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ARTICLE

Synthesis and antiproliferative evaluation of oxime, methyloxime, and amide-containing quinazolinones

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Certain oxime, methyloxime, and amide-containing quinazolinone derivatives were synthesized and evaluated *in vitro* for their antiproliferative activities against a panel of human cancer cell lines including nasopharyngeal carcinoma (NPC-TW01), lung carcinoma (NCI-H226), and leukemia (Jurkat). Quinazolinone **2** was inactive against all three cell lines tested, while quinazolinone **4** was weakly active against both Jurkat and H226 cancer cells with IC_{50} values of 6.55 and 12.27 μM, respectively, indicating that the oxime derivative **4** is more favorable than its ketone precursor **2**. Our results have also indicated that quinazolinone **8g** and its biphenyl counterpart **8f** exhibited more potent antiproliferative activities than the positive control methotrexate against all three cancer cell lines tested. Among these quinazolinone derivatives, **8g** was the most active against NPC-TW01 with an IC_{50} value of 4.78 μM. Further study on NPC-TW01 cell cycle distribution indicated that the compound **8g** induced cell arrest at the G1/G0 phase in a time- and concentration-dependent manner. Moreover, a characteristic hypo-diploid DNA content peak (sub-G1) was found to increase from 1 to 4% in NPC-TW01 cells treated with **8g** for 72 hr. These results indicate that **8g** can induce cells arrest in the G1/G0 phase and cause cell death. Further structural optimization of **8g** and detailed study of its antiproliferative mechanism are going on.

KEYWORDS
antiproliferative activities, nasopharyngeal carcinoma (NPC), quinazolinones

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC), a head and neck cancer that occurs between the top rear area of the throat and nose, is a rare cancer in Western society but is extremely common in Southeast Asia and Taiwan.[1–5] In Taiwan, NPC is the tenth leading cause of mortality in male cancer patients and the most common among males between 35 and 50 years of age.[6] Despite an initial response to chemotherapy, the majority of patients with advanced NPC succumb to this disease.[7,8] As a result, the impact of NPC on the family and social stability is quite devastating. Although pre-radiation chemotherapy may enhance the 5-year survival rates of NPC patients, the development of drug resistance often results in the failure of treatments. Besides, therapeutic outcome is still unsatisfactory for patients with refractory and relapsed NPC even in spite of receiving a second line of docetaxel-based chemotherapy.[9] Therefore, novel therapeutic drugs and protocols are urgently needed to overcome drug resistance in NPC patients.

For the past few years, we have been interested in the design and synthesis of novel heterocyclic compounds as

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potential anti-NPC agents.[10–13] Among them, *N*-(biphenyl-4-yl)-2-(2-oxo-1,2-dihydroquinolin-7-yloxy)acetamide (**I**)[10] and *N*-(naphthalen-2-yl)-2-(4-oxo-2-phenyl-4*H*-chromen-7-yloxy)acetamide (**II**)[11] were found to be selectively active against the growth of NPC-TW01 with IC_{50} values of <10 and 1.37 μM, respectively. More recently, we have prepared certain *N*-(naphthalen-2-yl)acetamide derivatives and evaluated *in vitro* for their antiproliferative activities against a panel of human cancer cell lines. Among them, *N*-(naphthalen-2-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)acetamide (**III**)[12] and 2-(9,10-dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-(naphthalen-2-yl)acetamide (**IV**)[13] were found to have selective antiproliferative activities against NPC-TW01 with IC_{50} values of 0.6 and 2.62 μM, respectively. In continuation of our studies to explore active and selective anti-NPC agents and establish structure–activity relationships, the present report describes the preparation of certain amide-containing quinazolinone derivatives (Figure 1). Our selection of quinazolinone derivatives as target compounds is based on the fact that the quinazolinone ring is an important and versatile motif of many anticancer drugs, especially epidermal growth factor receptor (EGFR) inhibitors such as gefitinib, erlotinib, and lapatinib.[14–17] The oxime-containing quinazolinone derivatives were also synthesized for antiproliferative evaluation.

2 | RESULTS AND DISCUSSION

2.1 | Synthesis

The preparation of oxime, methyloxime, and amide-containing quinazolinone derivatives is illustrated in Scheme 1. Reaction of 4-hydroxyquinazoline (**1**) with chloroacetone under basic conditions gave exclusively quinazolinone **2** in 88% yield. Alkylation of **1** occurred at N-3 but not at N-1 or the carbonyl oxygen was confirmed by NMR spectra. Structure of **2** was further proved by HMBC in which the coupling of H-2 (8.21 ppm) with C-2 (148 ppm, *J*-1), C-4 (148 ppm, *J*-3), and C-1' (55 ppm, *J*-3), respectively, was observed (Figure 2). Treatment of **1** with phenacyl bromide under basic conditions gave exclusively quinazolinone **3a** in 90% yield. Accordingly, compounds **3b–3g** were prepared from **1** and arylacyl bromide under the same reaction conditions.

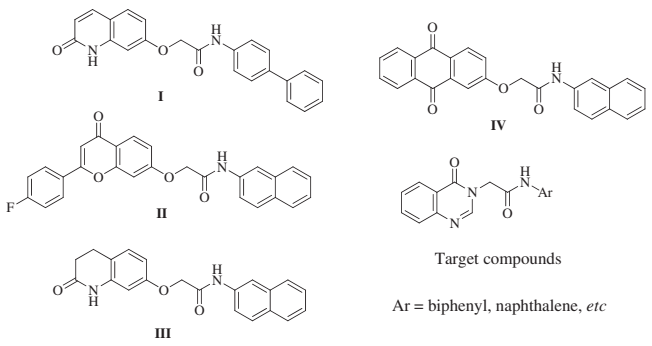


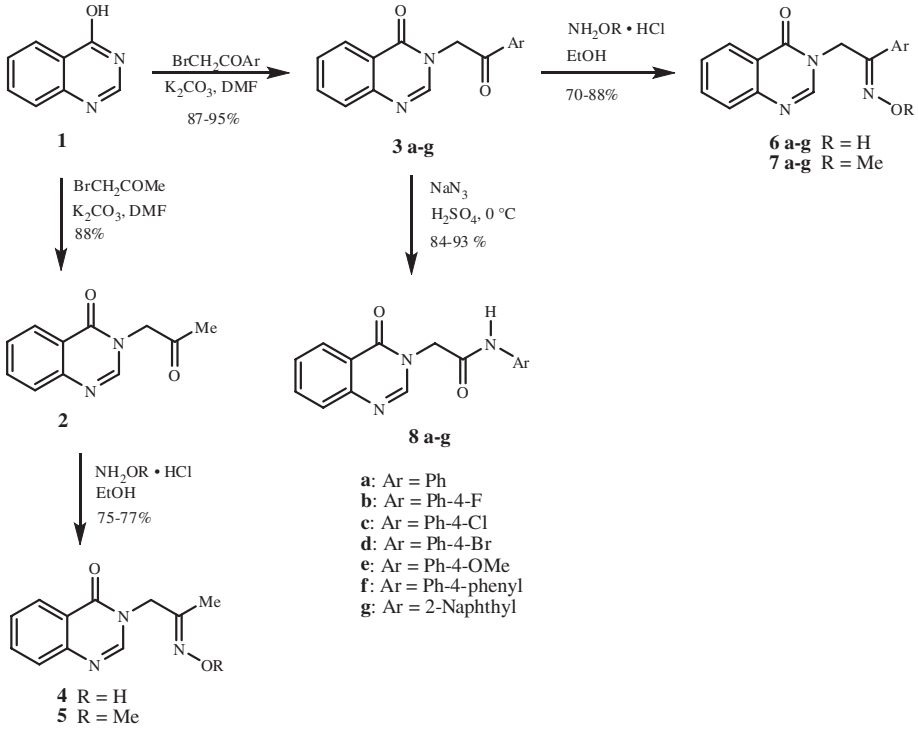
FIGURE 1 Structures of compounds **I–IV** and the target compounds

