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Synthesis of 4,6-Dichloro-3-[(1-*N*-Arylaminocarbonyl)-Hydrazono]-1,3-Dihydro-Indole-2-One as a Potential NMDA Receptor Glycine Site Antagonist

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A synthetic procedure for the preparation of indole-2,3-dione derivatives **6** as a potential NMDA receptor glycine site antagonist with improved pharmacological profile compared with 2-carboxyindole derivative **5**, starting from readily available 3,5-dichloroaniline (**7**), is described.

Key words: NMDA receptor, Glycine Site, Indole, Alzheimer

INTRODUCTION

The *N*-methyl-D-aspartate (NMDA) type of ionotropic glutamate receptors plays a major role in the neurotoxic cascade following cerebral ischaemia and hypoxic events (Meldrum, 1990; McCullough, 1992; Rothman *et al.*,1987). Additionally, the discovery that the glycine is a necessary coagonist for NMDA receptor activation (Johnson *et al., 1987*) has stimulated research into the development of antagonists for the NMDA receptor glycine site. In comparison with MNDA receptor anta-gonists acting competitively at the glutamate site or uncompetitively as channel blockers, glycine site antagonists have significantly improved side-effect profiles (Kemp *et al.*, 1993). Therefore, NMDA receptor antagonists acting at the glycine site have been actively sought for their therapeutic potential in the treatment of CNS disease such as Alzheimer disease, stroke, head injury, epilepsy and schizophrenia (Leeson *et al.*, 1994, Iverson *et al.*,1994, Kulagowski *et al.*, *1996* and Cai *et al.*, *1997*).

Structural examination of different series of glycine site antagonists revealed that benzofused heterocycles such as kynurenic acid (**1**) (Leeson *et al.*, 1991), 2-quinolone (**2**) (McQuaid *et al.*, 1992), 2-carboxy-tetrahydroquinoline (**3**) (Leeson *et al.*, 1992), quinoxalinedione (**4**) (Honore *et al.*, 1988 and Epperson *et al.*, 1993) and 2-carboxyindole (**5**) (Salituro *et al.*, 1992 and Fabio *et al.*, 1997) are the most representative glycine site antagonist. (Fig. 1). In spite of many classes of compounds mentioned above, most of these lack activity in the central nervous system following systemic dosing. Evidently, significant improvements in blood-brain barrier permeability and bioavailability are important factors to be considered as a good drug candidate.

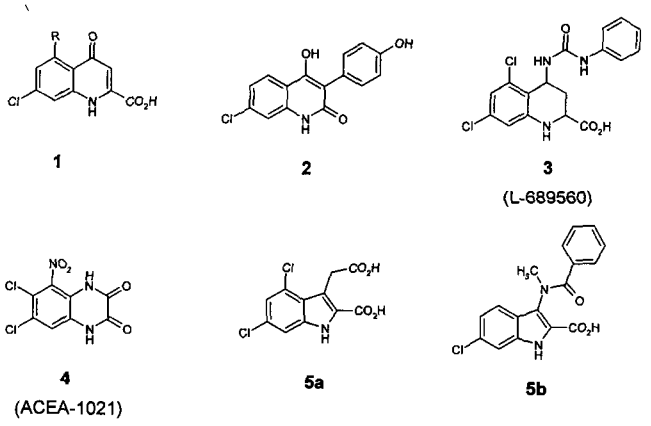

Fig. 1. *Structure of various glycine site antagonist*

Reported herein is the synthesis of indole-2,3-dione derivatives **6** as a potential lead compound for the NMDA receptor glycine site antagonist with improved pharmacological profile compared with 2-carboxyindole derivative **5**, starting from the readily available 3,5-dichloroaniline **7** (Scheme 1).

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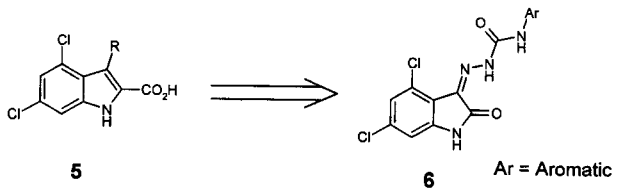


Fig. 2. A conceptual design for target compound

MATERIALS AND METHODS

Mass spectra were recorded on a Shimadzu QP-1000 spectrometer (20eV). High Resolution Mass Spectra (HRMS) were obtained on a JEOL JMS-DX-305 high resolution mass spectrometer. ^{1}H-NMR spectra were recorded either on a JEOL-60 or on a Varian Gemini-200 MHz spectometer. Chemical shifts were expressed in ppm downfield from TMS used as internal standard. Melting point was determined on an electrically heated Thomas-Hoover capillary melting point apparatus and uncorrected. All chromatographic separations were performed on Merck silica gel (Kieselgel 60, 230~400 mesh).

