermediate aldehyde which was subsequently reduced with sodium borohydride. Final formation of the amide moiety furnished the analogue **128** in 23.3% overall yield from nitrone **125** (7 steps).



Scheme 26. *Reagents and conditions:* (i) acrylonitrile, reflux, 4 h. (ii) L-cysteine ethyl ester · HCl, TEA, MeOH, rt, 3 hours. (iii) MnO_2, benzene, reflux, 12 h. (iv) EtOH, pTsOH, 60ºC, 4h. (v) CH_2Cl_2, aq NaIO4, rt, 15 min. (vi) $NaBH_4$, MeOH, 0ºC, 1 h. (vii) NH_3, MeOH, rt, 1 h.

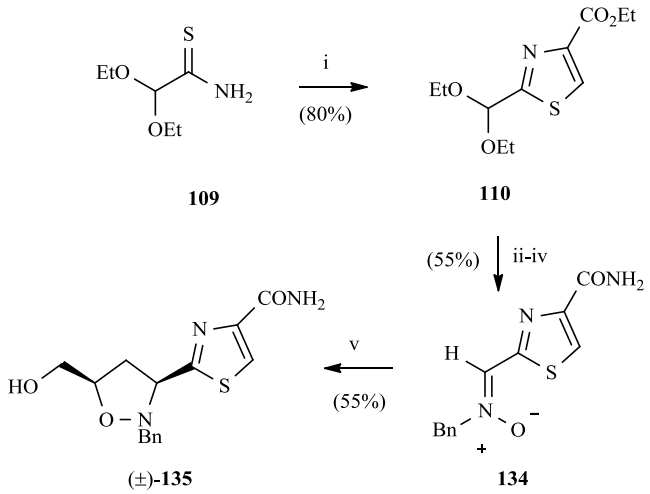
An enantiomeric unsubstituted derivative of **128** was prepared by the same authors [68] using nitrone **131** generated in situ. The opposite asymmetric induction exerted by chiral hydroxylamine **127** furnished intermediate **132** which was transformed into **133** following the same sequence of reactions illustrated in Scheme 26 and finishing with an acidic treatment to eliminate the chiral auxiliary. Thus, the analogue **133** was obtained in 8 steps and 36% overall yield from aldehyde **129** (Scheme 27).



Scheme 27. *Reagents and conditions:* (i) acrylonitrile, reflux, 4 h. (ii) L-cysteine ethyl ester · HCl, TEA, MeOH, rt, 3 hours. (iii) MnO_2, benzene, reflux, 12 h. (iv) EtOH, pTsOH, 60ºC, 4h. (v) CH_2Cl_2, aq $NaIO_4$, rt, 15 min. (vi) $NaBH_4$, MeOH, 0ºC, 1 h. (vii) NH_3, MeOH, rt, 1 h. (viii) 1.5% HCl in EtOH, rt, 3 h.

Compounds **128** and **133** presented the thiazole ring in a vicinal position to the oxygen atom of the isoxazolidine ring. The corresponding regioisomeric analogue in which the thiazole ring was placed vicinal to the nitrogen atom of the isoxazolidine ring was also synthesized. [69]

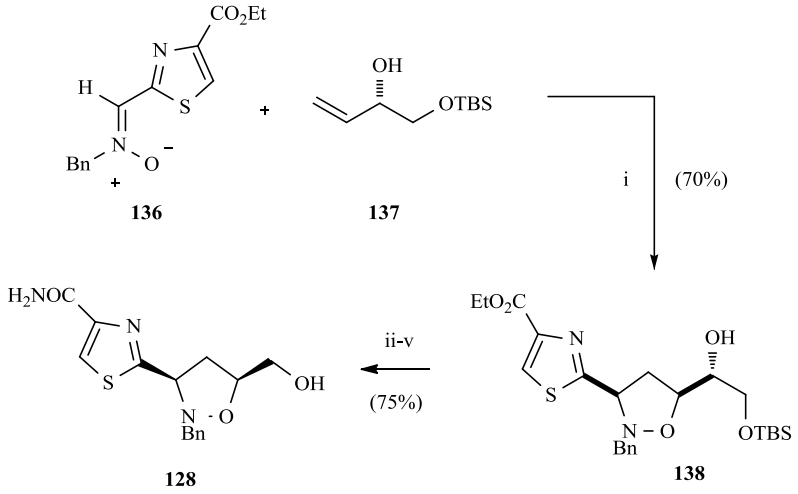
Racemic **135** was directly prepared from nitrone **134** synthesized by the Hantzsch's method from thioamide **109** and ethyl bromopyruvate. Cycloaddition of **134** with allylic alcohol under a variety of conditions furnished mixtures of *cis* and *trans* adducts. However, when the reaction was carried out in the presence of 1.0 eq of zinc (11) triflate and under microwave irradiation, only the desired *cis* isomer **135** was obtained (Scheme 28)



