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FULL PAPER

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Novel quinoline derivatives carrying nitrones/oximes nitric oxide donors: Design, synthesis, antiproliferative and caspase-3 activation activities

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Abstract

Novel quinoline derivatives carrying nitrones and oxime as nitric oxide donors were prepared and characterized using different spectroscopic techniques. Nitrones can release nitric oxide in larger amounts compared to corresponding oximes. Antiproliferative screening results showed that the 2-benzylthioquinoline nitrones **6e** and **6f** and the 2-methylthio analogues **6g** and **6h** exhibited promising antiproliferative activity especially against leukemia and colon cancer cell lines. Compounds **6c**, **6e**, and **6f** exhibited higher potency as anticancer agents compared to doxorubicin, with IC_{50} ranging from 0.45 to 0.91 μM. A remarkable overexpression of caspase-3 protein levels was observed in cells treated with the tested compounds. Compound **6e** exhibited more pre-G1 apoptosis and cell cycle arrest at the G2/M phase than in other phases. These results revealed that the tested compounds can cause programmed cell death through overexpression of caspase 3, which may be attributed to the release of nitric oxide.

KEYWORDS
antiproliferative, apoptosis, caspase 3, nitric oxide, nitrones, oximes

1 | INTRODUCTION

Quinoline is a significant nucleus which has attracted the attention of medicinal chemists due to its variable pharmacological activities. Easy functionalization of various ring positions of quinoline makes it an attractive synthetic building block for design and synthesis of new drugs. Additionally, quinolines are considered as an interesting group of compounds, many of which have widespread pharmacological actions such as anti-microbial,[1–4] anti-inflammatory,[5–8] anti-tubercular,[9–12] anti-convulsant,[13] antihypertensive,[14,15] antioxidant,[16–19] and anticancer[20] activities. Several mechanisms can explain the anticancer effect of quinoline derivatives including: topoisomerase inhibition,[21–23] DNA intercalation,[24] protein kinases inhibition,[25–27] tubulin polymerase inhibition,[28–31] and induction of apoptosis.[32,33] Quinoline derivative **I** exhibited potent anticancer activity against brain cancer cell line U87 with IC_{50} of 1.5 nM.[31] Compound **II** exhibits remarkable anticancer activity against HL60 cancer cell line with IC_{50} of 0.68 μM (Figure 1).[33] Incorporation of biologically active moieties into quinoline such as nitrones[34] and oximes[35] may produce biologically active anticancer agents. Compound **III** showed significant anticancer activity with IC_{50} of 31.42 μM against Hep-G_2 cancer cell line (Figure 1).[34] Nitrones are a

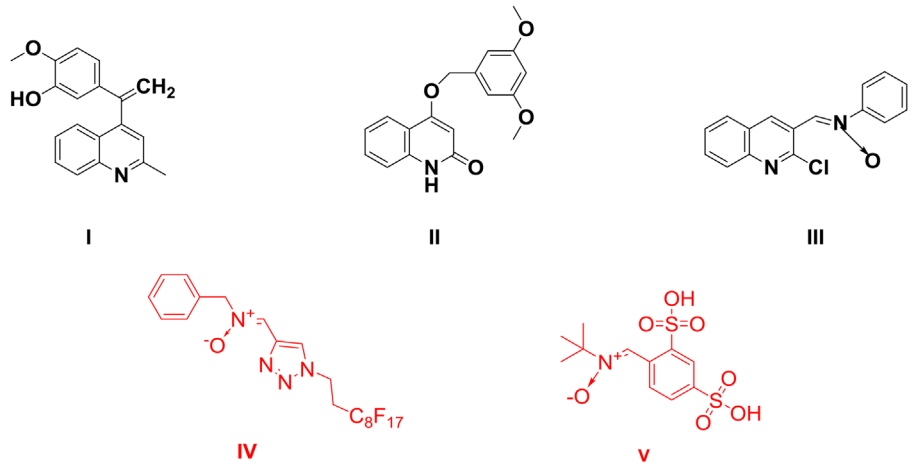


FIGURE 1 Structures of compounds **I–III**

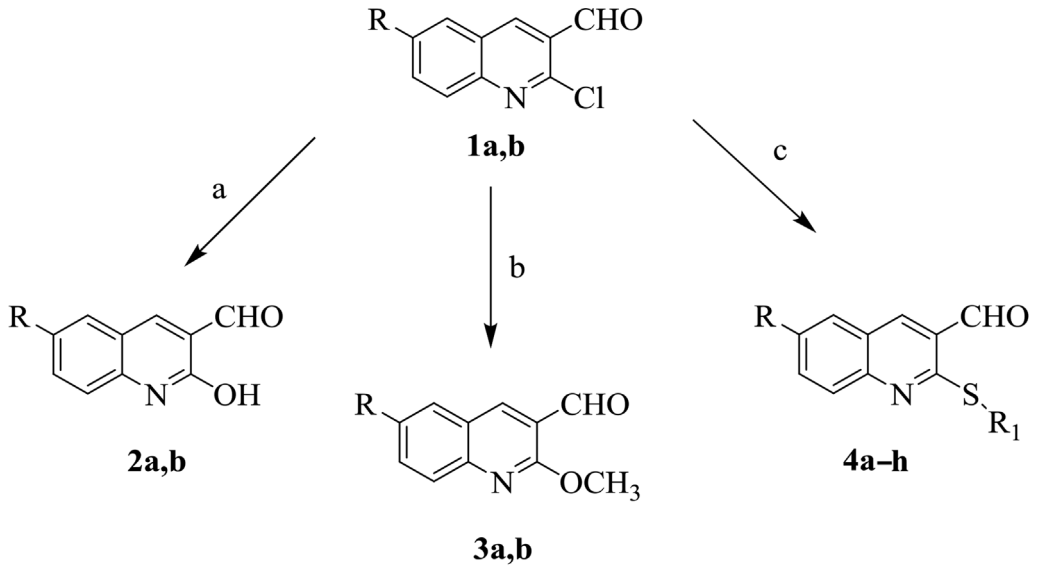
class of compounds with various biological activities including anti-inflammatory,[36] antioxidant,[37] anti-ischemic,[38] and antiproliferative[39] activities which may be attributed to nitric oxide release. Alpha-phenyl *N*-tertiary-butyl nitrone (PBN) is the most famous nitrone which is used as a spin trap and an antioxidant agent. Also, PNB showed a potent anticancer activity and caused shrinkage of cancer cells especially when administrated in early stage of cancer.[40]

Moreover, nitric oxide-releasing oximes have various potential activities that depend on releasing of NO from their structures. These activities include antihypertensive,[41] anti-inflammatory,[42] gastroprotective,[42] and antiproliferative[43] activities. Several mechanisms can explain the antiproliferative activity of nitrones and oximes, but the most accepted one is through the release of nitric oxide and/or induction of apoptosis.[44] NO may be converted inside the cell into reactive nitrogen species (RNS) such as NO_2 and N_2O_3, which targeted P53 causing cytochrome-c release and caspases activation.[45] Caspases are a group of vital mediators for apoptosis, but the most critical one is caspase-3, which can activate death protease leading to cleavage of many key cellular proteins.[46] 1,2,3-Triazole-substituted *N*-alkyl nitrone **IV** was reported as antiproliferative agent with IC_{50} of 8.1 μM against PC-3 cancer and also recorded caspase-3 induction.[36] Also, a disulfonyl derivative of phenyl-*tert*-butyl nitrone (OKN-007) **V** was established as antiproliferaive agent leading to regression of human glioma U87 through inhibition of caspases.[47] Based on the above-mentioned promising aspects, the strategy of this work includes gathering the two bioactive entities quinoline-nitrones or quinoline-oximes in one compact structure for the purpose of synergism and examined the prepared compounds as potential antiproliferative agents. The presence of nitrone and oxime moieties may synergize the antiproliferative activity of quinoline derivatives. The nitrones and oximes are the source of NO and the accumulation of NO in cancer cells subsequently will lead to apoptosis and arrest of cell cycle. The substituent in position two of quinoline was designed to be with different electronic and steric properties to investigate their effect on the antiproliferative activity of these derivatives. The target compounds were identified using different spectroscopic techniques including ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and elemental analysis. Moreover, nitric oxide release was determined using Griess method to evaluate the amount of NO released. The target compounds were screened for their antiproliferative activity. Furthermore, the IC_{50}, caspase-3 activation assay, cell cycle analysis, and apoptosis assay were established for the most active compounds of this series.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The intermediates quinoline aldehydes **1a**,**b**, **2a**,**b**, **3a**,**b** were synthesized through reported methods in literature,[48–50] Scheme 1. The 2-alkylthioquinoline-3-carbaldhyde derivatives **4a–h** were prepared by stirring of compounds **1a** or **1b** with sodium sulfide in DMF, further alkylation in the same reaction with different alkyl halides afforded the intermediates **4a–h**.[49] The structure of the new derivatives **4d–f** was confirmed by ^{1}H NMR, mass spectroscopy, and elemental analysis. ^{1}H NMR spectra of compounds **4d–f** exhibited a common singlet signal at δ 10.18–10.16 ppm related to –CHO. The aldehydic carbon appeared at δ 191.9–191.6 ppm in ^{13}C NMR spectrum. Additionally, a characteristic singlet signal appeared at δ 8.75–8.80 ppm related to H_4 of quinoline. Furthermore, spectrum of compound **4d** showed a singlet signal at δ 4.56 ppm related to benzylic protons, which confirmed by signal at δ 33.47 ppm in ^{13}C NMR spectrum. Reaction of 2-chloroquinoline-3-carbaldhyde derivatives **1a**,**b** with Na_2S in DMF followed by addition of propyl iodide afforded 2-isopropylquinoline-3-carbaldhyde **4e**,**f**. It is expected that the propyl iodide undergoes rearrangement into the more stable isopropyl carbocation. The same rearrangement occurred in a similar reaction of the propyl bromide in the presence of mercuric salts.[51] ^{1}H NMR spectra of compounds **4e**,**f** showed characteristic isopropyl pattern as a doublet at δ 1.43 and 1.42 ppm, and a septet at δ 4.18–4.25 ppm. ^{13}C NMR spectrum of compound **4e** exhibited the characteristic signals for the isopropyl.



