HETEROCYCLES, Vol. 92, No. 11, 2016, pp. 1983 - 1993. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 21st July, 2016, Accepted, 3rd October, 2016, Published online, 11th October, 2016
DOI: 10.3987/COM-16-13538

A CONCISE AND HIGHLY EFFICIENT SYNTHESIS OF PRAZIQUANTEL AS AN ANTHELMINTIC DRUG

Zhezhou Yang, Lin Zhang, Huirong Jiao, Rusheng Bao, Weiwei Xu, and Fuli Zhang*

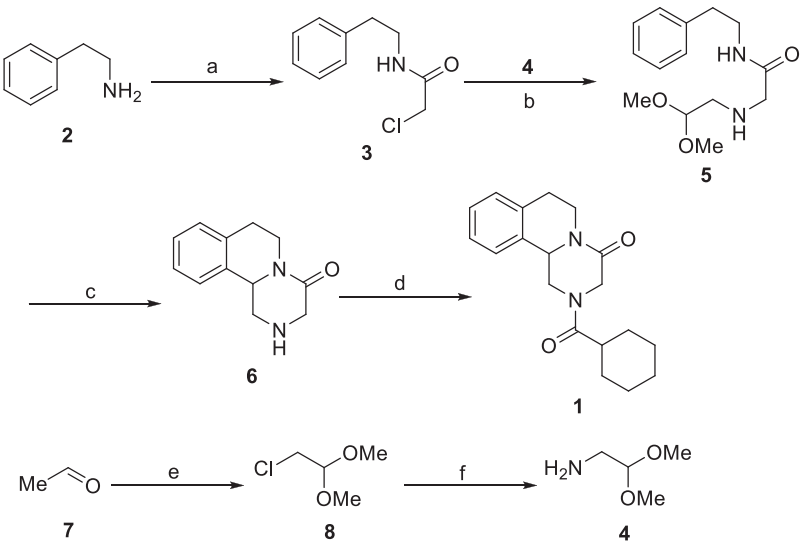
Shanghai Institute of Pharmaceutical Industry, China State Institute of Pharmaceutical Industry, 285 Gebaini Road, Shanghai 201203, China; E-mail: zhangfuli1@sinopharm.com

Abstract – A concise and practical synthesis of praziquantel as anthelmintic drug is described. The key steps include a monoalkylation of ethanolamine for the preparation of 2-(2-hydroxyethylamino)-*N*-phenethylacetamide and a mild oxidation protocol with SO_3-Py/DMSO as oxidant to transform alcohol into the corresponding aza-acetal. The telescoped synthesis is composed of five steps without purification of the intermediates, providing an overall yield of 80% with 99.8% purity after crystallization.

INTRODUCTION

Praziquantel (**1**) is a well known anthelmintic drug used in humans and animals with a broad activity against trematodes and schistosomes.[1] Since it was approved and especially recommended as the first choice for the treatment of schistosomiasis by World Health Organization in 1980, it has been accepted as the most effective drug to control helminthiasis.[2]

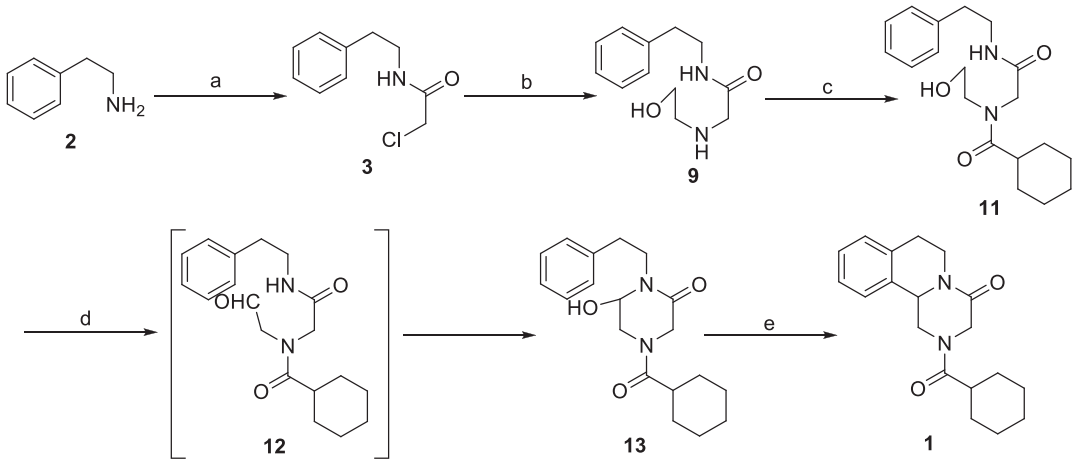
Although several methods for the synthesis of praziquantel were known in the literatures,[3] there are some drawbacks such as expensive cost and severe environmental pollution, e.g., the initial synthetic route required high pressure hydrogenation, highly toxic cyanide and huge amounts of phosphoric acid to produce praziquantel from isoquinnoline.[3a] Kim reported the synthetic pathway to praziquantel comprising only four steps from phenethylamine with a total yield of 50% (Scheme 1).[3g] Particularly, as both reagent and base, aminoacetaldehyde dimethyl acetal (**4**) played a key role in the concomitant formation of piperazine ring and isoquinoline ring. However, the route needed excess **4** which was obtained with poor yield and harsh reaction conditions through chlorination, acetalization and ammoniation from acetaldehyde.[4] Due to the similarity, Dömling had developed a three-step synthesis of praziquantel using Ugi four-component reaction, which resulted in an unacceptable yield of 39%.[3l]



