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One-pot synthesis of fluorescein based β-aminoglycosylketones and their biological and material applications

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Facile one-pot synthesis of fluorescein based β-aminoglycosylketones was carried out using 4,6-O-protected-C-glycoside, fluorescein-monoaldehyde and aromatic amines in presence of potassium carbonate as a catalyst. Studies reveal that the use of potassium carbonate resulted in good yield. All these compounds were characterized using different spectral techniques. The gelation properties of these compounds were studied in regard to their molecular structure by HRTEM, DSC and powder XRD techniques. Fluorescein based β-aminoglycosylketones show moderate antioxidant activities with maximum inhibitory activity.

Introduction

The β-aminocarbonyl compounds are important intermediate for the construction of various nitrogen containing natural products and pharmaceutically important products.[1-3] Though several carbon-carbon bond forming reactions are known in organic synthesis,[4] the use of Mannich reaction find prominent place and it affords synthetically and biologically important *β*-aminocarbonyl compounds (**4**) (Fig. 1) from aldehyde (**1**), amine (**2**) and carbonyl (**3**) derivatives.

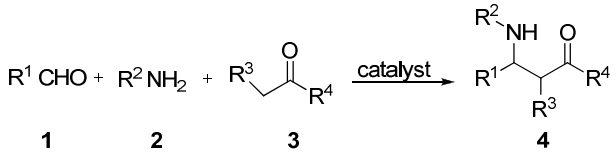

Figure 1. General synthesis of *β*-aminocarbonyl compounds (**4**).

In addition, *C*-glycosides has been extensively developed due to the diversity of biological and pharmaceutical applications.[5,6] *C*-Glycosides as subunits occur in a variety of biologically important natural products and also in synthetic compounds.[7] More recently, aryl-*C*-β-glycosides (**5** & **6**)[8,9] have been reported to possess potent SGLT2 inhibitor activity (Fig. 2). Multicomponent reactions emerged as a powerful tool for the construction of several novel and complex molecular structures with diversities of biological activities and pharmaceutical applications.[10] Several biologically important polysubstituted phenyl derivatives have been developed *via* multicomponent reactions.[11,12]

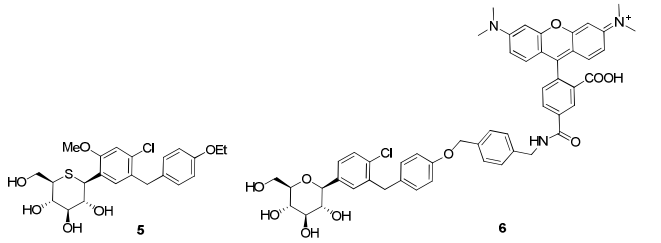

Figure 2. Representative examples of *C*-glycosides (**5**) and (**6**).[8,9]

Generally, the carbohydrate molecules to obtain low molecular weight gelators has been an interesting field of research in recent years.[13] Since carbohydrate molecules are biocompatible, the gels derived from these molecules have wide application in biology and also as functional materials.[14-16] Moreover, the self-assembly of sugar based-amphiphilic systems is thus emerging as a particular powerful strategy to direct the self-assembly of relatively simple glycosylamines into sophisticated materials possessing wide applications.[17,18] In addition the gels can be stabilized by intermolecular hydrogen

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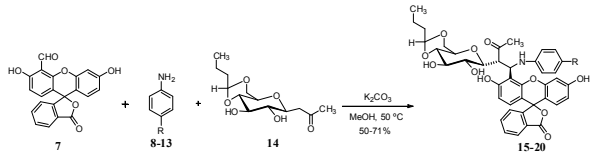
bonds between sugar-OH groups as well as van der Waals interactions between alkyl groups. In the search of new molecular entities with potential gelation ability, we have recently reported 4,6-*O*-protected-β-C-glycosides[19] as potential gelators with diverse applications. In the present study we report a novel class of fluorescein based β-amino glycosylketones as organogelators and antioxidant properties.

Result and discussion

Synthesis of fluorescein based *β*-aminoglycosylketones

Fluorescein-monoaldehyde[20-22] **7** and 1-(4,6-O-butylidene-β-D-glucopyranosyl)propan-2-one (BGP)[23] **14** were synthesized by adopting procedures reported in the literature. Fluorescein based β-aminoglycosylketones **15-20** were synthesized in one-step from the Mannich reaction of fluorescein-monoaldehyde (**7**) with aromatic amines **8-13** and 1-(4,6-*O*-butylidene-β-D-glucopyranosyl)propan-2-one **14** in the presence of potassium carbonate (K_2CO_3) as an inorganic catalyst (**Scheme 1**).



Scheme 1. Synthesis of fluorescein based β-aminoglycosylketones **(15-20)**

Optimization of reaction condition shows, use of 1 equiv of fluorescein-monoaldehyde **7**, 1 equiv of aromatic amines **8-13** and 1 equiv of 1-(4,6-O-butylidene-β-D-glucopyranosyl)propan-2-one **14** gives the desired fluorescein based β-aminoglycosylketones **15-20** in moderate yield. Details about the use of different solvents and temperature for the optimization of reaction conditions are given in ESI. The structures of the resulting fluorescein based β-aminoglycosylketones **15-20** were determined by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. The sugar β-anomeric center was easily confirmed by estimating the 3.80-4.62 ppm, (J = 7.0-8.7 Hz) as a doublet, as an evident from ^{1}H NMR studies (**Table 1**) and ^{13}C NMR spectra of the anomeric carbon was identified at 98.1-102.4 ppm. The anti isomers were identified by the coupling constants (J) of the vicinal protons adjacent to C=O and NH in their ^{1}H NMR spectra.

