CHAPTER 3

SYNTHESIS OF GLYCOSYLATED UREA
AND THIOUREA DERIVATIVES
SYNTHESIS OF GLYCOSYLATED UREA AND THIOUREA DERIVATIVES

3.1 INTRODUCTION

Glycosyl peptides or peptidic glycosides, a class of molecule of great medicinal value are very important in design and development of novel class of antitubercular compounds.\(^1\)-\(^2\) Many compound with condensed skeleton of ureas or thioureas and sugars are known to possess a variety of biological activities including herbicidal, insecticidal and glycosidase enzyme inhibitory activities.\(^3\)-\(^5\) The enzyme inhibitory activities of such compounds have been exploited in the development of antidiabetic,\(^6\)-\(^12\) antiviral,\(^13\)-\(^21\) anti AIDS,\(^22,23\) anti hyperglycemic,\(^24\) anti fungistatic,\(^25\) insect antifeedant,\(^26\)-\(^28\) anti obesity,\(^29,30\) antibacterial\(^31\) and anticancer\(^32\) agents. Further, a closure look into the chemical structures where urea and thiourea skeletons are responsible for antitubercular activity have prompted medicinal chemist to synthesize different analogs of this class of compound. Among them isoxyl (thiocarlide; 4,4'-diisoamyloxythiocarbanilide),\(^33\)-\(^35\) thiacetazone\(^36\)-\(^39\) and many analogs are known for their antitubercular activity (Figure 39). Several drawbacks associated with these molecules as drugs have opened new vista to synthesize hybrid molecules where thiourea and urea functionalities coupled with structural features offering less toxicity and better pharmacokinetics. These compounds are known to inhibit enzymes involved in *Mycobacterial* cell wall biosynthesis.\(^40\)-\(^48\)

![Figure 39: Thiacetazone and Isoxyl](image)

Further, hydrogen bonding and polarizability characteristics of thio compounds have contributed significantly in the molecular interaction (molecular recognition) process during inter- and intracellular interaction of biological events.\(^49,50\) Peptidyl glycosides are associated with a broad range of pharmacological activities and attempts are being made to develop compounds where amino acid portion of the peptide derivatives is replaced by...
uredyl and thiouredyl unit to get peptidomimetics. The latter could be beneficial not only as new active chemical entities but also as precursors for the synthesis of large number of pharmacologically active compounds. In view of the above facts and the well known characteristics of sugars to offer better stability, pharmacokinetics, transport and above all the less toxicity, syntheses of novel, selective and more potent glycosyl ureas and thioureas were undertaken both in conventional and combinatorial ways.51-53

3. 2 PRESENT WORK

3.2.1 CONVENTIONAL SYNTHESIS OF GLYCOSYL UREAS AND THIOUREAS

The glycosyl amino esters obtained in chapter-2 have been used as starting material for the synthesis of these compounds. Thus (1R, 2R, 3S, 4R) ethyl (5-amino-5,6-dideoxy-1,2-O-isopropylidene-3-O-methyl)-α-D-glucopyranosyl-β-L-idopyranosyl-4-epi-heptofuranurate 11 and (1R, 2R, 3S, 4R) ethyl (5-amino-3-O-benzyl-5,6-dideoxy-1,2-O-isopropylidene)-α-D-glucopyranosyl-β-L-idopyranosyl-4-epi-heptofuranurate 12 were reacted with different isocyanates or isothiocyanates in anhydrous dichloromethane or anhydrous acetonitrile to get the glycosylated urea or thiourea derivatives respectively (Scheme 10, Table 8).

Reagents & Conditions : (a) CH₂Cl₂, R₄NCO, r.t., 2-6 hr
(b) CH₃CN, R₄NCS, r.t., 2-6 hr

Scheme 10: Synthesis of Glycosylated Urea and Thiourea derivatives
Table 8: Glycosylated urea and thiourea derivatives

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<th>Comp. No.</th>
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Thus the reaction of glycosyl amino ester (11) with p-chlorophenyl isocynate in anhydrous dichloromethane resulted in the formation of ethyl [(1R, 2R, 3S, 4R, 5S)-5,6-dideoxy-1, 2-O-isopropylidene- 3-O-methyl-5- {N³-(4-chlorophenyl)-1-ureidyl} -1,4-heptofuranos-5-yl]-uronoate (95) in quantitative yield. The structure was ascertained by IR, MS and NMR spectral data and analysis. IR spectrum of compound 95 showed a strong absorption bands at 1661 cm⁻¹ and 1726 cm⁻¹ corresponding to N-C=O and O-C=O respectively. MS spectrum of the compound 95 showed (M+H)+ at m/z 443. The ¹H NMR spectrum of compound 95 showed three multiplets at δ 7.18 (Ar-H, 4H), 4.40 (H-4 and H-5, 2H) and at δ 2.69 (H-6, 2H). Two D₂O exchangeable peaks at δ 5.60 (m) and at δ 1.78 (s) corresponded to NH protons. H-1, H-2 and H-3 appeared as doublet at δ 5.91 (J = 3.8 Hz), 4.59 (J = 3.8 Hz) and at δ 3.70 (J = 2.2 Hz) respectively. One singlet at δ 3.38 was assigned for methoxy protons and other two signals at δ 1.47 and 1.31 were attributed for isopropylidene methyl protons. One quartet at δ 4.13 and a triplet at δ 1.25 (J = 7.1 Hz) correspond to OCH₂CH₃ protons. In ¹³C NMR spectrum, appearance of signals at δ 155.7 and 138.0 for NCO and Ar-qC respectively, while at δ 127.2 and 121.3 for Ar-CH confirmed the structure of glycosyl urea 95.

Similar reaction of the above glycosyl amino ester 11 with benzyl isocynate gave ethyl [(1R, 2R, 3S, 4R, 5S)- 5,6-dideoxy-1, 2-O-isopropylidene- 3-O-methyl-5- {N³-benzyl-1-ureidyl} -1,4-heptofuranos-5-yl]-uronoate (97). IR spectrum of compound 97 showed CO stretching frequency at νmax 1725 cm⁻¹ and 1685 cm⁻¹. In ¹H NMR spectrum of compound 97, five Ar-H were appeared at δ 7.28 as multiplet and NCH₂ appeared as multiplet at δ 4.35. In ¹³C NMR, signals at δ 158.4; 140.01, 128.79, 127.83, 127.34 and at δ 44.69 corresponded to NC=O, Ar-CH and NCH₂ respectively confirmed the structure of glycosyl urea 97. MS spectrum of the compound 97 showed (M+H)+ at m/z 423. The structures of others glycosyl ureas and thioureas were established on the similar way.

Reaction of N-1 substituted glycosyl amino esters viz 13 and 14 with p-chlorophenyl isocynate gave ethyl (1R, 2R, 3S, 4R)- 5-[N¹-benzyl-N³-(4-chlorophenyl) ureido]-5,6-dideoxy-1,2-O-isopropylidene-3-O-methyl/benzyl-α-D-glucos & β-L-idos-heptofuranuronate (107 and 108) respectively in quantitative yields. In ¹³C NMR spectrum of compound 107 and 108, Carbons adjacent to N-1 such as NCH₂Ph and C-5 were either not appeared or appeared with very little intensity on δ scale.
3.2.2 SOLID PHASE COMBINATORIAL SYNTHESIS OF GLYCOSYLATED UREAS

3.2.2.1 Introduction

Solid phase combinatorial synthesis (SPCS) has emerged as a powerful new technique with a set of novel strategies for generating library of compounds within a very short span. The biological evaluation of such compounds using *High throughput assay systems* (HTS) has reduced the time of lead optimization dramatically in drug discovery research.\(^{54-68}\) The synthetic aspect of this endeavor requires grafting a chemical scaffold on a solid phase followed by synthetic manipulations compatible with the solid support.\(^{69}\)

Combinatorial libraries containing several positions of diversity have been synthesized by the consecutive incorporation of multifunctional building blocks with orthogonal protecting groups. In the case of first building block, the solid support serves as a protecting group for one functionality following incorporation upon deprotection of the orthogonal protecting group, of subsequent building blocks, which are subsequently incorporated until all positions of diversity are added. In addition, the conformationally rigid and functionally rich carbohydrate system is unparallel in its value as a molecular scaffold. Thus effective methods and strategies for generating carbohydrate-based libraries would expand the utility of the combinatorial drug discovery paradigm.\(^{70}\)

A comprehensive carbohydrate-based combinatorial capability requires the ability to link or attach or protect sugars to a solid phase either as such or after modification to desired site. Since monosaccharides and their higher oligomers are conformationally rigid, chiral and highly functionalized molecules, therefore they provide a unique molecular system for appending functionality in a well-defined orientation. They have substantial value as either designed molecular scaffolds from which combinatorial lead optimization can proceed or scaffolds for the construction of primary screening libraries.\(^{71}\)

![Wang Resin](image)

*Figure 40: Wang Resin and Sieberamide Resin*
Although the monitoring of reaction products and intermediates formed during solid phase combinatorial synthesis is complicated as compared with solution phase synthesis yet the polymer-supported synthesis is beneficial than traditional method as it allows the removal of excess of reagents. It is also used to drive the reaction to completion by taking excess of reagents and purification of the reaction products at the end of the synthesis simply by washing the resin, minimizes the number of steps required in purification.

