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Synthesis of 5-Substituted Hexahydro-1H-1, 4-Diazepine Analogues

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Abstract: 5-Substituted hexahydro-1H-1,4-diazepine analogues were synthesized starting from N, N′-dibenzyl-1, 2-ethylenediamine and methyl 2, 4-dibromide butyrate through nucleophilic substitution, reduction, chlorination, debenzylation and amidation. Bioactivity tests showed that **9a** had the highest agonist activity.

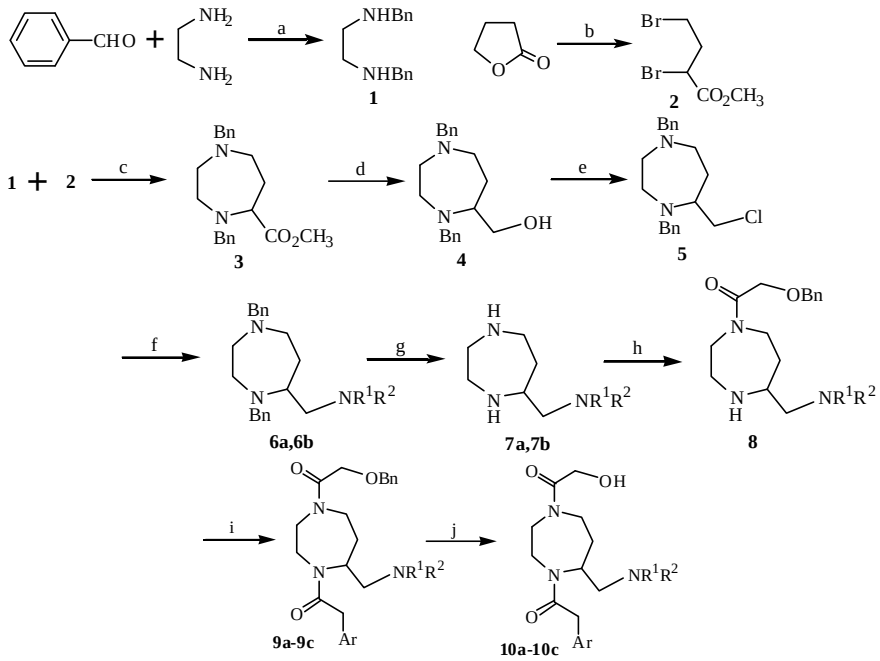
Key words: 5-Substituted hexahydro-1H-1, 4-diazepine analogues, synthesis, bioactivity.

Searching for new analgesic is still of great interesting for the researchers. Opioids have been a hot topic for their powerful pain relieving properties and their potential for recreational abuse[1,2]. In the previous paper[3] we have reported the synthesis of 2-substituted hexahydro-1H-1, 4-diazepine analogues. In order to get more selective κ-opioid receptor agonists, which can elicit analgesia while lacking serious side effects, a series of 5-substituted hexahydro-1H-1, 4-diazepine analogues carrying the segment of (1-arylacetamide-2-tertiaryamine) ethane have been synthesized in our laboratory. Herein, we report the synthesis of these novel target compounds (**9a-9c** and **10a-10c**) and the synthetic route (**Scheme 1**). The κ-opioid receptor antagonistic activity tests[4] showed that **9a** had the highest bioactivity among the target compounds.

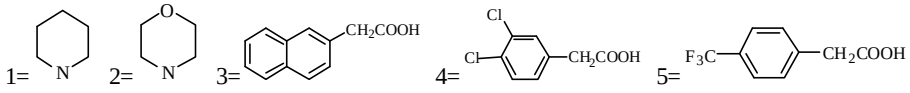
Compounds **1** and **2** were prepared according to the literatures[5,6] (yield, 76.3 and 93.7%). The mixture of **1** and **2** in toluene solution was stirred in the presence of triethylamine at 40-50°C for 24 hrs then at 55-60°C for 12 hrs. The extracted mixture was purified *via* silica gel with ethyl acetate- petroleum ether (5:1) as eluent to give yellow oil **3**, 1, 4-dibenzyl-5-methoxycarbonyl hexahydro –1H-1, 4-diazepine, in yield 46.8%.

The reduction of compound **3** was carried out in THF *via* the addition of $LiAlH_4$ at –10°C. Then the mixture was stirred at room temperature for 10 hrs and the resulting mixture was separated *via* silica gel with ethyl acetate-petroleum ether (3:1) as eluent to give colorless liquid **4**, 1, 4-dibenzyl-5-hydroxymethyl hexahydro-1H-1, 4-diazepine (yield, 87.1%).

