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# SYNTHESIS, STEREOCHEMISTRY AND CYTOTOXICITY OF PYRANONE DERIVATIVES ON HeLa AND A549 CELL LINES

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**ABSTRACT**

Pyranones have a range of biological actions including anticancer activities and hence a series of polyfunctionalized pyranones *i.e.*, 3,5-dialkyl-2,6-diaryltetrahydropyran-4-one derivatives **6a-h** were synthesized. The reports on analogous molecules with the alkyl and aryl substituents on the active methylene centers and either side on the heteroatom enhanced the anticancer activity with suppressed toxicity were also facilitated our focus on the poyfunctionalized pyranone derivatives **6a-h**. The synthesized pyranone derivatives were identified through CHN abundance, IR, Mass, and NMR. Stereochemical analysis of pyranone derivatives was carried out by $^1$H NMR studies, which indicated that compounds **6a-f** are in the chair whereas **6g-h** are in the twist-boat conformations. Then, the obtained heterocycles were examined for in vitro cytotoxicity on HeLa and A549 cells using the MTT assay. As an outcome of this study, we found that all the compounds exhibited their $IC_{50} \leq 50$ µM, and in fact, the oxime derivatives expressed better activity than their precursors **5a-h** against HeLa and A549 cell lines. The highly functionalized compound **6e** registered the best $IC_{50}$ of 11.8 µM against HeLa and 12.7 µM against A549 cells along with the absence of collateral toxicity on the normal healthy Chang liver cells, deserves further investigation of this molecule.

**Keywords:** Cervical Cancer; Lung Cancer; MTT Assay; Natural Product Derivative; Pyran-4-ones.

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## INTRODUCTION

Many reports reveal piperidin-4-one derivatives' anticancer properties over a range of cell lines[1-4] Compound **2** is the heterocyclic analog of the α,β-unsaturated ketone[5-7], known as curcumin **1** (Fig.-1).[9-10] Curcumin has been proven as an anticarcinogenic, antibacterial, anti-inflammation, and radical scavenging agent.[11-15] Compound **2** (Fig.-1), the 3,5-diarylpiperidin-4-one analogs of curcumin are Mannich bases, proved their improved efficiency than analogous chalcones by their selective toxicity to such cancer cells due to a better proportion of the compound dissociated in the tumors (in fact, tumors exist in comparatively lower pH than the healthy cells).[16] Earlier, we reported a range of 2,6-diaryl-3,5-dialkylpiperidin-4-ones **3** and their analogs with and without N-substitution beside diversity in the C-2, C-3, C-5, and C-6 substituents.[17-18] As a result, we found some lead molecules with good cytotoxicity on HeLa cells. The N-benzylated derivatives gave comparatively better results than the N-methylated or non-N-methylated Mannich bases. On the other hand, plenty of reports exist on the potential cytotoxic nature of many natural and synthetic coumarins **4**, which constitute the six-membered pyranone nucleus as an active pharmacophore.[19] Hence, we planned to make the oxygen analogs[20-21] by replacing the ring nitrogen of the established piperidones. Accordingly, we have synthesized the targeted poly-functionalized pyranones and their oxime ethers similar to that of the lead cytotoxic piperidone molecules with diverse substituents on the aryl. Earlier to our reports[17,22] on the diverse substitution of the heterocycle and the conversion of the carbonyl into oxime functionality to affect the biological actions, the improvement of anticancer activity, and along with suppressed toxicity of the six-membered heterocycles by the incorporation of alkyl/aryl substitutions on the heterocycle was witnessed by different researchers.[23-24]

## EXPERIMENTAL

The synthesis of target molecules viz., 3,5-dialkyl-2,6-diaryltetrahydropyran-4-ones **5a-h** and their oxime ethers **6a-h** are depicted in Scheme-1. The pyranones were synthesized by adopting the classical method[25]


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with some modifications to avoid/reduce the unreacted benzaldehydes and mono or di-benzylidene derivatives and reaction time as well.