Treatment of quinazolinone **2** with NH_2OH afforded exclusively quinazolinone **4** in 75% yield. The configuration of the oxime moiety was determined by through-space nuclear Overhauser effect spectroscopy (NOESY), which revealed a coupling connectivity to CH_3 protons. The stereospecific oximination to give the *E*-form product rather than the *Z*-isomer can be realized in which the hydroxyl group proximate to the methyl group is less sterically hindered.[18] Accordingly, quinazolinone **5** was prepared from **2** and NH_2OMe under the same reaction condition. Reaction of quinazolinone **3a** with NH_2OH afforded exclusively quinazolinone **6a** in 88% yield. The configuration of the oxime moiety was determined by its ^{13}C-NMR spectrum in which the *N*-CH_2 signal shifted upfield from 52.32 ppm (**3a**) to 42.19 ppm (**6a**).[19] The same synthetic procedures were applied for the synthesis of (*Z*)-**6b–g** from **3b–g** and (*Z*)-**7a–g** from **3a–g**.

The preparation of amide-containing quinazolinone via Schmidt rearrangement is also illustrated in Scheme 1. Quinazolinone **3a** was treated with H_2SO_4 and NaN_3 to afford quinazolinone **8a** in 90% yield. The same synthetic procedures were applied for the synthesis of **8b–8g**. The structures of the newly synthesized compounds were confirmed by NMR spectra and elementary analysis.

2.2 | Biological activity

All compounds were evaluated *in vitro* against a three-cell-line panel consisting of NPC-TW01 (human nasopharyngeal carcinoma), Jurkat (leukemia), and non-small-cell lung carcinoma (NCI-H226). Results from Table 1 indicate that quinazolinone **2** is inactive against all three cell lines tested, while its phenyl analog **3a** was weakly active against Jurkat cancer cells with an IC_{50} of 8.79 μM. Further substitution with the F atom at *para*-phenyl position enhanced cytotoxicities against both Jurkat and H226 cancer cells, while substitution with a Cl or a Br atom at the same position led to the inactive compounds of **3c** and **3d**. Substitution with an electron-donating group such as OMe, phenyl, or naphthyl moiety at the *para*-phenyl position did not significantly affect the inhibitory activity of Jurkat cancer cells in which compounds **3e**, **3f**, and **3g** exhibited IC_{50} in the range 6.08–9.28 μM. Quinazolinone **4** was weakly active against both Jurkat and H226 cancer cells, indicating that oxime is more favorable than its ketone precursor **2**. However, its methyloxime derivative **5** become inactive, indicating that a hydrogen-bond-donating group is required. The same trend was observed in most of the oxime derivatives **6a**, **6b**, and **6e–6g**, which were active against Jurkat cancer cells, while none of their methyloxime counterparts **7a–7g** exhibited cytotoxicity at 20 μM. Among these oxime derivatives **6a–6g**, the electron-withdrawing groups such as Cl and Br were



SCHEME 1 Synthesis of quinazolinone derivatives

unfavorable, so compounds **6c** and **6d** were inactive. However, compounds **6e**, **6f**, and **6g**, which bear electron-donating groups such as OMe, phenyl, and naphthyl, improved the antiproliferative activities against both Jurkat and H226 cancer cells. The same structure–activity relationship (SAR) was obtained for the amide-containing quinazolinone derivatives **8a**–**8g**, in which compounds **8c** and **8d** bearing the electron-withdrawing groups such as Cl and Br were inactive. Compounds **8a**, **8b**, and **8e** were weakly active against Jurkat cancer cells, while compounds **8f** and **8g**, which bear the electron-donating groups phenyl and naphthyl, respectively, were active against all three cancer cells tested. Our results indicate that quinazolinone **8g** and its biphenyl counterpart **8f** show more potent antiproliferative activities than the positive control methotrexate against all three cancer cell lines tested (Table 1). Among them, compound **8g** was the most active against NPC-TW01 with an IC_{50} value of 4.78 μM and therefore was subjected for further study on NPC-TW01 cell cycle distribution. Figure 3 shows that compound **8g** induced NPC-TW01 cell arrest at the G1/G0 phase in a time- and concentration-dependent manner. After 48 hr of treatment, significant G1/G0 (~70%) cell accumulation and a corresponding decrease in the G2/M and S phases cell population were detected. Moreover, a characteristic hypo-diploid DNA content peak (sub-G1) was found to increase from 1 to 3.6% and 4.4% in NPC-TW01 cells treated with **8g** for 48 and 72 hr (Table 2). These results indicate that **8g** can induce cells arrest in the G1/G0 phase and cause cell death. Further structural optimization of **8g** and detailed study of its antiproliferative mechanism are going on.

3 | EXPERIMENTAL

3.1 | General

Thin-layer chromatography (TLC) was carried out on precoated (0.2 mm) silica gel 60 F_{254} plates from EM Laboratories, Inc.; detection was by UV light (254 nm). Melting points were measured on an Electrothermal IA9100 digital melting point apparatus; the values are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Unity-400 spectrometer at 400 MHz or Varian Gemini-200 spectrometer at 200 MHz. The chemical shifts δ are reported in ppm with $SiMe_4$ as the internal standard (= 0 ppm); the coupling

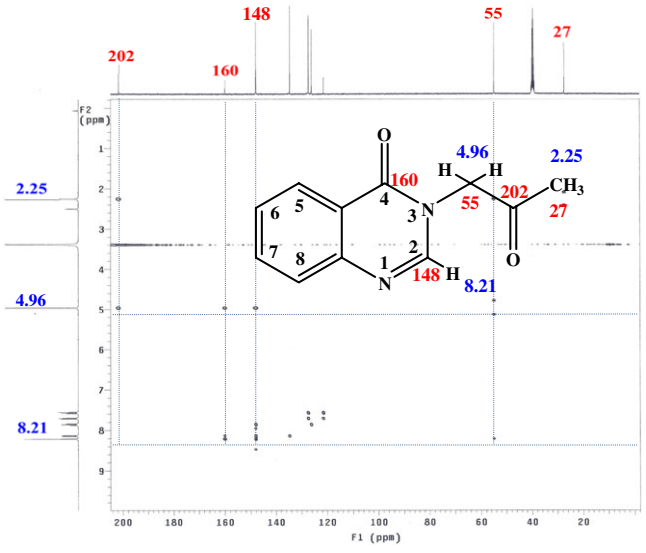


FIGURE 2 HMBC spectrum of 3-(2-oxopropyl)quinazolin-4(3*H*)-one (**2**)

TABLE 1 *In vitro* antiproliferative activity of quinazolinone bearing ketone, oxime, methyloxime, and amide derivatives

