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A series of 3-(allyloxy)-propylidene acetals **1a** to **6a** of some natural terpenoids like andrographolides **1**, **2**, forskolins **3-5** and arjunolic acid **6** were developed by novel one pot synthetic strategy using ceric (IV) ammonium nitrate as a catalyst. The method is both chemo and regioselective towards 1,3-acetal formation without effecting other poly functional groups of terpenoids. *O*-allylation is an important functional group transfaormation for alcohols and the resulted end allylic double bond may participate in a number of synthetically useful transformations like olefin metathesis. Acetal of andrographolide **1a** was further converted into **1b, 1c** and **1d** by dimerization, acetylation and epoxidation respectively. All the synthesized compounds were screened for *in vitro* antiproliferative activity against four cancer cell lines B16F10, THP-1, PC-3 and SKOV3. Derivatives of andrographolide **1a**, **1b**, **1c** and **2a,** forskolin **4a** and arjunolic acid **6a** have shown promising cytotoxicity (IC_{50} <10 μg/ml) in most of the tested cell lines. Also compounds **1b** (IC_{50} 0.83 μg/ml) and **5a** (IC_{50} 3.43 μg/ml) showed significant *α*-glucosidase inhibition in *in vitro* assay. Structures of all the synthesized compounds were confirmed by NMR, Mass, IR spectral data. A single crystal X-ray analysis of **5a** also confirmed the 3-(allyloxy)-propylidene acetal formation.

Introduction

Semisynthetic modification of natural products has gathered movement in recent times owing to its potential in generating molecules with promising biological activity, it can be achieved by functional group transformation or by introduction of moieties.[1–3] Protection of diol is one of the most important reactions in organic chemistry and many protecting groups and methods have been developed.

Cyclic acetal group is one of the most widely used protecting groups for diols. In general, the cyclic acetals are formed by acid-catalysed condensation (HCl, H_2SO_4, H_3PO_4, *p*-TSA) of diols with carbonyl compounds proceeded with azeotropic removal of water.[4–6] Although, many methods were reported for cyclic acetal protection, many of them were failed in protecting natural product acetals either due to harsh conditions or poly functional groups etc. Therefore, there is a need to develop safer and selective acetal protecting groups. *O*-allylation is another important protecting group for alcohols and the resulted end allylic double bond may participate in a number of synthetically useful transformations like epoxidation, hydroformylation, cycloaddition, ozonalasis, olefin metathesis etc. *O*-allylation of many of natural products enhanced their activity such as antimalarial C-16, C-10-*O*-allyl artemisinin derivatives (**A** & **B**),[7] anticancer 10-*β* taxane, 10-*α*-abeo-taxane acetals (**C** & **D**),[8] antibacterial *O*-allyl erythromycin (**E**)[9] and *O*-allyl tomatidine hydrochloride (**F**)[10] (Fig 1). Besides, allyl ethers have been widely utilized as versatile sources of allylic carbon unit for synthesis of dimers. The dimers of **A** and **B** were synthesised using self-cross-metathesis reaction (Grubbs catalyst), showed good selectivity and the potency against a few cancer cell lines.[7]

Fig. 1: Biological important some *O*-allyl derivatives of natural products **A-F.**

Andrographis paniculata has been used in traditional medicine in the Asian countries for centuries. Andrographolide, **1**, 14-deoxy-11,12-didehydroandrographolide **2** are major diterpene lactones with various biological potentials like analgesic, antipyretic, anti inflammatory[11,12] antimicrobial,[13] hepatoprotective,[14] antiviral,[15,16] antidiabetic[17] and antitumor activities.[18,19] Many of their synthetic analogues exhibited superior anticancer activity over the parent compounds in both

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in vitro and *in vivo* models. Interactions between α,β-unsaturated γ-butyrolactone moiety, C-12,13 & C-8,17 double bonds, the C-14 hydroxyl or its ester moiety and protection of 3,19-hyroxyl with acetyl or suitable acetals/ketals are crucial responsible for the cytotoxic activity exhibited by andrographolide and its analogues.[20–22] Recent reviews also revealed that **1** and its derivatives are versatile bioactive molecules for combating inflammation and cancer.[23]

Forskolin **3**, 7-deacetyl forskolin **4**, Isoforskolin **5** are the important major labdane diterpenoids present in *Coleus forskohlii.* The marker compound forskolin, possess remarkable biological properties. It is commonly used to stimulate cyclic AMP (by activating adenylyl cyclase enzyme), an important second messenger necessary for the proper biological response of cells to hormones and other extracellular signals. It results to cure numerous diseases including asthma, cardiovascular disease, eczema, psoriasis, hypertension, angina, obesity and cancer metastases. [24–27] Clinical study revealed that forskolin as a weight loss agent and for treatment of glaucoma.[28–30] Chemical modifications at C-6 and C-7 position has led to water soluble compounds, with modest selectivity for particular cyclase isoforms, including the cardiac type 5-AC.[31,32]

Arjunolic acid **6** (2,3,23-Trihydroxyolean-12-en-28-oic acid), a natural pentacyclic triterpenoid saponin isolated from the bark of *Terminalia Arjuna*, is a multifunctional therapeutic promise of alternative medicine,[33] used as an antioxidant,[34] hepatoprotective,[35] anti-bacterial,[36] and antitumor activities.[37] Arjunolic acid also plays beneficial role in the pathogenesis of diabetes and associated. [38–40]

All the above described terpenoids **1-6** are poly functionalized compounds. Structurally, **1-6** consist of three hydroxyl groups, and **5** has one more, four hydroxyl groups. Andrographolide **1** is having three hydroxyl groups at C-3, C-14 and C-19 and **2** is dehydrate (H & OH is removed from C-11, C-14) of **1**. Forskolin **3** contains three hydroxyl groups at C-1, C-6, C-9, with one 7-*O*-acetyl group. Compounds **4** and **5** are deacetyl analogues and regioisomer (having 6-*O*-Acetyl) of **3** respectively**.** Arjunolic acid **6** contains three hydroxyl groups at C-2, C-3 and C-23. The 1,3-hydroxyl groups in compounds **1** to **6** differ in special arrangement, i.e, 3,19-OH groups of **1**, **2** (andrographolides), 1,9-OH groups of **3-5 (**forskolins**)** are in *cis*-geometry and 3,23-OH groups of **6 (**Arjunolic acid**)** in *trans*-geometry.

