Synthesis, Antiproliferative, and Antiplatelet Activities of Oxime-containing 3,4-Dihydroquinolin-2(1*H*)-one Derivatives

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Some oxime-containing 3,4-dihydroquinolin-2(1*H*)-one derivatives were synthesized and evaluated for their antiplatelet and antiproliferative activities. These compounds were synthesized *via* alkylation of hydroxyl precursors followed by the reaction with NH_2OH. The preliminary assays indicated that (*Z*)-7-[2-(4-fluorophenyl)-2-(hydroxyimino)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**13c**) is the most active against U46619 induced platelet aggregation with an IC_{50} value of 3.51 μM. For the inhibition of AA-induced aggregation, (*E*)-6-[2-(hydroxyimino)propoxy]-3,4-dihydroquinolin-2(1*H*)-one (**15**) is the most potent with an IC_{50} value of 1.85 μM. These oxime-containing 3,4-dihydroquinolin-2(1*H*)-one derivatives were inactive against thrombin induced platelet aggregation with an IC_{50} value of greater than 26.78 μM. For the antiproliferative activity, most of these oxime-containing 3,4-dihydroquinolin-2(1*H*)-one derivatives were inactive while (*Z*)-7-[2-(hydroxyimino)-2-(naphthalen-2-yl)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**13a**) exhibited only marginal activities with GI_{50} value of 7.63, 7.34 and 6.36 μM against the growth of NPC-TW01, NCI-H661, and Jurkat respectively.

Keywords: Dihydroquinolinones; Antiproliferative activity; Antiplatelet activity.

INTRODUCTION

Certain quinolin-2(1*H*)-one (carbostyril) derivatives have been proved to possess antiplatelet, anti-inflammatory, anti-ulcer, vasodilatory, and phosphodiesterase inhibitory activities.[1-12] The cardiovascular and neuroprotective activities of certain 3,4-dihydroquinolin-2(1*H*)-ones substituted with various side chains have also been reported.[2,7,10,11,13] Recently, we have synthesized and evaluated the cardiovascular activities of certain α-methylene-γ-butyrolactones bearing heterocycles such as coumarins, flavones, xanthones, quinolines, and quinolin-2(1*H*)-ones.[14-18] Among these heterocycles, quinolin-2(1*H*)-ones proved to be the most active against platelet aggregation. One of the most potent antiplatelet agents, CCT-62, has been proved to be an inhibitor of phosphodiesterases, and its antiplatelet effect is mainly mediated by elevation of cyclic-AMP levels.[19] In the continuation of our search for more potent antiplatelet agents, a number of CCT-62 derivatives in which the α-methylene-γ-butyrolactone ring was replaced with an oxime moiety were synthesized and evaluated.[20,21] Among them, compound **1** was the most active against U46619 induced platelet aggregation with an IC_{50} of 0.56 μM. For the inhibition of AA induced aggregation, compound **2** exhibited very high activities with an IC_{50} of 0.58 μM and was inactive against cancer cell proliferation.[21] We have also synthesized certain 3,4-dihydroquinolin-2(1*H*)-one α-methylene-γ-butyrolactones (7HQ derivatives), saturated analogs of CCT-62, for pharmacological evaluation. The results indicated that 7HQ derivatives exert an inhibitory action on the expression of inducible nitric oxide synthase and cyclooxygenase-2 *via* the inhibition of IkB degradation and NF-kB activation.[22] The present report describes the preparation and antiplatelet evaluation of oxime-bearing 3,4-dihydroquinolin-2(1*H*)-ones which can be considered as reduced derivatives of compounds **1** and **2** or as 7HQ derivatives in which the α-methylene-γ-butyrolactone ring was replaced with an oxime moiety. Certain quinolin-2(1*H*)-one derivatives were previously reported to possess anticancer activity.[21,23,24] Therefore, these newly synthesized 3,4-dihydroquinolin-2(1*H*)-one derivatives

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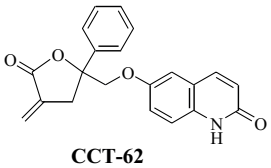
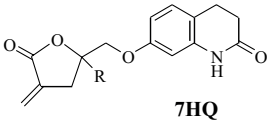
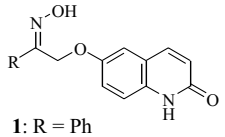
have also been evaluated *in vitro* against NPC-TW01 (nasopharygeal cancer), NCI-H661 and A549 (lung cancers), MKN45 (gastric cancer), and Jurkat (leukemia) since these cancers are very popular in Asia including Taiwan. Through structural modification, we expect to identify potential antiplatelet agents that are devoid of antiproliferative activity or potential anticancer agents that are devoid of antiplatelet activity.