Table 1. Synthesis of fluorescein based β-aminoglycosylketones (**15-20**)

Compounds	R	t (h)	δ (H-1) ($^3J_{H1,H2}$/Hz)	CGC (%) g mL^{-1}	Yield (%)
15	H (**8**)	5	4.13, 7.0	1.5	71
16	4-Br(**9**)	7	4.12, 7.5	1.5	55
17	4-NO_2(**10**)	4	3.80, 7.5	1.0	62
18	4-Cl(**11**)	5	3.81, 8.1	1.0	50
19	4-F(**12**)	8	4.52, 8.7	1.0	62
20	4-OMe(**13**)	5	4.12, 7.2	1.0	67

"*Anti*" isomer shows higher coupling constant than the "*syn*" one.[24,25] Moreover, methyl protons corresponding to the region of 0.89-0.95 ppm in ^{1}H NMR spectra, and the corresponding ^{13}C NMR signals are observed around 13.9 ppm. In addition, aromatic ring of the phenylamino core structure in the region of 8.06-6.58 ppm ensures the product formation. Structure of aromatic amines, fluorescein based β-aminoglycosyl ketones, reaction time and product yields are given in Table 1.

Gelation studies

Recently, we have reported the gelating abilities of different class of sugar derivatives,[17-19] and observed that fluorescein based β-aminoglycosylketones are better candidate for the gel formation (CGC: 1%) in Table 1. All gel samples were prepared by dissolving the gelator in a solvent in such a way that it forms a homogenous solution. The solution was allowed to cool down to room temperature, whereby the gel is formed.

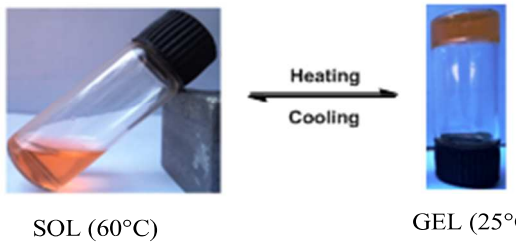


Figure 3. Demonstration of the thermoreversible organogel compound **16**.

The gelation ability of fluorescein based β-aminoglycosylketones **15-20** has been assessed by using ''stable to inversion of the container'' method.[19] The study includes six different fluorescein based β-aminoglycosylketones **15-20** in ten different solvents and the results of gelation are summarised in Table 2. These fluorescein based *β*-aminoglycosylketones are found to gelate both aliphatic (ethanol, methanol, chloroform, dichloromethane, ethyl acetate, hexane, acetone and tetrahydrofuran) and aromatic (benzene and toluene) solvents. Chloroform and dichloromethane were found to be the best solvents than other solvents studied for the gelation process, which may be attributed to a strong solvent interaction. Since the gelation ability of the organogelator has a significant dependence on the protecting group and the halogen substitutents present on the aromatic ring. Thus the greater gelation ability of BGP is due to

Table 2. Gelation studies of fluorescein based β-aminoglycosylketones (**15-20**)

Solvents/ Compounds	15	16	17	18	19	20
$CHCl_3$	G	G	G	G	G	G
EtOH	S	S	S	S	S	S
MeOH	S	PG	S	S	PG	P
THF	PG	G	G	PG	G	PG
DCM	G	G	G	G	G	G
EtOAc	PG	PG	G	G	S	P
Acetone	S	PG	G	PG	PG	PG
Benzene	S	P	G	PG	G	G
Toluene	G	P	G	G	PG	G
Hexane	PG	S	S	P	S	PG

G = good gelators; PG = partial gelators; S = solution; P = precipitation

London dispersion forces[18] which exist between the alkyl chain and halogen groups. Moreover, Hydrogen bonding, π-π stacking and dipole-dipole interactions were also responsible aggregation of LMOGs, allowing gel formation. The photograph of the gel derived from compound **16** in chloroform 1.5% is shown in Fig. 3.

HRTEM analysis

We prepared xerogels for HRTEM observations and found the gels of different compounds and the same compound in different solvents have different microstructures. Figure.4a illustrated that in the xerogel obtained from chloroform gel, the **17** self-assembled into nanorod with 50-85 nm in width and several micrometers in length, which further entangled into gel network. On the other hand, the arrangement of gelators in the gel of **17** led to lot of micronanorod (Fig. 4b). For instance, the toluene gel based on **17** exhibited twisted rod with a diameter of 18-20 nm, which intertwined into a spiderweb-like structure. For instance, the xerogel from compound **18** formed strips rod in chloroform (Fig.4c) with a width of 20-65 nm, and in toluene it formed quite a different microstructure as dense fibrous network (Fig.4d) with a thickness about 6-15 nm. As shown in Figure.4, the toluene gel of **20** showed a frizzy-like structure suggesting that **20** should aggregate in some two-dimensional morphology (Fig.4e). FESEM, the morphology of compound **17** is observed to be a fibrous network (Fig.4f). The HRTEM and FESEM images illustrated that the alkyl chain length has significant effect on the hierarchical growth of the compounds at the nanoscale and microscopic levels.

