Study on the Selective Reduction of 1*H*-Quinazoline-2,4-diones

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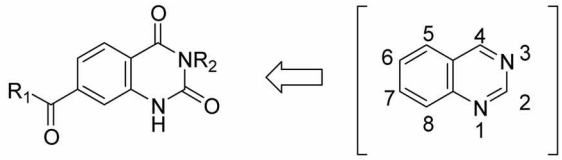
The 1*H*-quinazoline-2,4-dione derivatives have attracted interests on their various biological activities including the selective serotonin-S_2 antagonist.[1] These compounds are structurally similar with quinazoline and quinazolinone derivatives and conventionally synthesized by the coupling of isocyanate with the amine group as nucleophile and by cyclization under the heating and basic conditions.[2] From this main skeleton, the modified compounds had been synthesized for the desired biological activities. Of these, nonpeptide antagonists for the human gonadotropin-releasing hormone receptor were synthesized by modifying the C2 position and varying R2 derivatives.[3] Other example is the thymidylate synthase inhibitor, ZD9331, developed by AstraZeneca.[4] This compound was synthesized by modifying the C6 position. Recently, Ismail *et al.* designed and synthesized the carboxy-biphenylmethyl-quinazolin-4-one derivatives, on the basis of modeling and structure-activity studies, which could block the effects of angiotensin II by inhibiting the angiotensin-converting enzyme or rennin.[5]

According to these interesting structure-activity relationship, the development of new scaffold from 1*H*-quinazoline-2,4-dione has been issued by our program for the new drug discovery of Ca^{+2} channel blocker. For this purpose, according to our modeling team's suggestion, it was necessary to reduce selectively the C4 carbonyl function in 1*H*-quinazoline-2,4-dione to methylene group as shown in structure **4** and **6** (Scheme 2). Such a work as this C4 modified structure was reported by Desikan *et al.*[6] After obtaining these compounds, we can diversify this structure by modifying R1 and R2 groups, respectively. Although the various starting materials were employed to obtain this molecular scaffold, the method of direct reduction of C4 carbonyl function using synthetically well established 1*H*-quinazoline-2,4-dione compound will be simple and effective. These reactions have been accomplished by many research groups[7] and more recently, target-focused selective reductions were performed using the corresponding complex compounds.[8] But to our knowledge, no result was reported about the direct reduction of the compound **1** using reducing agent. Here we report the selective reduction of C4 carbonyl function among three carbonyl functions by the various reducing agents.



1*H*-quinazoline-2,4-dione derivatives **1** Quinazoline

Figure 1

Firstly, the compound **2**, which was prepared as described before,[3] was used as a substrate for reduction studies as shown in Scheme 1. It has three functional groups including ester, amide and urea. Sometimes amide bond is cleaved by the strong reducing reagent. Thus it is important to reduce C4 carbonyl group without the cleavage of amide bond. To try to find the appropriate reducing agent, the various reducing reagents were screened as shown in Table 1 and borane and aluminium hydride derivatives showed promising activities.

In THF solution, these reactions were tried at the different temperatures such as –10 °C and under the reflux conditions. Besides the above reducing agents, sodium cyanoborohydride, lithium 9-BBN, lithium borohydride, sodium borohydride and borane tetrahydrofuran complex were employed. But these reagents were too mild to reduce our substrate.

As shown in Table 1, the compound **2** was reduced at the ester carbonyl to give alcohol **3** under the conditions of –10 °C by six reducing agents. Next, it was further reduced at amide site to compound **4** under the reflux conditions. Lastly, it was fully reduced to the compound **5** by sodium bis(2-methoxyethoxy)aluminium dihydride and lithium aluminium hydride under the reflux conditions. Thus, among three active sites the urea showed the lowest reactivity according to the results of the condition of strong these reducing agents and reflux. In the case of diisobutylaluminium hydride and lithium tri-*tert*-buthoxyaluminium hydride, it was reduced to compound **4** even under the reflux