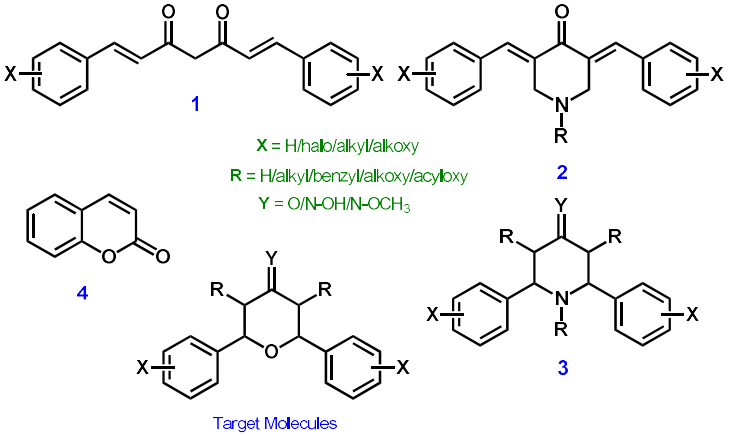
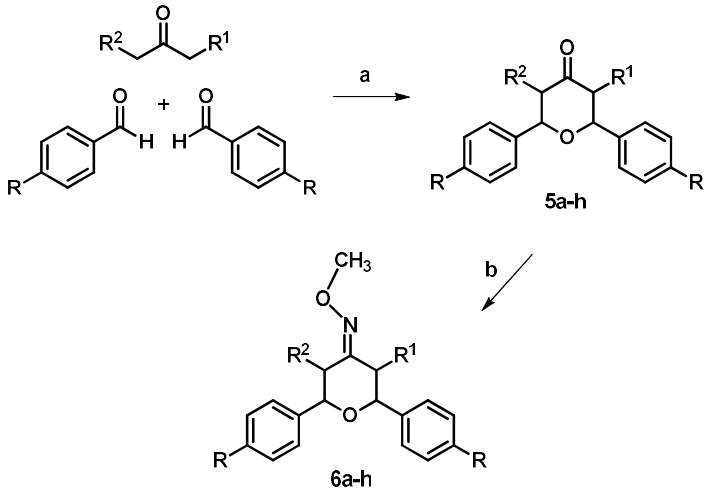



Fig.-1: Structures of Some Literature Precedents and Target Compounds

Thus the mixture of benzaldehyde (0.1 mol), 2-propanone or 3-propanone (0.05 mol), ethanol (0.6 mol), distilled water (3 mol) and potassium hydroxide (10%, 0.1 mol) was vigorously stirred with an excess addition of 10% KOH gradually till the completion, whereas the substituted benzaldehydes and 3-pentanone mixture afforded the product in a few hours by merely moderate stirring with calculated quantity of KOH.[22,26] Then the pyranones **5a** and **5b** were refluxed, respectively about 7 and 11 h with $CH_3ONH_2$. HCl and $CH_3COONa$. $3H_2O$, whereas **5d-h** required above 25 h to convert as oxime ethers; however, **5c** did not convert as oxime ether even up to 5 days. Neither the use of pyridine as a base nor other bases afford the desired product. The reaction was also performed even without base but no progress. During such prolonged reflux of 25 h, some compounds underwent epimerization, or else conformational change occurred however, the yield is good but the usage of pyridine or other bases notably diminished the product.




| Entry | R | $R^1$ | $R^2$ |
|---|---|---|---|
| 5a, 6a | H | $CH_3$ | H |
| 5b, 6b | H | $CH_2CH_3$ | H |
| 5c | H | $CH_3$ | $CH_3$ |
| 5d, 6d | F | $CH_3$ | $CH_3$ |
| 5e, 6e | Cl | $CH_3$ | $CH_3$ |
| 5f, 6f | Br | $CH_3$ | $CH_3$ |
| 5g, 6g | $CH_3$ | $CH_3$ | $CH_3$ |
| 5h, 6h | $OCH_3$ | $CH_3$ | $CH_3$ |

Scheme-1: Schematic Representation of the Target Compounds 6a-6h: (a) Aqueous KOH, Ethanol, Vigorous/Moderate Stirring; (b) $CH_3ONH_2$. HCl, $CH_3COONa$. $3H_2O$, $C_2H_5OH$, Reflux

