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CONCISE ARTICLE

Synthesis of new chromeno-annulated *cis*-fused pyrano[3,4-*c*]pyran derivatives *via* domino Knoevenagel–hetero-Diels–Alder reactions and their biological evaluation towards antiproliferative activity†

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A new series of chromeno-annulated *cis*-fused pyrano[3,4-*c*]pyran derivatives have been synthesized by intramolecular [4 + 2] domino Knoevenagel–hetero-Diels–Alder reactions of 1-oxa-1,3-butadienes derived *in situ* from 1,3-dicarbonyls/active methylenes and 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones in the presence of 20 mol% ethylenediamine diacetate (EDDA) in acetonitrile under reflux conditions in good to excellent yields. The structures were established based on spectroscopic data, and were further confirmed by X-ray diffraction analysis. These compounds were evaluated for their anti-proliferative activity using an *in vitro* MTT cytotoxicity assay. The results clearly demonstrated that compounds **4a**, **4b**, **4c**, **4j**, **4k**, **4l**, **4m** and **4n** exhibited significant anti-proliferative activity against human A549 lung cancer and non-cancer MRC-5 cell lines along with potent inhibitory activity against human neuroblastoma SK-N-SH cancer cell lines. Among these, compounds **4a**, **4b** and **4j** displayed the most potent anti-proliferative activity against human lung cancer A549 cell lines, while **4a** and **4b** displayed against neuroblastoma SK-N-SH cancer cell lines when compared to the standard doxorubicin.

Introduction

Cancer is one of the leading causes of death worldwide and accounted for 7.6 million deaths (nearly 13% of all deaths) in 2008. More than 70% of all cancer deaths occurred in low- and middle-income countries. Deaths from cancer worldwide are projected to continue to rise to over 11 million in 2030.[1] Among all cancers, lung cancer has been recognized to be one of the leading causes of death with 18.2% of all adulthood cancer deaths.[1] Neuroblastoma (NB), which is an embryonic malignancy of the sympathetic nervous system arising from neuroblasts, has been identified for 15 percent of all childhood cancer deaths among children younger than five years of age.[2] In recent years, understanding the biology of cancer has been exceptionally improved and new therapeutic agents have been developed connecting with the mechanisms of cancer cells' growth-inhibiting and differentiation-inducing or apoptosis-inducing abilities.[3–5] However, many clinically effective anti-cancer drugs used today have developed resistance in cancer therapy.[6] Therefore, there is still an impetus to identify and develop more potent anti-cancer therapeutic agents with improved properties such as enhanced and specific activity against various cancers in the field of medicinal chemistry.

In recent years, chromeno fused pyrano/pyranopyran heterocyclic natural products have attracted tremendous interest among researchers due to their potential applications in medicinal chemistry (Fig. 1).[7] Among these, chromeno fused pyranopyran derivatives exhibit significant biological activities, such as antitumour,[8] antimycobacterial[9] and antiviral.[10] In general these polycyclic heterocycles have been prepared by Lewis/Brønsted acid or ionic liquid [bmim]BF_4 catalysed intramolecular domino Knoevenagel–hetero-Diels–Alder (DKHDA) [4 + 2] cycloaddition of tethered oxadienes with non-activated olefins tethered to the diene system, and this has become one of the most powerful methods.[11,12] However, many of these synthetic methods suffer from drawbacks in reaction conditions, yields, regioselectivity and stereoselectivity. Therefore, the important biological properties of these chromeno fused pyranopyran derivatives along with our continuous efforts[13] in

