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Short communication

Synthesis and vasorelaxing evaluation of α-methylidene-γ-butyrolactone bearing quinolin-2(1*H*)-one and 3,4-dihydroquinolin-2(1*H*)-one derivatives

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Abstract – The main objective of this investigation was to explore the vasorelaxing structure–activity relationships of α-methylidene-γ-butyrolactone bearing quinolin-2(1*H*)-ones and their 3,4-dihydro derivatives. These target compounds were synthesised in two steps starting from aryl-OH which was treated with a bromomethyl ketone followed by a *Reformatsky*-type condensation. Quinolin-2(1*H*)-one α-methylidene-γ-butyrolactones exhibited less vasorelaxing activity than their 3,4-dihydro counterparts. Compounds with a methyl or a phenyl group at the C(γ) of the lactone were more vasorelaxant than the C(γ)-fluorophenyl derivatives in the 3,4-dihydroquinolin-2(1*H*)-one series. When comparing the positional isomers, α-methylidene-γ-butyrolactone substituted at the 7-position of the 3,4-dihydroquinolin-2(1*H*)-ones were more active than their 6-substituted counterparts, which in turn were more active than the 8-substituted derivatives. The vasorelaxing effect of these 3,4-dihydroquinolin-2(1*H*)-ones was proved to be dose dependent. Among them, 7-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenyfuran-2-yl)methoxy]-quinolin-2(1*H*)-one (**10b**) was the most potent with an IC_{50} of 9.2 μM on the KCl-induced vasoconstriction of pig coronary arteries. © 2001 Éditions scientifiques et médicales Elsevier SAS

vasorelaxant / α-methylidene-γ-butyrolactone / quinolin-2(1*H*)-one / 3,4-dihydroquinolin-2(1*H*)-one

1. Introduction

Since the discovery of carteolol as an β-adrenergic blocking agent, a vast number of quinolin-2(1*H*)-ones (carbostyril) and their 3,4-dihydro derivatives had been synthesised and proved to possess cardiovascular activities [1–15]. However, these cardiovascular activities of quinolin-2(1*H*)-one skeletons were influenced not only by the nature of the peripheral side chains but also by the anchoring position. For example, according to Nishi et al., the 6-substituted isomer exhibited the highest antiplatelet potency while the 7- and 8-substituted isomers were much less active when the side chains were maintained as $OCH_2CH_2CH_2$-COOEt, etc. in the 3,4-dihydroquinolin-2(1*H*)-one series [2–4]. They have also concluded that quinolin-2(1*H*)-ones possessed higher antiplatelet activity than that of their 3,4-dihydroquinolin-2(1*H*)-one counterparts [3–5]. Searching for novel positive inotropic quinolin-2(1*H*)-one drug candidates, Tominaga et al., revealed that a 6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-side chain substituted at the 6-position of the quinolin-2(1*H*)-one nucleus, exhibited the most potent positive inotropic effect among their positional isomers and both series of quinolin-2(1*H*)-ones and its 3,4-dihydro derivatives were active [6]. Although the 3,4-dihydroquinolin-2(1*H*)-ones exhibited less potent inotropic effect than that of their 3,4-dehydro counterparts, their lack of chronotropic side effect led to the discovery of a clinically useful drug, 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]quinolin-2(1*H*)-one (Vesnarinone), for the treatment of congestive heart failure. Later on, Fujioka et al. confirmed that the 6-substituted quinolin-2(1*H*)-ones exhibited the most potent positive inotropic effect but did not confirm that the 3,4-dihydroquinolin-2(1*H*)-one series was also active [10]. Over the past few years, we were particularly interested in synthesizing α-methylidene-γ-butyrolactones

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that were evaluated for their cardiovascular activities [12–20]. Our results demonstrated that quinolin-2(1*H*)-one α-methylidene-γ-butyrolactones **12a–d** were less active as antiplatelet agents than their 3,4-dihydro counterparts **10a–d**. Moreover, their inhibitory activities against arachidonic acid (AA)-induced platelet aggregation decrease in the order 7-substituted **10b–d** > 6-substituted **9b–d** > 8-substituted **11b–d** as shown in *table I* [14, 15]. We describe herein the preparation and vasorelaxing evaluation of certain α-methylidene-γ-butyrolactones bearing quinolin-2(1*H*)-ones and their 3,4-dihydro counterparts to classify further the structure–activity relationships in that series.