Linker, which connects the polymer support with the substrate and its choice especially important, upon cleavage, the linker functionality remains attached to the scaffold and may influence the biological activity. As carboxylic acids can be liberated by 50 % TFA treatment of wang resin while amides can be generated under relatively very mild condition i.e. 2 % TFA treatment of sieber amide resin. So a suitable linker is often selected by the functionality present in the specific class of target molecules. Besides above, the fluorenyl methoxy carbonyl protocol proved to be sufficiently mild for solid phase synthesis of glycopeptides using glycosyl amino acid as building blocks.

Antitubercular activity of glycosyl amino acids and glycosyl ureas were reported recently by us where glycosyl amino esters were found to be more active than their corresponding acids. Solid phase combinatorial synthesis of a library of glycoconjugates and C nucleosides have also been reported and the same approach may be utilized for the generation of glycoconjugates for biological interest. Hence glycosyl urea based libraries were generated in a parallel format manner on solid phase, using glycosyl amino acid on sieber amide resin followed by sequential reactions including reductive amination, reaction with substituted isocyanates and cleavage from resin under mild condition using 2 % TFA treatment.

3.2.2.2 SYNTHESIS OF LIBRARY

Aldehydes and isocyanates were used as monomers to build the library in a parallel format manner. Aldehydes used were 3-O-methyl-1,2- O-isopropylidene- α-D-xylofuran-5-ulose (7), 3-O-benzyl-1,2- O-isopropylidene- α-D-xylofuran-5-ulose (8), benzaldehyde, furfuraldehyde, 4-methoxy benzaldehyde, salisaldehyde and the isocyanates used were o-tolyl, p-tolyl, 3-chloro-4-methyl phenyl, 4-acetyl phenyl- and benzyl isocyanates. (Figure 41)
Glycosylated Fmoc amino acid (115a) was loaded on sieberamide resin by standard methods of amide coupling using diisopropylcarbodiimide (DIC), di-isopropylethylamine (DIPEA), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate (TBTU) and 1-Hydroxybenzotriazole (HOBT) as coupling agent. Completion of loading was determined by SBFT IR spectroscopy, where appearance of a band around 1700 cm\(^{-1}\) (amide linkage) and disappearance of band at 3300 cm\(^{-1}\) (NH\(_2\) of Sieberamide resin) indicates complete loading of the resin with Fmoc amino acid. Loading of the scaffolds was determined by taking initial and final weight of the resin and it was found to be more than 90 %. Usual deprotection of Fmoc group with piperidine-DMF followed by reductive alkylation/arylation with different aldehydes with sodium cyanoborohydride/trimethylorthoformate in the amino glycosylated resin bound compounds afforded the N-substituted resin bound glycosyl amino ester derivatives which latter on reaction with different isocyanates at room temperature gave resin bound glycosylated urea derivatives (119). Finally, treatment of 119 with 2 % TFA in DCM at ambient temperature afforded the desired glycosyl ureas derivatives [L-120(1-29)] in 60 -90 % yield. The structures of all the compounds were determined on the basis of FAB MS spectral data. However \(^{1}\)H NMR spectra of only few of the compounds were recorded.

![Figure 41a: Aldehydes used as monomers](image)

![Figure 42b: Isocynates used as monomers](image)
The glycosylated urea derivatives were prepared in a parallel format in the 96 well reaction vessel using Vantage millenium automated synthesizer (Advanced Chemtech). The steps involved for the synthesis of desired compounds are as follows:

(i) Deprotection of Fmoc group of sieber amide resin: Sieber amide resin was placed in desired reaction vessel in the machine and swelled in CH₂Cl₂ and DMF at ambient temperature under nitrogen atmosphere. Solvent was purged off and resin was dried in vacuo and then treated with 30 % piperidene in DMF twice for 20 minutes at ambient temperature under nitrogen atmosphere. The solvent was purged off and successively washed with DMF (3 x 2 min), CH₃OH (3 x 2 min) CH₂Cl₂ (3 x 2 min), isopropanol (3 x 2 min) and DMF (3 x 2 min) using wash chem file then dried in vacuo.

(ii) Loading of sugar amino acid on resin: Fluorenyl methoxy carbonyl -3-amino- [(1R, 2R, 3S, 4R)-3-O-methyl-1, 2-O-isopropylidene-1, 4-tetrahydrofuranos-4-yI]-propanoic acid (115) in dry DMF was added to the resin followed by addition of 1-Hydroxy benzotriazole, di-isopropyl ethyl amine, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl uranium tetrafluoro borate and di isopropyl carbodiimide in DMF with N₂ agitation for 4 hrs at room temperature. The solvents and excess reagents were purged off and the resin loaded compound was washed with DMF and again treated with 115 in presence of DIC, HOBT and DMAP for 3 hrs. Again the excess reagents and solvents purged off and resin was washed as above. The completion of reaction was monitored by Kaiser test. 84, 85

(iii) Deprotection of Fmoc group of resin bound compound: The resin bound 3-fluorenylmethoxycarbonyl-amino- [(1R, 2R, 3S, 4R)-3-O-methyl-1, 2-O-isopropylidene-1, 4-tetrahydrofuranos-4-yI)]-propanoyl resin (0.05 g, 0.031 mmol) was placed in 29 wells in reaction block and treated with 20 % piperidine: DMF (1.0 ml) twice for 5 min and 25 min respectively. After this the resin in each well was washed with DMF (3 x 2 min), MeOH (2 x 2 min) and DCM (3 x 2 min).

(iv) Reductive amination: A solution of desired aldehyde (0.31 mmol) of the above list in anhydrous trimethyl orthoformate (TMOF, 1.5 ml) was transferred to the reaction well and mixed for 2 hours followed by addition of a suspension of NaCNBH₃ (0.31 mmol) in
TMOF (0.5 ml) in each well and mixed for 30 minutes. This was followed by addition of glacial acetic acid (20 μl) in TMOF (80 μl) in each well and again mixed for 15 minutes. The resin bound compounds (118) were washed with DMF (3 x 2 min), MeOH (2 x 2 min) and DCM (3 x 2 min).

Reagents & conditions:
(i) LiOH, THF: H₂O:: 2:1, 1hr (ii) Fmoc-Osu, Na₂CO₃, THF, TDW, 8 hrs, 25 °C.
(iii) Sieber Amide Resin, DCC, DMAP, HOBT (iv) 20 % Piperidine/DMF, 15 min
(v) R₁CHO, TMOF, NaCNBH₃, AcOH (vi) R₂NCO, DCM (vii) 2 % TFA in DCM

Scheme 11: Solid phase Combinatorial Synthesis of Glycosyl Ureas
(v) **Reaction with substituted aromatic isocyanate:** A solution of desired isocyanates (0.31 mmol) in anhydrous DCM (2.0 ml) was dispensed in targeted wells and mixed at 25 °C under 50-psi N₂ pressure (inside reaction well) for 12 hours. The resin bound compounds (119) were washed with DMF (3 x 2 min), MeOH (2 x 2 min) and DCM (3 x 2 min).

(vi) **Cleavage with 2% TFA:** The reaction block was cooled to 15 °C by passing liquid N₂ through the block, cleavage vials were placed below the reaction block and the compounds were obtained in CH₂Cl₂ by emptying the reaction wells. Dichloromethane evaporated under N₂ and the compounds were lyophilized by dissolving in t-Butanol / water (4:1) and drying under freeze to give the title compounds L-120 (1-29). Purity of all the compounds were checked using HPLC and it was found to 50-80%.

All the twenty-nine glycosyl urea derivatives synthesized on solid support in parallel format manner and were characterized by spectral data. In FAB MS, all the twenty nine compounds showed [M+H]⁺. ¹H NMR spectra of few representative compounds were recorded. In the ¹H NMR spectrum of the representative compound L-120 [25], five aromatic protons appeared as multiplet at δ 7.30 and three D₂O exchangeable NH protons as broad singlets appeared at δ 7.02, 6.34 and 3.28. Three doublets at δ 5.82 (J = 3.3 Hz), 4.55 (J = 3.3 Hz) and at δ 3.67 (J = 3.0 Hz) were corresponded to H-1, H-2 and H-3 respectively. Besides other usual signals H-4 and H-5 were merged with NCH₂Ph and appeared as multiplet at δ 4.25. In FAB MS spectrum, appearance of molecular ion peak at m/z 394 (M+H)⁺ finally confirmed the proposed structure of glycosyl urea L-120 [25].