In our recently reported work on novel synthesis and biological evaluation of cyclic acetals of andrographolide and forskolins using ceric (IV) ammonium nitrate (CAN), the protection of diol with a suitable acetal moiety increases *in vitro* cytotoxicity against few cancer cell lines.[41,42] CAN is a most interesting one-electron oxidizing agent, environmentally benign, commercially available and inexpensive catalyst.[43] It is conveniently and widely used reagent for affecting a wide array of synthetic transformations due to advantages such as solubility in organic solvents, low toxicity, high reactivity and ease of handling. CAN is widely used for several synthetic transformation involving both C-C as well as C-X (X=hetero atom) bond forming reactions.[44–47]

Here, we report synthesis of novel 3-(allyloxy)-propylidene acetals of bioactive terpenoids by developing novel synthetic strategy. When the natural terpenoids **1-6** were treated with allyl alcohol in presence of CAN, 3-(allyloxy)-propylidene acetals were formed in one pot instead of acrolein acetals. All the compounds were evaluated for antiproliferative activity in *in vitro* mode against four cancer cell lines B16F10 (Mouse melanoma carcinoma), THP-1 (Human acute monocytic leukemia), PC-3 (Human prostate carcinoma), SKOV3 (Human ovarian carcinoma) cell lines and also evaluated for *in vitro* α-glucosidase inhibition.

Results and discussion

Chemistry

In Scheme 1, andrographolides **1** and **2** were treated with allyl alcohol (2 eq.) and CAN (2.1 eq.) in acetonitrile at room temperature for 24 h to result **1a** and **2a** in excellent yields (89 & 93 %). In **1a** the 3,19-diol was only acetalized and the labile 14-hydroxyl group, *exo*-methylene double bonds and lactone ring were undisturbed. It is also worthy to mention that any non-cyclized intermediate was not observed in the formation of **1a** (one pot reaction).

Scheme 1: Synthesis of 3,19-*O*-[(3-allyloxy)propylidene]andrographolides **1a** & **2a**

Latter, we applied this synthetic strategy to other similar type of terpenoids as shown in scheme 2 and scheme 3. Forskolins (**3-5),** arjunolic acid (**6),** when reacted with allyl alcohol, yielded compounds **3a**, **4a**, **5a** and **6a** in good yields (65-87 %). The regioselectivity in the formation of **4a** and **6a** may be due to formation of more stable six membered 1,3-acetal, compared to 1,2-acetal at these conditions.

Scheme 2: Synthesis of 1,9-*O*-[(3-allyloxy)propylidene]forskolins **3a**, **4a** & **5a**.

Scheme 3: Synthesis of 3,23-*O*-[(3-allyloxy)propylidene]arjunolic acid **6a.**

To confirm the formation of novel 3-(allyloxy)-propylidene acetal and also for SAR studies, **1a** was subjected to structural modification as shown in Scheme 4. In order to confirm newly formed end *O*-allylic double bond, **1a** was dimerized with Grubs catalyst (second generation), to result a homo dimer **1b** in good yields.[7] Also, to know the intact and contributions of C-14 hydroxyl group, C-8 exocyclic double bond, compound **1a** was acetylated with Ac_2O/TEA, epoxidation with *m*-CPBA in CH_2Cl_2 to yield **1c** and **1d** respectively.

Scheme 4: Synthesis of **1b-1d** from 3,19-*O*-[(3-allyloxy)-propylidene]andrographolide **1a.**

Structures of all the derivatives were elucidated by ^1H, ^{13}C NMR, Mass and IR spectral data. The stereochemistry of all the derivatives are assumed as per earlier reports.[48–50] Structure,

stereochemistry of compound **5a** was also confirmed by single crystal X-ray diffraction studies. The perceptive view of **5a** given in Fig 2 and the new stereo centre formed in cyclic acetal is in (*S*) configuration. The structure elucidation of new 3-(allyloxy)-propylidene group of compound **1a** was assigned as follows. **1a** showed characteristic stretching in IR spectra at 1646 cm^{-1} (C=C), confirmed the new allylic double bond. The molecular ion peaks m/z 447.03 $[M + H]^+$, 469 $[M + Na]^+$ observed in ESI-MS (positive) spectra. In the ^1H NMR spectrum, four signals in downfield region (with strong coupling interactions) at δ_H 5.79–5.92 (1H, m, H-5′), 5.22 (1H, d, J = 17.4 Hz, H_a-6′), 5.13 (1H, d, J = 10.2 Hz, H_b-6′) and 4.01-3.91 (2H, m, H-4′) were confirmed due to the end *O*-allylic (*O*-CH_2-CH=CH_{ab}) group. A triplet (overlapped) in the region of δ_H 4.90–4.93 (H-1′, *O*-C*H*-*O* acetal linkage), and also two overlapped multiplets at δ_H 3.51-3.36 (m, 2H, H-3′), 1.81–1.79 (m, 2H, H-2′) signals confirms propylidene *O*-CH-CH_2-CH_2-*O* linkage. In the ^{13}C, DEPT-135 NMR two new carbons at δ_C 93.31, 135.22 (CH-1′, CH-5′) and four new carbons at δ_C 117.28, 72.96, 65.90, 35.84 (CH_2-6′, CH_2-4′, CH_2-3′ & CH_2-2′) confirms the 3-(allyloxy)-propylidene group. Also, the structures of **1b**, **1c**, and **1d** confirmed the presence of 3-(allyloxy)-propylidene group, the intact of 14-hydroxyl group and C-8 exocyclic double bond respectively of **1a**. The step wise proposed mechanism for scheme 1-3 showed in Fig 3, it involves oxidation-addition-acetylation in one port method.

Fig. 2: The molecular structure of **5a** (ORTEP diagram), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30 % probability level and H atoms are shown as small spheres of arbitrary radius. The compound crystallized in orthorhombic $P2_12_12_1$ space group with two molecules (labelled A and B) in the asymmetric unit. For sake of clarity only one molecule (labelled A) is shown. The minor disordered component C28I has been omitted for clarity.

Fig. 3: Proposed mechanism for scheme 1-3.

Biological activity

***In vitro* antiproliferative activity**

All the natural products and its derivatives were screened for *in vitro* antiproliferative activity (tested concentrations: 1-100 µg/ml) by performing MTT assay against B16F10, THP-1 PC-3, SKOV3 cancer cell lines. 5-Fluorouracil was used as a reference compound.[51] Most of the derivatives exhibited a moderate to high degree of cytotoxicity with IC_{50} values ranging from 5.83±0.45 to 92.64±2.82 µg/ml against the tested cancerous cell lines (Table 1).

Table 1: *In vitro* cytotoxicity, *α*-glucosidase inhibition of terpenoids **1-6** and its derivatives.

