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Synthesis, antiproliferative, and antiplatelet activities of oxime- and amide-containing quinolin-2(1*H*)-one derivatives

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Abstract—Certain oxime- and amide-containing quinolin-2(1*H*)-one derivatives were synthesized and evaluated for their antiproliferative and antiplatelet activities. These compounds were synthesized via alkylation of hydroxyl precursors followed by the reaction with NH_2OH or NaN_3 (Schmidt reaction). The preliminary assays indicated that amide derivatives are either weakly active or inactive while the oxime counterparts exhibited potent inhibitory activities against platelet aggregation induced by collagen, AA (arachidonic acid), and U46619 (the stable thromboxan A_2 receptor agonist). Among them, (*Z*)-6-[2-(4-methoxyphenyl)-2-hydroxyiminoethoxy]quinolin-2(1*H*)-one (**7c**) was the most active against AA induced platelet aggregation with an IC_{50} of 0.58 μM and was inactive against cell proliferation. For the inhibition of U46619 induced aggregation, **7a** and **8a**–**c** exhibited very potent activities with IC_{50} values in a range between 0.54 and 0.74 μM. For the antiproliferative evaluation, *N*-(biphenyl-4-yl)-2-(2-oxo-1,2-dihydroquinolin-7-yloxy)acetamide (**11d**) was the most potent with GI_{50} values of <10, 10.8, and <10 μM against the growth of MT-2, NCI-H661, and NPC-Tw01, respectively, and possessed only a weak antiplatelet activity. Further evaluation of **11d** as a potential anticancer agent is on-going.
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1. Introduction

Certain quinolin-2(1*H*)-one (carbostyril) derivatives have been proved to possess antiplatelet, anti-inflammatory, anti-ulcer, vasodilatory, and phosphodiesterase inhibitory activities.[1–15] For example, carteolol is a β-adrenergic blocking agent has been used as a cardiovascular agent. However, the cardiovascular activities of quinolin-2(1*H*)-one skeleton were influenced not only by the kind of peripheral side chains but also by the position they substituted. For example, Tominaga et al. and Fujioka et al. revealed that 6-substituted quinolin-2(1*H*)-one exhibited the most potent positive inotropic effect among their positional isomers.[6] Therefore, their subsequent studies were focused only on 6-substituted quinolin-2(1*H*)-ones. Over the past few years, we were particularly interested in synthesizing α-methylene-γ-butyrolactones and evaluated their antiproliferative and cardiovascular activities.[12–21] Our results showed that the quinolin-2(1*H*)-one moiety is versatile and the inhibitory activity of quinolin-2(1*H*)-one α-methylene-γ-butyrolactones against arachidonic acid (AA)-induced platelet aggregation decreases in the order 7-substituted > 6-substituted > 8-substituted. Recently, we have reported antiproliferative and antiplatelet activities of certain oxime- and methyloxime-containing flavone and isoflavone derivatives.[22] To further study the structure–activity relationships of quinolin-2(1*H*)-one derivatives, we describe herein the preparation, antiproliferative, and antiplatelet activities of certain oxime- and amide-containing quinolin-2(1*H*)-one derivatives.

2. Chemistry

The preparation of oxime- and amide-containing quinolin-2(1*H*)-one derivatives is illustrated in Scheme 1. Alkylation of 6-hydroxyquinolin-2(1*H*)-one with phenyl bromomethylketone under basic conditions gave 6-(2-oxo-2-phenyl)quinolin-2(1*H*)-one (**4a**),[13] which was then treated with NH_2OH to afford exclusively (*Z*)-6-(2-(hydroxyimino)-2-phenylethoxy)quinolin-2(1*H*)-one (**7a**) in a good overall yield. The same synthetic procedure

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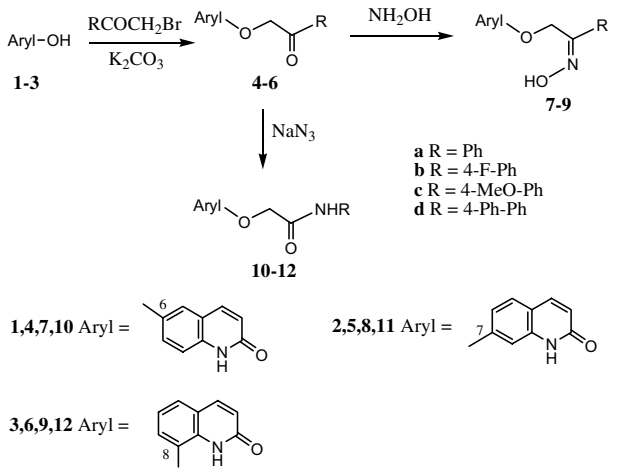


Scheme 1.

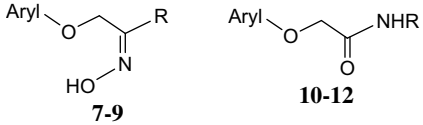
was applied for the synthesis of (*Z*)-**7b**–**d** from their respective ketone precursor **4b**–**d**. Accordingly, (*Z*)-**8a**–**d** and (*Z*)-**9a**–**d** were prepared from **5a**–**d**[14] and **6a**–**d**,[12] respectively. The configuration of the oxime moiety was confirmed by the ^{13}C NMR spectra. The carbon of 1′-CH_2 which is *anti* to the oxime moiety shifted downfield (δ approximately at 70.00 ppm), while that of the *syn* isomer shifted upfield (δ 59.78 for (*Z*)-**7a**, 59.83 for (*Z*)-**7b**, 59.80 for (*Z*)-**7c**, 59.71 for (*Z*)-**7d**, 59.73 for (Z)-**8a**, 59.81 for (*Z*)-**8b**, 59.71 for (*Z*)-**8c**, 59.68 for (*Z*)-**8d**, 60.22 for (Z)-**9a**, 60.18 for (*Z*)-**9b**, 60.18 for (*Z*)-**9c**, and 60.20 for (*Z*)-**9d**).[23] Treatment of **4a** with H_2SO_4 and NaN_3 afforded 2-(2-oxo-1,2-dihydroquinolin-6-yloxy)-*N*-phenylacetamide (**10a**) in a good overall yield. The same synthetic procedure was applied for the synthesis of **10b**–**d** from their respective ketone precursor **4b**–**d**. Accordingly, **11a**–**d** and **12a**–**d** were prepared from **5a**–**d** and **6a**–**d**, respectively.

