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Synthesis of Chromene 4 Aldehyde and 6-Phenyl-6h-Chromeno [4,3-B] Quinoline Derivatives as Anticancer and Apoptosis Inducing Agents

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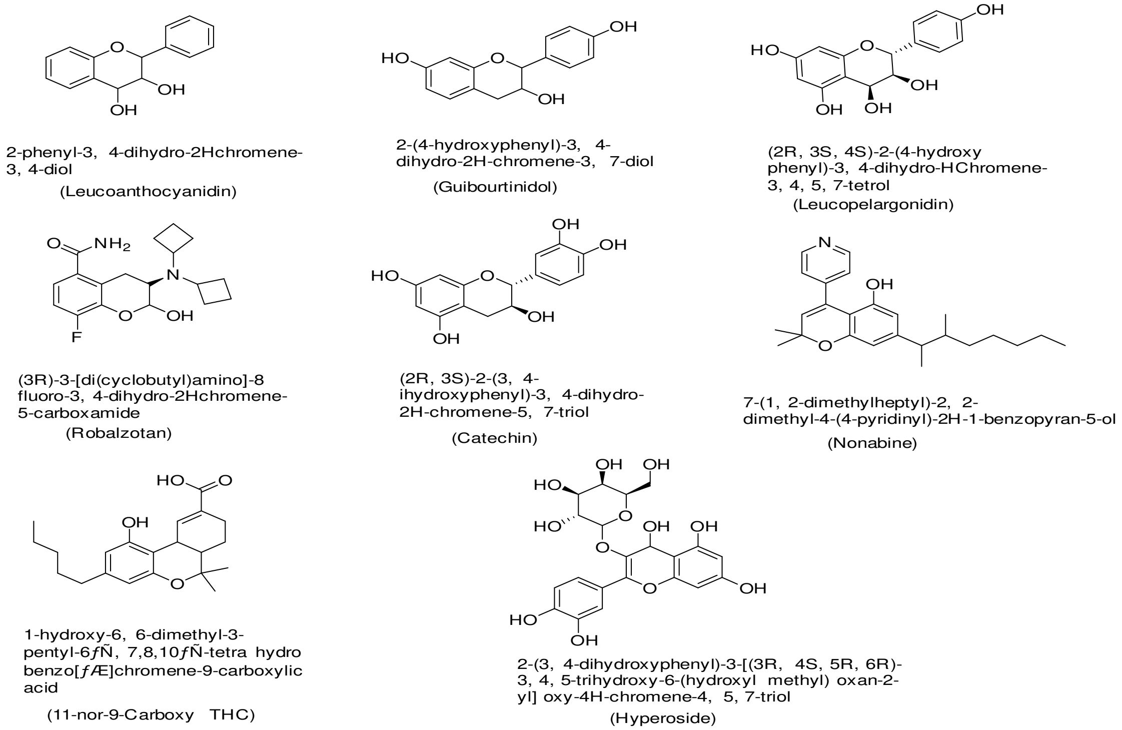
Abstract: A series of novel chromene 3-aldehyde and quinoline derivatives have been synthesized using diversely substituted nitroarenes in the presence of In, dil. HCl, H_2O (reductive amination) and evaluated for in vitro cytotoxic activity in three different cancer cell lines (MDA-MB-453, MCF-7, A549 and PC3). The synthetic strategy utilized to access these hybrids is operationally simple and works with great substrate scope. Interestingly, compound 6i was induced apoptosis to a significant extent in MDA-MB-453 cell lines. And these selected compounds 6i was led to morphological changes after treatment with MDA-MB-453 cell lines and found clear destabilization of mitochondrial membrane potential behind the observed anticancer activity. This strategy is operationally simple and works with a diverse range of substrates and warrants future investigations for further anticancer drug development.

I. INTRODUCTION

During the last twenty years, the study of the biological activities of chromene derivatives has been the aim of many scientists[1] recently, the antibacterial, anti-helminthic, anticoagulant, hypothermal and vasodilatory properties of chromene has been reviewed. Fused chromenes are interesting due to their significant anti-cancer activities[2].

Functionalized six-membered quinolines as structural motifs are found so often in many natural products and bioactive molecules. Quinoline structural motif is played key role in medicine as anti-malarial, antibiotics, antibacterial, anti-cancer, anti-HIV, ant-tuberculosis, anti-Alzheimer activities. They have also utilized to designing bio active drug candidates. In addition, they have applied as dyes, agrochemicals and corrosion inhibitors[3].



2-phenyl-3, 4-dihydro-2Hchromene-3, 4-diol
(Leucoanthocyanidin)

2-(4-hydroxyphenyl)-3, 4-dihydro-2H-chromene-3, 7-diol
(Guibourtinidol)

(2R, 3S, 4S)-2-(4-hydroxy phenyl)-3, 4-dihydro-HChromene-3, 4, 5, 7-tetrol
(Leucopelargonidin)

(3R)-3-[di(cyclobutyl)amino]-8 fluoro-3, 4-dihydro-2Hchromene-5-carboxamide
(Robalzotan)

(2R, 3S)-2-(3, 4-ihydroxyphenyl)-3, 4-dihydro-2H-chromene-5, 7-triol
(Catechin)