	IC_{50} (μM)[a]			
Compound	**R**	**TW01**	**Jurkat**	**H226**
2	Me	>20.00	>20.00	>20.00
3a	Ph	>20.00	8.79	>20.00
3b	Ph-4-F	>20.00	8.22	13.8
3c	Ph-4-Cl	>20.00	>20.00	>20.00
3d	Ph-4-Br	>20.00	>20.00	>20.00
3e	Ph-4-OMe	>20.00	9.28	>20.00
3f	Ph-4-phenyl	>20.00	7.64	>20.00
3g	Ph-4-naphthyl	>20.00	6.08	>20.00
4	Me	>20.00	6.55	12.27
5	Me	>20.00	>20.00	>20.00
6a	Ph	>20.00	7.16	>20.00
6b	Ph-4-F	>20.00	7.69	>20.00
6c	Ph-4-Cl	>20.00	>20.00	>20.00
6d	Ph-4-Br	>20.00	>20.00	>20.00
6e	Ph-4-OMe	>20.00	6.59	14.87
6f	Ph-4-phenyl	>20.00	6.41	10.41
6g	Ph-4-naphthyl	19.50	6.20	7.10
7a	Ph	>20.00	>20.00	>20.00
7b	Ph-4-F	>20.00	>20.00	>20.00
7c	Ph-4-Cl	>20.00	>20.00	>20.00
7d	Ph-4-Br	>20.00	>20.00	>20.00
7e	Ph-4-OMe	>20.00	>20.00	>20.00
7f	Ph-4-phenyl	>20.00	>20.00	>20.00
7g	Ph-4-naphthyl	>20.00	>20.00	>20.00
8a	Ph	>20.00	7.63	>20.00
8b	Ph-4-F	>20.00	7.05	>20.00
8c	Ph-4-Cl	>20.00	>20.00	>20.00
8d	Ph-4-Br	>20.00	>20.00	>20.00
8e	Ph-4-OMe	>20.00	6.69	>20.00
8f	Ph-4-phenyl	7.80	11.22	5.84
8g	Ph-4-naphthyl	4.78	8.52	7.88
Methotrexate		43.4	18.70	22.93

[a] Cancer cells were treated with different quinazolinone compounds of various concentrations for 72 hr, and cell survival was determined using MTT colorimetric assay. Representative data from three independent experiments performed in quadruplicate are shown.

constants *J* are in Hz. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer, and results were within ±0.4% of the calculated values.

3.2 | Syntheses

3.2.1 | Preparation of 2 and 3a-g

General procedure: 4-Hydroxyquinazoline (**1**) (10 mmol), K_2CO_3 (10 mmol), and dry DMF (50 mL) were stirred at room temperature (r.t.) for 30 min. To this solution was added chloroacetone/2-(bromoacetyl)naphthalene/substituted phenacyl bromide (10 mmol) in dry DMF (10 mL) in one portion. The resulting mixture was stirred at r.t. for 24 hr (TLC monitoring) and then poured into ice-water (100 mL).

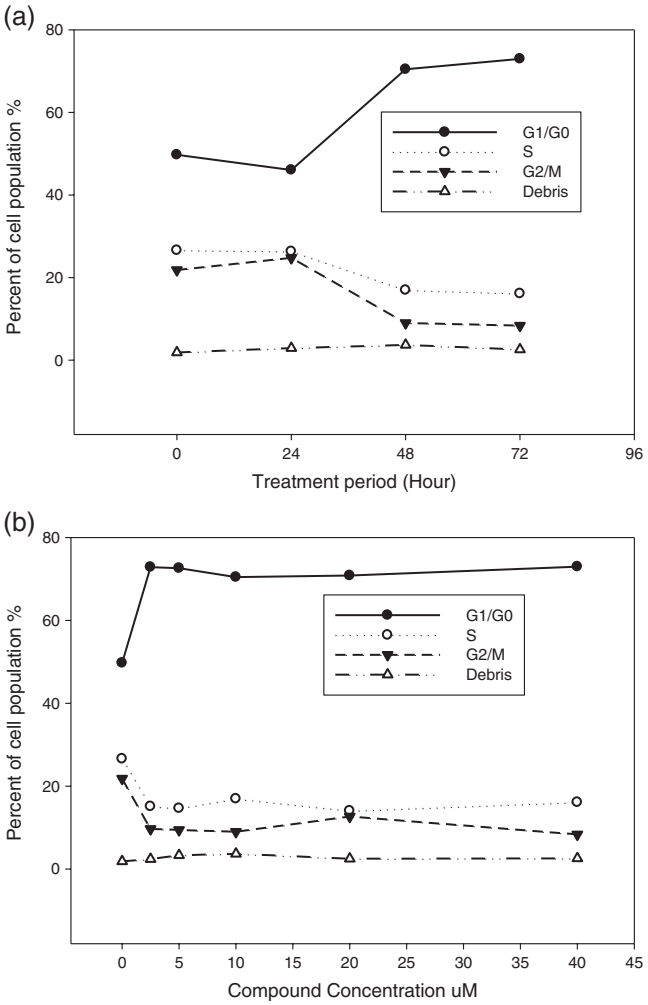


FIGURE 3 Compound **8g** inducing concentration- and time-dependent G1/G0 cell arrest in human NPC-TW01 cell line. NPC-TW01 cells were treated with 1 × IC_{50} (4.78 μM) of **8g** for 24, 48, and 72 hr (a) or different concentrations (2.5, 5, 10, 20, and 40 μM) for 48 hr (b). The cell population ratios were determined by flow cytometry

The yellow solid thus obtained was collected and purified by column chromatography on silica gel using *n*-hexane/ethyl acetate 1:2. The proper fractions were combined and evaporated to furnish a residual solid which was crystallized from Et_2O and CH_2Cl_2.

*3-(2-Oxopropyl)quinazolin-4(3*H*)-one (**2**)*: Yield 88%. mp 170–171 °C. ^{1}H-NMR (DMSO-d_6) 2.25 (s, 3H, Me), 4.96 (s, 2H, NCH_2), 7.56 (dd, J = 0.8, 8.0 Hz, 1H-C (8)), 7.71 (d, J = 8.0 Hz, 1H-C (7)), 7.85 (dd, J = 1.6, 8.0 Hz, 1H-C (6)), 8.15 (dd, J = 1.6, 8.0 Hz, 1H-C (5)), 8.21 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 27.19 (Me), 54.72 ($\underline{C}H_2CO$), 121.41, 126.08, 127.24, 127.29, 134.59, 148.01,

TABLE 2 Compound **8g** arrested NPC-TW01 cells at G_0/G_1 phase

Cell distribution (%)	Control	24 hr	48 hr	72 hr
G_0/G_1	49.73	46.04	70.43	71.97
G_2/M	26.61	26.32	16.94	15.63
S	21.82	24.74	8.97	8.00
Debris	1.84	2.90	3.66	4.40

148.1, 160.02 (C (4)), 201.73 ($CH_2\underline{C}O$). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C 65.34, H 4.98, N 13.85. Found: C 65.21, H 4.96, N 13.86.

*3-(2-Oxo-2-phenylethyl)quinazolin-4(3*H*)-one* (***3a***): Yield 90%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 5.64 (s, 2H, NCH_2), 7.57–7.64 (m, 3H, arom. H), 7.73–7.70 (m, 2H, arom. H), 7.90 (dd, J = 1.6, 8.0 Hz, 1H, arom. H), 8.11 (dd, J = 1.2, 8.0 Hz, 2H, arom. H), 8.17 (dd, J = 1.2, 8.0 Hz, 1H-C (5)), 8.35 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 52.32 ($\underline{C}H_2CO$), 121.51, 126.21, 127.45, 127.46, 128.24, 129.22, 134.38, 134.42, 134.81, 148.17, 148.44, 160.33 (C (4)), 192.96 ($CH_2\underline{C}O$). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C 72.72, H 4.58, N 10.60. Found: C 72.74, H 4.54, N 10.60.