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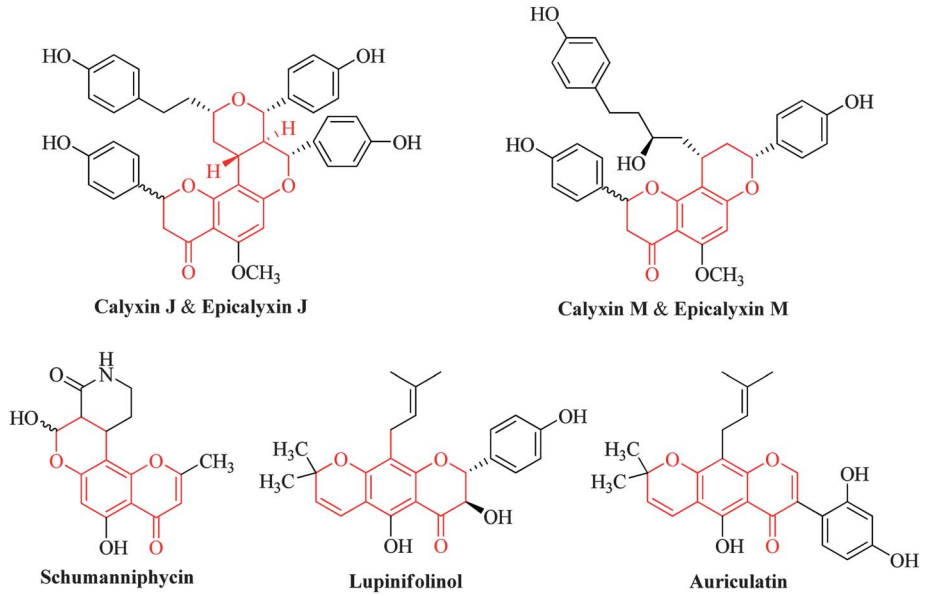


Fig. 1 Chromeno fused pyrano/pyranopyran heterocyclic natural products.

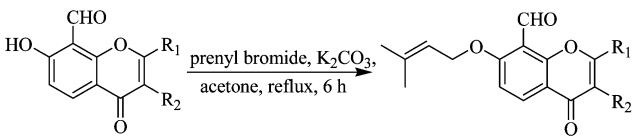
preparing biologically important compounds prompted us to synthesise a new series of chromeno *cis*-fused pyrano[3,4-*c*] pyrans in high yields with excellent regio- and stereo-selectivity and to investigate their primary biological activity against three different (MDA-MB-231, SK-N-SH, and A549) cancer cell lines and MRC-5 normal cell lines.

Results and discussion

Chemistry

According to our synthetic strategy, necessary precursors **2a–c** in synthesizing the anticipated chromeno *cis*-fused pyrano[3,4-*c*] pyrans (**4a–o**) have been prepared in high yields (89–93%) and purity by the reaction of substituted 7-hydroxy chromeno aldehydes **1a–c** and prenyl bromide in the presence of anhydrous potassium carbonate in dry acetone under reflux conditions (Scheme 1).

Having prepared the required 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones (**2a–c**) in adequate quantities, we have attempted the synthesis of a new series of chromeno *cis*-fused pyrano[3,4-*c*]pyrans (**4a–o**) in good to excellent yields (80–95%) by intramolecular [4 + 2] domino Knoevenagel–hetero-Diels–Alder reactions of 1-oxa-1,3-butadienes derived *in situ* from 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones (**2a–c**) and 1,3-dicarbonyl/active methylene compounds (**3a–h**). Accordingly, the treatment of the

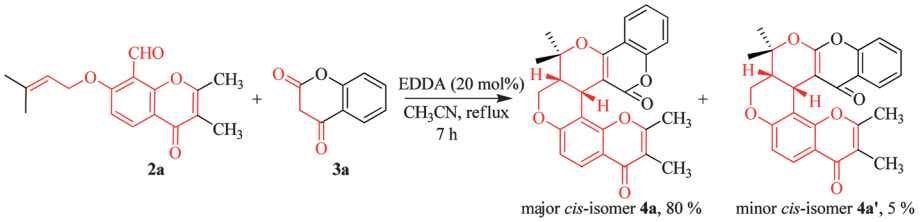


Scheme 1 7-*O*-prenyl-8-formyl-2,3-disubstituted chromenones.

7-*O*-prenyl derivative of 8-formyl-2,3-dimethyl chromenone **2a** with an unsymmetrical 1,3-diketone like 4-hydroxycoumarin **3a** in the presence of 20 mol% ethylenediamine diacetate (EDDA) in acetonitrile under reflux conditions resulted in the corresponding *cis*-major regioisomer **4a**, along with *cis*-minor regioisomer **4a′** (Scheme 2).