Compound **1a** showed improved cytotoxicity against B16F10 (IC_{50} 12.51), SKOV3 (IC_{50} 9.27) when compared to parent **1** (**(**IC_{50} 12.69-15.67). The cytotoxicity of **1a** derivative i.e., homo dimer **1b** showed better cytotoxicity in B16F10 (IC_{50} 8.49). The acetyl derivative of **1a**, i.e., **1c** was showed to be potential against all the cell lines B16F10 (IC_{50} 9.21), SKOV3 (IC_{50} 8.73) PC3 (IC_{50} 11.03) and THP-1 (IC_{50} 5.83). The epoxidation of **1a** i.e., **1d** reduced its cytotoxicity (IC_{50} >30). Compound **2** is not active in all the cell line (IC_{50}>50) but the derivative **2a** showed significant cytotoxicity against B16F10 (IC_{50} 8.93) cell line. Compound **4** showed no cytotoxicity against any of the cell line at <100 µg/ml. but its derivative **4a** showed potent cytotoxicity in all the cell lines B16F10 (IC_{50} 8.61), PC3 (IC_{50} 7.92). Compound **6a** was significantly inhibited PC-3 (IC_{50} 8.25) but in remaining cell lines it showed lesser activity compared to parent **6 (**IC_{50} 6.39-10.43). Compound **3** is moderately active against B16F10 (IC50 37.94), **3a** was inactive in all the cell lines (IC_{50} >50). Compound **5** is not active at tested concentrations (IC_{50} >50), but its derivative were moderately active against B16F10 (IC_{50} 43.15) and THP-1 (17.82). From the above results, the 3-(allyloxy)-propylidene acetal group significantly induced the cell proliferation compared to parent natural terpenoids.

It is noteworthy that the derivatives **1b**, **1c**, **2a** and **4a** have exhibited an excellent cytotoxic activity against B16F10 cell line compared to standard 5-flurouracil. Amongst all the synthesized compounds, **1c** is proved to be potential against SKOV3, THP-1 and **6a** against PC-3 respectively. The order of cytotoxicity among the tested cell lines based on the IC_{50} value of standard molecule was B16F10>PC3>THP-1>SKOV3.

***α*-Glucosidase inhibitory activity**

The compounds were also evaluated for rat intestinal *α*-glucosidase inhibitory activity (AGI), in *in vitro* mode and acarbose was used as standard.[42] The values are presented in table 1 and fig 3. It is evident from the results that, all the compounds exhibited varying degrees of *α*-glucosidase inhibitory activity (18.02 to 78.24 %) at primary screening concentrations of 100µg/ml. The percentages of AGI inhibition of **1a**, **2a**, **3a** and **5a** was increased when compared to parent compounds **1**, **2**, **3** and **5.** The inhibition profiles of **1a** was further increased by when derivatized to **1b** and **1c**. Derivatives **4a** and **6a** showed reduced inhibition profiles when compared with parents **4** and **6**. Compounds displaying more than 60 % inhibition were selected for concentration dependent activity evaluation and calculation of IC_{50} values. Based on IC_{50} values, dimer **1b** (IC_{50} 0.83 µg/ml) and Isoforskolin derivative **5a** (IC_{50} 3.43 µg/ml) have potentially inhibited the *α*-glucosidase enzyme. The protection with 3-(allyloxy)-propylidene group has added advantage in improving *α*-glucosidase inhibitory activity of selected natural products like andrographolide **1** and isoforskolin **5**.

Fig. 4: Rat intestinal *α*-glucosidase inhibitory activity shown by terpenoids **1-6** & its derivatives.

Experimental

Materials and equipments

The natural products, **1**, **2** from the areal parts of *A. paniculata*,[52] **3-5** from roots of *C. forskohlii*[53] and **6** from bark of *T. arjuna*[33] were isolated and characterized as per earlier reports. Solvent evaporations were conducted under reduced pressure. All non-aqueous reactions were carried out under N_2 atmosphere in flame-dried glassware. All reagents were

procured from Sigma Aldrich and were used as received. Precoated TLC plates made of Silica gel 60 F_{254} (Merck) was used for TLC. Visualization of the developed TLC was performed by UV light or 5% H_2SO_4 in Methanol. Melting points were measured using A. KRUSS OPTRONIC and are uncorrected. NMR spectra were recorded on Bruker Avance 300/400 MHz in $CDCl_3$ using TMS as internal standard. IR data are given only for compounds with significant functions and were recorded on KBr plate.

General procedure and spectral characterization for compounds 1a, 2a, 3a, 4a, 5a & 6a

Compound **1**/**2**/**3**/**4**/**5**/**6** (0.2 mmol) and allyl alcohol (0.4 mmol) were taken in to acetonitrile (10 ml). To this solution, CAN (0.42 mmol) in minimum amount of acetonitrile was added in drop wise at room temperature. The reaction mixture was further stirred at RT for another 24 h. After the completion of reaction (monitored by TLC), it was concentrated under vacuum and diluted with 10 ml of water and extracted with ethyl acetate (2 × 20 ml). The organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product so obtained was purified by column chromatography (silica gel 100-200 mesh) using different percentages of ethyl acetate in *n*-hexane as an eluting system to give pure compounds **1a**/**2a**/**3a**/**4a**/**5a**/**6a**.

3,19-*O*-[(3-allyloxy)propylidene]andrographolide (1a): Yield: 80 mg (89 %), white solid, mp = 120–122 °C; IR (KBr): 3417, 2938, 1753, 1673, 1367, 1098 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.86 (m, 1 H), 5.92–5.79 (m, 1 H), 5.22 (d, *J* = 17.4 Hz, 1 H), 5.13 (d, *J* = 10.2 Hz, 1 H), 4.93–4.90 (m, 2 H), 4.84 (s, 1 H), 4.58 (s, 1 H), 4.39 (dd, *J* = 10.2, 6.0 Hz, 1 H), 4.18 (d, *J* = 9.9 Hz, 1 H), 4.01–3.91 (brm, 3 H), 3.51–3.36 (brm, 4 H), 2.51 (brm, 2 H), 2.40–2.36 (m, 1 H), 2.24–2.20 (m, 1 H), 1.99–1.95 (m, 1 H), 1.81–1.79 (m, 5 H), 1.64–1.60 (brm, 1 H), 1.30 (s, 3 H), 1.19 (brm, 3 H), 0.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 170.90, 149.18, 146.94, 135.22, 128.46, 117.28, 109.58, 93.31, 80.40, 74.96, 72.96, 69.37, 66.33, 65.90, 56.12, 55.12, 39.21, 37.98, 37.32, 36.39, 35.84, 26.35, 25.09, 23.12, 22.16, 15.61; ESI-MS: positive ion mode: m/z = 447.03 $[M + H]^+$, 469.06 $[M + Na]^+$ (calculated mass M is 446.27). Elemental analysis for $C_{26}H_{38}O_6$, calculated: C, 69.93; H, 8.58 %. Found: C, 70.01; H, 8.59 %.