Scheme 1



6a NR^1R^2=1; **6b** NR^1R^2=2; **7a** NR^1R^2=1; **7b** NR^1R^2=2; **9a** NR^1R^2=1, Ar=3; **9b** NR^1R^2=1, Ar=4; **9c** NR^1R^2=1, Ar=5; **10a** NR^1R^2=1, Ar=3; **10b** NR^1R^2=1, Ar=4; **10c** NR^1R^2=1, Ar=5.



Reagents and conditions: a. CH_3OH, pTS then KBH_4; b. Br_2, PBr_3 then CH_3OH; c. $PhCH_3$, NEt_3; d. THF, $LiAlH_4$; e. $CHCl_3$, $SOCl_2$; f. MOA or DMF, HNR^1R^2; g. CH_3OH, H_2, Pd-C; h. $BnOCH_2COOH$, THF; i. $ArCH_2COOH$, THF; j. Pd-C, CH_3OH.

Thionyl chloride was added into the chloroform solution of **4** (satured by HCl previously) and the mixture was stirred for 1.5 hrs at 50°C. The resulting mixture was cooled at 0-5°C in acetonitrile for over 8 hrs and compound **5**, 1, 4-dibenzyl-5-chloromethyl hexahydro-1H-1, 4-diaze-pine, was obtained. Under nitrogen atmosphere, compound **5** reacted with piperidine (morpholine) in methoxy ethanol (DMF) in the presence of K_2CO_3, NaI at 110-120°C for 18 hrs. The extracted mixtures were isolated *via* silica gel with petroleum ether-ethyl acetate carried (3:1) as eluent to give oil **6a** in yield 84.0% (white crystal **6b** in yield 87.8%), which were then catalyzed hydrogenolysis by Pd-C in methanol at 50°C for 12 hrs. Compounds **7a, 7b** [**7a** 5-(1-piperidyl)methyl hexahydro-1H-1, 4-diazepine, **7b** 5-(1-morpholinyl)-methyl hexahydro-1H-1, 4-diazepine] were achieved[7] in 89.3-90.3% yield.

Isobutyl chloroformate was added dropwise into the THF solution of benzyloxyacetic acid and equimolar quantity of triethyl amine and the mixture was stirred for 1 hr at room temperature. Then the mixture was added dropwise into the

solution of chloroform, dichloromethane, triethyl amine and the hydrochloride of **7a**. The reaction system was stirred for 2 hrs at -78°C to give the pale yellow oil **8**[8], 1-benzyloxy acetyl-5-(1-piperidyl)methyl-hexahydro-1H-1, 4-diazepine, in yield 67.8%. The viscous oil **9a**, 1-benzyloxy acetyl-4-(2-naphthyl) acetyl-5-(1-piperidyl)methyl hexahydro-1H-1, 4-diazepine, was prepared by reaction of **8** with equimolar quantity of 2-naphthyl acetic acid and 1, 1′-carbonyldiimidazole in THF for 10 hrs with 75.0% yield. In a similar way as 2-naphthylacetic acid 3, 4-dichloro phenylacetic acid and 4-trifluoro methyl phenylacetic acid reacted with **8** to give[9] **9b**, **9c** [1-benzyloxy acetyl-4-(3, 4-dichlorophenyl) acetyl-5-(1-piperidyl)methyl-hexahydro-1H-1, 4-diazepine, 1-benzyl-oxy acetyl-4-(4-trifluoromethyl phenyl) acetyl-5-(1-piperidyl)methyl- hexahydro-1H-1, 4-diazepine] in yield 58.9 and 68.7%, respectively. **9a** could be converted into foam-like solid, the hydrochloride of **10a**, 1-hydroxymethyl carbonyl-4-(2-naphthyl) acetyl-5-(1-piperidyl)methyl-hexahydro-1H-1,4-diazepine by catalyzed hydrogenolysis with Pd-C at 50°C in MeOH for 8 hrs in the presence of few drops of hydrochloric acid, in 81.0% yield. **10b**, **10c** [1-hydroxymethyl carbonyl-4-(3,4-dichlorophenyl) acetyl-5-(1-piperidyl) methyl hexahydro-1H-1, 4-diazepine, 1-hydroxymethyl carbonyl-4-(4-tri-fluoromethyl phenyl) acetyl-5-(1-piperidyl)methyl hexahydro-1H-1, 4-diazepine] were prepared[10] from **9b**, **9c** in the same synthetic route of **10a** in yield 65.0 and 76.0%. All products were characterized by NMR, EIMS, IR and Elem. anal.

The receptor affinity of the target compounds of **9a-c** and **10a-c** were tested and their results were shown in **Table 1**. The IC_{50} value for inhibition the contraction of GPI of **9a** was 2.36 ± 0.45.