2. Chemistry

The preparation of the α-methylidene-γ-butyrolactones is illustrated in *figure 1*. Alkylation of 7-hydroxyquinolin-2(1*H*)-one (**4**) with bromoacetone under basic conditions provided 7-(2-oxopropoxy)quinolin-2(1*H*)-one (**8a**) which was then reacted with ethyl 2-(bromomethyl)acrylate and zinc powder in dry tetrahydrofuran (THF) to afford the Reformatsky product 7-[(2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxofuran-2-yl)methoxy]-quinolin-2(1*H*)-one (**12a**) in 53% overall yield. The same synthetic procedure was applied for the synthesis of **12d**. Synthesis of compounds **9a–d**, **10a–d**, **11a–d**, and **12b**, **c** were previously reported [12–15].

3. Biological investigation and discussion

The vasorelaxing effects of these compounds were represented as percentages of the reduction of the contraction height induced by 30 mM KCl (*table II*). Data are expressed as means ± S.E.M. The IC_{50} values represent the concentration at which 50% reduction in KCl-induced tone was observed. 6-[(2,3,4,5-Tetrahydro-2-methyl-4-methylene-5-oxofuran-2-yl)methoxy]-3,4-dihydroquinolin-2(1*H*)-one (**9a**) with an aliphatic Me substituent at the C(γ) lactone, and its Ph–C(γ) analogue (**9b**) possessed IC_{50} of 24.5 and 15.8 μM, respectively. The C(γ)-fluorophenyl substituted compound (**9c**) is less active while the C(γ)-biphenyl substituted one (**9d**) is completely inactive. The same pharmacological trend was observed for **12a–d** in which **12a** ($IC_{50} = 51.8$) and **12b** ($IC_{50} = 38.0$) were more active than **12c**, while **12d** was inactive. Results in *table II* also showed that C(γ)-biphenyl derivatives (**10d** and **11d**) were inactive whereas **10a**, **10b**, and **11a**

Table I. IC_{50} Values (μM) of α-methylidene-γ-butyrolactone derivatives on the platelet aggregation induced by AA and PAF.

	9a	**9b**	**9c**	**9d**	**10a**	**10b**	**10c**	**10d**
AA	1.64	0.57	0.60	3.29	2.31	0.23	0.28	1.91
PAF	13.3	2.33	1.83	6.23	51.4	6.13	3.54	11.4
	11a	**11b**	**11c**	**11d**	**12a**	**12b**	**12c**	**12d**
AA	35.7	4.39	3.75	7.73	3.90	0.50	0.40	2.40
PAF	>100	21.7	15.6	78.0	53.3	3.30	5.00	14.7

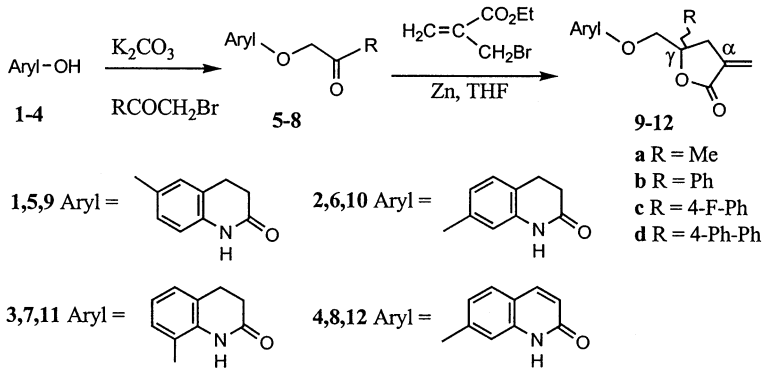

Figure 1.

