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An ultrasound assisted synthesis of spirooxindolo-1,2,4-oxadiazoles *via* [3+2] cycloaddition reaction and their anti-cancer activity

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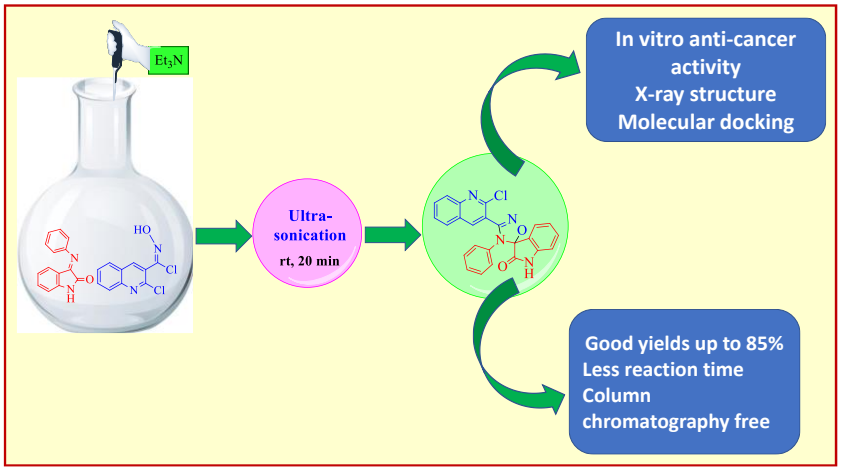
Abstract

A facile and ultrasound assisted green methodology was adopted to achieve spirooxindolo-1,2,4-oxadiazoles *via* a [3+2] cycloaddition of aryl nitrile oxides and isatin Schiff bases at room temperature with good yields and lesser reaction times. The proposed procedure avoids traditional column chromatography resulting in good to excellent yields. The synthesized compounds were evaluated for their anti-cancer activity against SK-OV-3, HeLa, HCT-116, DU-145, A549 and HEK-293 cell lines. Two of them showed significant anti-cancer activity against HeLa with IC_{50} value 10.75±0.39 µM and 12.43±0.77 µM respectively.



Keywords: Ultrasound irradiation, isatin Schiff bases, *N*-hydroxycarbimidoyl chloride, [3+2]cycloaddition, spirooxindolo-1,2,4-oxadiazoles, anti-cancer activity.

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Introduction

1,2,4-oxadiazole ring system has become a popular scaffold in the field of drug discovery and development.[1,2,3] The oxadiazole rings, which were an essential part of the pharmacophore for many different treatments present in the lead compounds to treat a wide range of disorders, including diabetes, obesity, inflammation, cancer, and infection.[4,5,6] Additionally, 1,2,4-oxadiazoles are being actively employed to create novel materials with beneficial features, including solar cells, fluorogenic chemosensory polymers, liquid crystals, organic light emitting diodes (OLEDs), and high energy materials (HEDM).[7,8] Due to these wide range of applications, synthetic organic chemists are particularly interested in developing efficient and effective methods for their production.[9,10,11] In the field of medicinal chemistry, heterocyclic compounds, notably spirooxindoles, have played a significant role. The [3+2] cycloaddition process is a highly regio-selective approach for the synthesis of spiroxindoles.[12,13,14,15] Spirooxindole alkaloids found in nature, such as horsfiline, extracted from Horsfieldia superba are used in traditional medicine (Figure 1).[16,17] However, the spiroxindoles having 1,2,4-oxadiazole ring systems are rare in the literature.

On the other hand, cancer is the second biggest cause of death after cardiovascular illnesses, despite the extensive research that has been done.[18] This remains a serious health threat and is one of the leading causes of mortality around the world.[19] Chemotherapy is the most cost-effective treatment option offered to patients across the world, but, can have severe side effects, and malignancies can develop resistance to some of the most regularly used medications leaving the patients with limited treatment alternatives.[20] As a result, more anti-cancer medications are needed with improved cancer cell selectivity.

Modern synthetic chemistry has recently paid increasing attention to ultrasonic irradiation (USI).[21] The use of mechanical and thermal energy for chemical reactions without significantly changing the reaction media is made possible by the acoustic cavitation that is caused by ultrasonication.[22] At room temperature, the energy produced by the cavity effect causes solubility, mass transfer, diffusivity, speeds up reactions, and shorten reaction time.[23] As far as we are aware, there were no reports on the synthesis of spirooxindolo-1,2,4-oxadiazoles using ultrasonic irradiation. Therefore, in this paper, we describe the use of ultrasound to aid in the [3+2] cycloaddition process to produce spirooxindolo-1,2,4-oxadiazoles, which were then examined for their anti-cancer potential as part of our continuing research into green chemistry and bio-active spirooxindoles.[24,25,26]