Table 1 The receptor affinity tests in guinea pig ileum (GPI) of the target compounds

Compd. (5×10^{-6}M)	**9a**	**9b**	**9c**	**10a**	**10b**	**10c**
Agonist activity (inhibition rate,%)	86	16	22	9	0	2
Reverse test	0	0	0	0	0	0

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8. Data of **9a-c**: **9a** mp (from formic acid-ethyl acetate) 108-101°C; EIMS *m/z*: 513 (M^+), 422, 400, 372, 141, 112, 98 (100%), 91; Anal.calcd.for $C_{32}H_{39}N_3O_3 \cdot C_4H_4O_4 \cdot 0.75H_2O$: C 67.22, H 6.97, N 6.53; found C 67.40, H 6.91, N 6.26. **9b:** ^{1}H NMR ($CDCl_3$, δ ppm and *J* in Hz): 1.41-1.94 (br, 8H, 5-CH_2, 3'-CH_2, 4'-CH_2, 5'-CH_2), 1.96-3.05 (br, 8H, 2'-CH_2,

6'-CH_2, $CHCH_2N$, 7-CH_2NCO), 3.60-4.45 (m, 4H, 2-CH_2NCO, 3-CH_2NCO), 3.70 (dd, 2H, J_1=16.37, J_2=16.88, $PhCH_2CO$), 4.30 (dd, 2H, J_1=37.98, J_2=15.42,$COCH_2O$), 4.55 (dd, J=12.46, 2H, $PhCH_2O$), 4.50 (*ca* 0.4H, C*H*CH_2N), 4.68-4.75 (*ca* 0.6H, br, $CHCH_2N$), 7.05-7.40 (8H, 8×ArH); IR (KBr) ν: 3500, 2950, 1645, 1471, 1140, 1030, 752cm^{-1}; HRMS *m/z*: 531 (M^+); Anal.calcd.for $C_{28}H_{35}N_3O_3Cl_2$ 531.2058, Obsd 531.2051 (delta=0.5, R+D=12). **9c** ^{1}H NMR ($CDCl_3$, δ ppm and J in Hz): 1.40-1.90 (m, 8H, 3'-CH_2, 4'-CH_2, 5'-CH_2, 6-CH_2), 2.10-2.60 (br, 6H, 2'-CH_2, 6'-CH_2, 7-CH_2), 2.70-3.00(dt, 2H, J_1=53.05, J_2=12.44, $CHCH_2N$), 3.50-4.40 (m, 4H, 2-CH_2, 3-CH_2), 4.05-4.25 (m, 4H, $ArCH_2CO$, $COCH_2O$), 4.45-4.60 (br, 2H, OCH_2Ph), 4.70-4.85 (*ca* 0.35H, 5-CH), 7.30-7.60 (m, 9H, 4×ArH, 5×PhH); EI MS *m/z:* 531(M^+), 440, 344, 159, 112, 98 (100%), 85.

9. Data of **10b-c**: **10b** ^{1}H-NMR($CDCl_3$, δ ppm and J in Hz): 1.45-1.95 (br, 6H, 3'-CH_2, 4'-CH_2, 5'-CH_2, 6-CH_2), 2.10-2.55 (br, 6H, 2'-CH_2N, 6'-CH_2N, 7-CH_2NCO), 2.60-3.10 (br, 3H, $CHCH_2N$, $COCH_2OH$) (could be exchanged by D_2O), 3.10-3.90 (br, 5H, 2-CH_2N, 3-CH_2N, H_2O) (could be exchanged by D_2O), 4.00-4.35 (br, 4H, $ArCH_2CO$, $COCH_2OH$), 4.55-4.85 (b, d, J=12.66, 1H, 5-Heq, 5-Hax), 7.20-7.40 (m, 10H, 10×ArH); EIMS *m/z*: 373(M^+), 316, 282, 254, 112, 98, 85. **10c** ^{1}H-NMR (D_2O, δppm): 1.45-2.12 (m, 8H, 3'-CH_2, 4'-CH_2, 5'-CH_2, 6-CH_2), 2.78-3.00 (m, 4H, 2'-CH_2, 6'-CH_2), 3.03-3.28 (d, t, 2H, J_1=54.70, J_2=11.61, $CHCH_2N$), 3.35-3.58 (br, 3H, 7-CHeq, 3-CHeq), 3.67-3.85 (m, 1H, 2-CHeq), 3.95-4.90 (m, 2H, 2-CHax, 3-CHax), 4.80 (br, 1H, C*H*CH_2N), 7.50-7.77 (m, 4H, 4×ArH); Anal.calcd. for $C_{22}H_3ON_3O_3F_3 \cdot HCl \cdot 3H_2O$: C 49.67, H 7.01, N 7.90; found C 49.69, H 6.60, N 7.56.

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