The reaction proceeds *via* a tandem Knoevenagel- and hetero-Diels–Alder pathway. This reaction is highly stereoselective affording exclusively chromeno *cis*-fused pyrano[3,4-*c*]pyran derivatives. These results can be explained nicely by assuming that the reactions are governed firstly by stereoelectronic and secondly by steric effects.[14] Thus more importantly stereospecificity of the formation of the major product **4a** may be explained by a stereoelectronic effect *via* an *endo-E-syn*-transition structure as shown in Fig. 2. The reaction proceeds *via* a tandem Knoevenagel- and hetero-Diels–Alder pathway. At first instance 7-*O*-prenyl-8-formyl-2,3-dimethyl chromenone **2a** reacted with unsymmetrical 1,3-diketone *i.e.*, 4-hydroxycoumarin **3a**, in the presence of EDDA to give Knoevenagel 1-oxa-1,3-butadiene, which undergoes an intramolecular hetero-Diels–Alder reaction with the dienophile *via endo-E-syn*-transition structure **I** to afford the *cis*-adduct **4a** exclusively. The *endo-E-syn*-transition structure **I** is more favorable than the *exo-Z-syn*-transition structure **II** due to an sp^2-geminal effect according to the phenomenon of 1,3-allylic strain, which has been already proved by Tietze's work.[15] In addition the regioselectivity of the major product **4a** formation over **4a′** may be explained as shown in Fig. 3. Accordingly, the Knoevenagel condensate 1-oxa-1,3-butadiene interacts with the dienophile in two ways as shown in **III** and **IV**. Compound **4a** was formed when the α,β-unsaturated ketone moiety in **III** acted as the heterodiene and **4a′** was formed when the α,β-unsaturated ester moiety in **IV** acted as the heterodiene. The Knoevenagel adduct **III** acts as a better heterodiene than **IV**, which is reflected in the higher yield of **4a** over **4a′**.

In addition, the stereochemistry of product **4a** was assigned on the basis of ^{1}H NMR *J*-coupling constants and NOE studies. In



Scheme 2 Synthesis of chromeno *cis*-fused pyrano[3,4-*c*]pyrans.

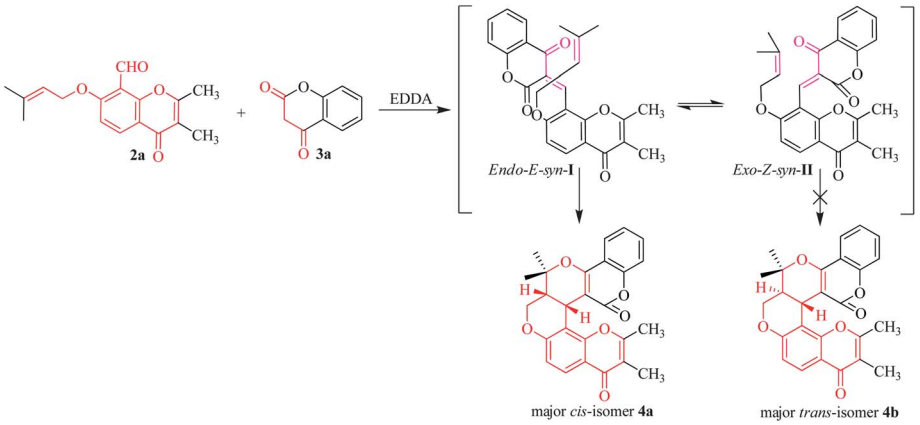


Fig. 2 Explanation of the observed stereochemistry.

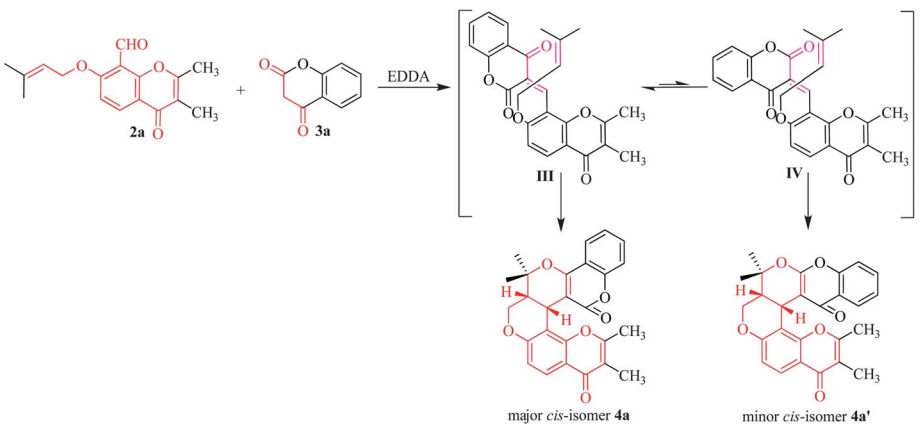


Fig. 3 Explanation of the observed regiochemistry.