Scheme 28. *Reagents and conditions:* (i) ethyl bromopyruvate, EtOH, molecular sieves, reflux, 90 min. (ii) NH_3, MeOH, r.t., 24 h. (iii) 1 M HCl, reflux, 1 h. (iv) $MgSO_4$, CH_2Cl_2, BnNHOH, rt, 6h. (v) allylic alcohol, CH_2Cl_2, $Zn(OTf)_2$, MW 90 watt, 160 ºC, 15 min.

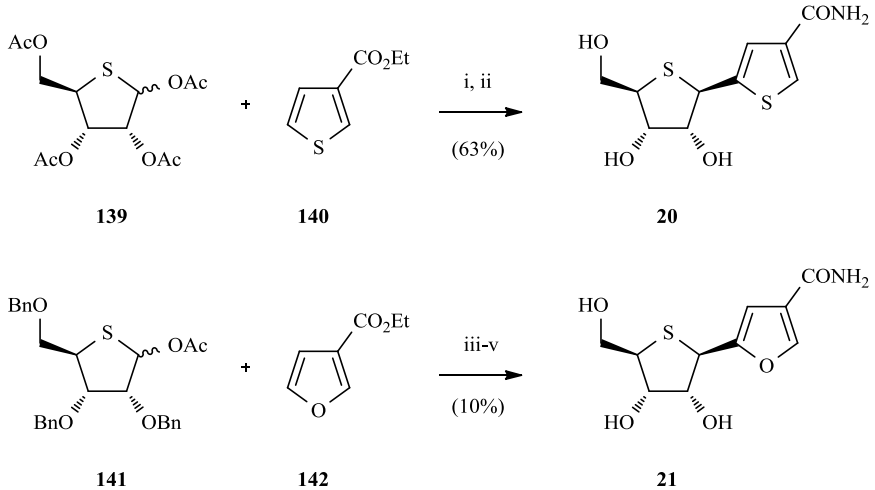
In order to introduce chirality in the process to obtain optically active derivatives, chiral hydroxylamines such as **130** was used to prepare the corresponding nitrones. However, any attempt of conducting the reaction in the presence of Lewis acids only afforded complex reaction mixtures of various compounds from which it was not possible to separate any adduct in a synthetically useful way.

On the other hand, the cycloaddition of nitrone **136**, obtained as illustrated in Scheme 28, with chiral nonracemic monoprotected diol **137** afforded a 4:1 mixture of isomers from which compound **138** was separated. After deprotection, diol cleavage and amide formation, compound **128** was obtained in 5 steps and 53% overall yield from nitrone **136** (Scheme 29).



Scheme 29. *Reagents and conditions:* (i) CH_2Cl_2, $Zn(OTf)_2$, MW 90 watt, 120 ºC, 2 min. (ii) Bu_4NF, THF, rt, 3 h. (iii) CH_2Cl_2, aq $NaIO_4$, rt, 15 min. (iv) $NaBH_4$, MeOH, 0ºC, 1 h.. (v) NH_3, MeOH, r.t., 24 h.

The synthesis of thiophenthiofurin **20** and furanthiofurin **21** have been reported by Franchetti and coworkers. [70] Compound **20** was prepared by direct glycosylation of tetraacetyl derivative **139** with ethyl thiophene-3-carboxylate (**140**). The reaction gave a mixture of 2- and 5-glycosylated regioisomers as α and β anomers in 56% yield. The mixture was treated with methanolic ammonia and the target **20** was separated by column chromatography (Scheme 30). Similarly, glycosylation of tribenzylated **141** with furan derivative **142** gave, after deprotection and amide formation, furanthiofurin **21**.



Scheme 30. *Reagents and conditions:* (i) $SnCl_4$, 1,2-dichloroethane, 0ºC, 30 min, rt, 24 h. (ii) NH_3, MeOH, then NH_4OH, rt, 24 h. (iii) TFA, CH_2Cl_2, 0ºC, 15 min, then warm to rt. (iv) BBr_3, CH_2Cl_2, -78ºC, 1h. (v) 30% NH_4OH, rt, 24h.

Acknowledgements

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