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# Stereoselective synthesis of natural product inspired carbohydrate fused pyrano[3,2-*c*] quinolones as antiproliferative agents†

Priti Kumari,[a] Chintam Narayana,[a] Shraddha Dubey,[b] Ashish Gupta[b] and Ram Sagar *[a,c]

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Pyrano[3,2-*c*]quinolone structural motifs are commonly found in natural products with diverse biological activities. As part of a research programme aimed at developing the efficient synthesis of natural product-like small molecules, we designed and developed the microwave assisted, facile stereoselective synthesis of two series of carbohydrate fused pyrano[3,2-*c*]quinolone derivatives (*n* = 23) starting from 2-*C*-formyl galactal and 2-*C*-formyl glucal, reacting with various 4-hydroxyquinolones in shorter reaction times (15–20 min). The antiproliferative activity of these synthesized pyrano[3,2-*c*]quinolones was determined against MCF-7 (breast) and HepG2 (liver) cancer cells. The selected library members displayed low micromolar (3.53–9.68 μM) and selective antiproliferative activity. These findings on carbohydrate fused pyrano[3,2-*c*]quinolone derivatives are expected to provide new leads for anticancer drug discovery.

## Introduction

Natural products and their derivatives have been a rich source of new leads in medicinal chemistry; therefore, the preparation of natural product-like molecules has been of interest to medicinal chemists and is an important area of research in modern drug discovery.[1–3] The syntheses of natural products or natural product-like molecules are often difficult due to the structural complexity with many stereogenic centers and intricate ring systems.[4] As part of a research programme aimed to develop the efficient synthesis of natural product-like small molecules, we identified pyrano[3,2-*c*]quinolone scaffolds as an important structural motif present in many bioactive natural products.[5] This structural motif is broadly represented by pyranoquinolone alkaloids, which are generally seen in the plant family Rutaceae, exhibiting diverse biological activities.[6]

Pyranoquinolones and fused pyrano[3,2-*c*]quinolone motifs are widely present in bioactive natural products, synthetic products as well as pharmaceutical agents.[7] Pyrano[3,2-*c*]quinolones are primarily known for their anticancer activity, along with antimalarial,[8] antibacterial,[9,10] antiinflammatory,[11] and antifungal[12] properties as well as inhibition of calcium signaling,[13] platelet aggregation,[14] and nitric oxide production.[15] Pyrano[3,2-*c*]quinolone is a core structural motif present in many alkaloids possessing significant pharmacological and therapeutic activities (Fig. 1).[16] For instance, huajiaosimuline (**A**), a potent and selective anticancer agent towards breast cancer, and zanthosimuline (**B**), an anticancer agent having

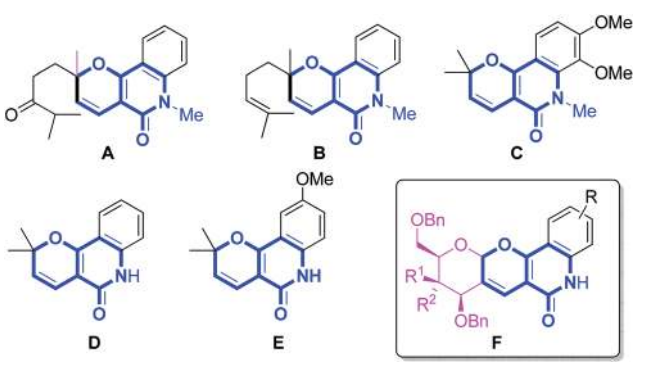


**Fig. 1** Naturally occurring and bioactive pyrano[3,2-*c*]quinolone molecules (A–E): (A) huajiaosimuline, a selective anticancer agent (breast); (B) zanthosimuline, an anticancer agent against multidrug resistant KB-VI cancer cells; (C) veprisine, antimycobacterial activity; (D) flindersine, antimicrobial and antifungal activity; (E) haplamine, anticancer activity; and (F) our anticancer pyrano[3,2-*c*]quinolone molecules presented in the current work.

[a]*Department of Chemistry, School of Natural Sciences, Shiv Nadar University (SNU), NH91, Tehsil-Dadri, Gautam Buddha Nagar, Uttar Pradesh, 201314, India. E-mail: ram.sagar@snu.edu.in*
[b]*Department of Life Sciences, School of Natural Sciences, Shiv Nadar University (SNU), NH91, Tehsil-Dadri, Gautam Buddha Nagar, Uttar Pradesh, 201314, India. E-mail: ashish.gupta@snu.edu.in*
[c]*Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, 221005, India*

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activity against multidrug resistant KB-VI cancer cells, were both isolated from *Zanthoxylum simulans*.[17] In addition, the natural product veprisine (**C**) possesses antimycobacterial activity; flindersine (**D**) isolated from *Toddalia asiatica* exhibits antimicrobial and antifungal activity;[18] and haplamine (**E**) isolated from *Haplophyllum villosum* displays good anticancer activity (Fig. 1).[19] These literature reports strongly support pyrano[3,2-*c*]quinolone as a privileged structural motif. We envisioned and designed a new carbohydrate fused pyrano[3,2-*c*]quinolone molecule (**F**) as a hybrid structural motif in anticipation of obtaining better anticancer candidates. Furthermore, when the natural product-like (privileged) molecules fused with carbohydrates, the resulting hybrid molecules possessed many additional pharmacological properties like better aqueous solubility, improved selectivity, improved cellular uptake, reduced cellular toxicity, *etc*.[20]

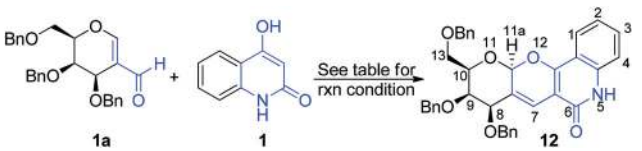
Considering the biological relevance of pyrano[3,2-*c*]quinolone structural motifs, several methods have emerged for their preparation and for the preparation of their derivatives over the past few decades.[21–31] These include multistep synthesis[22] and one-pot synthesis.[23] Hsung *et al.* developed a formal [3 + 3] cycloaddition reaction for the construction of pyrano[3,2-*c*]quinolones, but it requires 48 h of continuous refluxing in toluene.[24] A few other similar methods for the preparation of the pyranoquinolone skeleton are documented which mainly involve the reaction between 4-hydroxyquinolin-2-one and various 1,3-dielectrophiles like α,β-unsaturated aldehyde,[25] β-ketoester,[26] diethylmalonate,[27] arylidenemalononitrile and arylidenecyanoacetate under thermal reflux conditions. Lee *et al.* reported quite a few similar methods for the preparation of pyranoquinolones using iodine,[28] $InCl_3$,[29] and $Yb(OTf)_3$.[23] All the above-reported conditions required longer reaction times (12–24 h) and the reported yields were moderate. A greener approach has been reported with a few examples, where a similar structural motif can be constructed in 4–6 h in moderate to good yields by refluxing suitable substrates in water.[30] Recently, Hajra *et al.* reported the synthesis of pyrano[3,2-*c*]quinolin-2-ones catalyzed by Brønsted acidic ionic liquids (BAILs), which required 6 h of continuous refluxing at 110 °C.[31] The synthesis of some acetal fused pyrano[3,2-*c*]pyran-5(2*H*)-one derivatives was carried out earlier, which required 3–6 h of continuous heating at 80 °C.[32] We envisioned developing a method to construct a diverse and new carbohydrate fused pyrano[3,2-*c*]quinolone library with shorter reaction times and high yields under microwave conditions.

Herein we have developed the microwave assisted, facile stereoselective synthesis of carbohydrate fused pyrano[3,2-*c*]quinolones (**F**) derived from the hybrid structure of 4-hydroxyquinolone and 2-*C*-formyl glycals in good to very good yields in very short reaction times (15–20 min). The antiproliferative activity of these synthesized fused pyrano[3,2-*c*]quinolones was determined using cellular assays against MCF-7 and HepG2 cancer cell lines. The preliminary screening results show that selected carbohydrate fused pyrano[3,2-*c*]quinolones exhibited high growth inhibitory potencies with $IC_{50}$ in the range of 3.53–9.68 μM. The microwave assisted efficient synthesis of these pyrano[3,2-*c*]quinolones along with their preliminary antiproliferative activity are presented in this paper.