1a, 2a, 3a; R = H, 1b, 2b, 3b; R = CH_3

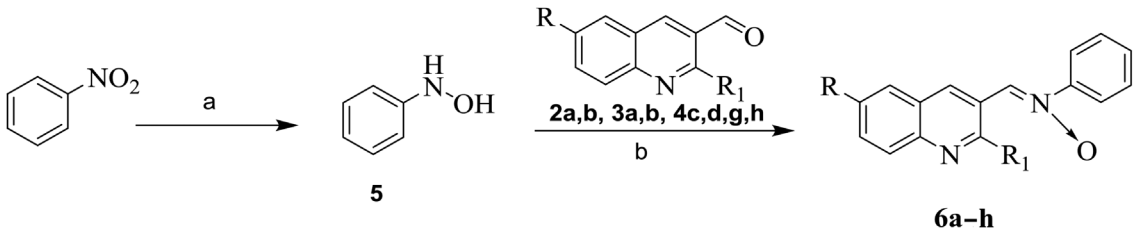
4a; R = H, R_1 = -$CH_2CH{=}CH_2$
4b; R = CH_3, R_1 = -$CH_2CH{=}CH_2$
4c; R = H, R_1 = -$CH_2C_6H_5$
4d; R = CH_3, R_1 = -$CH_2C_6H_5$
4e; R = H, R_1 = -$CH(CH_3)_2$
4f; R = CH_3, R_1 = -$CH(CH_3)_2$
4g; R = H, R_1 = -CH_3
4h; R = CH_3, R_1 = -CH_3

Reagent and conditions; a: 4 M HCl, 70°C, b: $NaOCH_3$, 60–70°C, c: DMF, Na_2S, RX, rt.

SCHEME 1 Synthesis of quinoline-3-carbaldhydes derivatives **2a**,**b**, **3a**,**b**, and **4a–h**

These results are an evidence that this reaction occurs through S_N1 mechanism and formation of the most stable secondary carbocation to form compounds **4e**,**f**.

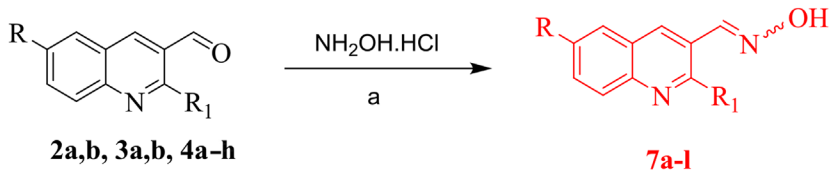
The nitrones **6a–h** were prepared as outlined in Scheme 2. Reduction of nitrobenzene using ammonium chloride and zinc dust in hot water afforded phenyl hydroxylamine **5**.[52] Heating of the appropriate quinoline-3-carbaldhyde **2a**,**b**, **3a**,**b**, **4c**,**d**,**g**,**h** with phenyl hydroxylamine **5** at 60°C in absolute ethanol afforded the corresponding quinoline nitrones **6a–h** using a procedure for synthesis of similar nitrones.[34] ^{1}H NMR spectra of nitrones **6a–h** showed a common singlet signal appearing at δ 10.26–10.00 ppm related to –N═CH proton of the formed nitrone moiety. The ^{13}C NMR spectra of nitrone derivatives **6a–h** showed disappearance of aldehydic carbonyl carbon and appearance of CH═N carbon. Also, the signals of the aromatic carbons appeared at their expected chemical shifts.



6a; R = H, R_1 = OH
6b; R = CH_3, R_1 = OH
6c; R = H, R_1 = OCH_3
6d; R = CH_3, R_1 = OCH_3
6e; R = H, R_1 = $SCH_2C_6H_5$
6f; R = CH_3, R_1 = $SCH_2C_6H_5$
6g; R = H, R_1 = SCH_3
6h; R = CH_3, R_1 = SCH_3

Reagent and conditions; a: Zinc dust, NH_4Cl, H_2O b: EtOH, 60°C.

SCHEME 2 Synthesis of quinoline nitrones **6a–h**



2a,b, 3a,b, 4a–h **7a-l**

7a; R = H, R_1 = OH
7b; R = CH_3, R_1 = OH
7c; R = H, R_1 = OCH_3
7d; R = CH_3, R_1 = OCH_3
7e; R = H, R_1 = SCH_2-CH=CH_2
7f; R = CH_3, R_1 = SCH_2-CH=CH_2

7g; R = H, R_1 = $SCH_2C_6H_5$
7h; R = CH_3, R_1 = $SCH_2C_6H_5$
7i; R = H, R_1 = $SCH(CH_3)_2$
7j; R = CH_3, R_1 = $SCH(CH_3)_2$
7k; R = H, R_1 = SCH_3
7l; R = CH_3, R_1 = SCH_3

Reagent and conditions; a: EtOH,TEA, rt.

SCHEME 3 Synthesis of quinoline oximes **7a–l**

The oxime derivatives **7a–l** were prepared as outlined in Scheme 3. Stirring at room temperature of quinoline aldhydes **2a**,**b**, **3a**,**b**, **4a–h** and hydroxylamine hydrochloride in ethanol using catalytic amount of TEA afforded the target quinoline oximes **7a–l** in a good yield.[35] ^{1}H NMR spectra of compounds **8a–l** showed a common singlet peak appearing at δ 11.81–11.48 ppm related to −OH proton of oxime and a common characteristic signal at δ 8.42–8.21 ppm related to −NCH proton. The allylthio derivatives **7e**,**f** showed the characteristic pattern of allyl group. Also, the isopropylthio derivatives **7i**,**j** exhibited the characteristic pattern of isopropylthio group. The ^{13}C NMR spectra of oxime derivatives **7a–l** showed disappearance of aldehydic carbon and appearance of CH═N carbon. Moreover, the aromatic carbons appeared at their expected chemical shifts. The purity of the newly prepared compounds was confirmed by elemental analysis; the results are consistent with the molecular formula of the products. Mass spectra of the target compounds are consistent with the calculated ones.

2.2 | Measurement of nitric oxide release

The amount of NO released from quinoline nitrones and oximes was measured quantitatively using modified Griess colorimetric method.[53] This method is used for the indirect determination of NO through spectrophotometric measurement of its stable decomposition products NO^{2-}. This reaction involves two steps; the first step is diazotization reaction in which the NO-derived nitrosating agent, dinitrogen trioxide (N_2O_3) generated from the auto-oxidation of NO, reacts with sulfanilamide to produce a diazonium ion. The second step is the coupling of diazonium ion with *N*-(1-naphthyl)ethylenediamine dihydrochloride (NEDD) to form a colorimetric azo product that absorbs strongly at λ_{max} 546 nm. In order to evaluate thiol-induced NO generation from the tested compounds, the NO-donating nitrones **6a–h** and oximes **7a–l**, were incubated in aqueous phosphate buffer of pH 7.4 in the presence of excess *N*-acetylcysteine which act as a source of thiols that are essential for release of NO from nitrones and oximes. The signal intensity of the dye is proportional to the amount of NO released. To quantify amount of NO released, a standard curve was made by measuring the change in absorbance of various concentration of standard sodium nitrite solutions treated by the same way. The results expressed as amount of NO released (mole/mole) are listed in Table 1. Results revealed that nitrone and oxime containing molecules are able to release NO at pH 7.4, where the NO-donating nitrones **6a–f** achieved maximum amount of NO released after 4 h. Compounds **6e** and **6f** released the highest amount of NO among this group (0.587 and 0.506 mole/mole), respectively. Also, compounds **6c**, **6d**, **6g**, and **6h** released a considerable amount of NO (0.441, 0.414, 0.433, and 0.418, respectively). On the other hand, the amounts of NO released from quinoline nitrones **6a–h** are more than those released from their corresponding oximes **7a–l** (Figure 2).