3,19-*O*-[(3-allyloxy)propylidene]-14-deoxy-11,12-didehydro-andrographolide (2a): Yield: 77.5 mg (91 %), pale yellow solid, mp = 38–40 °C; IR (KBr): 2873, 1750, 1643, 1367, 1084 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.16 (s, 1 H), 6.91 (dd, *J* = 15.6, 10.0 Hz, 1 H), 6.13 (d, *J* = 16 Hz, 1 H), 5.93–5.86 (m, 1 H), 5.26 (dt, *J* = 17.2, 1.6 Hz, 1 H), 5.16 (dd, *J* = 10.0, 0.8 Hz, 1 H), 4.81–4.79 (m, 3 H), 4.55 (s, 1 H), 4.09 (d, *J* = 11.6 Hz, 1 H), 3.96–3.95 (m, 2 H), 3.54–3.47 (m, 3 H), 3.44 (d, *J* = 11.6 Hz, 1 H), 2.48–2.04 (m, 4 H), 1.89–1.84 (m, 2 H), 1.78–1.75 (m, 1 H), 1.61–1.57 (m, 2 H), 1.36 (s, 3 H), 1.31–1.11 (brm, 3 H), 0.93 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.19, 147.97, 142.97, 135.86, 134.91, 129.24, 121.26, 116.80, 109.49, 93.02, 80.47, 71.89, 69.56, 69.10, 65.54, 61.56, 54.15, 38.53, 37.38, 37.04, 36.35, 35.51, 25.90, 21.97, 21.68, 16.01; ESI-MS: positive ion mode: m/z = 429.10 $[M+H]^+$, 451.09 $[M+Na]^+$, 474.19 $[M+2Na]^+$ (calculated mass M is 428.26). Elemental analysis for $C_{26}H_{36}O_5$, calculated: C, 72.87; H, 8.47 %. Found: C, 71.49; H, 8.44 %.

1,9-*O*-[(3-allyloxy)propylidene]forskolin (3a): Yield 88.5 mg (87 %), white solid, mp = 42–44 °C; IR (KBr): 3504, 2928, 1717, 1374, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.89–5.83 (m, 1 H), 5.77 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.40 (d, *J* = 4.0 Hz, 1 H), 5.28 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.24–5.12 (m, 2 H), 4.91 (dd, *J* = 10.8, 1.2 Hz, 1 H), 4.62 (dd, *J* = 6.0, 4.4 Hz, 1 H), 4.44 (t, *J* = 3.2 Hz, 1 H), 3.96–3.89 (m, 3 H), 3.63–3.45 (m, 2 H), 2.96 (d, *J* = 16.0 Hz, 1 H), 2.34 (d, *J* = 16.0 Hz, 1 H), 2.27 (d, *J* = 2.4 Hz, 1 H), 2.15 (s, 3 H), 2.04–2.01 (m, 1 H), 1.90–1.87 (m, 2 H), 1.75 (m, 1 H), 1.69 (s, 3 H), 1.50 (m, 4 H), 1.33 (s, 3 H), 1.26 (s, 3 H), 1.07–1.04 (m, 1 H), 1.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.33, 169.66, 146.01, 134.79, 116.53, 110.35, 94.84, 84.81, 80.75, 76.35, 75.52, 75.44, 71.51, 70.11, 64.95, 49.83, 42.98, 39.13, 36.50, 35.35, 34.38, 33.02, 31.53, 24.65, 23.54, 23.36, 21.17, 17.49; ESI-MS: positive ion mode: m/z = 529 $[M + Na]^+$ (calculated mass M is 506.6). Elemental analysis for $C_{28}H_{42}O_8$, calculated: C, 66.38; H, 8.36 %. Found: C, 65.98; H, 8.40 %.

1,9-*O*-(3-allyloxy)propylidene]-7-deacetylforskolin (4a): Yield 60 mg (65 %), white solid, mp = 70–72 °C; IR (KBr): 3561, 3487, 2929, 1717, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.98–5.82 (m, 2 H), 5.25–5.13 (m, 3 H), 4.96 (d, *J* = 9.0 Hz, 1 H), 4.62 (t, *J* = 3.0 Hz, 1 H), 4.22 (brs, 1 H), 4.03–3.91 (m, 3 H), 3.63 (m, 2 H), 2.92 (d, *J* = 18.0 Hz, 1 H), 2.52 (d, *J* = 3.0 Hz, 1 H), 2.39 (d, *J* = 18.0 Hz, 1 H), 2.21–2.16 (m, 2 H), 2.09–2.00 (m, 1 H), 1.95–1.79 (m, 2 H), 1.73–1.69 (m, 1 H), 2.04–1.64 (s, 3 H), 1.51 (m, 1 H), 1.46 (s, 3 H), 1.40 (s, 3 H), 1.26 (s, 3 H), 1.08–1.06 (m, 1 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 205.97, 147.05, 135.19, 117.04, 110.72, 95.17, 84.94, 82.34, 76.11, 76.03, 75.04, 72.06, 70.94, 65.42, 50.24, 43.44, 39.63, 36.93, 35.81, 34.71, 33.57, 31.32, 24.98, 23.99, 23.34, 18.02; ESI-MS: positive ion mode: m/z = 487.26 $[M + Na]^+$, 503.31 $[M + K]^+$ (calculated mass M is 464.6). Elemental analysis for $C_{26}H_{40}O_7$, calculated: C, 67.22; H, 8.68 %. Found: C, 67.04; H, 8.68 %.

1,9-*O*-[(3-allyloxy)propylidene]isoforskolin (5a): Yield 83.5 mg (82 %), white solid, mp = 110–112 °C; IR (KBr): 3466, 2927, 1741, 1715, 1232, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.95 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.90–5.84 (m, 2 H), 5.26–5.14 (m, 3 H), 4.97 (dd, *J* = 10.8, 1.2 Hz, 1 H), 4.64 (t, *J* = 4.8 Hz, 1 H), 4.20 (d, *J* = 4.0 Hz, 1 H), 4.02 (brs, 1 H), 3.94–3.93 (m, 2 H), 3.61–3.51 (m, 2 H), 2.95 (d, *J* = 16.4 Hz, 1 H), 2.43 (d, *J* = 16.8 Hz, 1 H), 2.36 (d, *J* = 2.8 Hz, 1 H), 2.10 (s, 3 H), 1.93–1.88 (m, 3 H), 1.75–1.72 (m, 1 H), 1.60 (s, 3 H), 1.54–1.53 (m, 1 H), 1.46 (s, 3 H), 1.40 (s, 3 H), 1.09–1.08 (m, 1 H), 1.09 (s, 3 H), 1.00 (s, 3 H); ESI-MS: positive ion mode: m/z = 529.27 $[M + Na]^+$, 552.35 $[M + 2Na]^+$; **Crystal data:** $C_{28}H_{42}O_8$, *M* = 506.62, colourless block, 0.19 × 0.17 × 0.12 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 9.9588(6), *b* = 11.4669(7), *c* = 47.914(3) Å, *V* = 5471.6(6) $Å^3$, *Z* = 8, D_c = 1.230 g/cm^3, F_{000} = 2192, Bruker SMART APEX CCD area-detector, MoKα radiation, λ = 0.71073 Å, T = 294(2)K, $2\theta_{max}$ = 50.0°, 53182 reflections collected, 9628 unique (R_{int} = 0.0612). Final *GooF* = 1.110, *R1* = 0.0833, *wR2*

