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Gabriel-Cromwell aziridination of amino sugars; chiral ferrocenoyl-aziridinyl sugar synthesis and their biological evaluation

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ABSTRACT

N-sugar substituted chiral aziridines were synthesized via Gabriel-Cromwell reaction. Novel pure diastereomers of aziridine derivatives (4 diastereomers) were readily obtained in high yields and their structures were confirmed by means of ^{1}H NMR, ^{13}C NMR, FT-IR, Mass and optical rotations. This is, to the best of our knowledge, the unique example of *N*-sugar aziridine synthesis. Diastereomeric effects for prostate (PC3) and cervix (HeLa) cancers were screened and it has been observed that the epimers bearing the same sugars showed different results against PC3 and HeLa cancer cells. The novel sugar aziridines were investigated as promising prodrug candidates for prostate cancer (PC3) therapy. Moreover, the drug likeness calculations (Lipinski's rule, physicochemical properties, lipophilicity, solubility, pharmacokinetics and bioavailability radar) have indicated that the sugar aziridines can be good candidates as oral drugs.

1. Introduction

Aziridine is a saturated three-membered heterocyclic amine containing one nitrogen atom in the ring [1–3]. The discovery of aziridines dates back to 1888 [4]. Its inherent reactivity, like its analogue epoxide, arises from the fact that the smallest strained three membered compounds have bond angle distortion and the dipole between carbon and hetero atom. Therefore, it has been used as a versatile building block in many organic transformations. They allow convenient access to amines, amino acids, amino alcohols, diamines, and other useful nitrogen-containing molecules [5,6]. Moreover, aziridine ring can be converted to azomethine ylides which can provide biologically important heterocyclic compounds with a dipolarophile such as alkene, alkyne, carbonyls and imines [7]. Although it has an inherent reactivity, many natural and synthetic compounds containing aziridines are sufficiently stable. Several natural aziridine alkaloids bearing the aziridine ring exhibit potential biological activity such as mitomycin, azirinomycin and madurastatin [8–10].

The synthesis of enantiomerically pure aziridines is one of the major areas of organic chemistry. Some of the common synthetic methods used in aziridine synthesis can be listed as follows; nitrene or nitrenoids addition to alkene [11], carbene addition to imine (Aza-Darzens reaction) [12], Michael type addition [13], 1,2-amino alcohols (intramolecular cyclization) [14] and enantioselective catalytic aziridination [15]. On the other hand, synthesis of aziridinyl sugar is limited due to the nature of sugars. Despite the numerous transformations of aziridines, few examples of synthetic methodologies have been described in carbohydrate chemistry. In other words, aziridine functionality has not received the attention it deserves in synthetic carbohydrate chemistry. One of the most used methods for aziridinyl sugar synthesis is the S_N2 reaction between the vicinal groups such as amino and the leaving group [16]. Reductive ring closure of azido-sugars by triphenylphosphine gave aziridine-sugars with inversion of configuration [17]. Keniche et al. synthesized aziridine-sugars from *N*-acyl-2-iodo-aziridines by nucleophilic displacement of iodine with amino-sugars [18]. Dhavale et al. synthesized the D-glucose derived aziridine by using Gabriel-Cromwell reaction from α-bromo-α,β-unsaturated ester sugar and primary benzyl amine [19] (Fig. 1b). Some sugar-derived aziridines are depicted in Fig. 1 [20–23].

Cancer is the most abundant and fatal disease in the world, the prostate and cervix cancer being among the most common for men and women, respectively. Stereoisomeric drugs that have different structures in three dimensional space operate differently towards chiral natural living systems. In this context, many studies have been reported in

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medicinal chemistry [24]. Due to the different activities of enantiomers, many disasters have occurred in medicinal treatments [25]. Moreover, we have envisaged that ferrocene unit could improve anti-cancer activity of sugar-aziridine diastereomers because many reports have been published about excellent anti-cancer activities of ferrocene-based molecules [26].

Many synthetic aziridines have been tested for their biological activity (Fig. 2). Vega-Peres at al. have synthesized aziridinyl galactopyranoside derivatives from alkenyl β-D-galacto pyranosides using Sharpless conditions and screened against lung cancer cell line. They found that some possess high and selective anti-cancer activities [27]. Within this work pure chiral ferrocenoyl-sugar-aziridine stereoisomers were synthesized and screened against PC3 and HeLa cancer cells.

2. Results and discussions

Novel *N*-sugar aziridines were obtained readily by employing the Gabriel-Cromwell reaction [33]. The synthesis starts with pure chiral sugars which are cheap and commercially available in large quantities. In this context, it can be called as "chiral pool asymmetric aziridine synthesis". Newly formed chiral center and the preserved absolute configuration of the sugars (1 and 5) afforded easily separable ferrocenoyl-aziridinyl-sugar diastereomers.

2.1. Chemistry

The synthetic part might be divided into three sections as follows; amino sugar synthesis, α,β-dibromopropanoylferrocene synthesis and aziridinyl sugar synthesis. In the first part, amino sugars (**4** and **8**) were obtained in three steps as we have reported [34] (Scheme 1). Firstly, commercially available sugars were tosylated with *p*-toluenesulfonyl chloride in pyridine at room temperature. Next, the tosylated sugars (**2** and **6**) were reacted with sodium azide, NaN_3, to give azido-deoxy sugars (**3** and **7**). Subsequently, azido-sugars (**3** and **7**) were reduced with $LiAlH_4$, into amino-sugars (**4** and **8**).

In the second part, acryloylferrocene was obtained from ferrocene and acryloyl chloride in the presence of an alkyl Lewis acid ($EtAlCl_2$ or $EtAlCl_2$–Me_3Al) [35]. Next, it was dibrominated according to the Dogan group procedure [36] (Scheme 2).

