

Synthesis of Praziquantel Derivatives and Their *In Vitro* Activity Against Adult *Clonorchis sinensis*

Choong Sup Kim¹ and Duk Young Min²

¹Division of Applied Science, Korea Institute of Science & Technology, Seoul 136-791, Korea and ²Department of Parasitology, College of Medicine, Hanyang University, Seoul 133-791, Korea

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Several praziquantel derivatives have been prepared by the acylation of compound **5**, and examined on their biological activity *in vitro* against adult *Clonorchis sinensis* collected from rabbits infected with metacercariae which was isolated from *Pseudorasbora parva*, a second intermediate host, captured in Nakdong river in Korea.

Key words : Praziquantel derivatives, Anthelmintic activity, *Clonorchis sinensis*

INTRODUCTION

Praziquantel is a synthetic drug exhibiting exceptional activity against all schistosomes affecting human beings and animals. Its pharmacological profile has well accepted in clinics as a drug of choice for the treatment of cestodiasis disease (Hardman *et al.*, 1996). In this point, several research groups have extensively investigated on the structure-activity relationship of this class of compounds and attempted to develop a more efficient synthetic route to praziquantel and its derivatives (Abo-Ghaila *et al.*, 1996; Day *et al.*, 1992; Hassanein, *et al.*, 1995; Pohlke, *et al.*, 1975; Yuste *et al.*, 1986).

Until praziquantel was marketed in early 1980's in Korea, clonorchiasis (Chinese liver fluke infection) was one of the most prevalent parasitic disease to inhabitants of rural area near rivers, especially in southern part of Korea. Accordingly, we have interested in development of less expensive synthetic pathway of praziquantel and its derivatives for the structure-activity relationship study.

As the result of our continuous efforts on this study, we reported a short and practical synthesis of praziquantel as shown in the following Scheme (Kim *et al.*, 1998). Our synthetic approach is a tandem one-pot amidoalkylation and cyclization of N-acyl imminium ion intermediate **4** generated *in situ* from compound **3** which can be easily prepared from readily available starting materials such as the corresponding phenethylamine **1**, monochloroacetyl chloride and amino-

acetaldehyde dimethylacetal. Unique feature of this synthetic route is to introduce various substituents to the phenyl ring of Praziquantel structure by using a substituted phenethylamine **1** as a starting material.

We prepared several derivatives of praziquantel by acylation and addition reaction of alkyliso (or alkylisothio) cyanate to a key intermediate **5**, and examined on their biological activity *in vitro* against adult *Clonorchis sinensis* (Chinese liver fluke) originated from *Pseudorasbora parva*, a second intermediate host, captured in Nakdong river in Korea.

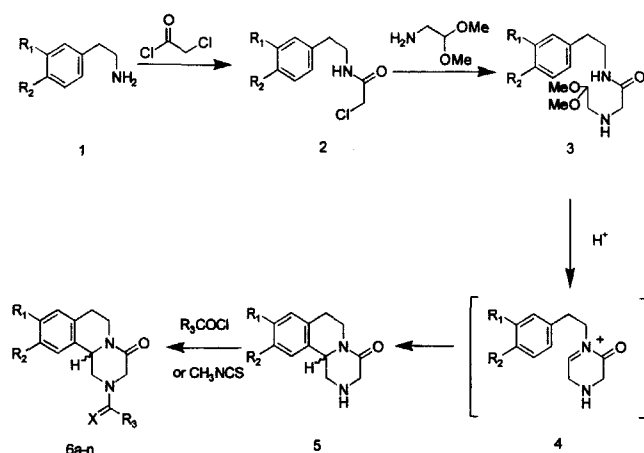
MATERIALS AND METHODS

Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on Varian A-60 (60 MHz) spectrometer. Chemical shifts (δ) were reported in ppm downfield from internal tetramethylsilane. Infrared (IR) spectra were recorded on Perkin-Elmer 137 spectrophotometer. All chemicals used for synthetic procedure were reagent grade.