= 0.1891, *R* indices based on 7271 reflections with I>2σ(I) (refinement on F^2), 644 parameters, 7 restraints., μ = 0.089 mm^{-1}. Absolute structure parameter = −1.7(15). CCDC 997472 contains supplementary crystallographic data for the structure.†

3,23-*O*-[(3-allyloxy)propylidene]arjunolic acid (6a): Yield 92 mg (79 %), white solid, mp = 66–68 °C; IR (KBr): 3425, 2947, 2863, 1720, 1389 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 5.92–5.85 (m, 1 H), 5.26 (dd, *J* = 17.2, 1.6 Hz, 1 H), 5.28 (d, *J* = 4 Hz, 1 H), 5.17 (dd, *J* = 10.4, 1.6 Hz, 1 H), 4.75 (t, *J* = 5.2 Hz, 1 H), 3.96 (dd, *J* = 5.6, 0.8 Hz, 2 H), 3.96 (td, *J* = 10.0, 4.4 Hz, 1 H), 3.73 (d, *J* = 10.0 Hz, 1 H), 3.57 (t, *J* = 6.4 Hz, 2 H), 3.27 (d, *J* = 10.4 Hz, 1 H), 3.08 (d, *J* = 9.6 Hz, 1 H), 2.81 (dd, *J* = 13.6, 3.6 Hz, 1 H), 2.05–1.90 (m, 6 H), 1.66–1.58 (m, 6 H), 1.43–1.22 (m, 7 H), 1.12 (s 3 H), 1.06 (m, 1 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.95 (m, 2 H), 0.92 (s, 3 H), 0.90 (s, 3 H), 0.86 (m, 1 H), 0.71 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 183.56, 143.49, 134.82, 122.27, 116.88, 100.85, 89.73, 78.25, 71.86, 65.43, 65.20, 51.33, 47.62, 46.44, 46.35, 45.80, 41.57, 40.90, 39.35, 38.09, 36.86, 35.11, 33.77, 33.02, 32.40, 32.01, 30.65, 27.60, 25.94, 23.54, 23.25, 22.79, 17.73, 17.55, 17.04, 14.23; ESI-MS: positive ion mode: m/z = 607.51 $[M + Na]^+$, 630.60 $[M + 2Na]^+$ (calculated mass M is 584.4). Elemental analysis for $C_{36}H_{56}O_6$, calculated: C, 73.93; H, 9.65 %. Found: C, 73.84; H, 9.65 %.

Synthetic procedure and characterization of compounds 1b-1d

Access to homo dimer 1b by self-cross metathesis of 1a: Compound **1a** (50 mg, 0.11 mmol), Grubs 2nd generation catalyst [$C_{46}H_{65}Cl_2N_2PRu$] (28.52 mg, 30 mol %) were taken in CH_2Cl_2 (5 ml) and stirred at room temperature for 24 h. After completion of reaction, it was filtered on a pad of silica and the filtrate was concentrated under reduced pressure. The crude was subjected to silica gel (100−200 mesh) column chromatography (70% EtOAc in *n*-Hexane), yielded a mixture of homo dimers **1b** (E:Z > 5:1; by HPLC analysis). Yield 70 mg (72 %), white solid, mp = 88–90 °C; IR (KBr): 3457, 2944, 1740, 1368, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.94 (t, *J* = 6.4 Hz, 2 H), 5.78 (brs, 2 H), 5.01–4.95 (m, 4 H), 4.89 (s, 2 H), 4.61 (s, 2 H), 4.55 (dd, *J* = 10.4, 6.0 Hz, 2 H), 4.24 (dd, *J* = 10.4, 1.4 Hz, 2 H), 4.05–3.93 (brm, 6 H), 3.54–3.43 (brm, 8 H), 2.99 (d, *J* = 5.6 Hz, 2 H), 2.57–2.41 (m, 6 H), 2.31–2.22 (m, 2 H), 1.99–1.98 (m, 2 H), 1.86–1.77 (m, 10 H), 1.69–1.67 (m, 2 H), 1.35 (s, 6 H), 1.23–1.16 (brm, 6 H), 0.80 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ (ppm) 170.12 (2 C), 148.73 (2 C), 146.54 (2 C), 129.30 (2 C), 128.04 (2 C), 109.13 (2 C), 92.90 (2 C), 80.01 (2 C), 74.37 (2 C), 70.85 (2 C), 69.01 (2 C), 66.07 (2 C), 65.59 (2 C), 55.74 (2 C), 54.75 (2 C), 38.83 (2 C), 37.56 (2 C), 36.93 (2 C), 36.05 (2 C), 35.47 (2 C), 25.96 (2 C), 24.72 (2 C), 22.72 (2 C), 21.79 (2 C), 15.24 (2 C); ESI-MS: positive ion mode: m/z = 866 $[M + H]^+$, 888 $[M + Na]^+$ (calculated mass M for $C_{50}H_{72}O_{12}$ is 865.11); **HPLC method:** The Waters HPLC system consisting of binary pump (Waters-1525), auto sampler (Waters-717 plus), Photodiode array detector (Waters- 2996) and Empower software v3.0 used for the analysis. The chromatographic separation carried out on a Waters Spherisorb ODS2 column (250 mm × 4.6 mm, 5µm particle size, Made in Ireland). The mobile phase used was water and acetonitrile (6:4). The mobile phase was degassed by sonication before use. Peak detection at 223 nm and the retention time were 14.74, 15.39 min. The column temperature fixed at RT and the injection volume was chosen to be 10 µl.

14-acetyl-3,19-O-[(3-allyloxy)propylidene]andrographolide (1c): Compound **1a** (100 mg, 0.22 mmol) and triethylamine (0.5 mL) and acetic anhydride (1 ml) were taken in to CH_2Cl_2 (10 ml) and stirred at RT for 20 min. The completion of the reaction monitored by TLC, then the mixture was diluted with cold water (25 ml), extracted with CH_2Cl_2 (2 × 20 ml). The separated organic layers were mixed, washed with 5 % $NaHCO_3$ solution, Brine solution, water successively. It was dried with Na_2SO_4 and concentrated. The obtained crude was column purified over silica gel (100-200 mesh) column chromatography using (30 % EtOAc in *n*-Hexane) yielded compound **1c** as white solid. Yield: 96 mg (87%), mp = 108–110 °C; IR (KBr): 2964, 1754, 1725, 1366, 1243, 1082 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.01 (td, *J* = 6.8, 1.6 Hz, 1 H), 5.93–5.85 (m, 2 H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.17 (dq, *J* = 10.4, 1.6 Hz, 1 H), 4.97 (t, *J* = 5.2 Hz, 1 H), 4.88 (s, 1 H), 4.55 (dd, *J* = 11.2, 6.0 Hz, 1 H), 4.52 (s, 1 H), 4.25 (dd, *J* = 11.2, 1.6 Hz, 1 H), 4.03 (d, *J* = 11.2 Hz, 1 H), 3.96 (dd, *J* = 6.0, 1.6 Hz, 1 H), 3.55–3.49 (m, 4 H), 3.42 (d, *J* = 11.2 Hz, 1 H), 2.47–2.22 (m, 3 H), 2.31–2.22 (m, 1 H), 2.13 (s, 3 H), 1.99–1.98 (m, 1 H), 1.88–1.78 (m, 5 H), 1.71–1.68 (m, 1 H), 1.35 (s, 3 H), 1.23–1.36 (m, 3 H), 0.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.19, 147.97, 142.97, 135.86, 134.91, 129.24, 121.26, 116.80, 109.49, 93.02, 80.47, 71.89, 69.56, 69.10, 65.54, 61.56, 54.15, 38.53, 37.38, 37.04, 36.35, 35.51, 25.90, 21.97, 21.68, 16.01; ESI-MS: positive ion mode: m/z = 489.16 $[M+H]^+$, 511.12 $[M+Na]^+$, 999.42 $[2M+Na]^+$ (calculated mass M is 488.28). Elemental analysis for $C_{28}H_{40}O_7$, calculated: C, 68.83; H, 8.25 %. Found: C, 69.01; H, 8.23 %.

