RSC Advances

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Journal:	*RSC Advances*
Manuscript ID:	RA-REV-05-2015-008059.R1
Article Type:	Review Article
Date Submitted by the Author:	17-Jun-2015
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Recent advances in multicomponent reactions involving carbohydrates

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Being an attractive class of naturally occurring molecules with fascinating properties sugars and their derivatives have wide applications in different fields especially in drug discovery. Due to their highly diverse nature they play various important key roles in biological system. In terms of providing both desirable structural diversity and compound libraries, multicomponent reactions (MCRs) are most efficient strategies. MCRs are widely employed by the chemists to generate sugar based derivatives with significantly extended variations having various benefits to the society. The advances on the synthesis of structurally diversified sugar based derivatives through new MCRs of the previous decade are reviewed.

Introduction

Carbohydrates are highly noticeable compounds due to the presence of a number of –OH functional groups with varying reactivity pattern which opens the path to access their potential derivatives.[1] Sugars are well known environmentally benign starting materials for having various interesting characteristics including availability, optical activity and high water solubility. These fascinating properties along with the site specific reactivity make them highly applicable in synthesis of biologically active compounds, designing of molecular recognition devices and as chiral auxilliariaries in asymmetric synthesis.[2] Besides this, carbohydrate derivatives display diverse biological activities such as antibiotics, antiviral drugs, and glycosylation inhibitors.[3] For example, iminosugars which are derived from reducing sugars are potentially very effective

therapeutic agents and has been reported to be significantly active against HIV infection, cancer, diabetes etc.[4] These are also useful for the treatment of other genetic and metabolic disorders[5] due to their powerful interference with glycosyltransferase. [6] Furthermore, glycoconjugates which mainly exist as glycolipids or glycoproteins uniquely participate in different processes such as cell adhesion, cell growth, inflammation, immune responses etc.[7] Therefore, the importance of glycobiology and subsequently the chemistry of glycoconjugates have gained enormous attention due to crucial functions played by carbohydrates in several biological events. Over the past decade, multicomponent reactions (MCRs)[8] have been emerged as one of the excellent strategy to meet the demands for organic synthesis such as biologically active carbohydrate derivatives. In this approach two or more easily accessible components are combined together in a single reaction vessel to produce a final product. The advantages of these reactions over conventional linear synthesis includes reduction of reaction time period, cost and energy, easily available starting materials, variable and high bond forming efficiency, resource effective, atom economical, eco-friendly and operational simplicity etc. Therefore, it has now a day become an important path for generating highly functionalized molecules with complexity and diversity by utilizing simply a straight forward single pot reaction without facing any problem in isolation and characterization of reaction intermediate. Owing to these benefits, MCRs are gaining popularity as well as particular interest for its application in combinatorial chemistry and drug discovery[9] by providing quite efficient construction of different arrays of heterocyclic compounds. Some popular MCRs involve Strecker amino acid synthesis, Hantsch synthesis, Biginelli dihydropyrimidine synthesis, Mannich reaction, Diels-Alder cycloaddition reactions, Ugi-4-component condensation, Passerini-3-component reaction, Ritter-Prins reaction etc.[10] As carbohydrates have occupied central place in different fields, therefore the molecules

of high interest are in demand which may be supplied through the present diversity oriented synthesis in combination with multicomponent reactions. Sugars or their derivative based MCR's are considered to be one of the most versatile methods for the preparation of libraries of such compounds simply by employing varieties of participating entities. Inspite of these advances, there is a further requirement to extend the scope of simple MCRs to carbohydrate based MCRs in combination with click chemistry. Dondoni and co-workers have made significant contribution towards sugar based MCRs.[11]

Combinatorial approach is, thus very helpful for designing and synthesis of modified form of biologically important molecules which are generally associated with sugars such as nucleic acids like DNA and RNA. These modified nucleosides attract significant interest because of their widespread applications as antiviral, antitumor and antibacterial agents.[12] A variety of synthetic nucleosides are also employed in gene-therapy, duplex stability and molecular probes for biological recognition. As far as medicinal point of view is concerned these molecules can play a very vital role for example acyclic, carbocyclic, C-nucleosides and other modified nucleosides have been used for the treatment of AIDS, herpes, hepatitis and cancers.[13] For example, the well-known modified nucleosides are AZT **1**, Floxuridine **2** and Nifidipine **3** have been used for treatment of HIV/AIDS and Cancer (Fig. 1). Analogues of these medicinally active modified nucleosides have been synthesized using multicomponent reactions. For instance modified nucleosides **4** and **5** were synthesized by combination of optically active dihydrofuran, ethyl acetoacetate and corresponding substituted Bis(trimethysilyl)thymine (Fig. 2).[14]

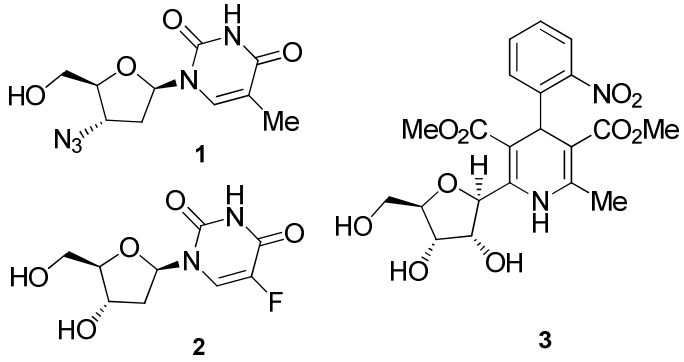


Fig. 1 Structure of AZT, Floxuridine and Nifidipine

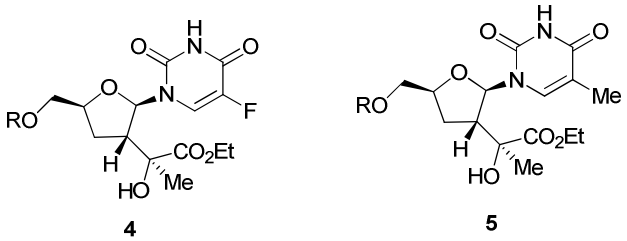


Fig. 2 Modified nucleosides synthesised by multicomponent reaction

Since carbohydrates have high degree of functionalization they can be used as templates by linking different active ends such as -NH_2, -CN, -COOH, -NC, -N_3 and multiple bonds etc to achieve several transformations for the generation of libraries containing huge varieties of molecules based on oligosaccharides or structurally related mimetics such as amide-linked saccharides (saccharide-peptide hybrids).

The main aim of this review is to take an overall look of new methodologies utilizing sugars as one of the component in recently developed new multicomponent approaches reported by chemical community from worldwide. The main content of this review covered the period from 2001 to 2015.

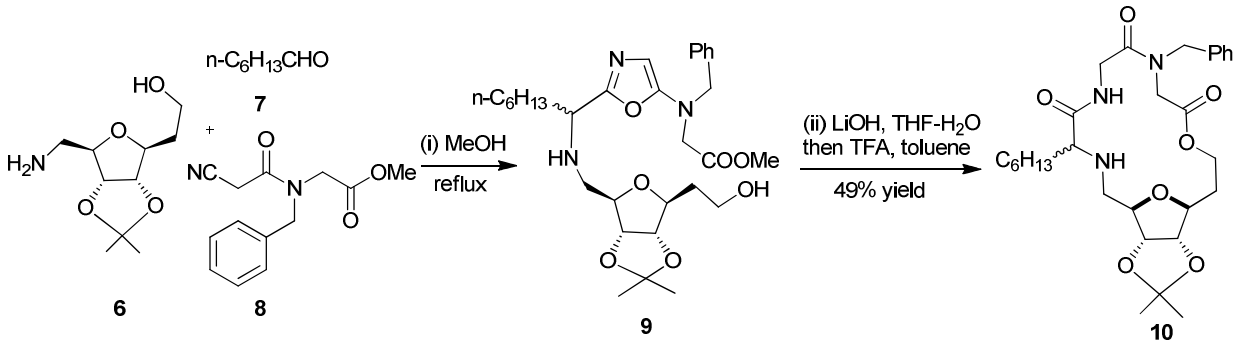
Multicomponent reactions involving carbohydrates

A large number of novel one pot multicomponent reactions utilizing carbohydrate and its derivatives have been developed by chemists all over the world. Being the interesting molecules,

researchers are making lot of efforts to obtain more efficient, environmental friendly and economical methodologies to synthesize carbohydrate derivatives. Based on the analysis of all known literatures on this topic, we classified these carbohydrate based MCRs into different categories according to the behavior of carbohydrates depending upon the active moieties present in the molecules.

(i) Sugar or sugar derived component acting as nucleophile

There are significant numbers of cases where sugar derivatives contain nucleophilic center when attached to electron rich groups such as -NH_2, -OH etc. To describe these kinds of reactions we begin with a rapid multicomponent synthesis of cyclodepsipeptide containing a sugar amino acid or a sugar amino alcohol reported by J. Zhu *et.al*. Wherein, a sugar amino acid (SAA) derivative **6** was combined with an aldehyde **7** and a dipeptide isonitrile **8** in refluxing methanol to afford the corresponding 5-aminooxazole **9** followed by the synthesis of cyclic sugar containing cyclopeptide **10**, after saponification of **9** via TFA or LiOH promoted macrocyclisation (Scheme 1).[15] Chiral amino alcohol was unable to provide sufficient chiral conditions to generate the diastereoslectivity in the key step i.e. carbon-carbon bond formation step. Therefore, a mixture of two diastereoisomers was obtained nearly in equal amounts.



Scheme 1 Multicomponent synthesis of 5-aminooxazole **9** followed by cyclisation to compound **10**

For macrolactonisation process, oxazole acted as an internal activator for the terminal carboxylic acid group[16] and involved as an integral part of peptide bond after cyclisation. Some other sugar containing cyclopeptides were also synthesized using corresponding aldehyde, SAA and isonitrile compounds (Fig. 3).

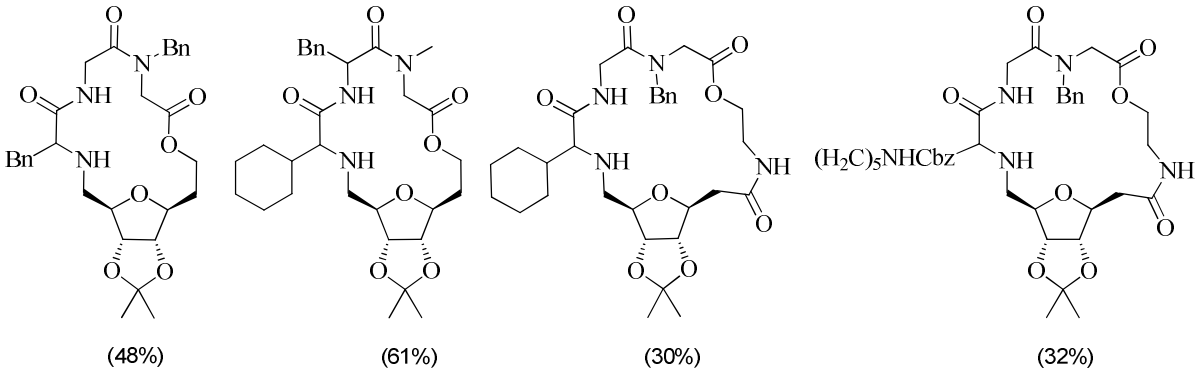
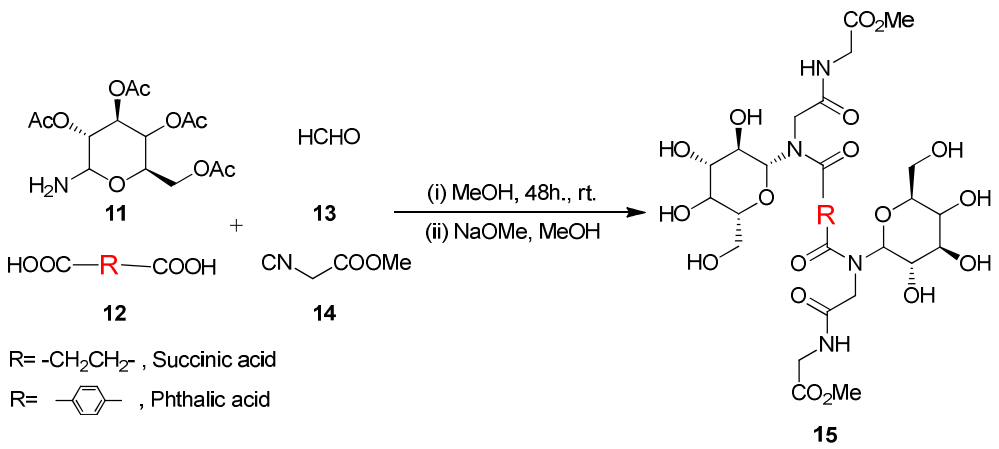


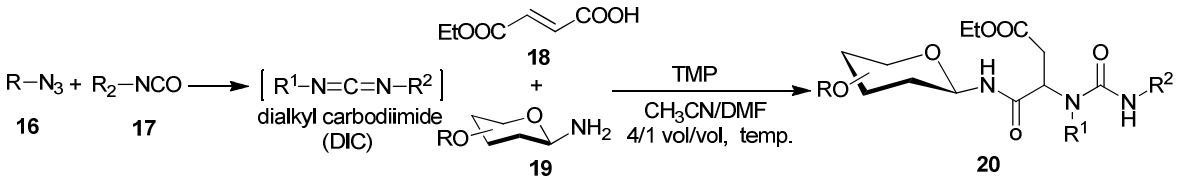
Fig. 3 Sythesised sugar containing cyclopeptides using different aldehyde,SAA and isonitrile

Another amino group substituted sugar moiety was utilized by Murphy and coworkers to develop an Ugi-based MCR for the synthesis of divalent galactose derivatives i.e. a divalent neoglycoconjugate **15**. This was synthesized by the reaction of sugar derivative **11**, diacid **12,** formaldehyde **13** and methyl cyanoacetate **14** (Scheme 2).[17]Two conformers were obtained in the ratio of 83:17, in which anti-conformer was the major isomer. The main aim of using diacid was to generate a bridge between glycopeptides. Succinic acid, terephthalic acid etc. can be employed as a suitable diacid.