N2-Methyl-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-2-carbothioamide (6b)

To a solution of 1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (5=HPI; R₁,R₂=H: 4.06 g, 0.02 mol) in CH₂Cl₂ (50 ml) was slowly added methylisothiocyanate (1.07 ml, 0.016 mol). The mixture was stirred for 1 h at room temperature and evaporated the solvent. The residue was triturated with ethyl acetate to obtain a pure product (5.06 g, 91.8%). m.p. 224~225°C; IR (KBr) 3310, 3290, 2900, 1650, 1640, 1540, 1460, 1440, 1410, 1330, 1290 cm⁻¹; ¹H NMR

Correspondence to: Choong Sup Kim, Biochemicals Research Center Korea Institute of Science and Technology, P.O. Box. 131, Cheongryang, Seoul 136-791, Korea



- Praziquantel 6a** ($R_1, R_2 = H, R_3 = \text{cyclohexyl}, X = O$);
6b ($R_1, R_2 = H, R_3 = \text{NHCH}_3, X = S$);
6c ($R_1, R_2 = H, R_3 = \text{cyclopropyl}, X = O$);
6d ($R_1, R_2 = \text{OCH}_3, R_3 = \text{CH}_3, X = O$);
6e ($R_1, R_2 = H, R_3 = 3,4,5\text{-trimethoxyphenyl}, X = O$);
6f ($R_1, R_2 = \text{OCH}_3, R_3 = 3,4,5\text{-trimethoxyphenyl}, X = O$);
6g ($R_1, R_2 = H, R_3 = \text{NHCH}_3, X = O$);
6h ($R_1, R_2 = \text{OCH}_3, R_3 = \text{cyclopropyl}, X = O$);
6i ($R_1, R_2 = \text{OCH}_3, R_3 = \text{cyclohexyl}, X = O$);
6j ($R_1, R_2 = \text{OCH}_3, R_3 = t\text{-butyl}, X = O$);
6k ($R_1, R_2 = \text{OCH}_3, R_3 = \text{NHCH}_3, X = O$);
6l ($R_1, R_2 = \text{OCH}_3, R_3 = \text{cyclopentyl}, X = O$);
6m ($R_1 = H, R_2 = \text{Br}, R_3 = \text{cyclohexyl}, X = O$);
6n (L-form of 6e)

Scheme

(DMSO- CDCl_3) δ 7.90 (1H, NH), 7.20~7.35 (m, 4H, phenyl protons), 5.15 (1H, dd, $J = 13.4, 2.8$ Hz, H-6') 4.83~4.92 (2H, m, H-1' and H-11b), 4.55 (1H, d, $J = 16.5$ Hz, H-3'), 4.15 (1H, d, $J = 16.5$ Hz, H-3), 3.40 (3H, s, NCH_3), 2.82~3.12 (4H, m, H-1, H-6 and 2 x H-7).

2-Cyclopropylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6c)

Cyclopropanecarbonyl chloride (3.0 ml, 0.033 mol) was slowly added dropwise to a solution of HPI (6.08 g, 0.02 mol) and triethylamine (6.28 ml, 0.045 mol) in CH_2Cl_2 (70 ml) in an ice-bath. After adding all of the chloride, the mixture was stirred for 1 h at room temperature and added water (80 ml). Organic layer was separated, washed with water, and dried. Solvent was evaporated, and the residue was triturated with ethyl acetate-hexane (1:1) mixture to obtain the product (7.12 g, 87.7%). A pure sample was recrystallized from CH_2Cl_2 -hexane. m.p. 142~144°C; IR (KBr) 1470, 1440, 1410, 1240 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.17~7.30 (m, 4H, phenyl protons), 5.05 (1H, dd, $J = 13.4, 2.8$ Hz, H-6') 4.73~4.85 (2H, m, H-1' and H-11b), 4.42 (1H, d, $J = 16.5$ Hz, H-3'), 4.08 (1H, d, $J = 16.5$ Hz, H-3), 2.82~3.12 (4H, m, H-1, H-6 and 2 x H-7), 1.66~1.78 (1H,

m, NCOCH_2), 0.83~1.05 (4H, m, cyclopropyl protons).
9,10-Dimethoxy-2-acetyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6d)