**Analytical and Spectral Data of the Compounds 6a-h**

**6a**: 3-Methyl-2,6-diphenyldihydro-*2H*-pyran-4(*3H*)-one *O*-methyloxime. White semi-solid, yield 96 %; $^1$H NMR: $\delta$= 4.35 (d, $J_{2a,3a}$ = 10.26 Hz, 1H, H-2a); 4.71 (dd, $J_{5a,6a}$ = 11.76; $J_{5e,6a}$ = 2.43 Hz, 1H, H-6a); 2.68 (sextet, 1H, H-3a); 2.22 (dd, $J_{5a,5e}$ = 14.36 Hz; $J_{5e,6a}$ = 2.44 Hz, 1H, H-5a); 3.71 (dd, 1H, H-5e); 3.86 (s, 3H,C=N-$OCH_3$); 0.97 (d, 3H, -$CH_3$ at C-3, $J$ = 6.60 Hz); 7.44-7.31 (10H, aryl protons) ppm; IR: 1630 (C=N stretching) cm$^{-1}$; MS (ES): *m/z*: 296.2 [*M*+1]; Anal. Cacld for $C_{19}H_{21}NO_2$: C 77.26, H 7.17, N 4.74, found C 77.25, H 7.19, N 4.75.

**6b**: 3-Ethyl-2,6-diphenyldihydro-*2H*-pyran-4(*3H*)-one *O*-methyloxime. White semi-solid, yield 95 %; $^1$H NMR: $\delta$= 4.31 (d, $J_{2a,3a}$ = 10.26 Hz, 1H, H-2a); 4.54 (dd, $J_{5a,6a}$ = 11.60; $J_{5e,6a}$ = 2.28 Hz, 1H, H-6a); 2.34 (m, 1H, H-3a); 1.99 (dd, $J_{5a,5e}$ = 13.96 Hz; $J_{5e,6a}$ = 2.24 Hz,1H, H-5a); 3.60 (dd, 1H, H-5e); 3.87 (s, 3H, C=N-O-$CH_3$); 1.61 (heptet, 1H, H of C-7); 1.23 (m, 1H, H' of C-7); 0.84 (t, 3H, -$CH_3$ at C-7, $J$ = 7.26 Hz); 7.44-7.24 (10H, aryl protons) ppm; IR: 1640 (C=N stretching) cm$^{-1}$; MS: *m/z*: 310.2 [$M$+1]; Anal. Cacld for $C_{20}H_{23}NO_2$: C 77.64, H 7.49, N 4.53, found C 77.67, H 7.50, N 4.54.

**6c**: No product.

**6d**: 2,6-*Bis*(4-fluorophenyl)-3,5-dimethyldihydro-*2H*-pyran-4(*3H*)-one *O*-methyloxime. Off-white solid, yield 77 %; $^1$H NMR: $\delta$= 4.18 (d, 1H, H-2a, $J_{2a,3a}$ = 10.42 Hz); 4.60 (d, 1H, H-6a, $J_{6a,5e}$ = 2.40 Hz); 3.57 (sextet, 1H, H-5e); 2.55 (sextet, 1H, H-3a); 3.89 (s, 3H, C=N-O-$CH_3$); 0.84 (d, 3H, $CH_3$ at C-3 (eq)), 0.86 (d, 3H, $CH_3$ at C-5 (ax)); IR: 1646 (C=N stretching) cm$^{-1}$; HRMS: *m/z*: 345.1 [$M^+$]; Anal. Cacld for $C_{20}H_{21}F_2NO_2$: C 69.55, H 6.13, N 4.06, found C 69.60, H 6.15, N 4.04.

**6e**: 2,6-*Bis*(4-chlorophenyl)-3,5-dimethyldihydro-*2H*-pyran-4(*3H*)-one *O*-methyloxime. Pale yellow semi-solid, yield 80 %; $^1$H NMR: $\delta$= 4.11 (d, 1H, H-2a, $J_{2a,3a}$ = 10.40 Hz); 4.67 (d, 1H, H-6a, $J_{6a,5e}$ = 2.36 Hz); 3.67 (sextet, 1H, H-5e); 2.57 (sextet, 1H, H-3a); 3.88 (s, 3H, C=N-O-$CH_3$); 0.83 (d, 3H, $CH_3$ at C-3 (eq)), 0.89 (d, 3H, $CH_3$ at C-5 (ax)); 7.50-7.37 (8H, aryl protons) ppm; HRMS: *m/z*: 377.1 [$M^+$]; Anal. Cacld for $C_{20}H_{21}Cl_2NO_2$: C 63.50, H 5.60, N 3.70, found C 63.55, H 5.65, N 3.67.

