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Synthesis, characterization and anti-cancer screening of modified Pyrano quinolines

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Abstract
Treatment of 8-hydroxy quinoline derivatives with various chalcones in presence of iodine and acetic acid under reflux condition various Pyrano [3,2-h] quinolines have been obtained. All the synthesized compounds were characterized with spectral study and screened for anti-cancer activity.

Keywords: quinoline, pyranoquinoline, michael addition and anti-cancer activity

1. Introduction
The plant family Balfourodedron riedelianum (Rutaceae) to be a prolific source of pyrano quinoline alkaloids [1]. Balfourodedron riedelianum (Rutaceae) is a small Brazilian tree which has been used as medicine for the treatment of gastrointestinal ailments [2]. The biological activity of these alkaloids depends not only on the bicyclic heteroaromatic pharmacophore but also on the nature of the peripheral substituent and their spatial relationship. They also exhibit antimalarial [3], antitumor [4], antioxidant [5], antileishmanial [6], anti inflammatory and anticancer [7] and antiplatelet activities [8]. In addition they function as pharmacologically active synthetic compounds [9] such as DNA binding capabilities [10] and DNA-intercalating carrier [11]. A series of compounds derived from 8-hydroxyquinoline as potential HIV-1 integrate inhibitors were synthesized recently [12, 13, 14, 15, 16, 17, 18]. In addition pyrano quinoline derivatives have gained strong attention recently due to their activities as perspective HIV integrase inhibitors [13], and also, for their extensive biological activities [14].
Prompted by these observations earlier we have reported some new pyrano [3,2-h] quinoline as newer antibiotics [15] and now in continuation of our interest in synthesizing newer modified pyrano [3,2-h] quinoline derivatives with anti-cancer activity, the present work has been conducted by Michael addition of some reported chalcones to 8-hydroxy quinolines. All the synthesised compounds were screened for anti-cancer activity.

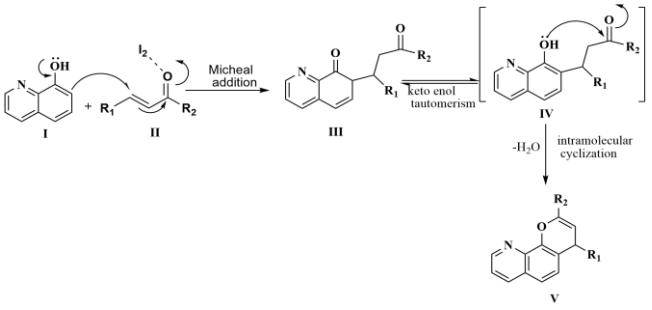
2. Materials and Methods
2.1 Synthesis and Characterisation
All chemicals were purchased from Sigma-Aldrich, Germany. Melting points were determined by the open capillary method and were uncorrected. FTIR spectra of the synthesized compounds were recorded on a Shimadzu-8400S, using KBr pellets in 10^{-4} resolution and 30 scans. ^{1}H NMR spectra were recorded on a Varian spectrometer, USA at 400 MHz at room temperature. Samples were prepared in $CDCl_3$ containing TMS as an internal standard. Splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Chemical shift values were given in parts per million (ppm). [13] C NMR were recorded on Varian 400 spectrometer, operating at 400 MHz. The Liquid Chromatography Mass Spectra (LC-MS) were recorded on a Varian Inc, USA, 410 Prostar Binary LC with 500 MS IT PDA detectors.

2.2 Cell lines
MCF-7 (breast cancer) cell line was collected from laboratory of VBCH, Silvassa. Cells were cultured in DMEM medium and supplemented with 10% of fetal bovine serum (FBS) then the culture flasks were incubated for 3-4 days at 37˚C in 5% CO_2 incubator.