In the third part, α,β-dibromopropanoylferrocene (**12**) and either amino sugar (**4** and **8**) were reacted for 3 days at ambient temperature (the protocol adapted from the Dogan group [36] (Scheme 3).

Finally, two diastereomeric aziridinyl-ferrocenoyl sugars (**13**, **14**, **15** and **16**) were obtained readily in high yields (up to 90%). The reaction mechanism (Gabriel–Cromwell reaction) for the last step is given in Scheme 4. During the work-up, the flash columns were applied easily because all the diastereomers (**13**, **14**, **15** and **16**) were colorful (Fig. 3). Consequently, the diastereomers were purified and separated. Unfortunately, single crystallization attempts failed. Therefore, the absolute configurations of the diastereomers could not be determined. We numbered the diastereomers in the order they came from the column.

The ^{1}H NMR (see the Experimental section and Supporting Information, respectively) of the compound **15** is chosen as a representative example for verifying the formation aziridinyl sugar. In the ^{1}H NMR spectrum of **15**, nine hydrogens of mono-substituted ferrocene resonate at 4.87 (s, 2H), 4.52 (s, 2H) and 4.16 (s, 5H) ppm. The seven hydrogens on the sugar ring appear at 5.92 (d, J = 3.6 Hz, $1H_{anomeric}$), 4.47 (m, $2H_{2,3}$), 4.13–4.09 (m, $1H_4$), 4.00 (dd, J = 9.2, 3.2 Hz, $1H_5$), 3.93 (dd, J = 8.5, 5.8 Hz, $1H_{6a}$) and 2.41 ppm (d, J = 3.1 Hz, $1H_{6b}$) respectively. In addition, the methyl hydrogens of isopropylidene groups appear at 1.44, 1.36, 1.32 and 1.23 ppm as sharp singlets. On the other hand, H_α of aziridine ring was observed at 2.59 (dd, J = 6.4, 3.3 Hz, $1H_\alpha$) while its diastereotopic hydrogens appear at 2.33 (d, J = 3.2 Hz, $1H_\beta$) and 2.15 (d, J = 6.6 Hz, $1H_{\beta'}$) ppm respectively.

2.2. Anticancer activity results

Anticancer activities of the compounds (**13**, **14**, **15** and **16**) against HeLa and PC3 cells were investigated at four different concentrations (100, 50, 25 and 5 μM). IC_{50} values of the compounds **13, 14, 15** and **16** against HeLa and PC3 cells are given in Table 1.

As can be seen from Table 1 all of the sugar aziridines (**13**, **14**, **15** and **16**) depicted significant toxic effect with IC_{50} values of 29.50 ± 0.02 μM, 23.55 ± 0.01 μM, 27.98 ± 0.05 μM and 29.32 ± 0.05 μM against PC3 cell with respect to the standard drug 5-FU (IC_{50}: 37.40 ± 0.01 μM). Of the four aziridines, **14** afforded the best cytotoxicity with IC_{50} value of 23.55 ± 0.01. On the other hand, these four compounds (**13**, **14**, **15** and **16**) showed very poor toxic effect against HeLa cancer with IC_{50} values of 39.57 ± 0.01 μM, 25.88 ± 0.01 μM, 39.25 ± 0.03 μM and 24.98 ± 0.01 μM against HeLa cell with respect to the standard drug 5-FU (IC_{50}: 2.51 ± 0.01 μM).

The anticancer activities of compounds **13**, **14**, **15**, **16** and 5-FU were

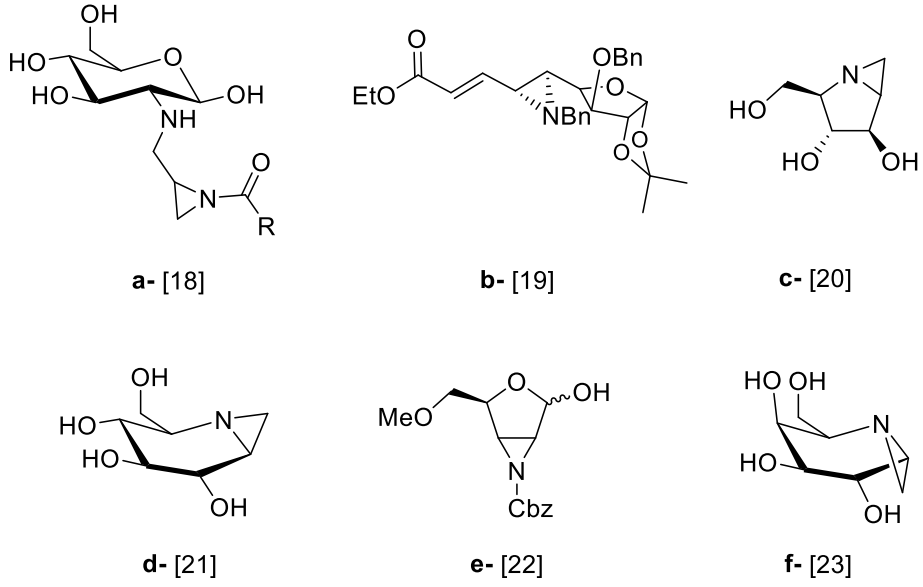


Fig. 1. Some selected sugar-derived aziridines.

