Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 14, pp. 1533-1536, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00244-8

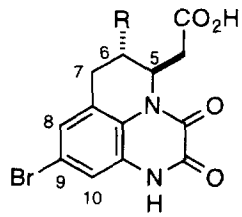
STRUCTURE-ACTIVITY RELATIONSHIPS OF TRICYCLIC QUINOXALINEDIONES AS POTENT ANTAGONISTS FOR THE GLYCINE BINDING SITE OF THE NMDA RECEPTOR 2.

Ryu Nagata,* Toru Kodo, Hiroshi Yamaguchi, and Norihiko Tanno

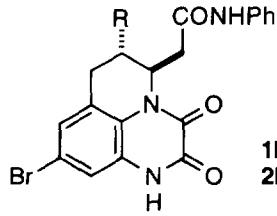
Sumitomo Pharmaceuticals Research Center, 1-98, Kasugadenaka-3-chome, Konohana-ku, Osaka 554 Japan

Abstract: Various modified compounds at the carbamoyl group of tricyclic quinoxalinedione **1b** and at the position of bromine atom of **1a,b** were synthesized and evaluated for their affinity for the glycine binding site of the NMDA receptor. Replacement of bromine atom of **1a,b** with chlorine atom (**14a,b**) retained the activity.

Antagonists acting at the glycine binding site of the NMDA receptor are potential therapeutics for neurodegerative disorders including not only stroke but also Huntington's and Alzheimer's diseases.[1] In the preceding paper,[2] we described the synthesis of a series of methyl substituted tricyclic quinoxalinediones based on **1a,b**[3] and evaluated their affinity for the glycine binding site of the NMDA receptor. Among them, C6 trans methyl derivatives **2a** (Ki = 3.3 nM) and **2b** (Ki = 3.0 nM) were well tolerated, compared with **1a** (Ki = 9.9 nM) and **1b** (Ki = 2.6 nM). These findings suggested that the corresponding hydrophobic pocket of the receptor would be expanded to the opposite side to the C5 side chain. According to the structural feature of **1a,b** and **2a,b**, additional two hydrophobic pockets will exist in the receptor. Namely, one is the region corresponding to the phenyl ring of the anilide group and another is the region of the bromine atom located in the south-western part of the quinoxalinediones. In this study, we examined the role of the phenyl ring and the size of the hydrophobic pocket in the bromine atom region.



1a: R = H
2a: R = Me

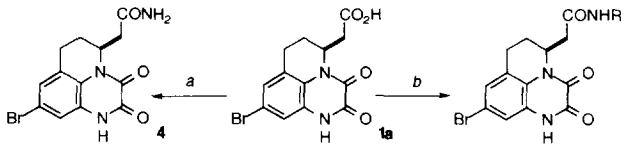


1b: R = H
2b: R = Me

Cyclohexylcarbamoyl derivative **3** was prepared by condensation of **1a** with cyclohexylamine using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC) and 1-hydroxybenzotriazole (HOBt). In a similar way, substituted anilide derivatives **5** - **11** were prepared. Amide **4** was synthesized by reaction of aqueous ammonia with mixed anhydride generated from **1a** and isobutyl chloroformate (Scheme 1). Hydrogenation of **1c** over Pd-C in a mixture of THF and acetic acid under an atmospheric pressure followed by column chromatography provided **12c** in 79% yield which was converted to the desired carboxylic acid **12a** and anilide **12b**. Treatment of **1c** with KI and CuI in HMPA at 160 °C[4] followed by column chromatography afforded **13c** (67%). Similarly, carboxylic acid **13a** and anilide **13b** were prepared. Chloro derivative **14c** could be obtained by reaction of **1c** with CuCl in DMSO at 160 °C (Scheme 2). More practically, **14c** was prepared by a modified sequence described in the synthesis of **1c**[3] as shown in Scheme 3. When 2-methoxycarbonylmethyl-1,2,3,4-tetrahydroquinoline was treated with N-chlorosuccinimide (NCS) in DMF at 0 °C, a 1 : 1 mixture of the desired