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**Synthesized Glycosyl Ureas:**

![L-120[1]](image1)

![L-120[2]](image2)

![L-120[3]](image3)
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### 1D NMR plot parameters

- **C1:** 20.00 cm
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- **F2P:** -2.885 ppm
- **F2:** -145.18 Hz
- **H2CM:** 11.14757 ppm/cm
- **H1CM:** 560.97620 Hz/cm
3.3 EXPERIMENTAL

The library was synthesized on sieber amide resin using a standard method of formation of amide linkage. Aromatic substituted isocyanates were purchased from Lancaster, Sigma and Aldrich. All other reagents and solvents were of standard quality and used after purification. Dichloromethane and acetonitrile were dried over P₂O₅ and calcium hydride respectively. The scaffolds 33 and 34 were synthesized by 1,4- conjugate addition of ammonia on sugar derived olefinic ester (9, 10) followed by the hydrolysis of amino ester (11, 12), with aqueous ethanolic triethylamine at room temperature or using LiOH.H₂O in THF/H₂O mixture as described in experimental part of Chapter 2. The free amino group in precursors of scaffold 116 was protected with Fmoc protecting group. NMR spectra were recorded on a Bruker 300 MHz instrument. HPLC was carried out using a Shimadzu LC 10 AS using a C₁₈ column (4.6 x 250 mm) with acetonitrile-water as mobile phase.

Combinatorial Synthesis of glycosylated urea derivatives:

Synthesis of library of glycosylated urea analogues was carried out on sieber amide resin (0.62 mmol / 1.0 g substitution), purchased from Novabiochem. Anhydrous solvents DMF and DCM were prepared by standard protocol. Coupling reagents DCC, DMAP and HOBt were dried over P₂O₅ in desiccator under vacuum. Loading of Fmoc-3-amino- [(1R, 2R, 3S, 4R)-3-O-methyl-1, 2-O-isopropylidene-1, 4-tetrahydrofuranos-4-yl]-propanoic acid (115a) on sieber amide resin was carried out in a sintered funnel specially designed for solid phase synthesis. Synthesis of library was carried out on Advanced Chemtech Vantage Millenium synthesizer 469 Ω in a parallel format manner.

Fluorenyl methoxy carbonyl -3-amino- [(1R, 2R, 3S, 4R) -3-O-methyl-1, 2-O-isopropylidene-1, 4-tetrahydrofuranos-4-yl]-propanoic acid [115a]

The amino acid derivative (1R, 2R, 3S, 4R) -5-amino-5, 6-dideoxy-1, 2-O-isopropylidene-3-O-methyl -β-L-ido- heptofuranuronic acid (33, 3.35 g, 11.59 mmol) and Na₂CO₃ (1.16 g, 11.60 mmol) were dissolved in triple distilled water (10 ml) and stirred at 0 °C for 5 min. A solution of the protecting agent N-(9-fluorenylmethoxycarbonyloxy) succinimide (3.92 g, 11.63 mmol) in THF (20 ml) was added and stirring was continued for 1 hr at 0 °C then at 25 °C for 12 hrs. The solvent was evaporated to dryness under reduced pressure. The crude product thus obtained was dissolved in water (100 ml) and extracted with ether (2 x 30 ml). The aqueous layer was acidified with KHSO₄ solution, white precipitate formed was dissolved in ethyl
acetate (3 x 100 ml) and washed with water (2 x 10 ml). The organic layer was dried over anhydrous \( \text{Na}_2\text{SO}_4 \) and evaporated under pressure to give compound 115a as colorless foam. (Yield 96%); m.p. = 85 °C. MS (FAB): 484 [M+H]^+; \(^1\)H NMR (CDCl\(_3\), 200 MHz): \( \delta \) 7.25-7.75 (m, 8H, fluorenyl-H), 5.91 (d, \( J = 3.5 \) Hz, 1H, H-1), 5.60 (bs, 1H, NH), 4.58 (d, \( J = 3.5 \) Hz, 1H, H-2), 4.21-4.26 (m, 5H, H-4, H-5, OCH\(_2\)CH\(_3\) and OCH\(_2\)CH), 3.71 (d, \( J = 3.0 \) Hz, 1H, H-3), 3.35 (s, 3H, OCH\(_3\)), 2.66 (m, 2H, H-6), 1.47 and 1.30 [each s, each 3H, C(CH\(_3\))\(_2\)].

Fluorenyl methoxy carbonyl -3-amino- [(1R, 2R, 3S, 4R) -1, 2-O-isopropylidene-3-O-methyl -1, 4-tetrahydrofuranos-4-yl]-propanamide resin [116]
Sieberamide resin (1.5 g, 0.93 mmol) was placed in a solid phase reaction vessel and treated with DMF (10 ml) twice for 5 minutes at ambient temperature, under nitrogen agitation. The resin was again swelled in DCM (15 ml) two times for 5 minutes at ambient temperature under nitrogen agitation. Fmoc-3-amino- [(1R, 2R, 3S, 4R)-1,2-O-isopropylidene -3-O-methyl-1, 4-tetrahydrofuranos-4-yl)]-propanoic acid (2.7 g, 5.58 mmol) was then added to the reaction vessel followed by addition of DIC (0.86 mL, 5.58 mmol), DMAP (0.23 g, 1.86 mmol) and HOBt (0.75 g, 5.58 mmol) in DMF (15 ml) and the reaction mixture was agitated with slow stream of nitrogen gas for 12 hr at room temperature. The solvents and excess of reagents were sucked off and the process of loading of the above compound 115a was repeated in order to have complete loading. The latter was washed with DMF (3 x 2 min), methanol (3 x 2 min) and DCM (3 x 2 min) and dried in vacuo to give amide resin (1.92 g). The loading was checked by means of ninhydrin test. 85

**PHYSICAL DATA OF PROTOTYPE COMPOUNDS:**

(1R, 2R, 3S, 4R, 5S)- 5,6-dideoxy-1, 2-O-isopropylidene- 3-O-methyl-5-N\(^\text{3}\)-2'-hydroxy benzyl (N\(^\text{3}\)-4'-chloro phenyl-1-ureidyl)-1,4-heptofuranos-5-yl - uronamide [L-120 (22)]
MS (FAB): 500 (M+H)^+; \(^1\)H NMR (CDCl\(_3\), 200 MHz): \( \delta \) 7.30, 7.16 and 7.05 (m, 10H, Ar-H and NH), 7.02 and 6.34 (bs, 2H, D\(_2\)O exchangeable NH), 5.82 (d, \( J = 3.3 \) Hz, 1H, H-1), 4.55 (d, \( J = 3.3 \) Hz, 1H, H-2), 4.30-4.19 (m, 4H, H-4, H-5 and NCH\(_2\)), 3.67 (d, \( J = 2.8 \) Hz, 1H, H-3), 3.39 (s, 3H, -OCH\(_3\)), 3.28 (bs, 1H, NH), 2.60 (m, 2H, H-6), 1.45 and 1.28 [each s, each 3H, C(CH\(_3\))\(_2\)].

(1R, 2R, 3S, 4R)- 5,6-dideoxy-1, 2-O-isopropylidene- 3-O-methyl-5- {N\(^\text{3}\)-benzyl-1-ureidyl}-1,4-heptofuranos-5-yl - uronamide [L-120 (25)]
MS (FAB): 394 (M+H)+; \(^1\)H NMR (CDCl₃, 200 MHz): \(\delta\) 7.30 (m, 5H, Ar-H), 7.02 and 6.34 (bs, 2H, D₂O exchangeable NH), 5.82 (d, \(J = 3.3\) Hz, 1H, H-1), 4.55 (d, \(J = 3.3\) Hz, 1H, H-2), 4.30-4.19 (m, 4H, H-4, H-5 and NCH₂), 3.67 (d, \(J = 2.8\) Hz, 1H, H-3), 3.39 (s, 3H, -OCH₃), 3.28 (bs, 1H, NH), 2.60 (m, 2H, H-6), 1.45 and 1.28 [each s, each 3H, C(CH₃)₂].

Ethyl \([(1R, 2R, 3S, 4R, 5S)-\text{5,6}-\text{dideoxy-1, 2-O-isopropylidene- 3-O-methyl-5-}\{\text{N}^3-(4\text{-chlorophenyl})-1\text{-ureidyl}\}-1,4\text{-heptofuranos-5-yl}]-\text{uronoate [95]}\]

To a magnetically stirring solution of glycosyl amino ester 11 (1.0 g, 3.46 mmol) in anhydrous dichloromethane (10 ml), 4- chloro phenyl isocyanate (0.42 ml, 3.46 mmol) was added at 30 °C and stirring continued for 4 h. The solvent was evaporated under reduced pressure and the residue thus obtained, was chromatographed over SiO₂ column using hexane: ethyl acetate (4:1) as eluent to give colorless foam. Yield 95 %; \([\alpha]_D^{25} - 26.66\) (c, 0.11, CHCl₃); MS (FAB): 443 (M+H)+; IR (Neat): \(\nu_{\text{max}}\) cm⁻¹ 3359 and 3019 (NH), 2834, 2937 and 2992 (CH₃ and CH₂ stretching), 1726.2 (ester), 1661.2 (amide); \(^1\)H NMR (CDCl₃, 200 MHz): \(\delta\) 7.18 (m, 4H, Ar-H), 5.91 (d, \(J = 3.8\) Hz, 1H, H-1), 5.60 (m, 1H, NH), 4.59 (d, \(J = 3.8\) Hz, 1H, H-2), 4.40 (m, 2H, H-4 and H-5), 4.13 (q, \(J = 7.1\) Hz, 2H, OCH₂CH₃), 3.70 (d, \(J = 2.2\) Hz, 1H, H-3), 3.38 (s, 3H, OCH₃), 2.69 (m, 2H, H-6), 1.78 (s, 1H, NH), 1.47 and 1.31 [each s, each 3H, C(CH₃)₂], 1.25 (t, \(J = 7.2\) Hz, 3H, OCH₂CH₃); \(^13\)C NMR (CDCl₃): \(\delta\) 172.2 (OC=O), 155.7 (NC=O), 138.2 (Ar-C), 127.12 and 121.3 (Ar-CH), 112.2 [C(CH₃)₂], 105.1 (C-1), 84.50 (C-2), 81.7 (C-4), 80.7 (C-3), 61.2 (OCH₂CH₃), 58.1 (OCH₃), 47.3 (C-5), 37.4 (C-6), 27.1 and 26.6 [2 x C(CH₃)₂], 14.4 (OCH₂CH₃); Anal. Calcd for C₂₀H₂₇N₂O₇Cl: C, 54.24; H, 6.14; N, 6.33; Found: C, 54.30; H, 5.88; N, 6.38 %.