## Results and discussion

For the efficient synthesis of carbohydrate-fused pyrano[3,2-*c*]quinolone hybrids, we identified 4-hydroxyquinolone **1** as the substrate which can be coupled with 2-*C*-formyl galactal **1a**[33] under microwave reaction conditions and to be transformed into the desired pyrano[2,3-*c*]quinolone hybrid **11** (Table 1) through selective C-1,2 nucleophilic addition followed by the 6π-electron electrocyclization reaction, *i.e.* formal [3 + 3] cycloaddition reaction. Although some earlier reports have described the synthetic methods for the preparation of pyranoquinolone alkaloids, these have limited substrate scope.[34] Later, improved synthetic methods have been reported for the synthesis of pyranoquinolone natural products and related biologically active molecules.[23–31,35] However, some of the transformations have faced challenges in terms of reaction time, isolated yield, substrate scope, *etc*. Therefore, there was a need to develop an efficient synthetic approach to this transformation reaction for better yields and shorter reaction times, which is an essential aspect in privileged library synthesis. In continuation of our work on the efficient synthesis of natural product-like molecules, we have developed the microwave assisted efficient synthesis of carbohydrate fused pyrano[3,2-*c*]quinolones. A library of twenty-three compounds was prepared

**Table 1** Reaction optimization using different organocatalysts and solvents




| S. no. | Reaction conditions[a] | Yield[b] (%) |
|---|---|---|
| 1 | Pyrrolidine, toluene : AcOH, Δ, 80 °C, 3 h | 40 |
| 2 | Pyrrolidine, toluene : AcOH, μW, 80 °C, 15 min | 66 |
| 3 | Pyrrolidine, EtOAc : AcOH, μW, 80 °C, 15 min | 71 |
| 4 | Pyrrolidine, benzene : AcOH, μW, 80 °C, 15 min | 60 |
| 5 | Pyrrolidine, xylene : AcOH, μW, 80 °C, 15 min | 41 |
| 6 | Pyrrolidine, ethanol : AcOH, μW, 80 °C, 20 min | 40 |
| 7 | Pyrrolidine, water : AcOH, μW, 80 °C, 20 min | NR |
| 8 | Pyrrolidine, PEG-200 : AcOH, μW, 80 °C, 20 min | NR |
| 9 | Piperidine, toluene : AcOH, μW, 80 °C, 15 min | 35 |
| 10 | Piperidine, EtOAc : AcOH, μW, 80 °C, 15 min | 52 |
| 11 | Piperidine, benzene : AcOH, μW, 80 °C, 15 min | 41 |
| 12 | Piperidine, xylene : AcOH, μW, 80 °C, 15 min | 42 |
| 13 | Proline, toluene : AcOH, μW, 80 °C, 15 min | 50 |
| 14 | Proline, EtOAc : AcOH, μW, 80 °C, 15 min | 55 |
| 15 | Proline, benzene : AcOH, μW, 80 °C, 15 min | 45 |
| 16 | Proline, xylene : AcOH, μW, 80 °C, 15 min | 42 |
| 17[c] | Pyrrolidine, EtOAc : AcOH, μW, 80 °C, 15 min | 68 |

[a] 0.5 equiv. of the organocatalyst was used in each case. [b] Isolated yield. Diastereomeric ratio (dr) was determined by crude $^1$H NMR; dr (α : β > 99 : 1). [c] 0.1 equiv. of the organocatalyst was used in this case. NR = no reaction.

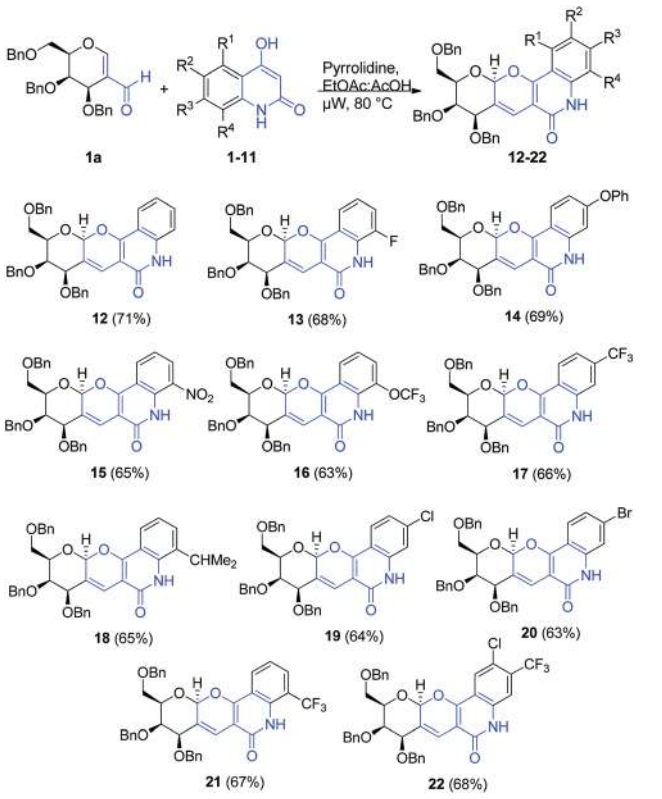
using the developed protocol and their preliminary anticancer activity was studied.

The initial reaction of 4-hydroxyquinolone **1** with 2-*C*-formyl galactal **1a** was performed under thermal conditions (80 °C) in toluene (3 h) but no product was seen, whereas the use of pyrrolidine as an organocatalyst furnished stereoselective product **12** after 3 h in a poor yield (entry 1, Table 1). When a similar reaction was undertaken under microwave heating conditions at 80 °C in the presence of pyrrolidine, carbohydrate fused pyrano[3,2-*c*]quinolone **12** was obtained in a better isolated yield (66%) in a highly stereoselective and regioselective manner (entry 2, Table 1). However, in the absence of pyrrolidine, the above reaction does not go to completion even after 20 min. This indicates that a secondary amine based organocatalyst (pyrrolidine) is required for this transformation, not only to accelerate the reaction but also to induce regioselectivity. The structure of the new pyrano[3,2-*c*] quinolone **12** was unambiguously established by 1D and 2D NMR (HSQC, COSY and NOE) experiments (ESI†). The stereochemistry of the newly generated chiral center was confirmed by a NOE correlation between the H-11a methine proton (new chiral center) and predefined chiral protons (H-10). This suggested that the H-11a proton is in the same face as the H-10 proton at the sugar part in compound **12**.

To optimize the reaction conditions and see the effect of reagents on stereoselectivity, we planned and tested a series of reaction conditions using various organocatalysts and solvent systems (Table 1). To enhance the reactivity of 2-*C*-formyl galactal **1a**, various secondary amine-based organocatalysts were tested. After screening a set of reaction conditions by using different organocatalysts under microwave conditions, it was found that the condensation of 4-hydroxyquinolone **1** with 2-*C*-formyl galactal **1a** in the presence of pyrrolidine (0.5 equiv.) in ethyl acetate at 80 °C affords **12** in 71% isolated yield with excellent diastereoselectivity (entry 3, Table 1). When we carried out the same transformation in the presence of 0.1 equiv. of pyrrolidine under similar conditions, compound **12** was obtained in 68% isolated yield (entry 17, Table 1); we obtained the identical product **12** without the loss of stereoselectivity when piperidine and proline were used as organocatalysts. The isolated yield varied with different organocatalysts without any significant difference in the reaction time (Table 1, entries 9–16).

To study the solvent effects for this transformation under microwave conditions, we screened 1% acetic acid in toluene, ethyl acetate, benzene, xylene, ethanol, water and poly(ethylene glycol)-200 (PEG-200) in the presence of pyrrolidine (Table 1, entries 2–8) keeping the other reaction parameters constant. In comparison, 1% acetic acid in ethyl acetate was found to be superior over toluene, benzene, xylene and ethanol. No reaction was observed when water and PEG-200 were used as the solvent on these substrates (Table 1, entries 7 and 8). When the same reaction was carried out using 1% citric acid or tartaric acid, as an alternative of acetic acid, in ethyl acetate as the solvent, only 10–15% conversion was noticed even after prolonged (25 min) heating under microwave conditions. The four solvent systems, *viz*. ethyl acetate, toluene, benzene and xylene, were screened with other organocatalysts (piperidine and proline) and the result showed that, indeed, 1% acetic acid in ethyl acetate was the best solvent among the others (Table 1, entries 9–16).

After having optimized the reaction conditions, we were interested in investigating the scope of this formal [3 + 3] cycloaddition reaction with different substituted 4-hydroxyquinolones. Therefore, various 4-hydroxyquinolones **1–11** were freshly prepared in the laboratory starting from the commercially available corresponding substituted anilines, reacting with Meldrum's acid followed by Eaton's reagent (Scheme S1, ESI†).[36] The diverse 4-hydroxyquinolone derivatives were then treated with 2-*C*-formyl galactal **1a** and 2-*C*-formyl glucal **1b** under optimized reaction conditions (μW, 80 °C, EtOAc : AcOH, pyrrolidine) in different sets of reactions. As shown in Scheme 1, 2-*C*-formyl galactal **1a** was successfully coupled with various substituted 4-hydroxyquinolones **1–11** to afford the respective carbohydrate fused pyrano[3,2-*c*]quinolones **12–22** in good to very good yields with excellent stereoselectivity (dr > 99 : 1). The substituents of the electron donating and electron withdrawing groups at the $R^1$, $R^2$, $R^3$ and $R^4$ positions on 4-hydroxyquinolones significantly affected neither the yield nor the reaction completion time. However, unsubstituted 4-hydroxyquinolone afforded a good yield (71%)




**Scheme 1** Synthesis of 2-*C*-formyl galactal fused pyrano[3,2-*c*]quinolones **12–22**.

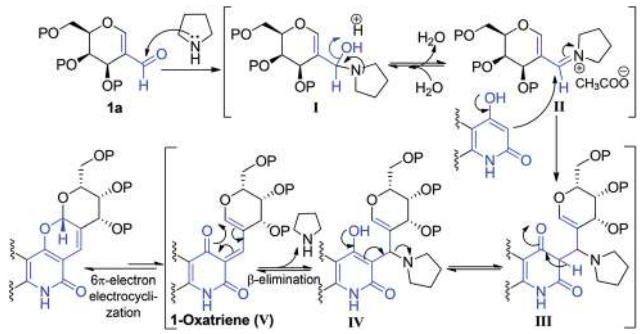
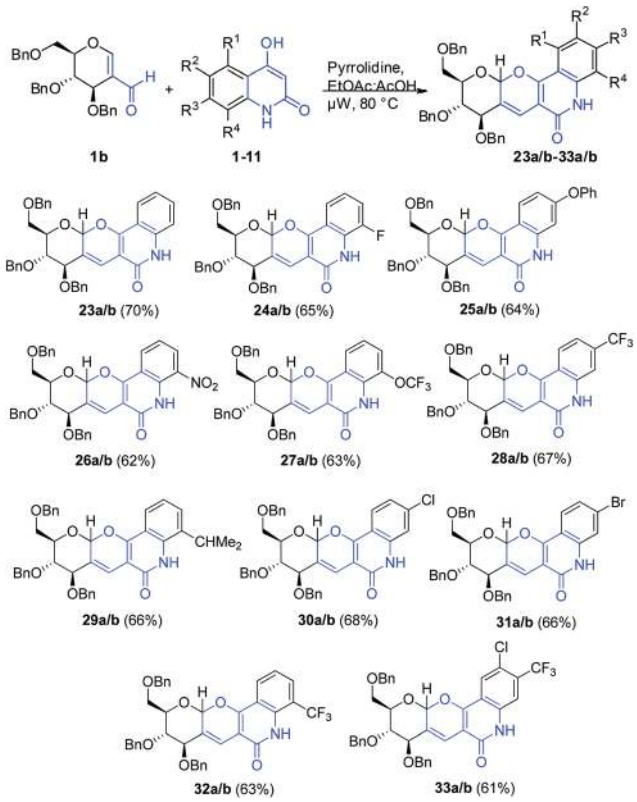



Fig. 2 Proposed reaction mechanism.

as compared to other mono- and di-substituted 4-hydroxyquinolones (Scheme 1).