2.3 Analysis of cell viability by MTT assay
Cell viability was measured quantitatively by using MTT, showed the activity of living cells [Plumb *et al*., 1989]. MCF-7 was seeded into 24 well plates and treated with 100µl/ml, 150µl/ml, 200µl/ml, 250µl/ml and 300µl/ml of various pyrano [3,2-h] qunolines mixture dissolved in $CHCl_3$. The treated mixture was then incubated at 37ºC with 5% CO_2 for 24 hours. After incubation, 2µl/ml of the labelled reagent was added to each well followed by incubation for 3 hours at 37ºC with 5% CO_2 and then the medium was discarded and the crystals were dissolved in 1.0 ml of 0.04N HCl. The absorbance of cells was measured at 570 nm with an ELISA reader. MTT assay was performed in the Department of Microbiology, SSR College of Arts, Commerce and Science, Silvassa.

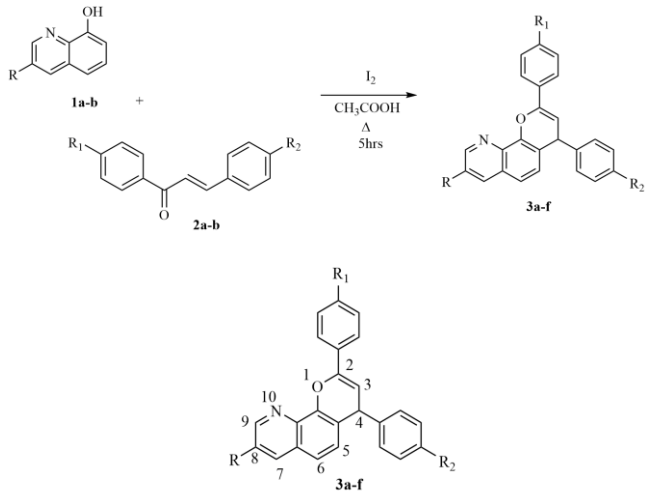
2.4 Statistical Analysis
Each data point was obtained by making at least 3 independent measurements. All data are expressed as mean + S.D. Data were analyzed by an analysis of variance ($p<0.05$) and the means separated by one-way ANOVA.

3. Experimental
3.1 Preparation of various pyrano quiniline (3a-f) (Scheme 2)
A possible mechanism is proposed in Scheme 1, where molecular iodine ligated with chalcone (II) activates Michael addition [15] with 8-hydroxyquinoline (I) and forms a 1,5-diketone (III) intermediate. The unstable intermediate is equilibrated in keto-enol (IV) forms. Further, the intermediate undergoes intramolecular cyclization by the loss of a water molecule to form the desired product (V).



Scheme 1

A mixture of a selected chalcones (0.5 mmol) [16], 8-hydroxy quinoline (0.5 mmol), and iodine (0.5 mmol) was dissolved in 15 mL acetic acid. Then, the mixture was stirred under reflux at 100℃ for three hours. The reaction mixture was cooled to room temperature and diluted with water, followed by $Na_2S_2O_3H_2O$ solution to quench excess iodine. The reaction mixture was filtered invacuo, and the residue was purified by column chromatography on silica gel (60-120 mesh) using $CHCl_3$: Pet-Ether (80:20) as an eluent to give the pure product.



3a	$R=R_1=R_2=H$	2,4-diphenyl-4*H*-pyrano[3,2-h]quinoline
3b	$R=R_1=H$, $R_2=Cl$	2-(phenyl)-4-(4-chloro-phenyl)-4*H*-pyrano[3,2-h]quinoline
3c	$R=R_1=H$, $R_2=Br$	2-(phenyl)-4-(4-bromo-phenyl)-4*H*-pyrano[3,2-h]quinoline
3d	$R=CH_3$, $R_1=R_2=H$	8-methyl-2,4-diphenyl-4*H*-pyrano[3,2-h]quinoline
3e	$R=CH_3$, $R_1=H$, $R_2=Cl$	8-methyl-2-(phenyl)-4-(4-chloro-phenyl)-4*H*-pyrano[3,2-]quinoline
3f	$R=CH_3$, $R_1=H$, $R_2=Br$	8-methyl-2-(phenyl)-4-(4-bromo-phenyl)-4*H*-pyrano[3,2-h]quinoline