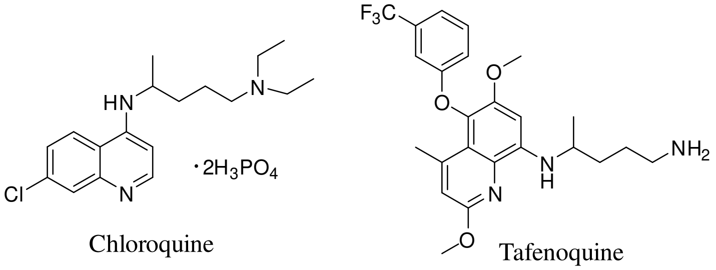
7-(1, 2-dimethylheptyl)-2, 2-dimethyl-4-(4-pyridinyl)-2H-1-benzopyran-5-ol
(Nonabine)

1-hydroxy-6, 6-dimethyl-3-pentyl-6ƒÑ, 7,8,10ƒÑ-tetra hydro benzo[ƒÆ]chromene-9-carboxylic acid
(11-nor-9-Carboxy THC)

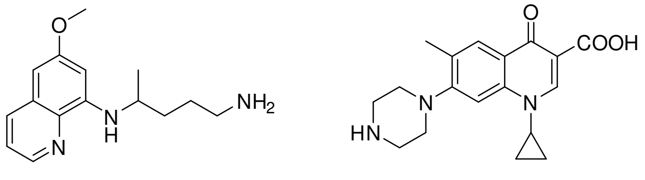
2-(3, 4-dihydroxyphenyl)-3-[(3R, 4S, 5R, 6R)-3, 4, 5-trihydroxy-6-(hydroxyl methyl) oxan-2-yl] oxy-4H-chromene-4, 5, 7-triol
(Hyperoside)

Figure 1: Chromone moiety containing drugs

Because of this ample range of applications in, modern medicinal chemistry, agriculture, biopharmaceutical industry numerous methods have been reported for the synthesis of these molecules[4]. The earlier methods reported harsh reaction conditions and utilization of costly reagents and catalysts draw backs in those methods.



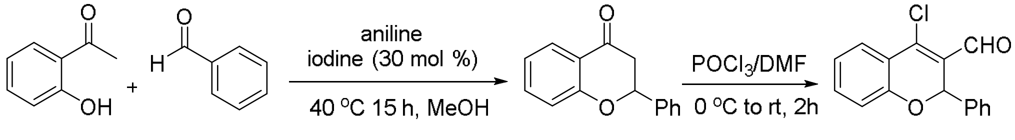
Chloroquine Tafenoquine



Primaquine Ciprofloxacin

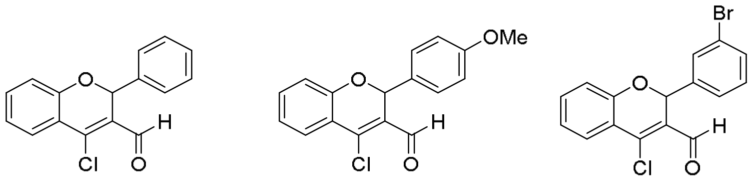
Figure 2: Quinoline moiety containing drugs

In continuation of our work[5] towards development of biologically active molecules, initially we have prepared 4-chloro-2-aryl-2*H*-3-chromene carbaldehyde **4**. Accordingly, flavone **3** was prepared from commercially available 2-hydroxy-acetophenone **1** and benzaldehyde **2** involving base catalyzed aldol-condensation and intramolecular oxa-Michael addition sequene. Flavone **3** was subjected Vilsmeier-Haack reaction[6, 7] using $POCl_3$ and DMF to furnish the desired 4-chloro-2-aryl-2*H*-3-chromene carbaldehyde **4** in good yield (Scheme 1). Utilizing similar synthetic sequence, we have prepared several analogues of **4** to access diverse chromene-quinoline hybrids (Scheme 1).



1 **2** **3** **4**

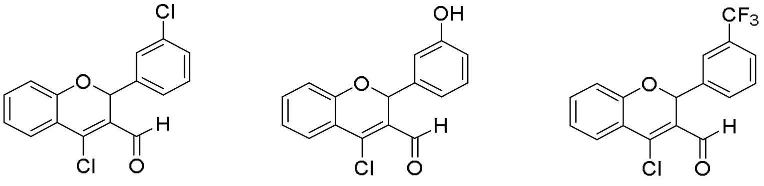
Scheme 2: Optimization of condition for the synthesis of chromene-quinoline hybrids



4a
Overall yield 45%

4b
Overall yield 34%

4c
Overall yield 38%



4d
Overall yield 32%

4e
Overall yield 35%

4f
Overall yield 37%

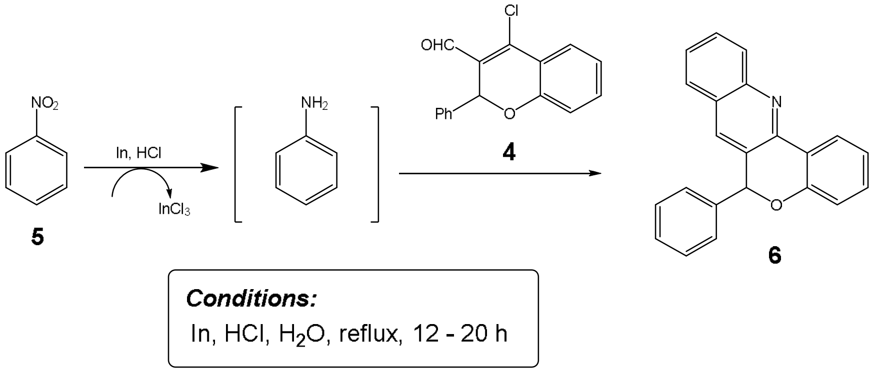
Figure 3: Synthesized chromene aldehyde derivatives

Table 2: Synthesis of Chrome 3 carbaldehyde derivatives.