3. Pharmacological results and discussion

3.1. Antiproliferative activity

All compounds were evaluated in vitro against a three-cell line panel consisting of Human T-cell leukemia (MT-2), Human lung carcinoma (NCI-H661), and Human Nasopharyngeal carcinoma (NPC-Tw01). Results from Table 1 indicated these compounds were either weakly active or inactive. For the oxime derivatives, antiproliferative activity decreased in an order of linked chromophore quinolin-2(1*H*)-one-7-yl **8a**–**d** > quinolin-2(1*H*)-one-8-yl **9a**–**d** > quinolin-2(1*H*)-one-6-yl **7a**–**d**. Among these quinolin-2(1*H*)-one-7-yl derivatives, (*Z*)-7-(2-(biphenyl-4-yl)-2-(hydroxyimino)ethoxy)quinolin-2(1*H*)- one (**8d**) was the most potent with GI_{50} values of

Table 1. Antiproliferative activity of quinolin-2(1*H*)-one derivatives



Compound	Substituents		GI_{50}[a,b] (μM)		
	Aryl	R	MT-2	NCI-H661	NPC-Tw01
7a	Quinolinone-6-yl	Ph	>50	44.3	>50
7b	Quinolinone-6-yl	4-F–Ph	>50	44.9	>50
7c	Quinolinone-6-yl	4-MeO–Ph	>50	47.0	>50
7d	Quinolinone-6-yl	4-Ph–Ph	>50	>50	>50
8a	Quinolinone-7-yl	Ph	24.6	36.1	43.7
8b	Quinolinone-7-yl	4-F–Ph	33.8	34.7	>50
8c	Quinolinone-7-yl	4-MeO–Ph	31.6	43.1	41.1
8d	Quinolinone-7-yl	4-Ph–Ph	30.3	12.2	30.5
9a	Quinolinone-8-yl	Ph	42.0	>50	>50
9b	Quinolinone-8-yl	4-F–Ph	49.2	44.2	46.3
9c	Quinolinone-8-yl	4-MeO–Ph	50.0	38.5	47.0
9d	Quinolinone-8-yl	4-Ph–Ph	42.0	>50	>50
10a	Quinolinone-6-yl	Ph	>50	43.5	>50
10b	Quinolinone-6-yl	4-F–Ph	>50	46.4	>50
10c	Quinolinone-6-yl	4-MeO–Ph	>50	39.1	>50
10d	Quinolinone-6-yl	4-Ph–Ph	>50	>50	25.6
11a	Quinolinone-7-yl	Ph	42.2	29.0	43.3
11b	Quinolinone-7-yl	4-F–Ph	>50	23.6	>50
11c	Quinolinone-7-yl	4-MeO–Ph	>50	39.3	>50
11d	Quinolinone-7-yl	4-Ph–Ph	<10	10.76	<10
12a	Quinolinone-8-yl	Ph	>50	>50	>50
12b	Quinolinone-8-yl	4-F–Ph	>50	45.7	>50
12c	Quinolinone-8-yl	4-MeO–Ph	>50	>50	>50
12d	Quinolinone-8-yl	4-Ph–Ph	>50	46.6	14.1

[a] GI_{50}, drug molar concentration causing 50% cell growth inhibition.
[b] NCI-H661, Human lung carcinoma; NPC-Tw01, Human Nasopharyngeal carcinoma; MT-2, Human T-cell leukemia.

Table 2. Effects of quinolin-2(1*H*)-one derivatives on the platelet aggregation induced by thrombin, AA, collagen, and U46619

Compound (100 μM)	Thrombin (0.1 U/mL)	Arachidonic acid (200 μM)	Collagen (10 μg/mL)	U46619 (2 μM)
Control	93.43 ± 0.60	90.62 ± 1.20	88.97 ± 1.72	90.13 ± 1.23
7a	65.84 ± 1.49	15.60 ± 2.09***	12.8 ± 1.1***	4.47 ± 2.92
7b	82.35 ± 2.15	5.18 ± 2.54***	80.75 ± 2.71	2.96 ± 2.41***
7c	70.05 ± 1.00	12.09 ± 1.66***	26.25 ± 2.51	1.42 ± 1.16***
7d	90.35 ± 1.64	10.74 ± 1.45***	51.25 ± 1.25***	7.26 ± 2.31***
8a	48.34 ± 2.72*	10.67 ± 6.25***	8.6 ± 2.3***	10.94 ± 4.44***
8b	50.61 ± 2.62	12.11 ± 5.74***	19.61 ± 5.24***	7.25 ± 2.75***
8c	59.79 ± 4.38	25.44 ± 1.70***	55.64 ± 6.70*	7.37 ± 3.09***
8d	91.42 ± 2.46	6.7 ± 2.85***	4.21 ± 1.25***	6.81 ± 3.35***
9a	91.05 ± 0.76	42.25 ± 17.58**	35.25 ± 9.32***	89.55 ± 1.38
9b	92.05 ± 2.42	9.96 ± 0.3***	5.67 ± 1.11***	7.29 ± 3.56***
9c	90.37 ± 0.48	8.35 ± 5.62***	12.64 ± 2.54***	4.67 ± 3.18***
9d	94.05 ± 2.17	13.5 ± 2.83***	10.31 ± 1.25***	90.23 ± 1.21
10a	82.15 ± 4.19	13.95 ± 0.71	11.25 ± 0.64***	5.36 ± 2.44***
10b	85.67 ± 2.72	8.88 ± 3.09***	5.65 ± 2.14***	4.35 ± 3.55
10c	91.27 ± 1.01	9.38 ± 1.43***	9.58 ± 3.54***	2.04 ± 1.67***
10d	91.41 ± 0.96	32.22 ± 16.52	12.52 ± 3.52***	5.78 ± 0.82***
11a	88.62 ± 1.12	28.21 ± 6.52	15.36 ± 2.45***	9.30 ± 3.27***
11b	91.35 ± 1.69	54.46 ± 2.64*	54.66 ± 2.52*	88.78 ± 0.36
11c	88.58 ± 1.48	14.71 ± 3.64***	69.69 ± 2.62*	3.97 ± 1.86***
11d	92.27 ± 1.19	56.35 ± 24.01	62.25 ± 5.32*	91.11 ± 1.32
12a	92.77 ± 1.53	91.66 ± 0.92	78.25 ± 3.21	88.26 ± 2.49
12b	93.93 ± 1.68	90.10 ± 1.45	78.65 ± 2.61	83.99 ± 4.08
12c	92.00 ± 0.77	90.02 ± 0.37	78.25 ± 4.25	90.64 ± 1.31
12d	93.35 ± 1.04	87.61 ± 2.62	80.21 ± 3.21	90.67 ± 0.94

* Significantly different from control value at $P < 0.05$ as compared with control.
** Significantly different from control value at $P < 0.01$ as compared with control.
*** Significantly different from control value at $P < 0.001$ as compared with control.

