RESEARCH PAPER

One Pot Synthesis of 4-Chloro-8-Methyl-1h-Quinolin-2-One Clubbed 1, 3, 4 Oxadiazoles Along With Thiophene, Furan and Pyrrole by Oxidative Iodocyclisation and Their Cytotoxicity Study Against Cervical Cancer Cells (Hela Cells)

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ABSTRACT
We have developed one pot methodology for synthesis of 4-chloro-8-methyl-1H-quinoline-2-one clubbed [1,3,4]-oxadiazoles along with thiophene, furan and pyrrole. This method involves conversion of (4-chloro-8-methyl-2-oxo-2H-quinolin-1-yl)acetic acid hydrazide into hydrazones by reacting with thiophene-2-carbaldehyde, furan-2-carbaldehyde and pyrrole-2-carbaldehydes. The resulting hydrazones, without isolation further oxidised into 2,5-disubstituted oxadiazoles via imine C-H bond using molecular iodine and base. This method gave very good yield of [1,3,4]-oxadiazoles. We have utilised bases K2CO3, Cs2CO3, DBU and NaH to optimise the conditions for iodocyclisation and found that, K2CO3, Cs2CO3, DBU gave good yield of thiophen and furan derivative of [1,3,4]-oxadiazoles and NaH gave moderate yield of pyrrole [1,3,4]-oxadiazole. In addition, newly synthesised compounds were screened for cytotoxicity against cervical cancer cells (HeLa cells) and found that thiophene derivative shown promising activity than furan and pyrrole [1,3,4]-oxadiazole derivatives.

Keywords: 4-chloro-8-methyl-1H-quinoline-2-one, (4-chloro-8-methyl-2-oxo-2H-quinolin-1-yl)acetic acid hydrazides, oxidative iodocyclisation, 2,5-disubstituted [1,3,4] oxadiazoles, HeLa cells.

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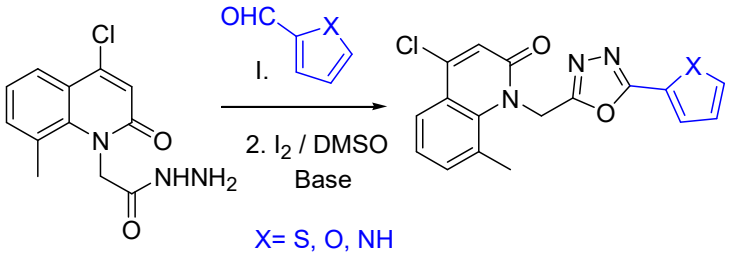
GRAPHICAL ABSTRACT



INTRODUCTION

Quinolines and oxadiazoles are promising scaffolds in medicinally active compounds particularly 2,5-disubstituted 1,3,4 oxadiazoles have been reported various biological activities including antioxidant,[1] T P inhibitory activity,[2] antiepileptic,[3] antimalarial,[4] anticonvulsant,[5] antimicrobial agents, [6,7] antiviral,[8] anticancer, [9-13] focal adhesion kinase inhibitors,[14] as axl kinase inhibitors,[15] anti-tubercular agents [16,17] anti-allergic.[18] Conversely, quinolin-2(1*H*)-one derivatives also reported to possess the activity of CDK5 inhibitors, [19] cytotoxic, [20] antifungal, [21] and inflammatory bowel disease. [22] These wide range of biological activities, tempted us to combine 4-chloro quinolin-2(1*H*)-one and 1,3,4 oxadiazoles along with five membered heterocycles furan, thiophen and pyrrole by oxidative iodocyclisation using molecular iodine and base. It is noteworthy to mention that quinoline combined 1,3,4 oxadiazoles also displayed notable biological activities such as potential inhibitors of DNA gyrase,[23] antimicrobial,[24] antitubercular, antimalarial,[25] and anticancer.[26]

Many reports available in the literature for the synthesis of 2,5-disubstituted oxadiazoles using molecular iodine [27-29] especially Nagula Shankaraiah *et al*[30] reported iodine-promoted one-pot synthesis of 1,3,4-oxadiazole via sp^3 C–