Table II. Inhibitory effects of α-methylidene-γ-butyrolactone derivatives on KCl induced contraction of pig coronary arteries.

	3 μM	10 μM	30 μM	100 μM	IC_{50}
Control	101.5 ± 5.2	103.8 ± 8.9	94.1 ± 7.6	70.0 ± 7.1	–
9a	91.0 ± .5.0	65.0 ± 9.0 [a]	27.0 ± 12.0 [a]	0.0 ± 0.0 [a]	24.5 ± 6.8
9b	1100.0 ± 2.0	54.0 ± 8.0 [a]	7.0 ± 6.0 [a]	0.0 ± 0.0 [a]	15.8 ± 3.9
9c	–	–	–	56.3 ± 3.1	–
9d	–	–	–	69.0 ± 8.1	–
10a	78.0 ± 6.6 [b]	58.0 ± 10.9 [a]	30.3 ± 12.4 [a]	0.0 ± 0.0 [a]	23.2 ± 9.8
10b	85.0 ± 7.8 [c]	28.5 ± 6.9 [a]	0.0 ± 0.0 [a]	0.0 ± 0.0 [a]	9.2 ± 1.2
10c	86.7 ± 11.3	52.4 ± 11.6 [a]	12.7 ± 13.0 [a]	0.0 ± 0.0 [a]	16.8 ± 7.2
10d	–	–	–	79.5 ± 6.4	–
11a	119.0 ± 10.1 [c]	84.3 ± 5.6 [b]	53.8 ± 12.3 [a]	0.0 ± 0.0 [a]	44.9 ± 7.0
11b	–	–	–	69.8 ± 9.6	–
11c	–	–	–	20.5 ± 1.7 [a]	–
11d	–	–	–	72.5 ± 9.0	–
12a	102.0 ± 5.2	82.0 ± 5.0 [b]	55.0 ± 6.5 [a]	0.0 ± 0.0 [a]	51.8 ± 9.0
12b	92.0 ± 5.7	78.0 ± 3.5 [a]	43.0 ± 9.9 [a]	0.0 ± 0.0 [a]	38.0 ± 7.1
12c	–	–	–	41.7 ± 10.2 [a]	–
12d	–	–	–	86.8 ± 8.3	–
Nifedipine	–	–	–	0.0 ± 0.0 [a]	–

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

were active vasorelaxants with IC_{50} of 23.2, 9.2, and 44.9 μM, respectively. These results are interesting, since earlier studies indicated that these compounds also have antiplatelet and cytotoxic activities, with the γ-fluorophenyl lactones being better antiplatelet agents than their corresponding γ-methyl counterparts [12–20] while the γ-biphenyl lactones were the most cytotoxic [21–23].

According to previous results [6, 10], 3,4-dihydroquinolin-2(1*H*)-one containing compounds were weaker inotropic agents than their unsaturated counterparts. However, we found here the opposite results for vasorelaxing and antiplatelet activities. Quinolin-2(1*H*)-ones **12a**–**c** exhibited less vasorelaxing activity than their 3,4-dihydro counterparts **10a**–**c**. Previous reports have also indicated that the peripheral aminoalcohol or ester type of side chain at the 6-position of the 3,4-dihydroquinolin-2(1*H*)-one moiety resulted in the most potent inotropic and antiplatelet activities [1–11]. However, according to our results, α-methylidene-γ-butyrolactones substituted at the 7-position of the 3,4-dihydroquinolin-2(1*H*)-ones, e.g. **10a**–**c**, were more active than their 6-substituted counterparts **9a**–**c**, which in turn were more active than the 8-substituted derivatives **11a**–**c**.