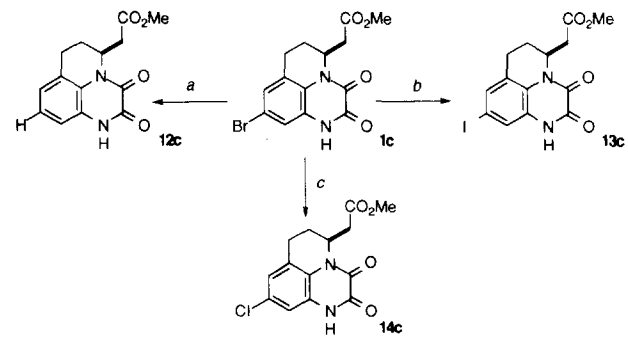
6-chloro derivative and the 8-chloro isomer was obtained. Reaction of N-ethoxalyl-2-methoxycarbonylmethyl-1,2,3,4-tetrahydroquinoline with NCS in DMF at 50 °C provided the desired 6-chloro derivative, exclusively. Methyl ester **14c** was converted to **14a**[5] and **14b**. By a similar sequence, **15a**[5] and **15b** were prepared starting from trans 2-methoxycarbonylmethyl-3-methyl-1,2,3,4-tetrahydroquinoline.

Scheme 1.



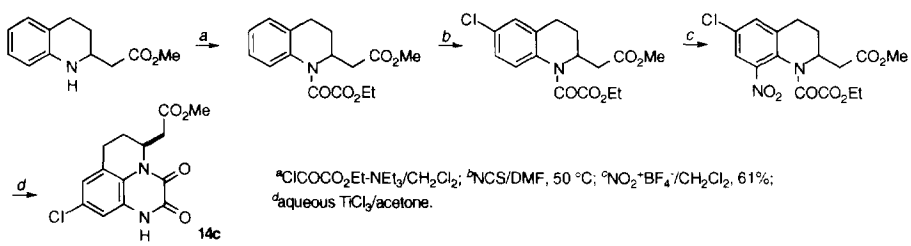
[a]1) NEt_3-*i*BuOCOCl/CH_2Cl_2 2) NH_3; [b]RNH_2, WSC-HOBt/DMF.

Scheme 2.



[a]1) H_2, Pd/C/THF-AcOH; [b]KI-CuI/HMPA, 160 °C; [c]CuCl/DMSO, 160 °C.

Scheme 3.



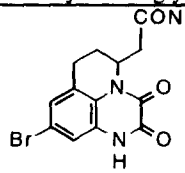
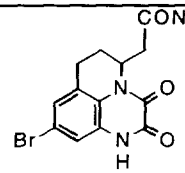
[a]$ClCOCO_2Et$-NEt_3/CH_2Cl_2; [b]NCS/DMF, 50 °C; [c]$NO_2^+BF_4^-/CH_2Cl_2$, 61%; [d]aqueous $TiCl_3$/acetone.

Tables 1 and 2 show the affinity of the compounds for the glycine site measured by the radio-ligand binding assay using [^{3}H] 5,7-dichlorokynurenic acid.[6] In addition to the Ki values of the selected compounds, % inhibition of the radio ligand at the concentration of the substrate (10 ng/mL) was listed for comparison.

Replacement of the phenyl ring of **1b** to a cyclohexane ring provided **3** which was much less active than **1b**. Taking a phenyl ring off from **1b** led to amide **4** which also showed significantly reduced activity. With respect to substituted anilide derivatives, compounds bearing an electron donating substituent (**5** - **8**) showed much higher affinity than those bearing an electron withdrawing substituent (**9** - **11**). Thus, the electron density

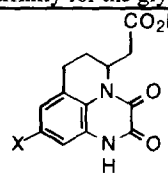
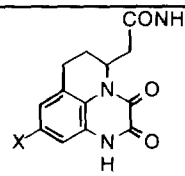
on the phenyl ring appears to largely influence the activity. This demonstrates the importance of the phenyl ring for the activity as a substituent of the carbamoylmethyl group at the C5 side chain and the origin of the high affinity of **1b** might be a π-π interaction between the anilide group and the receptor.

Table 1. The affinity for the glycine binding site[a]

compound	 R =	% inhibition (10 ng/mL) vs [^{3}H] DCKA[b]	compound	 R =	% inhibition (10 ng/mL) vs [^{3}H] DCKA[b]
1b	phenyl	92.9 ± 1.2 (Ki = 2.6 nM[c])	**7**	*p*-NH_2-phenyl	76.4 ± 2.6
3	cyclohexyl	23.8 ± 2.1	**8**	*p*-MeCONH-phenyl	73.0 ± 5.7
4	H	28.9 ± 2.6	**9**	*p*-CF_3-phenyl	1.0 ± 7.3
5	*p*-Me-phenyl	83.3 ± 2.3	**10**	*p*-NO_2-phenyl	21.5 ± 4.1
6	*p*-MeO-phenyl	67.5 ± 4.7	**11**	*p*-CN-phenyl	3.8 ± 6.5

[a]See refs 3 and 6. [b]DCKA: 5,7-dichlorokynurenic acid. [c]See ref. 3.