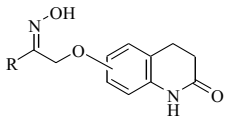
CCT-62



7HQ



1: R = Ph
2: R = 4-MeO-Ph



3,4-Dihydroquinolin-2(1*H*)-ones

RESULTS AND DISCUSSION

Synthesis

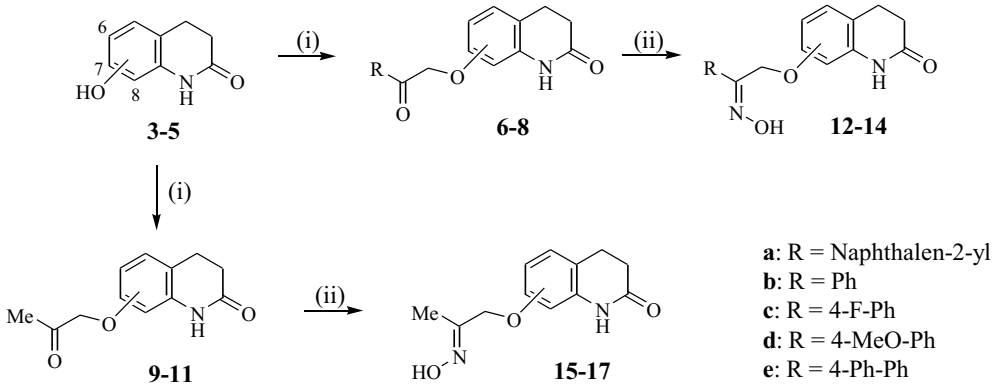
The preparation of oxime-containing 3,4-dihydroquinolin-2(1*H*)-one derivatives is illustrated in the Scheme I. Alkylation of 6-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**3**) with 2-(bromoacetyl)naphthalene under basic conditions gave 6-[2-(naphthalen-2-yl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**6a**), which was then treated with NH_2OH to afford exclusively (*Z*)-6-[2-(hydroxyimino)-2-(naphthalen-2-yl)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**12a**) in a good overall yield. The same synthetic procedure was applied for the synthesis of (*Z*)-**12b-e** from their respective ketone precursor **6b-e**.[12] Accordingly, (*Z*)-**13a-e** and (*Z*)-**14a-e** were prepared from **7a-e** and **8a-e**,[12] respectively. The configuration of the oxime moiety was confirmed by the ^{13}C-NMR spectra. For the *Z*-isomer, the 1'-CH_2 group is *syn* to the oxime OH group, which shifted the signal upfield to approximately 60.00 ppm.[25] Treatment of **3** with 2-bromoacetone under basic conditions gave 6-(2-oxopropoxy)-3,4-dihydroquinolin-2(1*H*)-one (**9**)[12] which was then reacted with NH_2OH to give exclusively (*E*)-6-[2-(hydroxyimino)propoxy]-3,4-dihydroquinolin-2(1*H*)-one (**15**). Accordingly, (*E*)-**16** and (*E*)-**17** were prepared from **10** and **11**,[12] respectively. The configuration of the oxime moiety was again confirmed by the ^{13}C-NMR spectra. For the *E*-isomer, the 1'-CH_2 group is *anti* to the oxime OH group, which shifted the signal downfield to approximately 70.00 ppm.[25]

Biological activities

1. Antiplatelet activity

The antiplatelet activities were evaluated in washed rabbit platelets. Platelet aggregation was induced by throm-

Scheme I



3-5 **6-8** **12-14** **9-11** **15-17**

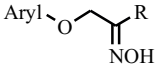
a: R = Naphthalen-2-yl
b: R = Ph
c: R = 4-F-Ph
d: R = 4-MeO-Ph
e: R = 4-Ph-Ph

3,6,9,12,15: 6-substituted
4,7,10,13,16: 7-substituted
5,8,11,14,17: 8-substituted

Reagents and conditions: (i) $RCOCH_2Br$, K_2CO_3; (ii) NH_2OH

bin (Thr, 0.1 U/mL), arachidonic acid (AA, 200 μM), and U46619 (thromboxan A2-like; 2 μM), respectively. The final concentration of compounds was 100 μM and the results are shown in Table 1. For the C-6 substituted 3,4-dihydroquinolin-2(1*H*)-one derivatives, **12b-12d** and **15** were capable of inhibiting thrombin, AA, and U46619 induced platelet aggregations completely at a concentration of 100 μM while at the same concentration, **12a** and **12e** were able to completely inhibit AA-induced aggregation but were inactive against thrombin and U46619 induced platelet aggregations. These results indicated that a less bulky substituent such as methyl, phenyl, 4-fluorophenyl, or 4-methoxyphenyl group is favorable for broad spectrum antiplatelet activities while a more bulky substituent such as naphthyl or biphenyl group is favorable for the selective antiplatelet activity. For the C-7 substituted 3,4-dihydroquinolin-2(1*H*)-one derivatives, compounds **13b-13d** possessed broad antiplatelet activities while **13a** and **16** were active against AA-induced aggregation only. The naphthyl derivative **13e** was inactive. For the C-8 substituted 3,4-dihydroquinolin-2(1*H*)-one derivatives, compounds **14a-14c** and **14e** were active against AA-induced aggregation while **14d** and **17** were inactive. In general, most of the 3,4-dihydroquinolin-2(1*H*)-one derivatives exhibited strong inhibitory activities against AA-induced aggregation, with few exceptions, in which compound **13c** was weekly active while **13e**, **14d**, and **17** were inactive. Compounds **12b-d**, **13b-d**, **14c**, and **15** were found to inhibit U46619-induced aggregation completely at a concentration of 100 μM. The effect on antiplatelet aggregation (IC_{50}) of oxime-containing 3,4-dihydroquinolin-2(1*H*)-one derivatives are given in Table 2. The thrombin-induced aggregation was the most resistant with an IC_{50} value of greater than 26.78 μM in each case while the AA-induced aggregation was the most susceptible and the inhibitory activity decreased in an order 3,4-dihydroquinolin-2(1*H*)-one-6-yl > 3,4-dihydroquino-

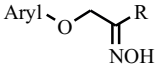
Table 1. Effect of oxime-containing 3,4-dihydroquinolin-2(1*H*)-one derivatives at a concentration of 100 μM on the platelet aggregation (%) induced by thrombin (Thr), arachidonic acid (AA), and U46619