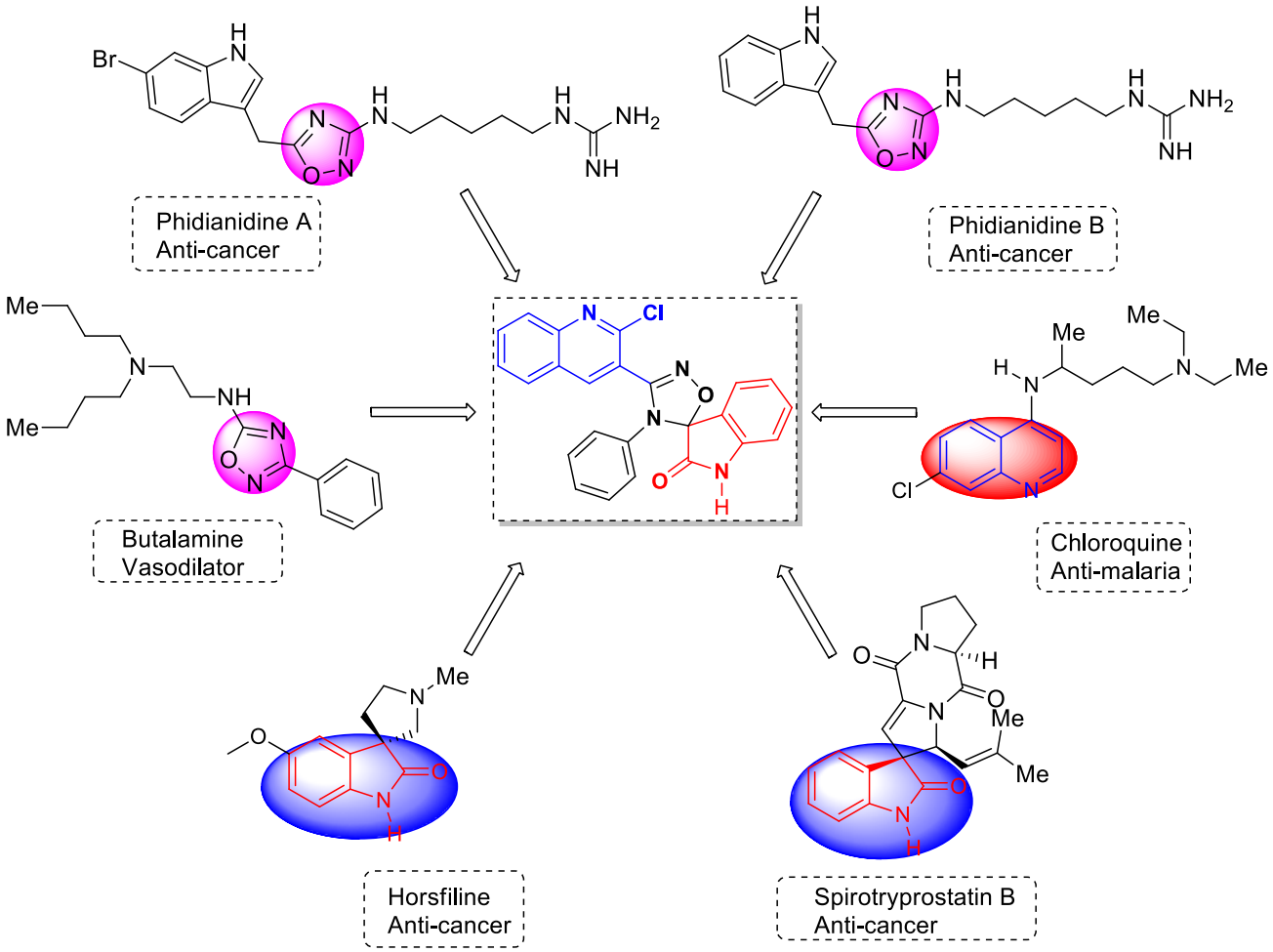


Figure 1. Design strategy for spirooxindolo-1,2,4-oxadiazoles for anti-cancer activity having 1,2,4-oxadiazole, oxindole, quinoline moieties as pharmacophores.

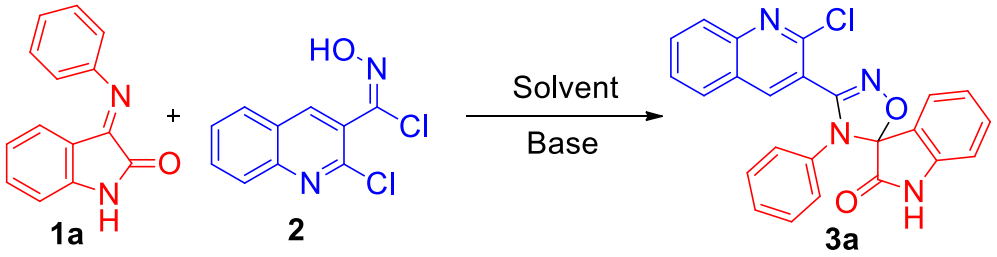
Results and Discussion

Chemistry

To optimize the reaction parameters, we used 3-(phenylimino)indolin-2-one **1a** and *N*-hydroxycarbimidoyl chloride **2**[27] as model reactants (Table 1). Initially, a reaction was carried out in methanol at room temperature, yielding a trace amount of the desired product **3a** (Table 1, entry 1). The reaction was then carried out in the presence of Et_3N in MeOH. To our pleasure, the required product **3a** was obtained with 40% yield (Table 1, entry 2). Solvents such as CH_3CN, DCM and $CHCl_3$ were tested to improve the yield. And the findings revealed that $CHCl_3$ is the optimum solvent to obtain the desired compound **3a** in 75% yield (Table 1, entries 3-5). Various bases such as DMAP, DABCO, DBU, and K_2CO_3 were investigated in order to determine the reaction efficiency (Table 1, entries 7-10), and Et_3N was discovered to be an efficient base for the formation of target compound **3a**. However, as it is a regular practice in our laboratory towards green methodologies, we tried the reaction in ultrasonication using $CHCl_3$, DCM and CH_3CN solvents (Table 1, entries 11-14), and found that $CHCl_3$ is the best solvent for the generation of title compound **3a** with 85% yield in 20 min (Table 1, entry11). Further when the reaction was proceeded beyond 20 min no improvement of the yield was observed (Table 1, entry 12). Further, we carried out the reaction at 60 °C in conventional as well as

ultrasonication but there was no significant effect on reaction yield (Table 1, entry 6 & 15). Variation of the base equivalents from 2.0 to 1.5 and then 2.5 was resulting a negative impact on product yield (Table 1, entries 16, 17). As a result, we decided that 1 mmol of **1a**, 1.1 mmol of **2**, and 2 equiv. of Et_3N in $CHCl_3$ (Table 1, entry11) at room temperature under ultrasound irradiation is the best reaction condition for the generation of target compounds.

Table 1. Optimization of the reaction conditions[a]

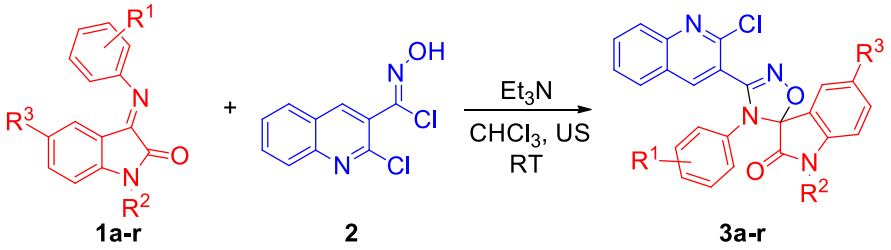


Entry	Solvent	Base	Method	Time	Yield (%)[b]
1	MeOH	--	Conventional	12 h	trace
2	MeOH	Et_3N	Conventional	12 h	40
3	CH_3CN	Et_3N	Conventional	8 h	65
4	DCM	Et_3N	Conventional	6 h	70
5	$CHCl_3$	Et_3N	Conventional	5 h	75
6[c]	$CHCl_3$	Et_3N	Conventional	1 h	70
7	$CHCl_3$	DMAP	Conventional	12 h	60
8	$CHCl_3$	DABCO	Conventional	12 h	45
9	$CHCl_3$	DBU	Conventional	12 h	50
10	$CHCl_3$	K_2CO_3	Conventional	12 h	30
11	$CHCl_3$	Et_3N	Ultrasonication	20 min	85
12	$CHCl_3$	Et_3N	Ultrasonication	25 min	85
13	DCM	Et_3N	Ultrasonication	30 min	80
14	CH_3CN	Et_3N	Ultrasonication	40 min	70
15[d]	$CHCl_3$	Et_3N	Ultrasonication	30 min	85
16[e]	$CHCl_3$	Et_3N	Ultrasonication	30 min	75
17[f]	$CHCl_3$	Et_3N	Ultrasonication	20 min	80

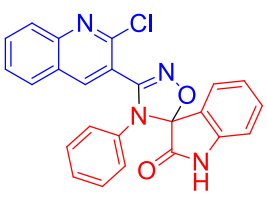
[a]Reaction condition: compound **1a** (1 mmol), *N*-hydroxycarbimidoyl chloride **2** (1.1 mmol), base (2 equiv) and solvent (3 mL) at room temperature. [b]Isolated yields. [c,d]at 60 °C .[e]1.5 equiv of base. [f]2.5 equiv of base.

Based on the optimized reaction conditions, we examined the substrate scope using several substituted isatin Schiff bases **1a-r** and *N*-hydroxycarbimidoyl chloride **2** (Table 2). The reaction was unaffected by the electron donating (-CH_3) and withdrawing (-Cl, -F, -Br) groups present on the isatin Schiff bases.