The mechanism of this formal [3 + 3] cycloaddition reaction can be proposed as shown in Fig. 2. Pyrrolidine attacks the 2-*C*-formyl galactal **1a** to form an intermediate **I**, which undergoes dehydration to form the iminium ion intermediate **II**. The resulting iminium ion (**II**) is a better electrophile than **1a** and undergoes selective nucleophilic *C*-1,2-addition with 4-hydroxyquinolone to furnish **III**. Intermediate **III** rearranges to **IV**, which transforms into 1-oxatriene intermediate **V** through β-elimination. Finally, **V** undergoes 6π-electron electrocyclization to afford the corresponding pyrano[3,2-*c*]quinolone with excellent diastereoselectivity. There is evidence for the reversibility of the 6π-electron electrocyclization of the ring closure of 1-oxatrienes reported in the literature.[37] Therefore, we can postulate that thermodynamically more stable diastereoisomers are formed and the final step equilibrium is shifted toward the product side (Fig. 2).

Furthermore, when 4-hydroxyquinolone **1** was reacted with 2-*C*-formyl glucal **1b** under optimized microwave reaction conditions (μW, 80 °C, EtOAc : AcOH, pyrrolidine), it afforded unexpectedly an epimeric mixture (1 : 1) of carbohydrate fused pyrano[3,2-*c*]quinolone **23a/b** in a good yield (70%). The stereoselectivity in this case could not be restored even after using different organocatalysts and different reaction conditions. As mentioned in the proposed mechanism, this type of reaction proceeds through a 1-oxatriene intermediate followed by 6π-electron electrocyclization and the reversibility of this cyclization was well studied and reported in the literature.[37] Based on the literature, we can presume that fused pyrano[3,2-*c*] quinolone **23a** is equilibrating with **23b** through a common 1-oxatriene intermediate in a reversible fashion and furnishing a mixture of epimers **23a/b**. We tried to isolate one stereoisomer **23a** through a column but it again becomes a mixture of epimers **23a/b** (NMR and TLC). This further confirmed that both isomers equilibrated in a reversible fashion. As shown in Scheme 2, 2-*C*-formyl glucal **1b** was successfully coupled with various other substituted 4-hydroxyquinolones **1–11** to afford the respective pyrano[3,2-*c*]quinolones **23a/b–33a/b** in acceptable to good yields as an epimeric mixture (dr ~ 1 : 1). Similarly, different substituents at the $R^1$, $R^2$, $R^3$ and $R^4$ positions on 4-hydroxyquinolone remarkably affect neither the yield nor




Scheme 2 Synthesis of 2-*C*-formyl glucal fused pyrano[3,2-*c*]quinolones **23a/b–33a/b**.

the reaction completion time when coupled with 2-*C*-formyl glucal **1b** (Scheme 2). Thus, a library of twenty-three different diverse carbohydrate fused pyrano[3,2-*c*]quinolone derivatives were prepared and the preliminary anticancer activity was examined *in vitro* through cellular assays using MCF-7 and HepG2 cancer cell lines and the bioactivity results are discussed below.

When *N*-protected 4-hydroxyquinolone **34** was reacted with 2-*C*-formyl galactal **1a** under optimized reaction conditions, it furnished carbohydrate fused *N*-methyl pyrano[3,2-*c*]quinolones **35** in 71% isolated yield (Scheme 3).

The antiproliferative activity of all synthesized carbohydrate-fused pyrano[3,2-*c*]quinolones **12–22** and **23a/b–33a/b** ($n$ = 22) was investigated at 25 μM concentration by cell viability assays against MCF-7 and HepG2 cell lines using doxorubicin (25 μM) as the positive control (Table 2). The results showed moderate activity with all tested compounds in MCF-7 (breast cancer cells). A better activity with compounds **19**, **24a/b**, **30a/b** and **33a/b** was observed with 54.8%, 47.1%,


Scheme 3 Synthesis of *N*-methyl pyrano[3,2-*c*]quinolones **35**.

Table 2 Anticancer screening results

| Compound[a] | Cell viability (%) ± SD | |
|---|---|---|
| | MCF-7 | HepG2 |
| **12** | 80.4 ± 1.13 | 93.6 ± 2.40 |
| **13** | 85.3 ± 1.06 | 81.9 ± 3.81 |
| **14** | 77.1 ± 1.62 | 99.4 ± 3.81 |
| **15** | 77.5 ± 2.82 | 37.6 ± 2.40 |
| **16** | 77.0 ± 1.41 | 89.9 ± 3.25 |
| **17** | 70.2 ± 1.06 | 91.3 ± 2.19 |
| **18** | 86.1 ± 2.12 | 92.7 ± 1.62 |
| **19** | 54.8 ± 2.61 | 84.6 ± 2.47 |
| **20** | 97.3 ± 0.91 | 97.8 ± 3.04 |
| **21** | 77.4 ± 1.20 | 92.5 ± 2.68 |
| **22** | 70.9 ± 1.90 | 94.2 ± 1.34 |
| **23a/b** | 84.3 ± 5.86 | 94.4 ± 2.26 |
| **24a/b** | 47.1 ± 2.96 | 93.8 ± 2.33 |
| **25a/b** | 82.1 ± 3.53 | 97.6 ± 3.39 |
| **26a/b** | 95.4 ± 4.87 | 82.0 ± 1.34 |
| **27a/b** | 96.1 ± 3.60 | 96.9 ± 2.89 |
| **28a/b** | 99.5 ± 2.12 | 80.6 ± 3.32 |
| **29a/b** | 98.9 ± 1.55 | 88.6 ± 1.90 |
| **30a/b** | 18.8 ± 1.83 | 49.8 ± 1.76 |
| **31a/b** | 76.8 ± 2.96 | 89.4 ± 3.25 |
| **32a/b** | 73.0 ± 2.26 | 74.4 ± 3.32 |
| **33a/b** | 42.3 ± 1.62 | 36.7 ± 3.60 |
| Doxorubicin | 15.3 ± 0.77 | 15.2 ± 0.84 |

[a] 25 μM concentration of each compound used for MCF-7 and HepG2 cells.

18.8% and 42.3% cell viability, respectively. However, the anticancer activity with compounds **15**, **30a/b** and **33a/b** against HepG2 cells was observed with cell viability of 37.6%, 49.8% and 36.7%, respectively (Table 2). These active compounds were then further tested at different lower concentrations, 1 μM, 5 μM, 10 μM and 20 μM (ESI†), against both cell lines in order to find out the $IC_{50}$ values of the active compounds.

From the study, it has been found that carbohydrate-fused pyrano[3,2-*c*]quinolone compounds **19** and **24a/b** exhibited growth inhibitory potencies selectively against MCF-7 cells, whereas compound **15** showed an inhibitory potency selective against HepG2 cells. Compounds **30a/b** and **33a/b** showed a high growth inhibition against the MCF-7 cell line with half-maximal inhibitory concentration ($IC_{50}$) values of 9.68 and 5.33 μM, respectively, whereas the $IC_{50}$ value for compound **33a/b** against HepG2 was 3.53 μM (Fig. 3).

## Conclusion

In summary, we have developed a new and efficient method for the synthesis of a natural product inspired library of carbohydrate-fused pyrano[3,2-*c*]quinolone hybrids. The method involves the microwave assisted, facile synthesis of carbohydrate-fused pyrano[3,2-*c*]quinolones, starting from freshly prepared diverse 4-hydroxyquinolones and 2-*C*-formyl glycals, in good to very good yields. The method is endowed with several unique merits including simple reaction conditions, shorter reaction time, broad substrate scope and no metal catalysis. The method has been successfully applied to diverse substituted 4-hydroxyquinolones bearing electron donating and withdrawing groups, and a library of twenty-three carbohydrate-fused pyrano[3,2-*c*]quinolone hybrid compounds were prepared. The carbohydrate part or free NH in these hybrid molecules can also be further modified and diversified to enhance their biological activities during the lead optimization process. We have shown that an *N*-methyl carbohydrate-fused pyrano[3,2-*c*]quinolone hybrid can be obtained by using this protocol. Subsequently, we demonstrated that the selected library members displayed low micromolar (3.53–9.68 μM) and selective antiproliferative activity.