Scheme 1. Regents and conditions: (a) chloroacetyl chloride, $NaHCO_3$, CH_2Cl_2, 0 °C, 3 h, 92%; (b) toluene, reflux, 2 h, 67%; (c) *conc.* H_2SO_4, rt, 3.5 h, 96%; (d) cyclohexanecarbonyl chloride, Na_2CO_3, CH_2Cl_2, rt, 2 h, 85%; (e) (i) Cl_2; (ii) MeOH, $CaCl_2$, 20-30 °C, 4 h, 50%; (f) 72.0 equiv liquid NH_3, MeOH, 140 °C, conducted in an airtight reactor for 10 h, 70%.

RESULTS AND DISCUSSION

In this paper we report an alternate synthesis of praziquantel, which utilized ethanolamine to replace the expensive aminoacetaldehyde dimethyl acetal and developed a practical telescoped process to obtain a high yield and purity product, eliminating some isolation and purification (Scheme 2).

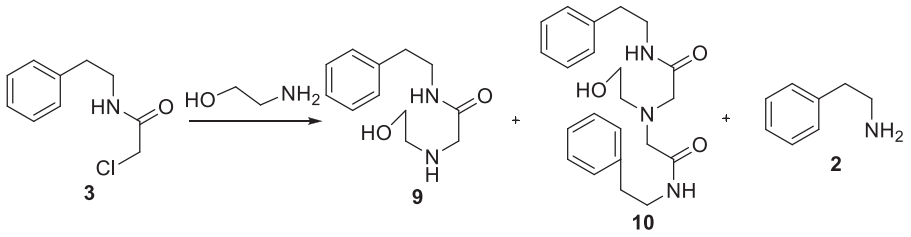


Scheme 2. Regents and conditions: (a) chloroacetyl chloride, NaOH, CH_2Cl_2, 0-10 °C, 4 h, quant.; (b) 8.0 equiv ethanolamine, 0-5 °C, 12 h; (c) cyclohexanecarbonyl chloride, NaOH, CH_2Cl_2, 0-10 °C, 5 h, 94% from **2**; (d) SO_3-Py, DMSO, Et_3N, 15-20 °C, 7 h; (e) *conc.* H_2SO_4, CH_2Cl_2, 0-5 °C, 4 h, 85% from **11**.

Commercially available phenethylamine **2** was reacted with chloroacetyl chloride in dichloromethane with sodium hydroxide as the base to give crude **3** in quantitative yield and 99.10% purity. In the preparation of **9**, an excess of ethanolamine was used as both reagent and base. In crude **9**, two major

impurities were identified as transamidation byproduct **2** and over-aminoalkylation byproduct **10**.[5] In an effort to minimize them, we investigated the amount of ethanolamine and temperature on the reaction performance. The results reported in Table 1 showed that the lower the reaction temperature, the lower the levels of the impurity **2** (Table 1, entries 1-5), and the proportion of **10** decreased if the quantity of ethanolamine was increased (Table 1, entries 4 and 6-9). Employing 8-fold excess of ethanolamine at low temperature was found to be suitable to achieve excellent conversion to **9** (Table 1, entry 5). Because of the similar partition in water and many organic solvents, ethanolamine was difficult to separate from compound **9** completely. After the completion of reaction, aqueous sodium hydroxide was added to the mixture, and xylene was added to remove the residual ethanolamine by azeotropic distillation *in vacuo*,[6] which can be recycled and reused into the process. HPLC examination of the crude product indicated that **9** has 96.10% purity along with 1.21% of **2** and 1.68% of **10**, which was subjected to the next step without further purification. Condensation of **9** with cyclohexanecarbonyl chloride in the presence of sodium hydroxide gave the crude **11**. After washing with methyl tert-butyl ether, **11** with 99.56% purity was obtained in 94% yield from phenethylamine. HPLC examination revealed the presence of the impurity **10** in less than 0.5%.