The vasorelaxing effects of these 3,4-dihydroquinolin-2(1*H*)-ones proved to be dose dependent. Among them, 7-[(2,3,4,5-Tetrahydro-4-methylidene-5-oxo-2-phenyfuran-2-yl)methoxy]-quinolin-2(1*H*)-one (**10b**) was the most potent, being able to completely inhibit pig coronary arterial contraction induced by 30 mM KCl at a concentration of 30 μM. Preparation of its pure enantiomers for biological evaluation is currently ongoing.

4. Conclusions

Some α-methylidene-γ-butyrolactones bearing quinolin-2(1*H*)-ones and their 3,4-dihydro derivatives **10a**, **10b**, **11a**, **12a**, and **12b** exhibited a complete inhibition of the contraction height induced by 30 mM KCl at a concentration of 100 μM while others **9d**–**12d** at the same concentration, were inactive. Their vasorelaxing activities were influenced not only by the nature of the peripheral lactones but also by the position of the lactone chains attached to it. The quinolin-2(1*H*)-one or its fragment 3,4-dihydro equivalent may be considered as the key determinant of the pharmacophore, while the lactones characterized both by the γ-substituents and their anchoring positions, are believed to play a modulatory role with a preference for a methyl or a phenyl group. In contrary to previous reports, 3,4-dihydroquinolin-2(1*H*)-one con-

taining compounds were more potent vasorelaxing agents than that of their unsaturated counterparts. These vasorelaxing activities decreased in the order 7-substituted > 6-substituted > 8-substituted.

5. Experimental protocols

5.1. Chemistry

Melting points (m.p.) were determined on an Yanaco micromelting-point apparatus and are uncorrected. The ultraviolet (UV) (λ_{max} (log ε) in nm) absorption spectra were obtained in a Beckman UV–vis spectrophotometer. Nuclear magnetic resonance (NMR) (^{1}H and ^{13}C) spectra were obtained with a Varian Gemini-200 spectrometer. Chemical shifts were expressed in parts per million (δ) with TMS as an internal standard. Thin-layer chromatography (TLC) was run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short wave UV light (254 nm) was used to detect the UV-absorbing spots. Elemental analyses (C, H, N) were carried out in a Heraeus CHN-O-Rapid elemental analyser and the results were within ±0.4% of theoretical values.

5.1.1. Synthesis of 7-(2-oxopropoxy)quinolin-2(1H)-one (8a)

7-Hydroxyquinolin-2(1*H*)-one (**4**; 1.61 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol) and dry DMF (50 mL) were stirred at room temperature (r.t.) for 30 min. To this solution was added bromoacetone (1.37 g, 10 mmol) in dry DMF (10 mL) in one portion. The resulting mixture was stirred continuously at r.t. for 24 h. (TLC monitoring) and then poured into ice water (100 mL). The white solid thus obtained was collected and crystallised from CH_2Cl_2 to afford **8a** (1.50 g, 69%); m.p.: 160–161 °C; ^{1}H-NMR (DMSO): δ 2.18 (s, Me), 4.87 (s, CH_2O), 6.31 (d, $J = 9.6$ Hz, H–C(3)), 6.71–7.59 (m, 3 arom. H), 7.81 (d, $J = 9.6$ Hz, H–C(4)), 11.55 (br s, NH); ^{13}C-NMR (DMSO): δ 26.20 (Me), 72.17 (CH_2O), 99.18, 110.30, 113.66, 118.83, 129.26, 139.91, 140.44 (arom. C), 159.41 (C-7), 162.14 (C-2), 203.51 (C-2′); Anal. Calc. for $C_{12}H_{11}NO_3 \cdot 0.125H_2O$: C, 65.67; H, 5.17; N, 6.38; Found: C, 65.82; H, 5.25; N, 6.45%.