## Experimental section

### General experimental methods

All experiments were performed in an oven-dried apparatus and in anhydrous solvents using a CEM microwave synthesizer. High resolution mass spectra were recorded on a quadrupole/TOF mass spectrometer with an ESI source. The solvents were distilled using a standard distillation procedure and

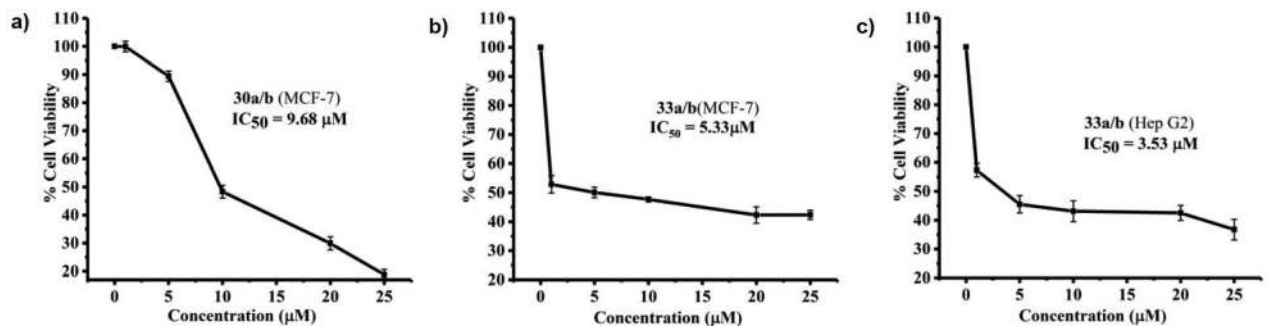



Fig. 3 Antiproliferative activity of carbohydrate fused pyrano[3,2-c]quinolones. To calculate the half-maximal inhibitory concentration ($IC_{50}$) values of compounds **30a/b** and **33a/b**, MCF-7 or HepG2 cells were treated with different concentrations (1, 5, 10, 20 and 25 μM) for 48 h. The percent cell viability was determined by cell viability assays. The $IC_{50}$ values were determined by plotting the values of percent cell viability against the concentration of each of these compounds. (a–b) The $IC_{50}$ values for compounds **30a/b** and **33a/b** against MCF-7 cells were 9.68, and 5.33 μM, respectively. (c) The $IC_{50}$ value for compounds **33a/b** against HepG2 cells was 3.53 μM. The experiments were performed in triplicates, $n$ = 3, and the ±SD value was calculated for each data point.

stored in 4 Å and 3 Å molecular sieves. $^1$H (400 MHz) and $^{13}$C (100 MHz) NMR spectra were recorded with a Bruker AMX-400 MHz instrument. The $^1$H and $^{13}$C chemical shifts are referenced to the solvent residual signals ($CDCl_3$: $\delta$ 7.26 for $^1$H NMR and $\delta$ 77.16 for $^{13}$C NMR) and reported in parts per million (ppm) at 25 °C; the peak at $\delta$ 1.56 corresponds to water (O–H) in $CDCl_3$. The coupling constants are expressed in hertz (Hz). The reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254); the spots were visualized with phosphomolybdic acid and 10% $H_2SO_4$ in ethanol. The melting points (m.p.) were uncorrected and recorded with an electrothermal melting point apparatus. 4-Hydroxyquinolones (**1–11** and **34**), 2-*C*-formyl galactal **1a** and 2-*C*-formyl glucal **1b** were freshly prepared in the laboratory as per reported procedures. Organocatalysts (L-prolin, pyrrolidine and piperidine) and different anilines used for preparing 4-hydroxyquinolones were purchased from Sigma-Aldrich.

**General experimental procedure for reaction optimization.** To a 10 mL microwave vial, 3,4,6-tri-*O*-benzyl-2-*C*-formyl D-galactal **1a** (100 mg, 0.225 mmol) and 4-hydroxyquinolone **1** (43.51 mg, 0.270 mmol) were added in different combinations of organocatalysts (pyrrolidine, piperidine and L-proline, 0.112 mmol) in 2 mL of various solvents (*viz*. 1% acetic acid in toluene, EtOAc and acetonitrile) and heated at 80 °C (100 W) for 15 min under microwave conditions. The completion of the reaction was monitored by TLC ($R_f$ = 0.56, 3 : 7 = ethyl acetate : hexane, v/v). After completion, the reaction was quenched by adding 5 mL of $NaHCO_3$ solution and the reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under vacuum to obtain the crude product. The crude product was purified by flash column chromatography, which furnished the desired product **12** in a good yield (71%) as an amorphous solid. Different organocatalysts and solvent combinations furnished the same product **12** in different yield percentages (Table 1).

### General experimental procedure for the synthesis of compounds 12–22, 35 and 23a/b–33a/b

A mixture of 3,4,6-tri-*O*-benzyl-2-*C*-formyl D-galactal **1a** (200 mg, 0.450 mmol), various 4-hydroxyquinolones **1–11** (0.540 mmol) and pyrrolidine (8 mg, 0.225 mmol) was heated in a microwave vial using 2 mL of EtOAc : AcOH (1 : 0.01) at 80 °C (100 W) for 15 min under microwave conditions. The progress of the reaction was monitored by TLC (3 : 7 = ethyl acetate : hexane, v/v). After completion, the reaction was quenched by adding 5 mL of $NaHCO_3$ solution and the reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under vacuum to obtain the crude product. The crude product was purified by flash column chromatography to obtain the pure products **12–22** in good to very good yields (Scheme 1). A similar reaction protocol was adopted for the synthesis of compounds **23a/b–33a/b** starting from 3,4,6-tri-*O*-benzyl-2-*C*-formyl D-glucal **1b** and the respective 4-hydroxyquinolones **1–11** (Scheme 2). The reaction time taken in the case of compounds **22** and **33a/b** was 20 min. Compounds **23a/b–33a/b** were isolated as an inseparable mixture (1 : 1) of two epimers. Therefore, in the $^1$H NMR spectra of these compounds, protons were integrated and reported as a doubled number.

**(8*R*,9*R*,10*R*)8,9-Bis(benzyloxy)10((benzyloxy)methyl)8,9,10,11a-tetrahydropyrano[3′,2′,5,6] pyrano[3,2-*c*]quinolin-6(5*H*)-one (12).** Purple amorphous solid, m.p.: 190 °C; yield 71%, $R_f$ = 0.56 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.58 (brs, 1H, NH), 7.95 (d, $J$ = 8.0 Hz, 1H, H-1), 7.47–7.19 (m, 18H, ArH), 7.17 (s, 1H, H-7), 6.10 (s, 1H, H-11a), 4.98 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.88 (d, $J$ = 12.4 Hz, 1H, $CH_2Ph$), 4.71 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.65 (d, $J$ = 12.4 Hz, 1H, $CH_2Ph$), 4.47 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.40 (d, $J$ = 11.2 Hz, 1H, $CH_2Ph$), 4.17 (brs, 1H, H-8), 4.00 (brs, 1H, H-9), 3.87 (t, $J$ = 6.8 Hz, 1H, H-10), 3.62 (dd, $J$ = 9.2 Hz and $J$ = 6.0 Hz, 1H, H-13a), 3.52 (dd, $J$ = 9.6 Hz and $J$ = 6.4 Hz, 1H, 13b), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.3, 154.8, 138.3, 137.8, 137.7, 137.4, 130.9, 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.6, 127.4, 125.8, 122.5, 122.3, 115.8, 114.1, 112.9 (C-7), 104.3, 97.0 (C-11a), 79.7 (C-8), 76.4 (C-9), 75.0 (C-10), 74.2, 73.5, 71.7 (3 × $CH_2Ph$), 68.8 (C-13), HRMS(ESI), calcd, $m/z$ $C_{37}H_{33}NO_6$, $[M + H]^+$ 588.2381; found: 588.2405.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-4-fluoro-8,9,10,11a-tetrahydro-pyrano[3′,2′,5,6]pyrano[3,2-*c*] quinolin-6(5*H*)-one (13).** Yellow amorphous solid, m.p.: 140 °C; yield 68%, $R_f$ = 0.64 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.79 (s, 1H), 7.72 (d, $J$ = 8.4 Hz, 1H, H-1), 7.39–7.09 (m, 17H, ArH), 7.19 (s, 1H, H-7), 6.09 (s, 1H, H-11a), 4.95 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.85 (d, $J$ = 12.4 Hz, 1H, $CH_2Ph$), 4.69 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.62 (d, $J$ = 12.4 Hz, 1H, $CH_2Ph$), 4.47 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.42 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.16 (brs, 1H, H-8), 4.00 (brs, 1H, H-9), 3.85 (m, 1H, H-10), 3.62(dd, $J$ = 8.8 Hz and $J$ = 6.4 Hz, 1H, H-13a), 3.52 (dd, $J$ = 9.6 Hz and $J$ = 6.4 Hz, 1H, C-13b), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 160.7, 146.5, 140.9, 140.0, 138.2, 137.6, 128.6, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.9, 126.7, 126.7, 122.0, 120.9, 118.3, 115.6, 114.7, 112.6 (C-7), 105.4, 96.9 (C-11a), 79.5 (C-8), 76.4 (C-9), 75.1 (C-10), 74.3, 73.6, 71.7 (3 × $CH_2Ph$), 68.8 (C-13). HRMS(ESI), calcd, $m/z$ $C_{37}H_{32}FNO_6$, $[M + H]^+$ 606.2286; found: 606.2277.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-3-phenoxy-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*] quinolin-6(5*H*)-one (14).** Off-white solid, m.p.: 172 °C; yield 69%, $R_f$ = 0.64 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.18 (s, 1H, NH), 7.88 (d, $J$ = 8.4 Hz, 1H, H-1), 7.39–7.05 (m, 20H, ArH), 6.86–6.76 (m, 3H, ArH), 6.07 (s, 1H, H-11a), 4.96 (d, $J$ = 12.4 Hz, 1H, $CH_2Ph$), 4.86 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.70 (d, $J$ = 11.2 Hz, 1H, $CH_2Ph$), 4.63 (d, $J$ = 12.4 Hz, 1H, $CH_2Ph$), 4.46 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.39 (d, $J$ = 11.2 Hz, 1H, $CH_2Ph$), 4.15 (brs, 1H, H-8), 3.98 (brs, 1H, H-9), 3.84 (t, $J$ = 4.8 Hz, 1H, H-10), 3.61 (dd, $J$ = 7.8 Hz and $J$ = 6.0 Hz, 1H, H-13a), 3.51 (dd, $J$ = 8.4 Hz and $J$ = 6.4 Hz, 1H, H-13b); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.3, 160.1, 154.8,