30.3, 12.2, and 30.5 μM against the growth of MT-2, NCI-H661, and NPC-Tw01, respectively, while the antiproliferative activity of **8a**–**c** is comparable. The same trend was observed for the amide counterparts in which quinolin-2(1*H*)-one-7-yl **11a**–**d** is preferred in comparison to their respective quinolin-2(1*H*)-one-6-yl **10a**–**d** and quinolin-2-(1*H*)-one-8-yl **12a**–**d**. Among these quinolin-2(1*H*)-one-7-yl derivatives, *N*-(biphenyl-4-yl)-2-(2-oxo-1,2-dihydroquinolin-7-yloxy)acetamide (**11d**) was the most potent with GI_{50} values of <10, 10.8, and

Table 3. IC_{50} values (μM) of oxime- and amide-containing quinolin-2(1*H*)-one derivatives on the platelet aggregation induced by AA, collagen, and U46619

Compound	Arachidonic acid (200 μM)	Collagen (10 μg/mL)	U46619 (2 μM)
Control	90.62 ± 1.20	88.97 ± 1.72	90.13 ± 1.23
7a	5.84 ± 0.28	38.3 ± 2.56	0.56 ± 0.03
7b	5.80 ± 0.07	n.d	5.41 ± 0.24
7c	0.58 ± 0.01	36.3 ± 3.12	5.37 ± 0.04
7d	60.30 ± 1.03	n.d	60.24 ± 2.45
8a	6.85 ± 3.55	3.53 ± 0.58	0.58 ± 0.02
8b	5.85 ± 1.57	9.95 ± 2.19	0.54 ± 0.01
8c	6.61 ± 0.22	n.d	0.74 ± 0.05
8d	52.82 ± 6.21	10.83 ± 2.46	5.45 ± 0.03
9a	n.d	n.d	n.d
9b	58.89 ± 0.83	38.3 ± 2.76	55.08 ± 3.81
9c	59.20 ± 3.95	52.3 ± 2.15	55.72 ± 2.52
9d	63.21 ± 2.40	35.5 ± 2.15	n.d
10a	67.8 ± 2.98	19.5 ± 3.21	57.18 ± 1.35
10b	53.21 ± 3.89	34.61 ± 2.85	5.20 ± 0.26
10c	49.71 ± 3.61	56.75 ± 2.54	54.63 ± 0.88
10d	68.98 ± 2.54	35.63 ± 1.25	56.18 ± 0.92
11a	62.31 ± 3.25	51.22 ± 1.52	59.31 ± 2.67
11b	n.d	n.d	n.d
11c	60.54 ± 7.52	n.d	36.59 ± 1.03
11d	n.d	n.d	n.d
12a	n.d	n.d	n.d
12b	n.d	n.d	n.d
12c	n.d	n.d	n.d
12d	n.d	n.d	n.d

n.d, not determined.

<10 μM against the growth of MT-2, NCI-H661, and NPC-Tw01, respectively. In general, the most preferred pharmacophore is quinolin-2(1*H*)-one-7-yl and the most active substituent (R group) is biphenyl for both series of amide and oxime derivatives.

3.2. Antiplatelet activity

The antiplatelet activities were evaluated in washed rabbit platelets. Platelet aggregation was induced by thrombin (Thr, 0.1 U/mL), arachidonic acid (AA, 200 μM), collagen (Col, 10 μg/mL), and U46619 (2 μM), respectively. The final concentration was 100 μM and the results are shown in Table 2. All of them are inactive against the platelet aggregation induced by thrombin. For the amides, quinolin-2(1*H*)-one-6-yl derivatives **10a–d** were weakly active on the platelet aggregation induced by AA, collagen, or U46619 while their positional isomers, **11a–d** and **12a–d**, were found to be inactive with an exception of **11c**. In general, oxime derivatives **7–9** are more active than their respective amide counterparts **10–12** as shown in Table 3. Among these oximes, quinolin-2(1*H*)-one-8-yl derivatives **9a–d** were less active than their respective quinolin-2(1*H*)-one-6-yl **7a–d** and quinolin-2(1*H*)-one-7-yl **8a–d**. For quinolin-2(1*H*)-one-6-yl derivatives **7a–d**, the potency of **7a– 7c** was comparable while **7d** was much less active against AA and U46619 induced platelet aggregation. The same trend was observed for the quinolin-2(1*H*)-one-7-yl **8a–d**, in which the potency of **8a–8c** was comparable while **8d** was much less active. Among them, (*Z*)-6-[2-(4-methoxyphenyl)-2-hydroxyiminoethoxy]quinolin-2(1*H*)-one (**7c**) was most active against AA induced platelet aggregation with an IC_{50} of 0.58 μM while the IC_{50} value for collagen induced platelet aggregation is 36.3 μM which indicated **7c** may interfere with the conversion of AA into thromboxane A2 but not affect intracellular signaling caused by collagen. On the contrary, (*Z*)-7-(2-(hydroxyimino)-2-phenylethoxy)quinolin-2(1*H*)-one (**8a**) was most active against collagen induced platelet aggregation with an IC_{50} of 3.53 μM. For the inhibition of U46619 induced aggregation, **7a** and **8a–c** exhibited very potent activities with IC_{50} values in a range of 0.54–0.74 μM. The intracellular signaling, such as intracellular calcium and phospholipase C activity, induced by U46619 is currently under investigation.