*3-(2-[4-Fluorophenyl]-2-oxoethyl)quinazolin-4(3*H*)-one* (***3b***): Yield 94%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 5.63 (s, 2H, NCH_2), 7.48 (dd, J = 2.4, 7.2 Hz, 2H, arom. H), 7.61 (d, J = 1.2, 7.2 Hz, 1H-C (6)), 7.75 (d, J = 7.6 Hz, 1H-C (8)), 7.90 (dd, J = 1.2, 7.2 Hz, 1H-C (7)), 8.14–8.21 (m, 3H, arom. H), 8.34 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 52.17 ($\underline{C}H_2CO$), 116.15, 116.37, 121.45, 126.14, 127.40, 131.11, 131.14, 131.27, 131.37, 134.73, 148.12, 148.33, 160.22 (C (4)), 164.38, 166.90, 191.56 ($CH_2\underline{C}O$). Anal. Calcd for $C_{16}H_{11}FN_2O_2{\cdot}0.2\ H_2O$: C 67.21, H 4.03, N 9.80. Found: C 66.85, H 4.02, N 9.73.

*3-(2-[4-Chlorophenyl]-2-oxoethyl)quinazolin-4(3*H*)-one* (***3c***): Yield 92%. mp 219–220 °C. ^{1}H-NMR (DMSO-d_6) 5.63 (s, 2H, NCH_2), 7.59 (dd, J = 1.2, 7.8 Hz, 1H-C (8)), 7.69–7.75 (m, 3H, arom. H), 7.85 (dd, J = 1.6, 8.0 Hz, 1H-C (7)), 7.91 (m, 1H, arom. H), 8.10–8.16 (m,3H, arom. H), 8.34 (s, 1H-C (2)). ^{13}C-NMR (DMSO): 52.16 ($\underline{C}H_2CO$), 121.39, 126.09, 127.33, 127.35, 129.24, 130.06, 133.0, 134.68, 139.16, 148.08, 148.24, 160.15 (C (4)), 192.0 ($CH_2\underline{C}O$). Anal. Calcd for $C_{16}H_{11}ClN_2O_2$: C 64.33, H 3.71, N 9.38. Found: C 64.32, H 3.88, N 9.26.

*3-(2-[4-Bromophenyl]-2-oxoethyl)quinazolin-4(3*H*)-one* (***3d***): Yield 95%. mp 211–212 °C. ^{1}H-NMR (DMSO-d_6) 5.68 (s, 2H, NCH_2), 7.59 (dd, J = 1.2, 7.8 Hz, 1H-C (8)), 7.82 (dd. J = 0.8, 8.0 Hz, 1H-C (7)), 7.97 (m, 3H, arom. H), 7.73–7.70 (m, 2H, arom. H), 7.90 (m, 1H, arom. H), 8.11 (dd, J = 1.2, 8.0 Hz, 2H, arom. H), 8.23 (dd, J = 1.2, 8.0 Hz, 1H-C (5)), 8.39 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 52.30 ($\underline{C}H_2CO$), 121.48, 126.24, 127.47, 127.55, 128.56, 130.27, 132.34, 133.42, 134.90, 148.16, 148.38, 160.34 (C (4)), 192.36 ($CH_2\underline{C}O$). Anal. Calcd for $C_{16}H_{11}BrN_2O_2$: C 56.00, H 3.23, N 8.16. Found: C 55.91, H 3.25, N 8.15.

*3-(2-[4-Methoxyphenyl]-2-oxoethyl)quinazolin-4(3*H*)-one* (***3e***): Yield 95%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 3.88 (s, 3H, OCH_3), 5.58 (s, 2H, NCH_2), 7.14 (dd, J = 2, 6.8 Hz, 2H, arom. H), 7.60 (d, J = 1.2, 8 Hz, 1H-C (6)), 7.75 (d, J = 8.0 Hz, 1H-C (8)), 7.88 (dd, J = 1.2, 7.2 Hz, 1H-C (7)), 8.09 (dd, J = 2.0, 6.8 Hz, 2H, arom. H), 8.16 (dd, 3H, arom. H), 8.34 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 51.89 ($\underline{C}H_2CO$), 55.79 (OCH_3), 114.37, 121.51, 126.17, 127.27, 127.37, 127.40, 130.61, 134.71, 148.17, 148.50, 160.30 (C (4)), 163.98 ($\underline{C}$-OCH_3), 191.17 ($CH_2\underline{C}O$). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C 69.38, H 4.79, N 9.52. Found: C 69.38, H 4.81, N 9.56.

*3-(2-[Biphenyl-4-yl]-2-oxoethyl)quinazolin-4(3*H*)-one* (***3f***): Yield 87%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 5.67 (s, 2H, NCH_2), 7.46–7.62 (m, 4H, arom. H), 7.74–7.81 (m, 3H, arom. H), 7.87–7.94 (m, 3H, arom. H), 8.16 (d, J = 1.2 Hz, 1H, arom. H), 8.18 (s, 1H, arom. H), 8.20 (d, J = 2.0 Hz, 1H, arom. H), 8.37 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 52.29 ($\underline{C}H_2CO$), 121.50, 126.18, 127.20, 127.28, 127.43, 128.77, 128.97, 129.30, 133.17, 134.77, 138.75, 145.58, 148.17, 148.43, 160.29 (C(4)), 192.48 ($CH_2\underline{C}O$). Anal. Calcd for $C_{22}H_{16}N_2O_2$: C 77.63, H 4.74, N 8.23. Found: C 77.48, H 4.67, N 8.16.

*3-(2-[Naphthalen-2-yl]-2-oxoethyl)quinazolin-4(3*H*)-one* (***3g***): Yield 90%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 5.76 (s, 2H, NCH_2), 7.59 (dd, J = 1.2, 8.0 Hz, 1H-C (6)), 7.63–7.74 (m, 3H, arom. H), 7.89 (dd, J = 1.6, 8.4 Hz, 1H, arom. H), 8.01–8.09 (m, 3H, arom. H), 8.18 (m, 2H, arom. H), 8.38 (s, 1H, arom. H), 8.87 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 52.29 ($\underline{C}H_2CO$), 121.51, 123.36, 126.19, 127.40, 127.42, 127.94, 128.83, 129.30, 129.81, 130.48, 131.67, 132.22, 134.77, 135.54, 148.17, 148.46, 160.32 (C (4)), 192.86 ($CH_2\underline{C}O$). Anal. Calcd for $C_{20}H_{14}N_2O_2$: C 76.42, H 4.49, N 8.91. Found: C 76.12, H 4.48, N 8.87.

3.2.2 | Preparation of 4 and 6a–g

General procedure: A solution of **2/3a–g** (1 mmol) was added a solution of hydroxylamine hydrochloride (2 mmol) in EtOH (20 mL). The mixture was heated at reflux for 4 hr (TLC monitoring) and evaporated to give a residual solid. The white solid thus obtained was collected, purified by flash column chromatography (FC; silica gel; CH_2Cl_2/MeOH 15:1), and recrystallized from Et_2O and CH_2Cl_2.