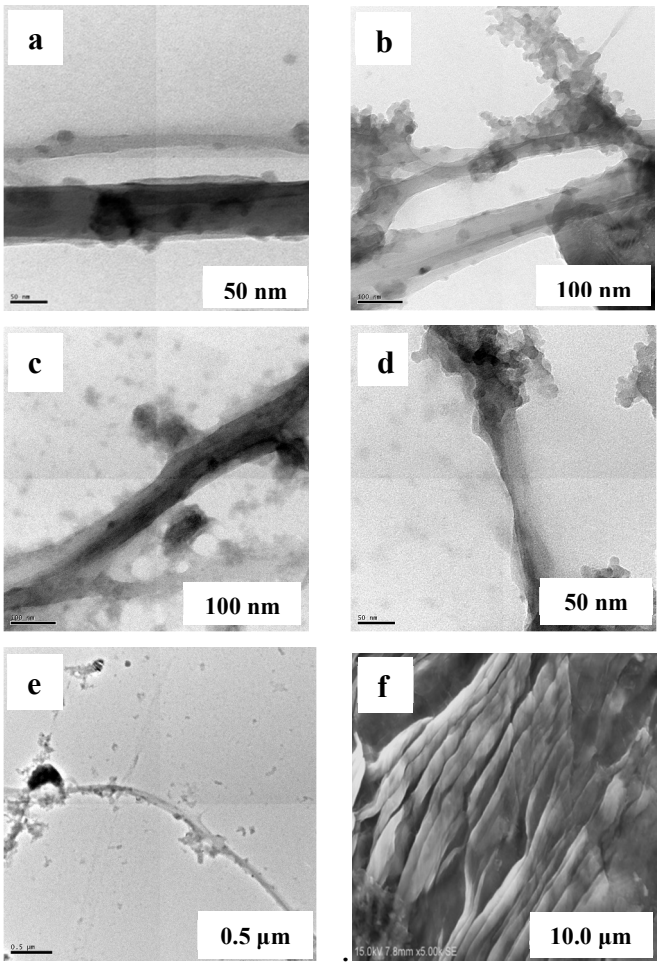


Fig 4. HRTEM images of gel derived from (a) compound **17** in chloroform (1.0 wt%); (b) compound **17** in toluene (1.0 wt%); (c) compound **18** in chloroform (1.0 wt%); (d) compound **18** in toluene (1.0 wt%); (d) compound **20** in toluene (1.0 wt%). SEM images of gel derived from (f) compound **17** in chloroform (1.0 wt%).

DSC analysis

The thermal properties of the organogelators have been analysed using differential scanning calorimetry (DSC). DSC data obtained for **17** and **18** are shown in Fig. 5. The melting point and enthalpy of organogelator **17** in the solid phase are 197.3 °C and ΔH = 102.6 $J\ g^{-1}$ and in gel phase the values are 125.6 °C and 121.8 $J\ g^{-1}$. The organogelator, **18** shows melting point and enthalpy in solid phase at 173.8 °C (ΔH = 116.2 $J\ g^{-1}$) and gel phase 169.1 °C (ΔH = 246.9 $J\ g^{-1}$), respectively. These results indicate that organogel **13** is more stable in the solid phase.[18,19] Compound **17** in nitrobenzene T_{gs} of gel phase was

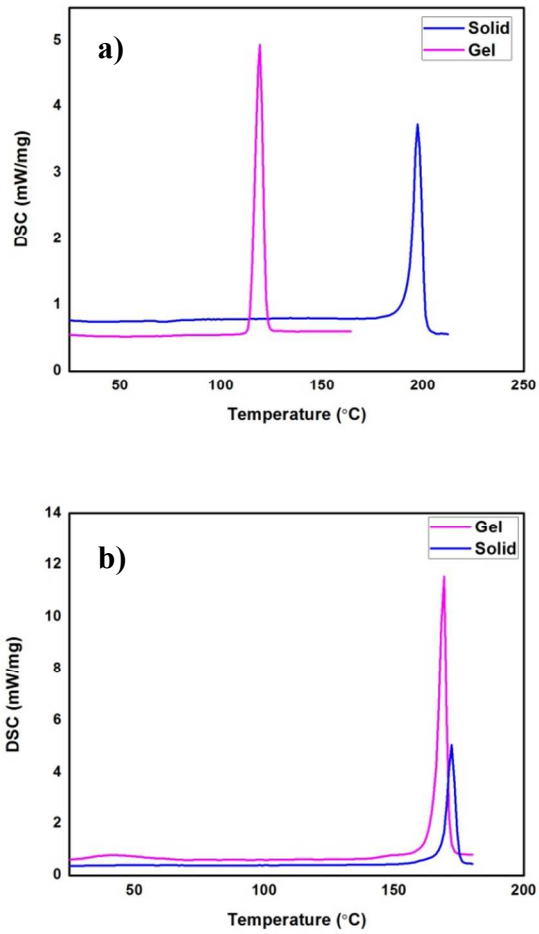


Fig 5. DSC spectra of (a), **17** (chloroform), (b), **18** (Toluene): (-) gel phase, (-) solid phase.

found to lower than the solid phase while for compound **18** the T_{gs} of gel phase was found to be greater than that of solid phase. These results indicate that the gel phase of Compound **17** has greater thermal stability than its corresponding solid phase, whereas for compound **18**, the solid phase has greater thermal stability than its corresponding gel phase (Table.3).

Table.3. Thermodynamic parameters for sol-gel transition of fluorescein based β-aminoglycosylketones (**17** and **18**)

Compounds	T_{gs} (°C)	ΔH ($J\ g^{-1}$)
17	125.6	121.8
18	169.1	246.9

Rheological Studies

The rheological behaviour of gel compound **17** in chloroform was shown in Figure 6. The results show linear regions of storage modulus (G') and loss modulus (G") with a frequency sweep (20-120 rad s^{-1}). There is no change and crossover observed in the storage modulus and loss modulus of either gel over the frequency range. The storage modulus (G') is the dominant variable in both cases, which is the most important characteristic of a molecular gel.[26,27] Moreover, both the storage and loss moduli are almost independent of the frequency, indicating a gel-like behaviour. The frequency measurements indicate that the gels did not show any change in rheological properties over the frequency range.

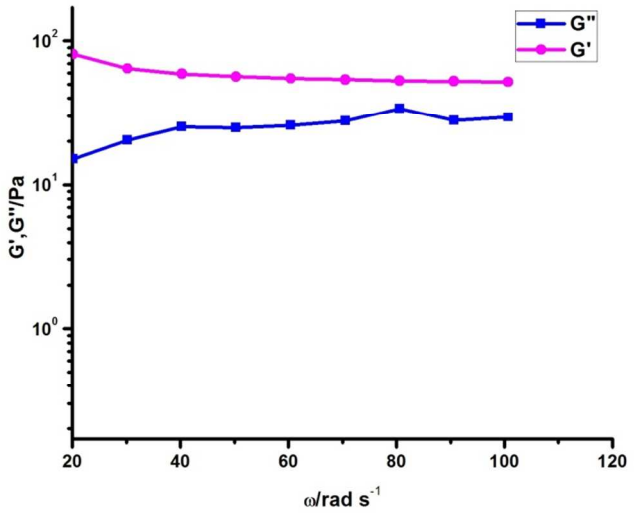


Fig 6. Angular frequency sweep (ω) dependencies of dynamic storage (G') and loss modulus (G") of gel compound **17** in chloroform.