3,19-*O*-[(3-allyloxy)propylidene]-8,17-epoxy-andrographolide (1d): *m*-CPBA (0.33 mmol) in CH_2Cl_2 (10 ml) was added to the solution of Compound **1a** (100 mg, 0.22 mmol) in CH_2Cl_2 (20 ml) at 0–5 °C for 10 min. Then the reaction mixture was stirred at RT for 1 h. The reaction was monitored by TLC and it was quenched with saturated aq. Na_2CO_3 (5 ml). The separated organic layer was washed with brine and water successively. It was dried with Na_2SO_4 and concentrated. The residue was purified through silica gel (100-200 mesh) column chromatography (40 % EtOAc in *n*-Hexane) to afford the desired product **1d**. Yield 75 mg (77 %), white solid, mp = 60–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.81 (t, *J* = 5.6 Hz, 1 H), 5.96–5.86 (m, 1 H), 5.27 (dd, *J* = 17.2, 1.6 Hz, 1 H), 5.18 (dd, *J* = 10.4, 1.2 Hz, 1 H), 5.00–4.96 (m, 2 H), 4.38 (dd, *J* = 10.0, 6.0 Hz, 1 H), 4.26 (dd, *J* = 10.4, 2.0 Hz, 1 H), 4.03 (d, *J* = 11.2 Hz, 1 H), 3.97 (dd, *J* = 5.6, 1.2 Hz, 2 H), 3.56–3.45 (m, 5 H), 2.89 (d, *J* = 2.0 Hz, 1 H), 2.67 (d, *J* = 3.6 Hz, 1 H), 2.33–2.27 (m, 1 H), 2.07–2.02 (m, 1 H), 1.90–1.86 (m, 3 H), 1.77–1.67 (m, 4 H), 1.47–1.43 (m, 2 H), 1.38 (s, 3 H), 1.28–1.19 (m, 3 H), 0.93 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 170.14, 146.14, 134.79, 128.95, 116.82, 92.91, 79.57, 73.66, 71.83, 68.71, 65.40, 65.16, 60.0, 54.12, 53.21, 51.05, 39.59, 36.67, 35.81, 35.69, 35.35, 25.84, 22.58, 20.88, 20.37, 15.08; ESI-MS: positive ion mode: m/z = 463.11

$[M+H]^+$, 485.13 $[M+Na]^+$, 947.40 $[2M+Na]^+$ (calculated mass M is 462.26). Elemental analysis for $C_{26}H_{38}O_7$, calculated: C, 67.51; H, 8.28 %. Found: C, 67.69; H, 8.25 %.

Cytotoxicity evaluation

Cell lines and cell culture: The cell lines B16F10 (Mouse Melanoma carcinoma), THP-1 (human acute monocytic leukemia), PC-3 (Human prostate carcinoma) and SKOV3 (Human ovarian carcinoma) were obtained from the National Centre for Cellular Sciences (NCCS), Pune, India. Cells were cultured in their respective selection media [RPMI-1640 (THP-1 and PC-3) and DMEM (B16F10 and SKOV3) that supplemented with 10% heat-inactivated Fetal Bovine Serum (FBS), 1 mM $NaHCO_3$, 2 mM-glutamine, 100 units/ml penicillin and 100 µg/ml of streptomycin. All cell lines were maintained in culture at 37 °C in humidified atmosphere of 5% CO_2

Test Concentrations: Stock solutions of each compound and positive control were prepared fresh prior to the start of every experiment. A stock solution of each compound was prepared at a concentration of 8 mg/ml in in 100% Dimethyl sulfoxide (DMSO, Sigma Chemical Co., St. Louis, MO). Working solutions of each test chemical were prepared by serial dilutions with the appropriate culture media. All the compounds were tested using the required concentrations that ranging from 1-100 µg/ml.

Cytotoxicity method: Cytotoxicity was measured using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium brome] assay. Briefly, the cells (2×10^4) were seeded in each well containing 100 µl of medium in 96 well plates. After overnight incubation (at 37 °C a humidified atmosphere of 5% CO_2), exactly 100 µl of media with different test concentrations (10 µg to 100 µg/ml) were added to the cell suspension, which is equivalent to 2 to 20 µl of assay volume. The viability of cells was assessed after 24h, by adding 10 µl of MTT (5 mg/ml) per well and incubated at 37 °C for additional three hours. The medium was discarded and the intensity of colour formation was measured at 570 nm in a spectrophotometer (Spectra MAX Plus; Molecular Devices; supported by SOFTMax PRO-5.4). The percent inhibition of cell viability was determined with reference to the control values (without test compound). Data were generated in three separate experiments and the mean values were subjected to linear regression analysis (Biostat 2008, professional statistical software) for the best straight-line fit.[54] IC_{50} concentrations (50% decreases in cell number as compared with that of the control values) were calculated using the respective regression equations.

α-Glucosidase inhibitory assay

α-Glucosidase inhibitory activities were determined as per earlier reported methods. Rat intestinal acetone powder in normal saline (100:1; w/v) was sonicated properly and the supernatant was used as a source of crude intestinal a-glucosidase after centrifugation. In brief, 10 µl of test samples (5 mg/ml DMSO solution) were reconstituted in 100 µl of 100 mM-phosphate buffer (p^H 6.8) in 96-well microplate and incubated with 50 µl of crude intestinal α-glucosidase for 5 min before 50 µl substrate (5 mM, *p*-nitrophenyl-α-D-glucopyranoside prepared in same buffer) was added. Release of *p*-nitrophenol was measured at 405 nm spectrophotometrically (Spectra Max plus 384, Molecular Devices Corporation, Sunnyvale, CA, USA) 5 min after incubation with substrate. Individual blanks for test samples were prepared to correct background absorbance where substrate was replaced with 50 µl of buffer. Control sample containg 10 µl of DMSO in place of test samples. Percentage of enzyme inhibition was calculated as $(1 - B/A) \times 100$, where [A] represents absorbance of control without test samples and [B] represents absorbance in presence of test samples. For calculation of 50% enzyme inhibitory activity (IC_{50}), five dilutions of primary screening concentration (5 mg/ml DMSO) of test compounds were prepared. The IC_{50} values were calculated applying logarithmic regression analysis.