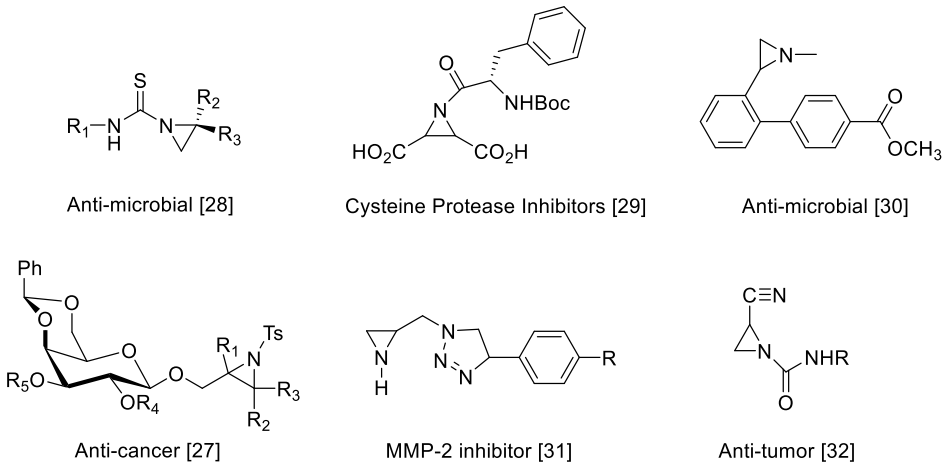
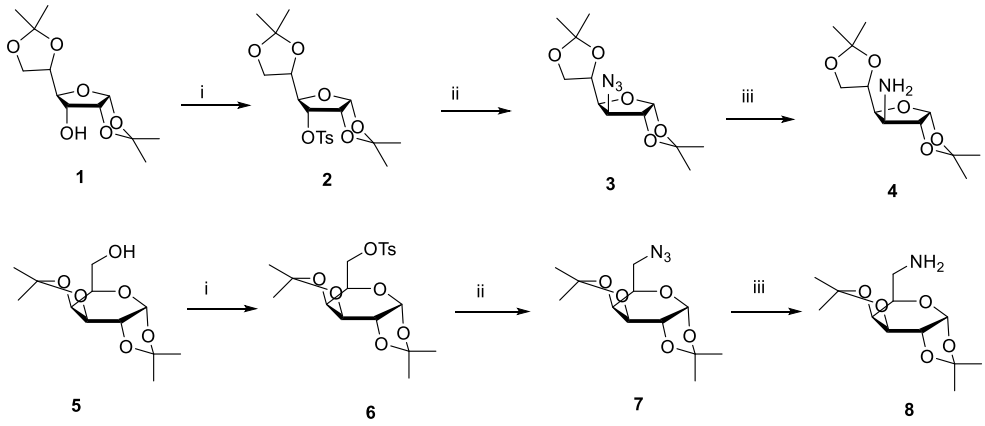
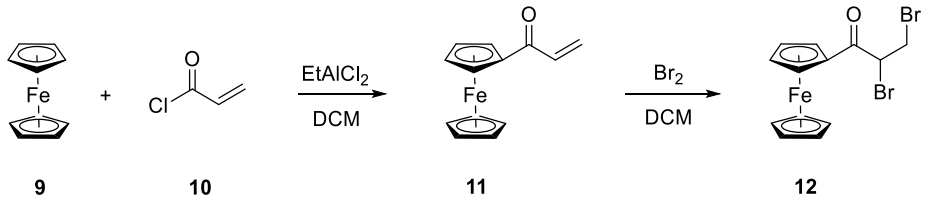


Fig. 2. Some selected biologically active aziridines [28–32].



Scheme 1. i) TsCl, Pyridine, rt ii) NaN_3, DMF, 150 °C iii) $LiAlH_4$, THF, −10 °C.



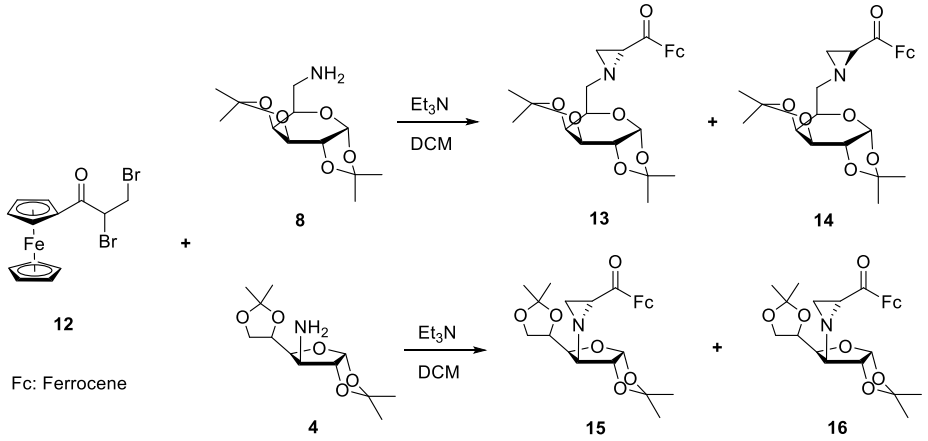
Scheme 2. α,β-dibromopropanoylferrocene synthesis.

determined to have the dose dependent effects against the PC3 cell lines (Fig. 4-A). Although at all doses, **13**, **14**, **15** and **16** were investigated to provide higher activities than 5-FU (standard compound) against PC3 cell, at the lowest dose (5 μM) remarkable activities were shown by **13** and **16** (10 times higher and 7 times higher inhibition than the standard 5-FU respectively). IC_{50} results of **13** and **16** also confirm these activities.