The product (6d) was prepared in 85% yield in the same manner as the compound (6c) with 9,10-dimethoxy-HPI (5; $R_1, R_2 = \text{OCH}_3$; 5.24 g, 0.02 mol). m.p. 120~122°C; IR (KBr) 1650, 1640, 1520, 1460, 1450, 1430, 1420, 1260, 1230 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 6.82 (1H, s, phenyl proton), 6.72 (1H, s, phenyl proton), 4.50~5.20 (2H, m, H-6 and H-11b), 3.97 (6H, s, OCH_3), 3.43~3.95 (3H, m, H-3 and H-1), 2.65~3.24 (4H, m, H-1, H-6 and H-7), 2.24 (3H, s, COCH_3).

2-(3,4,5-Trimethoxybenzoyl)-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6e)

The compound (6e) was obtained in 83.2% yield (9.90 g) by the same method as 6c using HPI (6.08 g, 0.03 mol) and trimethoxybenzoyl chloride (8.30 g, 0.036 mol). m.p. 146~147°C; IR (KBr) 1650, 1640, 1585, 1460, 1440, 1420, 1340, 1250, 1230, 1130 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.23~7.32 (m, 4H, phenyl protons), 6.81 (2H, s, acyl phenyl protons), 5.15 (1H, dd, $J = 13.4, 2.8$ Hz, H-6') 4.58~4.69 (2H, m, H-1' and H-11b), 4.38 (1H, d, $J = 16.5$ Hz, H-3'), 4.01 (1H, d, $J = 16.5$ Hz, H-3), 3.95 (9H, s, OCH_3), 2.72~3.02 (4H, m, H-1, H-6 and 2 x H-7).

9,10-Dimethoxy-2-(3,4,5-trimethoxybenzoyl)-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6f)

The desired compound (6f) was prepared by the same method as 6d in 93.1% yield. m.p. 148~150°C; IR (KBr); 1640, 1630, 1580, 1510, 1460, 1430, 1410, 1340, 1260, 1230, 1130 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 6.75 (1H, s, phenyl proton), 6.73 (1H, s, phenyl proton), 6.70 (2H, s, acyl phenyl protons), 5.23 (1H, dd, $J = 13.4, 2.8$ Hz, H-6'), 4.63~4.72 (2H, m, H-1' and H-11b), 4.41 (1H, d, $J = 16.5$ Hz, H-3'), 4.08 (1H, d, $J = 16.5$ Hz, H-3), 3.93 (9H, s, OCH_3), 2.73~3.08 (4H, m, H-1, H-6 and 2 x H-7).

N2-Methyl-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-2-carboxamide (6g)

Compound (6g) was obtained in quantitative yield (8.02 g) by a reaction of HPI (6.08 g, 0.03 mol) and methylisocyanate (2.12 ml, 0.036 mol) in the same manner as the compound (6b). m.p. 186~187°C; IR (KBr) 3370, 1660, 1630, 1540, 1480, 1410, 1260, 760 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.27~7.38 (m, 4H, phenyl protons), 5.25 (1H, dd, $J = 13.4, 2.8$ Hz, H-6') 4.88~4.97 (2H, m, H-1' and H-11b), 4.58 (1H, d, $J = 16.5$ Hz, H-3'), 4.23 (1H, d, $J = 16.5$ Hz, H-3), 2.84 (3H, s, NCH_3), 2.90~3.22 (4H, m, H-1, H-6 and 2 x H-7).