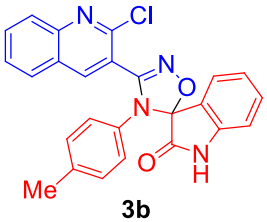
Table 2. Synthesis of spirooxindolo-1,2,4-oxadiazoles **3a-r**[a,b]



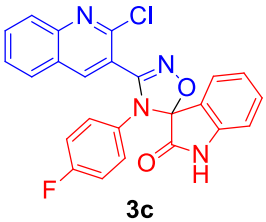
1a-r **2** **3a-r**



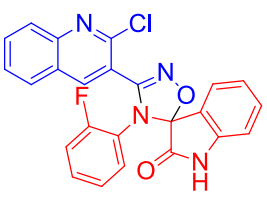
3a
20 min, 85%



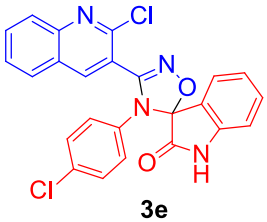
3b
20 min, 84%



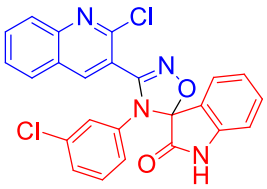
3c
30 min, 82%



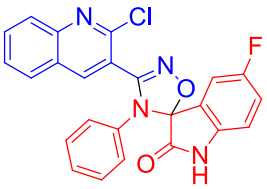
3d
30 min, 82%



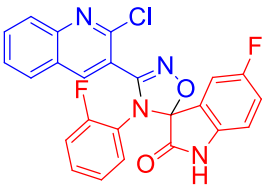
3e
20 min, 84%



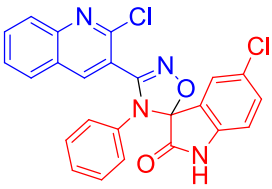
3f
25 min, 84%



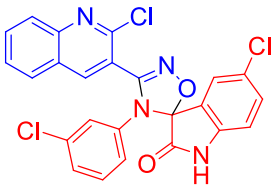
3g
30 min, 81%



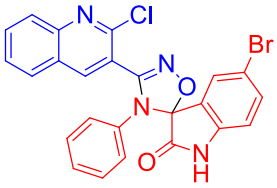
3h
40 min, 80%



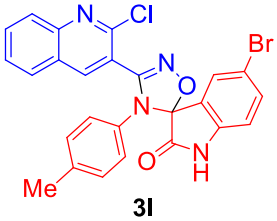
3i
25 min, 83%



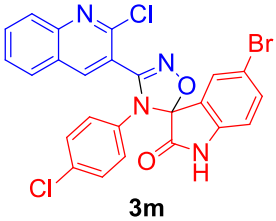
3j
30 min, 82%



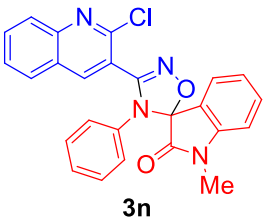
3k
40 min, 81%



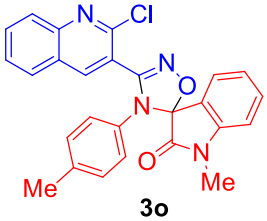
3l
35 min, 80%



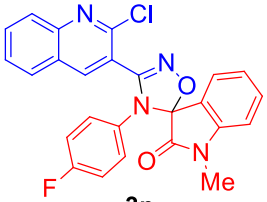
3m
35 min, 80%



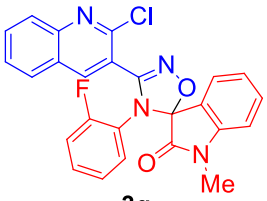
3n
25 min, 82%



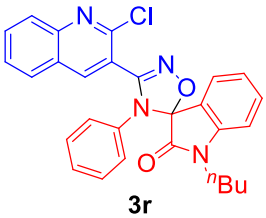
3o
25 min, 84%



3p
30 min, 82%



3q
30 min, 80%

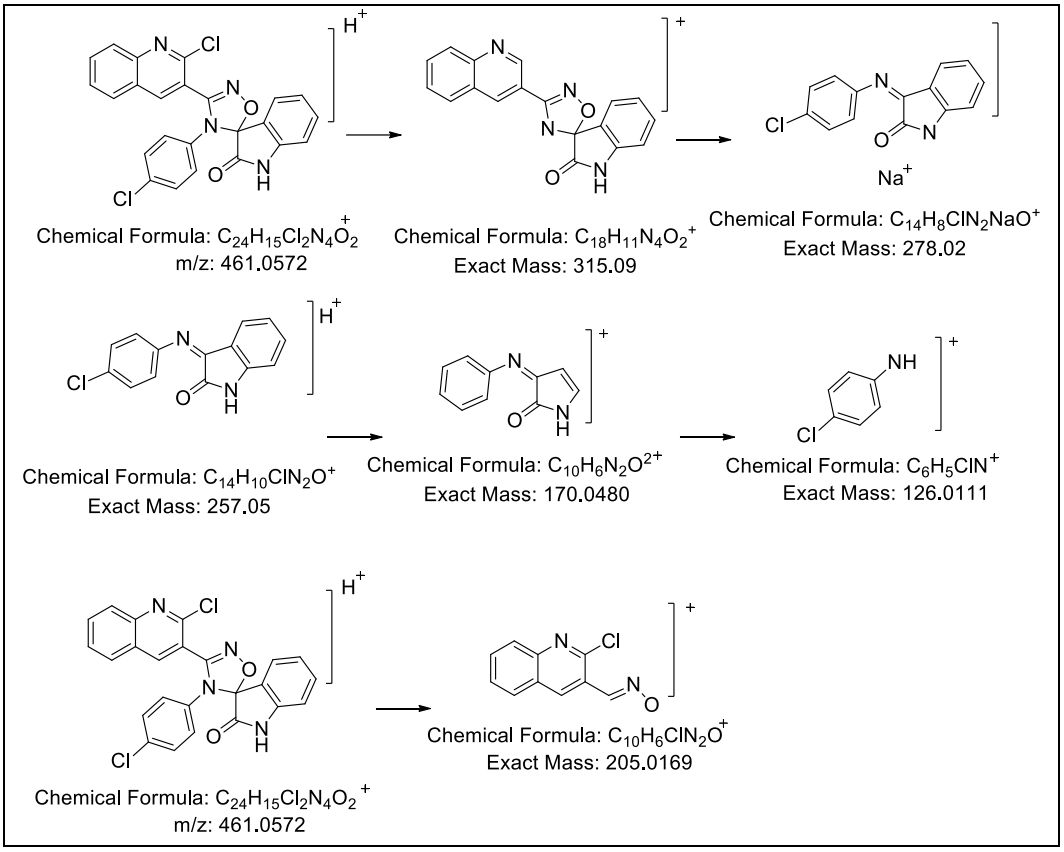


3r
30 min, 82%

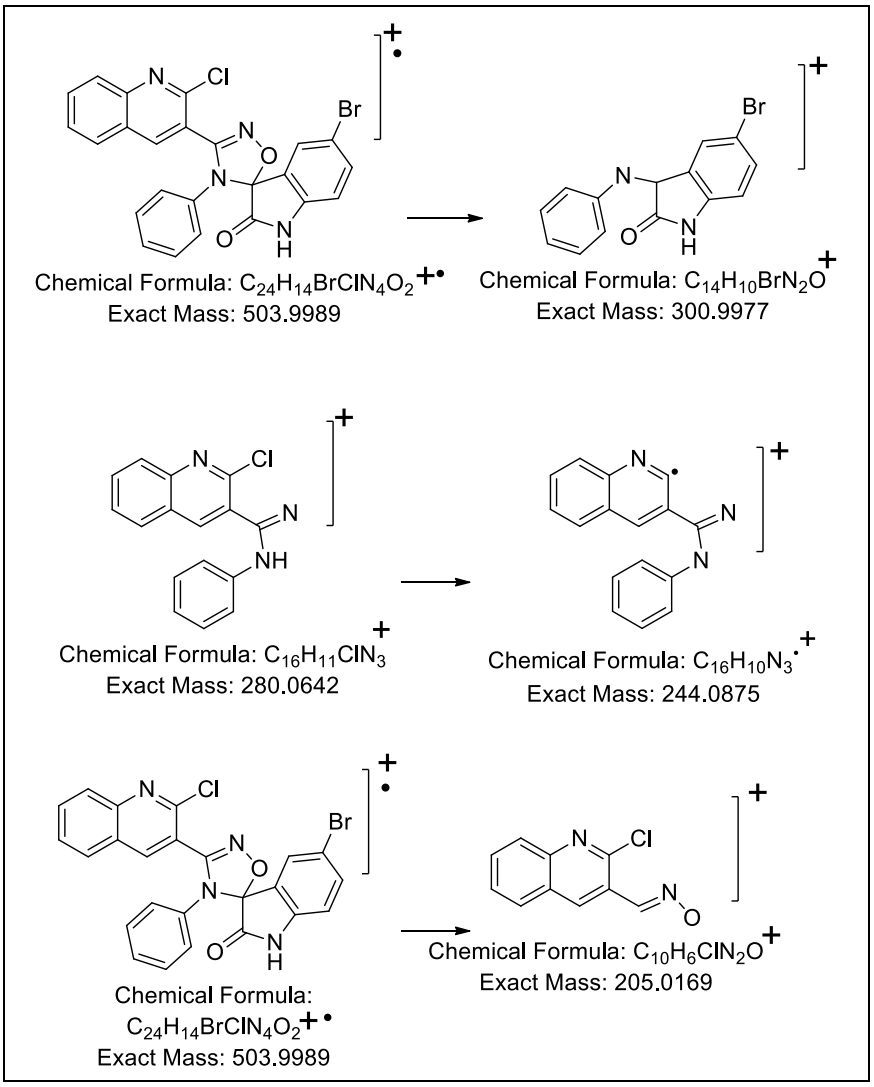
[a]Reaction conditions: compounds **1a-r** (1 mmol), *N*-hydroxycarbimidoyl chloride **2** (1.1 mmol), Et_3N (2 equiv) and $CHCl_3$ (3 mL) under ultrasonication at room temperature. [b]Isolated yields.

Spectral methods IR, ^1H, ^{13}C NMR and mass spectrometry were used to characterize the structures of synthesized compounds **3a-r**. The structures were also confirmed by single crystal X-ray diffraction method (**3r**). For instance, the peak at 1736 cm^{-1} in the IR spectrum of the compound **3o** corresponds to the stretching