Conclusions

A one-pot regio and chemo selective method for the synthesis of novel 3-(allyloxy)-propylidene acetals of bioactive natural terpenoids was developed by using allyl alcohol and CAN at room temperature. This method is being reported for the first time as an easy access to functionalized 1,3-diols. *In vitro* antiproliferative activity studies revealed that, andrographolide **1** is moderate cytotoxic but, the 3-(allyloxy)-propylidene acetal protection (**1a**) followed by homo dimerization (**1b**) and acetylation (**1c**) increased the cytotoxicity several folds. The compounds **1b**, **1c**, **2a** and **4a** seems to be promising as they shown better activity than the control (5-Fluorouracil) on B16F10 cells. Compound **1c** has shown promising cytotoxicity against SKOV3, THP-1 and **6a** against PC-3 respectively compared to parent in the series. The homo dimer compound **1d** and compound **4a** emerged as the most potent α-glucosidase inhibitors in present series. Thus, the reported synthetic strategy can find wide applications in semi synthesis of other complex bioactive natural products.

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Figures, Schemes and Table List

Fig. 1: Biological important some *O*-allyl derivatives of natural products **A-F.**

Fig. 2: The molecular structure of **5a** (ORTEP diagram), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30 % probability level and H atoms are shown as small spheres of arbitrary radius. The compound crystallized in orthorhombic $P2_12_12_1$ space group with two molecules (labelled A and B) in the asymmetric unit. For sake of clarity only one molecule (labelled A) is shown. The minor disordered component C281 has been omitted for clarity.

Fig. 3: Proposed mechanism for scheme 1-3.

Fig. 4: Rat intestinal α-glucosidase inhibitory activity shown by terpenoids **1-6** & its derivatives.

Scheme 1: Synthesis of 3,19-*O*-[(3-allyloxy)propylidene]andrographolides **1a** & **2a.**

Scheme 2: Synthesis of 1,9-*O*-[(3-allyloxy)propylidene]forskolins **3a**, **4a** & **5a**.

Scheme 3: Synthesis of 3,23-*O*-[(3-allyloxy)propylidene]arjunolic acid **6a**.

Scheme 4: Synthesis of **1b-1d** from 3,19-*O*-[(3-allyloxy)propylidene]andrographolide **1a**.

Table 1: *In vitro* cytotoxicity,α-glucosidase inhibition of terpenoids **1-6** and its derivatives.

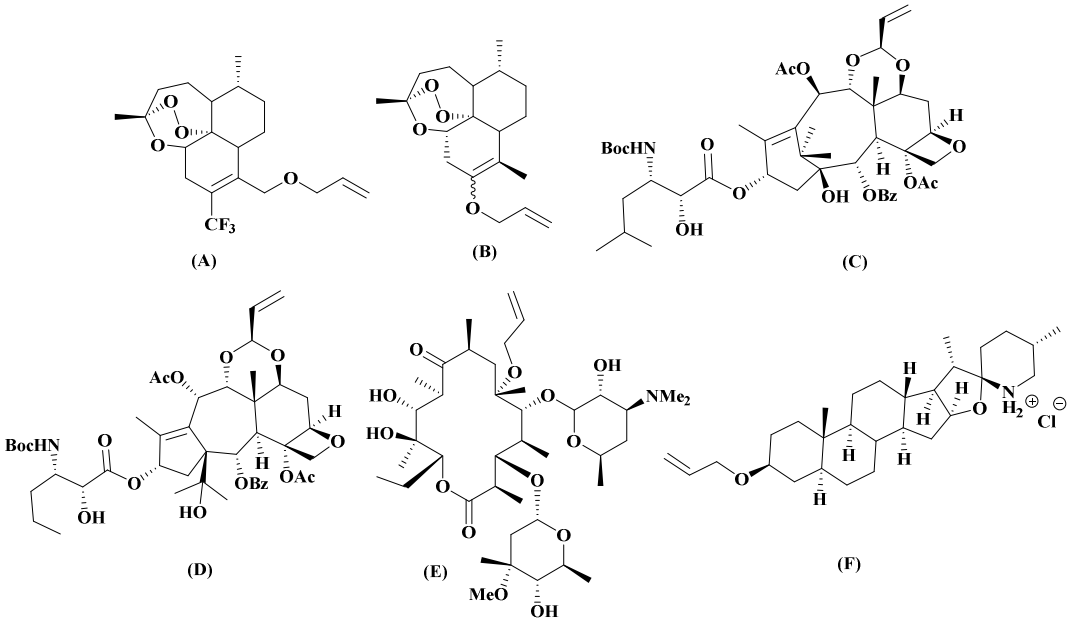
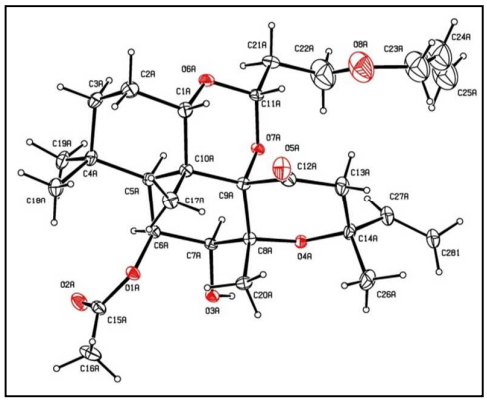


Fig. 1: Biological important some *O*-allyl derivatives of natural products **A-F.**



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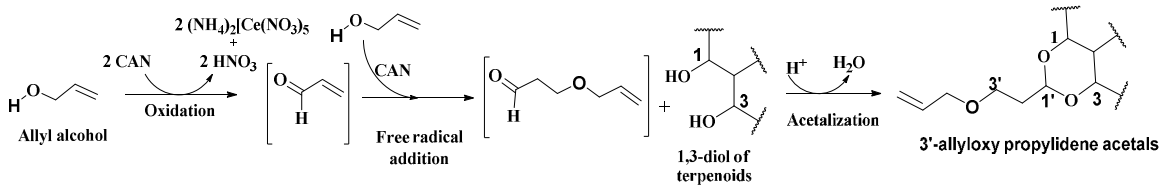