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H bond oxidation of 2-methyl quinoline followed by coupling with aryl hydrazide. Inspired from this work, we have developed, one pot methodology for synthesis of 4-chloro-8-methyl-1*H*-quinoline-2-one clubbed 1,3,4 oxadiazoles along with thiophene, furan and pyrrole using molecular iodine and base. This methodology involves formation of hydrazones from (4-chloro-8-methyl-2-oxo-2*H*-quinolin-1-yl)acetic acid hydrazides and five membered heterocyclic carbaldehydes such as thiophene, furan and pyrrole-2-carbaldehydes. Further, without isolation of intermediate hydrazones which were oxidised subsequently into 1,3,4-oxadiazoles by using molecular iodine and bases. This methodology offered very good yield and easy workout procedure.

MATERIALS AND METHODS

IR spectra in KBr pellets were recorded on a Shimadzu FT-IR 8201 PC spectrometer. ^{1}H and ^{13}C NMR spectra were acquired for DMSO-d^6 solutions on a Bruker AVIII spectrometer (400 and 100 MHz, respectively), using TMS as an internal standard. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage Max HRMS (ESI) ion trap mass Spectro meter. Elemental analysis was performed on a Vario EL III CHNS Analyzer and a Perkin Elmer 2400 Series II CHNS analyser. Melting points were determined by open capillary method using a Raga melting point apparatus and are uncorrected.

General Procedure for one pot synthesis of 8-methyl-4-chloro-quinolin-2(1*H*)- one clubbed 1,3,4 oxadiazole along with thiophene, furan and pyrrole (8-10): A solution of 4-chloro-8-methyl-2-oxo-2*H*-quinolin1-yl)-acetic acid hydrazide **1** (0.5 g) 0.0015 mol and five membered heterocyclic 2-aldehydes (0.0015 mol) in DMSO (20 mL) was stirred at room temperature for 4-5 hrs. The progress of the reaction was monitored by TLC, after completion of the reaction which was identified by disappearance of the starting compound spot in TLC, molecular iodine (0.0045 mol) (1.14 g) and base (0.0045 mol) (K_2CO_3-0.6219 g) (Cs_2CO_3-1.466 g) (NaH-0.108 g) (DBU-0.67 mL) were added to the rection mixture and the RB flask was heated for another 5-6 hrs. After completion of reaction again checked by TLC, the reaction mixture was quenched with thiosulphate solution and content was poured into crushed ice. The obtained crude product was filtered, washed, dried and then column chromatographed using a mixture of ethyl acetate (EA) and petroleum ether (PE) as eluent (20:80).

4-chloro-8-methyl-1-(5-thiophen-2-yl-[1,3,4]-oxadiazol-2-yl-methyl)-1*H*-quinolin-2-one (8): Yield: 0.4948 g **(**97 %). colourless solid. M.p.: 350°C >. IR (KBr), ν cm^{-1}: 1630(C=O), 1415 (C=N). ^{1}H NMR (500 MHz, DMSO-d$_6$, ppm), δ (ppm): 2.50 (s, 3H, 8-CH$_3$), 5.81 (s, 2H, N-CH$_2$), 7.28-8.32 (m, 7H, Ar H). ^{13}C NMR (100 MHz, DMSO-d$_6$), δ (ppm): 17.92, 57.84, 112.34, 121.11, 123.28, 124.19, 126.07, 130.98, 131.95, 132.25, 132.35, 135.69, 144.25, 144.84, 159.16, 163.11, Mass (HRMS): 375.0741(M+NH$_4$)$^+$. Elemental anal. for $C_{17}H_{12}ClN_3O_2S$, calcd.: C, 57.06; H, 3.38%; N,11.74; S, 8.96. found: C, 57.38; H, 3.62%; N,11.38; S, 8.66.