frequency of amide carbonyl of the isatin molecule and the peak at 1613 cm^{-1} corresponds to C=N stretching of 1,2,4-oxadiazole ring. The spiro carbon was represented by the signal at *δ* 98.03 in ^{13}C NMR. Further the presence of spiro carbon was confirmed by DEPT-135 NMR spectrum in which the peak at *δ* 98.03 was disappeared. The molecular weight of compound **3o** is determined from the molecular ion peak at *m/z* 455.1280 $[M+H]^+$ in the mass spectrum. Further, fragmentation pathway of the compounds **3e** and **3k** were supported by the MS/MS spectrum analysis (Scheme 1 and Scheme 2).

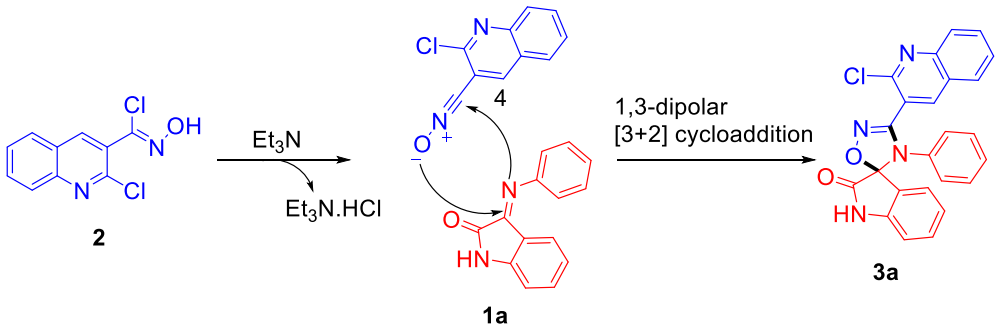


Scheme 1. Fragmentation pathway of the compound **3e**.



Scheme 2. Fragmentation pathway of the compound **3k**.

Furthermore, the regiochemistry of the produced compounds was demonstrated by single crystal X-ray diffraction method of compound **3r** (Figure 2) (CCDC: 2222697). Scheme 3 depicts the reaction process for the formation of target molecules **3a-r**. When *N*-hydroxycarbimidoyl chloride **2** reacts with the base, it produces *N*-oxide **4**.[28,29] The target product **3a** was obtained when this *in situ* produced *N*-oxide undergoes a [3+2] cycloaddition reaction with isatin Schiff base **1a**.[30,31]



Scheme 3. Plausible reaction pathway for the generation of target compound **3a.**

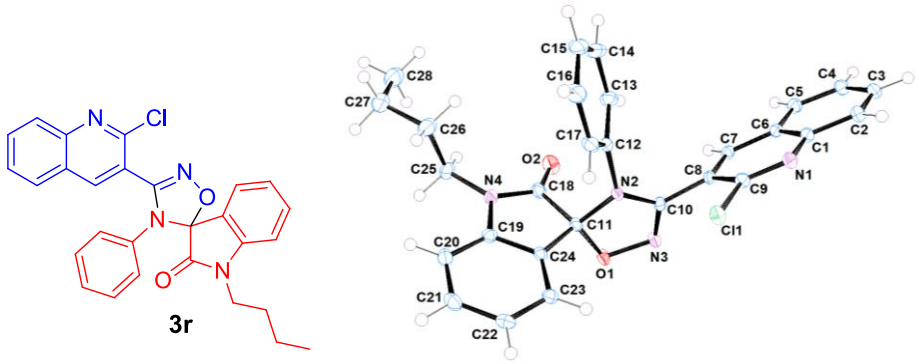


Figure 2. ORTEP representation of the compound **3r**. The thermal ellipsoids are drawn at 50% probability level.