Scheme 2

3.2 Characterization of synthesized compounds

3a: Yield 90%, mp 197°C, *IR (cm^{-1})*, ν_{max} 1612 and 1518 (aromatic C=C and C=N stretching), 3010 (aromatic C-H stretching), 751 and 972 (C-H bending vibrations of mono substituted benzene ring), 2930 (aliphatic C-H stretching), 1050 (C-O-C stretching of benzopyran ring). *^{1}H NMR (δ, ppm) ($CDCl_3$)* 7.26-8.89 (11H, multiplet, aromatic protons except C_3-H and C_4-H), 4.74(C_4-H) (1H, d, *J*=6.21Hz), 5.81(C_3-H) (1H, d, *J*=6.21Hz), ^{13}C NMR *(δ, ppm) ($CDCl_3$)* 42.43(CH), 93.34(CH), 120.94(CH), 120.23(CH), 121.37(C), 125.21(CH), 126.27(CH), 127.62(C), 127.91(CH), 128.23(CH), 128.45(CH), 128.66(CH), 129.21(CH), 135.32(C), 135.53(CH), 137.31(C), 144.75(C), 150.13(CH), 141.43(C), 151.82(C). Anal. Calcd. for $C_{24}H_{17}NO$: C, 85.94; H, 5.11; N, 4.18; O, 4.77%. Found: C, 85.88; H, 4.95; N, 4.10; O, 4.58%.

3b: Yield 90%, mp 197°C, *IR (cm^{-1})*, ν_{max} 1612 and 1518 (aromatic C=C and C=N stretchings), 3010 (aromatic C-H stretching), 751 and 972 (C-H bending vibrations of mono substituted benzene ring), 2930 (aliphatic C-H stretching), 1050 (C-O-C stretching of benzopyran ring).). *^{1}H NMR (δ, ppm) ($CDCl_3$)* 7.26-8.89 (10H, multiplet, aromatic protons except C_3-H and C_4-H), 4.74(C_4-H) (1H, d, *J*=6.21Hz), 5.81(C_3-H) (1H, d, *J*=6.21Hz), ^{13}C NMR *(δ, ppm) ($CDCl_3$)* 42.43(CH), 93.34(CH), 120.94(CH), 120.23(CH), 121.37(C), 125.21(CH), 127.62(C), 127.91(CH), 128.23(CH), 128.45(CH), 128.66(CH), 129.21(CH), 131.82(C), 135.32(C), 135.53(CH), 137.31(C), 144.75(C), 150.13(CH), 141.43(C), 151.82(C). Anal.Calcd.for $C_{24}H_{16}ClNO$: C, 77.94; H, 4.36; Cl, 9.59; N, 3.79; O, 4.33%. Found: C, 77.89; H, 4.11; Cl, 9.29; N, 3.62; O, 4.41%.

3c: Yield 90%, mp 197°C, *IR (cm^{-1})*, ν_{max} 1612 and 1518 (aromatic C=C and C=N stretching), 3010 (aromatic C-H stretching), 751 and 972 (C-H bending vibrations of mono substituted benzene ring), 2930 (aliphatic C-H stretching), 1050 (C-O-C stretching of benzopyran ring).). *^{1}H NMR (δ, ppm) ($CDCl_3$)* 7.26-8.89 (10H, multiplet, aromatic protons except C_3-H and C_4-H), 4.74(C_4-H) (1H, d, *J*=6.21Hz), 5.81(C_3-H) (1H, d, *J*=6.21Hz), ^{13}C NMR *(δ, ppm) ($CDCl_3$)* 42.43(CH), 93.34(CH), 120.31(C), 120.94(CH), 120.23(CH), 121.37(C), 125.21(CH), 127.62(C), 127.91(CH), 128.23(CH), 128.45(CH), 128.66(CH), 129.21(CH), 135.32(C), 135.53(CH), 137.31(C), 144.75(C), 150.13(CH), 141.43(C), 151.82(C). Anal. Calcd. for $C_{24}H_{16}BrNO$: C, 69.58; H, 3.89; Br, 19.29; N, 3.38; O, 3.86%. Found: C, 69.42; H, 3.75; Br, 19.21; N, 3.30; O, 3.81%.