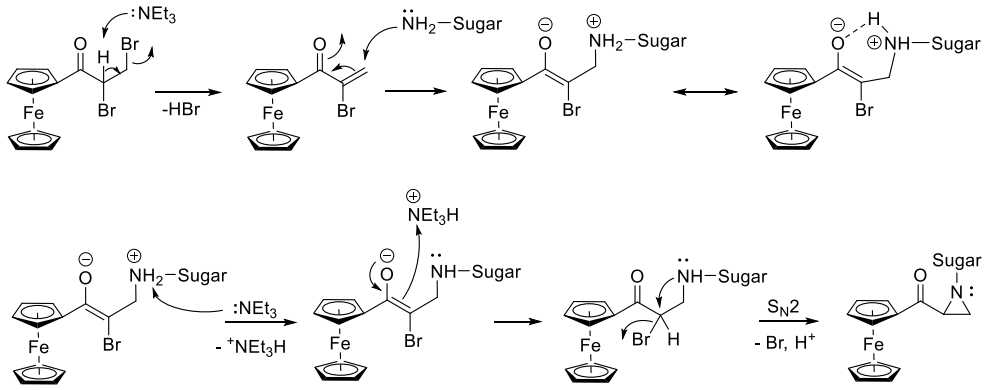
As with PC3, when the sugar aziridines (**13**, **14**, **15** and **16**) and 5-FU were screened with HeLa cells, they exhibited a dose-dependent effect (Fig. 4-B). In contrast to PC3 cancer cell, they afforded poor activities against HeLa cancer cell than the standard drug at all concentrations. High IC_{50} results at HeLa cancer cell support these results (Table 1).

2.3. Drug likeness properties

One of the aims for synthesis of molecules is related to their applications as drugs. Only five drug candidates can reach the stage of clinical testing as a result of screening of about 10,000 compounds. Before the discovery and drug development stages, it is necessary to acquire sufficient knowledge and physicochemical properties about the diseases and symptoms for which the considered drug can be used. Drug candidates that fit RO5 rules tend to have an increased chance of reaching the higher clinical stages. The four chiral azirdinyl-sugars (**13**, **14**, **15** and **16**) obey the Lipinski's rule as explained below. Their number of hydrogen bond acceptors (HBA) and donors (HBD) are within the Lipinski's rules; n-ON <10 and n-OHNH<5. Their calculated logP are smaller than 5 (logP <10, according to Lipinski's rules). The molecular weights of them are 497.36 g/mol which must be smaller than 500 g/mol according to Lipinski's rules. In drug design, the blood-brain barrier (BBB) score is valuable physicochemical information since it prevents toxic effects of drugs. As can be seen at Table 3, the BBB score of **13**, **14**, **15** and **16** ranges from 3.09 to 3.12 (the BBB score should be



Scheme 3. Synthesis of Sugar-aziridine-ferrocenoyl diastereomers.



Scheme 4. Gabriel-Cromwell aziridination mechanism.

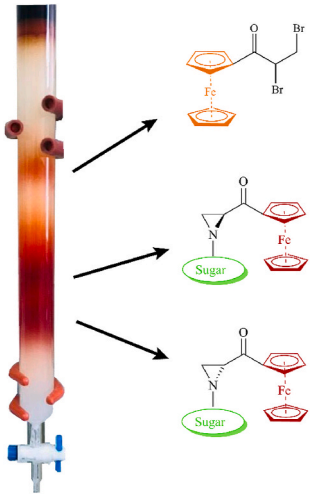


Fig. 3. Visible flash column for diastereomeric aziridinyl-ferrocenoyl sugar separation.

between 6-high and 0-low) [37]. The synthetic accessibility scores of the gluco-aziridine epimers (**13** and **14**) and galacto-aziridine (**15** and **16**) epimers have been found as 6.14 and 6.20 respectively (Table 2). The acceptable range for the synthetic accessibility is 1 (very easy) to 10 (difficult). Topological polar surface area (TPSA) values of **13**, **14**, **15** and **16** were smaller than 70 Å (66.23 Å). Moreover, the solubilities of the gluco-aziridine derivatives (**13** and **14**) and galacto-aziridine (**15** and **16**) were investigated as soluble and moderately soluble respectively. In addition, their skin permeations are equal and found as −7.32 which implies they have moderately skin permeations. As a result of Lipinski's rule of five (RO5) and other physicochemical calculations, **13**, **14**, **15** and **16** might be a new potential anticancer agents according to the calculated data (see Tables 2 and 3).

Table 1
IC_{50} values of compounds **13, 14, 15, 16** and 5-FU (standard drug).

Compound	PC3 (μM)	HeLa (μM)
13	29.50 ± 0.02	39.57 ± 0.01
14	23.55 ± 0.01	25.88 ± 0.01
15	27.98 ± 0.05	39.25 ± 0.03
16	29.32 ± 0.05	24.98 ± 0.01
5-FU	37.40 ± 0.01	2.51 ± 0.01

Fig. 5 shows the bioavailability radars of **13**, **14**, **15** and **16**. The pentagonal pink area represents the optimal range for each property (lipophilicity: LOGP between −0.7 and + 5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 $Å^2$, solubility: log S not higher than 6, saturation: fraction of carbons in the sp^3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds. Thus, it can be concluded that the compounds of **13**, **14**, **15** and **16** can be orally bioavailable.