139.0, 138.3, 137.8, 129.9, 128.6, 128.4, 128.1, 127.9, 127.8, 127.6, 127.4, 125.3, 125.0, 124.8, 124.3, 119.9, 119.1, 118.0, 113.4, 112.9 (C-7), 109.6, 103.8, 102.9, 97.0 (C-11a), 79.6 (C-8), 75.9 (C-9), 75.0 (C-10), 74.2, 73.5, 71.7 (3 × $CH_2$Ph), 68.8 (C-13), HRMS(ESI), calcd, *m*/*z* $C_{43}H_{37}NO_7$, $[M + H]^+$ 680.2643; found: 680.2634.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-1-((benzyloxy)methyl)-4-nitro-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (15).** Orange amorphous solid, m.p.: 180 °C; yield 65%, $R_f$ = 0.58 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 11.12 (brs, 1H, NH), 8.47 (d, *J* = 8.4 Hz, 1H, H-3), 8.32 (d, *J* = 7.6 Hz, 1H, H-1), 7.40–7.27 (m, 16H, ArH), 7.17 (s, 1H, H-7), 6.11 (s, 1H, H-11a), 4.93 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.85 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.68 (d, *J* = 11.2 Hz, 1H, $CH_2$Ph), 4.63 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.47 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.40 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.18 (brs, 1H, C-8), 4.00 (d, *J* = 2.0 Hz, 1H, H-9), 3.87 (m, 1H, H-10), 3.61 (dd, *J* = 9.6 Hz and *J* = 6.0 Hz, 1H, H-13a), 3.49 (dd, *J* = 9.6 Hz and *J* = 6.4 Hz, 1H, H-13b), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 160.1, 153.0, 140.0, 138.0, 137.6, 137.5, 132.9, 130.5, 128.6, 128.5, 128.4, 127.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 126.9, 121.0, 116.9, 112.0 (C-7), 105.7, 96.9 (C-11a), 79.5 (C-8), 76.58 (C-9), 75.24 (C-10), 74.4, 73.6, 71.8 (3 × $CH_2$Ph), 68.7 (C-13), HRMS(ESI), calcd, *m*/*z* $C_{37}H_{32}N_2O_8$, $[M + H]^+$ 633.2231; found: 633.2224.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-4-trifluoromethoxy-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (16).** Yellow amorphous solid, m.p.: 195 °C; yield 63%, $R_f$ = 0.71 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.92 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H, H-1), 7.39–7.26 (m, 16H, ArH), 7.18 (s, 1H, H-7), 6.09 (s, 1H, H-11a), 4.95 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.85 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.68 (d, *J* = 11.6 Hz, 1H, $CH_2$Ph), 4.62 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.46 (d, *J* = 11.6 Hz, 1H, $CH_2$Ph), 4.40 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.16 (brs, 1H, H-8), 3.99 (brs, 1H, H-9), 3.86 (t, *J* = 6.4 Hz, 1H, H-10), 3.61 (dd, *J* = 9.2 Hz and *J* = 6.4 Hz, 1H, H-13a), 3.50 (dd, *J* = 9.6 Hz and *J* = 6.4 Hz, 1H, H-13b), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 161.0 (C-6), 153.8, 138.2, 137.6, 136.1, 129.9, 128.3, 128.5, 128.4, 128.2, 127.9, 127.8, 127.8, 127.6, 127.3, 126.9, 121.7, 121.6, 121.1, 119.3, 116.1, 112.6 (C-7), 106.5, 96.9 (C-11a), 79.6 (C-8), 76.5 (C-9), 75.1 (C-10), 74.3, 73.6, 71.7 (3 × $CH_2$Ph), 68.8 (C-13), HRMS(ESI), calcd, *m*/*z* $C_{38}H_{32}F_3NO_7$, $[M + H]^+$ 672.2204; found: 672.2204.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-3-trifluoromethyl-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (17).** Yellow amorphous solid, m.p.: 139 °C; yield 66%, $R_f$ = 0.41 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz), $\delta$ 10.95 (s, 1H, NH), 8.04 (d, *J* = 7.6 Hz, 1H, H-1), 7.50–7.29 (m, 18H, ArH), 6.13 (s, 1H, H-11a), 4.97 (d, *J* = 10.4 Hz, 1H, $CH_2$Ph), 4.87 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.71 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.65 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.47 (d, *J* = 11.6 Hz, 1H, $CH_2$Ph), 4.41 (d, *J* = 11.2 Hz, 1H, $CH_2$Ph), 4.19 (brs, 1H, H-8), 4.02 (brs, 1H, H-9), 3.88 (m, 1H, H-10), 3.64 (dd, *J* = 9.6 Hz and *J* = 5.2 Hz, 1H, H-13a), 3.52 (dd, *J* = 9.0 Hz and *J* = 5.2 Hz, 1H, H-13b), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.4, 158.4, 153.8, 138.1, 138.0, 137.6, 137.4, 136.8, 128.6, 128.4, 128.2, 128.0, 127.7, 127.4, 126.1, 124.9, 123.5, 118.7, 112.4 (C-7), 106.0, 96.9 (C-11a), 89.6, 79.5 (C-8), 76.4 (C-9), 75.1 (C-10), 74.3, 73.6, 71.8 (3 × $CH_2$Ph), 68.7 (C-13), HRMS(ESI), calcd, *m*/*z* $C_{38}H_{32}F_3NO_6$, $[M + H]^+$ 656.2254; found: 656.2276.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-4-isopropyl-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (18).** Amorphous solid, m.p.: 175 °C; yield 65%, $R_f$ = 0.64 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.81 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H, H-1), 7.39–7.19 (m, 16H, ArH), 7.18 (s, 1H, H-7), 6.09 (s, 1H, H-11a), 4.96 (d, *J* = 11.6 Hz, 1H, $CH_2$Ph), 4.86 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.69 (d, *J* = 11.6 Hz, 1H, $CH_2$Ph), 4.63 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.46 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.40 (d, *J* = 11.6 Hz, 1H, $CH_2$Ph), 4.16 (brs, 1H, H-8), 3.99 (brs, 1H, H-9), 3.85 (t, *J* = 6.0 Hz, 1H, H-10), 3.62 (dd, *J* = 8.9 Hz and *J* = 6.4 Hz, 1H, H-13a), 3.52 (dd, *J* = 8.9 Hz and *J* = 6.4 Hz, 1H, H-13b), 3.16 (m, 1H, CH of isopropyl), 1.33 (d, 6H, $Me_2$),$^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 161.5, 155.1, 138.3, 137.8, 134.5, 133.3, 128.5, 128.4, 128.1, 127.9, 127.8, 127.6, 127.3, 127.2, 125.8, 122.2, 120.5, 114.3, 112.8 (C-7), 104.0, 97.0 (C-11a), 79.7 (C-8), 76.4 (C-9), 75.0 (C-10), 74.2, 73.5, 71.7 (3 × $CH_2$Ph), 26.8 (CH of –$CHMe_2$), 22.8 (Me), 22.7 (Me), HRMS(ESI), calcd, *m*/*z* $C_{40}H_{39}NO_6$, $[M + K]^+$ 668.2409; found: 668.2422.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-3-chloro-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (19).** Yellow amorphous solid, m.p.: 185 °C; yield 64%, $R_f$ = 0.60 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.02 (brs, 1H, NH), 7.94 (d, *J* = 8 Hz, 1H, H-1), 7.41–7.16 (m, 18H, ArH), 6.10 (s, 1H, H-11a), 4.97 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.87 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.71 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.64 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.46 (d, *J* = 11.6 Hz, 1H, $CH_2$Ph), 4.40 (d, *J* = 11.6 Hz, 1H, $CH_2$Ph), 4.17 (brs, 1H, H-8), 4.00 (brs, 1H, H-9), 3.87–3.84 (m, 1H, H-10), 3.62 (dd, *J* = 9.6 Hz and *J* = 5.6 Hz, 1H, H-13a), 3.52 (dd, *J* = 9.6 Hz and *J* = 6.4 Hz, 1H, H-13b), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.2, 154.8, 138.3, 137.8, 137.7, 137.3, 130.9, 128.6, 128.4, 128.2, 128.0, 129.9, 127.8, 127.7, 127.6, 127.4, 125.8, 122.6, 122.4, 115.8, 114.1, 112.9 (C-7), 104.3, 97.0 (C-11a), 79.6 (C-8), 76.4 (C-9), 75.0 (C-10), 74.2, 73.5, 71.7, 68.8 (C-13), HRMS(ESI), calcd, *m*/*z* $C_{37}H_{32}ClNO_6$, $[M + Na]^+$ 644.187; found: 644.1916.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-3-bromo-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (20).** Off-white amorphous solid, m.p.: 150 °C; yield 63%, $R_f$ = 0.45 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 9.71 (brs, 1H), 7.95 (d, *J* = 7.6 Hz, 1H, H-1), 7.45–7.18 (m, 17H, ArH), 7.17 (s, 1H, H-7), 6.10 (s, 1H, H-11a), 4.96 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.87 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.70 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.64 (d, *J* = 12.4 Hz, 1H, $CH_2$Ph), 4.46 (d, *J* = 12.0 Hz, 1H, $CH_2$Ph), 4.40 (d, *J* = 11.6 Hz, 1H, $CH_2$Ph), 4.17 (brs, 1H, H-8), 4.00 (brs, 1H, H-9), 3.86 (m, 1H, H-10), 3.62 (dd, *J* = 9.6 Hz and *J* = 5.6 Hz, 1H, H-13a), 3.51 (dd, *J* = 9.6 Hz and *J* = 6.7 Hz, 1H, H-13b), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.2, 154.8, 138.3, 137.8, 137.7,