Entry	**2(a-f)**	Product 4**(a-f)**	Overall Yield[a] (%)
1	Ph	**a**	45
2	Ph-4-OMe	**b**	34
3	Ph-3-Br	**c**	38
4	Ph-3-Cl	**d**	32
5	Ph-3-OH	**e**	35
6	Ph-3-CF_3	**f**	37

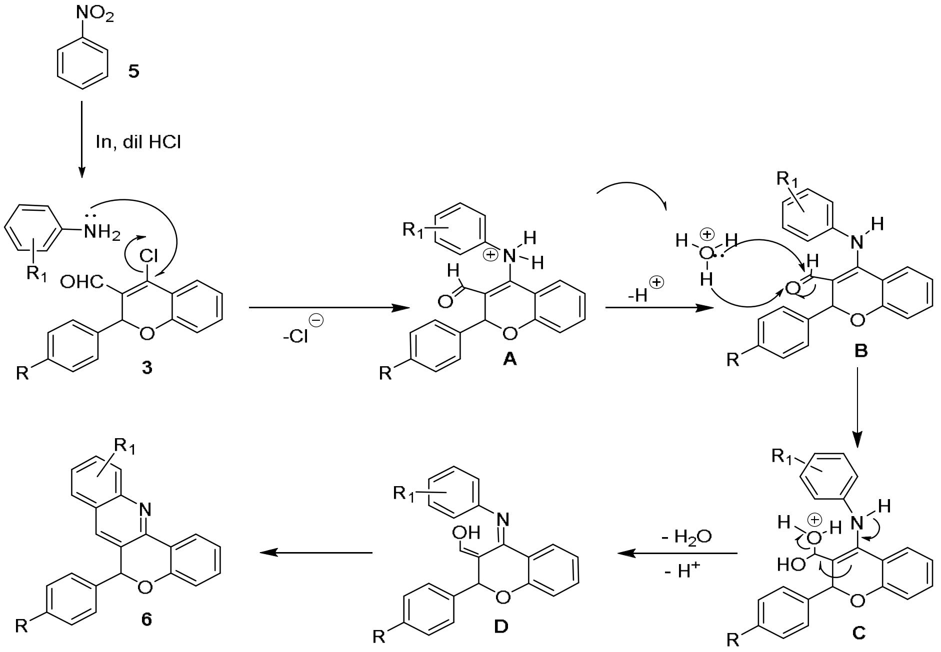
Nitroarenes possessing electron donating and withdrawing groups with various substitution patterns were tested in this reaction using method. Corresponding conditions of methodology was worked well and furnished desired products in excellent yields irrespective of electronic and steric nature of substrates (Table 2, entries 1-18). Chemical structures of all products were confirmed by 1H, 13C NMR, mass spectrometric data and the obtained data is in good agreement reported literature.

Formation of quinoline ring system always interesting in organic chemistry because of various applications in the synthesis of several compounds with six-membered rings. Here we have taken advantage of both chromene and quinoline architectures to make biologically potent molecules. The present method has proved to be a powerful tool for the intramolecular creation of carbon-carbon and carbon-nitrogen bonds. We herein report a protocol for the construction of chromene-quinoline hybrid comprising indium in dilute hydrochloric acid under reflux conditions. Reduction of nitroarenes is a widely fundamental organic transformation, which is highly demanding in pharmaceutical process development. These nitro arenes were readily reduced to corresponding amines via well protocols using In/dil. HCl in gram scale. In various organic synthesis water has been used as green solvent[8]. We hypothesized that, reduction of nitroarenes to anilines followed by subsequent condensation with the added chromene-3-carbaldehyde under these conditions (In, HCl, H_2O, reflux) would deliver the desired chromene-quinoline hybrid, in a straightforward manner (Scheme. 2).



Scheme 2. Synthesis of chromene-quinoline hybrids.

A plausible reaction mechanism was proposed based on reported literature and results obtained in this work, which is described in Scheme 3. As described in Scheme 2, under reaction conditions of methods A & B, nitroarenes **5** reduced to corresponding amine, which participated in the reaction cycle with chromene-3-carbaldehyde **4** and furnishes the imine **A**. Bronsted acid mediated (Indium/HCl/H_2O) formation of acetal **C** via **B** and subsequent rearrangement will provide the enol intermediate **D**, which undergo Fridel-Crafts type addition and aromatization steps to deliver the taget chromene-quinoline hybrid **6** (Scheme 3).



Scheme 3. The plausible reaction mechanism of the formation of the chromene-quinoline hybrid.

Table 2: Synthesis of the 6- phenyl-6*H*-chromeno [4,3-*b*] quinoline 6 (a-r) from Chrome 3 carbaldehyde.

Entry	R	R^1	Product 6	Time (h)	Yield^c(%)
1	H	H	a	8	80
2	H	3-Br	b	2	68
3	3-Cl	3-OMe, 4-OMe, 5-OMe	c	8	78
4	H	2-OMe, 3-OMe, 4-OMe	d	12	82
5	4-OMe	3-F	e	10	81
6	4-OMe	3-Cl	f	8	83
7	H	2-Me, 3-Br, 5-Cl	g	12	84
8	4-OMe	3-Me	h	8	72
9	H	3-NO_2	i	10	86
10	H	4-F	j	8	81
11	H	4-Cl	k	10	83
12	H	3-OMe, 4-OMe, 5-OMe	l	12	85
13	3-Cl	4-OH	m	10	86
14	H	3-Me, 4-OMe	n	12	87
15	3-Br	4-OH	o	12	81
16	4-OMe	4-OH	p	12	72
17	4-Br	H	q	8	67
18	3-Cl	H	r	12	82

[a] Reagents and conditions: nitroarene 1 (1.0 mmol), aldehyde 2 (1.0 mmol), In (2.0 mmol), 1 M aq HCl (1 mL), reflux.
[b] All the products were fully characterized by the usual spectroscopic techniques.