**6f**: 2,6-*Bis*(4-bromophenyl)-3,5-dimethyldihydro-*2H*-pyran-4(*3H*)-one *O*-methyloxime. Pale brown semi-solid, yield 82 %; $^1$H NMR: $\delta$= 4.12 (d, 1H, H-2a, $J_{2a,3a}$ = 10.36 Hz); 4.68 (d, 1H, H-6a, $J_{6a,5e}$ = 2.34 Hz); 3.67 (sextet, 1H, H-5e); 2.57 (sextet, 1H, H-3a); 3.88 (s, 3H, C=N-O-$CH_3$); 0.84 (d, 3H, $CH_3$ at C-3 (eq)), 0.87 (d, 3H, $CH_3$ at C-5 (ax)); 7.40-7.20 (8H, aryl protons) ppm; IR: 1648 (C=N stretching) cm$^{-1}$; HRMS: *m/z*: 465.0 [$M^+$]; Anal. Cacld for $C_{20}H_{21}Br_2NO_2$: C 51.72, H 4.53, N 3.00, found C 51.77, H 4.55, N 3.01.

**6g**: 2,6-*Bis*(4-methylphenyl)-3,5-dimethyldihydro-*2H*-pyran-4(*3H*)-one *O*-methyloxime. White semi-solid, yield 67%; $^1$H NMR: $\delta$=4.45 (d, 1H, H-2, $J_{2,3}$ = 5.60 Hz); 4.33 (d, 1H, H-6, $J_{6,5}$ = 9.22 Hz); 3.24 (sextet, 1H, H-5); 2.75 (sextet, 1H, H-3); 3.85 (s, 3H, C=N-O-$CH_3$); 1.29 (d, 3H, $CH_3$ at C-3, $J$ = 7.44 Hz); 1.18 (d, 3H, $CH_3$ at C-5, $J$ = 7.12 Hz); 2.23 (s), 2.22 (s) (6H, $CH_3$ at C-2"" and C-6""); 7.01-7.16 (8H, aryl protons) ppm; IR: 1650 (C=N stretching) cm$^{-1}$; HRMS: *m/z*: 337.2 [$M^+$]; Anal. Cacld for $C_{22}H_{27}NO_2$: C 78.30, H 8.06, N 4.15, found C 78.33, H 8.05, N 4.14.

**6h**: 2,6-*Bis*(4-methoxyphenyl)-3,5-dimethyldihydro-*2H*-pyran-4(*3H*)-one *O*-methyloxime. Off-white semi-solid, yield 71 %; $^1$H NMR: $\delta$= 4.45 (d, 1H, H-2, $J_{2,3}$ = 5.44 Hz); 4.29 (d, 1H, H-6, $J_{6,5}$ = 9.18 Hz); 3.22 (sextet, 1H, H-5); 2.73 (sextet, 1H, H-3); 3.85 (s, 3H, C=N-O-$CH_3$); 1.30 (d, 3H, $CH_3$ at C-3, $J$ = 7.34 Hz); 1.19 (d, 3H, $CH_3$ at C-5, $J$ = 7.12 Hz); 3.71 (s), 3.72 (s) (6H, $OCH_3$ at C-2"" and C-6""); 6.76-6.86 (dd, 4H, H-2"' and H-6"'), 7.26-7.35 (dd, 4H, H-2", H-6") ppm; IR: 1643 (C=N stretching) cm$^{-1}$; MS: *m/z*: 370.2 [$M$+1]; Anal. Cacld for $C_{22}H_{27}NO_4$: C 71.52, H 7.37, N 3.79, found C 71.50, H 7.40, N 3.78.

### Cytotoxicity Screening of the Synthesized Compounds

### Cell Types Used

The HeLa and A549 cell lines were acquired from the ATCC (USA). DMEM was procured from BioWhittaker®, FBS, and other cell culture tools were procured from Gibco BRL Life Technologies, USA, whereas, polyoxymethylene, PI, and Hoechst 33342 stain were obtained from Sigma–Aldrich.