Scheme 2 Ugi-MCR based synhesis of divalent neoglycoconjugates where diacid acting as bridge

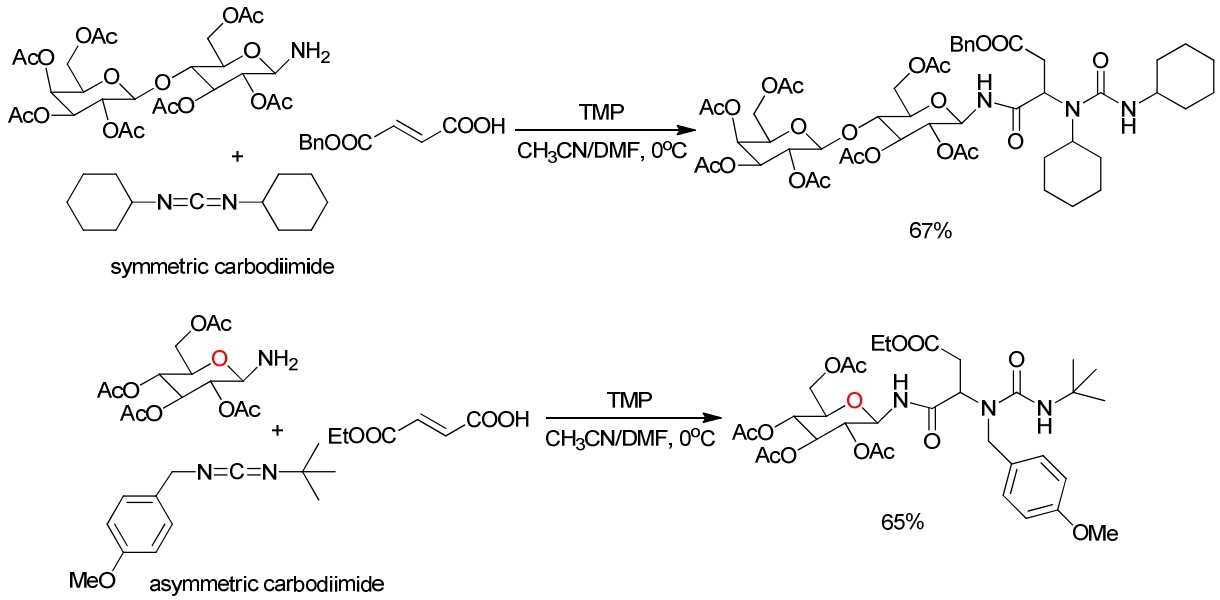
Further the similar amino group linked carbohydrate derivative was incorporated to synthesize a novel class of N-glycosyl conjugates by A. Volonterio and M. C. Bellucci *via* a multicomponent sequential domino process. N- glycosyl-Asp-Urea conjugate **20** was prepared by employing the reaction between fumaric acid monoethylester **18** and N-glycosylamine **19** with DIC (generated *in situ* from azides **16** and isocyanates **17**)(Scheme 3).[18]



Scheme 3 Four component synthesis of N-glycosyl-Asp-urea conjugate

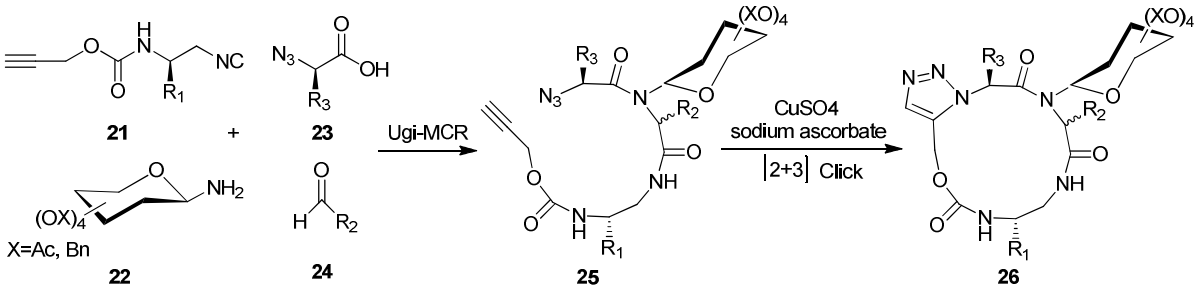
During the reaction, hydantoin was obtained as a byproduct along with the desired product. To increase the content of desired product, reaction was optimized in various solvents and co-solvents aiming to increase both the nucleophilicity and the solubility of the glycosyl amine reagent. By employing the solvent system, (4:1 (v/v) mix. of CH_3CN/MeOH) the formation of hydantoin intermediate was not observed. It has also been investigated that temperature plays a very significant role in process. At low temperature -30^{o}C, intermediate formation did not occur while at room temperature O-N acyl migration mechanism is followed with consequent

formation of hydantoin along with the desired product. It was also observed that symmetric carbodiimide reacted nicely to afford the desired conjugate product in good yield as a 2:1 diastereomeric mixture along with corresponding hydantoin. While asymmetric carbodiimide behaves differently depending on the nature of substituent attached, sterically hindered carbodiimide gave rise to a completely regioselective process (Scheme 4).



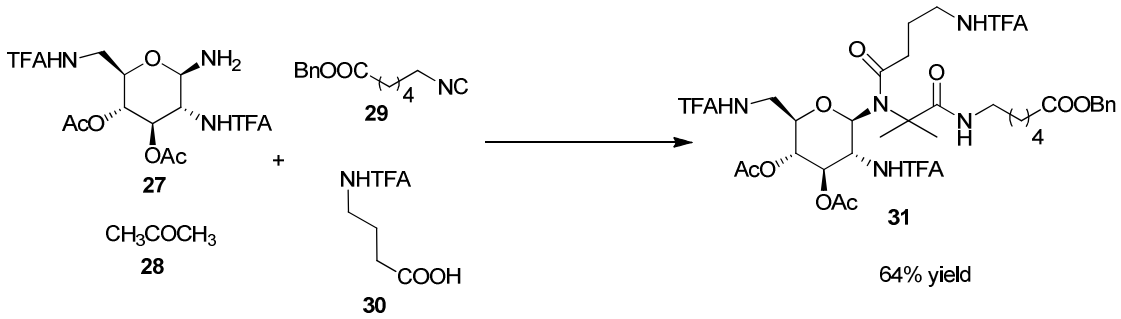
Scheme 4 Multicomponent reaction with symmetric and asymmetric carbodiimide

Exploring the utility of amino sugars in combinatorial approach Suresh *et.al*. have described a protocol involving propargyloxy carbonyl (POC) amino alkyl isonitriles **21**, glycosylamine **22**, azido acids **23** and simple aldehydes **24** as precursors to synthesise triazole linked cyclic glycopeptidomimetics **26** via sequential combination of Ugi-MCR and click chemistry (Scheme 5).[19] Compound **21** was used first time in MCR reaction, in which the POC group was demonstrated to perform dual function such as amine protection as well as a participant in cycloaddition reaction with an azide.



Scheme 5 Synthesis of Ugi-product **25** and triazole linked cyclic glycopeptidomimetics **26** via click chemistry

The chiral HPLC analysis revealed that the two diastereomers were present in 95:5 ratio. The choice of azido acid is very interesting as it serves as amino acid precursor in peptide bond formation. Azido acid was prepared by the reaction of amino acids with imidazole-1-sulfonyl azide as reported by Goddard-Borger[20]. For cyclisation process **25** was subjected to Cu catalyzed azide-alkyne cycloaddition. The designed triazole linked cyclic neoglycopeptide **26** was formed as major component along with only a small amount of dimer and meager quantities of other unidentified by products. A variety of catalytic system such as $CuSO_4.5H_2O$/sodium ascorbate in t-BuOH/water, CuBr/1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) in toluene, was employed to achieve cyclisation in order to get good yield as well as to reduce the duration of reaction. However, $CuSO_4.5H_2O$/sodium ascorbate was found to be satisfactory in providing better results. Other Structurally diverse multivalent amino glycoside mimics (neoglycoconjugates) was synthesized by Wastermann and Dornor by using 2, 6–diamino-2, 6-dideoxy glucose *via* Ugi multicomponent approach to obtain mono, di and trivalent carbohydrate clusters. Monovalent neoglycoconjugate product **31** was isolated in 64% yield *via* Ugi-MCR involving amine **27**, acetone **28**, isocyanide **29** and N-triflouroacetyl protected γ-amino butyric acid **30** (Scheme 6).[21] Similarly for divalent glycoconjugates **35**, compounds **28**, **29**, **32** and **33** were combined and for trivalent glycoconjugate **36**, a Ugi based Multicomponent reaction was utilized using compounds **29**, **32**, **33**, and **34** (Fig. 4).



Scheme 6 Synthesis of monovalent glycoconjugates *via* Ugi-MCR

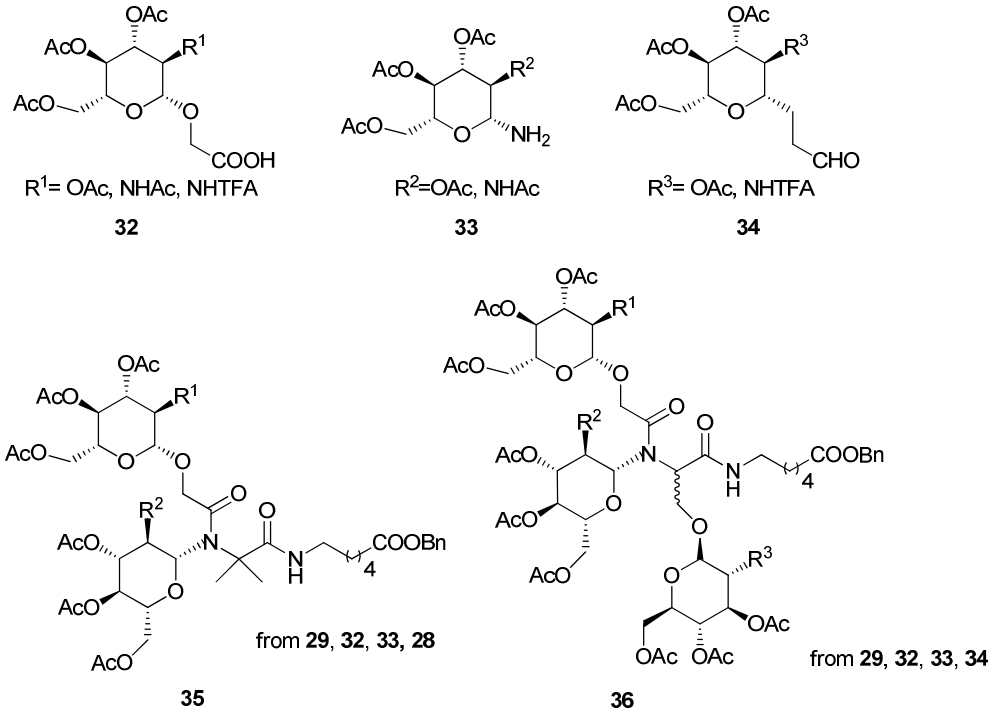
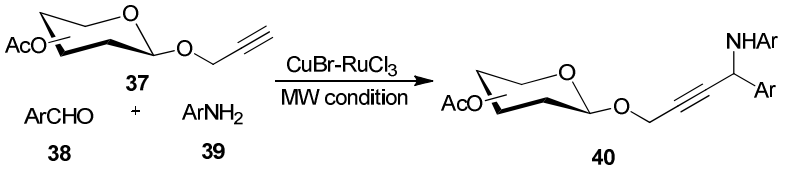


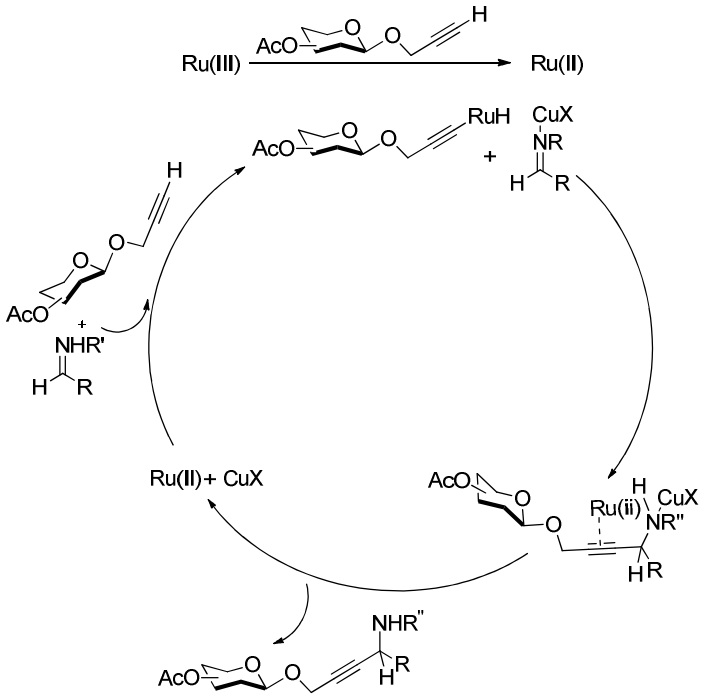
Fig. 4 Divalent and trivalent glycoconjugates **35** and **36** made from **28**, **29**, **32**, **33** and **34** *via* Ugi-MCR

Besides amino sugars various carbohydrate scaffolds with other potentially active nucleophilic centers have been used extensively by different research groups to design libraries of biologically active compounds and success was achieved by Mukhopadhay *et.al.* when they developed an efficient method for the synthesis of glycosylated propargyl amine **40** through Cu-Ru catalyzed A_3-coupling of propargyl glycosides **37**, aldehydes **38** and amines **39** under

microwave assisted conditions (Scheme 7).[22] A library of compounds was synthesized using this methodology by employing different aldehydes and amines.



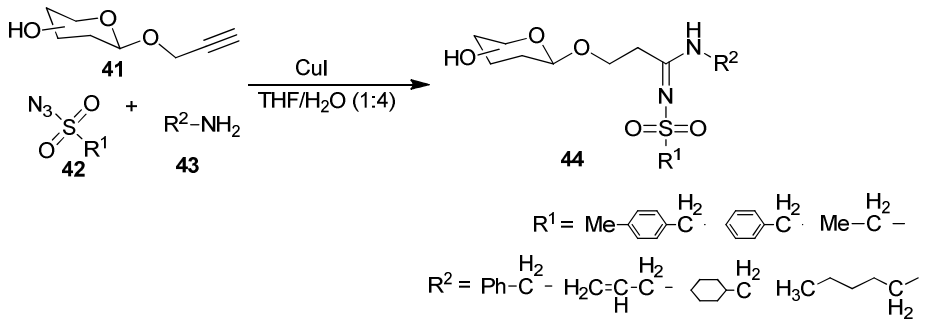
Scheme 7 Cu-Ru catalysed A^3-coupling of **37**, **38** and **39**



Scheme 8 Proposed mechanism for imine addition via C-H activation

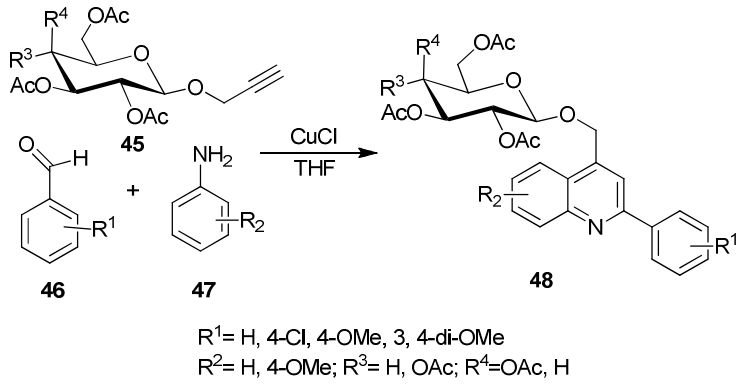
A tentative mechanism of the reaction was proposed displaying the activation of C-H bond of sugar alkyne by a Ru(II)[23] generated *in situ* from the reduction of Ru(III) by sugar alkyne as well as activation of imine with copper. The ruthenium intermediate thus generated then reacts immediately via Grignard type addition with activated imine to afford the corresponding nucleophilic addition product and the copper and ruthenium salts were released for further reaction (Scheme 8). It is noteworthy that when aliphatic amine and/or aliphatic aldehyde were

used, no significant products were isolated. Even aliphatic aldehyde devoid of any α-hydrogen failed to produce the desired product. Continuous efforts made by Mukhopadhyay *et. al.* lead them to develop an efficient Cu-catalyzed multicomponent reaction involving sugar alkynes **41**, sulphonylazides **42** and amines **43** to furnish glycosylated N-sulphonyl-amidines **44** (Scheme 9).[24] By employing different combination of sugar alkynes, sufonylazides and amines, a library containing a number of such compounds were obtained. This method is very simple and afforded the target compounds in high yield and purity.