Despite the above significant achievements, the design and development of synthetic processes, beginning with easily available materials to afforded densely functionalized quinine derivatives are still of great value. Compounds were evaluated for their anti-cancer activity against MDA-MB-453, MDA-MB-231, NCI, and HCT-15 cell lines. The cytotoxicity was verified in MDA-MB-453 cells.

Table 3: In vitro cytotoxicity (IC_{50} µM) against human cancer cell lines

Compound	^{a}MDA-MB-453	^{a}MDA-MB-231	^{c}NCI	^{d}HCT-15
4a	>40	>40	>40	>40
4b	>40	>40	>40	>40
4c	>40	>40	>40	>40
4d	>40	>40	>40	>40
4e	27±5.2	22.2±1.7	17.3±0.9	21.8±1.1
4f	>40	>40	>40	>40

50% Inhibitory concentration after 48 h of drug treatment, ^{a,b}breast cancer ^{c}lung cancer, ^{d}colon cancer

Table 4: In vitro cytotoxicity (IC_{50} µM) against human cancer cell lines

Compound	^{a}MDA-MB-453	^{a}MDA-MB-231	^{c}NCI	^{d}HCT-15
6a	>40	>40	>40	>40
6b	>40	>40	>40	>40
6c	26.5±0.5	17.9±2.2	35±6.7	32±6.7
6d	36±6.8	25.2±4.2	27.5±0.5	39.8±6.4
6e	17±5.2	22.2±1.7	32.9±5.4	21.8±1.1
6f	>40	>40	>40	>40
6g	25±4.6	24.2±4.2	12.6±0.9	32.9±5.4
6h	>40	>40	>40	>40
6i	6.3±0.9	27±5.2	22.2±1.7	21.8±1.1
6j	>40	>40	>40	>40
6k	>40	>40	>40	>40
6l	>40	>40	>40	>40
6m	>40	>40	>40	>40
6n	>40	>40	>40	>40
6o	32±6.7	17.9±2.2	26.5±0.5	39.8±6.1
6p	>40	>40	>40	>40
6q	>40	>40	>40	>40
6r	>40	>40	>40	>40

50% Inhibitory concentration after 48 h of drug treatment, ^{a,b}breast cancer ^{c}lung cancer, ^{d}colon cancer

II. PHARMACOLOGY

A. *In vitro anti-cancer activity*

A series of 6 different chromene 3 aldehydes (**4a-f**) and series of 18 different quinoline and chromene hybrids (**6a-r**) were synthesized and investigated for their cytotoxicity.

At first chromene 3 carbaldehyde derivatives **4(a-f)** were assessed in 4 different cell lines. Human breast (MDA-MB-453, MDA-MB-231), lung (NCI), colon cancer (HCT-15) based on % inhibition, the compounds were selected for IC_{50} evaluation (Table 3)[9]. Also % inhibition and IC_{50} was analyzed for chromene quinoline hybrids evaluated for their anti-cancer activity in 4 different cell lines (Table 4). Compared to chromene aldehyde series quinine derivatives more active against MDA-MB-453 cell lines.

The compounds **4(a-f)** against cell lines only one compound (4e) has considerable IC_{50} values from (Table 3). Most active compound found as 3-hydroxy substituted chromene-3-carbaldehyde **4e** on all cancer cell lines predominantly on NCI cancer cells IC_{50} values 17.3±0.9. Among quinoline series **6(a-r)** found lead molecule Thiophene scaffolds with flexible ester linkage not much active against HT29 and HCT116 cells. Compound **6i** was selected from the series of 18 chromene quinoline hybrids as the potential candidate based on IC_{50} (6.3±0.9) results. It showed sensitivity towards lung cancer cell line A549. Acridine orange/Ethidium bromide dye and DAPI staining were used to visualize morphological changes. Fluorescence microscope (Nikon Inc. Japan) was used to capture the images including phase contrast images in treated cells.

B. *Apoptosis Detection Studies*

1) *Morphological Changes (Phase Contrasted Imaging):* To examine whether the treatment with the compound could lead to loss of cell viability and prompted the induction of apoptosis, MDA-MB-453 cells were treated with different concentrations of the most potent compound **6i**. After 48 hrs of post-treatment, cells were ascertained under a phase contrast microscope (Nikon). The results from (Figure. 3) concludes that the treatment with compound **6i** showed reduced number of viable lung cancer cells dose dependently in comparison to the control cells where they appeared intact. Moreover, in the treated cells distinct and remarkable morphological features including detachment and cell shrinkage was observed[10].

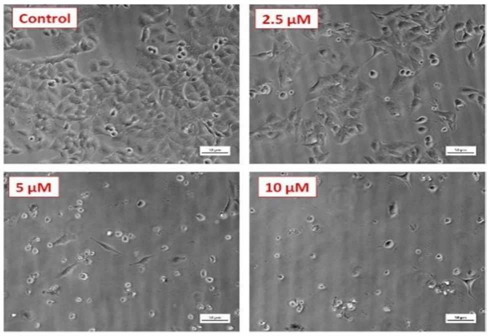


Figure 3. Morphological changes observed in breast cancer cells. MDA-MB-453 cells were treated with and without compound 6i for 48 h and images were captured by phase contrast microscope at 200X magnification.