Powder XRD analysis

The structures of the dry gels was generally investigated by XRD[26] and the XRD pattern obtained for **17** xerogel film it showed more reflections, that proved the presence of crystalline and lamellar nature in the film. This may be attributed to strong interaction between the neighboring molecules. The XRD patterns are shown in Figure 7a,b for **17** and **18**, respectively. The xerogel **17** showed seven reflection peaks and their corresponding space (*d*) are 9.39, 7.26, 5.74, 4.27, 3.75, 3.58 and 3.37 nm respectively, which are clearly indicative the presence of columnar arrangement of the molecules in the nanofibers. Because of they are π–π stacking[27] of the substituted aniline unit the self- assembled state molecules.

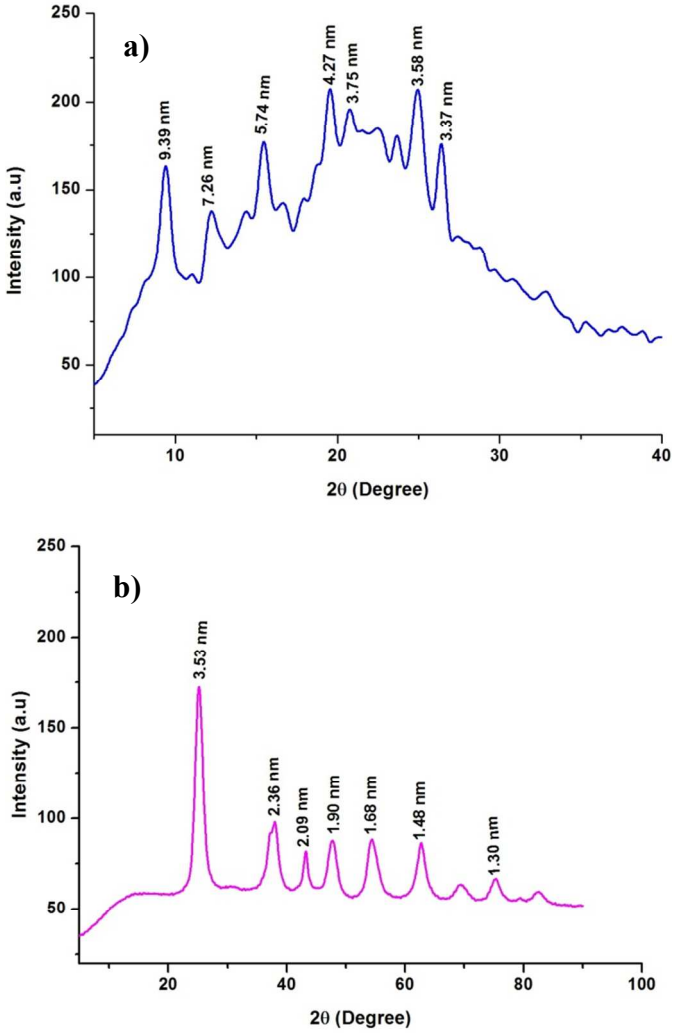


Fig 7. Powder XRD pattern of xerogel (a) **17** in Chloroform and (b) **18** in Toluene.

Whereas **18**, shows the seven reflection peaks of 3.53, 2.36, 2.09, 1.90, 1.68, 1.48, and 1.30 nm respectively, the peaks are clearly indicate the formation of a columnar arrangement[27]in the xerogel state. From the Figure 7a and 7b, it could be observed that the **18** have higher crystalline than **17** which may be due to the presence of functional group in the **18**.

Antioxidant studies

Free radical scavenging assay methodology has been employed to study the antioxidant potential of the fluorescein based β-aminoglycosylketones **15-20**. DPPH (1,1-diphenyl-2-picryl hydrazyl) known as stable free radical source has been used for

the determination of antioxidant property. DPPH has violet colour and has absorption band at 517 nm in ethanol. When DPPH is mixed with the fluorescein based β-aminoglycosylketones which can donate free electron, DPPH looses its colour and undergoes reduction to give diphenyl picryl hydrazine[22] as shown in ESI.

Fluorescein based β-aminoglycosylketones **15-20** were dissolved in MeOH with the concentrations of 10, 20, 30, 40, 50 and 60 μg/mL and used for the study. The test solution of the fluorescein based β-aminoglycosylketones **15-20** (0.1 mL) in MeOH was added to DPPH solution (0.5 mL) in ethanol and absorption was measured at 517 nm. Percentage activity was calculated from the following equation. Percentage Activity = [As - Ab/Ac - Ab] x 100, where As = absorbance of DPPH test solution. Ab = absorption of DPPH solution with blank without DPPH and Ac = control with DPPH solution without adding the fluorescein based *β*-aminoglycosylketones. Fig.8. shows the