Biological evaluation

We examined the synthesized compounds to elucidate their anticancer activity against ovarian cancer cell line (SK-OV-3), cervical cancer cell line (HeLa), colon cancer cell line (HCT-116), prostate cancer cell line (DU-145), lung cancer cell line (A549) and normal human embryonic kidney (HEK-293) cell lines.[32,33] The results were summarized in table S1 in supplementary material. The compounds **3h**, **3i** and **3p** against ovarian cancer cell line showed moderate anti-cancer activities with values IC_{50} 18.81±0.75 µM, 14.35±0.14 µM and 19.41±1.22 µM respectively when compared to the standard drug doxorubicin (IC_{50} 1.41±0.18 µM). The compound **3i** exhibited significant activity against cervical cancer HeLa cell line with IC_{50} value 10.75±0.39 µM whereas the compounds **3d**, **3h**, **3j**, **3k**, **3n** and **3p** showed moderate anti-cancer activity with IC_{50} values 16.61±0.61 µM, 15.14±0.96 µM, 12.43±0.77 µM, 18.80±1.54 µM, 18.53±0.91 µM and 16.69±1.15 µM respectively compared to the standard drug doxorubicin (IC_{50} 1.73±0.08 µM). Finally, compound **3i** exhibited moderate anti-cancer activity against prostate cancer cells DU-145 cell line with IC_{50} 19.27±0.62 µM when compared to the standard drug doxorubicin (IC_{50} 1.89±0.09 µM). No compound showed any significant activity against A549 and HEK-293 Cell lines. The structure activity relationships, *in silico* anti-cancer docking studies and ADME properties were presented in supplementary material.

Conclusions

An efficient green methodology using ultrasonication was developed for the synthesis of spirooxindolo-1,2,4-oxadiazole derivatives (**3a-r**) characterized by spectral methods and the structures were authenticated by SXRD. The methodology is advantageous to synthesize the target molecules with good yields and lesser reaction times. The *in-vitro* anti-cancer activities revealed that the compound **3i** and **3j** showed significant activity against cervical cancer HeLa cell lines. The compounds **3d**, **3h** and **3p** showed moderate activity against HeLa cell lines. The compound **3i** also exhibited a significant activity against ovarian cancer SK-OV-3 cell lines. The SAR analysis revealed that the compounds containing chlorine atom at R^3 position (**3i**, **3j**) showed significant activity whereas the compounds containing fluorine atom at R^1 (**3d**, **3h**, **3p**) showed moderate activity. The *in silico* anti-cancer molecular docking studies with the compounds **3m**, **3r** and **3o** showed least binding energy against histone deacetylases enzyme (PDB ID: 1VKG protein). These *in vitro* and *in silico* studies suggest that these compounds are promising hits for anti-cancer activity.

Experimental Section

General. All the chemicals and solvents were purchased from Aldrich/Spectrochem. All melting points were checked by using Stuart SMP30 melting point apparatus (Bibby Scientific Ltd. United Kingdom) and were uncorrected. Ultrasonication irradiation was performed on MAXSELL MX 200SH-6LQ Ultrasonic power 200 W. The reaction progress was checked with TLC plates (E. Merck, Mumbai, India). IR spectra were recorded on KBr disc by using Perkin-Elmer 100S spectrophotometer (Perkin-Elmer Ltd. United Kingdom) from 4000-400 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on Avance-III Bruker-400 MHz spectrometer (Bruker Corporation Ltd., Germany) using DMSO-d_6 as solvent and TMS as an internal standard and chemical shifts are expressed as ppm. Mass spectra were recorded on a Jeol JMSD-300 spectrometer (Jeol Ltd., Tokyo, Japan) in acetonitrile solvent. The SXRD data of the compound **3r** was collected and solved by using Bruker Kappa Apex II CCD diffractometer and ShelXT software.

General procedure for the synthesis of isatin Schiff bases (1a-r)[37, 38, 39, 40]

An oven dried 50 mL reaction flask with a magnetic stirring bar was charged with isatin (10 mmol), aniline (10 mmol) in EtOH (15 mL). At 60 °C, the mixture was agitated, and the catalytic quantity of glacial CH_3COOH was added. After the reaction was completed (as monitored by TLC), ice cold water was added, and the solid was filtered under vacuum, washed with cold methanol, and dried.

General procedure for the synthesis of *N*-hydroxycarbimidoyl chloride (2)[41]

Step1. **Preparation of 2-chloroquinoline-3-carbaldehyde oxime.** Hydroxylamine hydrochloride (5 mmol) and NaOAc (5mmol) were added to a solution of 2-chloroquinoline-3-carbaldehyde (5 mmol) in MeOH/H_20 (1:1, 10 mL), and the resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was extracted with ethyl acetate (2 × 20 mL). The organic phases were combined, washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The product 2-chloroquinoline-3-carbaldehyde oxime was used directly in the next step without further purification.

Step 2. **Preparation of *N*-hydroxycarbimidoyl chloride (2).** *N*-Chlorosuccinimide (7.5 mmol) was added to a solution of 2-chloroquinoline-3-carbaldehyde oxime (5 mmol) in DMF (10 mL), and the resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the reaction solution was poured into ice water. The mixture was then extracted with ethyl acetate (2 × 20 mL). The organic phases were combined, washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The product used directly in the next step without further purification. White solid. ^{1}H NMR (400 MHz, DMSO) δ 9.26 (s, 1H), 8.15 (d, *J* 8.0 Hz, 1H), 8.05 – 8.02 (m, 2H), 7.82 (t, *J* 6.8 Hz, 1H).

General procedure for the generation of target compounds 3a-r

Et_3N (2.0 equiv) was added dropwise during 10 minutes to a solution of isatin Schiff bases **1a-r** (1.0 mmol) and *N*-hydroxycarbimidoyl chloride **2** (1.1 mmol) in $CHCl_3$ (3 mL). For the proper period of time, the reaction was left at room temperature under ultrasound irradiation. The reaction mixture was concentrated under reduced pressure after completion of starting materials (TLC, EtOAc/*n*-hexane 1:10-1:8), and the residue was recrystallized from methanol to get the required products **3a-r**.

3'-(2-Chloroquinolin-3-yl)-4'-phenyl-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one) (3a). White solid. mp: 253-254 °C (from Methanol). IR (KBr, cm^{-1}): 3424, 1736, 1620, 1582, 1498. ^{1}H NMR (400 MHz, DMSO) δ 10.69 (s, 1H), 9.07 (s, 1H), 8.20 (d, *J* 8.0 Hz, 1H), 7.95 (q, *J* 8.0 Hz, 2H), 7.75 (dd, *J* 16.4, 8.0 Hz, 2H), 7.40 (t, *J* 7.6 Hz, 1H), 7.17 (d, *J* 7.2 Hz, 1H), 7.12 (t, *J 8.0 Hz,* 2H), 7.05 (t, *J* 6.8 Hz, 1H), 6.86 (t, *J* 8.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.1, 152.7, 147.8, 147.4, 143.4, 143.0, 135.3, 133.2, 133.0, 129.8, 129.2, 128.8, 128.2, 127.7, 126.7,

126.3, 124.7, 123.6, 118.2, 111.6, 98.2. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{16}ClN_4O_2$: 427.0962; found: 427.0965.