2) *Acridine Orange/ethidium Bromide (AO/EB) Staining:* Versatile fluorescent agents acridine orange/ethidium bromide dyes were used to identify dead and apoptotic cells[11]. EB stain only cells in the nuclei that have lost membrane integrity, whereas AO can stain the nuclei green which responsible for permeate the intact cell membrane. Experiment conducted in dose dependent manner at concentrations 2.5, 5 and 10 μM. In addition, early and late apoptotic cells can be determined by this assay. Thick orange spots indicated late stage apoptosis which determines chromatin condensation by ethidium bromide stain. Green to dark green colored areas represents chromatin condensation, fragmentation and cell shrinkage which is a sign of early stage apoptosis (Figure 5). Thus, apoptosis inducing confirmed with compound **6i** in breast cancer cells whereas control showed green color which represents normal morphology.

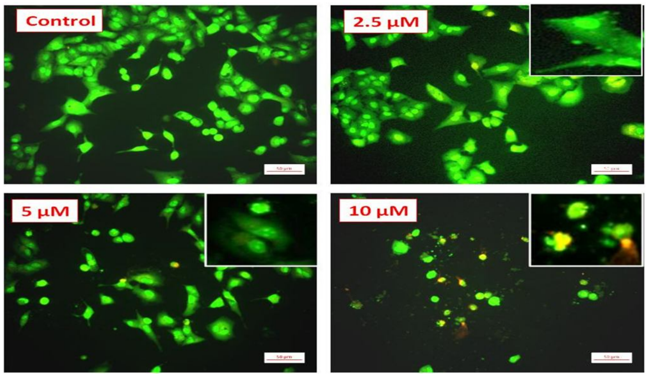


Figure 5. AO/EB staining of compound 6i on breast cancer cell line. MDA-MB-453 cells were treated with compound 6i with the 2.5, 5 and 10 μM concentrations and compared with control. All the representative images were captured by fluorescent microscope at 200X magnification.

3) *DAPI Nucleic Acid Staining:* Chromatin condensation or nuclear damage can be visualized by fluorescent dye DAPI (4',6-diamidino-2-phenylindole) which bind strongly to A-T rich sequences of DNA. We can determine apoptotic cells from live cells by giving bright blue color by staining the condensed nuclei. Hence, apoptotic property of compound **6i** was determined by this staining technique in MDA-MB-453 cell line. It was observed in Figure. 6 fragmented or horseshoe shaped, condensed nuclear structure at 5 and 10 µM concentrations[12].

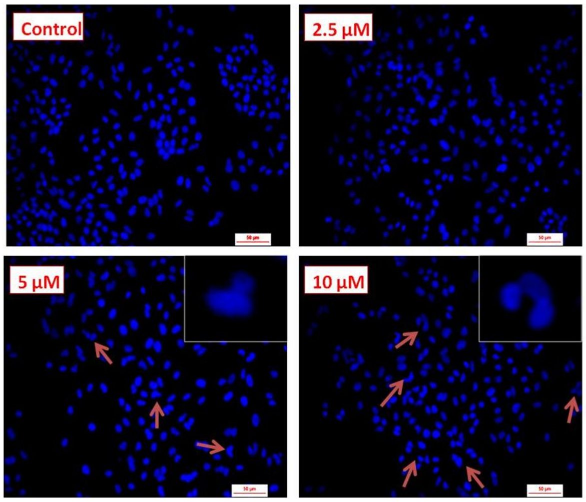


Figure 6. Nuclear morphology of breast cancer cells after DAPI staining. MDA-MB-453 cells were treated with compound 6i for 48 h and stained with DAPI. The control represents DAPI stain of without compound 6i. The images were captured with fluorescence microscope at 200X magnification. Arrows represent the changes in nuclear structure such as chromatin condensation and nuclear damage.

4) *JC-1 Staining:* Power house mitochondria play an important role in apoptotic signaling and regulates the electron transport chain by oxidative stress leads to depolarization of mitochondrial membrane potential ($\Delta\Psi_m$) reactive oxygen species (ROS) generation (4). Treatment of MDA-MB-453 cells with compound 6d showed reduction in the $\Delta\Psi_m$ compared to control as depicted in the Figure. 7. The compound represented collapse of $\Delta\Psi_m$ in dose dependent manner compared to the control. Therefore, lethal effects on mitochondria and subsequent events of apoptosis (Figure. 7)[13].

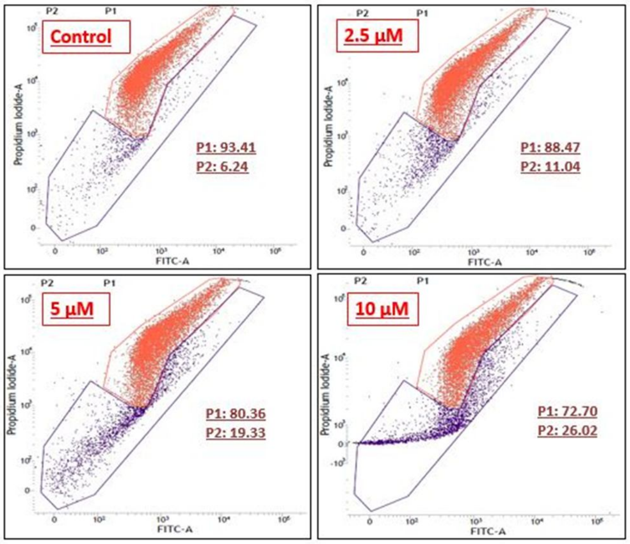


Figure 7. Mitochondrial membrane potential (ΔΨm) of MDA-MB-453 cells upon compound 6i exposure. A549 cells were treated with different concentrations of compound 6i for 48 h and stained with JC-1 followed by flow cytometric analysis.