Table 1. Optimization of **9** formation[a]

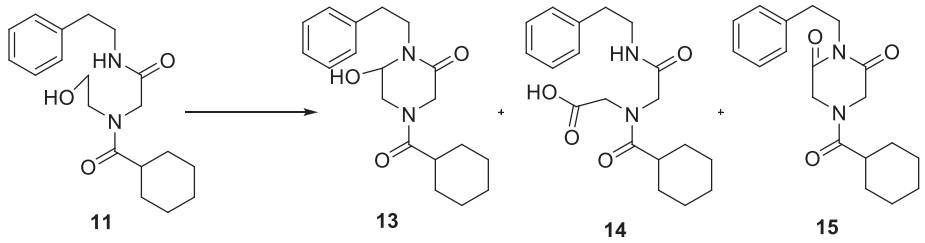


Entry	Ethanolamine (equiv)	Temp (°C)	**2** (%)[b]	**10** (%)[b]	**9** (%)[b]
1	8.0	65	6.62	0.65	90.51
2	8.0	55	2.61	0.88	96.12
3	8.0	40	1.22	1.73	95.72
4	8.0	20	0.72	2.41	95.86
5	8.0	5-10	0.32	2.73	96.27
6	6.0	20	0.73	2.95	94.75
7	5.0	20	0.82	3.91	93.80
8	4.0	20	0.79	5.38	92.23
9	3.0	20	0.73	8.36	89.81

[a] Reaction conditions: A mixture of **3** and ethanolamine was stired at the stated conditions. [b] Measured by HPLC analysis in area normalization.

The aldehyde **12** was easily formed by the oxidation of **11** with SO_3-Py/DMSO/Et_3N at 20 °C,[7] which was cyclized rapidly into the more stable aza-acetal **13**.[3e] Although other oxidation methods were also investigated,[8] including Swern oxidation,[9] Anelli oxidation,[10] TEMPO/Cu(I)/air,[11] $NaNO_2$/Ac_2O[12] and DMSO/Ac_2O,[13] only Parikh-Doering reaction using SO_3-Py/DMSO/Et_3N was able to achieve the required level of conversion and purity (Table 2). Swern oxidation usually required very low temperature condition, which was not acceptable for rapid large-scale synthesis. Treatment of **11** with TEMPO/NaOCl or $Ca(ClO)_2$ gave impure products containing over-oxidized impurities **14** and **15** (Table 2, entries 1-3).[3b] TEMPO/Cu(I) catalyst system with ambient air as the oxidant exhibited highly selective oxidation of primary alcohol **11** to the corresponding aldehyde, but unreacted alcohol was always observed as a major impurity from the slow oxidation (Table 2, entry 4). The $NaNO_2$/Ac_2O and DMSO/Ac_2O oxidation protocol is not a good choice, because the alcohol **11** tended to suffer acetylation (Table 2, entries 5 and 6). The Parikh-Doering oxidation gave product **13** in high conversion without carboxylic acid **14** and dicarboximide **15** (Table 2, entry 7). However, the highly volatile and malodorous dimethyl sulfide (DMS) as a byproduct in this reaction was a potential environmental issue. To control the DMS emission, nitrogen was sparged into the quenched reaction mixture and the off gas was trapped in a scrubber containing 5% H_2O_2 aqueous solution.[14]

Table 2. Synthesis of **13** using different oxidizing agents

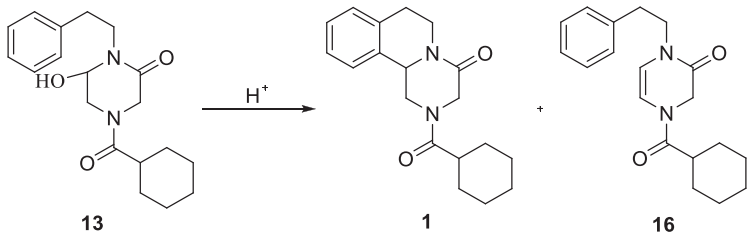


Entry	Oxidant	Reaction conditions	**11** (%)[a]	**13** (%)[a]	**14** (%)[a]	**15** (%)[a]
1	TEMPO/NaOCl/NaBr	$NaHCO_3$,[b] CH_2Cl_2, 5 °C, 14 h	0.57	51.63	42.24	3.40
2	TEMPO/NaOCl/NaBr	NaAcO/AcOH,[c] CH_2Cl_2, 5 °C, 20 h	0.80	47.91	39.35	1.02
3	TEMPO/$Ca(ClO)_2$/NaBr	CH_2Cl_2, 5 °C, 10 h	53.58	37.85	4.96	0.09
4	TEMPO/CuOTf/Air	MeCN, 15 °C, 48 h	40.60	48.48	ND[d]	0.84
5	$NaNO_2$/Ac_2O	0 °C, 2 h	55.24	ND	ND	ND
6	DMSO/Ac_2O	20 °C, 12 h	ND	0.27	ND	ND
7	SO_3-Py/DMSO/Et_3N	15-20 °C, 7 h	1.60	94.71	ND	ND

[a] Measured by HPLC analysis in area nomalization. [b] Adjusting the pH of the reaction system at 8.5-9.5 by addition of an aqueous solution of $NaHCO_3$. [c] Adjusting the pH of the reaction system at 4-6 by addition of an acetate buffer solution. [d] ND = not detected.