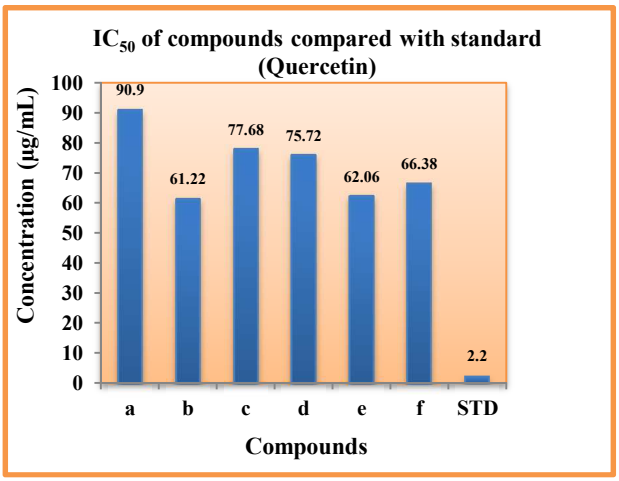


Fig 8. Antioxidant activities of fluorescein based β-aminoglycosylketones (**15-20**) as measured by the DPPH method: (a) **15**, (b) **17**, (c) **19**, (d) **18**, (e) **20**, (f) **16**, and standard Quercetin.

reduction of DPPH radical by fluorescein based β-aminoglycosylketones and also the concentration of β-aminoglycosylketones required to scavenge 50% (IC_{50}) the DPPH radical. The percentage of DPPH reduction with change in the concentration of the fluorescein based β-aminoglycosylketones **15-20** as shown in ESI. The second generation fluorescein based β-aminoglycosylketone **17** showed the excellent activity at all the concentration ranging from 10 to 60 μg/mL and hence **17** as the efficient antioxidant property.

However the antioxidant property of first and third generation fluorescein based β-aminoglycosylketones **16** and **18-20** alters depending on the concentration of the test solution. In fact zeroth generation fluorescein based *β*-aminoglycosylketone **18** has the lowest antioxidant property. The antioxidant property gradually increases with increasing the generation of fluorescein based β-aminoglycosylketones and hence **17** shows better antioxidant property than **15**, **16** and **18-20**. IC_{50} values were determined in order to confirm the reducing activity of the fluorescein based *β*-aminoglycosylketones synthesized.

All the fluorescein based β-aminoglycosylketones exhibited variation of free radical scavenging activity with respect to the variation of concentration. The activity is significant when compared with the standard antioxidant drugs, like standard Quercetin (with IC_{50} as 10-100 μg/mL respectively). The antioxidant property of the fluorescein based β-aminoglycosylketones **15-20** derived from fluorescein-aldehyde[29] is due to the presence of phenolic unit where as the antioxidant effect of the glycosides reported herein is due to the presence of the bioactive functionality. In general some of the glycosides have good bioavailability and biocompatibility, and hence they can be administrated by intravenous, oral, transdermal, and drug delivery systems.[18,30,31] Hence, in conclusion the fluorescein based β-aminoglycosylketones reported herein may have good biocompatibility, cytotoxicity and bioavailability.

Conclusion

In conclusion, we have designed and synthesized fluorescein based *β*-aminoglycosylketones from fluorescein-monoaldehyde, aromatic amines, and 1-(4,6-*O*-butylidene-β-D-glucopyranosyl)-propan-2-one in the presence of catalytic amount of potassium carbonate in good yield. The existence of the β-anomeric form in these sugar derivatives was identified from ^{1}H and ^{13}C NMR studies. These compounds have been found to be good organogelators. Morphological studies using HRTEM and PXRD analysis show fibrous networks in the gel state. The preliminary biological evaluation of these synthesized compounds showed moderate antioxidant properities.

Experimental section

D-Glucose, butyraldehyde, resorcinol, potassium carbonate and other solvents were obtained from SRL, Chennai, Tamil Nadu, India. Column chromatography was performed on Silica Gel (100-200 mesh). Melting points were measured on Sigma micro melting point apparatus and are uncorrected. NMR spectra were recorded on Bruker DRX 300 MHz in $CDCl_3$ or DMSO-d_6 at University of Madras (Chennai,Tamil Nadu, India). TMS was used as the internal standard (δ = 0.00 ppm) and all the *J* values are given in hertz. Optical rotation was performed by using Rudolph-Autopol II digital polarimeter. Elemental analyses were performed using Perkin-Elmer 2400 elemental analyzer. FESEM images were recorded on a Hitachi SU-6600 instrument and HRTEM was recorded using a JEOL, JEM 3010 model (LaB6 filament). Thermal transitions for gelators and gels were determined on a NETZSCH DSC 204 instrument. Rheological studies were recorded in Gemini 2000 using pp40. X-ray diffractograms of the dried films were recorded on XRD RINT 2500 diffractometer using Ni filtered Cu Kα radiation.

In vitro antioxidant activity

In vitro antioxidant activity for fluorescein based β-aminoglycosylketones **15-20** were evaluated by the DPPH radical scavenging method.[32] The principle of this assay is based on the measurement of the scavenging ability of the antioxidant towards the stable radical. The free radical of DPPH is reduced to the corresponding hydrazine when it reacts with hydrogen donors, and its stability is evaluated by the decolouration assay, which evaluates the decrease in absorbance at 517 nm produced by the addition of the antioxidant to a DPPH solution in ethanol. Assays were performed in 1.5 mL reaction mixtures containing 1 mL of 0.1 mM DPPH ethanol solution and 1 mL of different concentrations of fluorescein based β-aminoglycosylketones **15-20** (20-200 μg/mL)/0.5 mL of ethanol (as control). After 30 min of incubation at 37 °C in the dark, the absorbance of the reaction mixtures were measured at 517 nm. IC_{50} is the concentration of the sample required to scavenge 50% of the DPPH free radicals. The percentage of inhibition is calculated by subtracting the absorbance of the sample from the absorbance of the control divided by absorbance of the control. The lower the IC_{50}, the higher is the antioxidant activity of the examined compound. From the difference in the absorbance of DPPH, the percentage of inhibition was calculated as a function of antioxidant activity.

General procedure for the synthesis of fluorescein based *β*-aminoglycosylketone derivatives (15-20)

To a solution of the fluorescein-monoaldehyde **7**, (1.0 mmol), aromatic amines **8-13** (1.0 mmol), 1-(4,6-O-butylidene-*β*-D-glucopyranosyl)propan-2-one **14**, (1.0 mmol) and dry MeOH (10 mL) were added potassium carbonate (0.1 mmol). After stirring at 50 ºC for a given period of time, the reaction mixture was evaporated under reduced pressure and extracted by chloroform-water. The chloroform layer was dried over anhyd.Na_2SO_4 and concentrated to dryness. The product was further purified by flash column chromatography.