### Cell Culture

Cell culture was performed in a T-75 tissue culture apparatus at 37 °C in a 5% carbon dioxide damped incubator via DMEM boasting 10% sterile FBS, one hundred units per milliliter Penicillin, and one hundred micrograms per milliliter of Streptomycin.

## RESULTS AND DISCUSSION

### Conformational Analysis

The NMR assignments are executed with the comparison of corresponding pyran-4-ones and analogous piperidin-4-ones and their oxime derivatives. Initially, the 3,5-dimetyl-2,6-diarylpyran-4-ones **5a-h** were

identified with the earlier reports. All the pyran-4-ones adopt the chair conformation with the equatorial disposition of the attachments on active methylene centers and adjacent to the heteroatom, respectively.[22,26] The vicinal coupling constants $^3J_{2a,3a}$ and $^3J_{5a,6a}$ of **6a** and **6b** claim that both are in the chair and the attachments are equatorially oriented as their precursors **5a** and **5b**, which is in good agreement with the earlier reports as mentioned above. Further, the couplings between the alkyl groups and H-3a point out the conformation of the alkyl groups as envisaged in Fig.-2. The magnitude of vicinal couplings of pyranones **5c-h** proved their existence in the chair with equatorial substituents, whereas in oxime ethers **6d-f**, the observed couplings indicate that they are not by the diaxial vicinal couplings and they are due to $^3J_{2a,3a}$ and $^3J_{5e,6a}$. This designates the chair conformation for the pyranone ring with an axial positioning of the $CH_3$ at C-5. The observed vicinal couplings of **6g** and **6h** suggest that they adopt neither the chair nor the boat conformation. If they adopted the rigid boat conformation, the N-O completely eclipses the α-(C-H) bonds, and thus, three bonded interactions between the nuclei is about 4 Hz.

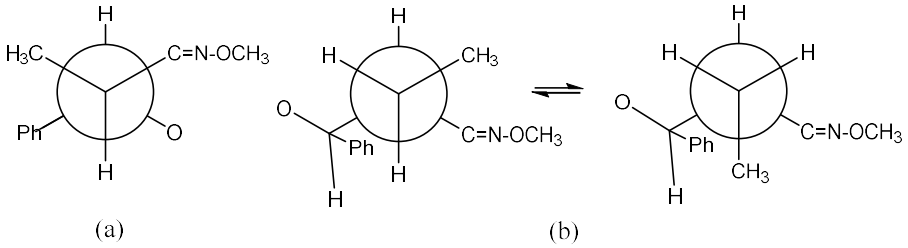



Fig.-2: (a) Conformation for the $CH_3$ at C-3 Attributed to Compound 6a. (b) Conformation of the $C_2H_5$ at C-3 Attributed to Compound 6b

## Epimerization

It is very interesting to study the effect on the stereochemistry of the insertion of $CH_3$ on C-3/C-5, which modifies the stereochemistry/conformation of the synthesized oximes ethers **6d-h** from their pyranone precursors **5d-h**, up to a significant level to severe change. The oxime derivatives **6d-f** experienced epimerization to hold on to the chair but to stabilize the chair conformation, the $CH_3$ on the same side as the $OCH_3$ of C=N underwent epimerization at C-5. Thus, those molecules are relieved from the severe $A^{1,3}$-interaction amongst the $CH_3$ and N-O. On the other hand, a rigorous change was observed on compounds **6g** and **6h** with a twist-boat conformation unlike the epimerization in analogous **6d-f** to hold on to the chair conformation. The conformation is well ascertained with our earlier report[17,22] on nitrogen analogs of the **6d-h**.