N-(3,5-Dichloro-phenyl)-2-hydroxyimino-acetamide (8)

To a solution of chloral hydrate(18.19 g, 0.11 mol) and sodium sulfate (25 g, 0.18 mol) in water (250 mL) was added a solution of 3,5-dichloroaniline (16.2 g, 0.1 mol) in water/C-HCl (150 mL/45 mL) while stirring vigorously over 0.5 h at room temperature. The reaction mixture was stirred at rt for another 0.5 h, added a solution of hydroxylamine. HCl (22.93 g, 0.33 mol) in water (100 mL) over 5 min and then heated at 100°C for 45 min. Upon colling the reaction mixture pale brown precipitate was obtained as crude product. The crude product was recrystallized from Ethyl Acetate/ Hexane (20 mL/200 mL) to get pure product (14.74 g, 63.3%); ^{1}H- NMR (200 MHz, DMSO-d_6) δ 7.30(s, 1H), 7.61(s, 1H), 7.80(s, 2H), 10.49(s, 1H), 12.32(s, 1H); MS: m/z 233(M^++1).

4,6-Dichloro-1*H*-indole-2,3-dione (9)

Compound **8** (1.17 g, 5 mmol) was added to c-H_2SO_4 (5.6 mL) at 10~15°C in a small portion over 10 min. The reaction mixture was heated at 80°C for 10 min and then poured into ice-water (50 mL). After stirring the mixture for 0.5 h, the precipitated white solid was filtered and dried to give desired product (0.99 g , 92.1%); ^{1}H-NMR (200MHz, DMSO-d_6) δ 6.90(s, 1H), 7.25(s, 1H), 11.32 (bs, 1H); MS: m/z 216(M^++1).

4,6-Dichloro-3-hydrazono-1,3-dihydro-indole-2-one (10)

To a solution of compound **9** (2.16 g, 20 mmol) in methanol (60 mL) was added hydrazine hydrate (1.5 mL, 30 mmol). The reaction mixture was heated at 50°C for 30 min. Upon cooling the mixture a white solid was obtained in quantitative yield.; mp 247°C; ^{1}H-NMR (200MHz, DMSO-d_6) δ 6.77(s, 1H), 7.04(s, 1H), 10.00 (m, 1H), 10.80~11.10(m, 2H); MS: m/z 230(M^++1).

General procedure for the preparation of compound 6

A solution of compound **10** (1 mmol), isocyanate (1.1 mmol) and triethylamine (1.1 mmol) in DMF (10 mL) was stirred at room temperature for 1 day. After removing solvent at reduced pressure the resulting slurry was treated with methanol/ethyl acetate (8 mL/2 mL) to get essentiallly pure products. Analytical samples were prepared by recrystallization from ethanol.

4,6-Dichloro-3-[(1-*N*-phenylaminocarbonyl)-hydrazono]-1,3-dihydro-indole-2-one (6a)

52.1% yield; mp 301~302°C; ^{1}H-NMR(200MHz, DMSO-d_6) δ 6.91(s,1H), 7.06 (m, 1H) 7.25(s, 1H), 7.30(m, 2H), 7.56(d, 2H), 9.75(s, 1H), 11.55(s, 1H), 12.51(s, 1H); MS: m/z 349(M^++1); HRMS: calcd. for $C_{15}H_{10}O_2N_4$ Cl_2: 348.0180, found: 348.0178.

4,6-Dichloro-3-[(1-*N*-benzenesulfonylaminocarbonyl)-hydrazono]-1,3-dihydro-indole-2-one (6b)

54.5% yield; mp 241~242°C; ^{1}H-NMR(200MHz, DMSO d_6) δ 6.90(s, 1H), 7.21(s, 1H), 7.65(m, 3H), 7.98(, 2H), 10.10(bs, 1H), 10.96(bs, 1H), 11.48(bs, 1H); MS: m/z 413 (M^++1); HRMS: calcd. for $C_{15}H_{10}O_4N_4$ Cl_2 S: 348.0180, found: 348.0178.

4,6-Dichloro-3-[(1-*N*-phenylaminocarbonyl)-hydrazono]-1,3-dihydro-indole-2-one (6c)

83.8% yield; mp 294~295°C; ^{1}H-NMR(200MHz, DMSO -d_6) δ 6.94(s, 1H), 7.36(s, 1H), 7.51(s, 4H), 9.96 (m, 1H), 11.56(bs, 1H), 12.55(bs, 1H); MS: m/z 427 (M^++1); HRMS: calcd. for $C_{15}H_9O_2N_4$ Cl_2 Br: 425.9286, found: 425.9292.