Scheme 9 Cu catalysed multicomponent synthesis of glycosylated N-sulfonyl amidines

Increasing popularity of these propargyl group substituted carbohydrates in multicomponent reactions encouraged Das and Kumar to synthesize quinoline based glycoconjugates **48** in good yield using propargyl glycosides **45** of D-glucose and D-galactose, aromatic aldehydes **46** and aromatic amines **47** *via* Cu(I) catalyzed one pot multi-component reaction (Scheme 10).[25] This catalytic system was used to generate a series of quinoline based glycoconjugates. It is quite interesting to note the effect of methoxy group substituted to aromatic aldehyde and amine in the synthesis of one pot product which not only favour the formation of product but also minimize the yield of by product i.e., propargyl amine. This observation was supported from the result obtained by Iqbal and cowerkers[26] with non-sugar hybrid of quinoline compounds.

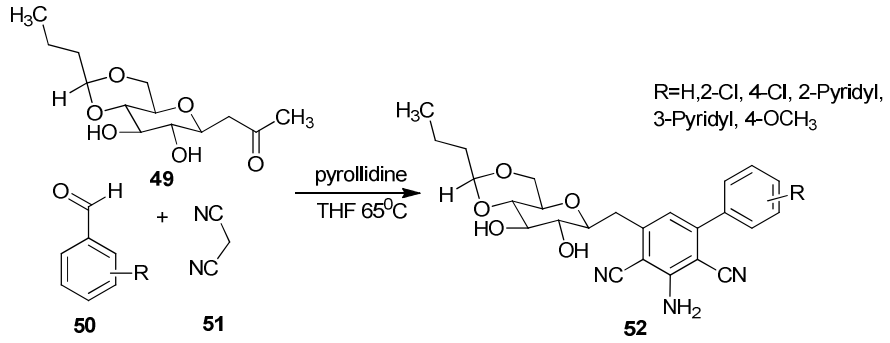


Scheme 10 One pot three component synthesis of quinoline based glycoconjugates

(ii) Carbohydrate moiety acting as electrophile

In this section, we covered a number of reported MCRs in which the carbohydrate derivatives seem to act as an electrophile. Common electrophilic center encountered in carbohydrates involved in MCRs are carbonyl groups and the groups which facilitates the easy attack of nucleophiles because of their better leaving ability.

Das *et.al.* synthesized biphenylmethyl-β-D-C-glycosides **52** *via* one-pot synthesis using 4,6-O-protected-C-glycoside **49**, aromatic aldehydes **50** and malononitrile **51** in presence of pyrollidine as an organocatalyst in THF at 65^{o}C (Scheme 11).[27]

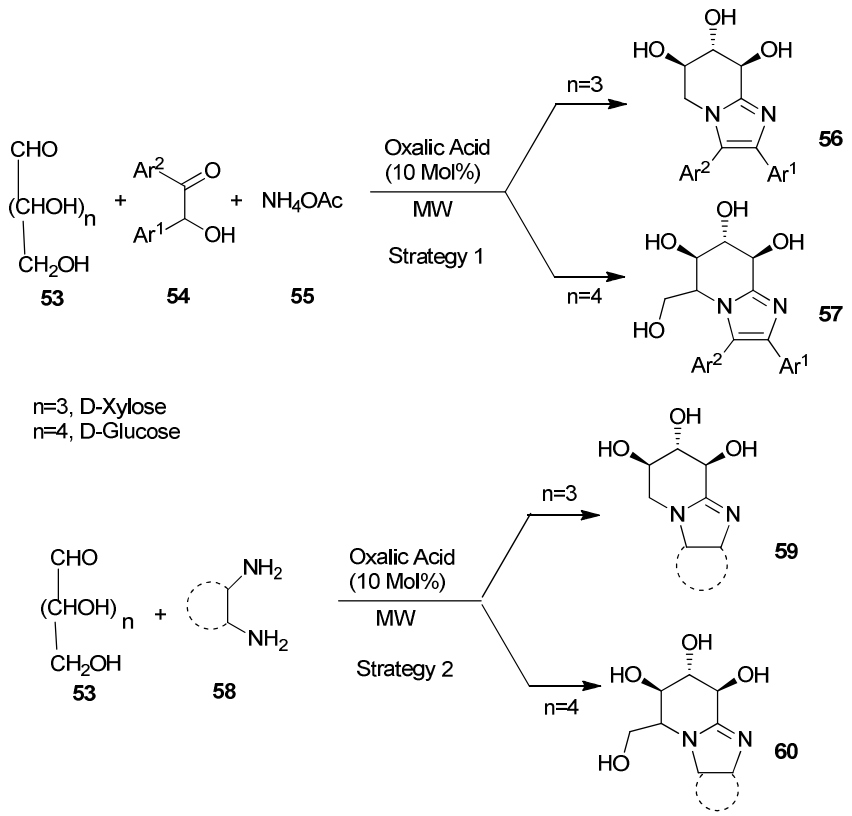


Scheme 11 One pot synthesis of biphenyl methyl-glycosides

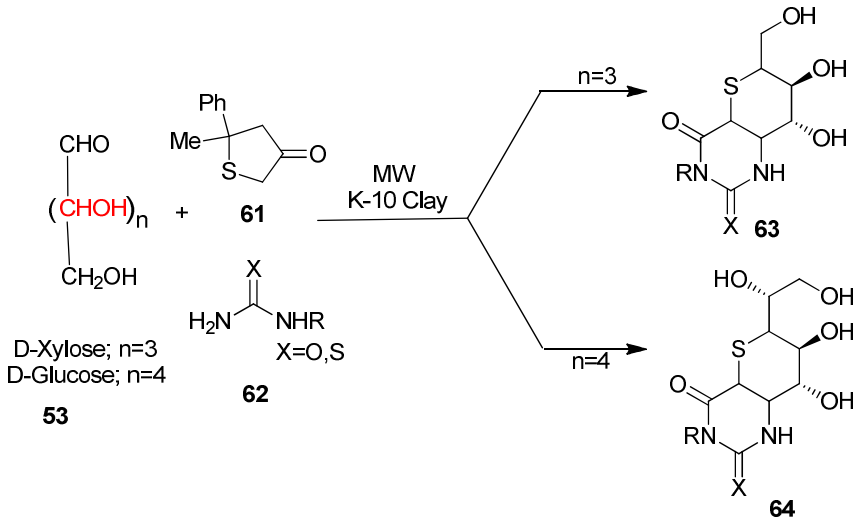
This method has opened a way to synthesize various C-glycosyl derivatives with several potential applications such as SGLT2 inhibitor, a sodium glucose transport protein abundant in

proximal convulated tubule portion of the nephron which contributes to renal glucose absorption therefore acting as anti-hyperglycemic agent.

A microwave assisted protocol developed by Yadav *et. al.* showing two highly yielding one-pot reactions using carbohydrate as one of the component to synthesize an iminosugar bearing imidazol [1,2-a] pyridin scaffold **56**, **57**, **59** and **60.** First approach involved a strategy in which MW assisted solvent free multicomponent reaction of D-glucose/D-xylose **53** benzoin **54** and ammonium acetate **55** was carried out using 10 mol% oxalic acid at around 80^{o}C for 9-13 minutes. While second approach also involved a similar kind of strategy where a solvent free intimate mixture of D-glucose/D-xylose and 1, 2 diamine **58** is irradiated with MW using same catalyst at 80^{o}C for about 8-14 minutes (Scheme 12).[28] Furthermore Yadav and coworkers have also developed a novel version of the Biginelli reaction using an unprotected aldose **53** as a biorenewable aldehyde component and 2-methyl-2-phenyl-1, 3-oxothiolan-5-one **61** as a mercaptoacetylating active methylene building block with urea/thiourea **62** for the synthesis of thiosugar-annulated multifunctionalised dihydropyrimidines **63** and **64** under MW irradiation in presence of nanoclay, Montmorillanite K-10 (a very soft phylosilicate group of minerals that typically in the form of microscopic crystals form a clay having catalytic properties) at 90^{o}C for 9-13 minutes (Scheme 13).[29] Isolation and purification by recrystallisation from ethanol afforded **63** and **64** in 76-89% yields with >95% diastereoselectivity in favor of cis.



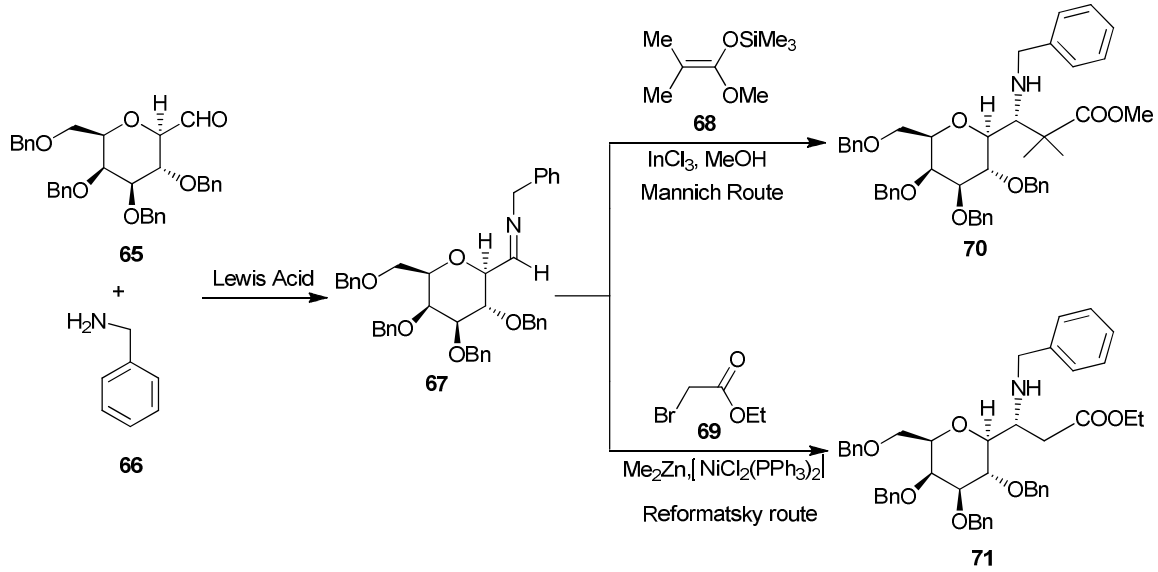
Scheme 12 MW assisted one pot synthesis of iminosugar **56**, **57**, **59** and **60**



Scheme 13 Synthesis of thiosugar annulated dihydropyrimidines **63** and **64**

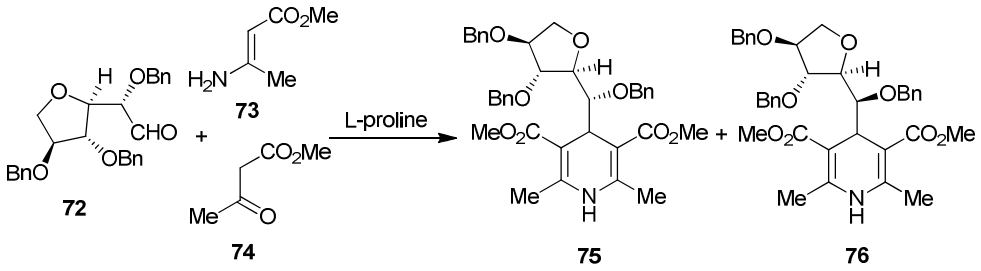
Dondoni contributed a lot to carbohydrate based multicomponent protocols by designing a range of compounds. C-glycosyl β-amino acid libraries with chemical and stereochemical diversity was

developed by Dondoni and coworkes by employing two complementary one pot three components Mannich-type and Reformatsky-type synthetic strategies.



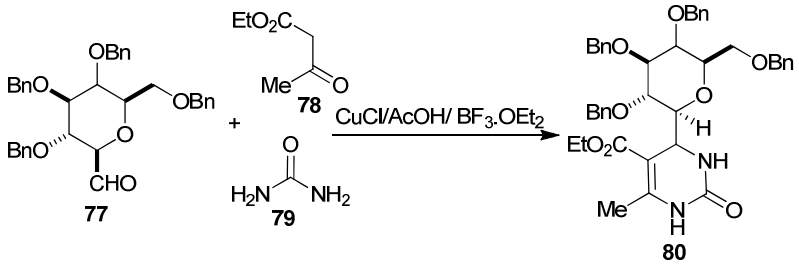
Scheme 14 Complementary Mannich and Reformatsky route for the synthesis of C-glycosyl aminoesters

Both strategies involved the construction of chiral C-glycosyl imine intermediate **67** fragments linked directly to the anomeric carbon of pyranose and furanose residue and involved the coupling of sugar aldehyde **65** to p-methoxybenzylamine **66** as initial step. Of course a different nucleophile, a ketene silylacetal **68** (Mannich route) or a bromozinc enolate **69** (Reformatsky route) was added successively. Individual β-C-glycosylated-β-amino acid ester **70** and **71** as single diastereomer was isolated in good yield (Scheme 14).[30] Again his interest in this area can be seen when Dondoni *et. al.* synthesized α-threofuranose C-nucleoside enantiomers in the light of organocatalytic Hantzsch cyclocondensation. The synthesis of dihydropyridine C-glycoconjugates (**75** & **76**) was reported using C-glycosyl aldehyde **72**, enamino ester **73** and β-keto ester **74** under L-proline catalyst (Scheme 15).[31] This protocol allows variation in all position of the dihydropyridine ring.