Compd.	Substituents		Inducer		
	Aryl	R	Thr (0.1 U/mL)	AA (200 μM)	U46619 (2 μM)
Control			91.69 ± 0.66	89.15 ± 0.88	89.53 ± 0.45
12a	Quinolinone-6-yl	Naph	86.76 ± 1.82[a]	4.81 ± 1.97[c]	87.65 ± 0.42[a]
12b	Quinolinone-6-yl	Ph	0 ± 0[c]	1.88 ± 1.53[c]	0 ± 0[c]
12c	Quinolinone-6-yl	4-F-C_6H_4	0 ± 0[c]	0 ± 0[c]	0 ± 0[c]
12d	Quinolinone-6-yl	4-MeO-C_6H_4	0 ± 0[c]	0 ± 0[c]	0 ± 0[c]
12e	Quinolinone-6-yl	4-Ph-C_6H_4	87.94 ± 0.98[a]	0 ± 0[c]	89.53 ± 0.45
13a	Quinolinone-7-yl	Naph	60.95 ± 1.99[c]	0 ± 0[c]	85.95 ± 2.24
13b	Quinolinone-7-yl	Ph	0 ± 0[c]	0 ± 0[c]	0 ± 0[c]
13c	Quinolinone-7-yl	4-F-C_6H_4	21.57 9.14[c]	17.34 ± 2.75[c]	0 ± 0[c]
13d	Quinolinone-7-yl	4-MeO-C_6H_4	22.02 ± 0.63[c]	0 ± 0[c]	0 ± 0[c]
13e	Quinolinone-7-yl	4-Ph-C_6H_4	75.27 ± 2.34[c]	82.92 ± 1.21[b]	82.07 ± 1.70[b]
14a	Quinolinone-8-yl	Naph	89.04 ± 1.30	0 ± 0[c]	87.53 ± 0.44[a]
14b	Quinolinone-8-yl	Ph	89.50 ± 1.00	2.11 ± 0.92[c]	87.68 ± 1.22
14c	Quinolinone-8-yl	4-F-C_6H_4	86.94 ± 1.34[a]	7.02 ± 3.74[c]	0 ± 0[c]
14d	Quinolinone-8-yl	4-MeO-C_6H_4	89.19 ± 0.55[a]	83.97 ± 0.84[b]	86.19 ± 1.03[a]
14e	Quinolinone-8-yl	4-Ph-C_6H_4	87.37 ± 1.57[a]	4.58 ± 5.74[c]	88.08 ± 0.45
15	Quinolinone-6-yl	Me	2.05 ± 1.67[c]	1.83 ± 0.75[c]	0 ± 0[c]
16	Quinolinone-7-yl	Me	87.60 ± 0.36[c]	0 ± 0[c]	86.60 ± 1.60
17	Quinolinone-8-yl	Me	87.12 ± 0.86[b]	83.14 ± 1.11[b]	83.40 ± 1.27[c]
Aspirin			91.70 ± 1.40	0 ± 0	88.80 ± 1.50

[a] Significantly different from control value at $p < 0.05$
[b] Significantly different from control value at $p < 0.01$
[c] Significantly different from control value at $p < 0.001$

Table 2. IC_{50} values (μM) of oxime-containing 3,4-dihydroquinolin-2(1*H*)-one derivatives on the platelet aggregation induced by thrombin (Thr), arachidonic acid (AA), and U46619



Compd.	Substituents		IC_{50}		
	Aryl	R	Thr (0.1 U/mL)	AA (200 μM)	U46619 (2 μM)
12a	Quinolinone-6-yl	Naph	-	8.63 ± 0.13	-
12b	Quinolinone-6-yl	Ph	29.97 ± 0.73	4.47 ± 0.34	14.15 ± 1.49
12c	Quinolinone-6-yl	4-F-C_6H_4	26.78 ± 0.88	4.49 ± 0.21	10.85 ± 1.67
12d	Quinolinone-6-yl	4-MeO-C_6H_4	28.35 ± 0.56	4.25 ± 0.13	6.70 ± 1.91
12e	Quinolinone-6-yl	4-Ph-C_6H_4	-	4.34 ± 0.14	-
13a	Quinolinone-7-yl	Naph	-	4.07 ± 0.04	-
13b	Quinolinone-7-yl	Ph	29.88 ± 0.63	4.13 ± 0.13	11.35 ± 1.13
13c	Quinolinone-7-yl	4-F-C_6H_4	46.42 ± 8.98	41.22 ± 2.30	3.51 ± 0.21
13d	Quinolinone-7-yl	4-MeO-C_6H_4	46.34 ± 9.04	6.24 ± 0.16	9.22 ± 2.42
13e	Quinolinone-7-yl	4-Ph-C_6H_4	-	-	-
14a	Quinolinone-8-yl	Naph	-	29.44 ± 0.12	-
14b	Quinolinone-8-yl	Ph	-	31.09 ± 0.28	-
14c	Quinolinone-8-yl	4-F-C_6H_4	-	34.03 ± 2.38	30.19 ± 0.68
14d	Quinolinone-8-yl	4-MeO-C_6H_4	-	-	-
14e	Quinolinone-8-yl	4-Ph-C_6H_4	-	33.54 ± 2.15	-
15	Quinolinone-6-yl	Me	31.17 ± 0.18	1.85 ± 0.40	10.37 ± 2.54
16	Quinolinone-7-yl	Me	-	28.18 ± 0.56	-
17	Quinolinone-8-yl	Me	-	-	-

lin-2(1*H*)-one-7-yl > 3,4-dihydroquinolin-2(1*H*)-one-8-yl. Among them, (*E*)-6-[2-(hydroxyimino)propoxy]-3,4-dihydroquinolin-2(1*H*)-one (**15**) was the most potent with an IC_{50} value of 1.85 μM against the platelet aggregation induced by AA.

2. Antiproliferative activity

All compounds were evaluated *in vitro* against a 5-cell line panel consisting of NPC-TW01, NCI-H661, A549, MKN45, and Jurkat. Results from Table 3 indicated that these compounds were either weekly active or inactive. For the C-6 substituted 3,4-dihydroquinolin-2(1*H*)-one derivatives, (*Z*)-6-[2-(hydroxyimino)-2-(naphthalen-2-yl)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**12a**) was the most active against the growth of NPC-TW01 and A549 with an GI_{50} value of 8.48 and 7.54 μM, respectively. For the C-7 substituted 3,4-dihydroquinolin-2(1*H*)-one derivatives, (*Z*)-7-[2-(hydroxyimino)-2-(naphthalen-2-yl)-ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**13a**) was the most active against the growth of NPC-TW01, NCI-H661, MKN45, and Jurkat with an GI_{50} value of 7.63, 7.34, 9.40, and 6.36 μM, respectively. The C-8 substituted 3,4-dihydroquinolin-2(1*H*)-one derivatives were inactive with an GI_{50} value of greater than 10.67 μM in each case.

EXPERIMENTAL SECTION

1. General

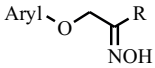
Melting points were determined on a Electrothermal IA9100 melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian-Unity-400 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co. The elemental analyses were performed in the Instrument Center of National Science Council at National Cheng-Kung University using Heraeus CHN-O Rapid EA, and all values are within ± 0.4% of the theoretical compositions.