4. Conclusion

A number of oxime and amide containing quinolin-2(1*H*)-one derivatives were synthesized and evaluated for their antiproliferative and antiplatelet activities. The results indicated quinolin-2(1*H*)-one-7-yl derivatives **8a–d** possess both antiproliferative and antiplatelet activities while quinolin-2(1*H*)-one-6-yl derivatives **7a–c** exhibited potent antiplatelet activities with less antiproliferative activity. The most potential compound was **7c** which exhibited potent activity against AA-induced platelet aggregation with an IC_{50} of 0.58 μM and was inactive against cell proliferation. On the contrary, **11d** exhibited potent antiproliferative activity with GI_{50} values of <10, 10.8, and <10 μM against the growth of MT-2, NCI-H661, and NPC-Tw01, respectively, and a weak antiplatelet activity. Further evaluation of **11d** as potential anticancer drug is on-going.

5. Experimental

5.1. General

TLC. Precoated (0.2 mm) silica gel 60 F_{254} plates from EM Laboratories Inc.; detection by UV light (254 nm). Mp: Electrothermal IA9100 digital melting-point apparatus; uncorrected. ^{1}H NMR spectra: Varian-Unity-400 spectrometer at 400, chemical shifts δ in ppm with $SiMe_4$ as an internal standard (=0 ppm), coupling constants J in Hz. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer, and results were within ±0.4% of calculated values.

5.1.1. (*Z*)-6-(2-(Hydroxyimino)-2-phenylethoxy)quinolin-2(1*H*)-one (7a). A solution of **4a** (0.28 g, 1 mmol) in EtOH (20 mL) was added a solution of hydroxylamine hydrochloride (0.14 g, 2 mmol) in EtOH (2 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 and purified by flash column chromatography (FC; silica gel; *n*-hexane/EtOAc 1:1) and recrystallized from CH_2Cl_2 to give **7a** (0.25 g, 84%). Mp 245–246 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 5.25 (s, OCH_2), 6.49 (d, J = 9.6, 1H–C(3)), 7.11 (dd, J = 9.2, 2.8, 1H–C(7)), 7.21 (d, J = 9.2, 1H–C(8)), 7.27 (d, J = 2.8, 1H–C(5)), 7.37–7.40 (m, 3H, arom. H), 7.63–7.66 (m, 2H, arom. H), 7.80 (d, J = 9.6, 1H–C(4)), 11.67 (s, NH), 11.94 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 59.78 (CH_2O), 111.13, 117.09, 120.31, 123.10, 127.03, 128.72, 129.02, 129.24, 129.59, 134.30, 134.98, 140.43, 153.41 (arom. C and C=N), 162.21 (C(2)). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.24; H, 4.81; N, 9.46.

The same procedure was applied to convert **4b–d** to **7b–d**; **5a–d** to **8a–d**; and **6a–d** to **9a–d**, respectively.

5.1.2. (*Z*)-6-(2-(4-Fluorophenyl)-2-(hydroxyimino)ethoxy)quinolin-2(1*H*)-one (7b). Yield: 64%. Mp 264–265 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 5.24 (s, OCH_2), 6.47(d, J = 9.6, 1H–C(3)), 7.09 (dd, J = 8.8, 2.8, 1H–C(7)), 7.19 (d, J = 8.8, 1H–C(8)), 7.22 (d, J = 2.8, 1H–C(5)), 7.24–7.26 (m, 2H, arom. H), 7.65–7.77 (m, 2H, arom. H), 7.79 (d, J = 9.6, 1H–C(4)), 11.64 (s, NH), 11.93 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 59.83 (CH_2O), 111.17, 115.58, 115.85, 116.07, 117.09, 120.29, 123.12, 129.22, 129.31, 131.77, 131.85, 134.34, 140.42, 150.62, 152.69, 153.27 (arom. C and C=N), 162.22 (C(2)). Anal. Calcd for $C_{17}H_{13}FN_2O_3 \cdot 0.25H_2O$: C, 64.45; H, 4.30; N, 8.84. Found: C, 64.53; H, 4.40; N, 8.80.

5.1.3. (*Z*)-6-(2-(Hydroxyimino)-2-(4-methoxyphenyl)ethoxy)quinolin-2(1*H*)-one (7c). Yield: 72%. Mp 244–245 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 3.76 (s, MeO), 5.22 (s, OCH_2), 6.49 (d, J = 9.2, 1H–C(3)), 6.92–6.95 (m, 2H, arom. H), 7.11 (dd, J = 8.8, 2.8,

1H–C(7)), 7.21 (d, $J = 8.8$, 1H–C(8)), 7.27 (d, $J = 2.8$, 1H–C(5)), 7.58–7.60 (m, 2H, arom. H), 7.79 (d, $J = 9.2$, 1H–C(4)), 11.65 (s, NH), 11.70 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 55.84 (MeO), 59.80 (CH_2O), 111.17, 114.45, 117.07, 120.32, 123.11, 127.39, 128.41, 134.30, 140.42, 152.96, 153.42, 160.51 (arom. C and C=N), 162.21 (C(2)). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.35; H, 5.02; N, 8.46.

5.1.4. (*Z*)-6-(2-(Biphenyl-4-yl)-2-(hydroxyimino)ethoxy)-quinolin-2(1*H*)-one (7d). Yield: 67%. Mp 242–243 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 5.26 (s, OCH_2), 6.47 (d, $J = 9.6$, 1H–C(3)), 7.12 (dd, $J = 9.2$, 2.4, 1H–C(7)), 7.22 (d, $J = 9.2$, 1H–C(8)), 7.29 (d, $J = 2.4$, 1H–C(5)), 7.35–7.37 (m, 1H, arom. H), 7.43–7.46 (m, 2H, arom. H), 7.66–7.74 (m, 6H, arom. H), 7.79 (d, $J = 9.6$, 1H–C(4)), 11.67 (s, NH), 11.99 (*s*, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 59.71 (CH_2O), 111.15, 117.10, 120.35, 120.75, 123.13, 126.97, 127.27, 127.42, 127.58, 128.40, 129.68, 130.01, 134.04, 134.34, 140.43, 141.15, 153.40 (arom. C and C=N), 162.21 (C(2)). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.19; H, 4.86; N, 7.50.