137.3, 130.9, 128.6, 128.4, 128.2, 128.0, 129.9, 127.8, 127.7, 127.6, 127.4, 125.8, 122.6, 122.4, 115.8, 114.1, 112.9 (C-7), 104.3, 97.0 (C-11a), 79.6 (C-8), 76.4 (C-9), 75.0 (C-10), 74.2, 73.5, 71.7 (3 × $CH_2Ph$), 68.8 (C-13), HRMS(ESI), calcd, *m*/*z* $C_{37}H_{32}BrNO_6$, $[M + H]^+$ 666.1486; found: 666.1500.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-4-trifluoromethyl-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (21).** Brown amorphous solid, m.p.: 130 °C; yield 67%, $R_f$ = 0.79 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.17 (d, *J* = 8.0 Hz, 1H, H-3), 7.75 (d, *J* = 7.6 Hz, 1H, H-1), 7.39–7.27 (m, 17 H, ArH), 7.17 (s, 1H, H-7), 6.10 (s, 1H, H-11a), 4.95 (d, *J* = 11.6 Hz, 1H, $CH_2Ph$), 4.85 (d, *J* = 12.4 Hz, 1H, $CH_2Ph$), 4.68 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.63 (d, *J* = 12.4 Hz, 1H, $CH_2Ph$), 4.47 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.40 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.16 (brs, 1H, H-8), 3.99 (brs, 1H, H-9), 3.86 (t, *J* = 6.4 Hz, 1H, H-10), 3.61 (dd, *J* = 9.2 Hz and *J* = 6.0 Hz, 1H, H-13a), 3.50 (dd, *J* = 9.2 Hz and *J* = 6.4 Hz, 1H, H-13b), $^{13}$C NMR, ($CDCl_3$, 100 MHz) $\delta$ 160.3 (C-6), 153.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 127.9, 127.9, 127.8, 127.6, 127.4, 127.2, 126.9, 121.4, 115.6, 112.3 (C-7), 106.2, 102.7, 96.9 (C-11a), 79.5 (C-8), 76.5 (C-9), 75.1 (C-10), 74.3, 73.6, 71.7 (3 × $CH_2Ph$), 68.7 (C-13). HRMS(ESI), calcd, *m*/*z* $C_{38}H_{32}F_3NO_6$, $[M + H]^+$ 656.2254; found: 656.2276.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-2-chloro-3-trifluoromethyl-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (22).** Off-white amorphous solid, m.p.: 182 °C; yield 68%, $R_f$ = 0.56 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 11.32 (brs, 1H, NH), 8.00 (s, 1H, H-4), 7.61 (s, 1H, H-1), 7.42–7.24 (m, 15H, ArH), 7.20 (s, 1H, H-7), 6.12 (s, 1H, H-11a), 4.99 (d, *J* = 11.6 Hz, 1H, $CH_2Ph$), 4.86 (d, *J* = 12.4 Hz, 1H, $CH_2Ph$), 4.72 (d, *J* = 11.6 Hz, 1H, $CH_2Ph$), 4.65 (d, *J* = 12.4 Hz, 1H, $CH_2Ph$), 4.48 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.41 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.19 (brs, 1H, H-8), 4.04 (brs, 1H, H-9), 3.89 (t, *J* = 5.6 Hz, 1H, H-10), 3.64 (dd, *J* = 9.2 Hz and *J* = 6.0 Hz, 1H, H-13a), 3.53 (dd, *J* = 9.6 Hz and *J* = 6.4 Hz, 1H, H-13b), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 161.6, 152.5, 138.0, 137.5, 128.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.4, 125.0, 112.3 (C-7), 106.9, 96.9 (C-11a), 79.4 (C-8), 76.4 (C-9), 75.1 (C-10), 74.4, 73.6, 71.8 (3 × $CH_2Ph$), 68.5 (C-13), HRMS(ESI), calcd, *m*/*z* $C_{38}H_{31}ClF_3NO_6$, $[M + K]^+$ 728.1424; found: 728.1420.

**(8*R*,9*S*,10*R*)8,9-Bis(benzyloxy)10((benzyloxy)methyl)8,9,10,11a-tetrahydropyrano [3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (23a/b).** Yellow amorphous solid, m.p.: 180 °C; yield 70%, $R_f$ = 0.41 (4 : 6 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 11.82 (s, 1H, NH), 8.00–7.95 (m, 2H), 7.49–7.18 (m, 37H, Ar H), 7.18 (s, 1H, H-7 of 23a), 7.07 (s, 1H, H-7 of 23b), 6.61 (s, 1H, H-11a of 23a), 6.01 (s, 1H, H-11a of 23b), 4.99 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.95 (d, *J* = 10.8 Hz, 1H, $CH_2Ph$), 4.75 (d, *J* = 12 Hz, 1H, $CH_2Ph$), 4.68 (d, *J* = 12.8 Hz, 1H, $CH_2Ph$), 4.62 (d, *J* = 12.8 Hz, 1H, $CH_2Ph$), 4.57 (d, *J* = 11.2 Hz, 1H, $CH_2Ph$), 4.54–4.49 (m, 3H, $CH_2Ph$), 4.50 (d, *J* = 11.2 Hz, 1H, $CH_2Ph$), 4.44 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.37 (d, *J* = 11.6 Hz, 1H, $CH_2Ph$), 4.26–4.23 (m, 2H), 3.86–3.67 (m, 8H), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.3, 157.8, 154.6, 138.1, 137.9, 137.8, 137.8, 137.7, 137.5, 128.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.9, 127.6, 127.6, 122.5, 122.4, 127.3, 126.2, 123.3, 123.2, 122.6, 122.5, 122.4, 120.9, 116.0, 115.9, 114.2, 114.0, 111.5, 109.7, 106.3, 104.3, 102.0, 98.5, 96.2, 82.3, 81.1, 79.0, 78.8, 76.4, 75.1, 73.5, 73.3, 73.3, 73.0, 72.9, 71.5, 70.1, 69.0, 68.7, HRMS(ESI), calcd, *m*/*z* $C_{37}H_{33}NO_6$, $[M + H]^+$ 588.2381; found: 588.2405.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-4-fluoro-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (24a/b).** Brown amorphous solid, m.p.: 120 °C; yield 65%, $R_f$ = 0.60 (1 : 1 = ethyl acetate : hexane, v/v), $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.62 (brs, 2H, NH), 7.77 (s, 2H), 7.42–7.15 (m, 34H, ArH), 7.10 (s, 1H, H-7 of 24a), 6.99 (s, 1H, H-7 of 24b), 6.59 (s, 1H, H-11a of 24a), 5.99 (s, 1H, H-11a of 24b), 5.01–4.89 (m, 2H, $CH_2Ph$), 4.71–4.62 (m, 4H, $CH_2Ph$), 4.59 (d, *J* = 12.0 Hz, 2H, $CH_2Ph$), 4.52 (d, *J* = 11.2 Hz, 1H, $CH_2Ph$), 4.44 (d, *J* = 12.4 Hz, 1H, $CH_2Ph$), 4.40 (d, *J* = 10.4 Hz, 1H, $CH_2Ph$), 4.33 (d, *J* = 11.2 Hz, 1H, $CH_2Ph$), 4.20 (s, 2H), 3.99 (s, 1H), 3.82–3.69 (m, 7H), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 160.9, 160.8, 156.8, 138.3, 137.8, 137.6, 137.4, 137.2, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.1, 126.9, 122.1, 116.0, 111.2, 104.9, 98.7, 96.1, 82.1, 81.0, 78.7, 75.1, 73.5, 73.3, 72.9, 72.4, 71.5, 70.6, 70.1, 68.3, 67.7; HRMS(ESI), calcd, *m*/*z* $C_{37}H_{32}FNO_6$, $[M + H]^+$ 606.2286; found: 606.2277.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-3-phenoxy-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (25a/b).** Light yellow amorphous solid, m.p.: 160 °C; yield 64%, $R_f$ = 0.66 (1 : 1 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.81 (brs, 1H, NH), 10.20 (brs, 1H, NH), 7.94–7.89 (m, 2H), 7.43–6.99 (m, 44H, ArH), 6.96 (s, 1H, H-7 of 25a) 6.75 (s, 1H, H-7 of 25b), 6.56 (s, 1H, H-11a of 25a), 5.97 (s, 1H, H-11a of 25b), 4.96 (d, *J* = 12.8 Hz, 1H, $CH_2Ph$), 4.90 (d, *J* = 8.8 Hz, 1H, $CH_2Ph$), 4.70 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.65 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.60–4.33 (m, 8H, $CH_2Ph$), 4.21–4.19 (m, 1H), 3.85–3.49 (m, 9H), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.4, 160.8, 160.2, 157.8, 156.7, 156.6, 154.6, 140.0, 139.1, 138.1, 137.9, 137.7, 137.3, 130.0, 129.6, 129.4, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 125.4, 124.5, 124.4, 123.4, 122.1, 120.1, 120.0, 119.9, 118.2, 116.7, 113.5, 111.6, 109.5, 104.0, 98.6, 96.1, 82.2, 81.0, 79.0, 78.7, 76.3, 75.1, 73.5, 73.3, 73.2, 72.7, 71.5, 70.0, 69.0, 68.6, HRMS(ESI), calcd, *m*/*z* $C_{43}H_{37}NO_7$, $[M + H]^+$ 680.2643; found: 680.2634.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-4-nitro-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (26a/b).** Yellow amorphous solid, m.p.: 179 °C; yield 62%, $R_f$ = 0.72 (1 : 1 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 11.11 (brs, 1H), 11.08 (brs, 1H), 8.48–8.44 (m, 2H), 8.33–8.31 (m, 2H), 7.40–7.08 (m, 30H, ArH), 7.05 (d, *J* = 1.6 Hz, 1H), 6.94 (d, *J* = 1.6 Hz, 1H), 6.80 (s, 1H, H-7 of 26a), 6.58 (s, 1H, H-7 of 26b), 6.36 (s, 1H, H-11a of 26a), 5.97 (s, 1H, H-11a of 26b), 4.91 (d, *J* = 11.6 Hz, 1H, $CH_2Ph$), 4.88 (d, *J* = 10.8 Hz, 1H, $CH_2Ph$), 4.70 (d, *J* = 10.2 Hz, 1H, $CH_2Ph$), 4.67 (d, *J* = 10.2 Hz, 1H, $CH_2Ph$), 4.61 (d, *J* = 12.0 Hz, 1H, $CH_2Ph$), 4.56 (d, *J* = 9.6 Hz, 1H, $CH_2Ph$), 4.53 (d, *J* = 9.6 Hz, 1H, $CH_2Ph$), 4.51 (d, *J* = 9.8 Hz, 1H, $CH_2Ph$), 4.48 (d, *J* = 9.8 Hz, 1H, $CH_2Ph$), 4.42 (d, *J* = 9.8 Hz, 1H, $CH_2Ph$), 4.38 (d, *J* = 9.8 Hz, 1H, $CH_2Ph$), 4.29