2. Syntheses

6-[2-(Naphthalen-2-yl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (6a)

6-Hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**3**, 0.82

Table 3. Antiproliferative activity of oxime-containing 3,4-dihydroquinolin-2(1*H*)-one derivatives



Compd.	Substituents		GI_{50} (μM)[a,b]				
	Aryl	R	NPC-TW01	NCI-H661	A549	MKN45	Jurkat
12a	Quinolinone-6-yl	Naph	8.48	16.14	7.54	14.65	18.14
12b	Quinolinone-6-yl	Ph	25.92	25.92	19.14	11.80	28.34
12c	Quinolinone-6-yl	4-F-C_6H_4	24.24	24.24	22.85	19.39	31.74
12d	Quinolinone-6-yl	4-MeO-C_6H_4	23.19	23.19	20.33	11.49	27.40
12e	Quinolinone-6-yl	4-Ph-C_6H_4	8.12	8.12	17.63	11.65	24.70
13a	Quinolinone-7-yl	Naph	7.63	7.34	11.56	9.40	6.36
13b	Quinolinone-7-yl	Ph	31.79	40.39	17.04	9.55	27.25
13c	Quinolinone-7-yl	4-F-C_6H_4	29.76	23.97	17.45	9.72	26.31
13d	Quinolinone-7-yl	4-MeO-C_6H_4	27.98	18.28	28.45	16.67	28.78
13e	Quinolinone-7-yl	4-Ph-C_6H_4	25.19	8.05	9.47	11.53	30.29
14a	Quinolinone-8-yl	Naph	28.83	30.86	29.30	17.41	29.00
14b	Quinolinone-8-yl	Ph	32.29	24.25	31.67	16.31	28.19
14c	Quinolinone-8-yl	4-F-C_6H_4	n.d	n.d.	n.d.	n.d.	n.d.
14d	Quinolinone-8-yl	4-MeO-C_6H_4	30.41	21.19	33.53	10.67	27.72
14e	Quinolinone-8-yl	4-Ph-C_6H_4	27.83	21.30	31.48	18.78	22.72
15	Quinolinone-6-yl	Me	33.03	25.17	28.34	20.34	29.88
16	Quinolinone-7-yl	Me	32.08	8.27	25.09	13.86	24.51
17	Quinolinone-8-yl	Me	34.93	35.28	36.68	22.21	31.73

[a] The concentration that inhibited the growth of 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%.

[b] These cell lines are: NPC-TW01 (Nasopharygeal carcinoma); NCI-H661 and A549 (Lung carcinoma); MKN45 (Gastric cancer); Jurkat (Leukemia).

n.d: not determined.

g, 5 mmol), K_2CO_3 (0.75 g, 5.5 mmol), and dry DMF (50 mL) were stirred at r.t. for 30 min. To this soln. was added 2-(bromoacetyl)naphthalene (1.37 g, 5.5 mmol) in dry DMF (10 mL) in one portion. The resulting mixture was stirred at r.t. for 24 h (TLC monitoring) and then poured into ice-water (100 mL). The white solid thus obtained was collected and crystallized from Et_2O to give **6a** (1.50 g, 91%). Mp 194-195 °C. ^{1}H-NMR (DMSO-d_6): 2.40-2.43 (m, 2H, H-C(3)), 2.77-2.81 (m, 2H, H-C(4)), 5.64 (s, 2H, OCH_2), 6.49 (d, 1H, J = 2.4 Hz, H-C(5)), 6.57 (dd, 1H, J = 8.4, 2.4 Hz, H-C(7)), 7.06 (d, 1H, J = 8.4 Hz, H-C(8)), 7.64-7.73 (m, 2H, arom. H), 7.99-8.06 (m, 3H, arom. H), 8.08-8.15 (m, 1H, arom. H), 8.76 (s, 1H, arom. H), 9.96 (s, 1H, NH). ^{13}C-NMR (DMSO): 24.68 (C(4)), 31.38 (C(3)), 70.92 (CH_2O), 102.76, 108.18, 116.77, 123.98, 127.83, 128.47, 129.02, 129.16, 129.61, 130.26, 130.51, 132.36, 132.80, 135.99, 139.90, 157.90, 170.94 (C(2)), 195.24 (C=O). *Anal.* Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 75.91; H, 5.21; N, 4.17.

7-[2-(Naphthalen-2-yl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (7a)

From 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**4**) as described for **6a**: 88% yield. Mp 184-185 °C. ^{1}H-NMR (DMSO-d_6): 2.39-2.42 (m, 2H, H-C(3)), 2.81-2.85 (m, 2H, H-C(4)), 5.63 (s, 2H, OCH_2), 6.77 (d, 1H, J = 8.4 Hz, H-C(5)), 6.81 (dd, 1H, J = 8.4, 2.4 Hz, H-C(6)), 6.89 (d, 1H, J = 2.4 Hz, H-C(8)), 7.64-7.73 (m, 2H, arom. H), 7.99-8.06 (m, 3H, arom. H), 8.08-8.15 (m, 1H, arom. H), 8.76 (s, 1H, arom. H), 9.92 (s, 1H, NH). ^{13}C-NMR (DMSO): 25.76 (C(4)), 31.01 (C(3)), 71.20 (CH_2O), 113.93, 114.88, 116.40, 124.01, 125.52, 127.80, 128.47, 129.13, 129.57, 130.26, 130.49, 132.42, 132.80, 135.97, 139.95, 153.88, 170.46 (C(2)), 195.36 (C=O). *Anal.* Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 75.83; H, 5.18; N, 4.12.

8-[2-(Naphthalen-2-yl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (8a)

From 8-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**5**)

as described for **6a**: 85% yield. Mp 159-160 °C. ^{1}H-NMR (DMSO-d_6): 2.47-2.51 (m, 2H, H-C(3)), 2.88-2.92 (m, 2H, H-C(4)), 5.73 (s, 2H, OCH_2), 6.82-6.91 (m, 3H, arom. H), 7.64-7.72 (m, 2H, arom. H), 7.96-8.05 (m, 3H, arom. H), 8.07-8.15 (m, 1H, arom. H), 8.78 (s, 1H, arom. H), 9.01 (s, 1H, NH). ^{13}C-NMR (DMSO): 24.85 (C(4)), 30.45 (C(3)), 71.77 (CH_2O), 112.04, 115.43, 120.63, 121.35, 122.11, 123.25, 125.99, 127.13, 127.78, 128.49, 128.96, 129.61, 130.03, 135.33, 139.56, 144.81, 169.59 (C(2)), 194.93 (C=O). *Anal.* Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 75.85; H, 5.17; N, 4.14.