5.1.5. (*Z*)-7-(2-(Hydroxyimino)-2-phenylethoxy)quinolin-2(1*H*)-one (8a). Yield: 80%. Mp 228–229 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 5.28 (s, OCH_2), 5.30 (d, $J = 9.6$, 1H–C(3)), 6.79 (dd, $J = 8.4$, 2.4, 1H–C(6)), 6.81 (d, $J = 2.4$, 1H–C(8)), 7.37–7.39 (m, 3H, arom. H), 7.54 (d, $J = 8.4$, 1H–C(5)), 7.63–7.65 (m, 2H, arom. H), 7.79 (d, $J = 9.6$, 1H–C(4)), 11.62 (s, NH), 11.94 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 59.73 (CH_2O), 99.88, 110.86, 114.43, 119.55, 127.10, 129.03, 129.64, 130.07, 134.81, 140.68, 141.18, 153.23, 160.35 (arom. C and C=N), 162.92 (C(2)). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.35; H, 4.83; N, 9.44.

5.1.6. (*Z*)-7-(2-(4-Fluorophenyl)-2-(hydroxyimino)ethoxy)-quinolin-2(1*H*)-one (8b). Yield: 82%. Mp 204–205 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 5.29 (s, OCH_2), 6.30 (d, $J = 9.2$, 1H–C(3)), 6.78 (dd, $J = 8.8$, 2.4, 1H–C(6)), 6.81 (d, $J = 2.4$, 1H–C(8)), 7.19–7.24 (m, 2H, arom. H), 7.54 (*d*, $J = 8.8$, 1H–C(5)), 7.66–7.70 (m, 2H, arom. H), 7.78 (d, $J = 9.6$, 1H–C(4)), 11.62 (s, NH), 11.9 6(s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 59.81 (CH_2O), 99.92, 110.91, 114.47, 115.86, 116.07, 119.55, 129.29, 129.37, 130.07, 131.23, 140.68, 141.17, 152.51, 160.26, 161.95, 162.95 (arom. C and C=N), 164.39 (C(2)). Anal. Calcd for $C_{17}H_{13}FN_2O_3$: C, 65.38; H, 4.20; N, 8.97. Found: C, 65.24; H, 4.25; N, 8.91.

5.1.7. (*Z*)-7-(2-(Hydroxyimino)-2-(4-methoxyphenyl)ethoxy)quinolin-2(1*H*)-one (8c). Yield: 78%. Mp 175–176 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 3.75 (s, MeO), 5.26 (s, OCH_2), 6.30 (d, $J = 9.6$, 1H–C(3)), 6.79 (dd, $J = 8.8$, 2.8, 1H–C(6)), 6.82 (*d*, $J = 2.8$, 1H–C(8)), 6.92–6.98 (m, 2H, arom. H), 7.54 (*d*, $J = 8.8$, 1H–C(5)), 7.56–7.60 (m, 2H, arom. H), 7.78 (d, $J = 9.6$, 1H–C(4)), 11.61 (s, NH), 11.71 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 55.82 (MeO), 59.71 (CH_2O), 99.92, 110.86, 114.09, 114.45, 119.50, 127.19, 128.45, 130.05, 131.17, 140.68, 141.18, 152.73, 160.51 (arom. C and C=N), 162.95 (C(2)). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.28; H, 5.10; N, 8.40.

5.1.8. (*Z*)-7-(2-(Biphenyl-4-yl)-2-(hydroxyimino)ethoxy)-quinolin-2(1*H*)-one (8d). Yield: 63%. Mp 233–234 °C. ^{1}H NMR(400 MHz, DMSO-d_6): 5.33 (s, OCH_2), 6.31 (d, $J = 9.6$, 1H–C(3)), 6.83 (dd, $J = 8.8$, 2.4, 1H–C(6)), 6.87 (d, $J = 2.4$, 1H–C(8)), 7.36–7.48 (m, 3H, arom. H), 7.56 (d, $J = 8.8$, 1H–C(5)), 7.67–7.74 (m, 6H, arom. H), 7.79 (d, $J = 9.6$, 1H–C(4)), 11.64 (s, NH), 12.02 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 59.68 (CH_2O), 99.97, 110.90, 114.48, 119.56, 127.27, 127.28, 127.63, 128.40, 129.67, 130.08, 133.90, 140.09, 140.67, 141.19, 141.22, 152.84, 160.40 (arom. C and C=N), 162.95 (C(2)). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.47; H, 5.04; N, 7.33.

5.1.9. (*Z*)-8-(2-(Hydroxyimino)-2-phenylethoxy)quinolin-2(1*H*)-one (9a). Yield: 71%. Mp 187–188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 5.39 (s, OCH_2), 6.45 (d, $J = 9.6$, 1H–C(3)), 7.05–7.21 (m, 3H, arom. H), 7.31–7.34 (m, 3H, arom. H), 7.76–7.78 (m, 2H, arom. H), 7.82 (d, $J = 9.6$, 1H–C(4)) 10.63 (s, NH), 12.03 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 60.22 (CH_2O), 112.37, 120.34, 120.81, 122.39, 123.14, 127.19, 128.87, 129.37, 129.62, 134.39, 140.90, 144.51, 153.27 (arom. C and C=N), 162.09 (C(2)). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.35; H, 4.83; N, 9.48.

5.1.10. (*Z*)-8-(2-(4-Fluorophenyl)-2-(hydroxyimino)ethoxy)quinolin-2(1*H*)-one (9b). Yield: 88%. Mp 185–186 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 5.39 (s, OCH_2), 6.46 (d, $J = 9.6$, 1H–C(3)), 7.06–7.21 (m, 5H, arom. H); 7.80–7.84 (m, 2H, arom. H), 7.82 (d, $J = 9.6$, 1H–C(4)), 10.72 (s, NH), 12.05 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 60.18 (CH_2O), 112.33, 115.67, 115.88, 120.36, 120.86, 122.38, 123.17, 129.38, 129.47, 130.84, 131.97, 132.06, 140.90, 140.95, 144.46, 152.46 (arom. C and C=N), 162.16 (C(2)). Anal. Calcd for $C_{17}H_{13}FN_2O_3$: C, 65.38; H, 4.20; N, 8.97. Found: C, 65.12; H, 4.32; N, 8.96.