The acid-catalyzed cyclization of **13** was carried out in the presence of $MeSO_3H$ or concentrated H_2SO_4 at room temperature.[3b] LC-MS analysis of the reaction mixture showed that cyclization of **13** to the desired praziquantel was accompanied by the formation of a byproduct, which was identified as enamide **16**.[3f] Since both reactions above were acid catalyzed, a study was initiated to investigate the effect of the acids in the transformation of **13** to **1**. As shown in Table 3, the use of catalytical amount of acid (Table 3, entries 1, 3 and 4) provided enamide **16** as the major product, while the use of acid as both catalyst and solvent (Table 3, entries 2, 5) surprisingly gave high levels of **1** without the formation of **16**. On the other hand, since $MeSO_3H$ can cause the genotoxic concern,[15] the process adopted concentrated H_2SO_4 for cyclization of **13** at 0-5 °C, and praziquantel was obtained in 85% yield from compound **11** and 99.8% purity through crystallization with $EtOH/H_2O$.

Table 3. Cyclization of **13** to praziquantel under various conditions



Entry	Acid	Solvent	Temp (°C)	Time (h)	**1** (%)[a]	**16** (%)[a]
1	$MeSO_3H$, 10 mol%	CH_2Cl_2	20	2	1.38	87.25
2	$MeSO_3H$	-[b]	20	4	97.19	ND[c]
3	*conc*. H_2SO_4, 10 mol%	CH_2Cl_2	20	2	4.20	89.24
4	*conc*. H_2SO_4, 10 mol%	toluene	60	1	11.20	83.47
5	*conc*. H_2SO_4[d]	CH_2Cl_2	0-5	1.5	97.76	ND

[a] Measured by HPLC analysis in area nomalization. [b] $MeSO_3H$ as both acid catalyst and solvent. [c] ND = not detected. [d] The volume ratio of conc. H_2SO_4 and CH_2Cl_2 was 1.5:1.

In summary, a concise and highly efficient synthesis of praziquantel has been developed by making use of ethanolamine instead of the relatively expensive aminoacetaldehyde dimethyl acetal. The telescoped process made the synthetic intermediates be directly treated into the next reaction without purification. The process produced praziquantel in 80% overyield from the cheap and readily available starting material phenethylamine.

EXPERIMENTAL

All solvents and reagents were purchased from the suppliers and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer. The solvents used for NMR spectroscopy were $CDCl_3$, using TMS as the internal reference. IR spectra were recorded on a Thermo Nicolet Nexus 670 FTIR spectrometer. Mass spectra were recorded on Agilent 6150B Series single quadrupole LC/MS. HRMS spectra were obtained on Bruker maXis 4G. Method of ionization was ESI (Elektron Spray Ionization). Melting points were measured on a Yice WRS-1B melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel 60 (54–74 μm). HPLC analyses were recorded with on a Dionex UItiMate 3000 chromatograph using a Waters XBridge C18, 4.6 mm × 150 mm, 3.5 μm column, acetonitrile and water (containing 0.1% TFA) as eluent, a column temperature of 35 °C, a flow rate of 1.0 mL/min, and measuring at 210 nm (Table 4). The purities of the compounds were based on the area of HPLC UV.

Table 4. The standard gradient

Time (min)	A[a] (%)	B[b] (%)
0	5	95
3	5	95
8	20	80
20	70	30
24	70	30
24.1	5	95
30	5	95

[a] Solvent A: acetonitrile. [b] Solvent B: water (containing 0.1% TFA).

2-Chloro-*N*-phenethylacetamide (3). To a solution of phenethylamine (316.6 g, 2.61 mol) in CH_2Cl_2 (3.0 L) was added a solution of NaOH (125.4 g, 3.13 mol) in water (1.5 L) at room temperature. Chloroacetyl chloride (309.8 g, 2.74 mol) was added dropwise within 2 h at 0-5 °C, followed by stirring the mixture at 5-10 °C for 2 h. The organic layer was separated, and washed with water (2 × 1.0 L). The solution was concentrated to afford **3** (517.4 g, quant.), which was used directly in the next step; a white solid; mp 65.4-65.6 °C (CH_2Cl_2) (lit.,[16] mp 65 °C); IR 3337, 3062, 3029, 2935, 2861, 1647, 1542, 1496, 1452, 1437, 1400, 1366, 1293, 1260, 1187, 1088, 1040, 1028, 1019, 926, 906, 777, 754, 699, 578, 559, 500, 426 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 5 H), 4.02 (s, 2 H), 3.58 (dd, J = 13.1, 7.0 Hz, 2 H), 2.87 (t, J = 7.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.86, 138.39, 128.75, 128.74, 126.72, 42.66, 40.99, 35.48; MS m/z 198 (M^+, 100). HRMS m/z $[M + Na]^+$ calcd for $C_{10}H_{12}ClNO$: 220.0500; found:

220.0501.