(*Z*)-6-[2-(Hydroxyimino)-2-(naphthalen-2-yl)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (12a)

To a soln. of **6a** (0.33 g, 1 mmol) in EtOH (20 mL) was added a soln. 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; CH_2Cl_2/AcOEt 2:1) and recrystallized from CH_2Cl_2 to give **12a** (0.25 g, 72%). Mp 230-231 °C. ^{1}H-NMR (DMSO-d_6): 2.36-2.40 (m, 2H, H-C(3)), 2.78-2.81 (m, 2H, H-C(4)), 5.29 (s, 2H, OCH_2), 6.74 (d, 1H, J = 8.4 Hz, H-C(8)), 6.77 (dd, 1H, J = 8.4, 2.4 Hz, H-C(7)), 6.84 (d, 1H, J = 2.4 Hz, H-C(5)), 7.52-7.54 (m, 2H, arom. H), 7.84-7.86 (m, 1H, arom. H), 7.89-7.96 (m, 3H, arom. H), 8.17 (m, 1H, arom. H), 9.91 (s, 1H, NH), 11.98 (s, 1H, NOH). ^{13}C-NMR (DMSO): 25.73 (C(4)), 30.94 (C(3)), 59.50 (CH_2O), 113.44, 114.84, 116.43, 124.40, 125.64, 126.72, 127.15, 127.35, 128.20, 128.42, 129.05, 132.51, 132.82, 133.34, 133,67, 153.59, 153.82, 170.53 (C(2)). *Anal.* Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.53; H, 5.23; N, 8.08.

The same procedure was applied to convert **7a** to **13a**; **8a** to **14a**; **6b-f** to **12b-f**; **7b-f** to **13b-f**; **8b-f** to **14b-f**; and **9-11** to **15-17**, respectively.

(*Z*)-6-[2-(Hydroxyimino)-2-phenylethoxy]-3,4-dihydroquinolin-2(1*H*)-one (12b)

Yield: 71%; Mp 229-230 °C. ^{1}H-NMR (DMSO-d_6): 2.37-2.40 (m, 2H, H-C(3)), 2.78-2.82 (m, 2H, H-C(4)), 5.17 (s, 2H, OCH_2), 6.74 (d, 1H, J = 8.4 Hz, H-C(8)), 6.77 (dd, 1H, J = 8.4, 2.4 Hz, H-C(7)), 6.80 (d, 1H, J = 2.4 Hz, H-C(5)), 7.37-7.39 (m, 3H, arom. H), 7.63-7.65 (m, 2H, arom. H), 9.91 (s, 1H, NH), 11.85 (s, 1H, NOH). ^{13}C-NMR (DMSO): 24.96 (C(4)), 30.18 (C(3)), 58.82 (CH_2O), 112.61, 114.01, 115.61, 124.80, 126.24, 128.18, 128.74, 132.06, 134.27, 152.83, 152.98, 169.65 (C(2)). *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.71; H, 5.40; N, 9.39.

(*Z*)-6-[2-(4-Fluorophenyl)-2-(hydroxyimino)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (12c)

Yield: 73%; Mp 233-234 °C. ^{1}H-NMR (DMSO-d_6): 2.34-2.38 (m, 2H, H-C(3)), 2.76-2.79 (m, 2H, H-C(4)), 5.15 (s, 2H, OCH_2), 6.68 (d, 1H, J = 8.0 Hz, H-C(8)), 6.73 (dd, 1H, J = 8.0, 2.0 Hz, H-C(7)), 6.78 (d, 1H, J = 2.0 Hz, H-C(5)), 7.17-7.23 (m, 2H, arom. H), 7.63-7.68 (m, 2H, arom. H), 9.90 (s, 1H, NH), 11.86 (s, 1H, NOH). ^{13}C-NMR (DMSO) δ: 25.74 (C(4)), 30.96 (C(3)), 59.67 (CH_2O), 113.43, 114.81, 115.80, 116.02, 116.41, 125.62, 129.19, 129.28, 131.47, 131.50, 132.90, 152.89, 153,65, 161.92, 164.36, 170.46 (C(2)). *Anal.* Calcd for $C_{17}H_{15}FN_2O_3 \cdot 0.25$ H_2O: C, 64.09; H, 4.91; N, 8.79. Found: C, 64.28; H, 4.93; N, 8.74.

(*Z*)-6-[2-(Hydroxyimino)-2-(4-methoxyphenyl)ethoxy]-quinolin-2(1*H*)-one (12d)

Yield: 71%; Mp 214-215 °C. ^{1}H-NMR (DMSO-d_6): 2.34-2.38 (m, 2H, H-C(3)), 2.76-2.79 (m, 2H, 2H-C(4)), 3.74 (s, 3H, MeO), 5.11 (s, 2H, OCH_2), 6.68 (d, 1H, J = 8.0 Hz, H-C(8)), 6.71 (dd, 1H, J = 8.0, 2.0 Hz, H-C(7)), 6.78 (d, 1H, J = 2.0 Hz, H-C(5)), 6.90-6.96 (m, 2H, arom. H), 7.55-7.69 (m, 2H, arom. H), 9.90 (s, 1H, NH) 11.63 (s, 1H, NOH). ^{13}C-NMR (DMSO): 24.65 (C(4)), 31.33 (C(3)), 55.81 (MeO), 59.38 (CH_2O), 102.78, 107.54, 114.41, 116.91, 127.30, 128.40, 129.12, 139.88, 153.09, 157.84, 160.46, 171.06 (C(2)). *Anal.* Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.21; H, 5.55; N, 8.57.

(*Z*)-6-[2-(Biphenyl-4-yl)-2-(hydroxyimino)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (12e)

Yield: 67%; Mp 240-241 °C. ^{1}H-NMR (DMSO-d_6): 2.35-2.39 (m, 2H, H-C(3)), 2.79-2.82 (m, 2H, H-C(4)), 5.32 (s, 2H, OCH_2), 6.77 (d, 1H, J = 8.0 Hz, H-C(8)), 6.88 (dd, 1H, J = 8.0, 2.0 Hz, H-C(7)), 6.97 (d, 1H, J = 2.0 Hz, H-C(5)), 7.35-7.48 (m, 3H, arom. H), 7.65-7.69 (m, 4H, arom. H), 7.82-7.84 (m, 2H, arom. H), 8.77 (s, 1H, NH), 12.02 (s, 1H, NOH). ^{13}C-NMR (DMSO): 24.76 (C(4)), 30.34 (C(3)), 59.75 (CH_2O), 110.77, 120.48, 122.16, 124.60, 126.48, 126.62, 127.09, 127.12, 127.71, 128.99, 133.03, 139.51, 140.47, 144.38, 152.64, 169.61 (C(2)). *Anal.* Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.96; H, 5.49; N, 7.49.