In conclusion, we have developed an efficient synthesis of quinoline derivatives by reductive amination reactions of nitroarenes and chromene aldehydes, by using indium in dilute hydrochloric acid. The direct application of nitroarenes and the conversion in water are the notable features of the present novel method. The conversion in water of nitroarenes are the remarkable features of the present work. In addition, these chromene aldehyde series and quinoline series evaluated for their *in vitro* anticancer potentials. The initial cytotoxicity evaluation of quinoline derived library identified lead molecule **6i** with IC_{50} 6.3±0.9 μM towards MDA-MB-453 breast cancer cell line. To accelerate further in detail conducted various assays like DAPI nuclear staining, AO/EB staining, and JC-1 staining which supported the apoptosis in MDA-MB-453 cells induced by compound **6i** in a concentration dependent manner. Our results demonstrate that prepared new chemical entities are capable of inducing apoptosis in targeting breast cancer. Thus, combining all these results shows the biological importance of quinoline derivatives and can be developed as anti-cancer agents.

III. ACKNOWLEDGEMENTS

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REFERENCES

[1] (a). Soine T. O; J. Pharm. Sci. **1964,** 53, 231.; (b) Badran M.M.; Ismail M.M.; El-Hakeem A; Egypt. J. Pharm. Sci. **1992,** 33, 1081.; (c) El-Farargy A.F. Egypt; J. Pharm. Sci. **1991,** 32, 625.; (d) 21. Tunek H. Monatsh. Chem.; **1962,** 93, 684.; (e) Nofal Z.M.; El-Masry H.; Fahmy H.H.; Sarhan I; Egypt J. Pharm. Sci. **1997,** 38, 1. (f) Nofal Z.M., El-Zahar M.I.; Abd-El-Karim S. S. Molecules **2000,** 5, 99. (j) Priepke H.; Kauffimann-Hefinar I.; Damm K.; Schnapp A. WO Patent, **2003**, 2003006443. (k) Vijaykumar P. R.; Vinod R.; Rajeswar R. V. Indian J. Chem. **2003,** 42, 1738.; (l) Venugopala K. N.; Jayashree B. S. Indian J. Heterocyclic Chem. **2003,** 12, 307.; (m) Vaccaro W.; Yang B.; Kim S.; Huynh T.; Leavitt K.; Li W. WO Patent 2004, 4009017.

[2] (a) Okumura K.; Ashino K.; Okuda T. Yakugaku Zasshi **1962,** 81, 1482, Chem. Abstr. **1962**, 56, 7938.; (b) Gingolani G. M.; Gaultrieri F.; Pigini J. Med. Chem. **1969,** 12, 531.; (c) Rao B.; Mouli C.; Reddy Y. D. Ind. J. Chem**.** **1983**, 2B, 176.; (d) El-Naggar A. M.; Ahmed F. S.; Abd El-Salam A. M.; Rady M. A.; Latif M. S. A. J.Heterocycl. Chem. **1981,** 18, 1203.; (e) Moustafa M.A, Scientica Pharmaceutica (Sci. Pharm.), **1991,** 59, 213.

[3] (a) Michael, J. P. Nat. Prod. Rep. **2005**, 22, 627. (b) Michael, J. P. Nat. Prod. Rep. **2007**, 24, 223. (c) Bray, P. G.; Ward, S. A.; O'Nell, P. M. Curr. Top. Microbiol. Immunol. **2005**, 295, 3. (d) Osiadacz, J.; Kaczmarek, L.; Opolski, A.; Wietrzyk, J.; Marcinkowska, E.; Biemacka, K.; Radzikowski, C.; Jon, M.; Peczynska-Czoch, W. Anticancer Res. **1999**, 19, 3333. (e) Martirosyan, A. R.; Rahim-Bata, R.; Freeman, A. B.; Clarke, C. D.; Howard, R. L.; Strobel, J. S. Biochem.Pharmacol. **2004**, 68, 1729. (f) Tsotinis, A.; Vlachou, M.; Zouroudis, S.; Jeney, A.; Timar, F.; Thruston, D. E.; Roussakis, C. Lett. Drug Des. Discovery **2005**, 2, 189. (g) Fakhfakh, M. A.; Fournet, A.; Prina, E.; Mouscadet, J. F.; Franck, X.; Hocquemiller, R.; Figadere, B. Bioorg. Med. Chem. **2003**, 11, 5013. (h) Franck, X.; Fournet, A.; Prina, E.; Mahieux, R.; Hocquemiller, R.; Figadere, B. Bioorg. Med. Chem. Lett. **2004**, 14, 3635. (i) Muruganantham, N.; Sivakumar, R.; Anbalagan, N.; Gunasekaran, V.; Leonard, J. T. Biol. Pharm. Bull. **2004**, 27, 1683. (j) Vangapandu, S.; Jain, M.; Jain, R.; Kaur, S.; Singh, P. Bioorg. Med. Chem. **2004**, 12, 2501. (k) Nayyar, A.; Malde, A.; Jain, R.; Coutinho, E. Bioorg. Med. Chem. **2006**, 14, 847. (l) Camps, P.; Gomez, E.; Munoz-Torrero, D.; Badia, A.; Vivas, N. M.; Barril, X.; Orozco, M.; Luque, F. J. J. Med. Chem. **2001**, 44, 4733. (m) Anzini, M.; Cappelli, A.; Vomero, S.; Giorgi, G.; Langer, T.; Hamon, M.; Merahi, N.; Emerit, B. M.; Cagnotto, A.; Skorupska, M.; Mennini, T.; Pinto, J. C. J. Med. Chem. **1995**, 38, 2692. (n) Hoemann, M. Z.; Kumaravel, G.; Xie, R. L.; Rossi, R. F.; Meyer, S.; Sidhu, A.; Cuny, G. Bioorg. Med. Chem. Lett. **2000**, 10¸ 2675. (o) Balsubramanian, M.; Keay, J. G. In Comprehensive Heterocyclic Chemistry II, Vol. 5; Katritzky, A. R.; Rees, C. W.; Seriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 245-300. (p) Kim, J. L.; Shin, I. S.; Kim, H. J. Am. Chem. Soc. **2005**, 127, 1614. (p) Zhang, X.; Shetty, A. S.; Jenekhe, S. A. Macromolecules **1999**, 32, 7422. (q) Jenekhe, S. A.; Lu, L.; Alam, M. M. Macromolecules **2001**, 34, 7315.