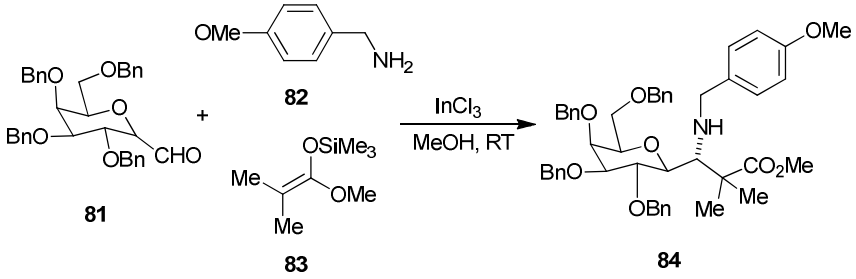
Scheme 15 Synthesis of furanose C-nucleoside enantiomer **75** and **76** *via* Hantzsch reaction

An asymmetric cyclo-condensation was also carried out using differentially substituted enamine, generated *in situ* from β-dicarbonyl components and formyl α-L-C-threofuranoside with α-D-isomer. Each reaction occurred with high but opposite stereoselectivity (de >95%) so that the pair of α-threofuranose C-nucleoside enantiomers was obtained. Furthermore, he also worked on the metal catalyzed multicomponent reaction. Dondoni *et.al.* prepared a collection of 13-mono and bis-C-glycosylated dihydropyrimidinones **80** using the three component promoter CuCl/AcOH/ $BF_3.OEt_2$ along with C-glycosylated reagents **77**, ethyl acetoacetate **78** and urea **79** with the aim of exploring potential entry to a library of dihydropyrimidinone glycoconjugates (Scheme 16). In case of mono glycosylated derivatives the sugar residues appeared at N_1, C_4 and C_6 while in bis glycosylated products with sugar residues at C_4 and C_6 were obtained as diastereomeric mixture. As the sugar residue itself show asymmetric induction, so good selectivity is achieved. Two C_4 epimer monastrol analogues bearing the ribofuranosyl moiety at C_6 were synthesized as a demonstration of this new concept in Biginelli reaction.[32]



Scheme 16 Biginelli reaction leading to 13-mono and bis-C-glycosylated dihydropyrimidinones

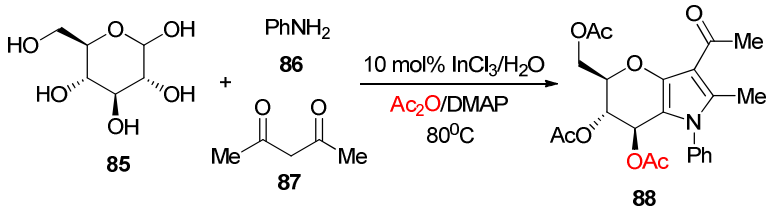
An efficient method involving the synthesis of C-galactosyl and C-ribosyl β-amino acids was introduced by Dondoni and coworkers. This method was actually the $InCl_3$ catalyzed one pot Mannich type three component condensation through the combination of corresponding formyl C-glycoside, p-methoxybenzylamine and a ketene silylacetal. For this, β-linked C-galactosyl formaldehyde **81** was first treated with p-methoxybenzylamine **82** using $InCl_3$ in methanol at room temperature followed by the addition of third partner, 1-methoxy-1-trimethylsilyloxy-2-methyl-1-propene **83**. A C-galactosyl β-amino ester **84** was obtained as a single diastereoisomer in 80% yield after 12 hour (Scheme 17).[33]



Scheme 17 Three component Mannich type synthesis of C-galactosyl beta amino ester **84**

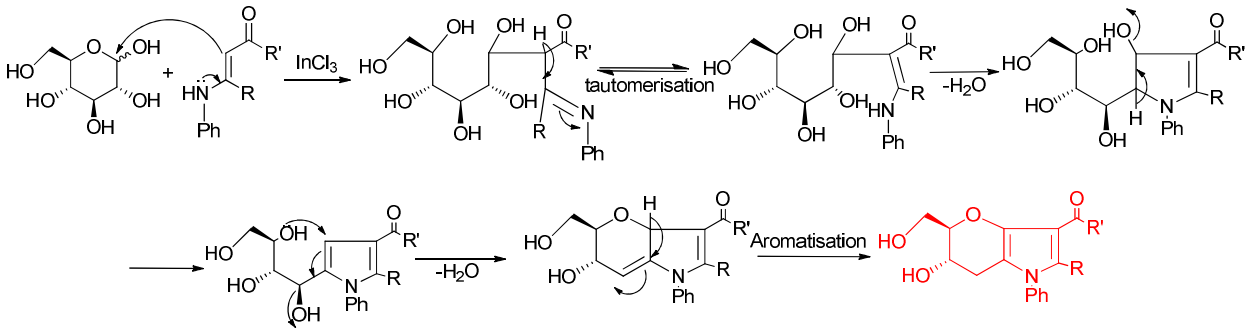
The key component in this synthesis are α and β linked formyl C-glycosides were obtained *via* thiazole based formylation of a variety of sugars.

There are significant numbers of examples of multicomponent reaction catalyzed by indium chloride. Yadav *et.al.*have made major contribution in this area utilising a three component coupling of aldose sugars, arylamine and β-diketones to synthesized annulated pyrroles using $InCl_3$ as catalyst in aqueous environment. In this methodology, aldose sugars **85** underwent smooth coupling with enamines generated *in situ* from arylamines **86** and 1,3 diketones **87** in presence of 10 mol% of $InCl_3$ in water at 80^0C to yield annulated pyrrole derivatives **88** in relatively good to high yields (Scheme 18).[34]



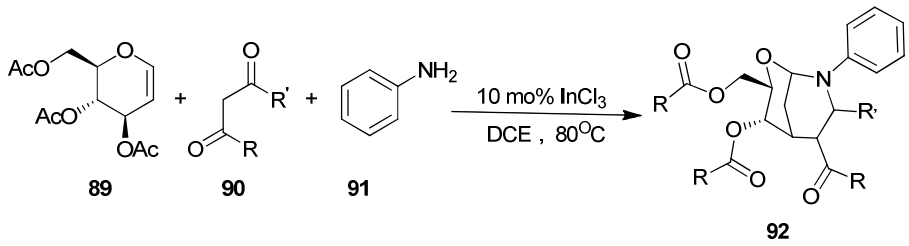
Scheme 18 Synthesis of annulated pyrroles *via* a three component coupling.

Scheme 19 shows the probable mechanism through which an annulated pyrrole was acheived *via* coupling of enamino ketone with sugar hemi-acetal to afford first an aldole kind of product which then undergoes subsequently cyclodehydration followed by the aromatization.



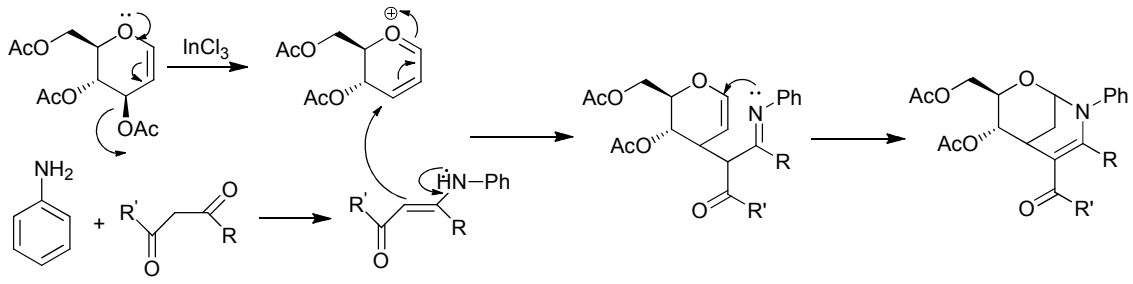
Scheme 19 A possible reaction mechanism showing condensation of enaminoketone with sugar hemiacetal

The use of $InCl_3$ and water assembly makes the procedure quite simple, convenient and environment friendly. Yadav *et.al.* also demonstrated the cyclisation of a glycal with enamines resulting to oxa-azabicyclononene scaffolds **92**. Glycal **89** was coupled with β-enamino ketones and β-enamino esters generated *in situ* from 1, 3dicarbonyl compounds **90** and aryl amine **91** in presence of $InCl_3$ (10 mol%) under refluxing conditios with dichloroethane (DCE) (Scheme 20).[35]



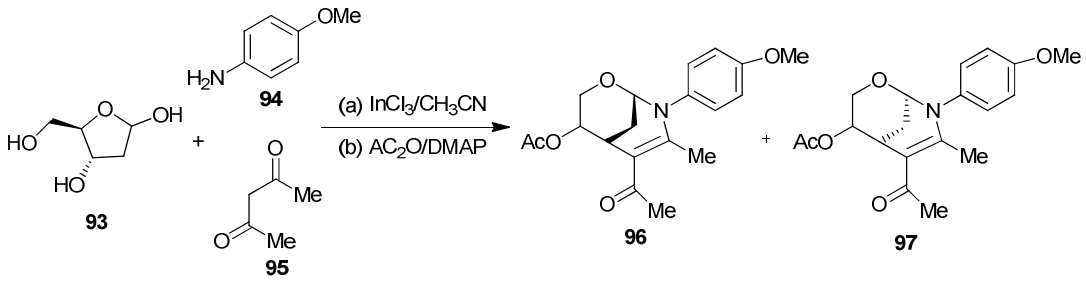
Scheme 20 Three component coupling of **89, 90** and **91.**

Scheme 21 shows a possible way for the formation of product. Enamines generated *in situ* from 1, 3-dione and arylamine reacted with glucal derivative including 3, 4, 6-tri-O-methyl- and 3, 4, 6-tri-O-allyl-D-glucal to afford cyclic products.



Scheme 21 A possible mechanism for the formation of product

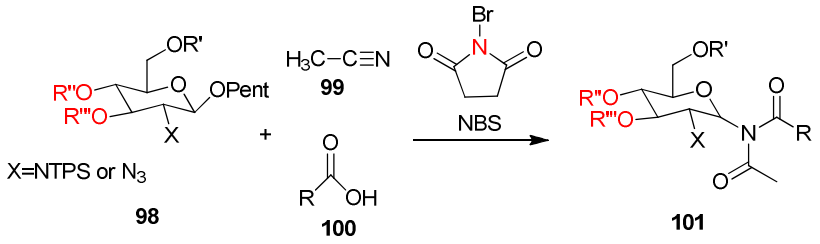
As another achievement in indium catalyzed MCRs Yadav *et.al* proposed a smooth cyclocondensation reaction involving 2-deoxyribose, an aryl amine and acetylacetone in presence of $InCl_3$ under mild conditions to yield the corresponding sugar derived bicyclic aminols in good yields with moderate diasteroselectivity. Scheme 22 shows an example of this kind of reaction involving 2-deoxyribose **93**, p-anisidine **94** and acetylacetone **95** in presence of 10 mol% $InCl_3$ using acetonitrile as solvent at room temperature to produce a mixture of **96** and **97** in 91% yield after acetylation.[36]



Scheme 22 $InCl_3$ catalysed synthesis of bicyclic aminol **96** and **97**

This reaction is analogues of the tropinone synthesis of Robinson with the help of this method one can get a wide range of sugar fused heterobicycles in a single step.

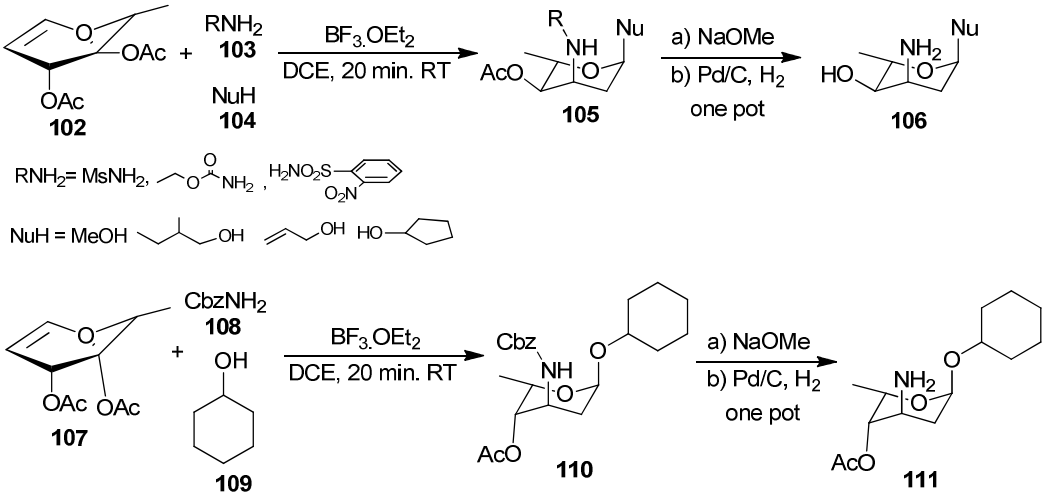
Bert *et.al*. developed a three component synthesis of N-acylated glycosylamines **101** involving n-pentyl glycosides **98**, acetonitrile **99** and carboxylic acids **100** under the effect of N-bromosuccinimide (NBS) (Scheme 23).[37]



Scheme 23 A three component synthesis of N-acylated glycosylamine **101**

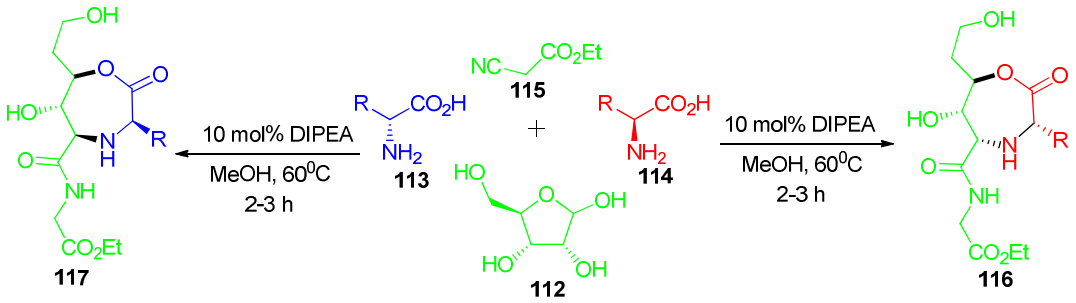
Anomeric stereoselectivity was controlled effectively by C_2 tetrachlorophthalamide and C_2 azido groups. An interesting thing is to be noted that the process was not dependent on the carboxylic acids strength. However, the rate was found to be affected by the substitution pattern of aromatic acid, while the presence of lone pair on the para substituents inhibited the process.

Liu and his coworkers have developed a highly efficient synthetic protocol to obtain L-ristosamine **106** and L-epi-daunosamine glycosides **111** *via* $BF_3.OEt_2$ promoted tandem hydroamination/ glycosylation of 3,4-di-O-acetyl-6-deoxy-L-glucal **102** and corresponding L-galactal **107** followed by the one pot deprotection of corresponding **105** and **110** (Scheme 24).[38] Advantages of this protocol include completely stereochemical nature of the reaction and short reaction time. This synthetic protocol also circumvents the problem of lack of stereoselectivity and thus neglecting labourious isolation of pure diastereomer.



Scheme 24 $BF_3.OEt_2$ promoted three component tandem hydroamination/glycosylation reaction

Recently, Benjamine *et.al.* presented a simple multicomponent reaction of unprotected carbohydrates **112** with amino acids **113** and **114** and isonitrile **115** in the form of extended Ugi-type reaction to yield novel glycopeptides **116** and **117** (Scheme 25).[39]



Scheme 25 Synthesis of novel glycopeptides using unprotected sugars via Ugi-3CR

This Ugi-type reaction does not require any catalyst or reagent at room temperature to work best. Although use of catalytic amount of tertiary amine and methanol as solvent result in shortening reaction time and increasing yield. An increase in yield was also observed with excess use of carbohydrate. Fig. 5 shows different glycoconjugates synthesized using a rang of D and L amino acids.