5.1.11. (*Z*)-8-(2-(Hydroxyimino)-2-(4-methoxyphenyl)ethoxy)quinolin-2(1*H*)-one (9c). Yield: 82%. Mp 203–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 3.71 (s, MeO), 5.37 (s, OCH_2), 6.47 (d, $J = 9.2$, 1H–C(3)), 6.85–6.94 (m, 2H, arom. H), 7.04–7.08 (m, 1H, arom. H), 7.15–7.20 (m, 2H, arom. H), 7.72–7.81 (m, 2H, arom. H), 7.82 (d, $J = 9.2$, 1H–C(4)), 10.66 (s, NH), 11.83 (s, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 55.77 (MeO), 60.18 (CH_2O), 112.35, 114.27, 120.35, 120.76, 122.41, 123.15, 126.78, 128.59, 129.46, 131.40, 140.92, 144.53, 152.78, 160.49 (arom. C and C=N), 162.12 (C(2)). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.62; H, 5.04; N, 8.57.

5.1.12. (*Z*)-8-(2-(Biphenyl-4-yl)-2-(hydroxyimino)ethoxy)-quinolin-2(1*H*)-one (9d). Yield: 83%. Mp 194–195 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 5.43 (s, OCH_2), 6.46 (d, $J = 9.6$, 1H–C(3)), 7.07–7.10 (m, 1H, arom. H), 7.19–

7.22 (m, 2H, arom. H), 7.34–7.36 (m, 1H, arom. H), 7.41–7.45 (m, 2H, arom. H), 7.61–7.68 (m, 4H, arom. H), 7.82 (d, J = 9.2, 1H–C(4)), 7.87–7.89 (m, 2H, arom. H), 10.74 (s, NH), 12.09 (m, NOH). ^{13}C NMR (100 MHz, DMSO-d_6): 60.20 (CH_2O), 112.43, 120.39, 120.85, 122.43, 123.18, 127.10, 127.27, 127.74, 128.37, 129.51, 129.66, 133.53, 140.13, 140.91, 141.18, 144.60, 152.90 (arom. C and C═N), 162.15 (C(2)). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.44; H, 4.96; N, 7.44.

5.1.13. 2-(2-Oxo-1,2-dihydroquinolin-6-yloxy)-*N*-phenylacetamide (10a). A solution of **4a** (0.28 g, 1 mmol) in H_2SO_4 (3 mL) was stirred at rt for 10 min. To this solution, sodium azide (0.13 g, 2 mmol) was added in one portion. The mixture was stirred at rt for 1 h (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; MeOH/EtOAc 1:1) and recrystallized from CH_2Cl_2 to give **10a** (0.25 g, 85%). Mp 243–244 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.74 (s, OCH_2), 6.30 (d, J = 9.6, 1H–C(3)), 6.83 (d, J = 2.4, 1H–C(5)), 6.86 (dd, J = 8.8, 2.4, 1H–C(7)), 7.05–7.08 (*m*, 1H, arom. H), 7.29–7.33 (*m*, 2H, arom. H), 7.58 (d, J = 8.8, 1H–C(8)), 7.60–7.62 (m, 2H, arom. H), 7.80 (d, J = 9.6, 1H–C(4)), 10.19 (s, NH), 11.66 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 67.71 (CH_2O), 99.83, 111.51, 114.48, 119.56, 120.39, 124.45, 129.45, 130.00, 139.02, 140.72, 141.14, 160.29 (arom. C), 162.98 (C(2)), 166.72 (CONH). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 68.99; H, 4.76; N, 9.84.

The same procedure was applied to convert **4b**–**d** to **10b**–**d**; **5a**–**d** to **11a**–**d**; and **6a**–**d** to **12a**–**d**, respectively.

5.1.14. *N*-(4-Fluorophenyl)-2-(2-oxo-1,2-dihydroquinolin-6-yloxy)acetamide (10b). Yield: 73%. Mp 259–260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.69 (s, 2H, CH_2O), 6.47 (d, J = 9.2, 1H–C(3)), 7.12 (d, J = 2.4, 1H–C(5)), 7.16 (dd, J = 8.8, 2.4, 1H–C(7)), 7.24–7.25 (m, 3H, arom. H), 7.64 (d, J = 8.8, 1H–C(8)), 7.65–7.66 (m, 1H, arom. H), 7.83 (d, J = 9.2, 1H–C(4)), 10.13 (s, NH), 11.67 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 62.23 (CH_2O), 111.42, 115.88, 116.11, 117.08, 120.24, 120.67, 122.32, 122.39, 123.13, 134.47, 135.40, 140.48, 153.26, 157.77, 160.15 (arom. C), 162.25 (C(2)), 167.13 (CONH). Anal. Calcd for $C_{17}H_{13}FN_2O_3$: C, 65.38; H, 4.20; N, 8.97. Found: C, 65.42; H, 4.26; N, 9.00.

5.1.15. *N*-(4-Methoxyphenyl)-2-(2-oxo-1,2-dihydroquinolin-6-yloxy)acetamide (10c). Yield: 93%. Mp 194–195 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 3.69 (s, MeO), 4.66 (s, OCH_2), 6.47 (d, J = 9.6, 1H–C(3)), 6.85 (d, J = 2.4, 1H–C(5)), 6.87 (dd, J = 8.8, 2.4, 1H–C(7)), 7.23–7.26 (m, 3H, arom. H), 7.52 (d, J = 8.8, 1H–C(8)), 7.52–7.53 (m, 1H, arom. H),7.82 (d, J = 9.6, 1H–C(4)), 9.97 (s, NH), 11.69 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 55.84 (MeO), 68.23 (CH_2O), 111.37, 114.50, 117.10, 120.26, 120.71, 122.15, 123.04, 132.01, 134.38, 140.55, 153.32, 156.25 (arom. C), 162.32 (C(2)), 166.71(CONH). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.84; H, 5.08; N, 8.57.