2.3 | Biological evaluation

2.3.1 | Evaluation of *in vitro* antiproliferative activity by NCI

The antiproliferative activity of quinolin nitrones **6a–h** and quinolin oximes **7a–l** was evaluated according to the protocol of the drug evaluation branch of the national cancer institute (NCI), Bethesda, USA, for *in vitro* anticancer activity (http://www.dtp.nci.nih.gov). Results for each tested compound were reported as the percentage of growth of the treated cells when compared to the untreated control cells (see supplementary data and Table 2).

The quinolin nitrones **6c–h** exhibited noteworthy antiproliferative activity and growth inhibition percentage while the 2-hydroxyl derivatives **6a**,**b** exhibited weak antiproliferative. Moreover, the 2-methoxy analogue **6c** showed complete cell death against leukemia cancer cell line HL-60 and remarkable growth inhibition activity against leukemia cancer cell line CCRF-CEM, K-562, MOLT-4, RPMI-8226, SR, colon cancer cell line HCT-116, HCT-15, SW-62 and breast cancer cell line MCF-7. Also, the 2-methoxy derivative **6d** revealed a remarkable growth inhibition activity against leukemia cancer cell line K-562 and colon cancer cell line HCT-116. Moreover, 2-benzylthio derivative **6e**

TABLE 1 Amount of NO released from synthesized compounds **6a–h** and **7a–l**

	Amount of NO released (mole/mole)					
Compound	**1 h**	**2 h**	**3 h**	**4 h**	**5 h**	**6 h**
6a	0.117 ± 0.014	0.121 ± 0.025	0.260 ± 0.028	0.301 ± 0.022	0.109 ± 0.019	0.097 ± 0.020
6b	0.123 ± 0.029	0.118 ± 0.012	0.286 ± 0.015	0.307 ± 0.015	0.166 ± 0.011	0.155 ± 0.024
6c	0.159 ± 0.009	0.204 ± 0.010	0.318 ± 0.029	0.441 ± 0.033	0.207 ± 0.039	0.113 ± 0.024
6d	0.189 ± 0.032	0.210 ± 0.021	0.390 ± 0.023	0.414 ± 0.022	0.205 ± 0.019	0.199 ± 0.016
6e	0.239 ± 0.007	0.311 ± 0.013	0.456 ± 0.027	0.58 ± 0.034	0.246 ± 0.017	0.180 ± 0.018
6f	0.179 ± 0.021	0.278 ± 0.026	0.344 ± 0.021	0.506 ± 0.024	0.287 ± 0.023	0.212 ± 0.014
6g	0.210 ± 0.022	0.298 ± 0.020	0.368 ± 0.039	0.433 ± 0.013	0.180 ± 0.021	0.111 ± 0.015
6h	0.191 ± 0.027	0.274 ± 0.015	0.377 ± 0.037	0.418 ± 0.014	0.212 ± 0.012	0.101 ± 0.033
7a	0.098 ± 0.012	0.133 ± 0.034	0.172 ± 0.039	0.191 ± 0.018	0.102 ± 0.033	0.084 ± 0.015
7b	0.134 ± 0.025	0.166 ± 0.032	0.197 ± 0.029	0.230 ± 0.016	0.136 ± 0.025	0.112 ± 0.023
7c	0.123 ± 0.027	0.147 ± 0.023	0.201 ± 0.027	0.290 ± 0.044	0.202 ± 0.017	0.173 ± 0.018
7d	0.131 ± 0.014	0.165 ± 0.019	0.187 ± 0.012	0.255 ± 0.010	0.214 ± 0.022	0.189 ± 0.011
7e	0.141 ± 0.003	0.179 ± 0.019	0.211 ± 0.015	0.277 ± 0.039	0.223 ± 0.018	0.160 ± 0.021
7f	0.149 ± 0.010	0.206 ± 0.017	0.255 ± 0.023	0.296 ± 0.025	0.208 ± 0.012	0.153 ± 0.037
7g	0.215 ± 0.032	0.211 ± 0.014	0.233 ± 0.034	0.282 ± 0.015	0.232 ± 0.036	0.186 ± 0.026
7h	0.171 ± 0.012	0.199 ± 0.023	0.240 ± 0.026	0.273 ± 0.019	0.211 ± 0.035	0.141 ± 0.013
7i	0.111 ± 0.011	0.153 ± 0.015	0.248 ± 0.018	0.261 ± 0.019	0.101 ± 0.009	0.067 ± 0.021
7j	0.178 ± 0.014	0.198 ± 0.006	0.206 ± 0.009	0.218 ± 0.021	0.197 ± 0.018	0.176 ± 0.030
7k	0.177 ± 0.033	0.198 ± 0.005	0.201 ± 0.019	0.232 ± 0.005	0.202 ± 0.027	0.144 ± 0.008
7l	0.179 ± 0.022	0.201 ± 0.020	0.288 ± 0.006	0.312 ± 0.029	0.189 ± 0.016	0.101 ± 0.015

showed the most promising results in this series, compound **6e** revealed a complete cell death against melanoma cancer cell line MDA-MB-435 and ovarian cancer cell line OVCAR-3. A remarkable growth inhibition activity was recorded for **6e** against leukemia cancer cell line CCRF-CEM, HL-60, MOLT-4, RPMI-8226, non-small cell lung cancer cell line HOP-62, HOP-92, colon cancer cell line HCT-116, HCT-15, HT-29, KM-12, SW-620, CNS cancer cell line SF-539, SNB-75, U251, melanoma cancer cell line LOX IMVI, M-14, SK-MEL-5, UACC-62, ovarian cancer cell line OVCAR-8, NCI/ADR-RES, renal cancer cell line SN12C and breast cancer cell line MCF-7. Furthermore, the other 2-benzylthio derivative **6f** revealed remarkable growth inhibition activity against leukemia cancer cell line RPMI-8226, colon cancer cell line HCT-116, HCT-15, HT-29, SW-620, melanoma cancer cell line LOX IMVI, MDA-MB-435, ovarian cancer cell line OVCAR-3 and breast cancer cell line MCF-7. Similarly, the 2-methylthio derivative **6g** showed complete cell death against leukemia cancer cell line HL-60 and remarkable growth inhibition activity against leukemia cancer cell line CCRF-CEM, K-562, MOLT-4, RPMI-8226, SR, colon cancer cell line HCT-116, HCT-15, SW-620, CNS cancer cell line SF-539, melanoma cancer cell line M-14, ovarian cancer cell line

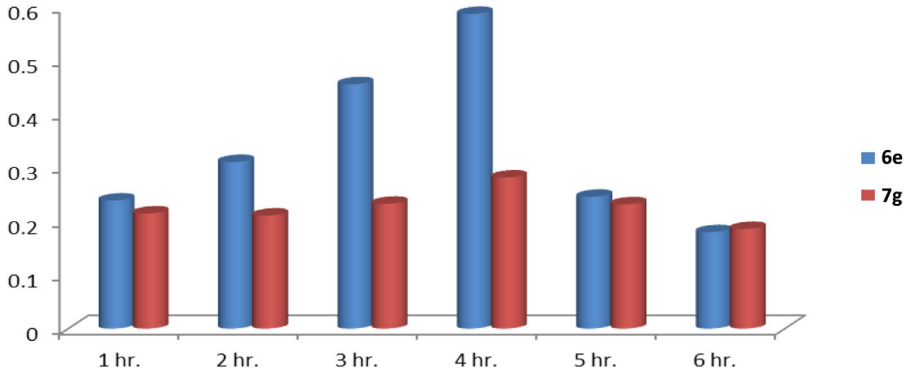


FIGURE 2 Amount of NO released from nitrone **6e** and corresponding oxime **7g**

TABLE 2 Growth inhibition percentage of compounds **6c–h**

		Growth inhibition percentage					
Panel	**Cell line**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**
Leukemia	CCRF-CEM	86.86	53.40	88.84	64.95	89.45	51.10
	HL-60	118.47	19.72	85.88	28.77	113.36	29.69
	K-562	86.52	66.46	59.63	52.31	84.92	69.12
	MOLT-4	70.51	17.25	72.79	46.29	88.03	50.62
	RPMI-8226	85.84	30.86	84.89	79.87	85.48	44.24
	SR	88.52	60.11	Nd	Nd	87.95	Nd
Non-small lung cancer	HOP-62	19.57	18.25	74.46	33.79	32.13	34.22
	HOP-92	35.58	27.52	80.88	38.66	46.79	53.25
Colon cancer	HCT-116	89.82	84.93	90.93	85.85	89.61	85.19
	HCT-15	81.04	32.80	88.52	71.74	81.33	44.26
	HT-29	30.00	4.88	90.00	83.88	19.84	47.93
	KM-12	15.98	9.5	74.98	59.79	−0.47	28.43
	SW-620	71.61	50.13	77.34	77.14	81.14	71.63
CNS cancer	SF-539	65.78	10.20	98.62	22.64	80.25	31.28
	SNB-75	26.97	20.45	88.58	45.26	32.72	37.18
	U 251	43.95	4.55	87.33	57.67	53.75	27.37
Melanoma	LOX IMVI	59.86	33.33	81.03	69.07	61.86	48.88
	M 14	60.44	13.22	93.09	70.78	82.39	25.05
	MDA-MB-435	57.83	3.10	124.09	70.78	54.13	22.26
	SK-MEL-5	26.91	3.82	82.43	20.27	47.51	5.13
	UACC-62	37.17	23.36	68.69	43.62	48.53	45.26
Ovarian cancer	OVCAR-3	13.76	3.44	112.04	68.49	33.14	36.72
	OVCAR-8	62.72	7.36	87.65	64.34	60.50	22.43
	NCI/ADR-RES	55.12	18.87	92.11	56.74	71.49	23.88
Renal cancer	SN12C	40.88	9.86	73.90	48.36	54.75	51.39
Breast cancer	MCF7	71.41	41.41	88.24	69.32	75.06	42.40

Nd, not detected.