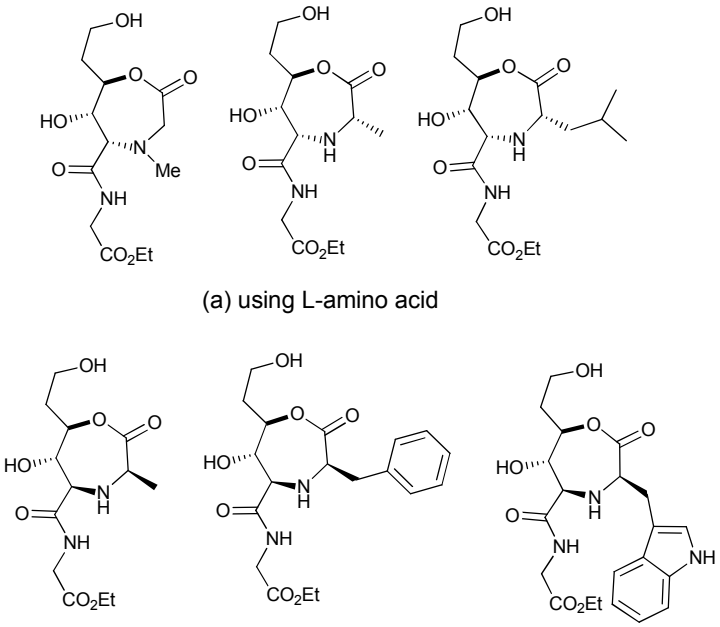
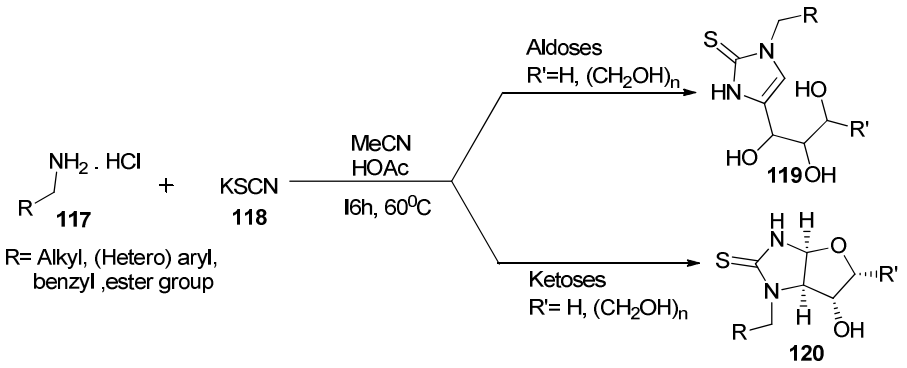


Fig. 5 Three component Ugi product using D-ribose, D/L amino acid and ethyl cyanoacetate

A modern variant of Maerckwald reaction used by Marcus *et. al.* to synthesise diversitly functionalized thioimidazoles **119** and **120** utilizing unprotected carbohydrates as well as simple amine salts **117** and potassium thiocynate **118** as biorenewable and sustainable starting materials.[40]



Scheme 26 Multicomponent synthesis of Polyhydroxyl thioimidazoles from aldoses and ketoses

Using aldoses such as D-(+)-xylose, D-(-)-ribose and D-(+)-galactose as carbohydrate component various thioimidazole structures were synthesized in high yield. On the other hand, in

the same reaction condition ketoses gave a very different outcome delivering bicyclic 6-hydroxytetrahydro-1*H*-furo[2,3-d]imidazole-2(5*H*)-thiones as major products (Fig. 6).

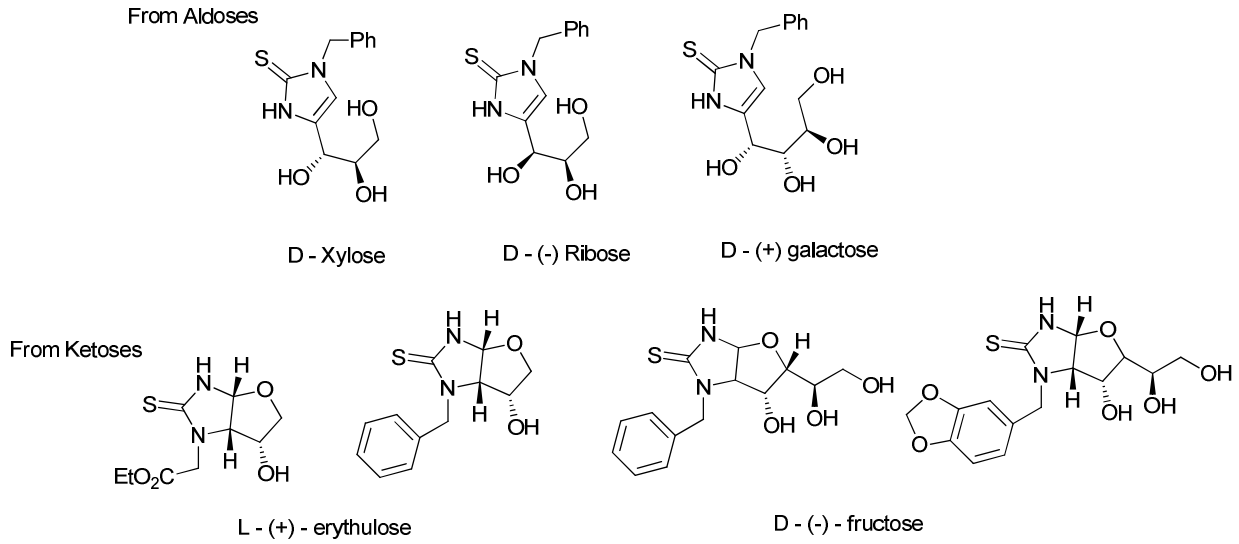
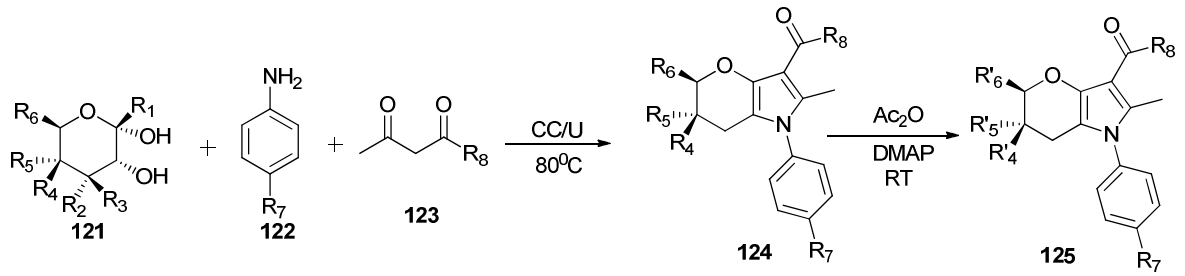


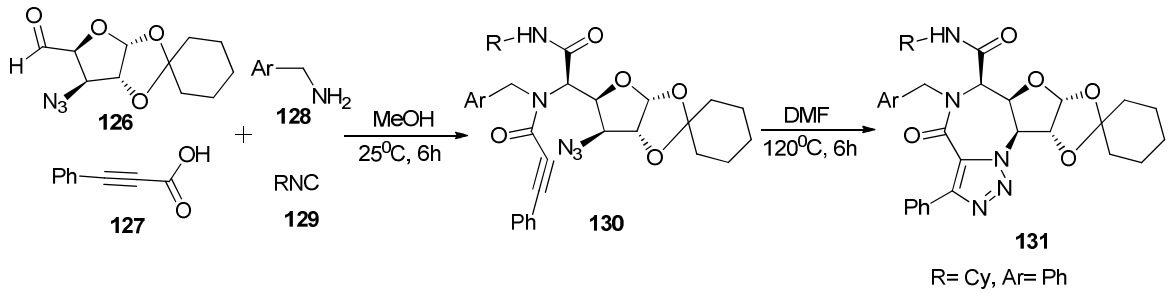
Fig 6 Synthesised polyhydroxy imidazoles using different Aldoses and Ketoses

Very recently, Sunil *et. al.* developed one pot three component synthesis of annulated pyrroles **124** by coupling of free sugars **121** with enamine, generated *in situ* from aryl amines **122** and 1,3-diketones **123** (Scheme 27).[41] The reaction condition is environmentally benign, do not require any additional bronsted or lewis acid catalyst and has been achieved by using a deep eutectic solvent[42].



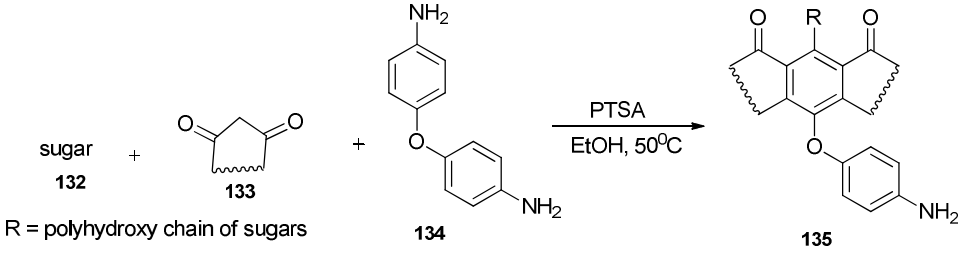
Scheme 27 Multicomponent synthesis of annulated pyrroles in choline chloride: urea (CC/U)

Reddy *et. al.* developed a four component and six centre Ugi reaction of sugar azidoaldehyde **126**, benzylamine **128**, alkyl isocyanide **129** and phenylpropioloic acid **127** to generate a novel class of hexahydro-4*H*-spiro{[1,3]dioxolo[4',5':4,5]furo[2,3-f][1,2,3]triazolo[1,5-a][1,4]di-azepine-9,1'-cyclohexane}-6-carboxamide derivatives **131**. Sugar derived triazolodiazepines was prepared from simple precursor through one pot two-step process (Scheme 28).[43]



Scheme 28 Multicomponent synthesis of sugar derived triaozolodiazepine

A novel series of poly-hydroxy functionalized acridine derivatives was synthesized by Zahra *et. at*. The synthesized compound incorporates three different substructures, namely a 4-(4-aminophenoxy) phenyl group **134**, an acridine moiety **133** and a polyhydroxy chain **132** (Scheme 29).[44] The inhibitory activity of the synthesised compounds against α-Glucosidase (α-Gls) and α-Amylase (α-Amy) were also evaluated which demonstrate the highest inhibitory activity for **139** compound with chromenol [3',4':5,6] pyrido [2,3-d] pyrimidine moiety.



Scheme 29 Synthetic approach for the synthesise of polyhydroxy functionalised acridine derivatives

This approach employed various sugars such as glucose, galactose, lactose etc. as a source of polyhydroxy chain to synthesis novel polyhydroxy substituted acridine derivatives. Some of the

synthesized compounds **136-139** with good inhibitory activity along with the sugars and acridine derivatives used are shown in Fig 7.

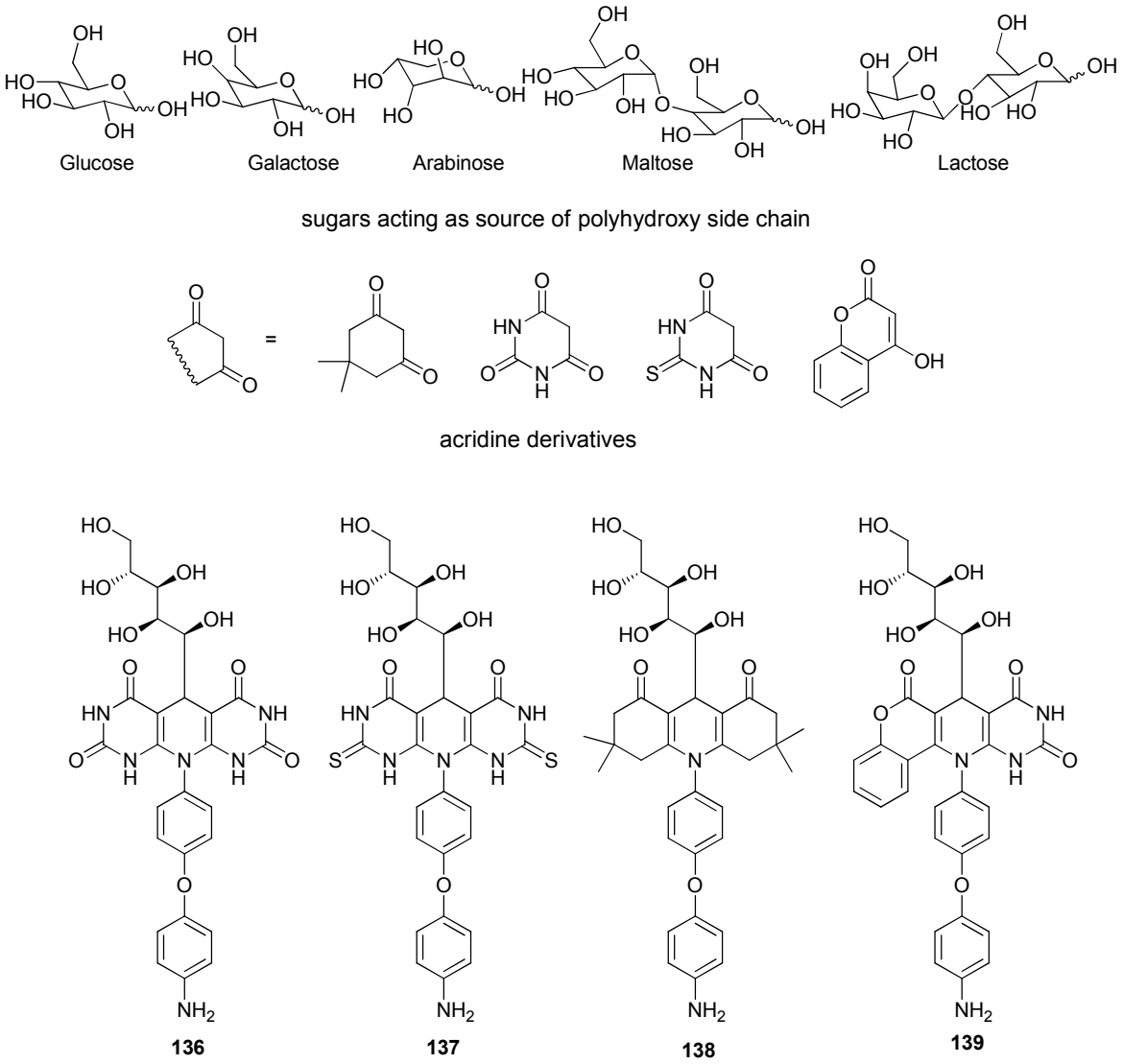
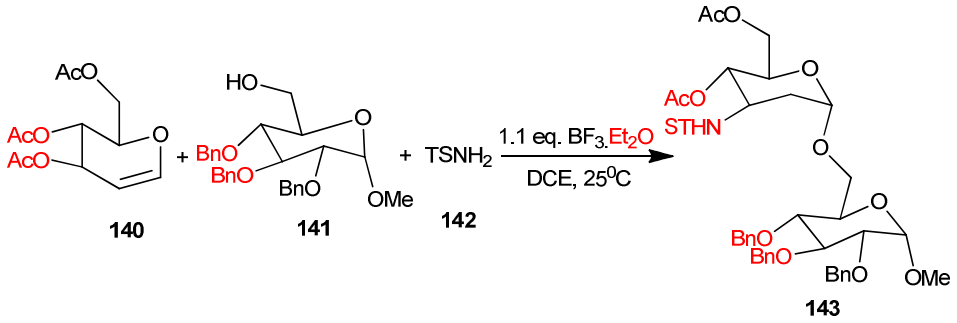


Fig. 7 Synthesised polyhydroxy functionalised acridine derivatives

(c) Miscellaneous reactions

In this section we include such multicomponent reactions, which are not covered in previous two classes because the nature of sugar components is not very clear or the same carbohydrate derivative exhibits dual role i.e., both the electrophilic and nucleophilic centers.