9,10-Dimethoxy-2-cyclopropylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6h)

The compound (6h) was prepared by the same method as the compound (6d) in 82.6 % yield. m.p. 127~128°C; IR (KBr); 1660, 1510, 1460, 1450, 1420, 1260, 1230, 1210, 1080, cm^{-1} ; ^1H NMR (CDCl_3) δ 6.78 (1H, s, phenyl proton), 6.70 (1H, s, phenyl proton), 5.25 (1H, dd, $J=13.4, 2.8$ Hz, H-6'), 4.65~4.74 (2H, m, H-1' and H-11b), 4.43 (1H, d, $J=16.5$ Hz, H-3'), 4.11 (1H, d, $J=16.5$ Hz, H-3), 3.90 (6H, s, OCH_3), 2.72~3.05 (4H, m, H-1, H-6 and 2 x H-7), 1.68~1.81 (1H, m, NCOCH-), 0.91~1.15 (4H, m, cyclopropane protons).

9,10-Dimethoxy-2-cyclohexylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6i)

The desired compound was obtained by the same method as the compound (6c) with cyclohexanecarbonyl chloride in 78% yield. m.p. 91~92°C; IR (KBr); 3530, 1650, 1600, 1470, 1440, 1260, 1220 cm^{-1} ; ^1H NMR (CDCl_3) δ 6.73 (1H, s, phenyl proton), 6.71 (1H, s, phenyl proton), 5.20 (1H, dd, $J=13.4, 2.8$ Hz, H-6'), 4.61~4.72 (2H, m, H-1' and H-11b), 4.42 (1H, d, $J=16.5$ Hz, H-3'), 4.10 (1H, d, $J=16.5$ Hz, H-3), 3.88 (6H, s, OCH_3), 2.76~3.11 (4H, m, H-1, H-6 and 2 x H-7), 1.76~1.98 (1H, m, NCOCH), 1.10~1.72 (10H, m, cyclohexane protons).

9,10-Dimethoxy-2-t-butylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6j)

The compound was prepared by acylation of dimethoxy substituted HPI with pivaloyl chloride as in the compound (6d). m.p. 116~118°C; IR (KBr); 3530, 1630, 1610, 1500, 1450, 1420, 1400, 1230, 1160 cm^{-1} ; ^1H NMR (CDCl_3) δ 6.70 (1H, s, phenyl proton), 6.75 (1H, s, phenyl proton), 5.23 (1H, dd, $J=13.4, 2.8$ Hz, H-6') 4.63~4.72 (2H, m, H-1' and H-11b), 4.45 (1H, d, $J=16.5$ Hz, H-3'), 4.14 (1H, d, $J=16.5$ Hz, H-3), 3.90 (6H, s, OCH_3), 2.79~3.13 (4H, m, H-1, H-6 and 2 x H-7), 1.40 (9H, s, 3CH_3).

9,10-Dimethoxy-N2-methyl-4-oxo-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-2-carboxamide (6k)

The desired compound (6k) was prepared as in the compound (6g) in 92.0% yield. m.p. 195~196°C; IR (KBr) 3400, 2950, 1670, 1650, 1550, 1530, 1480, 1440, 1390, 1370, 1350, 1330, 1290, 1270, 1220, cm^{-1} ; ^1H NMR (CDCl_3) δ 6.80 (1H, s, phenyl proton), 6.70 (1H, s, phenyl proton), 5.87 (1H, s, NH), 5.22 (1H, dd, $J=13.4, 2.8$ Hz, H-6') 4.87~4.95 (2H, m, H-1' and H-11b), 4.56 (1H, d, $J=16.5$ Hz, H-3'), 4.21 (1H, d, $J=16.5$ Hz, H-3), 3.90 (6H, s, OCH_3), 2.86 (3H, s, NCH_3), 2.85~3.02 (4H, m, H-1, H-6 and 2 x H-7).

9,10-Dimethoxy-2-cyclopentylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6l)

The desired compound (6l) was prepared as in the compound (6c) in 82.6% yield. m.p. 102~104°C; IR (KBr) 2950, 1670, 1660, 1650, 1430, 1265, 1230, cm^{-1} ; ^1H NMR (CDCl_3) δ 6.78 (1H, s, phenyl proton), 6.70 (1H, s, phenyl proton), 5.83 (1H, s, NH), 5.24 (1H, dd, $J=13.4, 2.8$ Hz, H-6'), 4.85~4.94 (2H, m, H-1' and H-11b), 4.57 (1H, d, $J=16.5$ Hz, H-3'), 4.25 (1H, d, $J=16.5$ Hz, H-3), 3.90 (6H, s, OCH_3), 2.84~3.05 (4H, m, H-1, H-6 and 2 x H-7), 1.62~1.93 (9H, m, NCOCH= and cyclohexane protons).