5.1.16. *N*-(Biphenyl-4-yl)-2-(2-oxo-1,2-dihydroquinolin-6-yloxy)acetamide (10d). Yield: 95%. Mp 385–386 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.74 (s, OCH_2), 6.50 (d, J = 9.6, 1H–C(3)), 7.27 (d, J = 2.4, 1H–C(5)), 7.28 (dd, J = 8.8, 2.4, 1H–C(7)), 7.30–7.32 (m, 2H, arom. H), 7.40–7.44 (m, 1H, arom. H), 7.61–7.63 (m, 5H, arom. H), 7.73 (d, J = 8.8, 1H–C(8)), 7.85–7.88 (m, 1H, arom. H),7.94 (d, J = 9.6, 1H–C(4)), 10.30 (s, NH), 11.68 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 68.27 (CH_2O), 111.37, 117.22, 120.42, 120.78, 122.80, 126.33, 126.84, 126.96, 127.68, 129.59, 134.36, 138.68, 140.42, 140.76, 147.50, 153.45 (arom. C), 162.25 (C(2)), 167.22 (CONH). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.65; H, 5.04; N, 7.20.

5.1.17. 2-(2-Oxo-1,2-dihydroquinolin-7-yloxy)-*N*-phenylacetamide (11a). Yield: 94%. Mp 228–229 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.69 (s, 2H, OCH_2), 6.47(d, J = 9.6, 1H–C(3)), 7.07 (d, J = 2.4, 1H–C(8)), 7.24 (dd, J = 8.8, 2.4, 1H–C(6)), 7.28–7.32 (m, 4H, arom. H), 7.60 (d, J = 8.8, 1H–C(5)), 7.61–7.63 (m, 1H, arom. H), 7.82 (d, J = 9.6, 1H–C(4)), 10.06 (s, NH), 11.66 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 68.23 (CH_2O), 111.38, 117.09, 120.26, 120.46, 120.66, 123.08, 124.45, 129.42, 134.42, 138.98, 140.51, 153.31 (arom. C), 162.28 (C(2)), 167.16 (CONH). Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.21; H, 4.84; N, 9.32.

5.1.18. *N*-(4-Fluorophenyl)-2-(2-oxo-1,2-dihydroquinolin-7-yloxy)acetamide (11b). Yield: 92%. Mp 273–274 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.74 (s, 2H, CH_2O), 6.29 (d, J = 9.6, 1H–C(3)), 6.83 (d, J = 2.4, 1H–C(8)), 6.85 (dd, J = 8.4, 2.4, 1H–C(6)), 7.13–7.17 (m, 2H, arom. H), 7.57 (d, J = 8.4, 1H–C(5)), 7.62–7.66 (m, 2H, arom. H), 7.79 (d, J = 9.6, 1H–C(4)), 10.32 (s, NH), 11.68 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 67.72 (CH_2O), 99.90, 111.45, 114.48, 115.88, 116.10, 119.61, 122.23, 122.31, 129.97, 135.43, 135.45, 140.65, 141.17, 157.76, 160.25 (arom. C), 162.93 (C(2)), 166.68 (CONH). Anal. Calcd for $C_{17}H_{13}FN_2O_3$: C, 65.38; H, 4.20; N, 8.97. Found: C, 65.21; H, 4.20; N, 8.97.

5.1.19. *N*-(4-Methoxyphenyl)-2-(2-oxo-1,2-dihydroquinolin-7-yloxy)acetamide (11c). Yield: 80%. Mp 237–238 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 3.70 (s, MeO), 4.71 (s, OCH_2), 6.30 (d, J = 9.6, 1H–C(3)), 6.83 (d, J = 2.4, 1H–C(8)), 6.85 (dd, J = 8.8, 2.4, 1H–C(6)), 6.86–6.89 (m, 2H, arom. H), 7.51–7.52 (m, 2H, arom. H), 7.57 (d, J = 8.8, 1H–C(5)), 7.80(d, J = 9.6, 1H–C(4)), 10.05 (s, NH), 11.67 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 55.84 (s, MeO), 67.71 (CH_2O), 99.84, 111.57, 114.48, 114.51, 119.51, 122.10, 129.96, 132.02, 140.77, 141.10, 156.25, 160.29 (arom. C), 163.03 (C(2)), 166.26 (CONH). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 67.04; H, 5.09; N, 8.64.

5.1.20. *N*-(Biphenyl-4-yl)-2-(2-oxo-1,2-dihydroquinolin-7-yloxy)acetamide (11d). Yield: 98%. Mp 367–368 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.77 (s, 2H, CH_2O), 6.31 (d, J = 9.6, 1H–C(3)), 6.84 (d, J = 2.4, 1H–C(8)), 6.88 (dd, J = 8.8, 2.4, 1H–C(6)), 7.40–7.44 (m, 2H, arom. H), 7.59 (d, J = 8.8, 1H–C(5)), 7.60–7.64(m, 5H, arom.

H), 7.71–7.74 (m, 2H, arom. H), 7.81(d, $J = 9.6$, 1H–C(4)), 10.28 (s, NH), 11.70 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 67.79 (CH_2O), 99.90, 111.53, 114.53, 119.52, 120.74, 126.28, 126.82, 126.97, 127.62, 127.69, 127.78, 129.59, 130.01, 140.74, 141.16, 160.32 (arom. C), 162.93 (C(2)), 166.77 (CONH). Anal. Calcd for $C_{23}H_{18}N_2O_3 \cdot 0.1H_2O$: C, 74.22; H, 4.87; N, 7.53. Found: C, 74.09; H, 4.94; N, 7.52.

5.1.21. 2-(2-Oxo-1,2-dihydroquinolin-8-yloxy)-*N*-phenylacetamide (12a). Yield: 96%. Mp 202–203 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.80 (s, 2H, OCH_2), 6.55 (d, $J = 9.6$, 1H–C(3)), 7.11–7.16 (m, 2H, arom. H), 7.22–7.24 (m, 1H, arom. H), 7.30–7.39 (m, 3H, arom. H), 7.59–7.61 (m, 2H, arom. H), 7.91 (d, $J = 9.6$, 1H–C(4)), 10.31 (s, NH), 11.46 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 68.67 (CH_2O), 113.49, 120.62, 121.48, 122.31, 122.56, 123.17, 125.18, 129.32, 129.41, 138.32, 141.15, 144.47 (arom. C), 162.60 (C(2)), 166.78 (CONH). Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.29; H, 4.82; N, 9.50.