We begin this section with the synthesis of 3-amino glycosides, a very common constituent of biologically active classes of glycoconjugates and naturally occurring oligosaccharides. Although number of the synthetic methods is available for the preparation of these compounds but each method is facing some drawbacks like low yields, long reaction times and annomeric mixtures. To overcome these limitations Ding *et.al.* developed a protocol for the synthesis of 1,3-cis-aryl-sulphonaminodeoxy disaccharides and oligosaccharides *via* α-selective glycosylation and hydroamination of glycal in a one pot manner using a promoter. They basically synthesized 3-aminoglycosides, 1,3-cis-3-tosylaminodeoxy disaccharides **143** by the treatment of glycosyl donor 3,4,6-tri-*O*-acetyl-D-glucal **140**, a glucose acceptor **141**, and PTSA **142** using 1.1 eq. of $BF_3.OEt_2$ as a promoter in 1,2, dichloroethane (DCE) at room temperature (Scheme 30).[45]

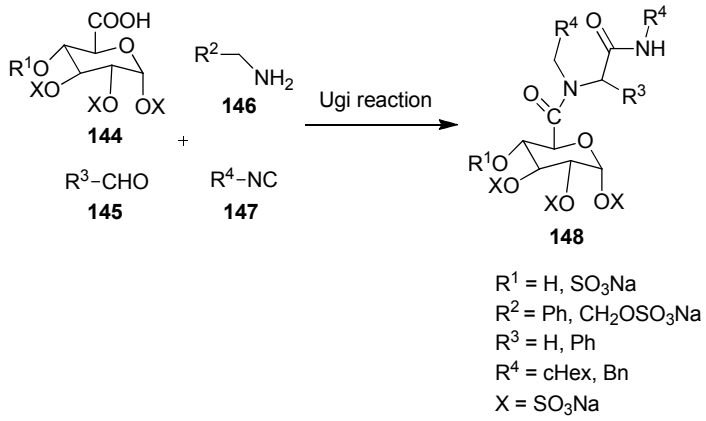


Scheme 30 One pot synthesis of a 3-amino glycosides **143** *via* glycosylation and hydroamination of glycal

This efficient multicomponent reaction methodology provides readily access to 1,3-cis-3-arylsulphonaminodeoxydisaccharides and oligosaccharides and allowed to synthesize a number of such compounds by variation of different components.

In the progress, Liu *et.al.* Synthesized a library of novel sulfated glycoconjugates using carbohydrate derived blocks by the application of Ugi-condensation. For monoseries, Sulfated monosaccharides are linked by various spacers to either an aromatic, aliphatic or negatively charged groups and for bis series to a second sulfated monosaccharide.[46] The monoseries

sulfated glycoconjugates **148** were constructed using a carbohydrate acid block **144** with commercially available carbonyl component **145**, amine **146** and isocyanide **147** (Scheme 31). The bis-series **149** and **150** were prepared by Ugi reaction incorporating either two carbohydrate blocks or single carbohydrate and a bis-amine (trans-1,4-diaminocyclohexane) or bis-acid(3,3-dimethyl glutaric acid) (Fig. 8). With the help of surface plasma resonance solution affinity assay (SPRSAA), the affinity of heparin sulfate mimetic was measured for the HS-binding fibroblast growth factor FGF-1 and FGF-2.



Scheme 31 Ugi-4CR synthesis of sulfated glycoconjugates **148**

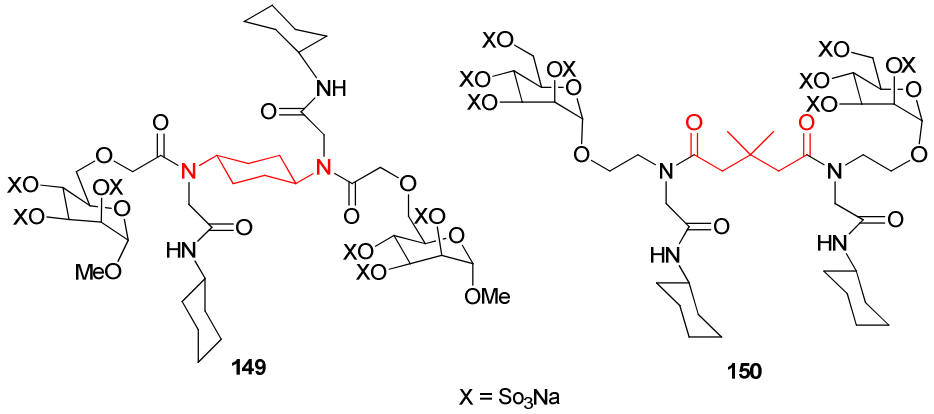
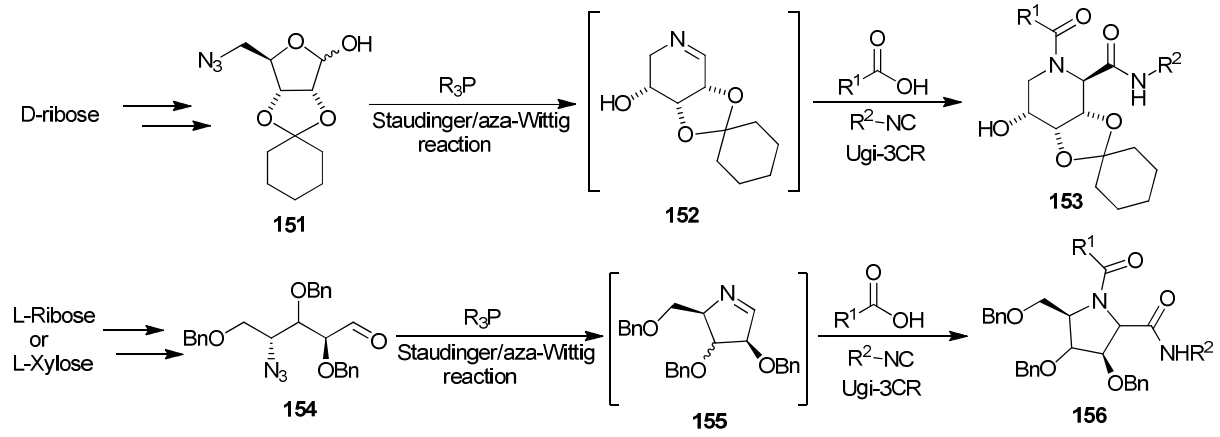


Fig. 8 Stucture of bis-sugars **149** and **150** incorporating trans-1,4-diaminocyclohexane and 3,3-dimethyl glutaric acid respectively as spacers.

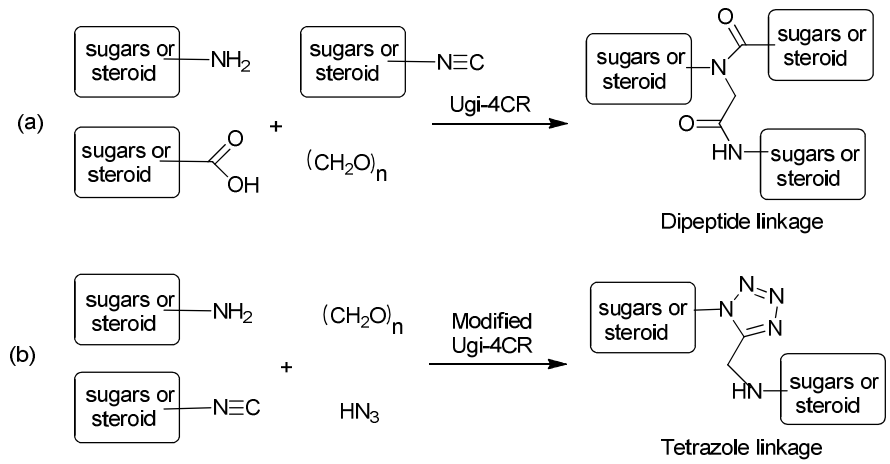
In further progress of his work, Liu *et.al*. synthesized the same library of small molecule heparin sulfate (HS) mimetics by employing Ugi-4CR of D-mannopyranoside derived isocyanides with

formaldehyde, carboxylic acids and amines followed by sulfonation. HS mimetics were used to probe the binding environment of some angiogenic H-S binding growth factors (FGF-1, FGF-2, VEGF) and showed a clear preference particularly an aromatic group for FGF-1 and VEGF.[47]

Following the advances in multicomponent reactions Herman *et.al*. have prepared a highly functionalized pyrollidines by a tandem Staudinger/Aza-Wittig/ Ugi three component reaction (SAWU-3CR). In this process, an azidoaldehyde was reacted with a trialkylphosphine (Staudinger reaction) to give an intermediate phosphazene, which then undergo an intramolecular aza-Wittig reaction with the aldehyde moiety to provide a cyclic imine. Addition of an isocyanide and a carboxylic acid at this stage provides a bisamide in an Ugi-3CR sequence. SAWU-3CR was applied on two different carbohydrate derived 4-azidopentanals (**151** and **154**) obtained from D-ribose and L-ribose or L-xylose respectively to generate **153** and **156** *via* the formation of corresponding cyclic imines **152** and **155** (Scheme 32).[48]

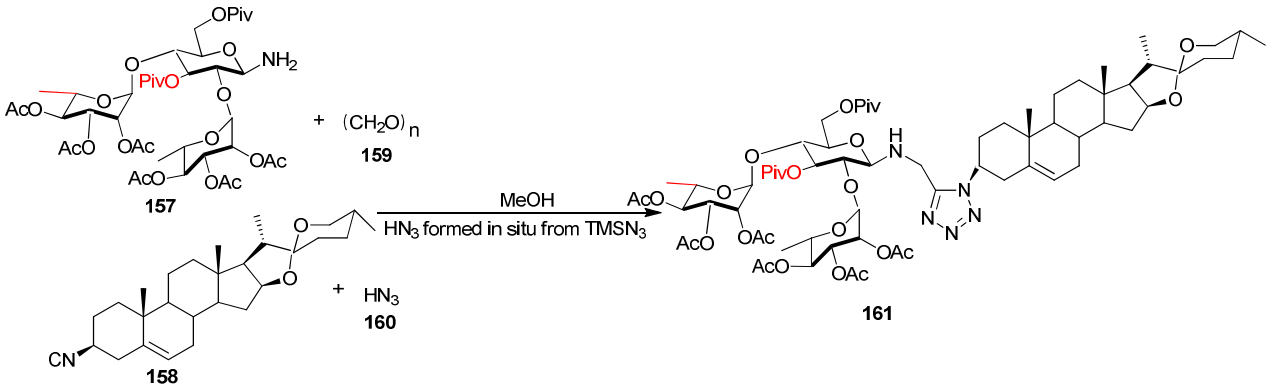


Scheme 32 Synthesis of highly functionalised heterocycles **153** and **156** *via* SAWU-3CR.



Scheme 33 Ugi-4CR and its modified version: Strategy behind sugar to steroid conjugation

A new carbohydrate-steroid conjugation approach based on Ugi four component reactions was implemented by Daniel *et.al*. to develop one pot synthesis of novel molecular chimeras incorporating sugar, pseudo-peptide and steroidal moieties. Glucose and chacotriose was ligated to spirostaine steroids. For the synthesis of tetrazole based chacotriose-diogenin conjugates two alternative strategies based on the (a) Ugi reaction and (b) its modified version, hydrazoic acid variant of Ugi reaction were employed (Scheme 33).[49]

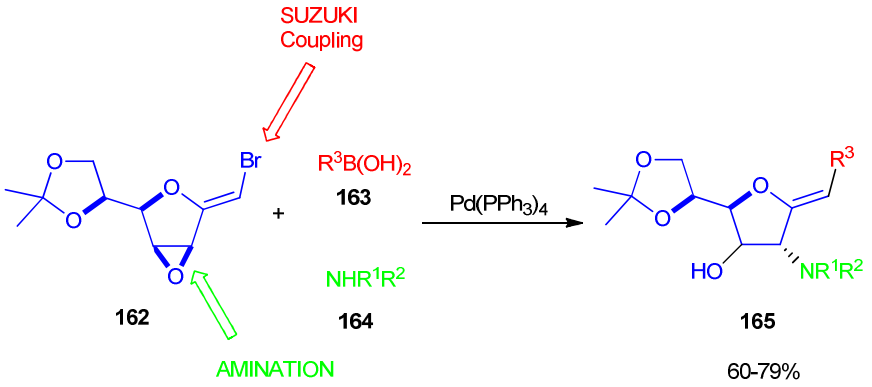


Scheme 34 Synthesis of tetrazole based spirostan saponin analogs **161**

This was the first time when triple sugar / pseudo peptide/ steroid hybrids were generated, thus opening a new path for the synthesis of these fascinating molecules and therefore, applicable in drug discovery and biological chemistry. Scheme 34 shows the synthesis of tetrazole spirostan

saponin analogs **161** using modified Ugi based (hydrazoic acid variant) reaction incorporating **157**, **158**, **159** and **160**.

Recently, furanose based carbohydrate template **165** have been developed by the Ana *et.al.* using a highly functionalized furanose derivative **162** possessing a halo-alkenyl allylic–oxirane system under a Pd catalyzed one pot three component assembly with boronic acids (R=H) or alkyl boranes **163** and amines **164** (Scheme 35).[50] This reaction has advantages of producing a completely regio and stereoselective sugar based derivatives with two sites of molecular diversity.



Scheme 35 Pd catalysed one pot three component reaction on functionalsed furanose **165**

Compound **162** seems to possess two sites namely the allylepoxide and the vinyl bromide susceptible enough to undergo activation by palladium catalyst through oxidative addition but which sites is more reactive is not known.

First total synthesis of antibacterial nucleoside natural product (-) muramycin (MRY) D_2 and its epimer was described by Satoshi and Akira utilizing Ugi 4-component reaction.[51] Basically the target MRY D_2 was retro synthetically divided into various important fragments which were combined readily to obtained the entire desired nucleoside molecule (Fig. 9). Key strategy involved the preparation of urea dipeptide moiety found in the muramycins containing an L-epi-capreomy-cidine *via* a nitrene. Further C-H insertion of sulfamate **166** and fully protected

muramycin skeleton with 10 mol % of Rh_2 $(esp)_2$ catalyst, the nitrene C-H insertion of sulfamate to give the cyclic sulfamates **167a** and **167b** in 47% yield in 1:2 ratio respectively. Cyclic guanidine skeleton was obtained *via* $HgBr_2$ promoted cyclisation of **169** followed by desufonylation upon acetolysis of the oxathiazinane ring to give **170** in good yield. MeSC(=O)-L-Val-O-t-Bu **168** was allowed to react with amine obtained by the selective removal of Cbz group of alcohol **171** to provide **172** which was then oxidized to **173**. Now, Ugi four-component reaction was allowed to occur between **174**, isonitrile **175**, isovaleraldehyde **176** and ammonia **177** to furnish the protected Ugi-products which was then unprotected to yield (-) MRY D_2 **178** and its epimer epi- MRY D_2 through HPLC separation of the diastereomers (Scheme 36).