4-chloro-1-(5-furan-2-yl-[1,3,4]-oxadiazol-2-yl-methyl)-8-methyl-1*H*-quinolin-2-one (9):

Yield: 0.4942 g **(**94 %). Colourless solid. M.p.: 350 °C >. IR (KBr), ν cm^{-1}: 1630(C=O), 1415(C=N). ^{1}H NMR (400 MHz, CDCl$_3$, ppm), δ (ppm): 2.52 (s, 3H, 8-CH$_3$), 5.89 (s, 2H, N-CH$_2$), 6.69(s, 1H, C$_3$H)7.58-8.38 (m, 6H, Ar H). ^{13}C NMR (80 MHz**,** CDCl$_3$-d$_6$), δ (ppm): 19.15, 36.37, 114.42, 120.45, 122.94, 128.08, 130.34, 131.16, 132.63, 138.67, 147.98, 161.47, Mass (HRMS): 342.7567. Elemental anal. for $C_{17}H_{12}ClN_3O_3$, calcd.: C, 59.75; H, 3.54%; N,12.30; found: C, 59.94; H, 3.32%; N,12.47.

4-chloro-8-methyl-1-[5-1*H*-pyrrol-2-yl)-[1,3,4]-oxadiazol-2-yl-methyl)-1*H*-quinolin-2-one (10) : Yield: 0.5365 g **(**87 %). Colourless solid. M.p.: 350°C >. IR (KBr), ν cm^{-1}: 3401(NH), 1630 (C=O),1424 (C=N). ^{1}H NMR (400 MHz, DMSO-d$_6$, ppm), δ (ppm): 2.42 (s, 3H, 8-CH$_3$), 5.09 (s, 1H, N-CH$_2$), 5.49 (s, 1H, N-CH$_2$), 7.45(s,1H, C$_3$H), 7,47-7.48 (m, 6H, Ar H), 11.8 (s, 1H, NH). ^{13}C NMR (80 MHz, DMSO-d$_6$), δ (ppm): 20.56, 43.83, 116.01, 118.37, 120.46, 123.26, 125.61, 127.85, 129.30, 130.27, 132.74, 134.44, 139.81, 144.72, 160.37, 168.37, Mass (HRMS): 341.0727 (M+H)$^+$. Elemental anal. for $C_{17}H_{13}ClN_4O_2$, calcd.: C, 59.92; H, 3.85%; N,10.40. found: C, 59.76; H, 3.72%; N,10.58.

General procedure for condensation of 4-chloro-8-methyl-2-oxo-2*H*-quinolin1-yl)-acetic acid hydrazide and thiophene, furan and pyrrole-2-carbaldehydes:

A solution of five membered heterocyclic 2-carbaldehyde (0.0014 mol) and (4-chloro-8-methyl-2-oxo-2*H*-quinolin1-yl)-acetic acid hydrazide (0.5 g) 0.0015 mol in DMSO (20 mL) was stirred at room temperature for 4-6 hrs. the progress of the reaction was monitored by TLC, after completion of the reaction, The mixture was poured into crushed ice. The resulting crude product was filtered, washed, dried and then column chromatographed using a mixture of ethyl acetate (EA) and petroleum ether (PE) as eluent (30:70).

4-chloro-8-methyl-2-oxo-2*H*-quinolin-1-yl)-acetic acid-thiophen-2-yl-methylenehydrazide (5): yield: 0.51 g **(**98 %). colourless solid. M.p.: 347-349 °C. IR (KBr), ν cm^{-1}: 3080 (NH), 1671(CO), 1583 (NH**CO**) ^{1}H NMR (500 MHz, DMSO-d$_6$, ppm), δ (ppm): 2.51 (s, 3H, 8-CH$_3$), 4.99 & 5,43 (s, 2H, N-**CH$_2$**), 7.12 (s,1H, C$_3$H) 7.14 to 8.51 (m, 7H, Ar H and N=**CH**) 11.58 (s, 1H, **NH**). ^{13}C NMR (100 MHz, DMSO-d$_6$), δ (ppm): 17.95, 62.94, 64.11, 112.78, 122.10, 123,07, 125.61, 128.40, 130.95, 131.67, 135.90, 139.08, 142.60, 143.12, 145.01, 159.91, 164.51, 168.91. Mass (HRMS): 359.0427 (M+H)$^+$. Elemental anal. for $C_{17}H_{14}ClN_3O_2S$, calcd.: C, 56.74; H, 3.92; N,11.68; S, 8.91% found: C, 56.60; H, 3.76%; N,11.48; S,8.64%.