Physicochemical and spectral data for 3-(fluorescein)-2-(4,6-*O*-butylidene-β-D-glucopyranosyl)-3-(phenylamino)-butan-1-one (15)

Compound, **15** was obtained by the reaction of fluorescein-monoaldehyde **7**, (1.0 mmol, 0.36 g), aniline **8**, (1.0 mmol, 0.2 mL), 1-(4,6-*O*-butylidene-β-D-glucopyranosyl)-propan-2-one **14**, (1.0 mmol, 0.12 g) as pale yellow solid: Yield: 0.50 g (71%); mp 156-158 ^oC; $[\alpha]_D^{31}$ + 87.8 (c 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, J = 7.3 Hz, -CH_3), 1.42 (q, 2H, J = 9.2 Hz, -CH_2), 1.62 (q, 2H, J = 9.0 Hz, -CH_2), 2.20 (s, 3H, -$COCH_3$), 2.67 (dd, 3H, J = 7.8 Hz, J = 7.8 Hz, Sac-H), 2.91 (d, 1H, J = 16.5 Hz, -CH), 3.22 (t, 1H, J = 9.0 Hz, Sac-H), 3.31-3.45 (m, 1H, Sac-H), 3.51 (d, 1H, J = 7.1 Hz, -CH), 3.69 (t, 1H, J = 8.4 Hz, Sac-H), 3.83 (s, 2H, Sac-OH), 4.13 (d, 1H, J = 7.2 Hz, Ano-H), 4.53 (t, 1H, J = 4.8 Hz, Sac-H), 6.59 (s, 1H, -NH), 6.77 (d, 2H, J = 8.4 Hz, Ar-H), 7.06 (d, 2H, J = 8.4 Hz, Ar-H), 7.14 (d, 2H, J = 7.2 Hz, Ar-H), 7.26 (t, 3H, J = 8.0 Hz, Ar-H), 7.34 (s, 2H, Ar-OH), 7.64-7.73 (m, 4H, Ar-H), 8.06 (d, 1H, J = 7.2 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.4, 169.0, 152.7, 151.1, 136.4, 135.5, 132.0, 130.2, 129.0, 125.8, 125.4, 124.7, 123.7, 117.4, 117.0, 110.6, 102.4, 81.2, 80.4, 76.0, 75.1, 74.2, 70.5, 68.2, 59.6, 36.2, 30.9, 28.0, 17.4, 13.9. ESI-MS: calc. for $C_{40}H_{39}NO_{11}$, 709.74; m/z found, 710.64 $[M + H]^+$; elemental Anal. Found: C, 67.84; H, 5.74; N, 1.87. Calc. For $C_{40}H_{39}NO_{11}$: C, 67.82; H, 5.70; N, 1.81.

Physicochemical and spectral data for 3-(fluorescein)-2-(4,6-*O*-butylidene-β-D-glucopyranosyl)-3-(4-bromophenylamino)-butan-1-one (16)

Compound, **16** was obtained by the reaction of fluorescein-monoaldehyde **7**, (1.0 mmol, 0.36 g), 4-bromoaniline **9**, (1.0 mmol, 0.17 g), 1-(4,6-*O*-butylidene-β-D-glucopyranosyl)-propan-2-one **14**, (1.0 mmol, 0.12 g) as brown solid: Yield: 0.48 g (62%); mp 162-164 ^oC; $[\alpha]_D^{31}$ + 58.5 (c 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, J = 7.4 Hz, -CH_3), 1.42 (q, 2H, J = 11.0 Hz, -CH_2), 1.62 (q, 2H, J = 9.1 Hz, -CH_2), 2.19 (s, 3H, -$COCH_3$), 2.54-2.67 (m, 1H, Sac-H), 2.90 (d, 1H, J = 11.2 Hz, -CH), 3.19-3.45 (m, 4H, Sac-H), 3.52 (d, 1H, J = 6.7 Hz, -CH), 3.67 (t, 1H, J = 8.7 Hz, Sac-H), 3.80 (d, 1H, J = 7.5 Hz, Ano-H), 4.12 (d, 1H, J = 3.6 Hz, Sac-H), 4.52 (t, 2H, J = 4.8 Hz, Sac-OH), 6.71 (s, 1H, -NH), 6.77 (t, 3H, J = 6.8 Hz, Ar-H), 7.05 (dd, 2H, J = 8.4 Hz, J = 8.4 Hz, Ar-H), 7.14 (t, 4H, J = 7.5 Hz, Ar-H), 7.34 (s, 2H, Ar-OH), 7.63-7.73 (m, 3H, Ar-H), 8.06 (d, 1H, J = 7.2 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 169.1, 152.8, 151.2, 145.7, 136.4, 135.5, 130.3, 129.0, 125.8, 125.4, 124.7, 123.7, 119.0, 117.4, 115.5, 102.5, 81.2, 80.5, 77.5, 77.0, 76.6, 76.0, 75.1, 74.2, 70.5, 68.2, 59.7, 36.2, 30.9, 29.5, 17.4, 13.9. ESI-MS: calc. for $C_{40}H_{38}BrNO_{11}$, 788.63; m/z found, 789.42 $[M + H]^+$; elemental anal. Found: C, 60.72; H, 4.76; N, 1.88. Calc. for $C_{40}H_{38}BrNO_{11}$: C, 60.79; H, 4.71; N, 1.82.