3. Conclusion

In summary, the present study reports the successful synthesis, characterization, cytotoxic, anticancer and drug likeness study of novel

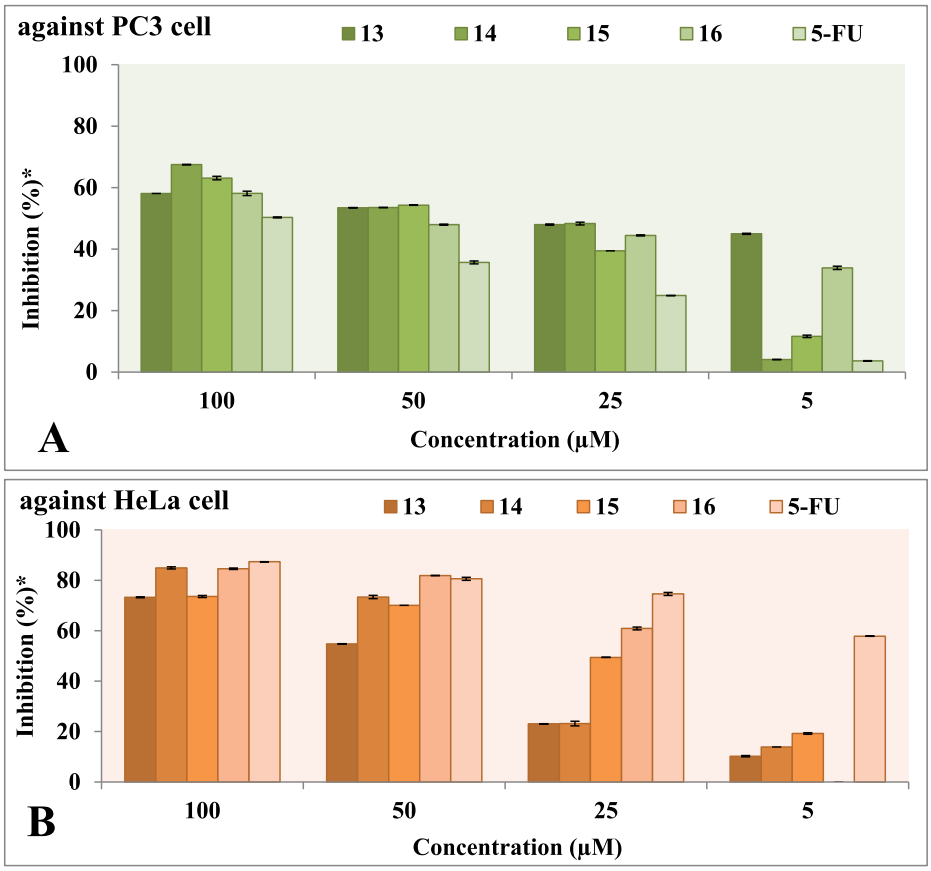


Fig. 4. Antiproliferative activity of **13, 14, 15, 16** and **5-FU** against PC3 (**A**) and HeLa (**B**) cells lines *Data are presented as mean ± SD (n = 6). Statistical significant difference ($p < 0.01$) was observed between treatments (ANOVA, Duncan).

aziridinyl sugar derivatives. Two different amino-sugars have been synthesized and reacted with freshly synthesized α,β-dibromo propanoylferrocene to give four different novel diastereomeric ferrocenoyl-aziridinyl sugars in high yields (80–90%). Of particular significance is reporting the first synthesis *N*-sugar substituted aziridine within this research. In addition, their separation is quite easy through flash column chromatography (without need TLC) since they are colorful and visible. Furthermore, their antiproliferative activity against PC3 and HeLa cancer cells were tested and found as good prodrug candidates for PC3 cancer cell. As a result of antiproliferative activities at the low dose (5 μM), **13** and **16** can be good drug candidates for prostate cancer with IC_{50} values of 29.50 ± 0.02 μM and 29.32 ± 0.05 μM respectively. IC_{50} results also confirm these activities. Compounds **13**, **14** and **15**, **16** are epimers among themselves and have given different anti-cancer activities. Thus, it can be interpreted that different absolute configurations of chiral compounds might give different biological evaluations. Finally, the drug likeness calculations were performed in order to find the ideal bioavailability. The molecular weight (MW), the number of hydrogen bond acceptors (HBA), the number of hydrogen bond donors (HBD), the number of rotatable bonds (RB) and the topological polar surface area (TPSA) for all the compounds are in good agreement with the Lipinski's rule of five.

4. Experimental

4.1. Chemistry (General methods)

All chemicals including 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**1**) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**5**) were supplied from Sigma-Aldrich Company. Acryloyl ferrocene (**11**) and 1,2-dibromoprapanoylferrocene (**12**) were prepared according to the literatures [34,35] respectively. 3-Amino-3-deoxy-1,2:5,6-di-*O*-isoproylidene-α-D-glucofuranose (**4**) and 6-Amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**8**) were prepared according to our previous report [33].

^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were measured on a Bruker spectrospin Avance DPX-400 Ultra shield instrument at 400 MHz and 100 MHz respectively (standard TMS). FT-IR spectra were obtained on Bruker Platinum ATR-IR instrument and reported in reciprocal centimeters (cm^{-1}). All solvents were dried and distilled prior to use. For measuring optical rotations, Rudolph Research Analytical Autopol III Polarimeter was used. Products were separated by flash column chromatography on Silica Gel 60 (Merck, 230–400 mesh ASTM). TLC analyses were applied on 250 μm Silica Gel 60 F254 plates. Mass spectra were recorded with GCMS-QP2010 Plus SHIMADZU instrument. The NMR spectra, FT-IR spectra and Mass spectra are given in Supplementary data section.