2-(2-Hydroxyethylamino)-*N*-phenethylacetamide (9). A mixture of **3** (517.4 g, 2.6 mol) and ethanolamine (1270.5 g, 20.8 mol) was stired at 0-10 °C for 12 h. To the reaction was added a solution of NaOH (109.6 g, 2.74 mol) in water (300 mL), and the mixture was stired at 20 °C for 0.5 h. Subsequently the residual water and ethanolamine was removed by azeotropic distillation *in vacuo* with xylene (700 mL), yielding a pale yellow oil compound **9** (96.10% area purity by HPLC). The crude product was used in the next reaction step without further purification. An analytical sample was obtained by column chromatography on silica gel eluting with MeOH/CH_2Cl_2 (3.5 : 100); a pale-yellow oil; IR 3314, 3085, 3027, 2932, 1951, 1879, 1652, 1603, 1537, 1497, 1454, 1363, 1333, 1267, 1201, 1138, 1059, 972, 888, 750, 701, 579, 505, 459, 449, 436, 427, 420, 416, 401 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 3 H), 7.22 – 7.17 (m, 2 H), 3.64 – 3.50 (m, 4 H), 3.24 (s, 2 H), 2.84 (t, J = 7.1 Hz, 2 H), 2.70 – 2.61 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 171.92, 138.90, 128.74, 128.59, 126.51, 61.24, 52.17, 51.66, 40.08, 35.61; MS *m*/*z* 223 (M^+, 100). HRMS *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{18}N_2O_2$: 223.1441; found: 223.1444.

***N*-(2-Hydroxyethyl)-*N*-(2-oxo-2-(phenethylamino)ethyl)cyclohexanecarboxamide (11).** To a solution of **9** prepared above in CH_2Cl_2 (4.5 L) was added a solution of NaOH (125.5 g, 3.14 mol) in water (2.0 L) at room temperature. Cyclohexanecarbonyl chloride (367.7 g, 2.51 mol) was added dropwise within 3 h at 0-5 °C, followed by stirring the mixture at 5-10 °C for 2 h. The organic layer was separated, and washed sequentially with 1 N HCl (500 mL) and water (2 × 1.5 L). After the solvent was removed under vacuum, the crude product was suspended in MTBE (3.0 L). The resulting slurry was stirred at 20 °C overnight. The solid was isolated by filtration, washed with cold MTBE (500 mL), and then dried under vacuum at 30 °C for 8 h to give **11** (813.8 g, 94% yield from phenethylamine **2**); a white solid; mp 99.8-100.6 °C (MTBE); IR 3429, 3278, 3094, 2932, 2855, 1641, 1568, 1444, 1405, 1360, 1315, 1270, 1206, 1181, 1085, 1062, 1024, 776, 760, 711, 593, 454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.29 (t, 2 H), 7.23 – 7.20 (m, 3 H), 3.85 (s, 2 H), 3.75 – 3.70 (m, 2 H), 3.56 – 3.48 (m, 4 H), 2.82 (t, J = 7.2 Hz, 2 H), 2.60 (tt, J = 11.3, 3.0 Hz, 1 H), 1.81 – 1.18 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 177.77, 170.88, 138.71, 128.76, 128.60, 126.51, 60.23, 52.45, 51.40, 40.82, 40.41, 35.42, 29.37, 25.79, 25.70; MS *m*/*z* 333 (M^+, 100). HRMS *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{28}N_2O_3$: 333.2173; found: 333.2175.

4-(Cyclohexanecarbonyl)-6-hydroxy-1-phenethylpiperazin-2-one (13). To a solution of **11** (212.0 g, 0.64 mol) in DMSO (600 mL) was added Et_3N (645.3 g, 6.38 mol) at ambient temperature. To the solution was added a solution of sulfur trioxide pyridine complex (609.0 g, 3.83 mol) in DMSO (1.6 L) was added at such a rate as to maintain the temperature between 15 and 20 °C for 4 h, and then the mixture was stirred at 20 °C for 3 h. The reaction mixture was poured into cold water (8.0 L), and sparged with N_2 for 6 h while the temperature was maintained below 20 °C. After removal of most of the DMS, water (2.0 L) was added into the reactor and the resultant solution was extracted with CH_2Cl_2 (2 × 1.0 L).