(d, $J$ = 11.2 Hz, 1H, $CH_2Ph$), 4.20–4.18 (m, 2H), 3.79–3.57 (m, 8H), $^{13}$CNMR ($CDCl_3$, 100 MHz) $\delta$ 160.0, 156.2, 152.9, 137.6, 137.5, 137.3, 137.1, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 121.2, 121.1, 110.6, 96.2, 95.4, 82.1, 81.0, 78.6, 78.5, 75.5, 75.2, 73.6, 73.5, 73.3, 73.0, 71.6, 71.2, 70.3, 68.9, 68.5; HRMS(ESI), calcd, $m/z$ $C_{37}H_{32}N_2O_8$, $[M + H]^+$ 633.2231; found: 633.2224.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-4-trifluoromethoxy-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (27a/b).** Light yellow solid, m.p.: 130 °C; m.p.: yield 63%, $R_f$ = 0.80 (1 : 1 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.98 (brs, 1H, NH), 10.95 (brs, 1H, NH), 7.96–7.91 (m, 2H, ArH) 7.46–7.15 (m, 34H, Ar H), 7.16 (s, 1H, H-7 of 27a), 7.06 (s, 1H, H-7 of 27b), 6.63 (s, 1H, H-11a of 27a), 6.01 (s, 1H, H-11a of 27b), 5.01 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.95 (d, $J$ = 10.8 Hz, 1H, $CH_2Ph$), 4.73 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.69 (d, $J$ = 12.4 Hz, 1H, $CH_2Ph$), 4.54–4.63 (m, 5H, $CH_2Ph$), 4.51 (d, $J$ = 11.2 Hz, 1H, $CH_2Ph$), 4.43 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.35 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.25–4.24 (m, 2H), 4.07–4.04 (m, 1H), 3.87–3.64 (m, 7H), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.4, 162.1, 157.0, 153.5, 153.3, 138.0, 137.8, 137.5, 137.4, 137.2, 136.9, 130.1, 128.5, 128.4, 128.3, 128.0, 127.9, 127.90, 127.7, 124.3, 122.45, 123.5, 118.7, 113.0, 111.4, 111.0, 106.9, 98.8, 96.1, 82.2, 81.0, 78.7, 76.4, 75.2, 73.5, 73.3, 73.0, 72.3, 71.5, 70.2, 68.9, 68.4, HRMS (ESI), calcd, $m/z$ $C_{38}H_{32}F_3NO_7$, $[M + H]^+$ 672.2204; found: 672.2231.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-3-trifluoromethyl-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (28a/b).** Off-white amorphous solid, m.p.: 140 °C; yield 67%, $R_f$ = 0.66 (1 : 1 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 12.04 (s, 1H, NH), 11.87 (s, 1H, NH), 8.15–8.10 (m, 1H), 7.95 (m, 1H), 7.94 (s, 1H), 7.74 (m, 1H), 7.57 (s, 1H), 7.53 (s, 1H), 7.50 (s, 1H), 7.43 (d, 3H, $J$ = 6.8 Hz), 7.15–7.38 (m, 26H, ArH), 6.63 (s, 1H, H-11a of 28a), 6.03 (s, 1H, H-11a of 28b), 4.94 (m, 2H, $CH_2Ph$), 4.70 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.67(d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.64 (brs, 1H, $CH_2Ph$), 4.58 (d, $J$ = 10.8 Hz, 1H, $CH_2Ph$), 4.44–4.53 (m, 4H, $CH_2Ph$), 4.39 (d, $J$ = 12.8, Hz, 1H, $CH_2Ph$), 4.34 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.20–4.24 (m, 2H), 3.63–3.99 (m, 8H), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 165.2, 162.1, 157.6, 157.0, 153.6, 143.5, 138.0, 137.8, 137.5, 137.4, 137.2, 136.8, 130.1, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.94, 124.3, 123.5, 118.7, 113.0, 106.9, 98.8, 96.1, 82.2, 81.0, 78.7, 76.4, 75.2, 73.5, 73.3, 73.0, 72.3, 71.5, 70.2, 68.9, 68.4, 68.3, HRMS(ESI), calcd, $m/z$ $C_{38}H_{32}F_3NO_6$, $[M + H]^+$ 656.2254; found: 656.2276.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-4-isopropy-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (29a/b).** Amorphous solid, m.p.: 110 °C; yield 66%, $R_f$ = 0.66 (1 : 1 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.22 (s, 1H, NH), 9.94 (s, 1H, NH), 8.00–7.85 (m, 2H), 7.44–7.12 (m, 33H, ArH), 7.11 (s, 1H, H-7 of 29a), 7.00 (s, 1H, H-7 of 29b), 6.56 (s, 1H, H-11a of 29a), 5.97 (s, 1H, H-11a of 29b), 4.96 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.91 (d, $J$ = 10.8 Hz, 1H, $CH_2Ph$), 4.71 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.64 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.59 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.54–4.45 (m, 5H, $CH_2Ph$), 4.40 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.33 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.21 (s, 2H), 4.00–3.99 (m, 1H), 3.83–3.60 (m, 7H), 3.47–3.37 (2H, CH of $CH(Me)_2$), 1.31 (d, $J$ = 4.8 Hz, 12H, $CH(Me)_2$), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 164.3, 161.7, 161.5, 158.1, 155.0, 138.2, 137.9, 137.8, 137.7, 137.4, 137.2, 135.4, 134.7, 133.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 126.9, 126.3, 123.3, 122.4, 122.3, 121.2, 120.9, 120.6, 114.4, 114.3, 111.4, 105.1, 104.1, 98.6, 96.3, 82.3, 81.2, 79.3, 78.8, 76.5, 75.1, 73.5, 73.3, 72.8, 71.5, 70.0, 69.0, 68.8, 68.4, 26.8, 26.8, 22.9, 22.8. HRMS(ESI), calcd, $m/z$ $C_{40}H_{39}NO_6$, $[M + K]^+$ 668.2409; found: 668.2422.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-3-chloro-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (30a/b).** Off-white amorphous solid, m.p.: 150 °C; yield 68%, $R_f$ = 0.57 (4 : 6 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 11.67 (brs, 2H, NH), 7.92–7.84 (m, 3H), 7.44–7.11 (m, 33H, Ar H), 7.12 (s, 1H, H-7 of 30a), 7.03 (s, 1H, H-7 of 30b), 6.60 (s, 1H, H-11a of 30a), 5.98 (s, 1H, H-11a of 30b), 4.98–4.92 (m, 1H, $CH_2Ph$), 4.73(d, $J$ = 10.2 Hz, 1H, $CH_2Ph$), 4.67 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.60–4.51 (m, 7H, $CH_2Ph$), 4.44 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.36 (d, $J$ = 12 Hz, 1H, $CH_2Ph$), 4.26–4.22 (m, 2H), 4.01–4.00 (m, 1H), 3.85–3.64 (m, 7H), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 160.1, 160.0, 155.8, 152.6, 137.0, 136.7, 136.6, 136.4, 136.2, 129.8, 129.1, 127.5, 127.4, 127.3, 126.9, 126.8, 126.6, 126.5, 126.2, 121.9, 121.3, 120.8, 120.7, 120.2, 115.0, 114.9, 110.1, 105.5, 104.5, 97.7, 95.1, 81.1, 80.0, 77.6, 77.5, 75.4, 74.1, 72.4, 72.3, 72.2, 71.7, 70.4, 69.0, 67.9, 67.6, HRMS(ESI), calcd, $m/z$ $C_{37}H_{32}ClNO_6$, $[M + Na]^+$ 644.187; found: 644.1916.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-3-bromo-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (31a/b).** Off-white amorphous solid, m.p.: 185 °C; yield 66%, $R_f$ = 0.62 (4 : 6 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 12.17 (brs, 1H NH), 7.63 (m, 1H), 7.47–7.05 (m, 37H, ArH), 7.05 (s, 1H, H-7 of 31b), 6.66 (s, 1H, H-11a of 31a), 6.03 (s, 1H, H-11a of 31b), 4.96 (d, $J$ = 10.4 Hz, 2H, $CH_2Ph$), 4.94 (m, 1H, $CH_2Ph$), 4.70 (d, $J$ = 10.4 Hz, 2H, $CH_2Ph$), 4.65 (d, $J$ = 9.6 Hz, 1H, $CH_2Ph$), 4.60 (d, $J$ = 9.8 Hz, 2H, $CH_2Ph$), 4.55 (d, $J$ = 10.4 Hz, 1H, $CH_2Ph$), 4.51 (d, $J$ = 9.4 Hz, 1H, $CH_2Ph$), 4.46 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.40 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.23–4.29 (m, 2H), 4.10–4.13 (m, 1H), 3.64–3.84 (m, 7H),$^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 160.5, 153.3, 139.2, 138.4, 137.2, 136.9, 136.7, 136.6, 136.3, 129.0, 127.5, 127.3, 127.2, 127.0, 126.9, 126.8, 126.7, 126.6, 126.4, 125.6, 120.3, 116.5, 112.1, 97.6, 94.6, 81.2, 80.1, 77.6, 76.1, 74.1, 72.4, 72.3, 72.1, 71.8, 70.5, 69.0, 68.1, 67.4, HRMS(ESI), calcd, $m/z$ $C_{37}H_{32}BrNO_6$, $[M + H]^+$ 666.1486; found: 666.1599.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-4-trifluoromethyl-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (32a/b).** Yellow amorphous solid, amorphous solid, m.p.: 155 °C; yield 63%, $R_f$ = 0.50 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 12.52 (s, 1H, NH), 12.18 (s, 1H, NH), 8.75 (d, $J$ = 15.6 Hz, 1H), 8.21 (d, $J$ = 7.6 Hz, 1H), 7.78 (m, 2H, ArH), 7.43–7.15 (m, 32H, ArH), 7.07 (s, 1H, H-7 of 32a), 6.97 (s, 1H, H-7 of 32b), 6.59 (s, 1H, H-11a of 32a), 5.99 (s, 1H, H-11b of 32b), 4.95 (d, $J$ = 12.8 Hz, 2H,