Physicochemical and spectral data for 3-(fluorescein)-2-(4,6-*O*-butylidene-β-D-glucopyranosyl)-3-(4-nitrophenylamino)-butan-1-one (17)

Compound, **17** was obtained by the reaction of fluorescein-monoaldehyde **7**, (1.0 mmol, 0.36 g), 4-nitroaniline **10**, (1.0 mmol, 0.13 g), 1-(4,6-O-butylidene-β-D-glucopyranosyl)-propan-2-one **14**, (1.0 mmol, 0.12 g) as pale yellow solid: Yield: 0.46 g (61%); mp 170-172 ^oC; $[\alpha]_D^{31}$ + 77.2 (c 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 7.2 Hz, -CH_3), 1.42 (q, 2H, J = 9.8 Hz, -CH_2), 1.60 (q, 2H, J = 9.0 Hz, -CH_2), 2.19 (s, 3H, -$COCH_3$), 2.65 (dd, 1H, J = 6.7 Hz, J = 6.6 Hz, Sac-H), 2.88 (d, 1H, J =11.5 Hz, -CH), 3.19-3.45 (m, 5H, Sac-H), 3.52 (d, 1H, J = 6.9 Hz, -CH), 4.12 (q, 2H, J = 3.6 Hz, Sac-H), 4.52 (d, 2H, J = 8.7 Hz, Ano-H), 6.62 (s, 1H, -NH), 6.77 (d, 2H, J = 8.4 Hz, Ar-H), 7.05 (d, 2H, J = 8.4 Hz, Ar-H), 7.15 (d, 4H, J = 6.9 Hz, Ar-H), 7.34 (s, 2H, Ar-OH), 7.64-7.73 (m, 2H, Ar-H), 8.06 (d, 3H, J = 8.7 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 169.2, 152.9, 152.6, 151.2, 138.7, 136.4, 135.6, 130.3, 129.0, 126.3, 125.8, 125.4, 124.7, 123.7, 117.4, 117.3, 113.3, 102.4, 81.3, 80.4, 77.5, 75.2, 74.3, 70.5, 68.2, 59.6, 36.2, 30.9, 29.8, 17.5, 13.9. Elemental Anal. Found: C, 63.56; H, 5.37; N, 3.61. Calc. for $C_{40}H_{38}N_2O_{13}$: C, 63.51; H, 5.32; N, 3.66.

Physicochemical and spectral data for 3-(fluorescein)-2-(4,6-*O*-butylidene-β-D-glucopyranosyl)-3-(4-chlorophenylamino)-butan-1-one (18)

Compound, **18** was obtained by the reaction of fluorescein-monoaldehyde **7**, (1.0 mmol, 0.36 g), 4-chloroaniline **11**, (1.0 mmol, 0.12 g), 1-(4,6-*O*-butylidene-β-D-glucopyranosyl)-propan-2-one **14**, (1.0 mmol, 0.12 g) as pale yellow solid: Yield: 0.40 g (54%); mp 148-150 ^{o}C; $[\alpha]_D^{31}$ + 56.8 (c 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, J = 7.2 Hz, -CH_3), 1.43 (q, 2H, J = 9.0 Hz, -CH_2), 1.63 (q, 2H, J = 5.2 Hz, -CH_2), 2.20 (s, 3H, -$COCH_3$), 2.65 (dd, 1H, J = 8.1 Hz, J = 8.1 Hz, Sac-H), 2.90 (d, 1H, J = 11.2 Hz, -CH), 3.22 (t, 1H, J = 9.0 Hz, Sac-H), 3.28-3.45 (m, 4H, Sac-H), 3.57 (d, 1H, J = 6.9 Hz, -CH), 3.69 (t, 1H, J = 8.7 Hz, Sac-H), 3.82 (d, 1H, J = 2.7 Hz, Sac-H), 4.12 (d, 1H, J = 8.7 Hz, Ano-H), 4.52 (t, 1H, J = 7.8 Hz, Sac-OH), 6.48 (t, 2H, J = 7.8 Hz, Ar-H), 6.77 (q, 4H, J = 7.4 Hz, Ar-H), 7.05 (s, 1H, -NH), 7.15 (q, 2H, J = 7.2 Hz, Ar-H), 7.34 (s, 2H, Ar-OH), 7.67 (q, 4H, J = 9.6 Hz, Ar-H), 8.06 (d, 1H, J = 7.2 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.1, 169.0, 152.8, 151.2, 146.7, 138.9, 135.5, 130.3, 129.0, 125.4, 124.7, 123.7, 119.9, 117.4, 114.7, 102.5, 84.2, 81.2, 80.4, 77.5, 77.0, 76.6, 75.9, 75.2, 74.3, 70.6, 68.2, 60.7, 36.2, 30.9, 28.9, 17.5, 13.9. ESI-MS: calc. for $C_{40}H_{38}ClNO_{11}$, 743.21; m/z found, 744.39 $[M + H]^+$; elemental Anal. Found: C, 64.76; H, 5.25; N, 1.68. Calc. for $C_{40}H_{38}ClNO_{11}$: C, 64.71; H, 5.29; N, 1.63.

Physicochemical and spectral data for 3-(fluorescein)-2-(4,6-*O*-butylidene-β-D-glucopyranosyl)-3-(4-fluorophenylamino)-butan-1-one (19)