4-chloro-8-methyl-2-oxo-2*H*-quinolin-1-yl)-aceticacid-furan-2-yl-methylenehydrazide (6): Yield: **0.52 g (**95 %). colourless solid. M.p.: 222-224 °C. IR (KBr), ν cm^{-1}: 3126(NH), 1685 (NC=O), 1601 (NHCO). ^{1}H NMR (500 MHz, DMSO-d$_6$, ppm), δ (ppm): 2.49 (s, 3H, 8-CH$_3$), 5,04 & 5 .38 (s, 2H, N-**CH$_2$**), 6.58 (s,1H, C$_3$H), 6.63(s, 1H,

CH=N) 6,65 to 7.86 (m, 6H, Ar H) 11.60 (s,1H, **NH**). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm):18.93, 42.94, 112.77, 114.43, 115.42, 120.01, 120.77, 121.88, 125.62, 131.19, 134.26, 137.01, 139.84, 145.22, 147.30, 149.17, 161.24, 164.07, 168.92. Mass (HRMS): 361.7046 $(M+NH_4)^+$. Elemental anal. for $C_{17}H_{14}ClN_3O_3$, calcd.: C, 59.40; H, 4.10%; N,12.22; found: C, 59.14; H, 4.32%; N,12.48.

4-chloro-2-oxo-8-methyl-2*H*-quinolin-1-yl)-aceticacid(1*H*-pyrrol-2-ylmethylene) hydrazide (7): Yield: **0.52 g (**95%). colourless solid. M.p.: 250-252 °C. IR (KBr), ν cm^{-1}: 3065(NH), 3061(NH), 1660(NC=O), 1652(NHCO). ^{1}H NMR (500 MHz, DMSO-d_6, ppm), δ (ppm): 2.42 (s, 3H, 8-CH_3), 5,01 & 5 .43 (s, 2H, N-**CH_2**), 6.14 (s,1H, C_3H), 6.48(s, 1H, CH=N) 7.32 to 7.89 (m, 6H, Ar H) 11.53 (s, 2H, **NH**). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm):20.35, 44.06, 109.57, 113.00, 115.80, 118.40, 120.48, 122.62, 125.15, 127.24. 132.18, 134.02, 137.02, 137.97, 143.80, 160.11, 163.10, 167.37. Mass (HRMS): 343.8496 $(M+H)^+$. Elemental anal. for $C_{17}H_{15}ClN_4O_2$, calcd.: C, 59.57; H, 4.41%; N,16.34. found: C, 59.79; H, 4.62%; N,16.18.

RESULTS AND DISCUSSION

We have recently reported 4-chloroquinolin-2(1*H*)- one and nitrophenyl appended 1,3,4 oxadiazoles from (4-chloro-2-oxo-2*H*-quinolin-1-yl)acetic acid hydrazides and nitro benzoic acid via dehydrative cyclisation method.[31] In continuation of that, we report new derivatives of 2,5-disubstitued 1,3,4 oxadiazoles having 8-methyl-4-chloroquinolin-2(1*H*)-one at 2nd position and five membered heterocycles thiophene, furan, and pyrrole at 5th position via sp^2 C-H bond oxidation of corresponding hydrazones.

Initially, we have planned to synthesis 2,5-disubstituted oxadiazoles via two steps. firstly, synthesis of hydrazones from (4-chloro-8-methyl-2-oxo-2*H*-quinolin-1-yl)acetic acid hydrazide **1** and five membered heterocyclic aldehydes such as thiophene, furan and pyrrole 2-carbaldehydes followed by oxidation with molecular iodine and base. Later we have developed one pot methodology, without isolation of hydrazones we proceeded oxidation reaction and obtained very good yield of 2,5-disubstituted 1,3,4 oxadiazoles.