The organic layer was washed with water (2 × 600 mL), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. And then CH_2Cl_2 (1.6 L) was stripped off under vacuum to afford **13** (94.71% area purity by HPLC) as a brown solution in CH_2Cl_2. The resulting solution was used directly in the next step without purification. An analytical sample was obtained by removing solvents under vacuum and crystallization with EtOAc; a white solid; mp 134.3-134.5 °C (EtOAc) (lit.,[3b] 134 °C); IR 3377, 3024, 2929, 2854, 1648, 1626, 1494, 1452, 1365, 1345, 1303, 1274, 1246, 1227, 1181, 1157, 1140, 1108, 1090, 1054, 1029, 985, 966, 936, 897, 869, 808, 786, 737, 703, 646, 614, 559, 503, 454, 409 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 5 H), 4.92 – 3.14 (m, 7 H), 3.04 – 2.89 (m, 2 H), 2.46 (t, J = 11.5 Hz, 1 H), 1.84 – 1.14 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 176.11, 166.41, 138.88, 128.92, 128.63, 126.62, 78.27, 49.06, 47.22, 46.38, 45.13, 40.75, 34.15, 28.99, 25.71; MS *m*/*z* 331 (M^+, 100). HRMS *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{26}N_2O_3$: 331.2016; found: 331.2014.

2-(Cyclohexylcarbonyl)-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (1). To a solution of *conc*. H_2SO_4 (600 mL) was added dropwise the above solution of **13** in CH_2Cl_2 at 0-5 °C for 2 h. After stirring at 0-5 °C for 2 h, the reaction mixture was poured into cold water (5.0 L), and extracted with CH_2Cl_2 (2 × 350 mL). The organic layer was washed with sequentially the saturated solution of sodium bicarbonate (2 × 300 mL) and water (2 × 300 mL), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure to afford crude **1** (195.5 g) as a off-white solid. The crude material was suspended in 55% EtOH (950 mL) and heated at 60 °C for 1 h. The mixture was cooled down to -6 °C and stirred for 8 h. The solids were collected by filtration, washed with cold 45% EtOH (3 × 100 mL) and dried under vacuum at 40 °C for 12 h to provide **1** (170.1 g, 85% yield from compound **11**) with 99.8% area purity by HPLC; a white solid; mp 138.4-139.2 °C (EtOH-H_2O) (lit.,[3a] 136-139 °C); IR 3444, 2929, 2853, 1649, 1628, 1447, 1421, 1357, 1326, 1300, 1245, 1211, 1177, 1126, 1088, 997, 894, 764, 693, 621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.10 (m, 4 H), 5.16 (dd, J = 13.2, 2.4 Hz, 1 H), 4.83 – 4.74 (m, 2 H), 4.47 (d, J = 17.4 Hz, 1 H), 4.08 (d, J = 17.4 Hz, 1 H), 2.99 – 2.76 (m, 4 H), 2.47 (m, 1 H), 1.82 – 1.16 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 174.79, 164.44, 134.80, 132.86, 129.33, 127.49, 127.02, 125.51, 55.00, 49.09, 45.22, 40.84, 39.15, 29.29, 29.07, 28.78, 25.77; MS *m*/*z* 313.1 (M^+, 100). HRMS *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{24}N_2O_2$: 313.1911; found: 313.1910.

2,2'-(2-Hydroxyethylazanediyl)bis(*N*-phenethylacetamide) (10). A mixture of **9** (4.55 g, 20.47 mmol), **3** (4.05 g, 20.49 mmol) and K_2CO_3 (2.83 g, 20.47 mmol) was stired at 50-60 °C for 5 h. The mixture was cooled down to room temperature and purified by column chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1.5 : 100) to give **10** (5.34 g, 68%); a white solid; mp 77.3-78.4 °C (MeOH-CH_2Cl_2); IR 3306, 3026, 2938, 2873, 2361, 2330, 1650, 1544, 1496, 1454, 1435, 1364, 1248, 1197, 1154, 1068, 984, 870, 750, 700, 668, 570, 497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.16 (m, 10 H), 3.54 (q, J = 6.9 Hz, 4 H), 3.45 – 3.36 (m, 2 H), 3.16 (s, 4 H), 2.83 (t, J = 7.0 Hz, 4 H), 2.64 – 2.55 (m, 2 H); ^{13}C NMR

($CDCl_3$) δ 171.02, 138.91, 128.73, 128.57, 126.51, 59.67, 59.43, 58.36, 40.48, 35.41; MS *m*/*z* 384.2 (M^+, 100). HRMS *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{29}N_3O_3$: 384.2282; found: 384.2278.