the ^{1}H NMR spectrum, the vicinal coupling constant $J_{Ha–Hb}$ = 4.7 Hz between H_a (δ 4.99 ppm) and H_b (δ 1.92 ppm) indicates that both these protons are on the same side, which consequently confirms that the two six membered tetrahydropyran rings are *cis* fused. Also the vicinal coupling constants like $J_{Hb–Hc}$ = 4.7 Hz, $J_{Hb–Hd}$ = 11.4 Hz and the presence of ω coupling of $J_{Ha–Hc}$ = 1.7 Hz further confirmed the positions of H_a, H_b, H_c and H_d as shown in Fig. 2. The presence of NOE correlation between H_a/H_b, H_b/H_c, H_a/Me-A and H_b/Me-A further supported the above observation. The energy-minimized structure of **4a** is in full agreement with the above NMR analysis (Fig. 4).

Encouraged by the above results obtained with 4-hydroxy-coumarin, next we have focused our attention on tandem Knoevenagel–hetero-Diels–Alder reactions between the 7-*O*-prenyl derivative of 8-formyl-2,3-dimethyl chromenone **2a**, the 7-*O*-prenyl derivative of 8-formyl-3-methyl chromenone **2b**, the 7-*O*-prenyl derivative of 8-formyl-2-methyl-3-phenyl chromenone **2c** and various symmetrical cyclic 1,3-diketones such as

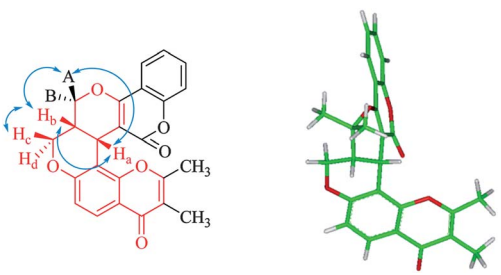
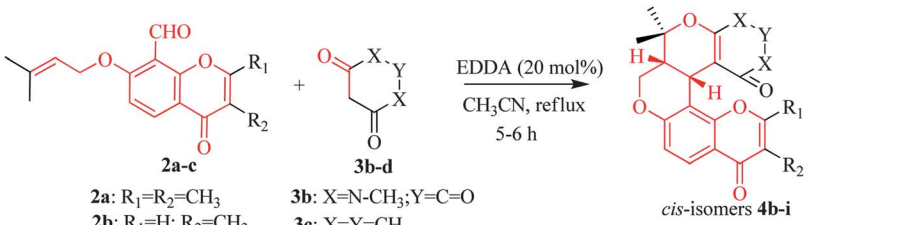


Fig. 4 Characteristic NOEs and energy-minimized structure of **4a**.



2a: R_1=R_2=CH_3
2b: R_1=H; R_2=CH_3
2c: R_1=CH_3; R_2=Ph

3b: X=N-CH_3;Y=C=O
3c: X=Y=CH_2
3d: X=CH_2;Y=$C(CH_3)_2$

4b: R_1=R_2=CH_3; X=N-CH_3;Y=C=O, 92%
4c: R_1=CH_3; R_2=Ph; X=N-CH_3;Y=C=O, 91
4d: R_1=R_2=CH_3; X=Y=CH_2, 95%
4e: R_1=H; R_2=CH_3; X=Y=CH_2, 93%
4f: R_1=CH_3; R_2=Ph; X=Y=CH_2, 92%
4g: R_1=R_2=CH_3; X=CH_2;Y=$C(CH_3)_2$, 91%
4h: R_1=H; R_2=CH_3; X=CH_2;Y=$C(CH_3)_2$, 91

Scheme 3 Synthesis of chromeno *cis*-fused pyrano[3,4-*c*]pyrans.