3'-(2-Chloroquinolin-3-yl)-4'-(p-tolyl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3b). Pale yellow solid. mp: 241-242 °C (from Methanol). IR (KBr, cm^{-1}): 3223, 1738, 1620, 1587, 1470. ^{1}H NMR (400 MHz, DMSO) *δ* 10.62 (s, 1H), 9.04 (s, 1H), 8.19 (d, *J* 8.4 Hz, 1H), 7.95 (t, *J* 9.2 Hz, 2H), 7.78-7.73 (m, 2H), 7.38 (t, *J* 8.0 Hz, 1H), 7.16 (t, *J* 7.6 Hz,1H), 6.91 (d, *J* 8.4 Hz, 2H), 6.85 (d, *J* 8.0 Hz, 1H), 6.77 (d, *J* 8.0 Hz, 2H), 2.06 (s, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 172.2, 152.9, 147.8, 147.5, 143.3, 143.0, 137.6, 133.2, 132.9, 132.4, 130.2, 129.2, 128.7, 128.2, 126.9, 126.8, 126.3, 124.7, 123.6, 118.3, 111.5, 98.3, 20.7. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{25}H_{18}ClN_4O_2$: 441.1118; found:441.1147.

3'-(2-Chloroquinolin-3-yl)-4'-(4-fluorophenyl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3c). Pale yellow solid. mp: 254-255 °C (from Methanol). IR (KBr, cm^{-1}): 3198, 1740, 1620, 1586, 1470. ^{1}H NMR (400 MHz, DMSO) *δ* 10.69 (s, 1H), 9.07 (s, 1H), 8.19 (d, *J* 8.0 Hz, 1H), 7.95 (q, *J* 8.4 Hz, 2H), 7.77 (t, *J* 7.2 Hz, 2H), 7.40 (t, *J* 8.0 Hz, 1H), 7.17 (t, *J* 7.6 Hz, 1H), 7.02-6.92 (m, 4H), 6.87 (d, *J* 7.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 172.1, 162.3 (d, *J* 244.3), 152.8, 147.8, 147.3, 143.5, 143.1, 133.3 (d, *J* 21.0), 131.4 (d, *J* 2.7), 129.4 (d, *J* 9.0), 129.2, 128.8, 128.2, 126.8, 126.3, 124.4, 123.7, 117.9, 116.9 (d, *J* 22.8), 111.6, 98.3. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{15}ClFN_4O_2$: 445.0868; found:445.0872.

3'-(2-Chloroquinolin-3-yl)-4'-(2-fluorophenyl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one(3d). White solid. mp: 267-268 °C (from Methanol). IR (KBr, cm^{-1}): 3203, 1742, 1621, 1590, 1503. ^{1}H NMR (400 MHz, DMSO) *δ* 10.67 (s, 1H), 8.99 (s, 1H), 8.20 (d, *J* 8.4 Hz, 1H), 7.96 – 7.92 (m, 2H), 7.77 – 7.73 (m, 1H), 7.56 (d, *J* 7.2 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.14 – 6.97 (m, 5H), 6.84 (d, *J* 7.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 172.2, 158.9 (d, *J* 248.3), 153.0, 147.8, 147.3, 143.3, 143.2, 133.4 (d, *J* 25.8), 130.7 (d, *J* 8.0), 129.7, 129.2, 128.8, 128.2, 126.7, 126.2, 125.5 (d, *J* 3.2), 123.4, 123.3, 123.1, 123.0, 117.7 (d, *J* 19.8), 116.9, 111.5, 98.0. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{15}ClFN_4O_2$: 445.0868; found:445.0898.

4'-(4-Chlorophenyl)-3'-(2-chloroquinolin-3-yl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3e). Yellow solid. mp: 241-242 °C (from Methanol). IR (KBr, cm^{-1}): 3231, 1744, 1619, 1587, 1493. 1H NMR (400 MHz, DMSO) *δ* 10.75 (s, 1H), 9.09 (s, 1H), 8.21 (d, *J* 8 Hz, 1H), 7.99 – 7.93 (m, 2H), 7.80 - 7.72 (m, 2H), 7.41(t, *J* 7.6 Hz, 1H), 7.22 (d, *J* 8 Hz, 2H), 7.16 (t, *J* 7.2Hz, 1H), 6.9 (d, *J* 8.4 Hz, 1H), 6.85 (d, *J* 8.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) *δ* 171.9, 152.5, 147.9, 147.2, 143.6, 143.0, 134.3, 133.4, 133.2, 132.1, 129.9, 129.3, 128.8, 128.2, 127.9, 126.8, 126.3, 124.2, 123.7, 117.8, 111.7, 98.2. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{15}Cl_2N_4O_2$: 461.0572; found: 461.0605.

4'-(3-Chlorophenyl)-3'-(2-chloroquinolin-3-yl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3f). White solid. mp: 260-261 °C (from Methanol). IR (KBr, cm^{-1}): 3414, 1746, 1620, 1588, 1472. ^{1}H NMR (400 MHz, DMSO) *δ* 10.82 (s, 1H), 9.13 (s, 1H), 8.22 (d, *J* 8.0 Hz, 1H), 8.01 – 7.94 (m, 2H), 7.80 (d, *J* 7.2 Hz, 1H), 7.75 (d, *J* 7.2 Hz, 1H), 7.43 (t, *J* 7.6 Hz, 1H), 7.20 – 7.14 (m, 3H), 6.92 (d, *J* 8.0 Hz, 1H), 6.84 (s, 1H), 6.80 (d, *J* 6.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 171.8, 152.2, 147.9, 147.2, 143.6, 143.0, 136.9, 133.7, 133.4, 133.3, 131.5, 129.2, 128.9, 128.2, 127.6, 126.8, 126.3, 125.3, 124.6, 124.1, 123.8, 117.8, 111.8, 98.2. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{15}Cl_2N_4O_2$: 461.0572; found: 461.0578.

3'-(2-Chloroquinolin-3-yl)-5-fluoro-4'-phenyl-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3g). White solid. mp: 247-248 °C (from Methanol). IR (KBr, cm^{-1}): 3177, 1744, 1619, 1585, 1487. ^{1}H NMR (400 MHz, DMSO) *δ* 10.66 (s, 1H), 8.99 (s, 1H), 8.20 (d, *J* 8 Hz, 1H), 7.97- 7.91 (m, 2H), 7.77 - 7.73 (m, 1H), 7.55 (d, *J* 7.2 Hz, 1H), 7.37- 7.33 (m, 1H), 7.15 - 6.98 (m, 5H), 6.84 (d, *J* 7.6 Hz, 1H), ^{13}C NMR (101 MHz, DMSO) *δ* 172.3, 160.1 (d, *J* 238.8 Hz), 152.7, 147.8, 147.4, 143.5 (d, *J* 19.2), 143.2, 139.2, 135.1, 133.3, 129.9 (d, *J* 14.4 Hz), 129.2, 129.2, 128.8, 128.2, 128.2, 127.9, 126.6, 126.3, 126.2, 126.0 (d, *J* 7.0 Hz), 119.7 (d, *J* 23.2 Hz), 118.0, 114.4, 114.1, 112.9 (d, *J* 8.0 Hz), 111.4, 98.2. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{15}ClFN_4O_2$: 445.0868; found:445.0882.