Ethyl \([(1R, 2R, 3S, 4R, 5R/S)-\text{3-O-benzyl-5, 6-dideoxy-1, 2-O-isopropylidene-5-}\{\text{N}^3-(4\text{-chlorophenyl})-1\text{-ureidyl}\}-1,4\text{-heptofuranos-5-yl}]-\text{uronoate [96]}\]

It was obtained by the reaction of compound 12 (1.0 g, 2.73 mmol) and 4-chloro phenyl isocyanate (0.33 ml, 2.73 mmol) as described above and isolated as colorless foam. Yield 90 %. \([\alpha]_D^{25} - 25.45\) (c, 0.14, CHCl₃); MS (FAB): 519 (M+H)+; IR (Neat): \(\nu_{\text{max}}\) cm⁻¹ 3361(NH), 2935 (CH), 1725 (C=O), 1661(NC=O); \(^1\)H NMR (CDCl₃, 200 MHz): \(\delta\) 7.32-7.10 (m, 9H, Ar-H), 5.92 (d, \(J = 3.8\) Hz, 1H, H-1), 5.55 (m, 1H, NH), 4.63 and 4.46 (each d, \(J = 12.0\) Hz, each 1H, OCH₂Ph), 4.62 (d, \(J = 3.8\) Hz, 1H, H-2), 4.30 (m, 1H, H-4), 4.12 (m, 3H, H-5 and OCH₂CH₃), 3.91 (d, \(J = 3.0\) Hz, 1H, H-3), 2.72 (m, 1H, H-6α), 2.56 (d, \(J = 5.5\) Hz, 1H, H-6β), 2.0 (s, 1H, NH), 1.46 and 1.30 [each s, each 3H, C(CH₃)₂], 1.25 (t, \(J = 7.2\) Hz, 3H, OCH₂CH₃);
$^{13}$C NMR (CDCl$_3$): $\delta$ (peaks were duplicated due to diastereoisomeric nature of product) 173.0 and 172.1 (OC=O), 155.5 (NC=O), 138.2, 138.1, 137.3 and 137.1 (Ar-C), 129.2, 129.0, 128.9, 128.5, 128.4, 128.1, 127.8, 121.3, 121.2 (Ar-CH), 112.3 and 112.2 [C(CH$_3$)$_2$], 105.3 and 105.1 (C-1), 82.4 and 82.3 (C-2), 82.1 and 819 (C-4), 80.8 and 80.6 (C-3), 72.5 and 72.2 (OCH$_2$Ph), 61.2 and 61.1 (OCH$_2$CH$_3$), 47.2 (C-5), 37.3 (C-6), 27.1 and 26.6 [2 x >C(CH$_3$)$_2$], 14.5 (OCH$_2$CH$_3$); Anal. Calcd for C$_{26}$H$_{31}$N$_2$O$_7$Cl: C, 60.17; H, 6.02; N, 5.40; Found: C, 58.89; H, 5.53; N, 5.94 %

Ethyl [(1R, 2R, 3S, 4R, 5S)-5,6-dideoxy-1, 2-O-isopropylidene- 3-O-methyl-5- {N$_3$-benzyl-1-ureidyl}-1,4-heptofuranos-5-yl]- uronoate [97]
It was obtained by the reaction of compound 11 (0.8 g, 2.77 mmol) and benzyl isocyanate (0.35 ml, 2.81 mmol) as described above and isolated as colorless foam. MS (FAB): 423 (M+H)$^+$; IR (Neat): $\nu_{max}$ cm$^{-1}$ 3340 (NH), 2970 and 2868 (CH$_3$ and CH$_2$ stretching), 1725 (C=O), 1685 (NC=O); $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 7.28 (m, 5H, Ar-H), 5.84 (d, $J = 3.8$ Hz, 1H, H-1), 5.32- 5.28 (m, 2H, H-5 and NH), 4.52 (d, $J = 3.8$ Hz, 1H, H-2), 4.40-4.29 (m, 3H, H-4 and NCH$_2$), 4.09 (q, $J = 7.1$ Hz, 2H, OCH$_2$CH$_3$), 3.64 (d, $J = 2.6$ Hz, 1H, H-3), 3.34 (s, 3H, -OCH$_3$), 2.61 (m, 2H, H-6), 1.44 and 1.28 [each s, each 3H, C(CH$_3$)$_2$], 1.22 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR (CDCl$_3$): $\delta$ 172.11 (OC=O), 158.41 (NC=O), 140.01, 128.79, 127.34 and 127.34 (Ar-C), 112.06 [C(CH$_3$)$_2$], 105.11 (C-1), 84.70 (C-2), 81.82 (C-4), 80.87 (C-3), 60.98 (OCH$_2$CH$_3$), 57.86 (OCH$_3$), 47.38 (C-5), 44.69 (NCH$_2$), 37.62 (C-6), 27.12 and 26.65 [2 x >C(CH$_3$)$_2$], 14.51 (OCH$_2$CH$_3$); Anal. Calcd for C$_{21}$H$_{30}$N$_2$O$_7$: C, 59.70; H, 7.16; N, 6.63; Found: C, 58.37; H, 7.58; N, 6.68 %

Ethyl [(1R, 2R, 3S, 4R, 5S)-3-O-benzyl - 5,6-dideoxy-1, 2-O-isopropylidene- 5- {N$_3$-benzyl-1-ureidyl}-1,4-heptofuranos-5-yl]- uronoate [98]
It was obtained by the reaction of compound 12 (1.1 g, 3.02 mmol) and benzyl isocyanate (0.38 ml, 3.06 mmol) as described above and isolated as colorless foam. Yield 90 %. [a]$_D^{25}$ - 30.68 (c, 0.08, CHCl$_3$); MS (FAB): 499 (M+H)$^+$; IR (Neat): $\nu_{max}$ cm$^{-1}$ 3370 (NH), 2928 and 2859 (CH$_3$ and CH$_2$ stretching), 1731 (C=O), 1644 (NC=O), 1560 (C=C); $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 7.33 (m, 10H, Ar-H), 5.90 (d, $J = 3.8$ Hz, 1H, H-1), 5.34 (bs, 1H, NH), 5.00 (m, 1H, H-5), 4.66 and 4.43 (each d, $J = 11.8$ Hz, each 1H, OCH$_2$Ph), 4.60 (d, $J = 3.8$ Hz, 1H, H-2), 4.42 - 4.28 (m, 3H, H-4 and NCH$_2$), 4.09 (q, $J = 7.1$ Hz, 2H, OCH$_2$CH$_3$), 3.89 (d, $J = 3.1$ Hz, 1H, H-3), 2.56 (d, $J = 6.7$ Hz, 1H, H-6A), 2.51 (d, $J = 6.3$ Hz, 1H, H-6B), 1.46 and 1.30 [each s,
Ethyl [(1R, 2R, 3S, 4R, 5S)-5,6-dideoxy-1, 2-O-isopropylidene- 3-O-methyl-5- {N\textsuperscript{3}-O-tolyl-1-ureidyl}-1,4-heptofuranos-5-yl]- uronoate [99]