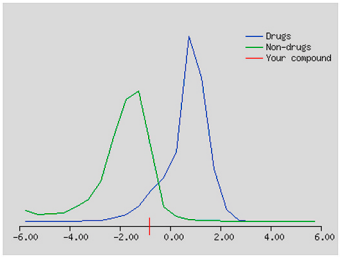
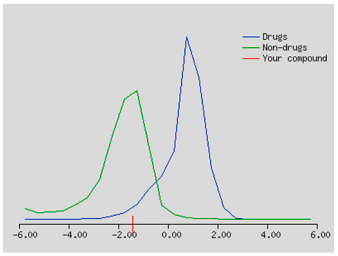
4.1.1. Procedure for aziridination of amino sugars

6-Amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**8**) (0.122 g, 0,4703 mmol) was dissolved in 1 mL of CH_2Cl_2 and stirred for 30 min. To this solution, 1,2-dibromoprapanoylferrocene (12) (0.150 g, 0.4703 mmol) and Et_3N (0.13 mL, 0,9406 mmol) were added. The reaction period was monitored via TLC. After mixing 2 days at ambient temperature (25 °C), It was directly added to the column (as eluent system: Hexane-EtOAc (1:1)) for separation and purification without doing any work-up. The colorful diastereomers (13 and 14) were readily collected without doing TLC. 0.130 g **13** and 0.081 g **14** were isolated. (90% total yield). The diastereomers were numbered in the order they came from the column.

Table 2
Physicochemical properties, lipophilicity, solubility, pharmacokinetics, druglikeness and medicinal chemistry of **13**, **14**, **15 and 16** predicted using Swiss ADME.

No	Physicochemical properties	Lipophilicity	Water solubility	Pharmacokinetics	Drug likeness	Medicinal Chemistry
13 and **14**	Formula: C25H31FeNO6 Moleculer weight: 497.36 g/mol Num. heavy atoms: 33 Num. arom.heavy atoms: 0 Fraction Csp3:0.64 Num. rotatable bon4ds: 6 Num. H-bond acceptors: 7 Num. H-bond donors: 0 Molar Refractivity: 120.22 TPSA: 66.23 Å	Log $P_{o/W}$ (iLOGP): 0.00 Log $P_{o/W}$ (XLOGP3):2.83 Log $P_{o/W}$ (WLOGP):2.54 Log $P_{o/W}$ (MLOGP):1.67 Log $P_{o/W}$ (SILICOS-IT):0.43 Consensus Log $P_{o/W}$: 1.49	Log *S* (ESOL): 4.31 Solubility:2.43e-02 mg/ml; 4.89e-05 mol/l Class:Moderately soluble Log *S* (Ali): 3.88 Solubility: 6.58e-02 mg/ml; 1.32e-04 mol/l Class: Soluble Log *S*(SILICOS-IT): 1.58 Solubility: 1.31e+01 mg/ml; 2.64e-02 mol/l Class: Soluble	GI absorption: High BBB permeant:Yes P-gpsubstrate:Yes CYP1A2 inhibitor:No CYP2C19 inhibitor:No CYP2C9 inhibitor:No CYP2D6 inhibitor:No CYP3A4 inhibitor:No Log Kp (skin permeation): 7.32 cm/s	Lipinski: Yes Ghose: No; 1 violation: MW > 480 Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: = 0 alert Brenk: 2 alers: Three-membered_heterocycle, heavy_metal Leadlikeness: No; 1 violation: MW > 350 Synthetic accessibility: 6.14
15 and **16**	Formula: C25H31FeNO6 Moleculer weight: 497.36 g/mol Num. heavy atoms: 33 Num. arom.heavy atoms: 0 Fraction Csp3:0.64 Num. rotatable bon4ds: 6 Num. H-bond acceptors: 7 Num. H-bond donors: 0 Molar Refractivity: 120.22 TPSA: 66.23 Å	Log Po/W (iLOGP): 0.00 Log Po/W (XLOGP3):2.83 Log Po/W (WLOGP):2.54 Log Po/W (MLOGP):1.67 Log Po/W (SILICOS-IT):0.51 Consensus Log Po/W: 1.51	Log S (ESOL): 4.31 Solubility:2.43e-02 mg/ml; 4.89e-05 mol/l Class:Moderately soluble Log S (Ali): 3.88 Solubility: 6.58e-02 mg/ml; 1.32e-04 mol/l Class: Soluble Log S(SILICOS-IT): 1.45 Solubility: 1.76e+01 mg/ml; 3.53e-02 mol/l Class: Soluble	GI absorption: High BBB permeant:Yes P-gpsubstrate:Yes CYP1A2 inhibitor:No CYP2C19 inhibitor:No CYP2C9 inhibitor:No CYP2D6 inhibitor:No CYP3A4 inhibitor:No Log Kp (skin permeation): 7.32 cm/s	Lipinski: Yes Ghose: No; 1 violation: MW > 480 Veber: Yes Egan: Yes Muegge: Yes Bioavailability Score: 0.55	PAINS: = 0 alert Brenk: 2 alers: Three-membered_heterocycle, heavy metal Leadlikeness: No; 1 violation: MW > 350 Synthetic accessibility: 6.20

Table 3
SMILES, Lipinski rule of five and drug-likeness of **13**, **14**, **15** and **16** predicted using molsoft programe.