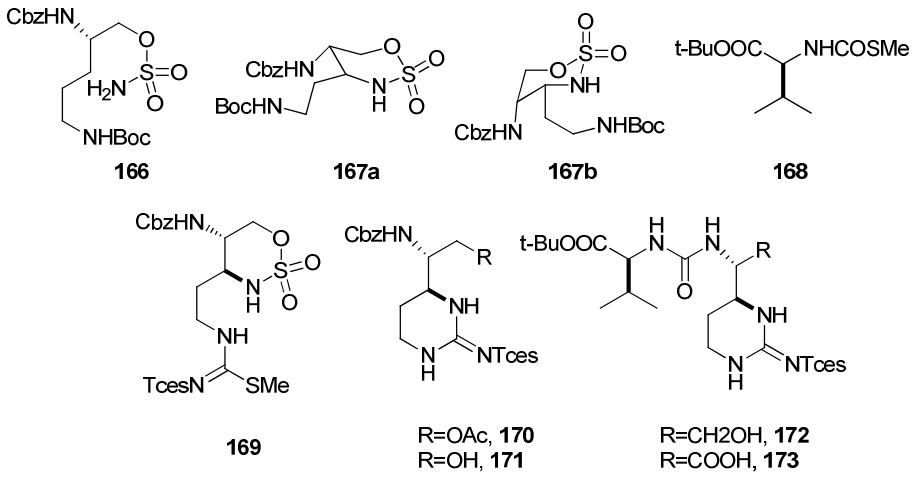
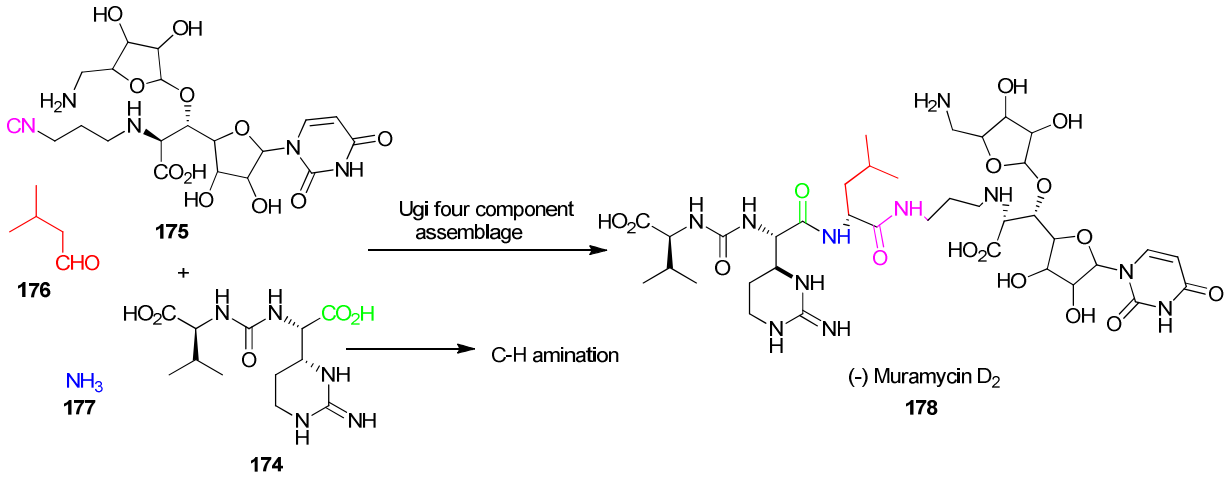


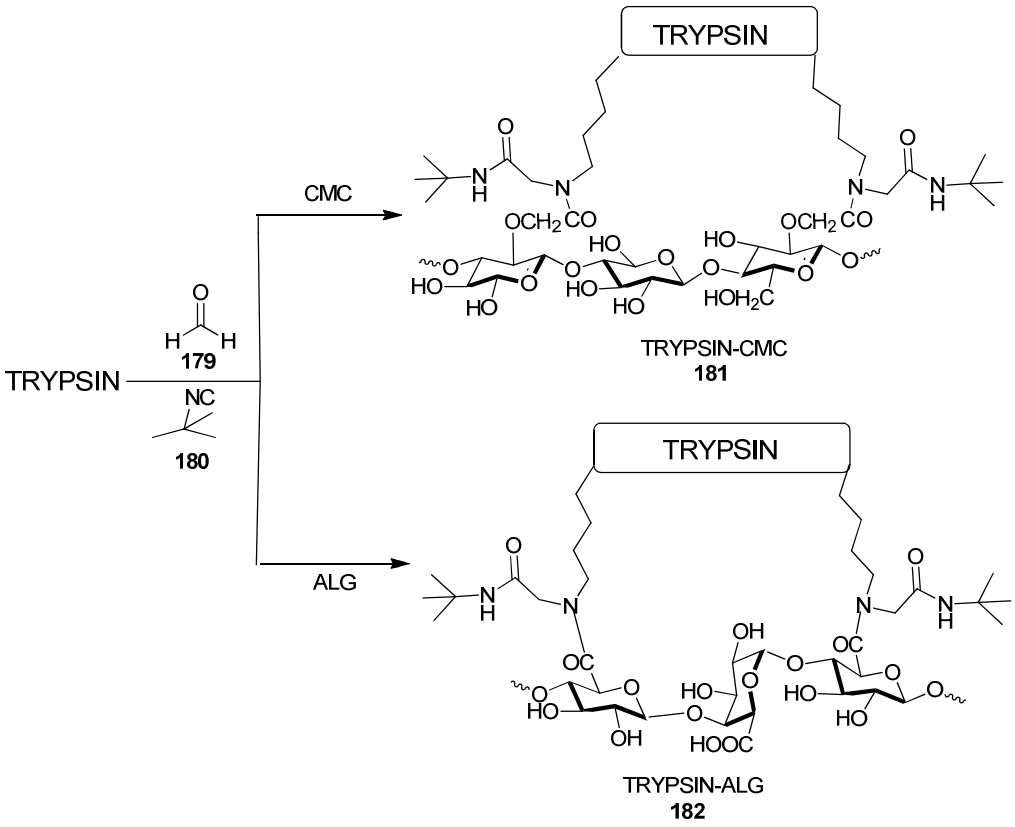
Fig. 9 Various fragments involve in the tatal synthesis of (-) muramycin and its epimer



Scheme 36 Total synthesis of (-) muramycin D_2 Ugi based multicomponent recation.

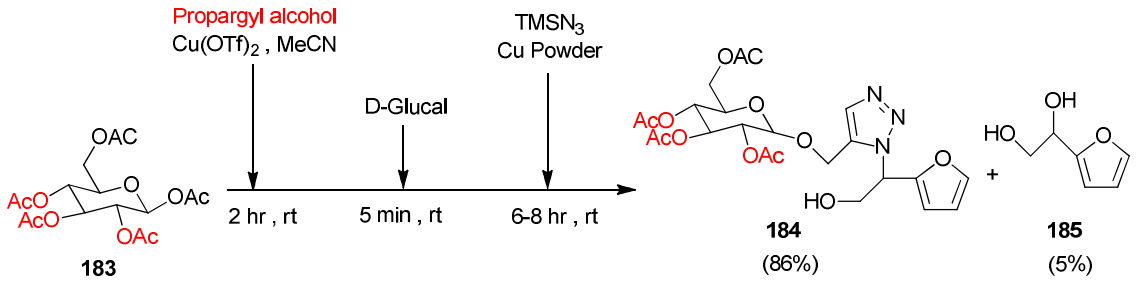
Ariel *et.al*. developed a synthetic method for the preparation of enzyme-polysaccharide derivatives **181** and **182** using Ugi multicomponent reaction. In this the target enzyme Bovine pancreatic trypsin was cross linked with the anionic polysaccharide O-carboxymethyl cellulose (CMC) and sodium alginate from *Laminaria Hyperboria* (ALG) in the presence of formaldehyde **179** and t-butyl isocyanide **180** (Scheme 37).[52]

It is interesting to note that the protease was found to retain 69-61% and 43-37% of its initial esterolytic and proteolytic activity after cross linking. Thermo stability of enzyme was also enhanced after modification from 49^0C to 57^0C. Resistant to inactivation and activation free energy of thermal inactivation was also increased after modification.

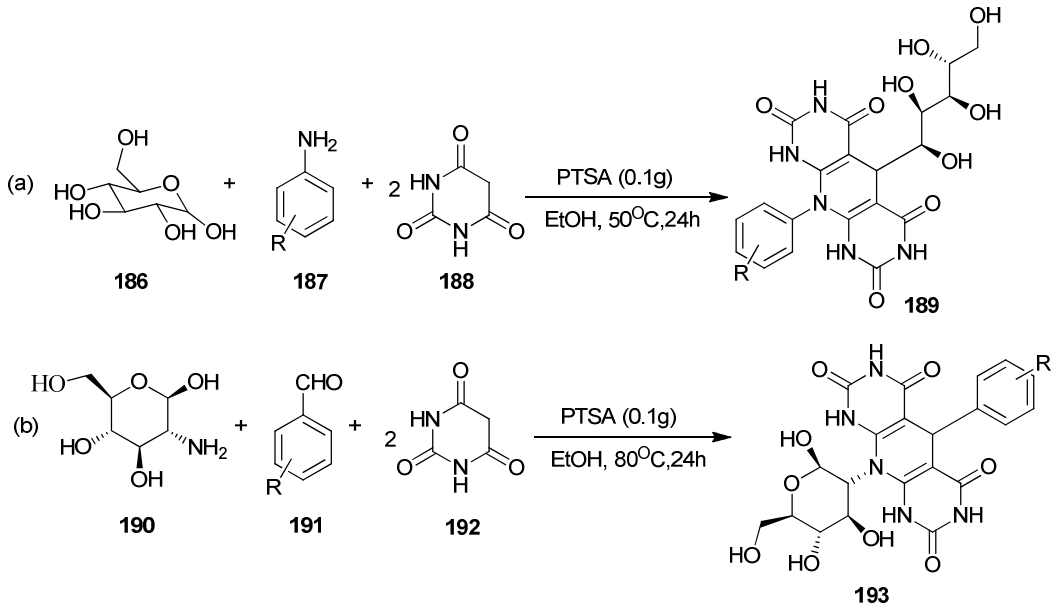


Scheme 37 Ugi-4CR synthesis of trypsin-CMC and trypsin-ALG conjugate

Mukherjee and his coworkers have reported a novel $Cu(OTf)_2$/Cu powder-mediated one-pot reaction for synthesizing furan based hydroxyl triazoles from the easily available glucopyranose peracetate **183** conjugates through sequential addition of the reagents. A solution of pentaacetylated D-mannose and propargyl alcohol in acetonitrile was subjected to O-glycosylation under $Cu(OTf)_2$ activation, followed by sequential addition of glucopyranose peracetate, $TMSN_3$, and finally copper powder to afford the triazole **184** as the major product (84% yield) along with furan diol **185** (5% yield) as by product (Scheme 38).[53]



Scheme 38 Multicomponent component synthesis of furan based hydroxy triazole glycoconjugates **184**



Scheme 39 Multicomponent synthesis of polyhydroxy substituted PFHs **189** and **193**

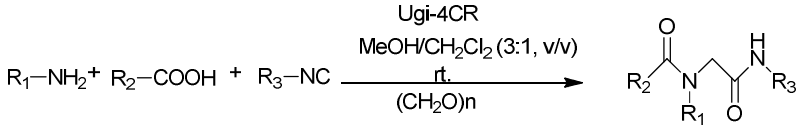
A new library of hydrophilic substituted pyrimidine fused hetereocycles was developed by Panahi *et.al.* They have synthesized of a set of polyhydroxy functionalized pyrimidine fused heterocycles (PFH_S) **189** and **193** by applying a multicomponent reaction in two sequences. One is sugar (glucose, glactose, arabinose and lactose) **186**, amines **187** and barbituric acid **188** (Scheme 39a) and other is D-glucosamine **190**, an aldehyde **191** and barbituric acid **192** (Scheme 39b).[54] These one pot protocols efficiently provide PFHs derivatives under mild and green conditions in good to excellent yields. The carbohydrate acts as carbonyl group source in one method and amine source in other method.

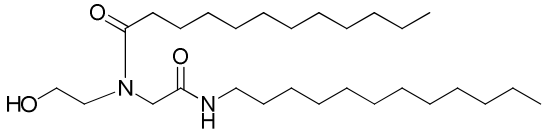
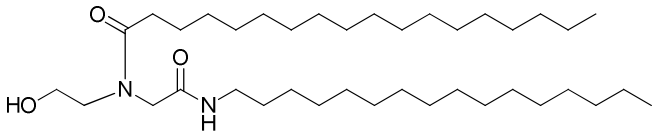
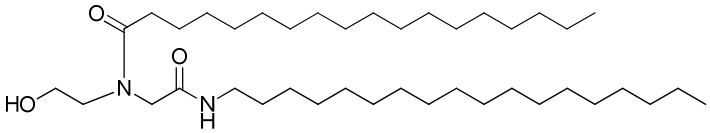
Recently, unique types of ceramides and glycolipids have been prepared based on Ugi reaction by Brokard *et.al.* involving lipidic isocyanides as surrogates of sphingolipids.[55] Two different strategies were implemented for this

(1) Formation of glycolipid skeleton *via* initial assembly of ceramide analogues followed by glycosylation

(2) One pot synthesis of glycolipid frameworks through the condensation of lipidic isocyanides either with lipidic amines and oligosaccharidic acids or with fatty acids and oligosaccharide amine

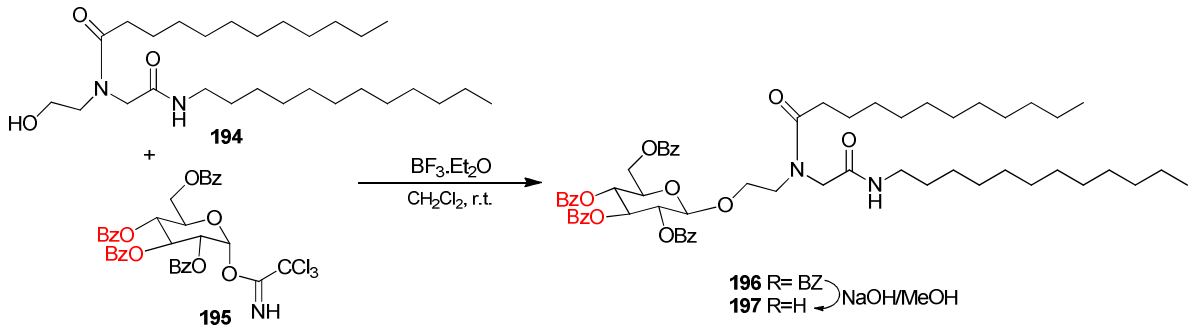
Table 1 Synthesis of ceramide analogous by the Ugi-4CR



Amine	Acid	Isocyanide	Ugi-type Ceramide Analogous
HO–CH2–CH2–NH2	$C_{11}H_{23}COOH$	$C_{12}H_{25}NC$	
HO–CH2–CH2–NH2	$C_{17}H_{35}COOH$	$C_{16}H_{33}NC$	
HO–CH2–CH2–NH2	$C_{17}H_{35}COOH$	$C_{18}H_{37}NC$	

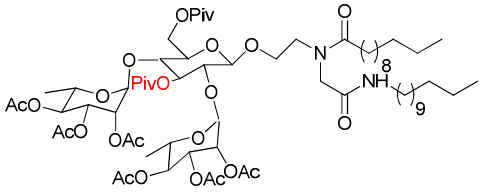
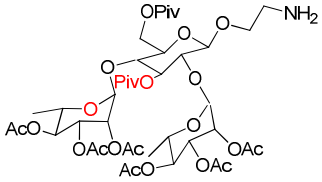
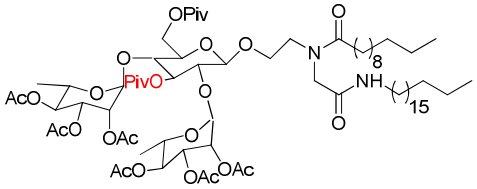
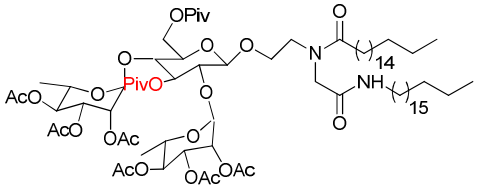
In first strategy, ethanolamine as the amino component was employed to provide the primary hydroxyl group required for the glycosylation. Thus lauric acid (dodecanoic acid) was combined with isocyanide to furnish the ceramide analogues, which was endowed with two lipidic chains of 12 carbon atoms each (Table 1). The important feature of this method includes that the length of lipid chain did not have any significant effect on the yield of product.