It was obtained by the reaction of compound 11 (1.0 g, 3.46 mmol) and O- tolyl isocyanate (0.435 ml, 3.50 mmol) as described above and isolated as colorless foam. \([\alpha]_D^{25} = -31.90\) (c, 0.10, CHCl\(_3\)); MS (FAB): 423 (M+H\(^+\)); IR (Neat): \(\nu_{\text{max}}\) cm\(^{-1}\) 3340 (NH), 2890 and 2836 (CH\(_3\) and CH\(_2\) stretching), 1726 (C=O), 1680 (NC=O); \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 7.57 (d, \(J = 8.2\) Hz, 1H, NH), 7.12 (m, 2H, Ar- H), 7.00 (d, \(J = 7.3\) Hz, 1H, Ar-H), 6.95 (m, 1H, Ar-\(\text{H}^1\)), 5.83 (d, \(J = 3.7\) Hz, 1H, H-1), 5.75 (s, 1H, -NH), 4.53 (d, \(J = 3.7\) Hz, 1H, H-2), 4.48 (m, 1H, H-5), 4.31 (dd, \(J = 7.1\) Hz and 3.0 Hz, 1H, H-4), 4.09 (q, \(J = 7.1\) Hz, 2H, OCH\(_2\)CH\(_3\)), 3.66 (d, \(J = 3.0\) Hz, 1H, H-3), 3.33 (s, 3H, OCH\(_3\)), 2.68 (dd, \(J = 16.6\) Hz and 6.0 Hz, 1H, H-6\(\alpha\)), 2.57 (dd, \(J = 16.6\) Hz and 6.5 Hz, 1H, H-6\(\beta\)), 2.22 (s, 3H, Ar-CH\(_3\)), 1.43 and 1.28 (each s, each 3H, C(CH\(_3\))\(_2\)), 1.20 (t, \(J = 7.1\) Hz, 3H, OCH\(_2\)CH\(_3\)); \(^1\)C NMR (CDCl\(_3\)): \(\delta\) 171.98 (OC=O), 156.54 (NC=O), 137.16, 131.39, 130.94, 127.01, 125.00 and 123.91 (Ar-C), 112.04 [C(CH\(_3\))\(_2\)], 105.17 (C-1), 84.78 (C-2), 81.78 (C-4), 80.56 (C-3), 61.02 (OCH\(_2\)CH\(_3\)), 57.88 (OCH\(_3\)), 47.24 (C-5), 37.51 (C-6), 27.14 and 26.67 [2 x >C(CH\(_3\))\(_2\)], 18.24 (Ar-CH\(_3\)), 14.53 \(\text{[OCH}_2\text{CH}_3]\); Anal. Calcd for C\(_{27}\)H\(_{34}\)N\(_2\)O\(_7\): C, 66.12; H, 6.49; N, 5.96 %

Ethyl [(1R, 2R, 3S, 4R, 5S)-3-O-benzyl -5,6-dideoxy-1, 2-O-isopropylidene- 5- {N\textsuperscript{3}-O-tolyl-1-ureidyl}-1,4-heptofuranos-5-yl]- uronoate [100]

It was obtained by the reaction of compound 12 (1.2 g, 3.30 mmol) and O- tolyl isocyanate (0.42 ml, 3.35 mmol) as described above and isolated as colorless foam. Yield 90 %. \([\alpha]_D^{25} = -41.56\) (c, 0.15, CHCl\(_3\)); MS (FAB): 499 (M+H\(^+\)); IR (Neat): \(\nu_{\text{max}}\) cm\(^{-1}\) 3362 (NH), 2990 and 2832 (CH\(_3\) and CH\(_2\) stretching), 1728 (C=O), 1660 (NC=O), 1602 (C=C); \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 7.31 (m, 5H, Ar-H), 7.14 - 7.01 (m, four lines having \(J = 8.4\) Hz, 4H, Ar- H), 6.33 (s, 1H, NH), 5.92 (d, \(J = 3.8\) Hz, 1H, H-1), 5.38 (d, \(J = 8.0\) Hz, 1H, -NH), 4.66 and 4.45 (each d, \(J = 11.8\) Hz, each 1H, OCH\(_2\)Ph), 4.61 (d, \(J = 3.8\) Hz, 1H, H-2), 4.38 (m, 2H, H-4 and H-5), 4.10
(q, J = 7.1 Hz, 2H, OCH₂CH₃), 3.91 (d, J = 3.2 Hz, 1H, H-3), 2.57 (m, 2H, H-6), 1.46 and 1.30 [each s, each 3H, C(CH₃)₂], 1.22 (t, J = 7.1 Hz, 3H, OCH₂CH₃); ¹³C NMR (CDCl₃): δ 172.02 (OC=O), 155.85 (NC=O), 137.27, 136.44, 133.41, 129.94, 128.99, 128.57 and 121.39 (Ar-C), 112.26 [C(CH₃)₂], 105.22 (C-1), 82.49 (C-2), 82.39 (C-4), 80.53 (C-3), 72.31 (OCH₂Ph), 61.06 (OCH₂CH₃), 47.14 (C-5), 37.56 (C-6), 27.19 and 26.70 [2 x >C(CH₃)₂], 21.15 (Ar-CH₃), 14.53 (OCH₂CH₃); Anal. Calcd for C₂₇H₃₄N₂O₇: C, 65.04; H, 6.87; N, 5.62; Found: C, 65.96; H, 6.37; N, 6.03 %

Methyl [(1R, 2R, 3S, 4R)- 5,6-dideoxy-1, 2-O-isopropylidene- 3-O-methyl-5- {N₃-3-acetyl phenyl-1-ureidyl}-1,4-heptofuranos-5-yl]- uronoate [101]

It was obtained by the reaction of (1R, 2R, 3S, 4R) methyl [5- amino -5,6-dideoxy -1,2-O- isopropylidene- 3-O- methyl- 1,4-pentofuranos- 4 - yl] - α- D- gluco & β- L-ido-heptanoate 11e (0.4 g, 1.45 mmol) and 3-acetyl phenyl isocyanate (0.2 ml, 1.45 mmol) as described above and isolated as colorless foam. [α]₀ ²⁵ - 38.52 (c, 0.12, CHCl₃); MS (FAB): 437 (M+H)⁺; IR (Neat): v max cm⁻¹ 3328 (NH), 2957 and 2879 (CH₃ and CH₂ stretching), 1724 (C=O), 1683 (NC=O); ¹H NMR (CDCl₃ 200 MHz): δ 7.84 (s, 1H, Ar-H), 7.63 - 747 (m, 2H, Ar- H), 7.29 (m, 1H, Ar-H), 6.10 (d, J = 7.8 Hz, 1H, NH), 5.90 (d, J = 3.7 Hz, 1H, H-1), 4.59 (d, J = 3.7 Hz, 1H, H-2), 4.55 - 4.45 (m, 2H, H-4 and H-5), 3.70 (d, J = 2.90 Hz, 1H, H-3), 3.66 (s, 3H, COOCH₃), 3.35 (s, 3H, OCH₃), 2.76 (m, 2H, H-6), 2.53 (s, 3H, COCH₃), 1.45 and 1.30 [each s, each 3H, C(CH₃)₂]; ¹³C NMR (CDCl₃): δ 199.17 (C=O), 172.55 (OC=O), 155.92 (NC=O), 140.28, 137.87, 129.55, 124.58, 122.80 and 119.33 (Ar-C), 112.16 [C(CH₃)₂], 105.36 (C-1), 84.54 (C-2), 81.77 (C-4), 80.72 (C-3), 57.90 and 52.21 (OCH₃), 47.14 (C-5), 37.22 (C-6), 27.08, 27.00 and 26.56 [2 x >C(CH₃)₂ and COCH₃]; Anal. Calcd for C₂₇H₃₄N₂O₇: C, 57.79; H, 6.47; N, 6.42; Found: C, 58.12; H, 7.01; N, 6.57 %

Ethyl [(1R, 2R, 3S, 4R, 5S)- 3-O-benzyl - 5,6-dideoxy-1, 2-O-isopropylidene- 5- {N₃-3-acetyl phenyl-1-ureidyl}-1,4-heptofuranos-5-yl]- uronoate [102]

It was obtained by the reaction of compound 12 (1.1 g, 3.02 mmol) and 3-acetyl phenyl isocyanate (0.42 ml, 3.05 mmol) as described above and isolated as colorless foam. Yield 90 %; [α]₀ ²⁵ - 43.90 (c, 0.13, CHCl₃); MS (FAB): 527 (M+H)⁺; IR (Neat): v max cm⁻¹ 3340 (NH), 1726 (C=O), 1686 (NC=O); ¹H NMR (CDCl₃, 200 MHz): δ 7.66 and 7.55 (each d, each J = 7.8 Hz, each 1H, Ar-H), 7.37-7.21 (m, 6H, Ar-H), 5.92 (d, J = 3.7 Hz, 1H, H-1), 5.78 (d, J = 8.0 Hz, 1H, NH), 4.66 - 4.48 (m, 4H, OCH₂Ph, H-2 and H-5), 4.36 (dd, J = 7.5 Hz and 3.0 Hz, 1H, 172
Ethyl [(1R, 2R, 3S, 4R, 5S)-5,6-dideoxy-1, 2-O-isopropylidenepy-3-O-methyl-5-\{N- naphthyl-1-ureidyl\}-1,4-heptofuranos-5-yl]-uroonoate \[103\]