No	SMILES	Molecular properties	Drug likeliness
13	[H][C@@]1(CN1CC1OC2OC(C)(C)OC2C2OC(C)(C)OC12)C(=O)C1=CC=CC1[Fe]C1C=CC=C1	Molecular formula:C25H31FeNO6 Molecular weight: 497.15 Number of HBA: 7 Number of HBD: 0 MolLogP: 3.72 MolLogS: 3.70 (in Log (moles/L)) 98.27 (in mg/L) MolPSA: 58.49 A^2 MolVol: 523.23 A^3 Number of stereo centers: 7 BBB Score: 3.09	 Drug-likeness model score: 0.82
14	[H][C@]1(CN1CC1OC2OC(C)(C)OC2C2OC(C)(C)OC12)C(=O)C1=CC=CC1[Fe]C1C=CC=C1		
15	[H][C@@]1(CN1C1C(OC2OC(C)(C)OC12)C1COC(C)(C)O1)C(=O)C1=CC=CC1[Fe]C1C=CC=C1	Molecular formula:C25H31FeNO6 Molecular weight: 497.15 Number of HBA: 7 Number of HBD: 0 MolLogP: 3.99 MolLogS: 4.02 (in Log (moles/L)) 47.37(in mg/L) MolPSA: 56.08 A^2 MolVol: 525.60 A^3 Number of stereo centers: 7 BBB Score: 3.12	 Drug-likeness model score: 1.41
16	[H][C@]1(CN1C1C(OC2OC(C)(C)OC12)C1COC(C)(C)O1)C(=O)C1=CC=CC1[Fe]C1C=CC=C1		

4.1.1.1. *(2R(or 2S))-1-(6-amino-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose) aziridin-2-yl)(ferrocenyl)methanone* ***(13)***. $[\alpha]_D^{25}$ = -291.7 (c = 0.0005, $CHCl_3$); FT-IR (neat): 2985, 2920, 1665, 1457, 1372, 1257, 1213, 1105, 1069, 1016, 841, 484. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (d, *J* = 4.9 Hz, $^1H_{anomeric}$), 4.85 (s, 1H-Fc), 4.83 (s, 1H-Fc), 4.52 (s, $1H_2$), 4.48 (d, *J* = 9.8 Hz, 2H-Fc), 4.25 (d, *J* = 8.0 Hz, $1H_3$)), 4.22 (dd, *J* = 4.9, 2.1 Hz, $1H_4$), 4.17 (s, 5H-Fc), 4.05 (m, $1H_5$), 2.73 (dd, *J* = 11.7, 7.5 Hz, $1H_{6a}$), 2.66 (dd, *J* = 6.2, 3.0 Hz, $1H_α$), 2.55 (dd, *J* = 11.7, 5.8 Hz, $1H_{6b}$), 2.30 (s, $1H_β$), 1.82 (d, *J* = 6.4 Hz, $1H_{β'}$), 1.48 (s, $3H_{ip}$), 1.39 (s, $3H_{ip}$), 1.25 (s, $3H_{ip}$), 1.22 (s, $3H_{ip}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 108.9, 108.6, 96.3, 78.6, 72.7, 72.5, 71.2, 70.6, 70.5, 70.1, 69.9, 69.1, 66.9, 59.7, 41.8, 35.6, 26.1, 24.9, 24.4. GC-Mass, *m/z* calcd. for

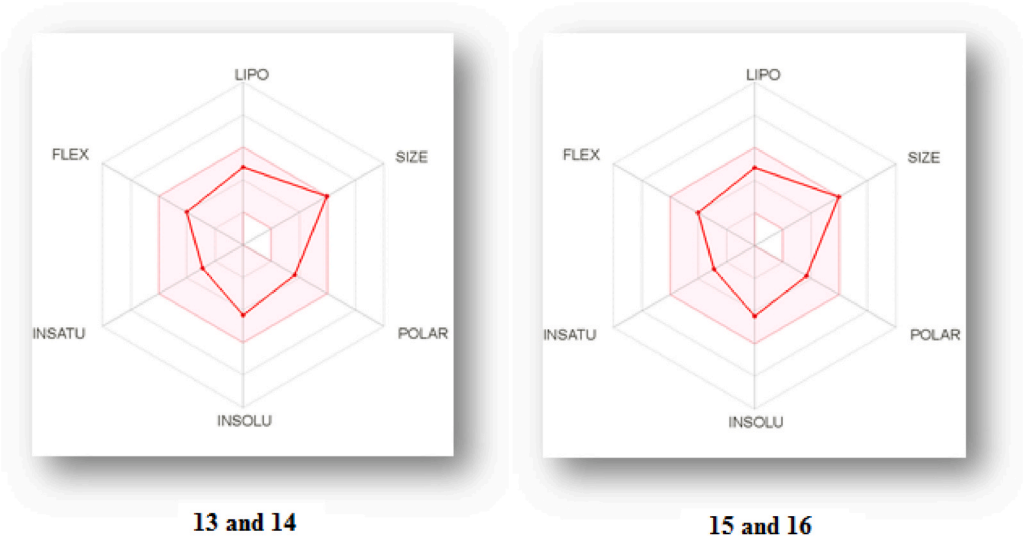


Fig. 5. Drug-likeness of **13, 14, 15** and **16** were predicted using Bioavailability radar. The pink area represents the optimal range for each properties (Lipo: Lipophilicity, Size: Moleculer weight, POLAR: Total Polar Surface Area, INSOLU: Insolubility, INSATU: Insaturation, FLEX: Flexibility). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

$C_{25}H_{31}FeNO_6$ [*m/z*]: 497.1, found: 497.0.