10-Bromo-2-cyclohexylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6m)

The compound was prepared by acylation of 10-bromosubstituted HPI (5, $\text{R}_1=\text{H}$, $\text{R}_2=\text{Br}$) with cyclohexanecarbonyl chloride in 78.1% yield. m.p. 81~83°C; IR (KBr); 2900, 1630, 1425, 1400, 1230 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.80 (1H, s, H-11), 7.75 (1H, d, $J=9.0$ Hz, H-9), 7.42 (1H, d, $J=9.0$ Hz, H-8), 5.29 (1H, dd, $J=13.4, 2.8$ Hz, H-6'), 4.69~4.78 (2H, m, H-1' and H-11b), 4.48 (1H, d, $J=16.5$ Hz, H-3'), 4.18 (1H, d, $J=16.5$ Hz, H-3), 2.86~3.31 (4H, m, H-1, H-6 and 2 x H-7), 2.40~2.01 (1H, m, NCOCH), 1.60~1.92 (9H, m, cyclohexane protons).

(-)-9,10-Dimethoxy-2-cyclohexylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (6n)

(-)-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one (5, $\text{R}_1=\text{R}_2=\text{OCH}_3$), which was obtained by resolution of a racemic mixture by the same method described in the literature (Pohlke *et al.*), was acylated as in the compound (6f). m.p. 141~147°C, $[\alpha]_{\text{D}}^{25}=-9.4$ The NMR and IR spectrum were coincided with its racemic mixture (6f).

Preparation of adult *Clonorchis sinensis* (Chinese liver fluke)

Metacercariae of *C. sinensis* were isolated from *Pseudorasbora parva* captured in Nakdong river, and infected orally to rabbits. The rabbits were sacrificed in two months later after infection, and adult *C. sinensis* were collected from bile ducts of the sacrificed rabbits. The collected adult worms washed with a sterilized incubation mixture of TC199 and normal saline (Rim *et al.*, 1980), and selected active ones for biological tests.

Anthelmintic activity test

Control test with praziquantel: Adult *C. sinensis* were treated with 0~0.3 $\mu\text{g}/\text{ml}$ concentration of praziquantel

Table I. *In vitro* activities of praziquantel against *Clonorchis sinensis*

Concentration ($\mu\text{g/ml}$)	Incubation time at 37°C						
	0	30 min	1 h	2 hrs	6 hrs	12 hrs	24 hrs
0.3	+++	-	-	-	-	-	-
0.1	+++	++	+	+	+	-	-
0.05	+++	++	++	++	++	+	-
0.03	+++	+++	+++	++	++	++	+
0.01	+++	+++	+++	++	++	++	+
0	+++	+++	+++	+++	++	+++	++

+++ : very active, ++ : active, + : sluggish, - : no movement

Table II. *In vitro* activities of praziquantel derivatives against adult *Clonorchis sinensis*