It was obtained by the reaction of compound 11 (1.0 g, 3.46 mmol) and naphthyl isocyanate (0.51 ml, 3.53 mmol) as described above and isolated as colorless foam. \([\alpha]_D^{25} - 46.56 (c, 0.19, CHCl_3); MS (FAB): 459 (M+H)^+; IR (Neat): v_{max} \text{ cm}^{-1} 3354 (NH), 2990, 2933 and 2856 (CH_3 and CH_2 stretching), 1728 (C=O), 1651 (NC=O), 1548 (C=C); ^1H NMR (CDCl_3, 200 MHz): \[8.04 \text{ and } 7.83 (each m, each H, naphthyl H), 7.66 (m, 2H, naphthyl H), 7.48 (m, 3H, naphthyl H), 7.12 (bs, 1H, NH), 5.81 (d, \(J = 3.8 \text{ Hz}, 1H, H-1\)), 5.57 (d, \(J = 8.4 \text{ Hz}, NH\)), 4.57 (m, 1H, H-5), 4.50 (d, \(J = 3.8 \text{ Hz}, 1H, H-2\)), 4.31 (dd, \(J = 6.8 \text{ Hz} \text{ and } 3.3 \text{ Hz}, 1H, H-4\)), 4.05 (q, \(J = 7.1 \text{ Hz}, 2H, OCH_2CH_3\)), 3.61 (d, \(J = 3.3 \text{ Hz}, 1H, H-3\)), 3.25 (s, 3H, OCH_3), 2.68 (dd, \(J = 16.4 \text{ Hz} \text{ and } 5.6 \text{ Hz}, 1H, H-6a\)), 2.57 (dd, \(J = 16.4 \text{ Hz} \text{ and } 6.4 \text{ Hz}, 1H, H-6b\)), 1.42 and 1.32 [each s, each 3H, C(CH_3)_2], 1.16 (t, \(J = 7.1 \text{ Hz}, 3H, OCH_2CH_3\)); ^13C NMR (CDCl_3): \[171.92 (OC=O), 156.97 (NC=O), 134.76, 134.16 (fused ring C), 129.15 (q C) 128.79, 126.62, 126.47, 126.17, 126.02, 122.59 and 122.22 (naphthyl-CH), 112.09 [C(CH_3)_2], 105.21 (C-1), 84.93 (C-2), 81.82 (C-4), 80.52 (C-3), 60.99 (OCH_2CH_3), 57.83 (OCH_3), 47.17 (C-5), 37.65 (C-6), 27.18 and 26.68 [2 x >C(CH_3)_2], 14.48 (OCH_2CH_3); Anal. Calcd for C_{21}H_{30}N_2O_7: C, 63.87; H, 6.51; N, 5.32; Found: C, 64.37; H, 7.15; N, 6.16 %

Ethyl [(1R, 2R, 3S, 4R, 5R)-5,6-dideoxy-1, 2-O-isopropylidenepy-3-O-benzyl-5-\{N- naphthyl-1-ureidyl\}-1,4-heptofuranos-5-yl]-uroonoate \[104\]

It was obtained by the reaction of compound 12 (1.0 g, 2.75 mmol) and naphthyl isocyanate (0.4 ml, 2.93 mmol) as described above and isolated as colorless foam. \([\alpha]_D^{25} - 42.59 (c, 0.19, CHCl_3); MS (FAB): 535 (M+H)^+; IR (Neat): v_{max} \text{ cm}^{-1} 3346 (NH), 2949, 2870 and 2943 (CH_3
and CH₂ stretching), 1726 (C=O), 1654 (NC=O), 1559 (C=C); ¹H NMR (CDCl₃, 200 MHz): δ 8.04, 7.70 and 7.57 (each m, each 1H, naphthyl H), 7.47 (m, 4H, naphthyl H), 5.31 (d, J = 8.4 Hz, 1H, NH), 4.63-4.57 (m, 3H, OCH₂Ph, H-2 and H-5), 4.39-4.33 (m, 2H, OCH₂Ph and H-4), 4.07 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 3.87 (d, J = 3.4 Hz, 1H, H-3), 2.58 (dd, J = 16.4 Hz and 5.7 Hz, 1H, H-6A), 2.50 (dd, J = 16.4 Hz and 6.1 Hz, 1H, H-6B), 1.44 and 1.30 [each s, each 3H, C(CH₃)₂], 1.25 (t, J = 7.1 Hz, 3H, OCH₂CH₃); Anal. Calcd for C₃₀H₃₄N₂O₇: C, 67.40; H, 6.41; N, 5.24; Found: C, 69.22; H, 7.02; N, 6.69 %

Ethyl [(1R, 2R, 3S, 4R, sS)-s,6-dideoxy-1,2-0-isopropylidene-3-O-methyl-5- {N³-p-fluoro-1-ureidyl}-1,4-heptofuranos-5-yl]- uronate [105]

It was obtained by the reaction of compound 11 (1.0 g, 3.81 mmol) and naphthyl isocyanate (0.44 ml, 3.85 mmol) as described above and isolated as colorless foam. Yield 95 %; [α]D²⁵ -28.73 (c, 0.11, CHCl₃); MS (FAB): 426 (M+H)⁺; IR (Neat): νmax cm⁻¹ 3346 (NH), 2938 and 2877 (CH₃ and CH₂ stretching), 1725 (ester), 1681 (amide); ¹H NMR (CDCl₃, 200 MHz): δ 7.30 and 6.95 (each m, each 2H, Ar-H), 6.70 (s, 1H, NH), 5.92 (d, J = 3.9 Hz, 1H, H-1), 5.29 (d, J = 8.6 Hz, 1H, NH), 4.59 (d, J = 3.9 Hz, 1H, H-2), 4.47-4.32 (m, 2H, H-4 and H-5), 4.11 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 3.69 (d, J = 3.1 Hz, 1H, H-3), 3.39 (s, 3H, OCH₃), 2.75 (dd, J = 16.2 Hz and 5.0 Hz, 1H, H-6A), 2.60 (dd, J = 16.2 Hz and 5.5 Hz, 1H, H-6B), 1.47 and 1.32 [each s, each 3H, C(CH₃)₂], 1.25 (t, J = 7.1 Hz, 3H, OCH₂CH₃); Anal. Calcd for C₂₉H₄₄N₂O₇: C, 56.33; H, 6.38; N, 6.57; Found: C, 58.03; H, 7.02; N, 6.71 %

Methyl [(1R, 2R, 3S, 4R, 5S)-3-O-benzyl -5,6-dideoxy-1, 2-O-isopropylidene-5- {N³-p-fluoro-1-ureidyl}-1,4-heptofuranos-5-yl]- uronate [106]

It was obtained by the reaction of (1R, 2R, 3S, 4R) methyl [3-O-benzyl-5-amino -5,6-dideoxy-1,2-O-isopropylidene-1,4-pentofuranos-4 - yl] - α- D-glucoside & β- L-idos-heptanoate 12c (0.35 g, 1.00 mmol) and p-fluorophenyl isocyanate (0.12 ml, 1.10 mmol) as described above and isolated as colorless foam. Yield 95 %; [α]D²⁵ -37.59 (c, 0.14, CHCl₃); MS (FAB): 503 (M+H)⁺; IR (Neat): νmax cm⁻¹ 3420 (NH), 2960 and 2886 (CH₃ and CH₂ stretching), 1720
Ethyl (1R, 2R, 3S, 4R, 5S)-5-[N-benzyl-N'-(4-chlorophenyl)ureido]5,6-dideoxy-1,2-O-isopropylidene-3-O-methyl-β-L-idono-heptofuranonate [107]

The glycosyl amino ester 13 (1.0 g, 2.64 mmol) and 4-chlorophenyl isocyanate (0.407 g, 2.65 mmol) in CH₂Cl₂ (15.0 ml) were magnetically stirred at 25 °C for 2 h. Solvent was evaporated and the reaction mixture was chromatographed over a SiO₂ column using a gradient of hexane: ethyl acetate (3:2) as eluent to give compound 107 as colourless foam; (Yield: 95 %). [α]₀D - 44.0 (c 0.2, CHCl₃). MS (FAB): 534 (M+H)+. IR (Neat): νmax cm⁻¹ 3370 and 3306 (NH), 2926, 2858 (CH₃ and CH₂ stretching), 1712 (COOEt), 1665 (CONH); ¹H NMR (200 MHz, CDCl₃): δ 7.42-7.34 (m, 9H, Ar-H), 5.97 (d, J = 3.8 Hz, 1H, H-1), 4.86 and 4.24 (each d, J = 15.3 Hz, each 1H, NCHA and -NCHB), 4.66 (d, J = 3.8 Hz, 1H, H-2), 4.42 (m, 2H, H-4, H-5), 4.08 (q, J = 7.1 Hz, 2H, -OCH₂), 3.63 (d, J = 2.8 Hz, 1H, H-3), 3.39 (s, 3H, -OCH₃), 2.82-2.76 (m, 1H, H-6ₐ), 2.47 (dd, J = 15.7 and 3.6 Hz, 1H, H-6ₖ), 1.47 and 1.31 [2 s, each 3H, C(CH₃)₂] 1.24 (t, J = 7.1 Hz, 3H, -OCH₂CH₂); ¹³C NMR (CDCl₃): δ 172.3 (OC=O), 157.8 (OCO), 129.1 and 122.3 (Ar-C), 112.2 [C(CH₃)₂], 105.0 (C-1), 84.3 (C-2), 81.3 (C-4), 79.7 (C-3), 61.4 (-OCH₂CH₃), 57.1 (-OCH₃), 34.9 (C-6), 27.1 and 26.5 [2 x C(CH₃)₂], 14.4 (CH₃). Anal. Calcd for C₂₇H₃₃N₂O₇Cl: C, 60.72; H, 6.43; N, 5.14 %.