The reaction commenced with (4-chloro-8-methyl-2-oxo-2*H*-quinolin-1-yl)acetic acid hydrazide **1** and thiophene-2 carbaldehyde **2** in DMSO under stirring condition for 4 hrs. This resulted in formation of (4-chloro-8-methyl-2-oxo-2*H*-quinolin-1-yl)acetic acid thiophen-2-yl-methylene hydrazides **5.** It was clearly confirmed by change in spot location in TLC and isolated the resulting hydrazone and characterized by spectroscopic techniques. The IR spectrum of compound **5** showed peaks at 3080 cm^{-1} for NH and 1671 cm^{-1} for N***C=O*** and 1583 cm^{-1} for NH***C=O***. In ^{1}H NMR spectrum of compound **5**, a singlet peak obtained at δ11.58 for ***NH*** and multiplets at δ 7.12-8.51 for all aromatic protons and N=***CH*** proton confirmed the formation compound **5**.

After having hydrazone **5,** it was cyclised by using of 3 equivalents of K_2CO_3 and 1 equivalent of iodine in DMSO at 150 °C for 4-5 hrs. After completion of reaction which was checked by TLC, we have isolated the cyclised compound **8** and studied by spectroscopically. In IR spectrum of compound **8**, the disappearance of peaks at 1583 cm^{-1} and 3080 cm^{-1} which are corresponding to ***NH***CO and ***NH*** peak of hydrazone **5** and in ^{1}H NMR spectrum of compound **8**, the disappearance of peak at δ 11.60 for NH which is present in hydrazone **5** confirmed the formation of cyclised compound **8**. In order to optimise the conditions, we have also examined the same cyclisation reaction with other bases including Cs_2CO_3, DBU and NaH. All the three bases yielded cyclised compound **8** with moderate to good yield.

Next, we have developed one pot methodology to synthesize compound **8**. Thus, (4-chloro-8-methyl-2-oxo-2*H*-quinolin-1-yl)acetic acid hydrazide **1** was stirred with thiophene-2 carbaldehyde for 4 to 5 hrs in DMSO, after completion of condensation which was checked by TLC (the complete disappearance of starting compound), we have added 3 equivalent of base and 1 equivalent of iodine to the same reaction mixture without isolating intermediate hydrazone and the round bottom flask was heated at 140-150 °C for another 5 to 6 hrs. This resulted in formation compound **8** successfully.