5.1.2. 7-[2-Oxo-2-(1,1′-biphenyl-4-yl)ethoxy]-quinolin-2(1H)-one (8d)

Prepared from 2-bromo-4′-phenylacetophenone by the same procedure as described for **8a** in 60% yield; m.p.: 194–195 °C; ^{1}H-NMR (DMSO): δ 5.69 (s, CH_2O), 6.31 (d, $J = 9.4$ Hz, H–C(3)), 6.78–8.14 (m, 12 arom. H), 7.81 (d, $J = 9.4$ Hz, H–C(4)), 11.50 (br s, NH); ^{13}C-NMR (DMSO): 70.35 (CH_2O), 99.34, 110.60, 113.68, 118.80, 127.06, 128.56, 128.64, 129.15, 129.25, 133.07, 138.80, 139.96, 140.48, 145.29 (arom. C), 159.72 (C-7), 162.18 (C-2), 193.72 (C-2′); Anal. Calc. for $C_{23}H_{17}NO_3 \cdot 0.25H_2O$: C, 76.76; H, 4.90; N, 3.89; Found: C, 76.43; H, 4.93; N, 3.88%.

5.1.3. Synthesis of 7-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]quinolin-2(1H)-one (12a)

To a solution of **8a** (0.65 g, 3 mmol) in dry THF (60 mL) were added activated Zn powder (0.26 g, 3.9 mmol), hydroquinone (6 mg), and ethyl 2-(bromomethyl)acrylate (0.78 g, 4 mmol). The mixture was refluxed under N_2 for 6 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl solution (300 mL) and extracted with CH_2Cl_2 (3×60 mL). The CH_2Cl_2 extracts were combined and washed with H_2O, dried (Na_2SO_4), and then evaporated to give a residual solid, which was crystallised from a 1:10 mixture CH_2Cl_2–Et_2O to afford **12a** (0.66 g, 77% yield); m.p.: 147–148 °C; UV: 248 (sh, 3.98), 333 (4.11) (0.1 N HCl–MeOH), 281 (3.67), 324 (4.04), 338 (3.93) (MeOH), 233 (sh, 4.51), 325 (3.94) (0.1 N NaOH–MeOH); ^{1}H-NMR (DMSO): δ 1.48 (s, Me), 2.80 (dt, $J = 17.4$ Hz, 2.8, H–C(3′)), 3.08 (dt, $J = 17.4$ Hz, 2.6, H–C(3′)), 4.11 (s, CH_2O), 5.75 (t, $J = 2.6$ Hz, 1H, CH_2=C(4′)), 6.07 (t, $J = 2.6$ Hz, 1H, CH_2=C(4′)), 6.31 (d, $J = 9.4$ Hz, H–C(3)), 6.74–7.59 (m, 3 arom. H), 7.81 (d, $J = 9.4$ Hz, H–C(4)), 11.59 (br s, NH); ^{13}C-NMR (DMSO): δ 23.34 (Me), 35.97 (C-3′), 72.78 (CH_2O), 81.70 (C-2′), 99.27, 110.45, 113.82, 118.92, 121.26, 129.46, 136.02, 140.06, 140.51 (arom. C), 159.84 (C-7), 162.30 (C-2), 169.29 (C-5′); Anal. Calc. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91; Found: C, 67.12; H, 5.28; N, 4.92%.

The same procedure was used to convert **8d** to **12d**.

5.1.4. 7-[(2,3,4,5-Tetrahydro-4-methylidene-5-oxo-2-(1,1′-biphenyl-4-yl)furan-2-yl)methoxy]quinolin-2(1H)-one (12d)

Yield: 76%; m.p.: 215–216 °C; UV: 250 (sh, 4.60), 333 (4.29) (0.1 N HCl–MeOH), 251 (4.54), 324 (4.24), 338 (4.13) (MeOH), 236 (sh, 4.81), 325 (4.11) (0.1 N NaOH–MeOH); ^{1}H-NMR (DMSO): δ 3.22 (dt, $J =$