3'-(2-Chloroquinolin-3-yl)-5-fluoro-4'-(2-fluorophenyl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3h). White solid. mp: 274-275 °C (from Methanol). IR (KBr, cm^{-1}): 3177, 1744, 1619, 1590, 1486. ^{1}H NMR (400 MHz, DMSO) *δ* 10.74 (s, 1H), 9.08 (s, 1H), 8.19 (d, *J* 8.0 Hz, 1H), 7.98 - 7.92 (m, 2H), 7.79 - 7.75 (m, 1H), 7.68 (dd, *J* 8.0, 4.0 Hz, 1H), 7.27 - 7.22 (m,1H), 7.16 (t, *J* 8.0 Hz, 2H), 7.09 (t, *J* 8.0 Hz, 1H), 6.92 (d, *J* 8.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) *δ* 172.2, 159.8 (d, *J* 238 Hz), 159.0 (d, *J* 249 Hz), 153.0, 147.8, 147.2, 143.4, 139.5, 133.4, 130.9 (d, *J* 7.0 Hz), 130.1, 129.2, 128.8, 128.2, 126.2, 125.6 (d, *J* 2.2 Hz), 124.9 (d, *J* 7.0 Hz), 122.8, 122.7, 119.9 (d, *J* 23 Hz), 117.5, 117.1 (d, *J* 20Hz), 114.3 (d, *J* 24.0 Hz), 112.7 (d, *J* 7 Hz), 97.9. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{14}ClF_2N_4O_2$: 463.0773; found:463.0782.

5-Chloro-3'-(2-chloroquinolin-3-yl)-4'-phenyl-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3i). White solid. mp: 237-238 °C (from Methanol). IR (KBr, cm^{-1}): 3388, 1748, 1619, 1583, 1495. ^{1}H NMR (400 MHz, DMSO) *δ* 10.88 (s, 1H), 9.10 (s, 1H), 8.18 (d, *J* 8.4 Hz, 1H), 7.97 – 7.93 (m, 2H), 7.83 (d, *J* 2.0 Hz, 1H), 7.79 – 7.75 (m, 1H), 7.44 (dd, *J* 8.4, 4.0 Hz, 1H), 7.17 – 7.12 (m, 2H), 7.09 – 7.05 (m, 1H), 6.92 – 6.88 (m, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 172.0, 152.7, 147.8, 147.3, 143.6, 141.9, 135.1, 133.3, 132.9, 129.9, 129.2, 128.8, 128.2, 127.9, 127.5, 126.7, 126.5, 126.3, 126.3, 118.0, 113.3, 98.0. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{15}Cl_2N_4O_2$: 461.0572; found:461.0584.

5-Chloro-4'-(3-chlorophenyl)-3'-(2-chloroquinolin-3-yl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3j). White solid. mp: 221-222 °C (from Methanol). IR (KBr, cm^{-1}): 3429, 1746, 1619, 1585, 1477. ^{1}H NMR (400 MHz, DMSO) *δ* 10.99 (s, 1H), 9.14 (s, 1H), 8.21 (d, *J* 8.0 Hz, 1H), 7.98 (t, *J* 10.0 Hz, 2H), 7.88 (s, 1H), 7.79 (t, *J* 7.2 Hz, 1H), 7.46 (d, *J* 8.4 Hz, 1H), 7.22 - 7.16 (m, 2H), 6.93 (d, *J* 8.8 Hz, 2H), 6.87 (d, *J* 8.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 171.8, 152.2, 147.9, 147.1, 143.9, 141.9, 136.6, 133.7, 133.5, 133.2, 131.7, 129.2, 128.9, 128.3, 127.9, 127.7, 126.8, 126.2, 125.7, 125.7, 124.8, 117.5, 113.4, 97.9. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{14}Cl_3N_4O_2$: 495.0182; found:495.0181.

5-Bromo-3'-(2-chloroquinolin-3-yl)-4'-phenyl-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3k). Yellow solid. mp: 234-235 °C (from Methanol). IR (KBr, cm^{-1}): 3392, 1748, 1618, 1589, 1498. ^{1}H NMR (400 MHz, DMSO) *δ* 10.90 (s, 1H), 9.11 (s, 1H), 8.18 (d, *J* 8.0 Hz, 1H), 7.99 – 7.93 (m, 3H), 7.79 – 7.75 (m, 1H), 7.57 (d, *J* 8.0 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.08 (d, *J* 7.6 Hz, 1H), 6.91 (d, *J* 7.2 Hz, 2H), 6.85 (d, *J* 8.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 171.9, 152.7, 147.8, 147.3, 143.6, 142.3, 135.8, 135.0, 133.3, 129.9, 129.4, 129.1, 128.8, 128.2, 128.0, 126.6, 126.4, 126.2, 117.9, 115.1, 113.7, 97.9. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{24}H_{15}BrClN_4O_2$:505.0067; found:505.0097.

5-Bromo-3'-(2-chloroquinolin-3-yl)-4'-(p-tolyl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3l). Pale yellow solid. mp: 240-241 °C (from Methanol). IR (KBr, cm^{-1}): 3368, 1748, 1618, 1588, 1472. ^{1}H NMR (400 MHz, DMSO) *δ* 10.83 (s, 1H), 9.09 (s, 1H), 8.18 (d, *J* 8.0 Hz, 1H), 7.95 (s, 3H), 7.79 – 7.75 (m, 1H), 7.56 (d, *J* 8.0 Hz, 1H), 6.94 (d, *J* 7.6 Hz, 2H), 6.86 – 6.81 (m, 3H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 172.0, 152.9, 147.8, 147.4, 143.6, 142.3, 137.9, 135.7, 133.8, 133.3, 132.2, 130.4, 129.5, 129.1, 128.8, 128.2, 127.0, 126.7, 126.2, 118.0, 115.0, 113.7, 98.0, 20.8. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{25}H_{17}BrClN_4O_2$: 519.0223; found:519.0222.

5-Bromo-4'-(4-chlorophenyl)-3'-(2-chloroquinolin-3-yl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3m). Yellow solid. mp: 201-202 °C (from Methanol). IR (KBr, cm^{-1}): 3238, 1746, 1619, 1588, 1471. ^{1}H NMR (400 MHz, DMSO) *δ* 10.76 (s, 1H), 9.09 (s, 1H), 8.21 (d, *J* 8.0 Hz, 1H), 8.0 - 7.93 (m, 2H), 7.80 - 7.76 (m, 1H), 7.73 (d, *J* 8.0 Hz, 1H), 7.44-7.40 (m, 1H), 7.22 (d, *J* 8.8 Hz, 2H), 7.16 (t, *J* 7.6 Hz, 1H), 6.9 (d, *J* 7.6 Hz, 1H), 6.85 (d, *J* 8.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 171.9, 152.5, 147.9, 147.2, 143.5, 143.0, 134.3, 133.4, 133.2, 132.2, 129.9, 129.2, 128.9, 128.2, 127.9, 126.8, 126.3, 124.1, 123.8, 117.8, 111.8, 98.2. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. For $C_{24}H_{14}BrCl_2N_4O_2$: 538.9677; found:538.9670.