[4] For some recent examples, see: (a) Horn, J.; Marsden, S. P.; Nelson, A.; House, D.; Weingarten, G. G. Org. Lett. **2008**, 10, 4117. (b) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. Org. Lett. **2007**, 9, 2645. (c) Luo, Y.; Li, Z.; Li, C.-J. Org.Lett. **2005**, 7, 2675. (d) Martinez, R.; Ramon, D. J.; Yus, M. J. Org. Chem. **2008**, 73, 9778. (e) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. J. Org. Chem. **2007**, 72, 6873. (f) Korivi, R. P.; Cheng, C.-H. J. Org. Chem. **2006**, 71, 7079. (g) Song, S. J.; Cho, S. J.; Park, D. K.; Kwon, T. W.; Jenekhe, S. A. Tetrahedron Lett. **2003**, 44, 255. (h) Zhang, W.; Jia, X.; Yang, L.; Liu, Z.-L. Tetrahedron Lett. **2002**, 43, 9433. (i) Kobayashi, K.; Yoneda, K.; Miyamoto, K.; Morikawa, O.; Konishi, H. Tetrahedron **2004**, 60, 11639. (j) Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B. A.; Ramesh, C. h.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Rao, V. J. Bioorg. Med. Chem. **2006**, 14, 4600. (k) Matrinez, R.; Ramon, D. J.; Yus, M. Eur. J. Org. Chem. **2007**, 1599. (l) Beller, M.; Thiel, O. R.; Trauthwein, H.; Hartung, C. G. Chem. Eur. J. **2000**, 6, 2513. (m) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. Chem. Commun. **2001**, 2576. (n) Luo, Z. Y.; Zhang, Q. S.; Oderaotoshi, Y.; Curran, D. P. Science **2001**, 291, 1766. (o) Jana, G. P.; Mukherjee, S.; Ghoray, B. K. Synthesis **2010**, 3179. (p) Rueping, M.; Sugiono, E.; Schoepke, F. R. Synlett **2010**, 852. (q) Georgescu, E.; Caira, M. R.; Georgescu, F.; Draghici, B.; Popa, M. M.; Dumitrascu, F. Synlett **2009**, 1795. (r) Yadav, J. S.; Reddy, B. V. S.; Yadav, N. N.; Gupta,M. K. Synthesis **2009**, 1131.

[5] (a) Synthesis of some new pulvinamides and their anti-inflammatory activity T. R. Reddy, P. Sreenivas, M. K. Reddy, Heterocycl. lett., **2013,** 3, 437-442; (b) Novel synthesis of 2-(2-(3-hydroxy-5-oxo-4-phenylthiophen-2(5H)-ylidene)-2-phenylacetamido) propanoic acid analogues and their anti-inflammatory properties M. K. Reddy, T. R. Reddy, K. R. Raju, PHOSPHORUS SULFUR, **2010,** 185, 313-318.

[6] (a) S. R. Moorty, V. Sundaramurthy, N. V. Subba Rao, Indian J. Chem Sec A, **1973**, 11**,** 854-856; (b) M. Venkati, R. S. Satyanarayana, G. Y. S. K. Swamy, K. Ravikumar, G. L. D. Krupadanam, Arkivok., **2012**, 355-364.

[7] (a) W. Baker, J. Chem.Soc, **1933**, 51, 1381-1389. (b) W.Baker, J. Chem. Soc, **1934**, 52, 1953-1954; (c) H, S. Mahal, K. Venkataraman, J. Chem. Soc, **1934**, 53, 1767-1769; (d) D. C. Bhalla, H. S. Mahal, K. Venkataraman, J. Chem. Soc, **1935**, 868-870; (e) J. A. Joule, K. Mills, Heterocycl.Chem, **2010**, 5th ed. Chichester, United Kingdom.

[8] (a) Minakata, S.; Komatsu, M. Chem. Rev. **2009**, 109, 711. (b) Lindström, U. M. Chem. Rev. **2002**, 102, 2751. (c) Liu, R.; Dong, C.; Liang, X.; Wang, X.; Hu, X. J. Org. Chem. **2005**, 70, 729. (d) Das, B.; Holla, H.; Venkatesh, K.; Majhi, A. Tetrahedron Lett. **2005**, 46, 8895.