5.1.22. *N*-(4-Fluorophenyl)-2-(2-oxo-1,2-dihydroquinolin-8-yloxy)acetamide (12b). Yield: 92%. Mp 201–202 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.81 (s, OCH_2), 6.55 (d, $J = 9.6$, 1H–C(3)), 7.10–7.15 (m, 1H, arom. H), 7.19–7.25 (m, 3H, arom. H), 7.30–7.32 (m, 1H, arom. H), 7.61–7.64 (m, 2H, arom. H), 7.92 (d, $J = 9.6$, 1H–C(4)), 10.40 (s, NH), 11.47 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 68.64(CH_2O), 113.50, 115.91, 116.13, 120.61, 121.48, 122.50, 123.22, 124.36, 124.44, 129.33, 134.67, 141.10, 144.43, 158.30, 160.69 (arom. C), 162.57 (C(2)), 166.74 (CONH). Anal. Calcd for $C_{17}H_{13}FN_2O_3 \cdot 0.25H_2O$: C, 64.44; H, 4.45; N, 8.84. Found: C, 64.50; H, 4.24; N, 8.89.

5.1.23. *N*-(4-Methoxyphenyl)-2-(2-oxo-1,2-dihydroquinolin-8-yloxy)acetamide (12c). Yield: 96%. Mp 183–184 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 3.73 (s, MeO), 4.77 (s, OCH_2), 6.55 (d, $J = 9.6$, 1H–C(3)), 6.92–7.96 (m, 2H, arom. H), 7.11–7.15 (m, 1H, arom. H), 7.23–7.25 (m, 1H, arom. H), 7.29–7.31 (m, 1H, arom. H), 7.47–7.50 (m, 2H, arom. H), 7.91 (d, $J = 9.6$, 1H–C(4)), 10.26 (s, NH), 11.55 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 55.88 (s, MeO), 68.65 (CH_2O), 113.44, 114.48, 120.60, 121.44, 122.49, 123.20, 124.34, 129.30, 131.18, 141.10, 144.44, 156.88 (arom. C), 162.60 (C(2)), 166.38 (CONH). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.34; H, 5.04; N, 8.48.

5.1.24. *N*-(Biphenyl-4-yl)-2-(2-oxo-1,2-dihydroquinolin-8-yloxy)acetamide (12d). Yield: 75%. Mp 268–269 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 4.86 (s, OCH_2), 6.58 (d, $J = 9.6$, 1H–C(3)), 7.14–7.18 (m, 1H, arom. H), 7.27–7.29 (m, 1H, arom. H), 7.29–7.38 (m, 2H, arom. H), 7.45–7.49 (m, 2H, arom. H), 7.67–7.77 (m, 6H, arom. H), 7.94 (d, $J = 9.6$, 1H–C(4)), 10.41 (s, NH), 11.49 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 68.74 (CH_2O), 113.56, 120.62, 121.49, 122.46, 122.50, 123.25, 127.04, 127.56, 127.91, 129.38, 129.63, 136.67, 137.89, 140.24, 141.10, 144.46 (arom. C), 162.52 (C(2)), 166.81(CONH). Anal. Calcds for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.57; H, 4.98; N, 7.52.

5.2. Antiproliferative activity

5.2.1. Cell culture. Human lung carcinoma (NCI-H661) was purchased from American Type Culture Collection (Rockville, MD); Human Nasopharyngeal carcinoma (NPC-Tw01) was purchased from Taiwan Food Industry Research and Development Institute (Hsinchu, Taiwan); Human T-cell leukemia (MT-2) was kindly provided by Dr. H.-S. Shiah (National Health Research Institutes, Hsinchu, Taiwan). Cell lines were maintained in the same standard medium, grown as a monolayer in DMEM (Gibco, USA), and supplemented with 10% fetal bovine serum (FBS) and antibiotics, that is, 100 IU/mL penicillin, 0.1 mg/mL streptomycin, and 0.25 μg/mL amphotericin. Culture was maintained at 37 °C with 5% CO_2 in a humidified atmosphere.

5.2.2. Antiproliferative assay. Cancer cells were treated as indicated for 48 h in medium containing 10% FBS. (3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, 2 mg/mL) (MTT, 20 mL) was added to the cultures and incubated during the final 1.5 h. The resultant tetrazolium salt was then dissolved by the addition of dimethylsulfoxide. Color was measured spectrophotometrically in a microtiter plate reader at 570 nm and used as a relative measure of viable cell number. The number of viable cells following treatment was compared to solvent and untreated control cells and used to determine the percent of control growth as $(Ab_{treated}/Ab_{control}) \times 100$, where Ab represents the mean absorbance ($n = 3$). The concentration that killed 50% of cells (GI_{50}) was determined from the linear portion of the curve by calculating the concentration of agent that reduced absorbance in treated cells, compared to control cells, by 50%.

5.3. Antiplatelet evaluation

The following reagents were used: collagen (type 1, bovine Achilles tendon; from Sigma) was homogenized in 25 mM AcOH and stored (1 mg/mL) at −70°. Arachidonic acid (AA), EDTA (*N*,*N*,*N*′*N*′-ethylenediamine tetraacetate), and bovine serum albumin (BSA) were purchased from Sigma and dissolved in $CHCl_3$. To test platelet aggregation, blood was collected from the rabbit marginal-ear vein, anticoagulated with EDTA (6 mM), and centrifuged for 10 min at 90*g* at rt. Platelet suspensions were prepared from the plasma according to a washing procedure previously described.[24] Platelet numbers were determined with a Coulter ZM counter and adjusted to 4.5×10^8 platelets/mL. The platelet pellets were suspended in Tyrode's solution of the following composition (in mM): NaCl (136.8), KCl (2.8), $NaHCO_3$ (11.9), $MgCl_2$ (2.1), NaH_2PO_4 (0.33), $CaCl_2$ (1.0), and glucose (11.2) containing BSA (0.35%). The platelet suspension was stirred at 1200 rpm, and the aggregation was measured at 37°C by the turbidimetric method described by O'Brien,[25] using a Chrono Log Lumi aggregometer. To eliminate solvent effects, the final concentration of dimethylsulfoxide (DMSO) was fixed at 0.5%. The percentage of aggregation was calculated based on the absorbances of a platelet suspension and that of Tyrode's solution, which were taken as 0% and 100% aggregated, respectively.

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