$CH_2Ph$), 4.92 (d, $J$ = 12.8 Hz, 1H, $CH_2Ph$), 4.64 (d, $J$ = 12.4 Hz, 2H, $CH_2Ph$), 4.60 (d, $J$ = 12.8 Hz, 1H, $CH_2Ph$), 4.55 (m, 3H, $CH_2Ph$), 4.47 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.39 (d, $J$ = 12.4 Hz, 1H, $CH_2Ph$), 4.33 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.20 (d, 2H, H-10), 3.98 (s, 1H), 3.82–3.59 (m, 7H), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 165.8, 164.0, 162.4, 161.2, 159.2, 159.1, 155.8, 152.6, 137.0, 136.7, 136.5, 136.4, 136.1, 134.9, 132.8, 132.2, 129.0, 127.5, 127.4, 127.3, 127.0, 126.9, 127.7, 127.6, 126.3, 125.5, 125.4, 117.7, 117.2, 114.6, 114.5, 114.1, 110.8, 109.8, 109.2, 105.1, 104.2, 97.8, 95.1, 81.1, 80.0, 77.6, 77.5, 75.5, 74.1, 72.5, 74.1, 72.5, 72.4, 72.3, 71.9, 70.5, 69.1, 67.9, 67.6, HRMS (ESI), calcd, $m/z$ $C_{38}H_{32}F_3NO_6$, $[M + H]^+$ 656.2254; found: 656.2276.

**(8*R*,9*S*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-2-chloro-3-trifluoromethyl-8,9,10,11a-tetrahydropyrano[3′,2′,5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (33a/b).** Yellowish amorphous solid, m.p.: 186 °C; yield 61%, $R_f$ = 0.67 (3 : 7 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 12.35 (s, 1H, NH), 11.64 (s, 1H, NH), 8.09 (s, 1H), 7.70 (d, $J$ = 8.4 Hz, 1H), 7.50–7.17 (m, 32H, ArH), 7.11 (s, 1H, H-7 of 33a), 7.01 (s, 1H, H-7 of 33b), 6.66 (s, 1H, H-11a of 33b), 5.95 (s, 1H, H-11a of 33a), 5.00–4.97 (m, 2H, $CH_2Ph$), 4.71–4.35 (m, 10H, $CH_2Ph$), 4.26–4.21 (m, 2H), 4.03–4.00 (m, 1H), 3.90–3.72 (m, 7H), $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 162.2, 161.0, 159.2, 155.8, 151.7, 150.9, 137.8, 137.5, 137.0, 134.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 124.4, 123.2, 123.2, 116.4, 115.5, 111.0, 106.9, 95.9, 82.1, 80.7, 77.2, 76.1, 75.3, 73.6, 73.5, 73.4, 73.3, 72.8, 71.6, 70.3, 68.8, 68.0, HRMS(ESI), calcd, $m/z$ $C_{38}H_{31}ClF_3NO_6$, $[M + K]^+$ 728.1424; found: 728.1420.

**(8*R*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-((benzyloxy)methyl)-5-methyl-8,9,10,11a-tetrahydro pyrano[3′,2′:5,6]pyrano[3,2-*c*]quinolin-6(5*H*)-one (35).** White amorphous solid, m.p.: 180 °C; yield 71%, $R_f$ = 0.56 (2 : 8 = ethyl acetate : hexane, v/v), $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.01 (d, $J$ = 6.4 Hz, 1H, H-1), 7.52 (m, 1H, 2H), 7.39–7.28 (m, 16H, ArH), 6.08 (s, 1H, H-11a), 4.95 (d, $J$ = 11.2 Hz, 2H, $CH_2Ph$), 4.86 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.69 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.63 (d, $J$ = 12.0 Hz, 1H, $CH_2Ph$), 4.47 (d, $J$ = 11.6 Hz, 1H, $CH_2Ph$), 4.40 (d, $J$ = 10.8 Hz, 1H, $CH_2Ph$), 4.16 (brs, 1H, H-9), 3.99 (brs, 1H, H-8), 3.85 (brs, 1H, H-10), 3.62 (brs, 1H, H-13a), 3.70 (s, 1H, N-$CH_3$), 3.54 (brs, 1H, H-13b); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 160.7, 152.9, 138.9, 138.3, 137.8, 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 125.9, 123.1, 121.8, 114.9, 113.9 (C-7), 113.7, 104.3, 96.9 (C-11a), 79.7 (C-8), 76.5(C-9), 75.0 (C-10), 74.2, 73.5, 71.7 (3 × $CH_2Ph$), 68.8 (C-13), 29.4 ($CH_3$); HRMS (ESI), calcd, $m/z$ $C_{38}H_{35}NO_6$, $[M + H]$+ 602.25; found: 602.26.

**Cell culture.** The human breast cancer cell line MCF-7 and liver cancer cell line HepG2 were cultured in Dulbecco's modified Eagle's medium (DMEM) (Gibco, St Louis, USA) supplemented with 10% heat inactivated FBS (fetal bovine serum, Gibco, USA) and 1% penicillin–streptomycin (Gibco, Canada) in a humidified $CO_2$ incubator at 37 °C. The cells were maintained as a monolayer in a 100 mm culture plate. The cells used for each experiment were of less than 8 passage number. The subculturing of the cells was performed every third day, followed by trypsin-EDTA treatment.

**Cell viability assay.** The cell viability assay was performed as per standard protocols. Briefly, MCF-7 and HepG2 cells were trypsinized (trypsin-EDTA, Invitrogen) and seeded at a density of 50 000 cells per well in complete media in a 12-well flat-bottomed plate, followed by incubation at 37 °C and 5% $CO_2$ for 12–14 hours. The cells were then treated with all synthesized carbohydrate-fused pyrano[3,2-*c*]quinolones ($n$ = 22) for 48 hours at five different concentrations, 1 μM, 5 μM, 10 μM, 20 μM and 25 μM. DMSO was used as the vehicle control and doxorubicin (a DNA damaging compound) was taken as the positive control. After treatment, the cells were observed under a microscope for 48 hours. After 48 hours, the medium from the plates was discarded and the cells were washed with phosphate buffer saline (PBS) followed by gentle shaking for the removal of dead cells. The cells were then trypsinized and resuspended in 1 mL DMEM. 10 μl of the cell suspension was added to a hemocytometer and viable cells were counted from each of the four quadrants followed by the calculation of the average cell viability for each compound. Percent viability was calculated as the number of cells in the treated well divided by the number of cells in the untreated well (DMSO treated) × 100. The $IC_{50}$ values were determined by plotting the values of percent cell viability against different concentrations of each of those most active compounds.

## Conflicts of interest

There are no conflicts of interest to declare.

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