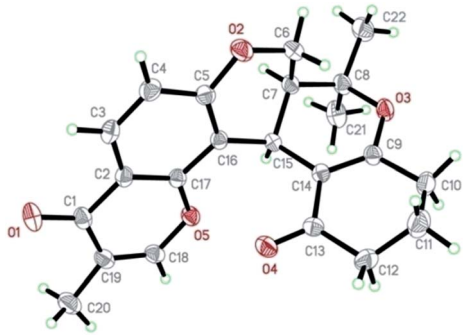


Fig. 5 ORTEP diagram for the compound **4e**, with displacement ellipsoids drawn at 30% probability level.

1,3-dimethylbarbituric acid **3b**, cyclohexane-1,3-dione **3c**, and dimedone **3d**. In all cases, the intramolecular [4 + 2] domino Knoevenagel–hetero-Diels–Alder reactions proceeded smoothly and yielded the corresponding novel chromeno pyrano[3,4-*c*] pyrans (**4b–i**) as single diastereomeric derivatives having the *cis*-configuration (Scheme 3). The stereospecificity of the formation of major products **4b–i** may be explained by the *endo-E-syn*-transition structure as shown in Fig. 2. Further the spatial stereochemistry of the products **4e** and **4g** was also confirmed by single crystal X-ray diffraction analysis (Fig. 5 and 6).[16,17]

Similarly, 7-*O*-prenylated chromeno aldehydes **2a** and **2b** on treatment with Meldrum's acid **3e** in the presence of 20 mol% ethylenediamine diacetate (EDDA) in acetonitrile under reflux conditions furnished the corresponding chromeno *cis*-fused pyrano[3,4-*c*]pyrans (**4j–k**) in excellent yields. Accordingly, the reaction proceeds *via* the intramolecular [4 + 2] domino Knoevenagel–hetero-Diels–Alder/elimination sequence (Scheme 4). Initially compounds **2a–b** reacted with **3e** to give Knoevenagel–hetero-Diels–Alder adducts **VIa–b** *via* the condensates **Va–b**. Under the same reaction conditions adducts **VIa–b** undergo retro Diels–Alder reaction to form ketenes **VIIa–b**, which trap water to form β-ketoacid acids **VIIIa–b** and subsequent *in situ* decarboxylation afforded **4j–k**.[18]

Furthermore, acyclic 1,3-dicarbonyls such as acetyl acetone **3f** and ethylacetoacetate **3g** also reacted well with 7-*O*-prenylated chromeno aldehyde **2a** to afford the corresponding chromeno *cis*-fused pyrano[3,4-*c*]pyrans (**4l–m**) in good yields under the similar reaction conditions (Scheme 5). Also the stereospecificity of the formation of major products **4l–m** may be explained by the *endo-E-syn*-transition structure as shown in Fig. 2.

Interestingly 3-methyl-1-phenyl-pyrazol-5-one **3h** also underwent smooth coupling with 7-*O*-prenylated chromeno aldehydes **2a** and **2c** to yield the corresponding chromeno *cis*-fused pyrano [3,4-*c*]pyrans (**4n–o**) in excellent yields (Scheme 6). Also the stereospecificity of the formation of major products **4n–o** may be explained by the *endo-E-syn*-transition structure as shown in Fig. 2.

Thus we have synthesized a novel series of chromeno *cis*-fused pyrano[3,4-*c*]pyrans (**4a–o**) in good to excellent yields.[19] All products are new and characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy. In addition the stereochemistry of these compounds was established based on the X-ray diffraction analysis. The purity of these compounds was further evaluated by high resolution mass spectroscopy.

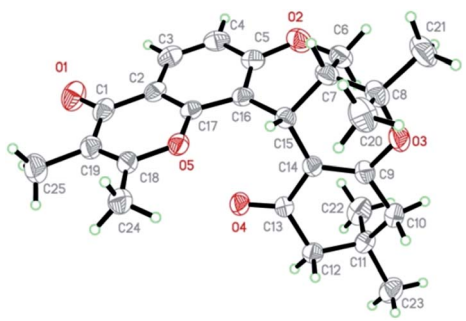
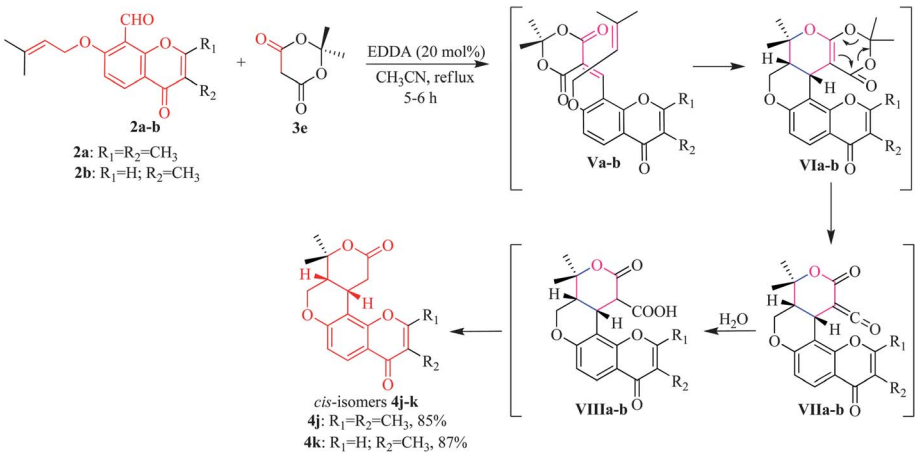