3'-(2-chloroquinolin-3-yl)-1-methyl-4'-phenyl-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3n):

White solid. mp: 251-252 °C (from Methanol). IR (KBr, cm^{-1}): 1735, 1612, 1589, 1489. ^{1}H NMR (400 MHz, DMSO) *δ* 9.09 (s, 1H), 8.20 (d, *J* 8.0 Hz, 1H), 7.98-7.92 (m, 2H), 7.79 - 7.75 (m, 2H), 7.51 - 7.47(m, 1H), 7.22 (t, *J* 7.6, 1H), 7.11-7.08 (m, 3H), 7.03 (t, *J* 7.6Hz, 1H), 6.83(d, *J* 7.2 Hz, 2H), 3.12 (s, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 170.5, 152.7, 147.8, 147.4, 144.4, 143.5, 135.2, 133.3, 133.1, 129.8, 129.2, 128.8, 128.2, 127.8, 126.4, 126.3, 124.2, 123.9, 118.1, 110.5, 98.0, 26.8. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{25}H_{18}ClN_4O_2$: 441.1118; found:441.1124.

3'-(2-Chloroquinolin-3-yl)-1-methyl-4'-(p-tolyl)-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3o). White solid. mp: 241-242 °C (from Methanol). IR (KBr, cm^{-1}): 1731, 1613, 1589, 1489. ^{1}H NMR (400 MHz, DMSO) *δ* 9.06 (s, 1H), 8.19 (d, *J* 6.0 Hz,1H), 7.94 (d, *J* 6.8 Hz, 2H), 7.77 (d, *J* 5.6 Hz, 2H), 7.48 (t, *J* 8.0 Hz, 1H), 7.22(t, *J* 7.2 Hz, 1H), 7.07 (d, *J* 6.8 Hz, 1H), 6.88 (d, *J* 5.6 Hz, 2H), 6.76 (d, *J* 6.4 Hz, 2H), 3.10 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 170.6, 152.9, 147.8, 147.5, 144.4, 143.4, 137.6, 133.3, 133.0, 132.3, 130.3, 129.2, 128.8, 128.2, 126.9, 126.4, 126.3, 124.2, 124.0, 118.2, 110.4, 98.0, 26.7, 20.7. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{26}H_{20}ClN_4O_2$: 455.1275; found:455.1280.

3'-(2-Chloroquinolin-3-yl)-4'-(4-fluorophenyl)-1-methyl-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3p). White solid. mp 231-232 °C (from Methanol). IR (KBr, cm^{-1}): 1734, 1613, 1583, 1490. ^{1}H NMR (400 MHz, DMSO) *δ* 9.09 (s, 1H), 8.19 (d, *J* 8.0 Hz ,1H), 7.99 - 7.92(m, 2H), 7.81 - 7.75 (m, 2H), 7.50 (t, *J* 8.0 Hz, 1H), 7.24 (t, *J* 7.6 Hz, 1H), 7.09(d, *J* 8.0 Hz, 1H), 7.0 - 6.91(m, 4H), 3.11 (s, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 170.4, 162.3 (d, *J* 244.4), 152.8, 147.9, 147.3, 144.5, 143.6, 133.3,133.2, 131.3 (d, *J* 3.0 Hz), 129.4 (d, *J* 9.1), 129.2, 128.8, 128.2, 126.4, 126.3, 124.2, 123.7, 117.8, 116.9 (d, *J* 23.0 Hz), 110.5, 98.0, 26.7. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{25}H_{17}ClFN_4O_2$: 459.1024; found:459.1029.

3'-(2-Chloroquinolin-3-yl)-4'-(2-fluorophenyl)-1-methyl-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3q). Brown solid. mp: 203-204 °C (from Methanol). IR (KBr, cm^{-1}): 1732, 1614, 1589, 1471. ^{1}H NMR (400 MHz, DMSO) *δ* 9.01 (s, 1H), 8.21 (d, *J* 7.6 Hz, 1H), 7.97-7.91 (m, 2H), 7.76 (t, *J* 6.8 Hz, 1H), 7.58 (d, *J* 7.2Hz, 1H), 7.47-7.42 (m, 1H), 7.15 - 7.10 (m, 2H), 7.07 (d, *J* 7.6Hz, 2H), 7.04 - 6.95 (m, 2H), 3.14 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.6, 158.9 (d, *J* 245.0 Hz), 153.1, 147.8, 147.2, 146.5, 144.8, 143.3, 133.4 (d, *J* 18.4 Hz), 130.6, 129.6, 129.2, 128.8, 128.2, 126.4 (d, *J* 10.8 Hz), 125.5, 123.8, 122.6, 117.6, 117.1 (d, *J* 25.0 Hz), 110.3, 97.7, 26.7. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. For $C_{25}H_{17}ClFN_4O_2$: 459.1024; found:459.1042.

1-Butyl-3'-(2-chloroquinolin-3-yl)-4'-phenyl-4'*H*-spiro[indoline-3,5'-[1,2,4]oxadiazol]-2-one (3r). Pale yellow solid. mp: 229-230 °C (from Methanol). IR (KBr, cm^{-1}): 1731, 1613, 1588, 1492.^{1}H NMR (400 MHz, DMSO) *δ* 9.07 (s, 1H), 8.20 (d, *J* 8.0 Hz, 1H), 7.98 - 7.91(m, 2H), 7.82 - 7.75 (m, 2H), 7.49 (t, *J* 7.6 Hz, 1H), 7.24 (t, *J* 7.2 Hz, 1H), 7.13 - 7.05 (m, 4H), 6.83 (d, *J* 6.8 Hz, 2H), 3.71-3.64 (m, 1H), 3.60 - 3.53 (m, 1H), 1.43 - 1.38 (m, 2H), 0.99-0.94 (m, 2H), 0.75 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 170.4, 152.8, 147.8, 147.3, 143.8, 143.4, 134.9, 133.3, 133.1, 129.7, 129.2, 128.8, 128.2, 128.0, 126.8, 126.6, 126.3, 124.3, 124.1, 118.1, 110.6, 98.0, 28.9, 19.4, 13.9. HRMS (ESI, *m/z*): $[M+H]^+$ calcd. for $C_{28}H_{24}ClN_4O_2$: 483.1588; found:483.1597.

Anticancer activity

The anticancer activity of the compounds was determined using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) reduction assay.[42] Around $1x10^4$ cells/well were seeded in 100 µl DMEM (Dulbecco's Modified Eagle's Medium) supplemented with 10% FBS in each well of 96-well plates and were incubated for 24 h at 37 °C in a CO_2 incubator. After 24 h of incubation, cells were treated with the test compounds for 48 h. After the treatment, 10 µl of MTT (5 mg/mL) was added to each well and the plates were further incubated for 4 h. After incubation, supernatant from each well was carefully removed and formazon crystals were dissolved in 100 µl of dimethyl sulfoxide (DMSO). Finally, the absorbance was measured at 540 nm.

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Conflicts of interest

There are no conflicts to declare

Supplementary Material

Copies of NMR, Mass, FTIR spectra of all prepared compounds are given in the Supplementary Material file associated with this manuscript.

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