Ethyl [(1R, 2R, 3S, 4R, 5S)-3-O-benzyl-5, 6-dideoxy-1, 2-O-isopropylidene-5-{N₁-benzyl-N³-(4-chlorophenyl)ureido}-1,4-heptofuranos-5-yl]- uronate [108]

It was obtained by the reaction of compound 14 (1.24 g, 2.72 mmol) and 4-chloro phenyl isocyanate (0.33 ml, 2.73 mmol) as described above and isolated as colorless foam. Yield 90 %. [α]₀D 25 - 25.45 (c, 0.14, CHCl₃); MS (FAB): 609 (M+H)+; IR (Neat): νmax cm⁻¹ 3343 (NH), 175
2986, 2935 and 2833 (CH₃ and CH₂ stretching), 1734 (C=O), 1672 (NC=O), 1596 (C=C);

!H NMR (CDCl₃ 200 MHz): δ 7.31 and 7.15 (m, 14H, Ar-H), 5.96 (d, J = 3.8 Hz, 1H, H-1), 4.75-4.66 (m, 4H, CH₂Ph, NCH₂ and H-2), 4.48-4.33 (m, 3H, CH₃Ph, H-4 and H-5), 4.07 (d, J = 7.1 Hz, 2H, OCH₂CH₃), 3.77 (d, J = 3.0 Hz, 1H, H-3), 2.88 (d, J = 12 Hz, 2H, H-6), 1.66 (bs, 1H, NH), 1.40 and 1.29 [each s, each 3H, CCCH₃], 1.19 (t, J = 7.1 Hz, 3H, OCH₂CH₃);

!3C NMR (CDCl₃): δ 171.81 (OC=O), 157.38 (NC=O), 138.86, 136.96, 129.09, 129.00, 128.96, 128.77 and 128.66 (Ar-C), 112.34 [C(CH₃)₂], 105.16 (C-1), 82.16 (C-2), 81.06 (C-4), 79.59 (C-3), 71.86 (OCH₂Ph), 61.50 (OCH₂CH₃), 35.08 (C-6), 27.17 and 26.67 [2 x >CCCH₃];

Anal. Calcd for C₃₃H₃₇ClN₂O₇: C, 65.07; H, 6.12; N, 4.60; Found: C, 65.85; H, 6.93; N, 5.19 %.

Ethyl [(1R, 2R, 3S, 4R, 5S)-5,6-dideoxy-1,2-O-isopropyldene-3-O-methyl-5-{N₃-phenyl-1-thioureidyl}-1,4-heptofuranos-5-yl]- uronoate [109]

Reaction of glycosyl amino ester 11 (0.8 g, 2.77 mmol) with phenyl isothiocyanate (0.34 ml, 2.84 mmol) in anhydrous acetonitrile (10 ml) and workup as described above gave the title compound 109 as colorless foam. Yield 95 %; [α]D²⁵ - 37.58 (c, 0.13, CHCl₃); MS (FAB): 425 (M+H)+; IR (Neat): νmax cm⁻¹ 2973 and 2877 (CH₃ and CH₂ stretching), 1726 (C=O), 1682 (C=S); 

!H NMR (CDCl₃ 200 MHz): δ 8.22 (bs, 1H, NH), 7.33 (m, 5H, Ar-H), 6.84 (d, J = 8.4 Hz, 1H, H-1), 5.10 (m, 1H, H-5), 4.53 (d, J = 3.7 Hz, 1H, H-2), 4.38 (m, 1H, H-4), 4.11 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 3.72 (d, J = 3.2 Hz, 1H, H-3), 3.36 (s, 3H, OCH₃), 2.79 (d, J = 5.9 Hz, 2H, H-6), 1.44 and 1.30 [each s, each 3H, C(CH₃)₂], 1.22 (t, J = 7.1 Hz, 3H, OCH₂CH₃); 

!3C NMR (CDCl₃): δ 180.04 (C=S), 171.63 (C=O), 137.04, 130.15, 126.96 and 124.84 (Ar-C), 112.36 [C(CH₃)₂], 105.13 (C-1), 85.22 (C-2), 82.09 (C-4), 79.68 (C-3), 61.07 (OCH₂CH₃), 58.37 (OCH₃), 51.27 (C-5), 36.97 (C-6), 27.23 and 26.71 [2 x >C(CH₃)₂]; Anal. Calcd for C₁₈H₂₆N₂O₆S: C, 56.59; H, 6.65; N, 6.60; Found: C, 57.48; H, 6.97; N, 5.78 %.

Ethyl [(1R, 2R, 3S, 4R, 5S)-3-O-benzyl-5,6-dideoxy-1,2-O-isopropyldene-5- {N₃-phenyl-1-thioureidyl}-1,4-heptofuranos-5-yl]- uronoate [110]

It was obtained by the reaction of compound 12 (1.0 g, 2.75 mmol) and phenyl isothiocyanate (0.34 ml, 2.84 mmol) as described above and isolated as colorless foam. Yield 95 %; [α]D²⁵ - 38.6 (c, 0.09, CHCl₃); MS FAB: 475 (M+H)+; IR (Neat): νmax cm⁻¹ 3380 (NH), 3021 and 2982 (CH₃ and CH₂ stretching), 1725 (C=O), 1685 (C=S); 

!H NMR (CDCl₃ 200 MHz): δ 8.19 (bs, 1H, H-1), 7.39-7.15 (m, 7H, Ar-H), 6.84 (d, J = 8.4 Hz, 1H, H-2), 4.38 (m, 1H, H-4), 4.11 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 3.72 (d, J = 3.2 Hz, 1H, H-3), 3.36 (s, 3H, OCH₃), 2.79 (d, J = 5.9 Hz, 2H, H-6), 1.44 and 1.30 [each s, each 3H, C(CH₃)₂], 1.22 (t, J = 7.1 Hz, 3H, OCH₂CH₃); 

!3C NMR (CDCl₃): δ 180.04 (C=S), 171.63 (C=O), 137.04, 130.15, 126.96 and 124.84 (Ar-C), 112.36 [C(CH₃)₂], 105.13 (C-1), 85.22 (C-2), 82.09 (C-4), 79.68 (C-3), 61.07 (OCH₂CH₃), 58.37 (OCH₃), 51.27 (C-5), 36.97 (C-6), 27.23 and 26.71 [2 x >C(CH₃)₂]; Anal. Calcd for C₁₈H₂₆N₂O₆S: C, 56.59; H, 6.65; N, 6.60; Found: C, 57.48; H, 6.97; N, 5.78 %.
1H, NH), 7.38-7.16 (m, 10H, Ar-H), 6.86 (d, J = 7.7 Hz, 1H, NH), 5.77 (d, J = 3.6 Hz, 1H, H-1), 5.12 (m, 1H, H-5), 4.62-4.46 (m, 3H, OCH2Ph and H-2), 4.39 (t, J = 3.6 Hz, 1H, H-4), 4.09 (q, J = 7.1 Hz, 2H, OCH2CH3), 3.97 (d, J = 3.1 Hz, 1H, H-3), 2.85 (dd, J = 16.6 Hz and 4.5 Hz, 1H, H-6A), 2.70 (dd, J = 16.6 Hz and 7.6 Hz, 1H, H-6B), 1.42 and 1.29 [each s, each 3H, C(CH3)2], 1.24 (t, J = 7.1 Hz, 3H, OCH2CH3); 13C NMR (CDCl3): δ 179.72 (C=S), 171.54 (C=O); 137.28, 136.95, 130.01, 128.91, 128.62, 126.84 and 124.83 (Ar-C), 112.49 [C(CH3)2], 105.12 (C-1), 83.01 (C-2); 82.77 (C-4), 79.75 (C-3); 72.83 (OCH2Ph), 61.01 (OCH2CH3), 51.08 (C-5); 37.24 (C-6), 27.28 and 26.76 [2 x >C(CH3)2], 14.50 (OCH2CH3); Anal. Calcd for C24H30N2O6S: C, 60.74; H, 6.37; N, 5.90; Found: C, 59.80; H, 6.92; N, 5.47 %.

Ethyl [(1R, 2R, 3S, 4R, 5R/S)-5,6-dideoxy-1, 2-O-isopropylidene-3-O-methyl-5-{N3-chloro phenyl-1-thioureidyl}-1,4-heptofuranos-5-yl]-uronoate [111]

It was obtained by the reaction of compound 11 (0.9 g, 3.11 mmol) and 3-chlorophenyl isothiocyanate (0.42 ml, 3.20 mmol) as described above and isolated as colorless foam. Yield 95 %; [α]D 25 - 31.8 (c, 0.08, CHCl3); MS (FAB): 459 (M+H)+; IR (Neat): v_{max} cm^{-1} 3339 (NH), 3015 and 2936 (CH3 and CH2 stretching), 1728 (C=O); 1H NMR (CDCl3, 200 MHz): δ 7.23 (m, 4H, Ar-H), 6.90 (s, 1H, NH), 5.92 and 5.88 (each d, each J = 3.2 Hz, each 1H, diastereomeric H-1), 5.06 (m, 1H, H-5), 4.59 and 4.53 (each d, each J = 3.7 Hz, each 1H, diastereomeric H-2), 4.38 (m, 1H, H-4), 4.14 (q, J = 7.0 Hz, 2H, OCH2CH3), 3.82 and 3.78 (each d, each J = 3.2 Hz, each 1H, diastereomeric H-3), 3.43 (s, 3H, OCH3), 2.82 (m, 2H, H-6), 1.46 and 1.32 [each s, each 3H, C(CH3)2], 1.25 (t, J = 7.1 Hz, 3H, OCH2CH3); Anal. Calcd for C20H27N2O6SCl: C, 52.34; H, 5.93; N, 6.10; Found: C, 54.14; H, 6.56; N, 5.48 %.