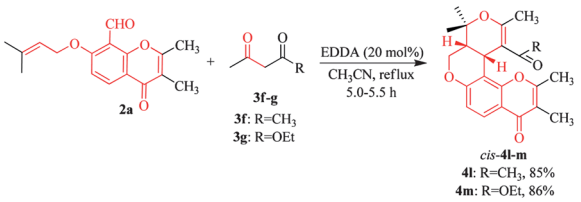
Fig. 6 ORTEP diagram for the compound **4g**, with displacement ellipsoids drawn at 30% probability level.

Biological evaluation

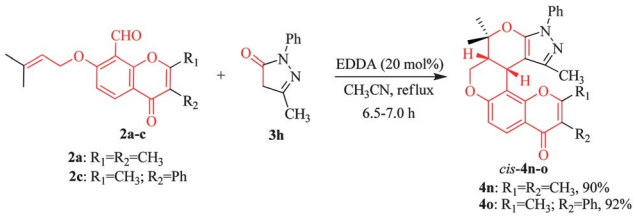
Inhibitory efficiency was tested for some of these *cis*-fused pyrano[3,4-*c*]pyrans against three different cancer cell lines (MDA-MB-231, SK-N-SH and A549) and a normal cell line (MRC-5) and the results are summarized in Table 1. The MTT assay was performed following the previously reported protocol in the 96 well plate.[13c] Compounds **4a**, **4b**, **4j**, **4k** and **4m** exhibited significant anti-proliferative activity against human A549 lung cancer cell lines, while **4a**, **4j** and **4m** were active against human lung non-cancer MRC-5 cell lines. In addition, compounds **4a**, **4b**, **4c**, **4l**, **4m** and **4n** displayed potent inhibitory activity against human



Scheme 4 Synthesis of chromeno *cis*-fused pyrano[3,4-*c*]pyrans.



Scheme 5 Synthesis of chromeno *cis*-fused pyrano[3,4-*c*]pyrans.



Scheme 6 Synthesis of chromeno *cis*-fused pyrano[3,4-*c*]pyrans.

neuroblastoma SK-N-SH cancer cell lines. Compounds **4a**, **4b** and **4j** are most promising leads, suggesting that aromatic dimethyl substituents and heterocyclic dienophiles have good activity. On the pyranopyran ring, an ester displays a better cytotoxicity than the ketone as shown by **4l** and **4m**. In general, compounds with 2,3-dimethyl substitution on the chromenone moiety seem to be a better fit than a phenyl group at the 3-position. Surprisingly, none of the compounds in the current study displayed any toxicity against the MDA-MB-231 cell line. Overall, our current cytotoxicity data suggest that some of the molecules presented in this study have good anti-cancer properties. Further studies are in progress to understand the molecular target for these molecules which will help in understanding the structure–activity relationship.

Conclusions

In conclusion we have synthesized a series of novel chromeno-annulated *cis*-fused pyrano[3,4-*c*]pyran derivatives and evaluated their anti-proliferative activity against human lung adenocarcinoma epithelial A549, human lung non-cancer fibroblast MRC-5, human neuroblastoma SK-N-SH and human breast adenocarcinoma MDA-MB-231 cell lines using an *in vitro* cytotoxicity assay. Among these, compounds **4a**, **4b** and **4j** displayed the most potent anti-proliferative activity against the human lung cancer A549 cell line, while **4a** and **4b** exhibited potent anti-proliferative activity against neuroblastoma SK-N-SH cancer cell lines when compared to the standard doxorubicin. Further work is in progress in biotinylation of some of the lead compounds to identify the molecular targets in the tested cell lines.