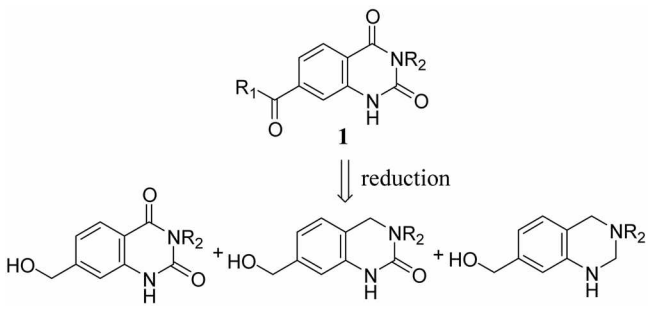
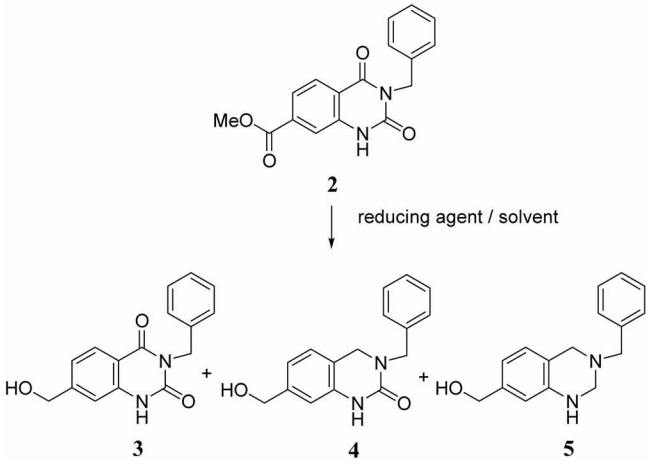


Figure 2



Scheme 1

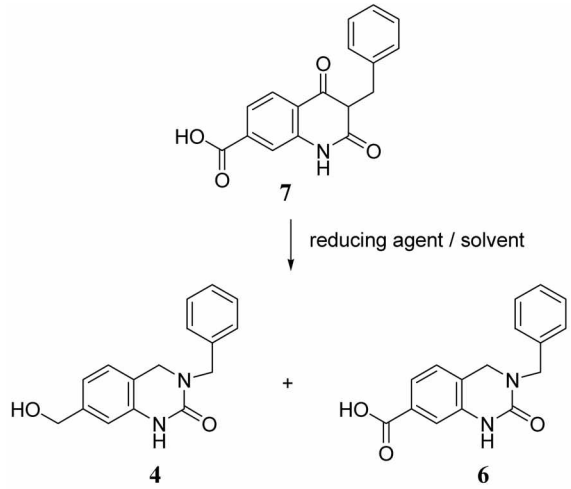
Table 1. Reduction of ester **2** by some reducing agents in THF solvent

Reducing agent	Temperature (°C)	Reaction time (h)	Yield (%)[a]		
			3	**4**	**5**
Super-H	−10	0.5	95	–	–
Super-H	reflux	8	nd[b]	85	–
L-Selectride	−10	0.5	92	–	–
L-Selectride	reflux	6	nd	40	
Vitride	−10	0.5	90	–	–
Vitride	reflux	4.5	nd	39	–
Vitride	reflux	5.5	nd	nd	85
LAH	−10	0.5	92	–	–
LAH	reflux	5	nd	35	–
LAH	reflux	6	nd	nd	80
DIBAL-H	−10	0.5	90	–	–
DIBAL-H	reflux	9	nd	80	–
LBAH	−10	0.5	85	–	–
LBAH	reflux	8.5	nd	70	–

[a]isolated yield by column chromatography and maximum yield as the respective compound; [b]nd: not determined; Super-H:Lithium triethyl borohydride; L-Selectride Lithium tri-*sec*-butyl borohydride. Vitride: Sodium bis-(2-methylethoxy) aluminium dihydride; LAH; Lithium aluminium hydride; DIBAL-H; Diisobutylaluminium hydride; LBAH; Lithium tri-*tert*-buthoxyaluminium hydride.

conditions. Both of lithium triethyl borohydride and lithium tri-*sec*-butyl borohydride reduced it to the compound **4** under the reflux conditions as well. As these results showed, we were able to reduce the compound **2** selectively to either the compound **4** or **5** depending on the choice of reducing agents. Next, we needed to oxidize the alcohol compound **4** to the carboxylic acid **6**, which were planned to couple with the various amines to obtain drug candidates. But this process was tedious.