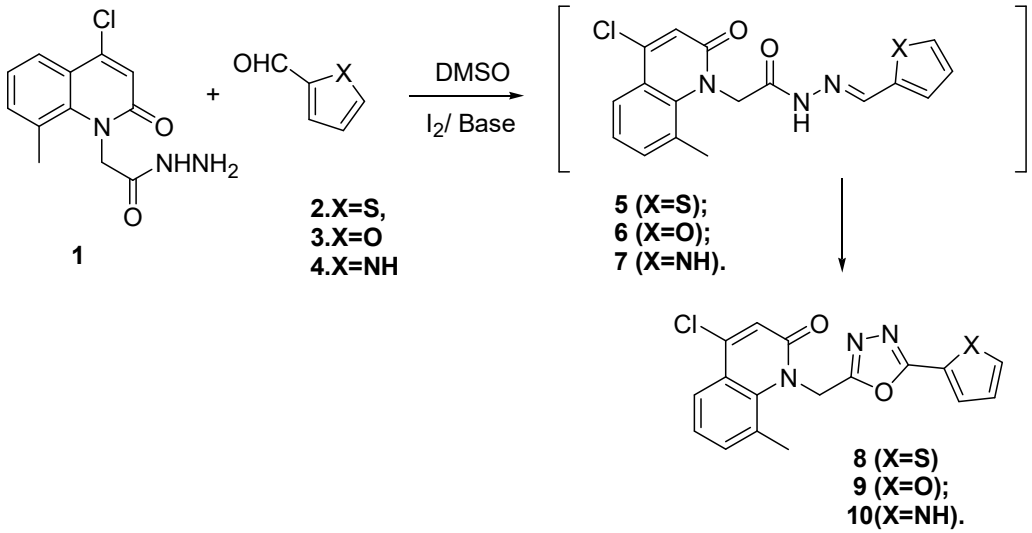
we have extended the same reaction sequences and one pot methodology with other aldehydes such as furan-2-carbaldehyde and pyrrole-2-carbaldehyde to access furan and pyrrole substituted 1,3,4-oxadiazoles. Thus, as in the case of thiophene, we have synthesised (4-chloro-8-methyl-2-oxo-2*H*-quinolin-1-yl)acetic acid-furan-2-ylmethylene-hydrazide **6** and (4-chloro-8-methyl-2-oxo-2*H*-quinolin-1-yl)acetic acid-1*H*-pyrrol-2-ylmethylene-hydrazides **7** by using compound **1** and furan-2-carbaldehyde and pyrrole 2-carbaldehyde respectively. The resulting compounds were confirmed by spectral studies. The ^{1}H NMR spectrum of compound **6** showed peak at δ 11.6 for *NH* and δ 6.63 for *CH=N* confirmed the formation of compound **6** and for compound **7** there are peaks in the ^{1}H NMR spectrum of compound **7** at δ 11.53 corresponding to two *NH* and δ 6.14 for *CH=N* confirmed the formation of hydrazone **7**.

Next, the resulting hydrazones **6** and **7** were cyclised by using molecular iodine and bases K_2CO_3, $C_{S2}CO_3$, DBU and NaH. For hydrazone **6** from furan-2-carbaldehyde, all the bases provided cyclised 1,3,4-oxadiazoles **9** with good to moderate yield and products were confirmed by spectral studies. In the IR spectrum of compound **9**, the disappearance of peak at 1601cm^{-1} corresponding to NH*CO* and 3126 cm^{-1} corresponding to NH peak of hydrazone **6** confirmed the cyclisation. In the ^{1}H NMR spectrum of compound **9**, the disappearance of NH peak at δ 11.60 of hydrazone **6** also confirmed the oxidative cyclisation.

For cyclisation of hydrazone **7** from pyrolle-2-carbaldehyde, weak bases K_2CO_3, Cs_2CO_3 and DBU were

unsuccessful even on prolong heat conditions. However, strong base NaH yielded cyclised 1,3,4-oxadiazoles **10** with moderate yield at 150-155 °C. the cyclised compounds were confirmed by spectral studies. In the IR spectrum of compound **10**, the disappearance of two peaks at 3065 cm^{-1} and 3061 cm^{-1} for NH which are present in corresponding hydrazone **7** and appearance of a new peak at 3401 cm^{-1} for NH confirmed the cyclisation. Further, In ^1H NMR spectrum of compound **10**, the disappearance of peak for two NH proton at δ 11.53 which is present in corresponding hydrazone **7** and appearance of a peak at δ 11.8 for a NH confirmed the iodocyclisation.

Finally, we have also developed one pot methodology for furan and pyrrole containing 1,3,4 oxadiazoles by using suitable base identified as above method and obtained moderate to good yield. The total reaction sequences are summarised in **scheme 1** conditions were tabulated in **Table 1.**



Scheme 1: Synthesis of 2,5-disubstitutued-[1,3,4]-oxadiazoles

Table:1 Conditions for 2,5-disubstitutued-[1,3,4]-oxadiazoles

Entry	X	Base (3 equiv)	Temp(°C)	Time (h)	Yield (%)
1	S (8)	K_2CO_3	145-150	3	97
2	S (8)	Cs_2CO_3	145-150	4	96
3	S (8)	DBU	145-150	4	90
4	S (8)	NaH	100-105	2	92
5	O (9)	K_2CO_3	155-160	10	94
6	O (9)	Cs_2CO_3	155-160	13	88
7	O (9)	DBU	155-160	10	86
8	O (9)	NaH	110-115	6	90
9	NH (10)	K_2CO_3	150-155	No reaction	
10	NH (10)	Cs_2CO_3	150-155	No reaction	
11	NH (10)	DBU	150-155	No reaction	
12	NH (10)	NaH	150-155	6	87