Table 1 *In vitro* antiproliferative activity[a] of novel chromeno pyrano [3,4-*c*]pyrans against human A549, MDA-MB-231, and SK-N-SH cancer cell lines and MRC-5 non-cancer cell lines using MTT assay

	Breast	Neuroblastoma	Lung-cancer	Lung-normal
Compound ($\mu g\ mL^{-1}$)	MDA-MB-231	SK-N-SH	A549	MRC-5
4a	>100	1.05 ± 0.006	0.1 ± 0.002	0.6 ± 0.001
4b	>100	1.06 ± 0.02	0.1 ± 0.004	>100
4c	>100	10.51 ± 0.09	>100	>100
4d	>100	>100	>100	>100
4e	>100	>100	>100	>100
4f	>100	>100	>100	>100
4g	>100	>100	>100	>100
4h	>100	>100	>100	>100
4i	>100	>100	>100	>100
4j	>100	>100	0.09 ± 0.001	0.6 ± 0.001
4k	>100	>100	11.24 ± 0.008	>100
4l	>100	10.7 ± 0.07	>100	>100
4m	>100	10.85 ± 0.03	10.94 ± 0.002	0.9 ± 0.001
4n	>100	10.58 ± 0.06	>100	>100
4o	>100	>100	>100	>100
Doxorubicin (Standard)	8.14 ± 0.14	0.97 ± 0.03	15.07 ± 0.13	14.84 ± 0.25

[a] Results are expressed as IC_{50} values in μM concentrations.

Acknowledgements

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16 The CCDC deposition number for **4e** is 848040 Crystal data: $C_{22}H_{22}O_5$, M = 366.40, monoclinic, space group $P2_1/n$, a = 15.4539(11) Å, b = 7.4613(5) Å, c = 16.2148(11) Å, β = 106.214(1)°, V = 1795.3(2) Å^3, Z = 4, D_{calcd} = 1.356 mg m^{-3}, T = 294(2) K, μ = 0.096 mm^{-1}, F(000) = 776, λ = 0.71073 Å. Data collection yielded 16 576 reflections resulting in 3161 unique, averaged reflections, 2889 with $I > 2\sigma(I)$. Full-matrix least-squares refinement led to a final R = 0.0462, wR = 0.1298 and GOF = 1.043. Intensity data were measured on a Bruker Smart Apex with a CCD area detector.

17 The CCDC deposition number for **4g** is 839 724. Crystal data: $C_{25}H_{28}O_5$, M = 408.47, monoclinic, space group $P2_1/c$, a = 11.7974(15) Å, b = 13.9420(18) Å, c = 13.4238(17) Å, β = 101.254(2)°, V = 2165.5(5) Å^3, Z = 4, D_{calcd} = 1.253 mg m^{-3}, T = 294(2) K, μ = 0.086 mm^{-1}, F(000) = 872, λ = 0.71073 Å. Data collection yielded 20 554 reflections resulting in 3806 unique, averaged reflections, 3113 with $I > 2\sigma(I)$. Full-matrix least-squares refinement led to a final R = 0.0431, wR = 0.1198 and GOF = 1.035. Intensity data were measured on a Bruker Smart Apex with a CCD area detector.