*(E)-3-(2-[Hydroxyimino]propyl)quinazolin-4(3*H*)-one* (***4***): Yield 75%. mp 170–171 °C. ^{1}H-NMR (DMSO-d_6) 1.82 (s, 3H, Me), 4.74 (s, 2H, NCH_2), 7.58 (dd, J = 1.2, 8.0 Hz, 1H-C (6)), 7.69 (d, J = 8.4 Hz, 1H-C (8)), 7.86 (dd, J = 1.6, 8.4 Hz, 1H-C (7)), 8.17 (dd, J = 1.6, 8.0 Hz, 1H-C (5)), 8.30 (s, 1H-C (2)), 10.80 (s, NOH). ^{13}C-NMR (DMSO) 12.36 (Me), 48.28 ($N\underline{C}H_2$), 121.64, 126.11, 127.11, 127.14, 134.43, 147.50, 148.35, 150.74 (C=NOH), 159.99 (C=O). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C 60.82, H 5.10, N 19.34. Found: C 60.86, H 5.10, N 19.33.

*(Z)-3-(2-[Hydroxyimino]-2-phenylethyl)quinazolin-4(3*H*)-one* (***6a***): Yield 88%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 5.24 (s, 2H, NCH_2), 7.29–7.36 (m, 3H, arom. H), 7.53 (d, J = 1.2, 8.4 Hz, 1H-C (6)), 7.62–7.65 (m, 3H, arom. H), 7.82 (dd, J = 1.2, 8.4 Hz, 1H-C (7)), 8.08 (dd, J = 1.2, 8.0 MHz, 1H-C (5)), 8.43 (s, 1H-C (2)), 11.80 (s, NOH). ^{13}C-NMR (DMSO) 42.19 ($N\underline{C}H_2$), 121.25, 125.96, 126.73, 127.11, 128.23, 128.85, 134.40, 134.51, 147.62, 148.48, 152.64 (C=O), 159.98 (C=NOH).

Anal. Calcd for $C_{16}H_{13}N_3O_2$: C 68.81, H 4.69, N 15.05. Found: C 68.82, H 4.69, N 14.94.

*(Z)-3-(2-(4-Fluorophenyl)-2-(hydroxyimino)ethyl)quinazolin-4(3*H*)-one (**6b**)*: Yield 77%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 5.22 (s, 2H, NCH_2), 7.16–7.21 (m, 2H, arom. H), 7.57 (d, J = 1.2, 8.0 Hz, 1H-C (6)), 7.65 (dd, J = 0.8, 8.2 Hz, arom. H), 7.70–7.83 (m, 3H, arom. H), 8.09 (dd, J = 1.6, 8.0 Hz, 1H-C (5)), 8.46 (s, 1H-C (2)), 11.83 (s, NOH). ^{13}C-NMR (DMSO) 42.46 ($N\underline{C}H_2$), 115.07, 115.29, 121.23, 125.97, 127.12, 127.14, 128.95, 129.03, 131.1, 131.13, 134.44, 147.63, 148.60, 151.82, 160.03 (C=O), 161.19 (C=NOH), 163.63. Anal. Calcd for $C_{16}H_{12}FN_3O_2$: C 64.64, H 4.07, N 14.13. Found: C 64.58, H 4.08, N 14.13.

*(Z)-3-(2-(4-Chlorophenyl)-2-(hydroxyimino)ethyl)quinazolin-4(3*H*)-one (**6c**)*: Yield 76%. mp 210–211 °C. ^{11}H-NMR (DMSO-d_6) 5.19 (s, 2H, NCH_2), 7.39–7.43 (m, 2H, arom. H), 7.53 (dd, J = 1.2, 8.0 Hz, 1H-C (8)), 7.63–7.70 (m, 3H, arom. H), 7.82 (m, 1H, arom. H), 8.07 (dd, J = 1.6, 8.0 Hz, 1H-C (5)), 8.44 (s, 1H-C (2)), 11.94 (s, NOH). ^{13}C-NMR (DMSO) 42.68 ($N\underline{C}H_2$), 121.32, 126.12, 127.26, 127.4, 128.47, 128.69, 133.72, 133.78, 134.71, 147.73, 148.84, 151.9 (C=NOH), 160.24 (C=O). Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C 61.25, H 3.86, N 13.39. Found: C 61.20, H 3.82, N 13.37.

*(Z)-3-(2-(4-Bromophenyl)-2-(hydroxyimino)ethyl)quinazolin-4(3*H*)-one (**6d**)*: Yield 75%. mp 194–195 °C. ^{1}H-NMR (DMSO-d_6) 5.24 (s, 2H, NCH_2), 7.56–7.3662 (m, 3H, arom. H), 7.66–7.71 (m, 3H, arom. H), 7.89 (dd, J = 1.2, 8.4 Hz, 1H-C (7)), 8.13 (dd, J = 1.2, 8.0 MHz, 1H-C (5)), 8.50 (s, 1H-C (2)), 12.04 (s, NOH). ^{13}C-NMR (DMSO) 42.73 ($N\underline{C}H_2$), 121.37, 122.57, 126.20, 127.31, 127.52, 129.02, 131.47, 134.16, 134.82, 147.76, 148.90, 152.07 (C=O), 160.34 (C=NOH). Anal. Calcd for $C_{16}H_{12}BrN_3O_2$: C 53.65, H 3.38, N 11.73. Found: C 53.73, H 3.41, N 11.60.

*(Z)-3-(2-(Hydroxyimino)-2-(4-methoxyphenyl)ethyl)quinazolin-4(3*H*)-one (**6e**)*: Yield 77%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 3.73 (s, 3H, OCH_3), 5.21 (s, 2H, NCH_2), 6.92 (dd, J = 2.0, 7.2, 2H, arom. H), 7.54 (d, J = 1.2, 8.0 Hz, 1H-C (6)), 7.60–7.65 (m, 3H, arom. H), 7.83 (dd, J = 1.6, 8.0 Hz, 1H-C (7)), 8.10 (dd, J = 1.2, 8.0 Hz, 1H-C (5)), 8.40 (s, 1H-C (2)), 11.64 (s, NOH). ^{13}C-NMR (DMSO) 41.77 ($N\underline{C}H_2$), 55.12 (OCH_3), 113.7, 121.3, 126.01, 126.8, 127.12, 128.08, 134.41, 147.61, 148.4, 152.11 (C=O), 159.79 ($\underline{C}$-OCH_3), 159.99 (C=NOH). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C 66.01, H 4.89, N 13.58. Found: C 66.01, H 4.92, N 13.60.

*(Z)-3-(2-(Biphenyl-4-yl)-2-(hydroxyimino)ethyl)quinazolin-4(3*H*)-one (**6f**)*: Yield 75%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 5.27 (s, 2H, NCH_2), 7.34–7.54 (m, 4H, arom. H), 7.64–7.69 (m, 5H, arom. H), 7.78–7.83 (m, 3H, arom. H), 8.11 (dd, J = 1.2, 8.0 Hz, 1H-C (5)), 8.47 (s, 1H–C (2)), 11.88 (s, NOH). ^{13}C-NMR (DMSO) 42.03 ($N\underline{C}H_2$), 121.3, 125.0, 126.48, 126.59, 127.12, 127.14, 127.19, 127.71, 128.96, 133.69, 1,349.44, 139.28, 140.42, 147.64, 148.55, 152.13 (C=O), 160.05 (C=NOH). Anal. Calcd for $C_{22}H_{17}N_3O_2$: C 74.35, H 4.82, N 11.82. Found: C 74.17, H 4.82, N 11.81.