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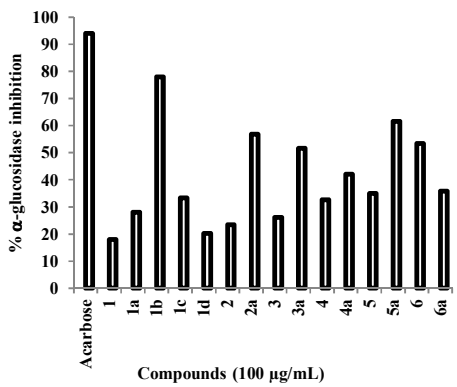

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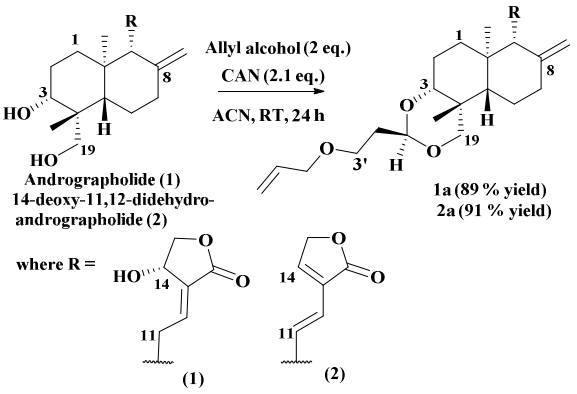

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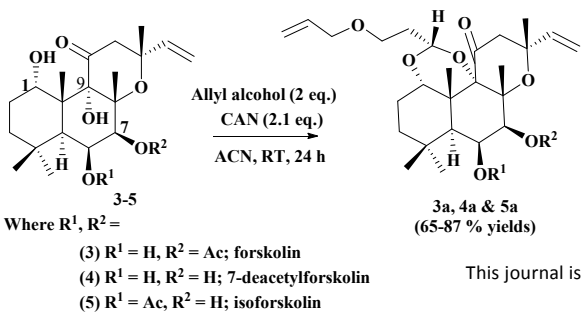

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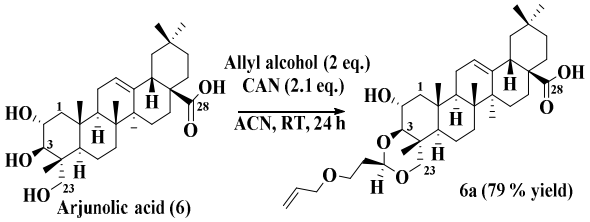

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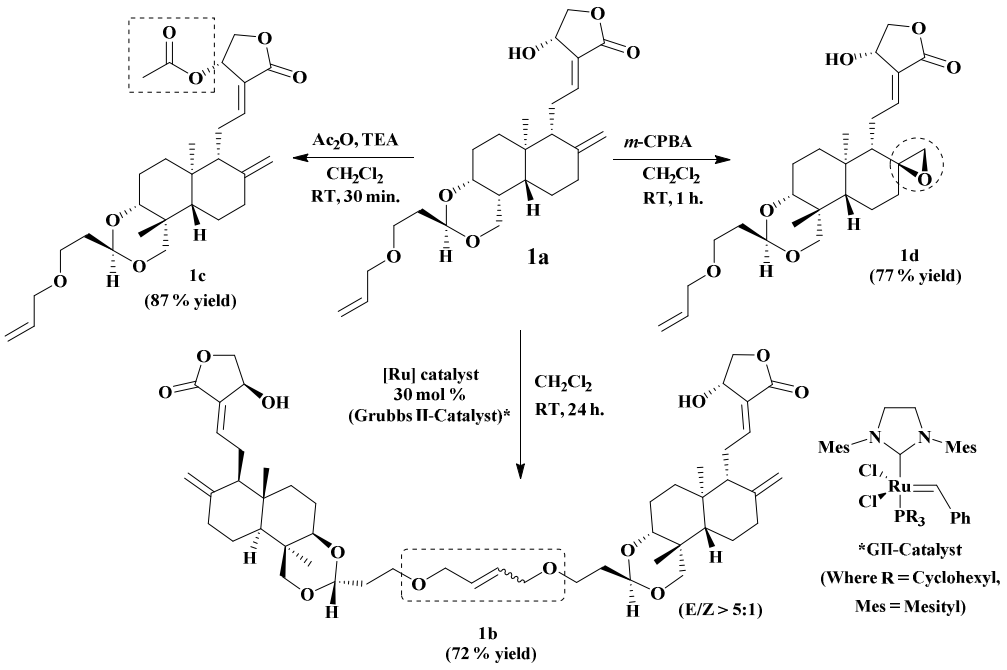

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Table 1: *In vitro* cytotoxicity,α-glucosidase inhibition of terpenoids **1-6** and its derivatives.

Compound	AGI % inhibition at 100 µg/ml (IC_{50} µg/ml)	Cell growth inhibition in IC_{50} (µg/ml)[a]			
		B16F10	THP-1	PC-3	SKOV3
1	18.02	15.67±0.29	13.85±0.63	16.27±0.57	12.69±0.89
1a	28.08	12.51±0.62	11.47±0.72	15.39±0.29	9.27±0.48
1b	78.24 (0.83)[b]	8.49±0.82	32.86±1.89	29.15±1.09	9.61±0.42
1c	33.27	9.21±0.91	5.83±0.45	11.03±0.63	8.73±0.72
1d	20.13	45.17±1.72	38.27±1.67	29.14±1.84	37.28±1.98
2	23.37	52.89±1.37	NA	NA	82.17±2.59
2a	56.82	8.93±0.63	41.64±2.86	NA	56.49±2.59
3	26.17	37.94±1.04	NA	NA	74.38±2.90
3a	51.62	NA	NA	75.92±2.87	NA
4	32.65	NA	NA	NA	NA
4a	42.04	8.61±0.29	11.04±0.57	7.92±2.87	13.17±0.41
5	34.97	92.64±2.82	NA	NA	NA
5a	61.52 (3.43)[b]	43.15±1.89	17.82±0.32	67.31±1.93	51.83±1.69
6	53.41	6.39±0.71	8.43±0.91	10.43±0.98	10.29±0.79
6a	35.87	26.84±1.20	13.69±0.57	8.25±0.35	13.96±0.94
5-FU[c]	--	9.93±0.54	0.64±0.08	1.56±0.14	0.57±0.06
Acarbose[c]	93.97 (0.68)	--	--	--	--

[a]Exponentially growing cells were treated with different concentrations of all compounds for 24h and cell growth inhibition was analyzed through MTT assy. IC_{50} is defined as the concentration, which results in a 50% decrease in cell number as compared with that of the control cultures in the absence of an inhibitor and were calculated using the respective regression analysis. The values represent the mean ± SE of three individual observations. [b]Values in parentheses represent IC_{50} in ug/ml for the respective compounds showing >60 % inhibition. [c]5-Fluorouracil (5-FU)/Acarbose were employed as positive controls. NA indicates that the compounds are not active at 100 µg/ml concentration.