Drugs	Concentration ($\mu\text{g/ml}$)	Incubation time at 37°C						
		0	30 min	1 h	2 hrs	6 hrs	12 hrs	24 hrs
Control	0	+++	+++	+++	+++	+++	++	++
Praziquantel	0.1 $\mu\text{g/ml}$	+++	++	+	+	+	-	-
	0.3 $\mu\text{g/ml}$	+++	-	-	-	-	-	-
6b	0.1 $\mu\text{g/ml}$	+++	+++	++	++	++	++	++
	0.3 $\mu\text{g/ml}$	+++	+++	+++	++	++	++	+
6c	0.1 $\mu\text{g/ml}$	+++	+++	++	++	++	++	+
	0.3 $\mu\text{g/ml}$	+++	+++	++	++	++	++	+
6d	0.1 $\mu\text{g/ml}$	+++	+++	++	++	++	++	+
	0.3 $\mu\text{g/ml}$	+++	+++	++	++	++	++	++
6e	0.1 $\mu\text{g/ml}$	+++	+++	+++	++	++	++	+
	0.3 $\mu\text{g/ml}$	+++	+++	+++	+++	++	++	+
6f	0.1 $\mu\text{g/ml}$	+++	+++	++	++	+	++	++
	0.3 $\mu\text{g/ml}$	+++	+++	++	++	++	++	++
6g	0.1 $\mu\text{g/ml}$	+++	+++	+++	++	+	+	+
	0.3 $\mu\text{g/ml}$	+++	+++	+++	++	+	+	+
6h	0.1 $\mu\text{g/ml}$	+++	+++	+++	+++	++	++	+
	0.3 $\mu\text{g/ml}$	+++	+++	+++	+++	++	++	+
6i	0.1 $\mu\text{g/ml}$	+++	+++	+++	+++	+	++	++
	0.3 $\mu\text{g/ml}$	+++	+++	+++	++	++	++	++
6j	0.1 $\mu\text{g/ml}$	+++	+++	+++	++	+	+	+
	0.3 $\mu\text{g/ml}$	+++	+++	++	++	+	+	+
6k	0.1 $\mu\text{g/ml}$	+++	+++	+++	++	++	++	++
	0.3 $\mu\text{g/ml}$	+++	+++	+++	++	++	+	+
6l	0.1 $\mu\text{g/ml}$	+++	++	++	++	++	++	+
	0.3 $\mu\text{g/ml}$	+++	++	++	++	++	+	+
6m	0.1 $\mu\text{g/ml}$	+++	++	++	+	+	+	-
	0.3 $\mu\text{g/ml}$	+++	++	++	+	+	-	-
6n	0.1 $\mu\text{g/ml}$	+++	+++	++	++	++	++	+
	0.3 $\mu\text{g/ml}$	+++	+++	+++	++	++	++	+

at 37°C as shown in Table I. Anthelmintic activity was observed from 30 min. to 24 hrs, and graded activity by triple plus symbol (+++) for control or very active, double plus (++) for active, single plus (+) for sluggish, and minus symbol (-) for no movement. At a concentration of 0.3 $\mu\text{g/ml}$, all flukes were dead within 30 minutes, and 6 hours at 0.1 $\mu\text{g/ml}$ concentration. However, about 30% of worms were still alive

even after 24 hours at below 0.01 $\mu\text{g/ml}$ concentration (Table I).

Activity test with samples: Compounds (**6b-n**) were incubated with flukes in the same manner as the control test group with praziquantel. Concentration of the compounds was 0.1 and 0.3 $\mu\text{g/ml}$, and compared their activity with results of the same concentration of praziquantel as shown in Table II.

RESULTS AND DISCUSSION

Synthesis

The acylation of **5** with a corresponding acyl chloride was smoothly accomplished in the presence of organic base such as triethylamine in methylene chloride. Thiourea and urea compounds **6b**, **6g** and **6k** were also obtained in almost quantitative yield by reaction of compound **5** with methylisothiocyanate or methylisocyanate. Racemic mixture of the intermediate **5** was resolved to obtain L-form by the known method reported in the literature (Pholke *et al.*, 1975) and acylated to prepare corresponding L-form derivatives. For substituent of phenyl ring of Praziquantel structure substituted phenethylamines **1** were selected in the beginning of the synthesis.

Biological activity

Most of derivatives, even at high concentration (0.3 µg/ml), were negligibly active against adult *C. sinensis* except that the compound **6m** possessing a bromine atom on the phenyl ring of praziquantel shows weak activity. This finding suggests that a substitution of phenyl ring decreases the activity, and cyclohexane carbonyl moiety is the most favorable acyl group for anticestocidal activity of Praziquantel structure.

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