2-(*N*-(2-Oxo-2-(phenethylamino)ethyl)cyclohexanecarboxamido)acetic acid (14). To a mixture of **11** (12.67 g, 38.11 mmol), TEMPO (0.18 g, 1.15 mmol), NaBr (0.41 g, 4.0 mmol) and $NaHCO_3$ (27.14 g, 323.06 mmol) in CH_2Cl_2 (100 mL)–H_2O (175 mL) was added dropwise NaOCl (5% w/w, 65.48 g, 43.98 mmol) at 5 °C for 4 h, followed by stirring the mixture at 5 °C for 10 h. After separation of the phases, the aqueous phase was washed with CH_2Cl_2 (2 × 30 mL), adjusted the pH at 2-3 by the addition of 1 N HCl, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1 : 20) to afford **14** (4.55 g, 34.5%); a white solid; mp 116.6-117.2 °C (MeOH-CH_2Cl_2); IR 3427, 3263, 3097, 3029, 2929, 2857, 2659, 1764, 1650, 1623, 1570, 1496, 1470, 1451, 1400, 1368, 1312, 1265, 1209, 1189, 1137, 1084, 1035, 1006, 964, 879, 745, 700, 583, 558, 493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.17 (m, 5 H), 4.21 (s, 1 H), 4.08 (s, 1 H), 4.00 (s, 1 H), 3.94 (s, 1 H), 3.65 – 3.52 (m, 2 H), 2.86 (t, *J* = 7.1 Hz, 2 H), 2.42 – 2.25 (m, 1 H), 1.85 – 1.16 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 178.06, 172.72, 169.85, 138.44, 128.67, 128.63, 126.62, 53.84, 52.97, 51.93, 41.10, 40.66, 35.15, 29.20, 25.47; MS *m*/*z* 347 (M^+, 100). HRMS *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{26}N_2O_4$: 347.1965; found: 347.1965.

4-(Cyclohexanecarbonyl)-1-phenethylpiperazine-2,6-dione (15). To a solution of **14** (6.77 g, 19.54 mmol) in toluene (60 mL) was added Et_3N (2.50 g, 24.71 mmol) and Ac_2O (8.12 g, 79.54 mmol) at room temperature, and then the mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled down to room temperature and washed sequentially with 2 N NaOH (100 mL) and water (2 × 100 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. After the solvent was removed under vacuum, the crude product was suspended in heptane (30 mL). The resulting slurry was stirred at 20 °C overnight. The solid was isolated by filtration, washed with heptane (10 mL), and then dried under vacuum at 40 °C for 8 h to give **15** (6.29 g, 98%); a white solid; mp 86.4-86.9 °C (heptane) (lit.,[3b] 90 °C); IR 2930, 2854, 1737, 1682, 1496, 1452, 1391, 1347, 1266, 1173, 997, 749, 700, 613, 429 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.14 (m, 5H), 4.40 (s, 4H), 4.14 – 3.94 (m, 2H), 2.95 – 2.78 (m, 2H), 2.43 (tt, *J* = 11.4, 3.4 Hz, 1H), 1.94 – 1.16 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 174.34, 167.65, 137.79, 128.92, 128.51, 126.68, 48.82, 45.42, 40.64, 40.33, 33.72, 29.10, 25.56; MS *m*/*z* 329.2 (M^+, 100). HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{24}N_2O_3$: 351.1679; found: 351.1683.

4-(Cyclohexanecarbonyl)-1-phenethyl-3,4-dihydropyrazin-2-one (16). To a solution of **13** (6.42 g, 19.43 mmol) in CH_2C1_2 (100 mL) was added $MeSO_3H$ (0.20 g, 2.08 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was washed sequentially with 1 N NaOH (25 mL) and water (2 × 50 mL) . The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized from EtOAc to afford **16** (4.73 g, 78%); a white solid; mp

132.0-132.6 °C (EtOAc) (lit.,[3f] 128-130 °C); IR 2929, 2853, 1660, 1644, 1496, 1453, 1428, 1406, 1344, 1295, 1224, 1136, 998, 890, 809, 740, 724, 701, 555, 500, 450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.14 (m, 5H), 6.39 (dd, *J* = 213.7, 6.1 Hz, 1H), 5.46 (dd, *J* = 58.5, 6.1 Hz, 1H), 4.32 (s, 2H), 3.75 (t, *J* = 7.3 Hz, 2H), 2.90 (t, *J* = 7.3 Hz, 2H), 2.47 (tt, *J* = 11.5, 3.3 Hz, 1H), 1.89 – 1.19 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 173.77, 163.58, 138.07, 128.88, 128.61, 126.67, 113.91, 108.90, 47.71, 45.88, 40.85, 34.55, 28.92, 25.71, 25.66; MS *m/z* 313.2 (M^+, 100). HRMS *m/z* $[M + Na]^+$ calcd for $C_{19}H_{24}N_2O_2$: 335.1730; found: 335.1729.