17.2 Hz, 2.8, H–C(3′)), 3.65 (dt, $J = 17.2$ Hz, 2.8, H–C(3′)), 4.34, 4.46 (AB type, $J = 10.4$ Hz, CH_2O), 5.82 (t, $J = 2.6$ Hz, 1H, CH_2=C(4′)), 6.14 (t, $J = 2.6$ Hz, 1H, CH_2=C(4′)), 6.31 (d, $J = 9.4$ Hz, H–C(3)), 6.77–7.77 (m, 12 arom. H), 7.80 (d, $J = 9.4$ Hz, H–C(4)), 11.53 (br s, NH); ^{13}C-NMR (DMSO): δ 37.11 (C-3′), 73.32 (CH_2O), 84.09 (C-2′), 99.44, 110.40, 113.84, 118.95, 121.63, 125.77, 126.73, 126.90, 127.69, 128.97, 129.38, 134.92, 139.42, 139.94, 140.14, 140.42 (arom. C), 159.60 (C-7), 162.16 (C-2), 168.90 (C-5′); Anal. Calc. for $C_{27}H_{21}NO_4 \cdot 0.125H_2O$: C, 76.18; H, 5.03; N, 3.29; Found: C, 75.99; H, 5.08; N, 3.34%.

5.2. Biology

5.2.1. In vitro antiplatelet evaluation

5.2.1.1. Reagents

Arachidonic acid (AA), EDTA, and bovine serum albumin were purchased from Sigma Chem. Co. Platelet-activating factor (PAF) was purchased from Calbiochem-Behring Co.

5.2.1.2. Platelet aggregation

Blood was collected from the rabbit marginal ear vein, anticoagulated with EDTA (6 mM) and centrifuged for 10 min at $90 \times g$ and at room temperature. Platelet suspensions were prepared from the plasma according to the washing procedures previously described [24]. Platelet numbers were determined with a Coulter counter (Model ZM) and adjusted to 4.5×10^8 platelets mL^{-1}. 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 °C by the turbidimetric method as described by O'Brien [25] using a Chrono-Log Lumi-aggregometer. To eliminate solvent effects on aggregation, the final concentration of dimethylsulfoxide (DMSO) was fixed at 0.5%. The 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.

The IC_{50} values (μM) for **12a** and **12d** were as follows: 3.90 and 2.40, respectively, on the platelet aggregation induced by AA; 53.3 and 14.7, respectively, that of induced by PAF.

5.2.2. In vitro vasorelaxing evaluation [26]

Porcine hearts were obtained from a local abattoir within 30 min of slaughter and were transported to the laboratory in Krebs-Henseleit (KH) buffer solution with the following composition (mM): NaCl (120), KCl (5.2), KH_2PO_4 (1), $MgSO_4$ (1.3), $CaCl_2$ (2.5), $NaHCO_3$ (15.5), glucose (11.3), and pyruvate (1). The pH value of the KH buffer solution was adjusted to 7.4. The right coronary and anterior descending branch of the left coronary arteries were dissected from each heart and stored overnight at 4 °C in an oxygenated KH buffer solution. On one of the two following days, these arteries were cleaned of any remaining connective tissue and cut into 3-mm rings.

Coronary arterial rings were suspended in organ bath filled with 20 mL KH solution. The bath solution was gassed with a mixture of 95% O_2 and 5% CO_2 and the temperature was maintained at 37 °C throughout the experiment. Each ring was suspended by two fine stainless-steel wire clips; one clip was anchored inside the organ bath and the other was connected to a force transducer (model FT03, Grass Instrument, USA). Isometric tension was measured by Cyber 380 and Digidata 1320A (Axon Instrument, USA) and recorded in a computer.

Tissues were allowed to equilibrate for a minimum of 1 h before testing had begun. KCl (30 mM) was then added into the organ chamber to contract these rings. When the contraction reached a stable plateau (usually 15 min), compounds (100 μM) were added in organ bath to screen the activity of relaxation. Concentration–response curves for some more potent compounds were established by cumulative addition at doses of 3, 10, 30 and 100 μM.

Contractile responses were calculated as the difference between resting tension and maximum tension developed in response to KCl stimulation. Data are expressed as mean ± S.E.M. from a number ($n = 4$–6) of experiments. Statistical analyses were performed using Student test. $P \leqq 0.05$ was considered significant.

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