To resolve this problem, the carboxylic acid **7** was employed. The acid function would be more resistant to the reducing agent than the ester function. To reduce C4 carbonyl function selectively, the above five reducing agents such as boron and aluminium hydride derivatives were used under the THF reflux conditions and the results were shown in Table 2.



Scheme 2

Table 2. Reduction of carboxylic acid **7** by some reducing agents in THF solvent

Reducing agent	Temperature (°C)	Reaction time (h)	Yield (%)[a]	
			4	**6**
Super-H	reflux	6	–	93
L-Selectride	reflux	6	–	25
Vitride	reflux	5	nd[b]	39
Vitride	reflux	8	60	nd
LAH	reflux	7	nd	35
LAH	reflux	9	70	nd
DIBAL-H	reflux	9	–	85

[a]isolated yield by column chromatography and maximum yield as the respective compound; [b]nd: not determined

As expected, the compound 7 was selectively reduced at C4 carbonyl site by borane agents and DIBAL-H without the reduction of carboxyl group. But the others reduced both of C4 carbonyl and carboxyl group to alcohol **4** under the reflux conditions. Interestingly, any of these reducing agents did not produce the compound **5**. When R2 is *p*-chlorobenzyl or *p*-fluorobenzyl group, the similar results were obtained. Although DIBAL-H selectively produced the compound **6** in high yield, the next work-up procedure was tedious. Thus we selected two borane reducing agents, Super-H and L-selectride, to obtain the compound **6**. Of these two agents, Super-H gave higher yield and was easy to handle.

To optimize the reduction condition, solvent effect was investigated under the reflux conditions using Super-H. Although we used some solvents such as THF, 1,4-dioxane, toluene and methylene chloride, the best result was obtained in THF and the carboxylic acid **7** was obtained in 93% yield.

In conclusion, we could achieve the selective reduction of the substrates **2** and **7** to the corresponding products. To get C4 reduction selectively, we could use borane hydride derivatives. To reduce both of C2 and C4 carbonyl function, aluminium hydride derivatives could be employed. Especially, the selective reduction of the substrate **7** to the compound **6** is very important to transform it to final amide products.

The resulted products would be used for the synthesis of Ca^{+2} channel blocker.

Experimental Section

3-Benzyl-7-hydroxymethylquinazolin-2,4-dione (3). To a solution of the compound **2** (100 mg, 0.32 mmol) in THF (50 mL) under a nitrogen atmosphere was added the reducing agent (5 equivalents) and the mixture was stirred at −10 °C or heated under reflux. After the completion of the reaction, the mixture was quenched with saturated aqueous NH_4Cl and extracted with methylene chloride (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the compound **3**: mp 228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 8.0 Hz, 1H), 7.26-7.23 (m, 4H), 7.22-7.18 (m, 1H), 7.10 (s, 1H), 7.08 (d, J = 0.8 Hz, 1H), 5.06 (s, 2H), 4.55 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 151.2, 150.9, 140.2, 137.9, 128.7, 127.9, 127.7, 127.5, 120.8, 112.6, 62.7, 43.5; IR (KBr) 3205, 1708, 1655, 1598, 1491, 1220, 772 (cm^{-1}); HRMS (ESI) Calcd. for $C_{16}H_{14}N_2NaO_3$ [M+Na] ; 305.0902. Found: *m/z* 305.0908.

3-Benzyl-7-hydroxymethyl-3,4-dihydroquinazolin-2-one (4). mp 240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.30-7.25 (m, 5H), 6.83 (s, 1H), 6.81 (s, 1H), 4.61 (s, 2H), 4.62 (s, 2H), 4.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 141.6, 136.8, 136.5, 130.9, 128.6, 128.3, 128.0, 127.5, 125.4, 120.4, 116.2, 112.3; IR (KBr) 3221, 1659, 1601, 1491.767 (cm^{-1}); HRMS (ESI) Calcd for $C_{16}H_{16}N_2NaO_2$ [M+Na] : 291.1109. Found: *m/z* 291.1102.