ACKNOWLEDGEMENTS

We are grateful to China State Institute of Pharmaceutical Industry and Zhejiang Hisun Pharmaceutical Co., Ltd. for financial support. We also thank Prof. Weicheng Zhou for reviewing and improving this manuscript.

REFERENCES

1. (a) J. Kusel and P. Hagan, *Parasitology Today*, 1999, **15**, 352; (b) M. J. Doenhoff, G. Kimani, and D. Cioli, *Parasitology Today*, 2000, **16**, 364.
2. M. Woelfle, P. Olliaro, and M. H. Todd, *Nature Chemistry*, 2011, **3**, 745.
3. (a) J. Seubert, R. Pohlke, and F. Loehich, *Experientia*, 1977, **33**, 1036; (b) D. Frehel and J.-P. Maffrand, *Heterocycles*, 1983, **20**, 1731; (c) F. Yuste, Y. Pallás, H. Barrios, B. Ortíz, and R. Sánchez-Obregón, *J. Heterocycl. Chem.*, 1986, **23**, 189; (d) W. F. Berkowitz and T. V. John, *J. Org. Chem.*, 1984, **49**, 5269; (e) O. V. Shekhter, O. B. Kuklenkova, N. L. Sergovskaya, and Yu. S. Tsizin, *Chem. Heterocycl. Compd.*, 1993, **29**, 170; (f) J. H. Kim, Y. S. Lee, and C. S. Kim, *Heterocycles*, 1998, **48**, 2279; (g) J. H. Kim, Y. S. Lee, H. Park, and C. S. Kim, *Tetrahedron*, 1998, **54**, 7395; (h) M. H. Todd, C. Ndubaku, and P. A. Bartlett, *J. Org. Chem.*, 2002, **67**, 3985; (i) C. Ma, Q.-F. Zhang, Y.-B. Tan, and L. Wang, *J. Chem. Res.*, 2004, **2004**, 186; (j) S. El-Fayyoumy, W. Mansour, and M. H. Todd, *Tetrahedron Lett.*, 2006, **47**, 1287; (k) P. Roszkowski, J. K. Maurin, and Z. Czarnocki, *Tetrahedron: Asymmetry*, 2006, **17**, 1415; (l) H. Cao, H. Liu, and A. Dömling, *Chem. Eur. J.*, 2010, **16**, 12296; (m) P. S. Sadhu, S. N. Kumar, M. Chandrasekharam, L. Pica-Mattoccia, D. Cioli, and V. J. Rao, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1103; (n) A. S.-K. Tsang, K. Ingram, J. Keiser, D. B. Hibbert, and M. H. Todd, *Org. Biomol. Chem.*, 2013, **11**, 4921; (o) L. Balaya, M. Manjathuru, Y. Derambala, P. K. Vasudeva, and T. Arulmoli, 'Process for the preparation of praziquantel', U.S. Patent 2013/0289275, 2013; (p) M. Seki and T. Ogiku, *Tetrahedron*, 2014, **70**, 3864; (q) S. Dhanasekaran, A. Suneja, V. Bisai, and V. K. Singh, *Org. Lett.*, 2016, **18**, 634.
4. (a) R. B. Woodward and W. E. Doering, *Org. Synth.*, 1944, **24**, 3; (b) J. K. Lawson, *J. Am. Chem.*

Soc., 1953, **75**, 3398; (c) M. S. Malik, N. K. Sangwan, O. P. Malik, and K. S. Dhindsa, *Org. Prep. Proced. Int.*, 1991, **23**, 764.

5. M. E. Freed, W. F. Bruce, R. S. Hanslick, and A. Mascitti, *J. Org. Chem.*, 1961, **26**, 2378.
6. The Dow Chemical Co., 'Azeotropic Data-III', ed. by L. H. Horsley, American Chemical Society, Washington, DC, 1973, p 151.
7. J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505.
8. S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan, and D. H. B. Ripin, *Chem. Rev.*, 2006, **106**, 2943.
9. A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
10. P. L. Anelli, C. Biffi, F. Montanari, and S. Quici, *J. Org. Chem.*, 1987, **52**, 2559.
11. J. M. Hoover and S. S. Stahl, *J. Am. Chem. Soc.*, 2011, **133**, 16901.
12. B. P. Bandgar, V. S. Sadavarte, and L. S. Uppalla, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3559.
13. J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, 1967, **89**, 2416.
14. T. B. Douglas, *J. Am. Chem. Soc.*, 1946, **68**, 1072.
15. G. Szekely, M.-C. Amores de Sousa, M. Gil, F. C. Ferreira, and W. Heggie, *Chem. Rev.*, 2015, **115**, 8182.
16. S. A.-L. Laurent, J. Boissier, F. Coslédan, H. Cornitzka, A. Robert, and B. Meunier, *Eur. J. Org. Chem.*, 2008, **2008**, 895.