3d: Yield 90%, mp 197°C, *IR (cm^{-1})*, ν_{max} 1730 (C=O stretching of δ-lactone of coumarin), 1612 and 1518 (aromatic C=C and C=N stretchings), 3010 (aromatic C-H stretching), 751 and 972 (C-H bending vibrations of mono substituted benzene ring), 2930 (aliphatic C-H stretching), 1050 (C-O-C stretching of benzopyran ring).). *^{1}H NMR (δ, ppm) ($CDCl_3$)* 2.35 (1 × CH_3, s), 7.26-8.89 (10H, multiplet, aromatic protons except C_3-H and C_4-H), 4.74(C_4-H) (1H, d, *J*=6.21Hz), 5.81(C_3-H) (1H, d, *J*=6.21Hz), ^{13}C NMR *(δ, ppm) ($CDCl_3$)* 18.47(CH_3), 42.43(CH), 93.34(CH), 120.23(CH), 121.37(C), 125.21(CH), 126.27(CH), 127.62(C), 127.91(CH), 128.23(CH), 128.45(CH), 128.66(CH), 129.21(CH), 130.43(C), 135.32(C), 135.53(CH), 137.31(C), 144.75(C), 150.13(CH), 141.43(C), 151.82(C). Anal.Calcd.for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01; O, 4.58%. Found: C, 85.88; H, 5.20; N, 3.94; O, 4.31%.

3e: Yield 90%, mp 197°C, *IR (cm^{-1})*, ν_{max} 1730 (C=O stretching of δ-lactone of coumarin), 1612 and 1518 (aromatic C=C and C=N stretchings), 3010 (aromatic C-H stretching), 751 and 972 (C-H bending vibrations of mono substituted benzene ring), 2930 (aliphatic C-H stretching), 1050 (C-O-C stretching of benzopyran ring).). *^{1}H NMR (δ, ppm) ($CDCl_3$)* 2.25 (1 × CH_3, s), 7.26-8.89 (9H, multiplet, aromatic protons except C_3-H and C_4-H), 4.74(C_4-H) (1H, d, *J*=6.21Hz), 5.81(C_3-H) (1H, d, *J*=6.21Hz), ^{13}C NMR *(δ, ppm) ($CDCl_3$)* 17.67(CH_3), 42.43(CH), 93.34(CH),

120.23(CH), 121.37(C), 125.21(CH), 126.27(CH), 127.62(C), 127.91(CH), 128.23(CH), 128.45(CH), 128.66(CH), 129.21(CH), 131.11(C), 135.32(C), 135.53(CH), 137.31(C), 144.75(C), 150.13(CH), 141.43(C), 151.82(C). Anal.Calcd.for $C_{25}H_{18}ClNO$: C, 78.22; H, 4.73; Cl, 9.24; N, 3.65; O, 4.17%. Found: C, 78.17; H, 4.58; Cl, 9.13; N, 3.48; O, 4.10%.