Compound, **19** was obtained by the reaction of fluorescein-monoaldehyde **7**, (1.0 mmol, 0.36 g), 4-fluoroaniline **12**, (1.0 mmol, 0.2 mL), 1-(4,6-O-butylidene-β-D-glucopyranosyl)-propan-2-one **14**, (1.0 mmol, 0.12 g) as pale yellow solid: Yield: 0.38 g (52%); mp 166-168 ^{o}C; $[\alpha]_D^{31}$ + 34.7 (c 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, J = 7.2 Hz, -CH_3), 1.42 (q, 2H, J = 9.2 Hz, -CH_2), 1.62 (q, 2H, J = 8.5 Hz, -CH_2), 2.19 (s, 3H, -$COCH_3$), 2.64 (q, 1H, J = 8.1 Hz, Sac-H), 2.91 (d, 1H, J = 10.2 Hz, -CH), 3.19-3.45 (m, 4H, Sac-H), 3.52 (d, 1H, J = 6.6 Hz, -CH), 3.69 (t, 1H, J = 8.7 Hz, Sac-H), 3.81 (d, 1H, J = 8.1 Hz, Ano-H), 4.12 (d, 1H, J = 5.7 Hz, Sac-H), 4.53 (t, 2H, J = 4.5 Hz, Sac-OH), 6.76 (s, 1H, -NH), 7.04 (d, 3H, J = 7.5 Hz, Ar-H), 7.14 (d, 4H, J = 7.2 Hz, Ar-H), 7.34 (s, 2H, Ar-OH), 7.64-7.73 (m, 5H, Ar-H), 8.05 (d, 1H, J = 7.2 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 169.1, 152.8, 151.2, 136.4, 135.5, 130.3, 130.2, 129.0, 126.9, 125.8, 125.5, 124.7, 123.6, 119.4, 117.4, 115.6, 102.5, 81.2, 80.4, 75.2, 74.3, 70.5, 68.2, 58.5, 36.2, 32.0, 30.9, 17.4, 17.3, 13.9. Elemental Anal. Found: C, 66.27; H, 5.46; N, 1.72. Calc. for $C_{40}H_{38}FNO_{11}$: C, 66.22; H, 5.42; N, 1.77.

Physicochemical and spectral data for 3-(fluorescein)-2-(4,6-*O*-butylidene-β-D-glucopyranosyl)-3-(4-methoxy phenylamino)-butan-1-one (20)

Compound, **20** was obtained by the reaction of fluorescein-monoaldehyde **7**, (1.0 mmol, 0.36 g), 4-methoxyaniline **13**, (1.0 mmol, 0.12 g), 1-(4,6-*O*-butylidene-β-D-glucopyranosyl)-propan-2-one **14**, (1.0 mmol, 0.12 g) as brown solid: Yield: 0.50 g (68%); mp 160-162 ^{o}C; $[\alpha]_D^{31}$ + 23.6 (c 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 7.3 Hz, -CH_3), 1.45 (q, 2H, J = 9.4 Hz, -CH_2), 1.65 (q, 2H, J = 9.4 Hz, -CH_2), 2.19 (s, 3H, -$COCH_3$), 2.55-2.66 (m, 1H, Sac-H), 2.87 (d, 1H, J = 11.7 Hz, -CH), 3.18-3.40 (m, 6H, Sac-H), 3.44 (s, 2H, Sac-OH), 3.75 (s, 3H, -OCH_3), 4.12 (d, 1H, J = 7.2 Hz, Ano-H), 4.52 (t, 1H, J = 7.9 Hz, Sac-H), 6.70 (s, 1H, -NH), 6.77 (d, 5H, J = 8.4 Hz, Ar-H), 7.06 (d, 2H, J = 8.4 Hz, Ar-H), 7.14 (d, 3H, J = 6.9 Hz, Ar-H), 7.34 (s, 2H, Ar-OH), 7.63-7.72 (m, 2H, Ar-H), 8.06 (d, 1H, J = 9.0 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 169.0, 153.3, 152.8, 151.2, 138.8, 136.3, 135.4, 130.2, 129.0, 125.9, 125.4, 124.7, 123.7, 117.0, 114.8, 102.5, 81.4, 80.4, 75.2, 74.3, 70.5, 68.2, 60.0, 55.7, 36.2, 32.0, 30.9, 17.4, 13.9. Elemental Anal. Found: C, 66.87; H, 5.49; N, 1.69. Calc. for $C_{41}H_{41}NO_{12}$: C, 66.81; H, 5.44; N, 1.62.

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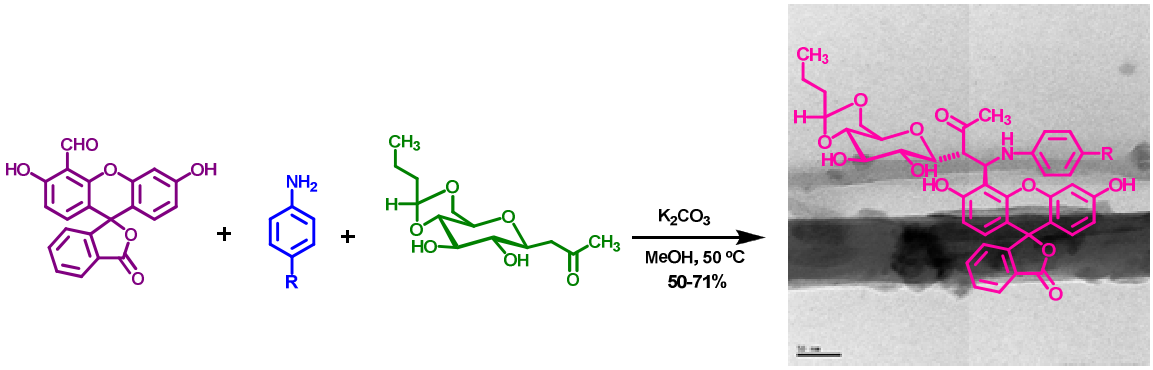
Graphical Abstract



Abstract

Facile one-pot synthesis of fluorescein based β-aminoglycosylketones was carried out using 4,6-O-protected-*C*-glycoside, fluorescein-monoaldehyde and aromatic amines in presence of potassium carbonate as a catalyst. Studies reveal that the use of potassium carbonate resulted in good yield. All these compounds were characterized using different spectral techniques. The gelation properties of these compounds were studied in regard to their molecular structure by HRTEM, DSC and powder XRD techniques. Fluorescein based β-aminoglycosylketones show moderate antioxidant activities with maximum inhibitory activity.

***Keywords*:** Fluorescein monoaldehyde, Mannich-type reaction, Morphological studies, DSC analysis, Antioxidant activities,