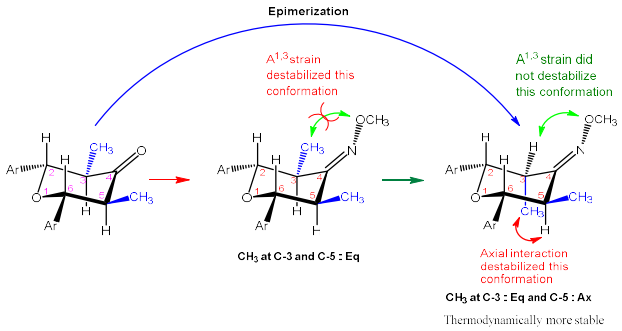



Fig.-3: Epimerization was Observed in Compounds 6d-f During the Conversion of Ketone into Oxime Functionality

### In Vitro Anticancer Study

All the synthesized pyranone derivatives **5a-h** and **6a-h** were examined to expose their cytotoxicity on cervical and lung cancer cell lines by the MTT method (Table-1). For a better perception, the activities of all compounds are compared with the standard drugs, which were also screened similarly.

Data from Table-1 is helpful in finding the more active molecules and rationalizing them for further view. The entire panel of synthesized compounds exhibits the antiproliferation $IC_{50}$ of <50 μM, except compounds **5a** and **5b** against HeLa cells, they also inhibited the proliferation by 54 and 51 μM, respectively. The activity is improved with an increase of alkyl chain length at C-3 of **5b** than **5a**, however, it is better by the

attachment of another $CH_3$ at C-5 of **5a**, which afforded **5c** with an $IC_{50}$ of 47 µM. Hence, to get further improvement, we have incorporated F, Cl, Br, $CH_3$, and $OCH_3$ substituents on the aryl groups, which pave the oxygen of **5c** of **5a-c**.

Table-1: Cytotoxic effect of pyranones **5a-h** and oxime ethers **6a-h**

| Compound | $IC_{50}$ in µM | |
|---|---|---|
| | HeLa | A549 |
| 5a | 54.5±0.6 | - |
| 5b | 51.3±1.0 | - |
| 5c | 47.4±0.7 | - |
| 5d | 21.6±0.8 | - |
| 5e | 17.3±1.1 | - |
| 5f | 19.4±0.5 | - |
| 5g | 44.9±0.5 | - |
| 5h | 39.4±1.2 | - |
| 6a | 48.3±0.9 | 24.8±0.4 |
| 6b | 32.7±0.1 | 18.2±1.4 |
| 6d | 13.4±0.7 | 13.5±0.7 |
| 6e | 11.8±0.9 | 12.7±0.2 |
| 6f | 17.4±0.5 | 17.5±0.6 |
| 6g | 38.4±0.7 | 40.4±0.7 |
| 6h | 34.9±0.5 | 26.6±0.4 |
| Camptothecin | 3.1±0.1 | 2.1±0.3 |
| Etoposide | 13.7±0.5 | 5.7±0.4 |

Accordingly, a significant improvement was noticed by the halo-substituted compounds **5d-f** (≤20 µM against HeLa) rather than the methyl/methoxy compounds **5g/5h** (45/39 µM). Then the oxime ethers **6a-h** of the above tested pyranones were screened for their cytotoxicity and a similar trend was observed for oxime ethers as well. The same as the halo compounds **5d-f**, corresponding oxime ethers **6d-e** also showed better activity between 12 and 17 µM than others, particularly, **6e** exhibited its best cytotoxicity against HeLa at an $IC_{50}$ of 11.78 µM. Overall, all oxime ethers **6a-h** revealed a marginal improvement in their $IC_{50}$ than their corresponding pyranones **5a-h**. Hence, we directly tested all oxime ethers **6a-h** against A549 cells. Similar to HeLa, the halo compounds **5d-f** showed good cytotoxicity of 13 to 17 µM against A549 cells as well.

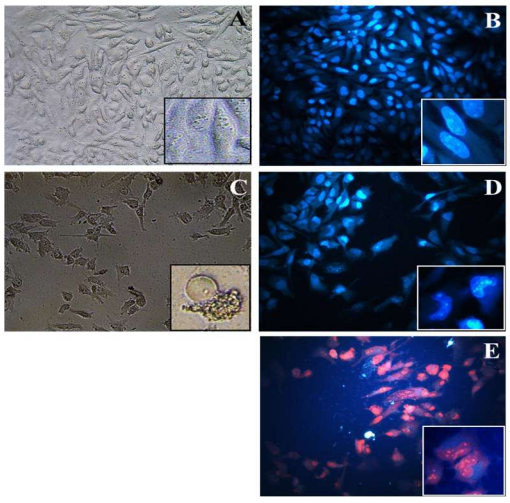



Fig.-4: Microscopic Portraits of Normal (A and B) and Treated (C, D and E) HeLa Cells, Obtained by Fluorescence (360/470 nm) and Light Microscopy (535/617 nm) for Hoechst and Propidium Iodide Stains, Separately

Also, **6e** registered its best at an $IC_{50}$ of 12.69 µM. Moreover, among the methyl/methoxy compounds **6g/6h**, the methoxy compound **6h** exhibited comparatively a better antiproliferation $IC_{50}$ of 26.60 against A549 than the required 34.94 µM for HeLa cells.