NCI/ADR-RES and breast cancer cell line MCF-7. In addition, compound **6h** exhibited remarkable growth inhibition activity against leukemia cancer cell line K562, colon cancer cell line HCT-116 and SW-620. On the other hand, all the screened quinolone oximes **7a–l** showed moderate to weak antiproliferative activity on all tested cancer cell lines. Also, leukemia, colon cancer cell lines HCT-116, HCT-15, HT-29, KM-12, SW-620 and breast cancer cell line MCF7 are the most affected types by tested nitrones (see the Supporting Information).

According to the above-mentioned results, it is obvious that quinoline nitrones exhibited higher antiproliferative activity than corresponding quinoline oximes. Moreover, the substitution of quinoline nitrones at position two with benzylthio or methylthio groups increases the antiproliferative activity greatly. On the other hand, anticancer activity will be abolished when the position two of quinoline is occupied by hydroxyl group. It is obvious that the presence of 2-benzylthio derivatives can increase the antiproliferative activity greater than the corresponding methylthio analogue. Moreover, results indicated that substitution of quinoline ring in position two with hydroxyl group can drastically decrease the antiproliferative activity of quinoline nitrones.

2.3.2 | Cytotoxic activity using MTT assay and evaluation of IC_{50}

Cell viability assay

Cell viability assay was carried out for selected most active quinoline nitrones **6c**, **6e–g** using human mammary gland epithelial cell line (MCF-10A). Compounds were treated with MCF-10A cells for 4 days and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was applied to evaluate the viability of cells. Tested compounds were revealed to be non-toxic where exhibiting more than 91% MCF-10A cell viability.

TABLE 3 IC_{50} values of compounds **6c**, **6e–g**, and doxorubicin against RPMI-8226 and HCT-116 cell lines

	IC_{50} (μM) ± SEM	
Compound number	Against RPMI-8226	Against HCT-116
6c	0.81 ± 0.11	1.32 ± 0.05
6e	0.45 ± 0.03	2.10 ± 0.12
6f	0.79 ± 0.06	2.98 ± 0.17
6g	1.35 ± 0.08	0.98 ± 0.05
Doxorubicin	0.91 ± 0.1	0.41 ± 0.03

Evaluation of IC_{50}

The most active compounds from NCI results, compounds **6c**, **6e–g** were selected to evaluate cytotoxicity using MTT assay and IC_{50} value was evaluated for each compound against RPMI-8226 leukemia and HCT-116 colon cancer cell lines. Doxorubicin was used as a reference drug and all of IC_{50} values in micromolar (μM) are listed in Table 3.

The results in Table 3 showed that all of the tested compounds showed potent antiproliferative activity against RPMI-8226 leukemia cancer cell line compared to doxorubicin. Compounds **6c**, **6e**, and **6f** exhibited remarkable antiproliferative activity with IC_{50} values of 0.81, 0.45, and 0.79 μM, respectively. Moreover, compound **6g** showed a comparable activity to doxorubicin with IC_{50} value of 1.35 μM. These results indicated that 2-benzylthioquinoline-nitrones **6e** and **6f** exhibited the highest activity among the tested compounds and the lowest IC_{50} values rather than 2-methoxy and 2-methylthioquinoline nitrones **6c** and **6g**, respectively. Concerning HCT-116 colon cancer cell line, all of the tested compounds showed a comparable activity to doxorubicin with IC_{50} values of 1.32, 2.10, 2.98, and 0.98 μM, respectively. Also, the 2-methylthioquinoline-nitrone **6g** exhibited the highest antiproliferative activity among all tested compounds against colon cancer with IC_{50} of 0.98 μM.

2.3.3 | Apoptotic proteins activation assay

Cytochrome c and caspases concentration in the cell can be used as valuable markers for apoptosis induction. Quinoline–nitrones **6c**, **6e–g** were evaluated as cytochrome c and caspase-3 activators against RPMI-8226 leukemia cancer cell line and the results are listed in Table 4.

Leukemia cell RPMI-8226 was treated with compounds **6c**, **6e–g** and doxorubicin (0.81, 0.45, 0.79, 1.35, and 0.91 μM), respectively, then cytochrome c and caspase-3 concentrations were evaluated. Results in Table 4 indicated that a remarkable overexpression of both cytochrome c and caspase-3 protein levels were observed in treated cells. The overexpression of caspase-3 by 2-benzylthioquinoline-nitrones **6e** and **6f** were 577.9 and 626.9 pg/mL higher than that of doxorubicin 565.1 pg/mL. On the other hand, the methoxy quinoline–nitrone **6c** and methylthio derivative **6g** showed a comparable induction of caspase-3 (538.8 and 513 pg/mL, respectively) compared to doxorubicin, but less than that obtained by benzylthio derivatives **6e** and **6f**. Also, overexpression of cytochrome c by 2-benzylthioquinoline-nitrones **6e** was 0.6665 pg/mL higher than that of doxorubicin 0.6042 pg/mL. The most active compound **6e** causes overexpression of both cytochrome c and caspase-3 protein levels in leukemia cell RPMI-8226 about 12- and 13-fold, respectively, higher than control. So, the above results may be considered as a suggestion that apoptosis may be attributed to over-expression of both cytochrome c and caspase-3 induced by the tested compounds.

2.3.4 | Cell cycle analysis and apoptosis

Cell cycle analysis was performed for the most active compound **6e** (0.45 and 0.90 μM) and doxorubicin (0.91 μM) as standard drug against leukemia RPMI-8226 cell line. In accordance of IC_{50} concentration (0.45 μM), the percentages of cells of RPMI-8226 cell in G0/G1 phase of the cell cycle in the control was 46.89% which recorded a noteworthy decrease to 23.59 and 25.18% upon treatment with compound **6e** and doxorubicin, respectively (Figures 3 and 5). These percentages were markedly increased at the G2/M phase to 44.13% and 44.06% for compound **6e** and doxorubicin, respectively, due to accumulation of cells at this phase. Furthermore, it is obvious that the apoptotic cell percentage was increased from 2.34% for control untreated leukemia RPMI-8226 cell to 18.64% and 22.17% in treated cells with compound **6e** and doxorubicin, respectively (Figures 3 and 5). The results indicated that the percentage of the late apoptosis is more than that of early apoptosis which a good evidence for irreversible apoptosis caused by compounds **6e** (Figures 4 and 5). In accordance of IC_{50} concentration duplicate (0.90 μM), the same results

TABLE 4 Cytochrome c and caspase-3 levels for compounds **6c**, **6e–g**, doxorubicin, and control untreated leukemia RPMI-8226 cell

	Cytochrome c		Caspase-3	
Compound number	Conc (pg/mL)	Fold change	Conc (pg/mL)	Fold change
6c	0.4435	4.30	538.8	11.60707
6e	0.6665	6.47	577.9	12.44938
6f	0.4769	4.63	626.9	13.50495
6g	0.5051	4.98	513	11.05127
Doxorubicin	0.6042	5.86	565.1	12.17363
Cont	0.1035	1.00	46.42	1.0000

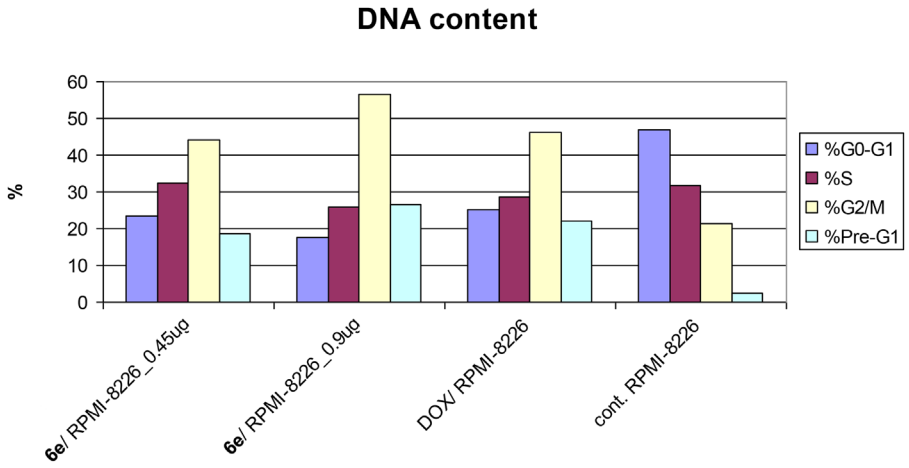


FIGURE 3 Cell cycle analysis on RPMI-8226 treated with compound **6e** and doxorubicin

in cell cycle phases were observed which reflect that changes occurred during different phases are dose dependent.