*(Z)-3-(2-(Hydroxyimino)-2-(naphthalen-2-yl)ethyl)quinazolin-4(3*H*)-one (**6g**)*: Yield 80%. mp 228–229 °C. ^{1}H-NMR (DMSO-d_6) 5.34 (s, 2H, NCH_2), 7.46–7.52 (m, 3H, arom. H), 7.62 (dd, J = 0.4, 8.4 Hz, 1H, arom. H), 7.75–7.93 (m, 5H, arom. H), 8.07 (dd, J = 1.6, 8.0 Hz, 1H-C (5)), 8.24 (d, J = 1.2 Hz, arom. H), 8.49 (s, 1H-C (2)), 11.94 (s, NOH). ^{13}C-NMR (DMSO) 42.25 ($N\underline{C}H_2$), 121.31, 124.14, 126.02, 126.31, 126.6, 126.8, 127.15, 127.23, 127.58, 127.81, 128.34, 132.13, 132.6, 132.94, 134.51, 147.66, 148.66, 152.48 (C=O), 160.14 (C=NOH). Anal. Calcd for $C_{20}H_{15}N_3O_2$: C 72.94, H 4.59, N 12.76. Found: C 72.56, H 4.54, N 12.67.

3.2.3 | Preparation of 5 and 7a–g

General procedure: A solution of **2/5a–g** (1 mmol) was added a solution of *O*-methylhydroxylamine hydrochloride (2 mmol) in EtOH (20 mL). The mixture was heated at reflux for 4 h (TLC monitoring) and evaporated to give a residual solid. The white solid thus obtained was collected, purified by flash column chromatography (FC; silica gel; *n*-hexane/EtOAc 1:3), and recrystallized from Et_2O and CH_2Cl_2.

*(E)-3-(2-[Methoxyimino]propyl)quinazolin-4(3*H*)-one (**5**)*: Yield 77%. mp 69–70 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.81 (s, 3H, CH_3), 3.64 (s, 3H, $NOCH_3$), 4.73 (s, 2H, NCH_2), 7.58 (ddd, J = 1.6, 8.0, 1.2 Hz, 1H-C (6)), 7.70 (dd, J = 0.8, 8.0 Hz, 1H-[C7]), 7.86 (ddd, J = 1.2, 8.0, 0.8 Hz, 1H-C (8)), 8.16 (dd, 1H, J = 1.2, 8.0 Hz, 1H-C (8)), 8.28 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 13.02 ($\underline{C}H_3$), 48.27 ($NO\underline{C}H_3$), 61.43 ($N\underline{C}H_2$), 121.61, 126.33, 127.34, 134.7, 148.0, 148.27, 152.71 (C=O), 160.17 (C=$NOCH_3$). Anal. Calcd for $C_{12}H_{13}N_3O_2$: C 62.33, H 5.67, N 18.17. Found: C 62.37, H 5.70, N 18.08.

*(Z)-3-(2-[Methoxyimino]-2-phenylethyl)quinazolin-4(3*H*)-one (**7a**)*: Yield 70%. mp 97–98 °C. ^{1}H-NMR (DMSO-d_6) 3.91 (s, 3H, $NOCH_3$), 5.22 (s, 2H, NCH_2), 7.31–7.33 (m, 3H, arom. H), 7.47–7.62 (m, 4H, arom. H), 7.80 (ddd, J = 1.6, 8.0, 2.0 Hz, 1H-C (8)), 8.04 (dd, J = 1.2, 8.0 Hz, 1H-C (8)), 8.41 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 43.34 ($NO\underline{C}H_3$), 62.41 ($N\underline{C}H_2$), 121.27, 126.13, 127.28, 127.47, 128.47, 129.53, 133.52, 134.75, 147.71, 148.58, 154.31 (C=O), 160.22 (C=$NOCH_3$). Anal. Calcd for $C_{17}H_{15}N_3O_2$: C 69.61, H 5.15, N 14.33. Found: C 69.71, H 5.18, N 14.33.

*(Z)-3-(2-(4-Fluorophenyl)-2-(methoxyimino)ethyl)quinazolin-4(3*H*)-one (**7b**)*: Yield 71%. mp 102–103 °C. ^{1}H-NMR (DMSO-d_6) 3.90 (s, 3H, $NOCH_3$), 5.19 (s, 2H, NCH_2), 7.13–7.19 (m, 2H, arom. H), 7.52 (dd, J = 1.2, 8.0 Hz, 1H-C (6)), 7.62–7.67 (m, 3H, arom. H), 7.81 (dd, J = 1.6, 8.0 Hz, 1H-C (7)), 8.05 (dd, J = 1.6, 8.0 Hz, 1H-C (8)),

8.42 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 43.5 ($NOCH_3$), 62.45 (NCH_2), 115.35, 115.60, 121.24, 126.12, 127.32, 127.49, 129.57, 129.65, 130.12, 130.15, 134.78, 147.72, 148.61, 153.41 (C=O), 160.25, 161.58, 164.03 ($C=NOCH_3$). Anal. Calcd for $C_{17}H_{14}FN_3O_2$: C 65.59, H 4.53, N 13.50. Found: C 65.57, H 4.55, N 13.49.

*(Z)-3-(2-(4-Chlorophenyl)-2-(methoxyimino)ethyl)quinazolin-4(3*H*)-one (**7c**)*: Yield: 80%. mp 145–146 °C. ^{1}H-NMR (DMSO-d_6) 3.91 (s, 3H, $NOCH_3$), 5.19 (s, 2H, NCH_2), 7.42 (dd, J = 2.8, 8.4 Hz, 2H, arom. H), 7.52 (ddd, J = 1.2, 8.0, 1.2 Hz, 1H-C (8)), 7.65 (dd, J = 2.8, 8.4 Hz, 3H, arom. H), 7.82 (m, 1H, arom. H), 8.16 (dd, 1H, J = 1.2, 8.0 Hz, 1H-C (5)), 8.43 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 43.40 ($NOCH_3$), 62.57 (NCH_2), 121.23, 126.12, 127.33, 127.51, 128.56, 129.07, 132.59, 134.3, 134.81, 147.72, 148.63, 153.29 (C=O), 160.26 ($C=NOCH_3$). Anal. Calcd for $C_{17}H_{14}ClN_3O_2$: C 62.30, H 4.31, N 12.82. Found: C 62.17, H 4.31, N 12.78.

*(Z)-3-(2-(4-Bromophenyl)-2-(methoxyimino)ethyl)quinazolin-4(3*H*)-one (**7d**)*: Yield: 83%. Mp 142–143 °C. ^{1}H-NMR (DMSO-d_6) 3.91 (s, 3H, $NOCH_3$), 5.18 (s, 2H, NCH_2), 7.45–7.58 (m, 5H, arom. H), 7.64 (d, J = 8.0 Hz, 1H-C (8)), 7.82 (m, 1H, arom. H), 8.04 (dd, 1H, J = 1.6, 8.0 Hz, 1H-C (5)), 8.42 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 43.34 ($NOCH_3$), 62.58 (NCH_2), 121.23, 123.05, 126.12, 127.33, 127.52, 129.31, 131.48, 132.97, 134.82, 147.72, 148.63, 153.36 (C=O), 160.26 ($C=NOCH_3$). Anal. Calcd for $C_{17}H_{14}BrN_3O_2$: C 54.86, H 3.79, N 11.29. Found: C 54.89, H 3.85,N 11.31.