4,6-Dichloro-3-[(1-*N*-methoxyphenylaminocarbonyl)-hydrazono]-1,3-dihydro-indole-2-one (6d)

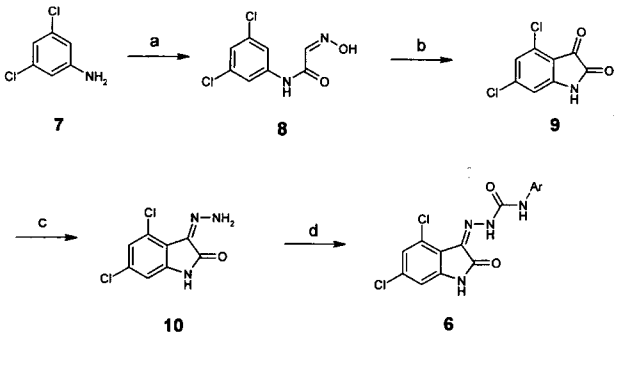
42.0% yield; mp 269~270°C; ^{1}H-NMR(200MHz, DMSO -d_6) δ 3.70(s, 3H), 6.90(m, 3H), 7.30(s, 1H), 7.45(d, 2H), 9.67(s, 1H), 11.54(bs, 1H), 12.49(bs, H); MS: m/z 379 (M^++1); HRMS: calcd. For $C_{16}H_{12}O_3N_4Cl_2$: 378.0286, found: 378.0280.

RESULTS AND DISCUSSION

The essential kynurenate-type glycine antagonist pharmacophore is also found in indole-2-carboxylic acid (Huettner *et al.*, 1989). 6-Chloro substitution enha-nces

binding and a number of workers have shown that introduction of hydrogen-bond-accepting 3-sub-stituents leads to improved activity (Salituro *et al.*, 1992 and Fabio *et al.*, 1997). Substantial structural tolerance at the 3-position of the indoles is shown by compound **5b**. It is also known that the modification of kynurenic acid (**1**) by introducing ureido group at 4-position led to a highly potent series of 4-substituted-2-carboxytetrahydroquinoline (**3**) (code; L-689560, IC_{50}=7.8 nm) with affinies in the nanomolar range(Leeson *et al.*, 1992).

Those findings suggests a broadly parallel structure-activity requirement to the 4-position of tetrahydro-quinoline series (Leeson *et al.*, 1992) and 3-position of indole series (Rowley *et al.*, 1992). Also a series of 2-quinolone derivatives **2** have designed with the goal of combining structural features present in the kynurenic acid 1 and quinoxalinedione **4**. By appling aforementioned concepts (e.g. introduction of urea functionality and keto (oxo)group) it was envisioned that structural modification at the 3-position of 2-carboxyindole **5** to its urea type derivative **6** may provide a new lead compound for the glycine site antagonist (Fig. 2). The synthesis started from the preparation of isatin (**9**). Thus, isatin (**9**) was synthesized according to the Sandmeyer procedure (Lackey *et al.*, 1995) whereby the α-oximino-anilide (**8**) formed by condensation of chloral hydrate, hydroxylamine and aniline was cyclized by concentrated H_2SO_4. The overall yield for the two steps was 58.2%. The isatin (**9**) was transformed into its hydrazone **10** almost in quantitative yield simply by treating methanol solution of **9** with hydrazine hydrate at 50°C. Finally, 4,6-dichloro-3-hydra-zono-1,3-dihydro-indole-2-one (**10**) was treated with aryliso-cyanates to give target compounds **6** in 50~82% yield. By no means the derivatization of **9** was not thorough at this stage, and either expansion or extention of this chemistry will highly depend on their biological evaluation for the NMDA receptor glycine site.



Reagent: a) (i)$CCl_3CHO.H_2O$, 2N-HCl, rt, 20min
(ii)$NH_2OH.HCl$, reflux, 30min, 58.2% overall
b) c-H_2SO_4, 80°C, 10min, 92.1%
c) $NH_2NH_2.H_2O$, MeOH, 50°C, 99%
d) Ar-N=C=O, DMF, Et_3N, rt, 10h, 52 ~ 82%

6a: Ar = Phenyl
6b: Ar = Benzenesulfonyl
6c: Ar = 4-Bromophenyl
6d: Ar = 4-Methoxyphenyl

Scheme 1. Synthesis of 4,6-dichloro-1*H*-indole-2,3-dione-3-*N*-(arylaminocarbonyl)hydrazones

In conclusion we synthesized 4,6-dichloro-3-[(1-*N*-arylaminocarbonyl)-hydrazono]-1,3-dihydro-indole-2-one (**6**) via fairly routine chemistry, and their biological activity for the NMDA receptor glycine site will be awaited.

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