Ethyl [(1R, 2R, 3S, 4R, 5S)-3-O-benzyl -5,6-dideoxy-1, 2-O-isopropylidene-5- {N3-chloro phenyl-1-thioureidyl}-1,4-heptofuranos-5-yl]-uronoate [112]

It was obtained by the reaction of compound 12 (1.0 g, 2.75 mmol) and 3-chlorophenyl isothiocyanate (0.37 ml, 2.82 mmol) as described above and isolated as colorless foam. Yield 95 %; [α]D 25 - 33.9 (c, 0.1, CHCl3); MS (FAB): 535 (M+H)+; IR (Neat): v_{max} cm^{-1} 3377 and 3192 (NH), 2985 and 2936 (CH3 and CH2 stretching), 1727 (C=O), 1591 (C=S), 1527 (C=C); 1H NMR (CDCl3, 200 MHz): δ 8.16 (bs, 1H, NH), 7.41-7.10 (m, 7H, Ar-H), 6.95 (m, 2H, 2H, ArH), 5.87 (d, J = 3.6 Hz, 1H, H-1), 5.00 (bs, 1H, NH), 4.67-4.57 (m, 3H, OCH2Ph and H-2), 4.40 (t, J = 3.0 Hz, 1H, H-4), 4.12 (q, J = 7.1 Hz, 3H, OCH2CH3 and H-5), 3.97 (d, J =3.1 Hz, 1H, H-3), 2.85 (dd, J = 16.6 Hz and 4.2 Hz, 1H, H-6A), 2.70 (dd, J = 16.6 Hz and 8.1 Hz, 1H,
H-6\textsubscript{a}), 1.44 and 1.31 [each s, each 3H, C(CH\textsubscript{3})\textsubscript{2}], 1.21 (t, J = 7.1 Hz, 3H, OCH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): \delta 179.70 (C=S), 171.49 (C=O); 138.32, 137.02, 135.37, 131.00, 128.93, 128.82, 128.61, 126.49, 124.14 and 122.22 (Ar-C), 112.58 [C(CH\textsubscript{3})\textsubscript{2}], 105.16 (C-1), 83.14 (C-2), 82.71 (C-4), 79.79 (C-3), 72.90 (OCH\textsubscript{2}Ph), 61.14 (OCH\textsubscript{2}CH\textsubscript{3}), 50.96 (C-5), 37.35 (C-6), 27.27 and 26.71 [2 x >C(CH\textsubscript{3})\textsubscript{2}], 14.51 (OCH\textsubscript{2}CH\textsubscript{3}); Anal. Calcd for C\textsubscript{26}H\textsubscript{31}N\textsubscript{2}O\textsubscript{6}SCLI: C, 58.36; H, 5.84; N, 5.24; Found: C, 59.49; H, 6.64; N, 5.81 %.

**Ethyl [(1R, 2R, 3S, 4R, 5R/5)- 5,6-dideoxy-1, 2-O-isopropylidene- 3-O-methyl-5- {N\textsuperscript{3}-benzoyl-1-thioureidyl}-1,4-heptofuranos-5-yl]- uronoate [113]**

It was obtained by the reaction of compound 11 (1.40 g, 4.84 mmol) and benzoyl isothiocyanate (0.66 ml, 4.90 mmol) as described above and isolated as colorless foam. Yield 95 %; [\alpha]_D\textsubscript{25} = -38.92 (c, 0.15, CHCl\textsubscript{3}); MS (FAB): 453 (M+H\textsuperscript{+}); IR (Neat): \nu_{max} \text{ cm}^{-1} 3265 (NH), 2987, 2937 and 2834 (CH\textsubscript{3} and CH\textsubscript{2} stretching), 1730 (ester), 1676 (amide); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz): \delta 8.96 (bs, 1H, NH), 7.84 and 7.54 (m, 5H, Ar-H), 5.99 and 5.92 (each d, each J = 3.8 Hz, each 1H, diastereomeric H-1), 5.23 (m, 1H, H-5), 4.60-4.54 (m, 2H, H-2 and H-4), 4.19 (q, J = 7.1 Hz, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 3.87 and 3.78 (each d, each J = 3.3 Hz, each 1H, diastereomeric H-3), 3.48 and 3.42 (each s, each 3H, OCR\textsubscript{3}), 2.96 (dd, J = 6.7 Hz and 16.5 Hz, 1H, H-6\textsubscript{a}), 2.82 (dd, J = 5.7 Hz and 16.5 Hz, 1H, H-6\textsubscript{b}), 1.71 (bs, 1H, NH), 1.49 and 1.32 [each s, each 3H, C(CH\textsubscript{3})\textsubscript{2}], 1.28 (t, J = 7.1 Hz, 3H, OCH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): \delta 179.86 and 179.75 (C=S), 171.32 and 171.25 (C=O), 166.81 and 166.56 (C=O), 133.75, 132.35, 129.39, 129.16, 128.46 and 127.89 (Ar-C), 112.24 [C(CH\textsubscript{3})\textsubscript{2}], 105.46 and 105.31 (C-1), 85.19 and 84.52 (C-2), 81.93 and 81.68 (C-4), 79.43 and 79.35 (C-3), 61.20 (OCH\textsubscript{2}CH\textsubscript{3}), 58.28 and 58.08 (OCH\textsubscript{3}), 52.07 and 51.73 (C-5), 36.86 and 35.39 (C-6), 27.26 and 26.71 [2 x >C(CH\textsubscript{3})\textsubscript{2}], 14.55 (OCH\textsubscript{2}CH\textsubscript{3}); Anal. Calcd for C\textsubscript{21}H\textsubscript{28}N\textsubscript{2}O\textsubscript{7}S: C, 55.74; H, 6.24; N, 6.19; Found: C, 56.89; H, 6.86; N, 5.78 %.

**Ethyl [(1R, 2R, 3S, 4R, 5S)- 3-O-benzyl- 5,6-dideoxy-1, 2-O-isopropylidene- 5- {N\textsuperscript{3}-benzoyl-1-thioureidyl}-1,4-heptofuranos-5-yl]- uronoate [114]**

It was obtained by the reaction of compound 12 (1.0 g, 2.75 mmol) and benzoyl isothiocyanate (0.37 ml, 2.75 mmol) as described above and isolated as colorless foam. Yield 95 %; [\alpha]_D\textsubscript{25} = -34.6 (c, 0.12, CHCl\textsubscript{3}); MS (FAB): 529 (M+H\textsuperscript{+}); IR (Neat): \nu_{max} \text{ cm}^{-1} 3170 (NH), 2988 and 2838 (CH\textsubscript{3} and CH\textsubscript{2} stretching), 1730 (C=O), 1673 (C=S); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz): \delta 8.79 (bs, 1H, NH), 7.70, 7.50 and 7.29 (m, 10H, Ar-H), 6.06 (d, J = 3.7 Hz, 1H, H-1), 5.24 (m, 1H, H-5), 178
4.66 (two d, \( J = 11.4 \) Hz and \( 3.7 \) Hz, 2H, OCH\(_A\)Ph and H-2), 4.54 (m, 2H, OCH\(_B\)Ph and H-4), 4.14 (q, \( J = 7.1 \) Hz, 2H, OCH\(_2\)CH\(_3\)), 4.04 (d, \( J = 3.4 \) Hz, 1H, H-3), 2.86 (d, \( J = 6.2 \) Hz, 2H, H-6), 1.49 and 1.32 [each s, each 3H, C(CH\(_3\))\(_2\)], 1.24 (t, \( J = 7.1 \) Hz, 3H, OCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 179.82 (C=S), 171.29 (C=O); 166.63 (C=O), 137.50, 133.79, 129.43, 128.86, 128.53, 128.21, 127.17, 127.91 and 127.85 (Ar-C), 112.35 [C(CH\(_3\))\(_2\)], 105.43 (C-1), 83.17 (C-2), 82.65 (C-4), 79.51 (C-3), 72.47 (OCH\(_2\)Ph), 61.16 (OCH\(_2\)CH\(_3\)), 52.01 (C-5), 36.09 (C-6), 27.29 and 26.75 [2 x >C(CH\(_3\))\(_2\)], 14.56 (OCH\(_2\)CH\(_3\)); Anal. Calcd for C\(_{27}\)H\(_{32}\)N\(_2\)O\(_7\)S: C, 61.35; H, 6.10; N, 5.30; Found: C, 62.73; H, 6.84; N, 5.89 %

### 3.4 REFERENCES


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