Anti-cancer study

Evaluation of in vitro cytotoxicity against HeLa cell lines carried out for newly synthesized 8-methyl derivative of 2,5-disubstituted-1,3,4 oxadiazoles (compounds **8**, **9** and **10)** using MTT assay. The IC 50 value revealed that quinoline and thiophene clubbed 1,3,4-oxadiazole **8** showed better activity than quinoline and furan clubbed 1,3,4-oxadiazole **9** and quinoline and pyrrole clubbed 1,3,4-oxadiazole **10**. The IC50 values of the tested compounds are summarized in **Table 2**. Nuclear morphology of HeLa cells with compound **8**, **9** and **10** are given in **figure 1.**

Table 2: MTT Assay IC_{50} – Values. Standard Used: Doxorubicin

S.No	**Sample**	**HeLa cells (IC_{50})** (µg/ml)
1	4-chloro-8-methyl-1-(5-thiophen-2-yl-[1,3,4]-oxadiazol-2-yl-methyl)-1*H*-quinolin-2-one. **(8)**	10 ±0.7
2	4-chloro-1-(5-furan-2-yl-[1,3,4]-oxadiazol-2-yl-methyl)-8-methyl-1*H*-quinolin-2-one. **(9)**	19 ±0.4
3	4-chloro-8-methyl-1-[5-1*H*-pyrrol-2-yl)-[1,3,4]-oxadiazol-2-yl-methyl)-1*H*-quinolin-2-one. (**10)**	23 ±0.5

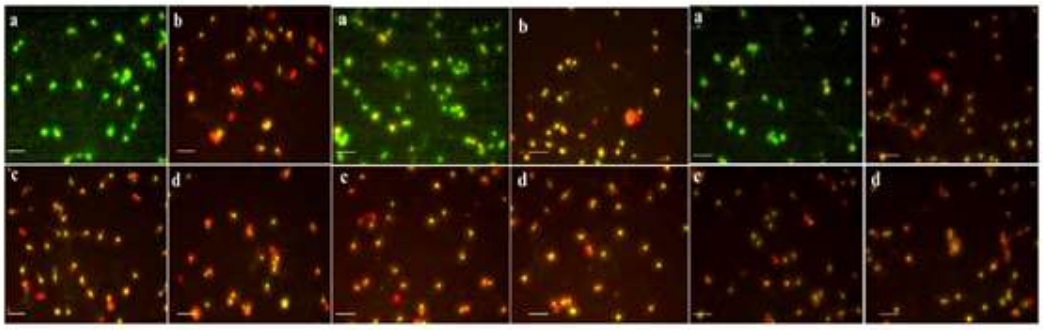


Figure 1: Nuclear morphology of HeLa cells with (i) compound **8** (ii) compound **9** and (iii) compound **10**: In the pictures: a – control, b – 10 µM concentration, c –25 µM concentration, d – 50 µM concentration. (for all three compounds)

CONCLUSION

In conclusion, we have developed one pot methodology for synthesise of 4-chloro-8-methyl-1*H*-quinoline-2-one combined 1,3,4 oxadiazoles along with thiophene, furan and pyrrole. We have optimised conditions and bases for iodocyclisation. Thus, bases K_2CO_3, Cs_2CO_3, DBU were efficient bases for synthesis of thiophene and furan derivatives and not suitable for pyrrole derivative and NaH provided moderate yield of pyrrole derivative. Further, the resulting compounds were screened for cytotoxicity against cervical cancer cells (HeLa cells) and resulted thiophene containing 1,3,4 oxadiazole **8** shown promising activity than furan **9** and pyrrole **10** derivatives.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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