According to the above results, it is clear that the compound **6e** exhibited pre-G1 apoptosis and cell cycle arrest at G2/M phase. Moreover, it is obvious that the tested compounds are not cytotoxic but antiproliferative causing programmed cell death and cell cycle arrest.

3 | CONCLUSIONS

Two nitric oxide donating series, quinolone nitrones and quinoline oxime derivatives were prepared and identified by different spectroscopic techniques including ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental microanalysis. Nitric oxide release measurements using modified Griess colorimetric method revealed that the target nitrone and oxime are able to release NO at pH 7.4 with maximum amount of NO released after 4 h. In general, nitrones can release larger amount than their corresponding oximes. Antiproliferative activity screening of the target compounds showed that the nitrone derivatives are more active than the oxime analogues. The quinolin nitrones **6c–h** exhibited promising antiproliferative activity and growth inhibition percentage against most of the tested cell lines while the quinoline oximes **7a–l** exhibit weak activity. The IC_{50} was determined for compounds **6c**, **6e–g** against RPMI-8226 leukemia and HCT-116 colon cancer cell lines. Compounds **6c**, **6e**, **6f** exhibited more potency than standard drug doxorubicin against RPMI-8226 leukemia cancer cell line with IC_{50} value of 0.81, 0.45, 0.79, and 0.91 μM, respectively. Moreover, all of the tested compounds showed a comparable activity to doxorubicin with IC_{50} value of 1.32, 2.10, 2.98, and 0.98 μM, respectively, against HCT-116 colon cancer cell line. Furthermore, the quinoline nitrones **6c**, **6e–g** were evaluated as caspase-3 activators against RPMI-8226 leukemia cancer cell line where a remarkable overexpression of caspase-3 protein level was observed in treated cells. Also, compound

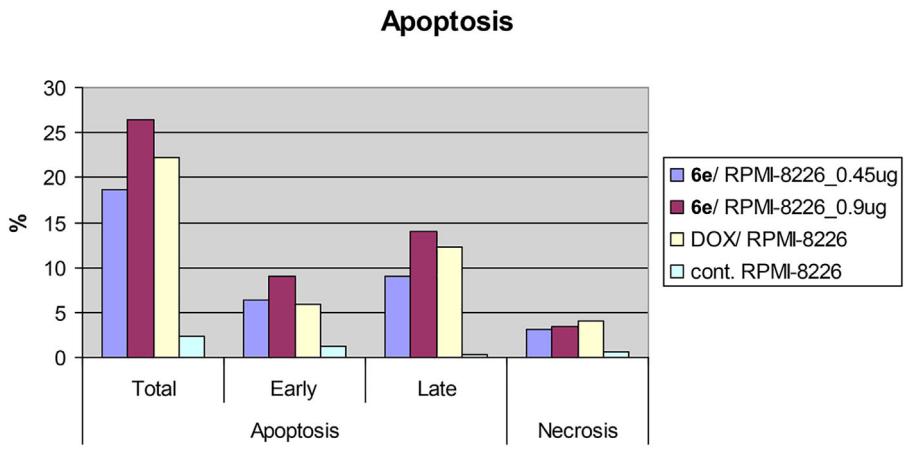


FIGURE 4 Percentage of apoptosis and necrosis for compounds **6e** and doxorubicin on RPMI-8226 cells

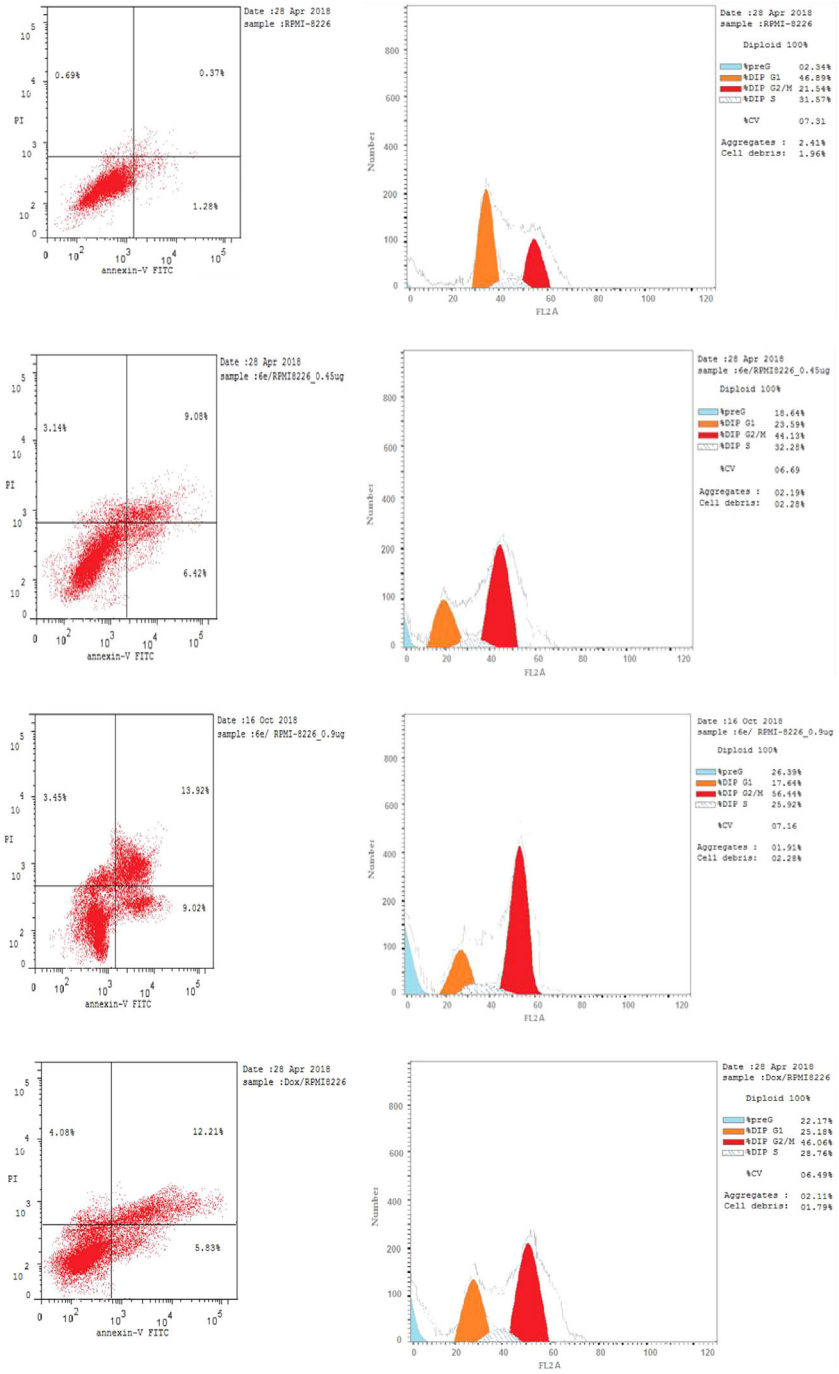


FIGURE 5 Cell cycle analysis and apoptosis induction analysis using Annexin V/PI of compound **6e**, doxorubicin and control untreated RPMI8226 cell

6e exhibited pre-G1 apoptosis and cell cycle arrest at G2/M phase {apoptosis is occurred in pre-G1 phase and the proportion of cells (cell accumulation) is the highest in G2/M phase than other phases}. It is obvious that there is a direct relationship between nitric oxide release, potency as antiproliferative agents and caspase-3 protein overproduction. The nitric oxide donating 2-benzylthioquinoline nitrones **6e** and **6f**; the 2-methylthioquinoline nitrones **6g** and **6h** represent novel highly potent antiproliferative agents that require further *in vivo* studies.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

Chemicals and solvents used in the preparation of the target compounds are of commercial grade and purchased from Sigma–Aldrich, Alfa Aesar, Merck, Fluka and El-Nasr pharmaceutical chemicals

companies. Chemicals and solvents were used without purification. Thin layer chromatography (TLC) was used for monitoring chemical reactions and was carried out using silica gel 60 F_{254} precoated sheet 20 × 20 cm, layer thickening 0.2 mm (E, Merck, Germany), and were visualized using UV-lamp at 254 nm. Melting points (mp) were determined using Stuart electrochemical melting point apparatus (Stuart Scientific, England) and were uncorrected. ^{1}H NMR spectra were carried out on 400 MHz Bruker spectrometer, using TMS as an internal reference. Chemical shift (δ) values are given in parts per million (ppm) relative to DMSO-d_6 (2.5) and coupling constants (*J*) in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet. ^{13}C NMR spectra were carried out on Bruker spectrometer (100 MHz). Shimadzu GC MS and LC-MS/MS Agilent Technologies, 6420 TripleQuad apparatus, Faculty of Pharmacy, Minia University, were used for mass spectroscopy. Vario EL III German CHN Elemental analyzer model was used for elemental analysis. The intermediate compounds were prepared as reported: **1a**,**b**,[49] **2a**,**b**,[48,54] **3a**,**b**,[50] and **5**.[52]

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

4.1.2 | General procedure for the synthesis of 2-alkylthio-6-substituted-quinoline-3-carbaldehyde 4a–h

To a solution of compounds **1a**,**b** (0.01 mol) in DMF (10 mL), sodium sulfide (1.7 g, 0.015 mole) was added and stirred overnight at room temperature (monitored by TLC). After the reaction completion, alkyl halide (0.01 mol) was added and stirred for further 1 h. The reaction mixture was poured into crushed ice and the precipitated solid obtained was filtered, washed with water, dried, and crystallized from methanol/water. Structures of compounds **4a**,[55] **4b**,[56] **4c**,[49] **4g**,[49] and **4h**[56] were confirmed by melting point as reported in literature.