*(Z)-3-(2-(Methoxyimino)-2-(4-methoxyphenyl)ethyl)quinazolin-4(3*H*)-one (**7e**)*: Yield: 75%. mp 113–114 °C. ^{1}H-NMR (DMSO-d_6) 3.70 (s, 3H, OCH_3), 3.89 (s, 3H, $NOCH_3$), 5.18 (s, 2H, NCH_2), 6.89 (dd, J = 2.4, 9.2 Hz, 2H, arom. H), 7.48–7.57 (m, 3H, arom. H), 7.63 (dd, J = 0.8, 8.0, Hz, 1H-C (6)), 7.81 (ddd, J = 1.6, 8.0, 1.2 Hz, 1H-C (7)), 8.06 (dd, J = 1.6, 8.0 Hz, 1H-C (8)), 8.39 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 42.98 ($NOCH_3$), 55.33 (OCH_3), 62.24 (NCH_2), 113.9, 121.32, 125.80, 126.17, 127.30, 127.46, 128.71, 134.75, 147.71, 148.54, 153.69 (C=O), 160.21, 160.26 ($C=NOCH_3$). Anal. Calcd for $C_{18}H_{17}N_3O_3$: C 66.86, H 5.30, N 13.00. Found C 66.68, H 5.37, N 13.04.

*(Z)-3-(2-(Biphenyl-4-yl)-2-(methoxyimino)ethyl)quinazolin-4(3*H*)-one (**7f**)*: Yield: 71%. mp 146–147 °C. ^{1}H-NMR (DMSO-d_6) 3.93 (s, 3H, $NOCH_3$), 5.24 (s, 2H, NCH_2), 7.32–7.52 (m, 4H, arom. H), 7.62–7.66 (m, 5H, arom. H), 7.71–7.81 (m, 3H, arom. H), 8.07 (dd, J = 1.2, 8.0 Hz, 1H-C (8)), 8.45 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 43.17 ($NOCH_3$), 62.49 (NCH_2), 121.32, 126.17, 126.66, 126.79, 127.32, 127.48, 127.80, 128.05, 129.20, 132.71, 134.78, 139.25, 141.04, 147.74, 148.64, 153.69 (C=O), 160.28 ($C=NOCH_3$). Anal. Calcd for $C_{23}H_{19}N_3O_2$: C 74.78, H 5.18, N 11.37. Found: C 74.62, H 5.16, N 11.29.

*(Z)-3-(2-(Methoxyimino)-2-(naphthalen-2-yl)ethyl)quinazolin-4(3*H*)-one (**7g**)*: Yield 78%. mp 173–174 °C. ^{1}H-NMR (DMSO-d_6) 3.99 (s, 3H, $NOCH_3$), 5.36 (s, 2H, NCH_2), 7.47–7.55 (m, 3H, arom. H), 7.63 (dd, J = 0.4, 8.0, 1H-C (6)), 7.75–7.80 (m, 2H, arom. H), 7.87–7.94 (m, 3H, arom. H), 8.06 (dd, J = 1.2, 8.0 Hz, 1H-C (8)), 8.23 (d, J = 1.2 Hz, 1H, arom. H), 8.52 (s, 1H-C (2)). ^{13}C-NMR (DMSO) 43.08 ($NOCH_3$), 62.44 (NCH_2), 121.21, 124.28, 126.0, 126.72, 126.86, 127.06, 127.20, 127.30, 127.61, 127.89, 128.38, 130.99, 132.49, 133.08, 134.59, 147.63, 148.52, 153.86 (C=O), 160.15 ($C=NOCH_3$). Anal. Calcd for C20H15N3O2: C 72.94, H 4.59, N 12.76. Found: C 72.56, H 4.54, N 12.67.

3.2.4 | Preparation of 8a–g

General procedure: A solution of **3a**–**g** (1 mmol) in H_2SO_4 (3 mL) was stirred at r.t. for 10 min. To this solution, was added sodium azide (2 mmol) in one portion. The mixture was stirred continuously at r.t. for 1 hr (TLC monitoring) and then poured into ice-water (100 mL). The white solid thus obtained was collected and purified by flash column chromatography (FC; silica gel; CH_2Cl_2/MeOH 30:1). The proper fractions were combined and evaporated to furnish a residual solid which was crystallized from Et_2O and CH_2Cl_2.

*2-(4-Oxoquinazolin-3[4*H*]-yl)-*N*-phenylacetamide (**8a**)*: Yield 90%. mp 252–253 °C. ^{1}H-NMR (DMSO-d_6) 4.83 (s, 2H, NCH_2), 7.29 (s, 1H, arom. H), 7.33 (d, J = 7.6, 2H, arom. H), 7.53–7.57 (m, 3H, arom. H), 7.72 (d, J = 8.0 Hz, 1H, arom. H), 7.83–7.85 (m, 1H, arom. H), 8.12–8.15 (m, 1H, arom. H), 8.33 (s, 1H-C (2)), 10.51 (s, 1H, CONH). ^{13}C-NMR (DMSO) 49.34 (NCH_2), 119.68, 121.73, 124.35, 126.52, 127.63, 127.91, 129.46, 135.29, 138.84, 148.33, 149.02, 160.94 (C=O), 165.94 (CONH). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C 68.81, H 4.69, N 15.05. Found: C 68.66, H 4.54, N 15.01.

*N-(4-Fluorophenyl)-2-(4-oxoquinazolin-3[4*H*]-yl)acetamide (**8b**)*: Yield 91%. mp 244–245 °C. ^{1}H-NMR (DMSO-d_6) 4.85 (s, 2H, NCH_2), 7.14–7.19 (m, 2H, arom. H), 7.55–7.62 (m, 3H, arom. H), 7.73 (d, J = 7.6 Hz, 1H, arom. H), 7.84–7.88 (m, 1H, arom. H), 8.16 (dd, J = 1.2, 8.0 Hz, 1H-C (8)), 8.37 (s, 1H-C (2)), 10.54 (s, 1H, CONH). ^{13}C-NMR (DMSO) 48.84 (NCH_2), 115.48, 115.70, 120.9, 120.98, 121.49, 126.11, 127.30, 127.34, 134.68, 135.06, 135.08, 148.15, 148.66, 157.03, 159.42, 160.41 (C=O), 165.47 ($C=NOCH_3$). Anal. Calcd for $C_{16}H_{12}FN_3O_2$: C 64.64, H 4.07, N 14.13. Found: C 64.57, H 4.06, N 14.13.

*N-(4-Chlorophenyl)-2-(4-oxoquinazolin-3[4*H*]-yl)acetamide (**8c**)*: Yield 89%. mp 262–263 °C. ^{1}H-NMR (DMSO-d_6) 4.84 (s, 2H, NCH_2), 7.39 (dd, J = 2.8, 9.2 Hz, 2H, arom. H), 7.55–7.60 (m, 3H, arom. H), 7.72 (d, J = 8.0 Hz, 1H-C (7)), 7.88 (m, 1H, arom. H), 8.15 (dd, J = 1.2, 8.0 Hz, 1H-C (5)), 8.34 (s, 1H-C (2)), 10.64 (s, 1H, CONH). ^{13}C-NMR (DMSO) 49.18 (NCH_2), 121.08, 121.62, 126.35, 127.52,

127.64, 127.68, 129.17, 135.07, 137.72, 148.26, 148.83, 160.72 (C=O), 165.96 (CONH). Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C 61.25, H 3.86, N 13.39. Found: C 60.91, H 3.88, N 13.32.