Glycosylation of ceramide analogue **194** with 2,3,4,6-tetra-O-bezoyl-α-D-glycopyranosyltrichloroacetimidate **195** to give a conjugate **196** was carried out followed by the deprotection with NaOMe/MeOH to produce neoglycolipid **197** (Scheme 40), a new class of cerebroside mimetic.



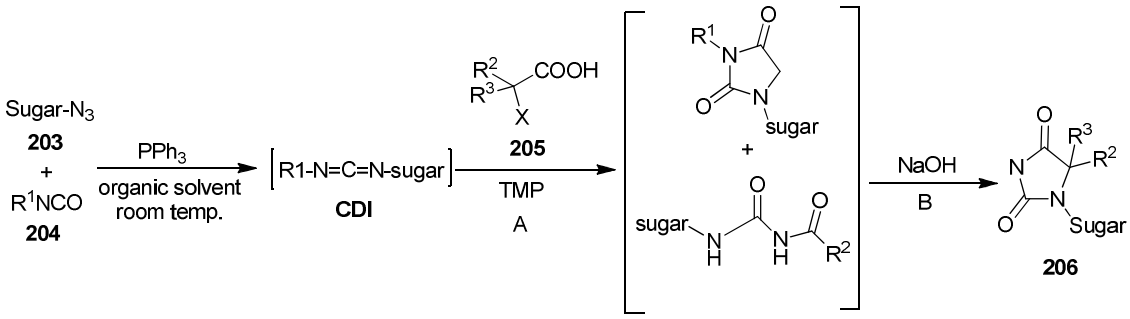
Scheme 40 Synthesis of neoglycolipid by glycosylation of ceramide analogues

Table 2.One-pot multicomponent synthesis of neoglycolipids from fatty acids, lipidic isocyanides and an amino-containing oligosaccharide.

Amine	Acid	Isocyanide	Glycolipids
	$C_{11}H_{23}COOH$ **199**	$C_{12}H_{25}NC$ **201**	
 **198**	$C_{11}H_{23}COOH$ **199**	$C_{18}H_{37}NC$ **202**	
	$C_{17}H_{35}COOH$ **200**	$C_{18}H_{37}NC$ **202**	

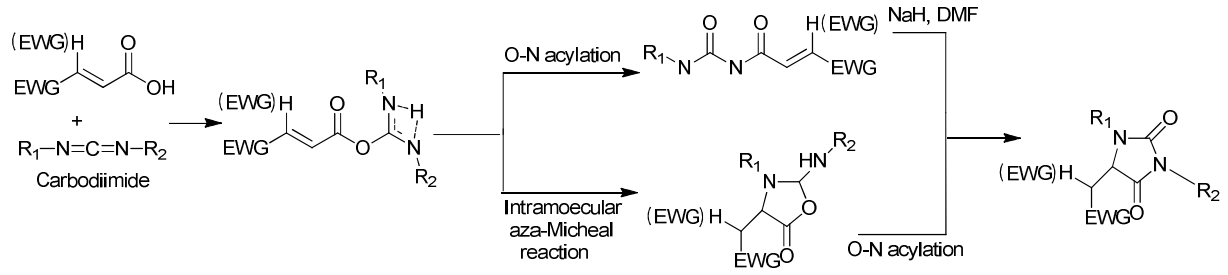
Second approach involved a one pot multicomponent reaction where 2-aminoethyl β-chacotrioside **198** was combined with lauric acid **199** and stearic acid **200** as well as lipidic isocyanides (**201** and **202)** and paraformaldehyde as oxo component (Table 2).

To describe a method of linking sugars to heterocycles and peptides Volonterio *et.al.* reported a one pot sequential synthesis of a novel class of glycoconjugates i.e., glycol hydantoin conjugates **206**. Initially, glycoazides **203** were reacted with isocyanates **204** to generate carbodiimide intermediate (CDI) which is then combined with suitable carboxylic acids **205** (step A) (Scheme 41).[56] Total regioselectivity was observed in almost all cases when both strong and weak carbodiimide intermediates are involved.

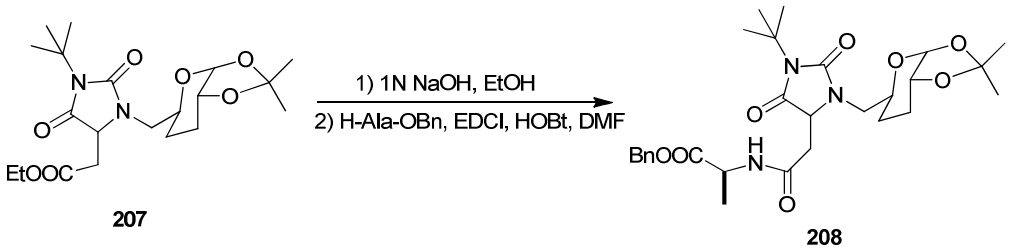


Scheme 41 Three component sequential synthesis of glyco-hydantoin conjugates

Regioisomeric N-acylurea derivative (carbodiimide) was prepared by Staudinger reaction between galactose-azide and isocyanate in high yield through the favourable O-N acyl migration process compared to slow intramolecular aza-Michael step (Scheme 42). Cyclisaton step (B) was easily achieved by adding the base solution to the reaction mixture once N-acylurea intermediate was formed.



Scheme 42 Mechanism showing the favourable O-N acyl migration and slow intramolecular aza-Micheal step

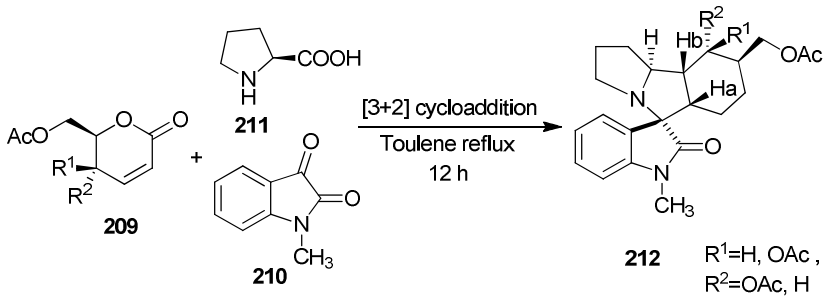


207 **208**

Scheme 43 Conversion of glyco-hydantoin conjugates into sugar-pseudopeptide

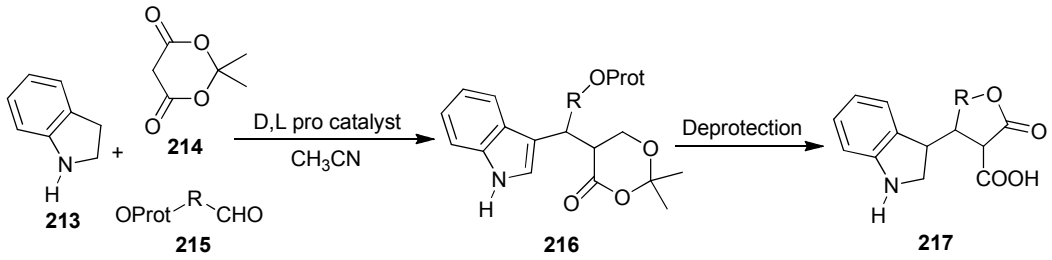
Glycol-hydantoin conjugates **207** was then converted into sugar-pseudopeptide **208** conjugates by treating with an aqueous solution of NaOH and the resulting acid then allowed to couple with alanine benzyl ester (Scheme 43). Glycol-hydantion conjugates formation worked well with fumaric acid monoethyl, monobenzyl and mono t-butyl ester, so ester group was hydrolysed chemoselectively by chosing suitable reagent maintaining the protecting group on glycol moiety or *vice versa* while this was not nessassary for the pseudo glycopeptides.

Rao and Raghunathan have developed a diasteroselective synthetic protocol to synthesize pyrrolidinyl spirooxindoles fused to sugar lactone **212** *via* [3+2] cycloaddition of azomethine ylides. A unique kind of dipolarophile (α-β-unsaturated lactone) derived from D-glucose/ D-glactose **209** was allowed to react with azomethine ylide generated *in situ* from isatin/ N-substituted isatin **210** and secondary amino acids **211** to give the corresponding products in good yield (Scheme 44) and this cycloaddition was observed to be highly regio and diasteroselective.[57]



Scheme 44 Synthesis of sugar lactone fused spiropyrrolizidine oxindole

Dardennes *et.al.* described a trimolecular condensation of indole **213**, Meldrum's acid **214** and chiral sugar derived aldehyde **215** to obtain compound **216** which was allowed to undergo subsequent deprotection step to yield **217** (Scheme 45).[58] The absolute configuration of the α-carbon in the chiral aldehydes was used as the basis to control the stereochemistry of the newly created stereogenic centre. However, a completely opposite stereochemistry in case of trimolecular condensation with bicyclic O-benzyl-protected aldehyde was observed probably due to less congested conformer of the intermediate Knoevenagel product.



Scheme 45 Diastereoselective condensation of Indole, Meldrum's acid and chiral sugar derived aldehyde

Fig. 10 shows the structure of various chiral sugar derived aldehyde used in the condensation process.

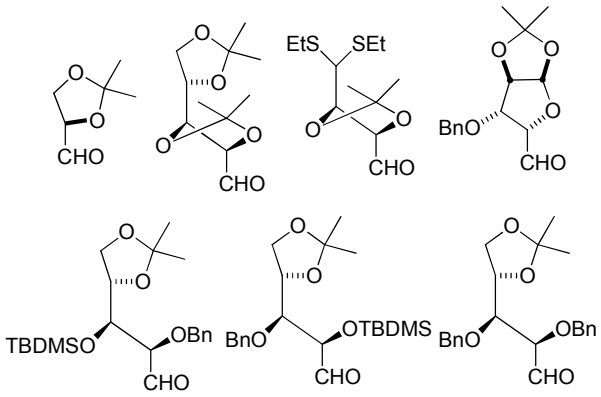
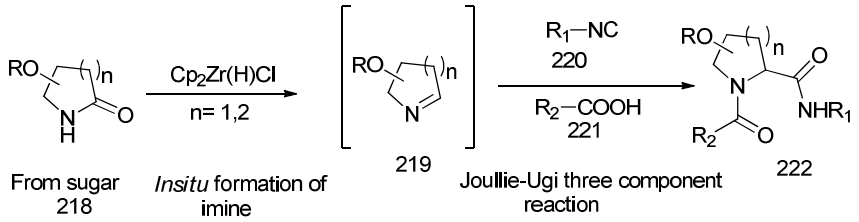


Fig. 10 Structure of various chiral sugar derived aldehyde used

Very recently Piotr *et. al.* developed a strategy based on the one pot reduction of sugar derived lactams with Schwartz's reagent followed by multicomponent Ugi-Joullie reaction. Upon treatment with the Schwartz's reagent ($Cp_2Zr(H)Cl$), five or six membered lactams derived from sugars **218** was converted into imines **219** under mild condition. Further this imine was allowed to undergo Jouliie-Ugi reaction with isonitrile **220** and acid **221** to generate compound **222** (Scheme 46).[59]



Scheme 46 Sequential Lactam Reduction/Joullie-Ugi Three-Component Reaction

Fig 11 shows structure of some of the lactam **223-226** and their corresponding polyhydroxylated piperidine/pyrrolidine peptidomimetics **223a-226a** formed by the sequential reduction of lactam by Schwartz's reagent to imine which *insitu* allowed to involved in further three component Joullie-Ugi reaction with isonitrile and trifluoroacetic acid.

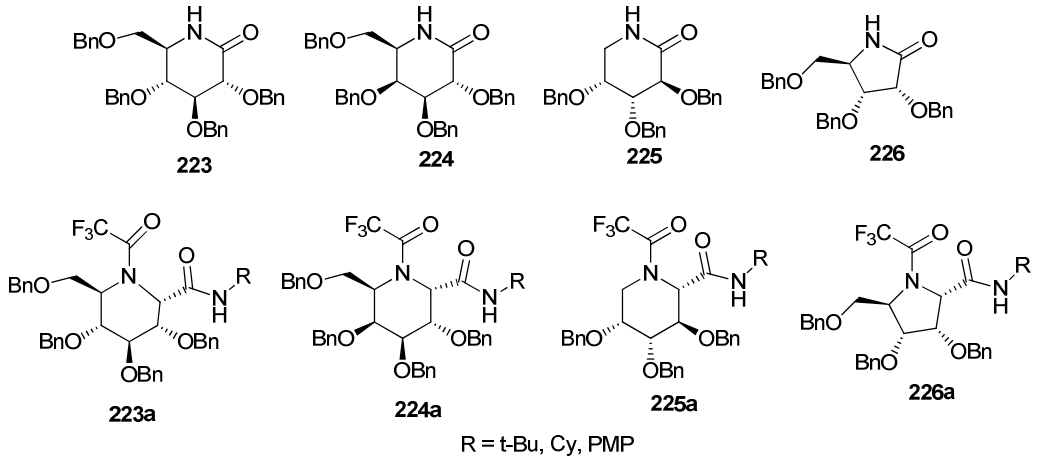


Fig 11. structure of some of the lactam used and their corresponding products

Conclusion

As a class of typical widely occurring natural compounds with number of biological and pharmacological importance, sugar based derivatives have been regarded as very important targets of organic synthesis. In this review, we presented remarkable characteristics of multicomponent reactions on the synthesis of a number of sugar based derivatives as main theme. The concept of MCRs has allowed an easy access to desirable compounds with great molecular complexity. Other advantages include often excellent level of selectivity with quite simple operational procedures, as well as savings time, energy and costs. MCRs proceed generally under relatively mild conditions and bear wide variety of functional groups, thus avoiding functional group protection chemistry. A noticeable number of MCRs have been employed to generate the highly functionalized sugar based derivatives with potentially active ends which can be further manipulated accordingly. Among MCRs, Ugi-4CR has been widely used to incorporate significant amount of complexity in the molecules as well as in the total synthesis of some of the biologically important mimetics. Thus, we hope with this review to have provided appropriate background for such developments and the encouragement to synthetic organic chemists to employ this valuable information to synthesize other biologically and

medicinally active sugar based derivatives or to discover efficient methodologies having at least some benefits over the existing one.

Acknowledgements

We gratefully acknowledge the financial support from the University Grant Commission, New Delhi for fellowship. MMK is also thankful to UGC, New Delhi for Start-up Grant [F-20-1/2012(BSR)/20-2(15)/2012(BSR)].

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