Table 2. The affinity for the glycine binding site[a]

compound	 X =	% inhibition (10 ng/mL) vs [^{3}H] DCKA[b]	compound	 X =	% inhibition (10 ng/mL) vs [^{3}H] DCKA[b]
1a	Br	68.7 ± 1.6 (Ki = 9.9 nM[c])	**1b**	Br	92.9 ± 1.2 (Ki = 2.6 nM[c])
12a	H	30.3 ± 7.2	**12b**	H	52.7 ± 3.7
13a	I	76.2 ± 3.9 (Ki = 46.6 nM)	**13b**	I	46.7 ± 7.1 (Ki = 134 nM)
14a	Cl	90.3 ± 5.6 (Ki = 5.1 nM)	**14b**	Cl	79.3 ± 2.3 (Ki = 6.6 nM)
15a	Cl, C6-trans Me	(Ki = 4.4 nM)	**15b**	Cl, C6-trans Me	(Ki = 3.1 nM)

[a]See refs 3 and 6. [b]DCKA: 5,7-dichlorokynurenic acid. [c]See ref. 3.

Compounds having a much smaller substituent (H, **12ab**) and larger substituent (I, **13ab**) at the C9 position than bromine (**1ab**) showed reduced affinity in both the carboxylic acid and anilide series. However,

chloro derivatives **14a** (Ki = 5.1 nM) and **14b** (Ki = 6.6 nM) retained the activity. Along the line, chloro substituted 6-trans methyl derivatives **15a** (Ki = 4.4 nM) and **15b** (Ki = 3.1 nM) also had excellent activity. Thus, the hydrophobic pocket in this region appears to be size-limited and chlorine and bromine atom are most favorable as a substituent at the C9 position.

Acknowledgments. We are grateful to Prof. Y. Yoneda and Dr. K. Ogita of Setsunan University for evaluation of the biological activities. We thank Mr. N. Ae for his synthetic contribution. We appreciate Dr. M. Nakamura for his valuable discussion. We also express appreciation to Dr. M. Sunagawa for encouragement and stimulating discussion.

References and notes

(1) Reviews: (a) Carter, A. J. *Drugs of the Future* **1992**, *17*, 595. (b) Kemp, J. A.; Leeson, P. D. *Trends Pharmacol. Sci.* **1993**, *14*, 20. (c) Leeson, P. D.; Iversen, L. L. *J. Med. Chem.* **1994**, *37*, 4053.

(2) Nagata, R.; Ae, N.; Tanno, N. *Bioorg. Med. Chem. Lett.*, preceding paper in this issue.

(3) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Nishimura, T.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, H.; Nakamura, M.; Ogita, K.; Yoneda, Y. *J. Med. Chem.* **1994**, *37*, 3956.

(4) Suzuki, H.; Kondo, A.; Ogawa, T. *Chem. Lett.* **1985**, 411.

(5) **14a**: mp 287.5 ~ 288 °C (dec); ^{1}H NMR (270 MHz, DMSO-d_6) δ 12.06 (bs, 1 H), 7.08 (d, 1 H, J = 2 Hz), 7.02 (d, 1 H, J = 2 Hz), 5.02 ~ 5.13 (m, 1 H), 2.95 (ddd, 1 H, J = 17.1, 13.5, 4.5 Hz), 2.78 (dm, 1 H, J = 17.1 Hz), 2.41 ~ 2.60 (m, 2 H), 2.14 (dm, 1 H, J = 13.5 Hz), 1.88 ~ 1.95 (m, 1 H). **15a**: mp > 280 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 12.05 (br, 1 H), 7.06 (d, 1 H, J = 2.0 Hz), 7.02 (d, 1 H, J = 2.0 Hz), 4.77 - 4.83 (m, 1 H), 3.13 (dd, 1 H, J = 5.0, 17.2 Hz), 2.29 - 2.63 (m, 4 H), 0.85 (d, 3 H, J = 6.9 Hz).

(6) Yoneda, Y.; Suzuki, T.; Ogita, K.; Han, D. *J. Neurochem.* **1993**, *60*, 634.

(*Received in Japan* 13 *April* 1995; *accepted* 5 *June* 1995)