(*Z*)-7-[2-(Hydroxyimino)-2-(naphthalen-2-yl)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (13a)

Yield: 72%; Mp 198-199 °C. ^{1}H-NMR (DMSO-d_6):

2.37-2.41 (m, 2H, H-C(3)), 2.75-2.78 (m, 2H, 2H-C(4)), 5.29 (s, 2H, OCH_2), 6.43 (d, 1H, J = 2.4 Hz, H-C(8)), 6.58 (dd, 1H, J = 8.4, 2.4 Hz, H-C(6)), 7.05 (d, 1H, J = 8.4 Hz, H-C(5)), 7.52-7.55 (m, 2H, arom. H), 7.83-7.96 (m, 4H, arom. H), 8.16 (m, 1H, arom. H), 9.97 (s, 1H, NH), 11.98 (s, 1H, NOH). ^{13}C-NMR (DMSO): 23.89 (C(4)), 30.56 (C(3)), 58.58 (CH_2O), 102.04, 106.86, 116.17, 123.64, 125.96, 126.35, 126.56, 127.41, 127.62, 128.26, 128.33, 131.63, 132.55, 132.89, 139.16, 152.72, 157.10, 170.15 (C(2)). *Anal.* Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.43; H, 5.18; N, 7.96.

(*Z*)-7-[2-(Hydroxyimino)-2-phenylethoxy]-3,4-dihydroquinolin-2(1*H*)-one (13b)

Yield: 71%; Mp 167-168 °C. ^{1}H-NMR (DMSO-d_6): 2.38-2.42 (m, 2H, H-C(3)), 2.75-2.79 (m, 2H, H-C(4)), 5.17 (s, 2H, OCH_2), 6.40 (d, 1H, J = 2.8 Hz, H-C(8)), 6.53 (dd, 1H, J = 8.4, 2.8 Hz, H-C(6)), 7.04 (d, 1H, J = 8.4 Hz, H-C(5)), 7.37-7.40 (m, 3H, arom. H), 7.62-7.64 (m, 2H, arom. H), 9.98 (s, 1H, NH), 11.85 (s, 1H, NOH). ^{13}C-NMR (DMSO): 23.89 (C(4)), 30.56 (C(3)), 58.70 (CH_2O), 102.01, 106.78, 116.16, 126.28, 128.19, 128.33, 128.76, 134.18, 139.16, 152.79, 157.07, 170.18 (C(2)). *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.07; H, 5.46; N, 9.46.

(*Z*)-7-[2-(4-Fluorophenyl)-2-(hydroxyimino)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (13c)

Yield: 73%; Mp 172-173 °C. ^{1}H-NMR (DMSO-d_6): 2.38-2.42 (m, 2H, H-C(3)), 2.75-2.79 (m, 2H, 2H-C(4)), 5.18 (s, 2H, OCH_2), 6.40 (d, 1H, J = 2.4 Hz, H-C(8)), 6.52 (dd, 1H, J = 8.4, 2.4 Hz, H-C(6)), 7.04 (d, 1H, J = 8.4 Hz, H-C(5)), 7.20-7.24 (m, 2H, arom. H), 7.65-7.69 (m, 2H, arom. H), 9.98 (s, 1H, NH), 11.87 (s, 1H, NOH). ^{13}C-NMR (DMSO): 23.89 (C(4)), 30.56 (C(3)), 58.75 (CH_2O), 102.01, 106.81, 115.02, 115.24, 116.22, 128.33, 128.45, 128.52, 130.59, 130.62, 139.17, 152.06, 156.95, 161.13, 163.58, 170.17 (C(2)). *Anal.* Calcd for $C_{17}H_{15}FN_2O_3$: C, 64.96; H, 4.81; N, 8.91. Found: C, 65.04; H, 4.95; N, 9.21.

(*Z*)-7-[2-(Hydroxyimino)-2-(4-methoxyphenyl)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (13d)

Yield: 74%; Mp 165-166 °C. ^{1}H-NMR (DMSO-d_6): 2.35-2.39 (m, 2H, H-C(3)), 2.72-2.76 (m, 2H, H-C(4)), 3.74 (s, 3H, MeO), 5.11 (s, 2H, OCH_2), 6.38 (d, 1H, J = 2.8 Hz, H-C(8)), 6.51 (dd, 1H, J = 8.4, 2.8 Hz, H-C(6)), 6.90-6.92 (m, 2H, arom. H), 7.02 (d, 1H, J = 8.4 Hz, H-C(5)), 7.53-7.56 (m, 2H, arom. H), 9.97 (s, 1H, NH), 11.63 (s, 1H, NOH). ^{13}C-NMR (DMSO): 24.65 (C(4)), 31.33 (C(3)), 55.81 (MeO), 59.38 (CH_2O), 102.78, 107.54, 114.41, 116.91, 127.30, 128.40, 129.12, 139.88, 153.09, 157.84, 160.46, 171.06 (C(2)). *Anal.* Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.16; H, 5.67; N, 8.57.

(*Z*)-7-[2-(Biphenyl-4-yl)-2-(hydroxyimino)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (13e)

Yield: 73%; Mp 190-191 °C. ^{1}H-NMR (DMSO-d_6): 2.38-2.42 (m, 2H, H-C(3)), 2.76-2.79 (m, 2H, H-C(4)), 5.21 (s, 2H, OCH_2), 6.44 (d, 1H, J = 2.8 Hz, H-C(8)), 6.57 (dd, 1H, J = 8.4, 2.8 Hz, H-C(6)), 7.06 (d, 1H, J = 8.4 Hz, H-C(5)), 7.36-7.40 (m, 1H, arom. H), 7.46-7.49 (m, 2H, arom. H), 7.69-7.75 (m, 6H, arom. H), 9.99 (s, 1H, NH), 11.92 (s, 1H, NOH). ^{13}C-NMR (DMSO): 24.68 (C(4)), 31.35 (C(3)), 59.41 (CH_2O), 102.83, 107.58, 116.99, 127.22, 127.29, 127.59, 128.39, 129.14, 129.68, 134.02, 139.97, 140.13, 141.12, 153.22, 157.87, 170.97 (C(2)). *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.15; H, 5.40; N, 7.52.