3-Benzyl-7-hydroxymethyl-1,2,3,4-tetrahydroquinazoline (5). mp 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 6.88 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 1.2 Hz, 1H), 6.59 (s, 1H), 4.58 (s, 2H), 4.07 (s, 2H), 3.86 (s, 2H), 3.74 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 140.2, 138.3, 129.1, 128.4, 127.8, 127.2, 119.3, 116.9, 113.5, 65.3, 62.7, 57.0, 53.0; IR (KBr) 3306, 1623, 1589, 803, 748 (cm^{-1}); HRMS (ESI) Calcd. for $C_{16}H_{18}N_2NaO$ [M+Na]: 277.1317. Found: *m/z* 277.1321.

3-Benzyl-7-carboxy-3,4-dihydroquinazolin-4-one (6). mp 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 7.40 (s, 2H), 7.33-7.24 (m, 5H), 7.11 (d, J = 8.0 Hz, 1H), 4.52 (s, 2H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.4, 153.7, 138.2, 137.6, 130.9, 129.0, 128.1, 127.7, 126.3, 122.8, 122.5, 114.5, 49.7, 47.9; IR (KBr) 3197, 3104, 3027, 2511, 1689, 1649, 1601, 1528, 1495, 717 (cm^{-1}); HRMS (ESI) Calcd for $C_{16}H_{14}N_2NaO_3$ [M+Na]: 305.0902. Found: *m/z* 305.0907.

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References

1. Wouters, W.; Janssen, C. G. M.; Dun, J. V.; Thijssen, J. B. A.; Laduron, P. M. *J. Med. Chem.* **1986**, *29*, 1663.
2. Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153.
3. Betz, S. F.; Reinhart, G. J.; Lio, F. M.; Chen, C.; Struthers, R. S. *J. Med. Chem.* **2006**, *49*, 637.
4. Moseley, J. D.; Bansal, P.; Bowden, S. A.; Couch, A. E. M.; Hubacek, I.; Weingartner, G. *Org. Process Res. Dev.* **2006**, *9*, 153.
5. Ismail, M. A. H.; Barker, S.; Abou El Ella, D. A.; Abouzid, K. A. M.; Toubar, R. A.; Todd, M. H. *J. Med. Chem.* **2006**, *49*, 1526.
6. Desikan, S.; Parsons, R. L.; Davis, W. P.; Ward, J. E.; Marshall, W. J.; Toma, P. H. *Org. Process Res. Dev.* **2006**, *9*, 933.
7. (a) Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1998**, *90*, 2927. (b) Curran, W. V.; Angier, R. B. *J. Org. Chem.* **1966**, *31*, 3867. (c) Konet, M. J.; Thio, P. A.; Tan, S. I. *ibid* **1968**, *33*, 3637. (d) Brown, H. C.; Heim, P. *ibid* **1973**, *38*, 912. (e) Borch, R. F. *Tetrahedron Lett.* **1968**, *9*, 61. (f) Rerick, M. N.; Trottier, C. H.; Daignault, R. A.; Defos, J. D. *ibid* **1963**, *4*, 629. (g) Adachi, K.; Tsuru, E.; Banjo, E.; Doe, M.; Shibata, K.; Yamashita, T. *Synthesis* **1998**, *11*, 1623.
8. (a) O'Mahony, G.; Nieuwenhuyzen, M.; Armstrong, P.; Stevenson, P. J. *J. Org. Chem.* **2004**, *69*, 3968. (b) Hu, W. P.; Tsai, P. C.; Hsu, M. K.; Wang, J. J. *ibid* **2004**, *69*, 3983. (c) Jensen, C. M.; Lindsay, K. B.; Andreasen, P.; Skrydstrup, T. *ibid* **2005**, *70*, 7512.