2-(Benzylthio)-6-methylquinoline-3-carbaldehyde 4d

Yellowish white powder; yield: 85%; mp: 107–109°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.16 (s, 1H, CHO), 8.79 (s, 1H, Ar-H), 7.95–7.92 (m, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.77 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.52 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.31–7.29 (m, 2H, Ar-H), 7.23 (d, *J* = 7.0 Hz, 1H, Ar-H), 4.56 (s, 2H, −CH_2), 2.51(s, 3H, −CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 191.9, 156.9, 147.6, 145.3, 138.6, 136.5, 136.1, 129.8, 128.8, 128.7, 127.7, 127.4, 127.3, 124.8, 33.8, 21.4. GC MS: *m/z* calcd.: 293.09, found: 293.23. Anal. calcd. for $C_{18}H_{15}NOS$ (293.09): C, 73.69; H, 5.15; N, 4.77. Found: C, 73.51; H, 5.28; N, 4.90.

2-(Isopropylthio)quinoline-3-carbaldehyde 4e

Yellowish white powder; yield: 74%; mp: 100–102°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.49 (s, 1H, CHO), 8.29 (s, 1H, Ar-H), 7.85–7.11 (m, 4H, Ar-H), 4.41–4.10 (m, 1H, −C<u>H</u>$(CH_3)_2$), 1.50 (d, *J* = 6.8 Hz, 6H, −CH($C\underline{H}_3$)$_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 191.7, 157.9, 147.5, 144.6, 136.6, 136.0, 129.0, 127.6, 127.1, 124.8, 34.0, 23.1. GC MS: *m/z* calcd.: 231.07, found: 231.93. Anal. calcd. for $C_{13}H_{13}NOS$ (231.07): C, 67.50; H, 5.66; N, 6.06. Found: C, 67.41; H, 5.89; N, 6.23.

2-(Isopropylthio)-6-methylquinoline-3-carbaldehyde 4f

Yellowish white powder; yield: 71%; mp: 98–99°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.17 (s, 1H, CHO), 8.75 (s, 1H, Ar-H), 7.84–7.73 (m, 3H, Ar-H), 4.25–4.24. (m, 1H, −C<u>H</u>$(CH_3)_2$), 2.49(s, 3H, −CH_3), 1.42 (d, *J* = 6.8 Hz, 6H, −CH($C\underline{H}_3$)$_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 191.6, 157.7, 147.8, 144.5, 136.4, 135.9, 128.7, 127.6, 127.5, 124.6, 33.9, 23.1, 21.4. GC MS: *m/z* calcd.: 245.09, found: 245.80. Anal. calcd. for $C_{14}H_{15}NOS$ (245.09): C, 68.54; H, 6.16; N, 5.71. Found: C, 68.76; H, 6.34; N, 5.78.

4.1.3 | General procedure for the synthesis of quinoline nitrones 6a–h

A mixture of substituted quinoline aldhydes **2a**,**b**, **3a**,**b**, **4c**,**d**,**g**,**h** (0.001 mole) and phenylhydroxylamine **5** (0.001 mol) in absolute ethanol (5 mL) was heated in water bath at 60°C for 6 h. After cooling the formed precipitate was filtered off, washed, dried, and crystallized from methanol to give the corresponding nitrones[34] **6a–h**.

N-((2-Hydroxyquinolin-3-yl)methylene)aniline oxide 6a

Yellow powder; yield: 79%; mp: 115–117°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.17 (s, 1H, OH), 10.06 (s, 1H, NCH), 8.49 (s, 1H, Ar-H), 7.88 (dd, *J* = 8.0, *J* = 4.0 Hz, 2H, Ar-H), 7.80 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.59–7.55 (m, 4H, Ar-H), 7.33 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.25–7.21 (m, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 160.9, 149.0, 139.2, 136.9, 132.2, 130.6, 129.9, 129.8, 128.2, 123.1, 122.8, 121.7, 119.6, 115.6. GC MS: *m/z* calcd.: 264.09, found $[M+H]^+$: 265.01. Anal. calcd. for $C_{16}H_{12}N_2O_2$ (264.09): C, 72.72; H, 4.58; N, 10.60. Found: C, 72.89; H, 4.72; N, 10.48.

N-((2-Hydroxy-6-methylquinolin-3-yl)methylene)aniline oxide 6b

Yellow powder; yield: 77%; mp: 111–113°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.10 (s, 1H, OH), 10.00 (s, 1H, N═CH), 8.48 (s, 1H, Ar-H), 7.88–7.87 (m, 2H, Ar-H), 7.58–7.57 (m, 4H, Ar-H), 7.41 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.24 (d, *J* = 7.4 Hz, 1H, Ar-H), 2.37 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 160.8, 149.0, 137.3, 136.7, 133.5, 132.2, 130.6, 129.8, 129.2, 128.3, 122.7, 121.7, 119.5, 115.6, 20.8. GC MS: *m/z* calcd.: 278.11, found $[M+H]^+$: 279.13. Anal. calcd. for $C_{17}H_{14}N_2O_2$ (278.11): C, 73.37; H, 5.07; N, 10.07. Found: 73.68; H, 5.19; N, 10.23.

N-((2-Methoxyquinolin-3-yl)methylene)aniline oxide 6c

Yellow powder; yield: 75%; mp: 99–101°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.26 (s, 1H, NCH), 8.50 (s, 1H, Ar-H), 8,01 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.93–7.91 (m, 2H, Ar-H), 7.80 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.76–7.72 (m, 1H, Ar-H), 7.62–7.57 (m, 3H, Ar-H), 7.51–7.48 (m, 1H, Ar-H), 4.10 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 158.8, 149.2, 146.1, 136.3, 131.7, 130.7, 129.8, 129.6, 127.4, 126.9, 125.5, 125.0, 122.0, 116.0, 54.4. GC MS: *m/z* calcd.: 278.11, found $[M+H]^+$:

279.00. Anal. calcd. for $C_{17}H_{14}N_2O_2$ (278.11): C, 73.37; H, 5.07; N, 10.07. Found: C, 73.60; H, 5.13; N, 10.29.

N-((2-Methoxy-6-methylquinolin-3-yl)methylene)aniline oxide 6d

Yellow powder; yield: 71%; mp: 97–99°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.15 (s, 1H, N═CH), 8.45 (s, 1H, Ar-H), 7.91–7.89 (m, 2H, Ar-H), 7.74 (s, 1H, Ar-H), 7.68 (d, J = 8.4 Hz, 1H, Ar-H), 7.59–7.56 (m, 4H, Ar-H), 4.06 (s, 3H, OCH_3), 2.46 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 158.4, 149.2, 144.5, 135.7, 134.7, 133.5, 130.7, 129.8, 128.5, 127.4, 126.7, 124.9, 121.8, 115.7, 54.3, 21.1. GC MS: *m/z* calcd.: 292.12, found $[M+H]^+$: 293.06. Anal. calcd. for $C_{18}H_{16}N_2O_2$ (292.12): C, 73.95; H, 5.52; N, 9.58. Found: C, 74.12; H, 5.70; N, 9.35.

N-((2-(Benzylthio)quinolin-3-yl)methylene)aniline oxide 6e

Yellow powder; yield: 73%; mp: 100–102°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.13 (s, 1H, N═CH), 8.39 (s, 1H, Ar-H), 8.05 (d, J = 8.0 Hz, 1H, Ar-H), 7.99 (d, J = 8.0 Hz, 1H, Ar-H), 7.90–7.88 (m, 2H, Ar-H), 7.84–7.81 (m, 1H, Ar-H), 7.58–7.54 (m, 6H, Ar-H), 7.34–7.30 (m, 2H, Ar-H), 7.26–7.23 (m, 1H, Ar-H), 4.69 (s, 2H, $-CH_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.1, 149.2, 147.3, 138.1, 134.1, 132.0, 130.9, 129.9, 129.8, 129.7, 128.9, 127.8, 127.7, 127.6, 126.9, 125.5, 122.8, 122.0, 34.2. GC MS: *m/z* calcd.: 370.11, found: 370.12. Anal. calcd. for $C_{23}H_{18}N_2OS$ (370.11): C, 74.57; H, 4.90; N, 7.56. Found: C, 74.13; H, 5.24; N, 7.89.