(*Z*)-8-[2-(Hydroxyimino)-2-(naphthalen-2-yl)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (14a)

Yield: 69%; Mp 185-186 °C. ^{1}H-NMR (DMSO-d_6): 2.33-2.36 (m, 2H, H-C(3)), 2.77-2.80 (m, 2H, H-C(4)), 5.41 (s, 2H, OCH_2), 6.75-6.76 (m, 1H, arom. H), 6.86-6.89 (m, 1H, arom. H), 6.99-7.01 (m, 1H, arom. H), 7.51-7.53 (m, 2H, arom. H), 7.86-7.92 (m, 3H, arom. H), 7.98-8.00 (m, 1H, arom. H), 8.34 (m, 1H, arom. H), 8.84 (s, 1H, NH), 12.10 (s, 1H, NOH). ^{13}C-NMR (DMSO): 25.39 (C(4)), 30.97 (C(3)), 60.28 (CH_2O), 111.33, 121.11, 122.81, 124.30, 125.23, 127.03, 127.04, 127.32, 127.76, 128.13, 128.29, 129.15, 132.01, 133.43, 133,66, 144.99, 153.47, 170.29 (C(2)). *Anal.* Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.63; H, 5.21; N, 8.05.

(*Z*)-8-[2-(Hydroxyimino)-2-phenylethoxy]-3,4-dihydroquinolin-2(1*H*)-one (14b)

Yield: 72%; Mp 146-147 °C. ^{1}H-NMR (DMSO-d_6): 2.37-2.41 (m, 2H, H-C(3)), 2.79-2.83 (m, 2H, H-C(4)), 5.28 (s, 2H, OCH_2), 6.76-6.96 (m, 3H, arom. H), 7.35-7.38 (m, 3H, arom. H), 7.72-7.74 (m, 2H, arom. H), 8.66 (s, 1H, NH), 11.95 (s, 1H, NOH). ^{13}C-NMR (DMSO): 24.66 (C(4)), 30.24 (C(3)), 59.72 (CH_2O), 110.67, 120.37, 122.07, 124.46, 126.44, 126.98, 128.16, 128.82, 133.87, 144.25, 152.89, 169.50 (C(2)). *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.20; H, 5.48; N, 9.47.

(*Z*)-8-[2-(4-Fluorophenyl)-2-(hydroxyimino)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (14c)

Yield: 70%; Mp 166-167 °C. ^{1}H-NMR (DMSO-d_6):

2.37-2.41 (m, 2H, H-C(3)), 2.80-2.83 (m, 2H, 2H-C(4)), 5.29 (s, 2H, OCH_2), 6.76-6.78 (m, 1H, arom. H), 6.84-6.93 (m, 2H, arom. H), 7.16-7.21 (m, 2H, arom. H), 7.76-7.79 (m, 2H, arom. H), 8.75 (s, 1H, NH), 11.98 (s, 1H, NOH). ^{13}C-NMR (DMSO): 25.40 (C(4)), 30.99 (C(3)), 60.40 (CH_2O), 111.34, 115.70, 115.91, 121.16, 122.83, 125.26, 127.71, 129.38, 129.47, 131.02, 131.05, 144.91, 152.89, 161.93, 164.38, 170.35 (C(2)). *Anal.* Calcd for $C_{17}H_{15}FN_2O_3$: C, 64.96; H, 4.81; N, 8.91. Found: C, 64.69; H, 5.00; N, 9.13.

(*Z*)-8-[2-(Hydroxyimino)-2-(4-methoxyphenyl)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (14d)

Yield: 67%; Mp 152-153 °C. ^{1}H-NMR (DMSO-d_6): 2.35-2.39 (m, 2H, H-C(3)), 2.77-2.81 (m, 2H, H-C(4)), 3.73 (s, 3H, MeO), 5.23 (s, 2H, OCH_2), 6.73-6.93 (m, 5H, arom. H), 7.64-7.66 (m, 2H, arom. H), 8.67 (s, 1H, NH), 11.74 (s, 1H, NOH). ^{13}C-NMR (DMSO) δ: 25.40 (C(4)), 30.99 (C(3)), 55.80 (MeO), 60.37 (CH_2O), 111.36, 114.33, 121.08, 122.84, 125.20, 127.68, 128.58, 131.25, 145.01, 153.17, 160.48, 170.33 (C(2)). *Anal.* Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.20; H, 5.83; N, 8.46.

(*Z*)-8-[2-(Biphenyl-4-yl)-2-(hydroxyimino)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (14e)

Yield: 67%; Mp 200-20 °C. ^{1}H-NMR (DMSO-d_6): 2.36-2.40 (m, 2H, H-C(3)), 2.79-2.83 (m, 2H, H-C(4)), 5.33 (s, 2H, OCH_2), 6.77-6.79 (m, 1H, arom. H), 6.87-6.90 (m, 1H, arom. H), 6.96-6.98 (m, 1H, arom. H), 7.36-7.40 (m, 1H, arom. H), 7.45-7.49 (m, 2H, arom. H), 7.65-7.69 (m, 4H, arom. H), 7.82-7.85 (m, 2H, arom. H), 8.76 (s, 1H, NH), 12.04 (s, 1H, NOH). ^{13}C-NMR (DMSO) δ: 25.40 (C(4)), 30.97 (C(3)), 60.42 (CH_2O), 111.43, 121.16, 122.88, 125.27, 127.14, 127.27, 127.72, 127.76, 128.38, 129.68, 133.65, 140.15, 141.15, 145.02, 153.38, 170.38 (C(2)). *Anal.* Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.83; H, 5.42; N, 7.48.