4.1.1.2. *(2S(or 2R))-1-(6-amino-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose) aziridin-2-yl)(ferrocenyl)methanone* ***(14)***. $[\alpha]_D^{25} = +85.4$ (c = 0.0005, $CHCl_3$); FT-IR (neat): 2981, 1660, 1460, 1374, 1257, 1169, 1075, 1015, 824, 509. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (d, *J* = 4.9 Hz, $1H_{anomeric}$), 4.86 (s, 1H-Fc), 4.80 (s, 1H-Fc), 4.54 (dd, *J* = 7.9, 2.0 Hz, $1H_2$), 4.48 (s, 2H-Fc), 4.30 (d, *J* = 7.9 Hz, $1H_3$), 4.20 (dd, *J* = 4.9, 2.2 Hz, $1H_4$), 4.19–4.15 (m, 5H), 2.75 (dd, *J* = 11.9, 6.6 Hz, $1H_5$), 2.68 (dd, *J* = 6.3, 3.1 Hz, $1H_{6a}$), 2.51 (dd, *J* = 11.9, 6.1 Hz, $1H_{6b}$), 2.42 (s, $1H_\alpha$), 2.21 (d, *J* = 14.7 Hz, $1H_\beta$), 1.82 (d, *J* = 6.4 Hz, $1H_{\beta'}$), 1.41 (s, $3H_{ip}$), 1.39 (s, $3H_{ip}$), 1.21 (s, $3H_{ip}$), 1.18 (s, $3H_{ip}$).^{13}C NMR (101 MHz, $CDCl_3$) δ δ 199.9, 109.0, 108.6, 96.2, 78.6, 72.5, 71.5, 70.6, 70.3, 70.1, 69.9, 69.1, 7.2, 60.1, 41.4, 36.1, 29.7, 26.1, 26.1, 24.9, 24.3. GC-Mass, *m/z* calcd. for $C_{25}H_{31}FeNO_6$ [*m/z*]: 497.1, found: 497.0.

3-Amino-3-deoxy-1,2:5,6-di-*O*-isoproylidene-α-D-glucofuranose (**4**) (0.122 g, 0,4703 mmol) was dissolved in 1 mL of CH_2Cl_2 and mixed for ½ of an hour. To this solution, 1,2-dibromoprapanoylferrocene (12) (0.150 g, 0.4703 mmol) and Et_3N (0.13 mL, 0,9406 mmol) were added. The reaction period was monitored via TLC. After mixing 2 days at ambient temperature (25 °C), It was directly added to the column (as eluent system: Hexane-EtOAc (1:1)) for separation and purification without doing any work-up. The colorful diastereomers (13 and 14) were readily collected without doing TLC. 0.078 g **15** and 0.090 g **16** were isolated. (85% total yield). The diastereomers were numbered in the order they came from the column.

4.1.1.3. *(2R(or 2S))-1-(3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose) aziridin-2-yl)(ferrocenyl)methanone* ***(15)***. $[\alpha]_D^{25} = +45.0$ (c = 0.0008, $CHCl_3$); FT-IR (neat): 2923, 1646, 1455, 1375, 1257, 1210, 1105, 1066, 1001, 802, 484. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (d, *J* = 3.6 Hz, $1H_{anomeric}$), 4.87 (s, 2H-Fc), 4.52 (s, 2H-Fc), 4.47 (m, $2H_{2,3}$), 4.16 (s, 5H-Fc), 4.13–4.09 (m, $1H_4$), 4.00 (dd, *J* = 9.2, 3.2 Hz, $1H_5$), 3.93 (dd, *J* = 8.5, 5.8 Hz, $1H_{6a}$), 2.59 (dd, *J* = 6.4, 3.3 Hz, $1H_\alpha$), 2.41 (d, *J* = 3.1 Hz, $1H_{6b}$), 2.33 (d, *J* = 3.2 Hz, $1H_\beta$), 2.15 (d, *J* = 6.6 Hz, $1H_{\beta'}$), 1.44 (s, $3H_{ip}$), 1.36 (s, $3H_{ip}$), 1.32 (s, $3H_{ip}$), 1.23 (s, $3H_{ip}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6, 111.7, 109.3, 105.3, 84.9, 81.5, 78.1, 74.9, 72.9, 72.8, 72.6, 69.9, 69.8, 69.5, 68.2, 40.5, 37.8, 26.9, 26.8, 26.3, 25.4. GC-Mass, *m/z* calcd. for $C_{25}H_{31}FeNO_6$ [*m/z*]: 497.1, found: 497.0.

4.1.1.4. *(2S (or 2R)-1-(3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose) aziridin-2-yl)(ferrocenyl)methanone* ***(16)***. $[\alpha]_D^{25} = -140.0$ (c = 0.0027, $CHCl_3$); FT-IR (neat): 2924, 2854, 1743, 1650, 1542, 1455, 1374, 1256, 1210, 1116, 1106, 1067, 1002, 860, 821, 484. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (d, *J* = 3.6 Hz, $1H_{anomeric}$), 4.89–4.83 (m, 2H-Fc), 4.55 (d, *J* = 3.6 Hz, 1H-Fc), 4.51 (s, 1H-Fc), 4.46 (d, *J* = 1.2 Hz, $1H_2$), 4.25–4.16 (m, $1H_3$), 4.14 (s, 5H-Fc), 4.00–3.87 (m, $3H_{4,5,6a}$), 2.88 (dd, *J* = 6.5, 3.3 Hz, $1H_\alpha$), 2.34 (d, *J* = 3.3 Hz, $1H_\beta$), 2.30 (d, *J* = 1.7 Hz, $1H_{6b}$), 1.84 (d, *J* = 6.6 Hz, $1H_{\beta'}$), 1.43 (s, $3H_{ip}$), 1.31 (s, $3H_{ip}$), 1.26 (s, $3H_{ip}$), 0.98 (s, $3H_{ip}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 111.5, 109.3, 105.1, 84.9, 81.4, 78.3, 74.9, 72.8, 72.5, 72.4, 71.1, 69.9, 68.6, 67.9, 43.8, 33.6, 26.9, 26.8, 26.3, 24.9. GC-Mass, *m/z* calcd. for $C_{25}H_{31}FeNO_6$ [*m/z*]: 497.1, found: 497.0.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2021.108430.

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