N-*(4-Bromophenyl)-2-(4-oxoquinazolin-3[4*H*]-yl)acetamide (8d)*: Yield 92%. mp 244–245 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.84 (s, 2H, NCH_2), 7.48–7.59 (m, 5H, arom. H), 7.72 (d, J = 7.6 Hz, 1H-C (7)), 7.88 (m, 1H, arom. H), 8.12 (dd, J = 1.2, 8.0 Hz, 1H-C (5)), 8.33 (s, 1H-C (2)), 10.64 (s, 1H, CONH). ^{13}C-NMR (DMSO) 49.19 ($N\underline{C}H_2$), 115.67, 121.47, 121.61, 126.35, 127.52, 127.68, 132.06, 135.07, 138.13, 148.25, 148.82, 160.72 (C=O), 165.98 ($\underline{C}$=NOCH$_3$). Anal. Calcd for $C_{16}H_{12}BrN_3O_2$: C 53.65, H 3.38, N 11.73. Found: C 53.71, H 3.50, N 11.52.

N-*(4-Methoxyphenyl)-2-(4-oxoquinazolin-3[4*H*]-yl)acetamide (**8e**)*: Yield: 84%. mp 230–231 °C. ^{1}H-NMR (DMSO-d_6) 4.83 (s, 2H, NCH_2), 6.90 (dd, J = 2.0, 6.8 Hz, 2H, arom. H), 7.48–7.59 (m, 3H, arom. H), 7.73 (dd, J = 0.8, 7.6 Hz, 1H-C (6)), 7.88 (dd, J = 1.6, 7.2 Hz, 1H-C (7)), 8.16 (dd, J = 1.2, 8.0 Hz, 1H-C (8)), 8.36 (s, 1H-C (2)), 10.33 (s, 1H, CONH). ^{13}C-NMR (DMSO) 48.75 ($N\underline{C}H_2$), 55.24 (OCH_3) 114.07, 120.68, 121.52, 126.11, 127.27, 127.33, 131.82, 134.65, 148.16, 148.73, 155.46, 160.41 (C=O), 164.99 ($\underline{C}$=NOCH$_3$). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C 66.01, H 4.89, N 13.58. Found: C 65.90, H 4.91, N 13.55.

N-*(Biphenyl-4-yl)-2-(4-oxoquinazolin-3[4*H*]-yl)acetamide (**8f**)*: Yield: 93%. mp 307–308 °C. ^{1}H-NMR (DMSO-d_6) 4.90 (s, 2H, NCH_2), 7.30–7.34 (m, 1H, arom. H), 7.42–7.45 (m, 2H, arom. H), 7.56–7.74 (m, 8H, arom. H), 7.85–7.89 (m, 1H-C (7)), 8.17 (dd, J = 1.2, 8.0 Hz, 1H-C (8)), 8.39 (s, 1H-C (2)), 10.59 (s, 1H, CONH). ^{13}C-NMR (DMSO) 48.94 ($N\underline{C}H_2$), 119.56, 121.51, 126.12, 126.35, 127.17, 127.22, 127.31, 127.36, 129.03, 134.70, 135.31, 138.14, 139.61, 148.17, 148.69, 160.42 (C=O), 165.59 ($\underline{C}$=NOCH$_3$). Anal. Calcd for $C_{22}H_{17}N_3O_2$: C 74.35, H 4.82, N 11. 82. Found: C 74.23, H 4.85, N 11.82.

N-*(Naphthalen-2-yl)-2-(4-oxoquinazolin-3[4*H*]-yl)acetamide (**8g**)*: Yield: 89%. mp 294–295 °C. ^{1}H-NMR (DMSO-d_6) 4.40 (s, 2H, NCH_2), 7.39–7.49 (m, 2H, arom. H), 7.56–7.62 (m, 2H, arom. H), 7.73–7.80 (m, 2H, arom. H), 7.85–7.90 (m, 3H, arom. H), 8.17 (dd, J = 1.2, 8.0 Hz, 1H-C (8)), 8.27 (d, J = 2.0 Hz, 1H, arom. H), 8.41 (s, 1H-C (2)), 10.70 (s, 1H, CONH). ^{13}C-NMR (DMSO) 48.99 ($N\underline{C}H_2$), 115.42, 119.77, 121.52, 124.90, 126.12, 126.65, 127.30, 127.35, 127.40, 127.59, 128.70, 129.95, 133.45, 134.68, 136.23, 148.17, 148.7, 160.44 (C=O), 165.83 ($\underline{C}$=NOCH$_3$). Anal. Calcd for $C_{20}H_{15}N_3O_2$: C 72.94, H 4.59, N 12.76. Found: C 72.62, H 4.60, N 12.71.

3.3 | Antiproliferative activity

3.3.1 | Cell lines

Human leukemia (Jurkat) and non-small-cell lung carcinoma (NCI-H226) were obtained from the American Type Culture Collection (Rockville, MD). A nasopharyngeal carcinoma (NPC-TW01) cell line was purchased from the Taiwan Food Industry Research and Development Institute (Hsinchu, Taiwan). All the tumor cell lines were maintained in MEM, RPMI 1640, or DMEM medium supplied with 10% fetal bovine serum at 37 °C in a humidified atmosphere of 5% CO_2/95% air in the presence of antibiotics.

3.3.2 | Growth inhibition assay (MTT assay)

The colorimetric assay for cellular growth and survival was performed as described by Hansen et al., with slight modifications.[20] Pre-determined numbers of cells were seeded in a 96-well microplate, and designated compounds at various concentrations were added for the indicated time period. The MTT-containing solution was added after compound treatment, and conversion of MTT to formazan by metabolically viable cells was measured by absorbance at 490 nm in a 96-well microtiter plate reader. The percentage of conversion by mock-treated control cells was used to evaluate the effect of the chemicals on cell growth and to determine the IC_{50} values.

3.4 | Cell cycle analysis

Treated or control cells were trypsinized and collected for overnight fixation with 70% ice-cold ethanol in 1 × phosphate-buffered saline (1 × PBS) at −20 °C. After centrifugation and washing with 1 × PBS for depleting ethanol, cells were permeabilized with 0.1% triton X-100 in 1 × PBS for 15 min at room temperature and then stained with propidium iodide (PI) (40 μg/mL) containing RNase A (0.1 mg/mL) in PBS for 30 min at 37 °C. After centrifugation and washing with 1 × PBS for removing free PI, the samples were instantly analyzed on a Canto II flow cytometer (BD Biosciences, San Jose, CA) and the distribution of each cell cycle phase was thus evaluated by the FCS express software (De Novo software, Los Angeles, CA).

4 | CONCLUSIONS

We have synthesized certain oxime, methyloxime, and amide-containing quinazolinone derivatives for antiproliferative evaluation against NPC-TW01, Jurkat, and NCI-H226 cancer cells. Among them, *N*-(naphthalen-2-yl)-2-(4-oxoquinazolin-3[4*H*]-yl)acetamide (**8g**) showed the highest activity against NPC-TW01 cell lines with an IC_{50} value of 4.78 μM. Flow cytometric analysis indicated that **8g** induced NPC-TW01 cell arrest at the G1/G0 phase in a time- and concentration- dependent manner. Collectively, this work provided solid evidence that **8g** might be a potential lead compound capable of inducing nasopharyngeal cancer cell death and is worthy of advanced development and investigation.

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Conflict of interest

All the authors have declared that they have no conflict of interest.

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