(*E*)-6-[2-(Hydroxyimino)propoxy]-3,4-dihydroquinolin-2(1*H*)-one (15)

Yield: 68%; Mp 200-201 °C. ^{1}H-NMR (DMSO-d_6): 1.82 (s, 3H, Me), 2.38-2.42 (m, 2H, H-C(3)), 2.80-2.84 (m, 2H, H-C(4)), 4.48 (s, 2H, OCH_2), 6.72 (d, 1H, J = 8.4 Hz, H-C(8)), 6.78 (dd, 1H, J = 8.4, 2.4 Hz, H-C(7)), 6.83 (d, 1H, J = 2.4 Hz, H-C(5)), 9.92 (s, 1H, NH), 10.90 (s, 1H, NOH). ^{13}C-NMR (DMSO) δ: 11.37 (Me), 24.97 (C(4)), 30.20 (C(3)), 69.74 (CH_2O), 113.35, 114.46, 115.61, 124.74, 132.06, 152.02, 153.17, 169.66 (C(2)). *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.54; H, 6.05; N, 11.98.

(*E*)-7-[2-(Hydroxyimino)propoxy]-3,4-dihydroquinolin-2(1*H*)-one (16)

Yield: 73%; Mp 215-216 °C. ^{1}H-NMR (DMSO-d_6): 1.82 (s, 3H, Me), 2.39-2.43 (m, 2H, H-C(3)), 2.76-2.80 (m, 2H, H-C(4)), 4.48 (s, 2H, OCH_2), 6.46 (d, 1H, J = 2.4 Hz, H-C(8)), 6.54 (dd, 1H, J = 8.4, 2.4 Hz, H-C(6)), 7.05 (d, 1H, J = 8.4 Hz, H-C(5)), 10.00 (s, 1H, NH), 10.91 (s, 1H, NOH). ^{13}C-NMR (DMSO): 11.36 (Me), 23.90 (C(4)), 30.59 (C(3)), 69.38 (CH_2O), 102.20, 107.60, 116.08, 128.27, 139.13, 151.81, 157.23, 170.18 (C(2)). *Anal.* Calcd for $C_{12}H_{14}N_2O_4$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.35; H, 6.04; N, 11.88.

(*E*)-8-[2-(Hydroxyimino)propoxy]-3,4-dihydroquinolin-2(1*H*)-one (17)

Yield: 68%; Mp 147-148 °C. ^{1}H-NMR (DMSO-d_6): 1.85 (s, 3H, Me), 2.41-2.44 (m, 2H, H-C(3)), 2.82-2.86 (m, 2H, H-C(4)), 4.55 (s, 2H, OCH_2), 6.76-6.78 (m, 1H, arom. H), 6.83-6.89 (m, 2H, arom. H), 9.10 (s, 1H, NH), 10.92 (s, 1H, NOH). ^{13}C-NMR (DMSO): 12.23 (Me), 25.56 (C(4)), 31.19 (C(3)), 70.71 (CH_2O), 111.66, 120.87, 122.79, 125.48, 127.75, 145.44, 152.90, 170.54 (C(2)). *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.55; H, 6.20; N, 11.94.

3. Antiproliferative Activity

1. *Cell Lines* - Human non-small cell lung carcinoma (NCI-H661, A549), gastric cancer (MKN45), and T-cell leukemia (Jurkat) was purchased from American Type Culture Collection (ATCC; Rockville, MD). Nasopharyngeal carcinoma (NPC-TW01) was purchased from Bioresource Collection and Research Center (BCRC, Taiwan). All the tumor cell lines were maintained in either RPMI-1640 or Modified essential medium (MEM) supplied with 10% fetal bovine serum at 37 °C in a humidified atmosphere of 5% CO_2/95% air in the absence of antibiotics.

2. *Growth Inhibition Assay* - Logarithmic phase cells were seeded in a 96-well plate and incubated overnight prior to addition of the designated compounds. After incubation with different concentrations of the tested compounds for 72 h, cells were incubated with MEM containing 0.4 mg/mL MTT for 2 h. The conversion of MTT to formazan by metabolically viable cells was measured by the absorbance at 570 nm in a 96-well microtiter plate reader. The percentage conversion by mock-treated control cells was used to evaluate the effect of the chemicals on cell

growth and to determine the concentration that inhibited 50% of growth (GI_{50}).

4. Antiplatelet Evaluation

Reagents: Collagen (type 1, bovine *Achilles* tendon) obtained from *Sigma Chem. Co*. was homogenized in 25 mM AcOH and stored (1 mg/mL) at -70°. Arachidonic acid (AA), EDTA, and bovine serum albumin were purchased from *Sigma Chem. Co*. and dissolved in $CHCl_3$.

Platelet aggregation: Blood was collected from the rabbit marginal ear vein, anticoagulated with EDTA (6 mM) and centrifuged for 10 min at 90 × g and at r.t. Platelet suspensions were prepared from the plasma according to the washing procedures previously described.[26] Platelet numbers were determined with a Coulter counter (Model ZM) and adjusted to 4.5×10^8 platelets/mL. The platelet pellets were suspended in *Tyrode's* solution of the following composition (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 bovine serum albumin (0.35%). The platelet suspension was stirred at 1200 rpm and the aggregation was measured at 37° by the turbidimetric method as described by O'Brien[27] using a *Chrono-Log Lumi-aggregometer.* To eliminate solvent effects on aggregation, the final concentration of dimethylsulfoxide (DMSO) was fixed at 0.5%. Percentage of aggregation was calculated using the absorbance of a platelet suspension as 0% aggregation and the absorbance of *Tyrode's* solution as 100% aggregation.

CONCLUSION

A number of oxime-containing 3,4-dihydroquinolin-2(1*H*)-one derivatives were synthesized and evaluated for their antiplatelet and antiproliferative activities. The preliminary results indicated that (*Z*)-7-[2-(4-fluorophenyl)-2-(hydroxyimino)ethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**13c**) was the most active against U46619 induced platelet aggregation with an IC_{50} value of 3.51 μM while (*E*)-6-[2-(hydroxyimino)propoxy]-3,4-dihydroquinolin-2(1*H*)-one (**15**) was the most active against AA-induced aggregation with an IC_{50} value of 1.85 μM. Both **13c** and **15** exhibited very weak antiproliferative effects implied their highly potential to be developed as antiplatelet agents. Further structural optimization is on-going.

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