Further, we have repeated the cytotoxicity assay with the lead test compounds on the normal healthy cells of the Chang liver cell line. There is no indication of cell death in these cells up to 50 µM concentration of the test compound **6e**. Hence, these preliminary data suggest that **6e** can be considered as a lead to explore further study to propose as a medicinally important molecule. The Hoechst and Propidium Iodide-stained cells were pictured in a fluorescence microscope (CTR 6000; Germany) and manifested in Fig.-4 (HeLa) and 5 (A549) cells. The cell morphology irregularities ensued by the test molecules were detected using a phase contrast as well as fluorescence microscopes. The representative effects of the lead compound **6e** ($IC_{50}$ concentration) were micrographed by light and fluorescence microscopes to assess the cytotoxic nature of these compounds. The control group appeared as normal, and intact nuclei that were free from cytomorphological irregularities as observed in Fig.-4 and 5 (A and B). The cells were examined through high cytotoxic molecule **6e** at its $IC_{50}$ (24 hours) to explore the morphological changes which include a bulge of the plasma membrane of the cell, chromatin shortening, segmentation, and emergence of apoptotic blebs. Most of them expressed the signs of apoptosis with harsh destruction as the cytolysis and the consequent discharge of cytoplasm as perceived in the C of Fig.-4 and 5.

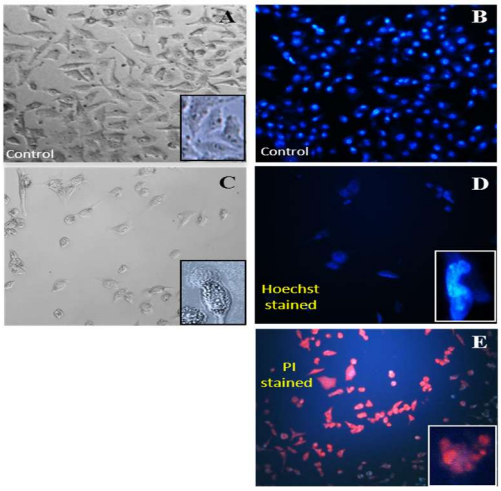



Fig.-5: Microscopic Portraits of Normal (A and B) and Treated (C, D and E) A549 Cells, Obtained by Fluorescence (360/470 nm) and Light Microscopy (535/617 nm) for Hoechst and PI Stains, separately.

The premature apoptosis of the cells observed in this study is due to nucleus shortening. The collapsed nuclear cytoplasmic congruousness is accompanied by trimmed karyon to a horseshoe curve image. In some treated cells, devastating parts of the nucleus (karyorrhexis and karyolysis) caused cytological aberration (pyknosis).[27]

## CONCLUSION

The present study involves the synthesis of pyranone derivatives with good yield and stereoselectivity. The 3-alkylated oxime ethers **6a** and **6b** adopt chair conformers through equatorial attachments as their precursors. Also, the 3,5-dimethyl compounds **6c-f** retained their chair conformation except the C-5 position $CH_3$, which epimerized to adopt an axial disposition to circumvent the 1,3-spatial interaction of the *syn* $CH_3$ and oxime functionality, whereas the compounds **6g** and **6h** turned as twist-boat. The new molecules registered a noteworthy activity against both HeLa and A549 cells, and particularly, oxime ethers expressed comparatively a better profile than pyranones. The preliminary investigation pointed out that compound **6e** is a lead molecule with good cytotoxicity of 11.78 µM for HeLa and 12.69 µM for A549 with the absence of collateral toxicity on normal healthy cells of Chang liver cells up to a 50 µM concentration. Thus, this molecule deserves further investigation.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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