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19 *General procedure*: *Chemistry*: A mixture of 7-*O*-prenyl derivatives of 8-formyl-2,3-disubstituted chromenones (**2a–c**) (1.0 mmol) and 1,3-diketones (**3a–h**) (1.0 mmol) in acetonitrile (5 mL) was stirred in the presence of EDDA (20 mol%) under reflux conditions for an appropriate time. After completion of the reaction as indicated by TLC, the excess acetonitrile was distilled off and the residue was poured into water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (100–200 mesh) with eluent hexane–ethyl acetate to yield the corresponding pure chromeno *cis*-fused pyrano[3,4-*c*]pyrans (**4a–o**) as solids (yields: 80–95.0%). Data of the representative compounds are as follows. For full characterization data, see the ESI†. (1*S*,14*R*)-5,6,15,15-Tetramethyl-4,12,16,24-tetraoxahexacyclo[12.12.0.0^{2,11}.0^{3,8}.0^{17,26}.0^{18,23}]hexacosa-2,5,8,10,17(26),18(23),19,21-octaene-7,25-dione (**4a**): Yield 79.9%; White solid; mp 220–223 °C; IR (KBr): ν_{max} 3557, 3450, 2923, 1712, 1608, 1437, 1370, 1326, 1294, 1259, 1192, 1131, 1089, 1021, 832, 756, 604, 455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 3H), 1.64 (s, 3H), 2.06 (s, 3H), 2.29–2.36 (m, 1H), 2.41 (s, 3H), 4.07 (t, J = 11.7 Hz, 1H), 4.53 (ddd, J = 11.7, 5.3, 2.1 Hz, 1H), 4.63 (d, J = 4.2 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 7.14–7.30 (m, 2H), 7.50 (td, J = 7.5, 1.1 Hz, 1H), 7.80 (dd, J = 7.5, 1.1 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.92, 160.84, 160.24, 158.29, 156.74, 156.56, 152.65, 131.94, 125.88, 123.56, 122.99, 116.25, 116.15, 115.32, 114.03, 108.49, 100.18, 78.34, 63.35, 36.80, 29.67, 27.10, 25.62, 24.24, 18.41, 10.00; MS–ESIMS: m/z 431 [M + H]$^+$; HRMS calcd for $C_{26}H_{23}O_6$, 431.1494; found, 431.1498; (1*S*,14*R*)-5,6,15,15,18,20-hexamethyl-4,12,16-trioxa-18,20-diazapentacyclo[12.8.0.0^{2,11}.0^{3,8}.0^{17,22}]docosa-2,5,8,10,17(22)-pentaene-7,19,21-trione (**4b**): Yield 92%; White solid; mp 169–174 °C; IR (KBr): ν_{max} 3449, 2924, 1707, 1664, 1611, 1439, 1365, 1295, 1258, 1189, 1128, 1079,

1024, 825, 788, 742, 652, 604, 470 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.57 (s, 3H), 1.61 (s, 3H), 2.05 (s, 3H), 2.15–2.23 (m, 1H), 2.39 (s, 3H), 3.16 (s, 3H), 3.36 (s, 3H), 4.06 (t, J = 11.2 Hz, 1H), 4.48 (ddd, J = 11.0, 4.9, 1.1 Hz, 1H), 4.53 (d, J = 3.3 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.91, 161.27, 160.77, 156.45, 156.40, 154.40, 150.84, 125.67, 116.27, 115.96, 114.05, 109.32, 86.48, 80.50, 62.98, 36.83, 28.87, 28.05, 27.01, 25.53, 23.18, 18.51, 10.10; MS–ESIMS: m/z 425 $[M + H]^+$; HRMS calcd for $C_{23}H_{25}N_2O_6$, 425.1712; found, 425.1715; (13*R*,18*S*)-4,5,14,14-tetramethyl-3,11,15-trioxatetracyclo [8.8.0.0^{2,7}.0^{13,18}]octadeca-1,4,7,9-tetraene-6,16-dione (**4j**): Yield 85%; Violet solid; mp 153–155 °C; IR (KBr): ν_{max} 3428, 2923, 1726, 1644, 1606, 1467, 1437, 1406, 1357, 1326, 1274, 1250, 1190, 1132, 1092, 1064, 1021, 956, 831, 784, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 1.54 (s, 3H), 1.64 (s, 3H), 2.02 (s, 3H), 2.18–2.24 (m, 1H), 2.43 (s, 3H), 2.49 (dd, J = 18.7, 9.3 Hz, 1H), 3.23 (dd, J = 18.7, 8.5 Hz, 1H), 3.80–3.90 (m, 1H), 4.04 (t, J = 11.6 Hz, 1H), 4.54 (ddd, J = 11.6, 3.8, 1.5 Hz, 1H), 6.82 (d, J = 9.3 Hz, 1H), 7.96 (d, J = 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.59, 177.18, 169.09, 160.61, 156.80, 125.80, 116.98, 116.50, 114.87, 111.56, 81.15, 62.39, 36.82, 32.38, 29.28, 26.27, 24.01, 18.51, 9.95.; MS–ESIMS: m/z 329 $[M + H]^+$.