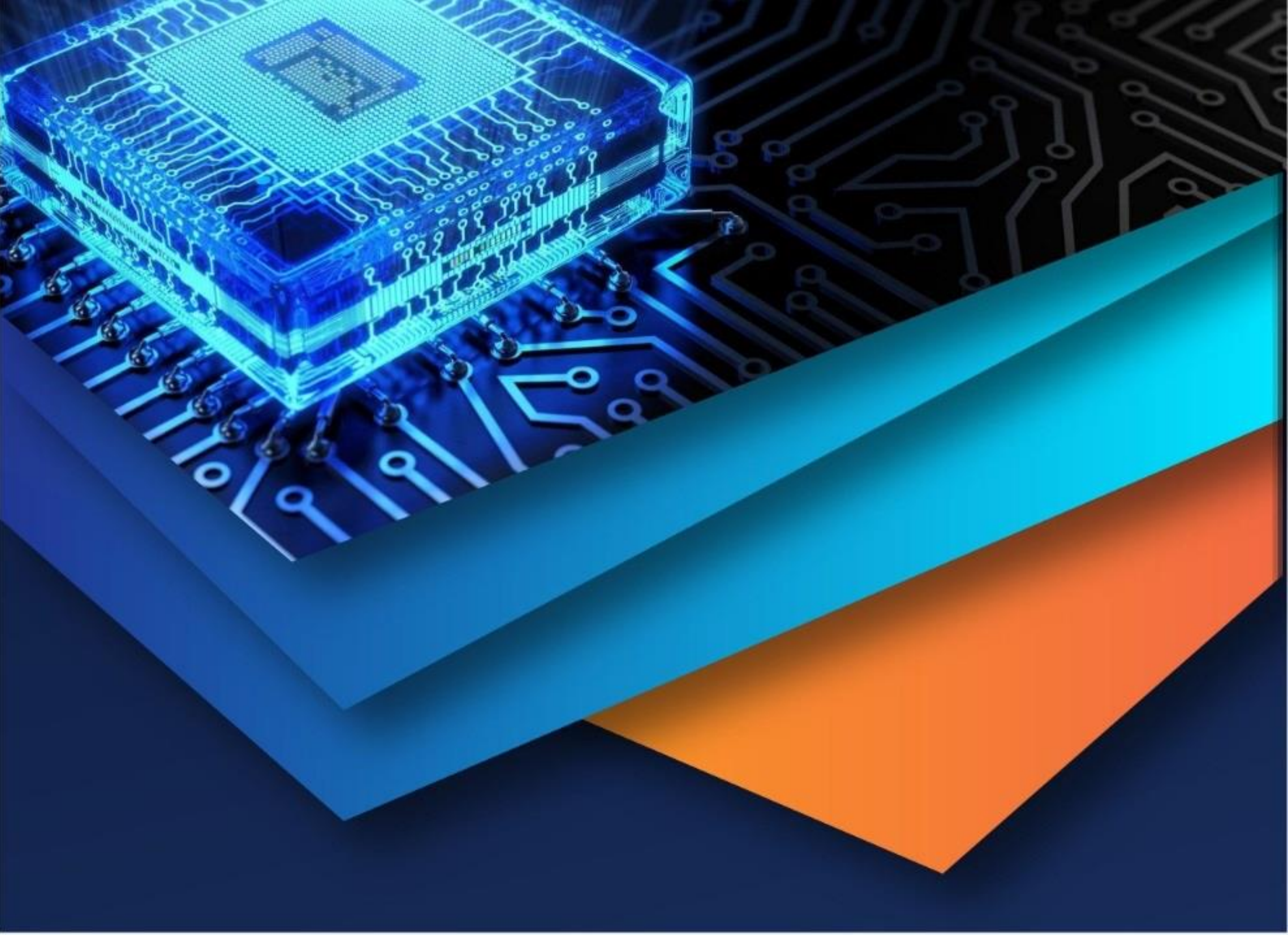
[9] S. Shrivastava, P. Kulkarni, D. Thummuri, M. K. Jeengar, V. G. M. Naidu, M. Alvala, G. B. Reddy, S. Ramakrishna, Piperlongumine, an alkaloid causes inhibition of PI3 K/Akt/mTOR signaling axis to induce caspase-dependent apoptosis in human triple-negative breast cancer cells. Apoptosis, **2014**, 19, 1148-1164.

[10] S. Vishal, C. Ashun, A. Saroj, K. S. Ajit, P. S. I. Mohan, Eur J Med Chem, **2013**, 69, 310-319.

[11] E-R. Hahm, M. B. Moura, E. E. Kelley, B. V. Houten, S. Shiva, S. V. Singh, Withaferin A-Induced Apoptosis in Human Breast Cancer Cells Is Mediated by Reactive Oxygen Species, PLos One, **2011**, 6, e23354.

[12] S. G. Kennedy, E. S. Kandel, T. K. Cross, N. Hay, Akt/Protein kinase B inhibits cell death by preventing the release of cytochrome c from mitochondria, Mol. Cell Biol. **1999**, 19, 5800-5810.

[13] T. S. Reddy, H. Kulhari, V. G. Reddy, A. V. S. Rao, V. Bansal, A. Kamal, R. Shukla, Synthesis and biological evaluation of pyrazolo–triazole hybrids as cytotoxic and apoptosis inducing agent, Org. Biomol. Chem, **2015**, 13, 10136-10149.



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