N-((2-(Benzylthio)-6-methylquinolin-3-yl)methylene)aniline oxide 6f

Yellow powder; yield: 68%; mp: 103–105°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.03 (s, 1H, N═CH), 8.36 (s, 1H, Ar-H), 7.90–7.87 (m, 3H, Ar-H), 7.79 (s, 1H, Ar-H), 7.60–7.56 (m, 3H, Ar-H), 7.54–7.52 (m, 2H, Ar-H), 7.33–7.22 (m, 4H, Ar-H), 4.66 (s, 2H, $-CH_2$), 2.49 (s, 3H, $-CH_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.0, 145.9, 138.1, 136.4, 134.1, 133.6, 130.9, 129.9, 129.8, 128.7, 128.4, 128.0, 127.6, 127.5, 125.4, 122.8, 122.0, 121.5, 34.1, 21.4. *m/z* GC MS: *m/z* calcd.: 384.13, found: 384.09. Anal. calcd. for $C_{24}H_{20}N_2OS$ (384.13): C, 74.97; H, 5.24; N, 7.29. Found: C, 74.63; H, 5.38; N, 7.40.

N-((2-(Methylthio)quinolin-3-yl)methylene)aniline oxide 6g

Yellow powder; yield: 69%; mp: 93–94°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 1H, N═CH), 8.42 (s, 1H, Ar-H), 8.03 (d, J = 7.6 Hz, 1H, Ar-H), 7.92–7.89 (m, 3H, Ar-H), 7.81–7.77 (m, 1H, Ar-H), 7.63–7.60 (m, 3H, Ar-H), 7.58–7.54 (m, 1H, Ar-H), 2.72 (s, 3H, SCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 158.1, 149.2, 147.41, 133.6, 131.9, 131.0, 130.0, 129.7, 127.9, 127.7, 126.7, 125.3, 123.0, 122.0, 13.4. GC MS: *m/z* calcd.: 294.08, found $[M+H]^+$: 295.01. Anal. calcd. for $C_{17}H_{14}N_2OS$ (294.08): C, 69.36; H, 4.79; N, 9.52. Found: C, 69.02; H, 4.56; N, 9.67.

N-((6-Methyl-2-(methylthio)quinolin-3-yl)methylene)-anilineoxide 6h

Yellow powder; yield: 66%; mp: 90–92°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.00 (s, 1H, NCH), 8.37 (s, 1H, Ar-H), 7.90–7.88 (m, 2H, Ar-H), 7.79–7.74 (m, 2H, Ar-H), 7.62–7.59 (m, 4H, Ar-H), 2.69 (s, 3H, SCH_3), 2.47 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.9, 149.2, 146.0, 136.2, 133.8, 133.2, 130.9, 129.9, 128.4, 128.0, 127.5, 125.2, 122.9, 122.0, 21.4, 13.3. LC-MS/MS: *m/z* calcd.: 308.10, found: 308.90. Anal. calcd. for $C_{18}H_{16}N_2OS$ (308.10): C, 70.10; H, 5.23; N, 9.08. Found: C, 70.38; H, 5.31; N, 9.31.

4.1.4 | General procedure for the synthesis of quinoline oximes 7a–l

A mixture of appropriate quinoline aldhydes **2a**,**b**, **3a**,**b**, and **4a–h** (0.001 mole), hydroxylamine hydrochloride (0.001 mol) and TEA (0.002 mol) in absolute ethanol (10 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into crushed ice and the formed precipitate was filtered off, washed, dried, and crystallized from methanol/water to give the corresponding oximes[35] **7a–l**.

2-Hydroxyquinoline-3-carbaldehyde oxime 7a

Yellowish white powder; yield: 90%; mp: 157–159°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.02 (s, 1H, OH), 11.50 (s, 1H, OH), 8.28 (s, 1H, N═CH), 8.22 (s, 1H, Ar-H), 7.76 (d, J = 8.0 Hz, 1H, Ar-H), 7.53–7.49 (m, 1H, Ar-H), 7.32 (d, J = 8.0 Hz, 1H, Ar-H), 7.21–7.17 (m, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 161.1, 143.7, 139.2, 134.7, 131.3, 129.1, 124.6, 122.7, 119.4, 115.5. LC-MS/MS: *m/z* calcd.: 188.06, found $[M+H]^+$: 189.00. Anal. calcd. for $C_{10}H_8N_2O_2$ (188.06): C, 63.82; H, 4.28; N, 14.89. Found: C, 63.65; H, 4.35; N, 15.04.

2-Hydroxy-6-methylquinoline-3-carbaldehyde oxime 7b

Yellowish white powder; yield: 87%; mp: 152–154°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.94 (s, 1H, OH), 11.48 (s, 1H, OH), 8.21 (s, 1H, N═CH), 8.19 (s, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 7.34 (d, J = 8.4 Hz, 1H, Ar-H), 7.22 (d, J = 8.4 Hz, 1H, Ar-H), 2.33 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 161.0, 143.8, 137.3, 134.4, 132.6, 131.7, 128.5, 124.5, 119.4, 115.5, 20.8. LC-MS/MS: *m/z* calcd.: 202.07, found $[M+H]^+$: 203.00. Anal. calcd. for $C_{11}H_{10}N_2O_2$ (202.07): C, 65.34; H, 4.98; N, 13.85. Found: C, 65.70; H, 5.12; N, 14.13.

2-Methoxyquinoline-3-carbaldehyde oxime 7c

Yellowish white powder; yield: 89%; mp: 147–149°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.63 (s, 1H, OH), 8.52 (s, 1H, NCH), 8.30 (s, 1H, Ar-H), 7.96 (d, J = 8.0 Hz, 1H, Ar-H), 7.78 (d, J = 8.4 Hz, 1H, Ar-H), 7.70–7.66 (m, 1H, Ar-H), 7.46–7.43 (m, 1H, Ar-H), 4.04 (s, 3H, $-OCH_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 159.4, 146.3, 143.3, 134.8, 130.8, 128.8, 126.7, 125.2, 125.1, 117.7, 54.1. LC-MS/MS: *m/z* calcd.: 202.07, found $[M+H]^+$: 203.00. Anal. calcd. for $C_{11}H_{10}N_2O_2$ (202.07): C, 65.34; H, 4.98; N, 13.85. Found: C, 65.11; H, 5.16; N, 14.19.

2-Methoxy-6-methylquinoline-3-carbaldehyde oxime 7d

Yellowish white powder; yield: 88%; mp: 154–156°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.60 (s, 1H, OH), 8.39 (s, 1H, N═CH), 8.28 (s, 1H, Ar-H), 7.68–7.65 (m, 2H, Ar-H), 7.49 (d, J = 8.8 Hz, 1H, Ar-H), 4.01 (s, 3H, $-OCH_3$), 2.43 (s, 3H, $-CH_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 158.9, 144.7, 143.4, 134.3, 134.2, 132.7, 127.6, 126.8, 125.0, 117.6,

54.0, 21.3. LC-MS/MS: *m/z* calcd.: 216.09, found $[M+H]^+$: 217.10. Anal. calcd. for $C_{12}H_{12}N_2O_2$ (216.09): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.91; H, 5.70; N, 13.24.

2-(Allylthio)quinoline-3-carbaldehyde oxime 7e

Yellowish white powder; yield: 86%; mp: 143–145°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.80 (s, 1H, OH), 8.42 (s, 1H, N═CH), 8.37 (s, 1H, Ar-H), 7.97 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.89 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.76–7.72 (m, 1H, Ar-H), 7.53 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.03–5.96 (m, 1H, $-CH_2-C\underline{H}CH_2$), 5.39 (d, *J* = 16.8 Hz, 1H, $-CH_2-CH{=}C\underline{H}_2$), 5.13 (d, *J* = 10.0 Hz, 1H, $-CH_2-CHC\underline{H}_2$), 4.03 (d, *J* = 7.2 Hz, 2H, $-C\underline{H}_2-CHCH_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.6, 147.3, 145.2, 134.8, 134.3, 131.2, 128.8, 127.7, 126.5, 125.6, 125.2, 118.6, 32.8. LC-MS/MS: *m/z* calcd.: 244.07, found: 244.90. Anal. calcd. for $C_{13}H_{12}N_2OS$ (244.07): C, 63.91; H, 4.95; N, 11.47. Found: C, 64.24; H, 5.12; N, 11.80.