3f: Yield 90%, mp 197°C, *IR (cm^{-1})*, ν_{max} 1730 (C=O stretching of δ-lactone of coumarin), 1612 and 1518 (aromatic C=C and C=N stretchings), 3010 (aromatic C-H stretching), 751 and 972 (C-H bending vibrations of mono substituted benzene ring), 2930 (aliphatic C-H stretching), 1050 (C-O-C stretching of benzopyran ring).). *^{1}H NMR (δ, ppm) ($CDCl_3$)* 2.19 (1 × CH_3, s), 7.26-8.89 (9H, multiplet, aromatic protons except C_3-H and C_4-H), 4.74(C_4-H) (1H, d, *J*=6.21Hz), 5.81(C_3-H) (1H, d, *J*=6.21Hz), ^{13}C NMR *(δ, ppm) ($CDCl_3$)* 18.68(CH_3), 42.43(CH), 93.34(CH), 120.23(CH), 121.37(C), 125.21(CH), 126.27(CH), 127.62(C), 127.91(CH), 128.23(CH), 128.45(CH), 128.66(CH), 129.21(CH), 130.43(C), 135.32(C), 135.53(CH), 137.31(C), 144.75(C), 150.13(CH), 141.43(C), 151.82(C). Anal.Calcd.for $C_{25}H_{18}BrNO$: C, 70.10; H, 4.24; Br, 18.66; N, 3.27; O, 3.74%. Found: C, 69.16; H, 3.98; Br, 18.70; N, 3.21; O, 3.11%.

4. Results and Discussion

Pyrano [3,2-h] quinolines (3a-f) were screened at concentration of 100 µl/ml, 150 µl/ml, 200 µl/ml, 250 µl/ml and 300 µl/ml. The most of compounds significantly reduced the growth of MCF-7 cell line. The data are shown in chart-1.

The compound 3a at 150 µl/ml shows lower cell viability 44, compound 3c at 150 µl/ml and 300 µl/ml shows lower cell viability 55 and 44 and compound 3f at 150 µl/ml and 250 µl/ml shows lower cell viability 41 and 46, Which are the lowest. But the compound 3b at 150 µl/ml and 200 µl/ml shows excellent cell viability 92.2 and 93.1, compound 3d at 150 µl/ml and 300 µl/ml shows excellent cell viability 92 and 93.2 and compound 3f at 200 µl/ml and 300 µl/ml shows excellent cell viability 92.7 and 91.8. The rest of compounds at various concentrations show moderate cell viability.

Thus, to gain a better understanding of the beneficial biological activities of pyrano[3,2-h]quinolines upon cancer prevention, a greater knowledge of the metabolism of pyrano[3,2-h]quinolines is needed. More research is clearly needed to identify and characterize additional pyrano[3,2-h]quinolines metabolites and their biological activities, which will potentially provide invaluable insights into the mechanisms underlying the beneficial effects of pyrano[3,2-h]quinolines to humans, especially in terms of cancer prevention. If such studies succeed in identifying an active pyrano[3,2-h]quinolines derivative, it could be used as a parent compound for the development of potent anticancer drugs.

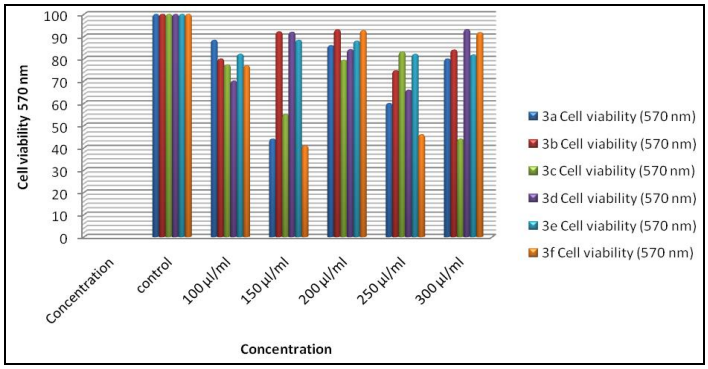


Fig 1: Evaluation of reduction for MCF-7 cell line treated with pyrano[3,2-h]quinolines(3a-f) mixture at 570nm using ELISA reader

5. Acknowledgements

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