2-(Allylthio)-6-methylquinoline-3-carbaldehyde oxime 7f

Yellowish white powder; yield: 84%; mp: 144–146°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.77 (s, 1H, OH), 8.35 (s, 1H, N═CH), 8.30 (s, 1H, Ar-H), 7.78 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 7.56 (dd, *J* = 8.6, *J* = 4.0 Hz, 1H, Ar-H), 6.02–5.97 (m, 1H, $-CH_2-C\underline{H}{=}CH_2$), 5.39 (d, *J* = 16.8 Hz, 1H, $-CH_2-CHC\underline{H}_2$), 5.12 (d, *J* = 10.0 Hz, 1H, $-CH_2-CH{=}C\underline{H}_2$), 4.01 (d, *J* = 7.2 Hz, 2H, $-C\underline{H}_2-CH{=}CH_2$), 2.46 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 155.4, 146.0, 145.2, 135.9, 134.4, 134.1, 133.18, 127.5, 127.5, 125.5, 125.2, 118.5, 32.8, 21.4. LC-MS/MS: *m/z* calcd.: 258.08, found: 258.90. Anal. calcd. for $C_{14}H_{14}N_2OS$ (258.08): C, 65.09; H, 5.46; N, 10.84. Found: C, 64.89; H, 5.31; N, 10.97.

2-(Benzylthio)quinoline-3-carbaldehyde oxime 7g

Yellowish white powder; yield: 85%; mp: 161–163°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.78 (s, 1H, OH), 8.42 (s, 1H, N═CH), 8.35 (s, 1H, Ar-H), 7.97 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.79–7.75 (m, 1H, Ar-H), 7.56–7.51 (m, 3H, Ar-H), 7.35–7.19 (m, 3H, Ar-H), 4.60 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.8, 147.2, 145.4, 138.5, 135.2, 131.2, 129.8, 128.8, 127.7, 127.4, 126.5, 125.6, 125.0, 34.2. GC MS: *m/z* calcd.: 294.08, found $[M+H]^+$: 295.07. Anal. calcd. for $C_{17}H_{14}N_2OS$ (294.08): C, 69.36; H, 4.79; N, 9.52. Found: C, 69.12; H, 4.95; N, 9.84.

2-(Benzylthio)-6-methylquinoline-3-carbaldehyde oxime 7h

Yellowish white powder; yield: 81%; mp: 164–166°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.75 (s, 1H, OH), 8.33 (s, 1H, N═CH), 8.30 (s, 1H, Ar-H), 7.86 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 7.59 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.51–7.49 (m, 2H, Ar-H), 7.32–7.28 (m, 2H, Ar-H), 7.24–7.20 (m, 1H, Ar-H), 4.57 (s, 2H, CH_2), 2.47 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 155.7, 145.9, 145.5, 138.5, 135.9, 134.5, 133.3, 129.8, 128.8, 127.5, 127.5, 127.4, 125.6, 125.0, 34.2, 21.4. GC MS: *m/z* calcd.: 308.10, found $[M+H]^+$: 309.01. Anal. calcd. for $C_{18}H_{16}N_2OS$ (308.10): C, 70.10; H, 5.23; N, 9.08. Found: C, 70.48; H, 5.16; N, 9.19.

2-(Isopropylthio)quinoline-3-carbaldehyde oxime 7i

Yellowish white powder; yield: 82%; mp: 141–143°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.76 (s, 1H, OH), 8.41 (s, 1H, N═CH), 8.33 (s, 1H, Ar-H), 7.96 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.86 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.75–7.71 (m, 1H, Ar-H), 7.54–7.50 (m, 1H, Ar-H), 4.27–4.20 (m, 1H, $-C\underline{H}-(CH_3)_2$), 1.43 (d, *J* = 6.8 Hz, 6H, $-CH-(C\underline{H}_3)_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.6, 147.6, 145.0, 134.2, 131.1, 128.9, 127.7, 126.3, 125.4, 125.3, 35.1, 23.2. LC-MS/MS: *m/z* calcd.: 246.08, found $[M+H]^+$: 247.00. Anal. calcd. for $C_{13}H_{14}N_2OS$ (246.08): C, 63.39; H, 5.73; N, 11.37. Found: C, 63.04; H, 5.51; N, 11.58.

2-(Isopropylthio)-6-methylquinoline-3-carbaldehyde oxime 7j

Yellowish white powder; yield: 83%; mp: 139–141°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.74 (s, 1H, OH), 8.31 (s, 1H, N═CH), 8.30 (s, 1H, Ar-H), 7.76 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.71 (s, 1H, Ar-H), 7.57–7.52 (m, 1H, Ar-H), 4.25–4.18 (m, 1H, $-C\underline{H}-(CH_3)_2$), 2.46 (s, 3H, CH_3), 1.42 (d, *J* = 7.8 Hz, 6H, $-CH-(C\underline{H}_3)_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.4, 146.29, 145.1, 135.8, 133.6, 133.1, 127.5, 125.4, 125.2, 35.0, 23.2, 21.4. LC-MS/MS: *m/z* calcd.: 260.10, found $[M+H]^+$: 261.00. Anal. calcd. for $C_{14}H_{16}N_2OS$ (260.10): C, 64.58; H, 6.19; N, 10.76. Found: C, 64.51; H, 6.40; N, 10.89.

2-(Methylthio)quinoline-3-carbaldehyde oxime 7k

Yellowish white powder; yield: 86%; mp: 137–139°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.81 (s, 1H, OH), 8.40 (s, 1H, N═CH), 8.37 (s, 1H, Ar-H), 7.96 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.89 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.75–7.71 (m, 1H, Ar-H), 7.53–7.50 (m, 1H, Ar-H), 2.65 (s, 3H, SCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.8, 147.5, 145.2, 134.4, 131.1, 128.8, 127.7, 126.3, 125.4, 125.2, 13.4. LC-MS/MS: *m/z* calcd.: 218.05, found: 218.90. Anal. calcd. for $C_{11}H_{10}N_2OS$ (218.05): C, 60.53; H, 4.62; N, 12.83. Found: C, 60.17; H, 4.88; N, 13.01.

6-Methyl-2-(methylthio)quinoline-3-carbaldehyde oxime 7l

Yellowish white powder; yield: 87%; mp: 131–133°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.77 (s, 1H, OH), 8.35 (s, 1H, −CH═N), 8.28 (s, 1H, Ar-H), 7.78 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 7.57–7.55 (m, 1H, Ar-H), 2.63 (s, 3H, SCH_3), 2.46 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.6, 146.1, 145.2, 135.7, 133.7, 133.1, 127.5, 125.4, 125.1, 21.4, 13.4. GC MS: *m/z* calcd.: 232.07, Found: 232.10. Anal. calcd. for $C_{12}H_{12}N_2OS$ (232.07): C, 62.04; H, 5.59; N, 12.96. Found: C, 61.87; H, 5.70; N, 13.24.

4.2 | Nitric oxide release measurement

The nitrite calibration curve in addition to the absorbance of the tested compounds were measured on Spectronic Genesys UV-VIS spectrophotometer connected to an IBM computer loaded with the Winspec application software (Milton Roy, USA) (see Appendix A, Supporting Information).

4.3 | Biological screening

4.3.1 | The NCI-60 anticancer drug screen

The methodology of the NCI for primary anticancer assay was performed at 60 human tumor cell lines panel derived from nine

neoplastic diseases, according to the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda (see Appendix A, Supporting Information).

4.3.2 | Cell culture protocol

Cell line cells were obtained from American Type Culture Collection, cells was cultured using DMEM (Invitrogen/Life Technologies) supplemented with 10% FBS (Hyclone), 10 µg/mL of insulin (Sigma), and 1% penicillin–streptomycin. All of the other chemicals and reagents were from Sigma or Invitrogen (see Appendix A, Supporting Information).

4.3.3 | MTT assay

The MTT method of monitoring *in vitro* cytotoxicity is well suited for use with multiwell plates. For best results, cells in the log phase of growth should be employed and final cell number should not exceed 10^6 cells/cm^2. Each test should include a blank containing complete medium without cells (see Appendix A, Supporting Information).

4.3.4 | Cytochrome c assay

Cells were obtained from American Type Culture Collection, cells were grown in RPMI 1640 containing 10% fetal bovine serum at 37°C, stimulated with the compounds to be tested for cytochrome c, and lysed with Cell Extraction Buffer. This lysate was diluted in Standard Diluent Buffer over the range of the assay and measured for cytochrome c content (cells are plated in cells/well in a volume of 100 µL complete growth medium + 100 µL of the tested compound + 50 µL of 1× biotin-conjugated antibody + 100 µL of 1× streptavidin-HRP + 100 µL TMB substrate soln of per well in a 96-well plate for 24 h before assay).

4.3.5 | Caspase-3 activation assay

Cells were obtained from American Type Culture Collection; cells were grown in RPMI 1640 containing 10% fetal bovine serum at 37°C (see Appendix A, Supporting Information).

4.3.6 | Cell cycle analysis

The RPMI 8226 cell line was treated with 0.45 µM of compound **6e** for 24 h. After treatment, the cells were suspended in 0.5 mL of PBS (see Appendix A, Supporting Information).

4.3.7 | Apoptosis assay

The RPMI 8226 was treated with 0.45 µM of compound **6e** for 24 h (see Appendix A, Supporting Information).

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