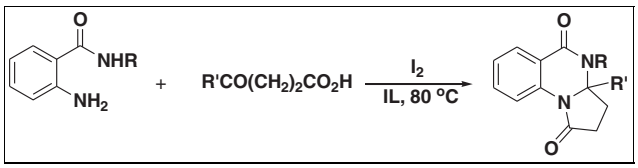
An Efficient Synthesis of Pyrrolo[1,2-*a*]quinazoline Derivatives in Ionic Liquid Catalyzed by Iodine

Lian Lu,[a] Ke Yang,[a] Mei-Mei Zhang,[b] and Xiang-Shan Wang[a]*

[a]School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou Jiangsu 221116, People's Republic of China
[b]The Key Laboratory of Biotechnology on Medical Plant of Jiangsu Province, Jiangsu Normal University, Xuzhou Jiangsu 221116, People's Republic of China
*E-mail: xswang1974@yahoo.com

Received May 31, 2011
DOI 10.1002/jhet.1116
Published online 26 November 2013 in Wiley Online Library (wileyonlinelibrary.com).



A mild, green, and facile method for the synthesis of 2,3,3*a*,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione derivatives is described in high yields by using ionic liquids as green media. The method involves the reaction of 2-aminobenzamides with 4-oxopentanoic acid or 4-aryl-4-oxo-butanoic acid catalyzed by iodine and has the advantages of mild reaction conditions, high yields, one-pot, operational simplicity, and environmentally benign.

J. Heterocyclic Chem., **51**, 841 (2014).

INTRODUCTION

Pyrroloquinazolines are important core structures found in a variety of natural products and other biologically important molecules [1]. They often possess a wide range of biological activities, such as antitumor [2], modulators of chemokine activity [3], and anti-inflammatory activity [4]. Some of them may be useful for optimization of thrombin receptor antagonistic activity [5].

Although a number of useful synthetic procedures to prepare these compounds have been developed [6], still several limitations remain. For example, most reported procedures are several steps, low yields, or in flammable organic solvents. Moreover, the starting materials are not often readily available. Thus, a simple, efficient, and green method to synthesize pyrroloquinazolines would be attractive.

Room temperature ionic liquids, especially those based on the 1-*N*-alkyl-3-methylimidazolium cation, have shown great promise as attractive alternative to conventional solvents [7]. The unique property of room temperature ionic liquids is that they have essentially no vapor pressure, which makes them optimal replacements for the volatile organic solvents traditionally used as industrial solvents. Another nice feature of ionic liquid is its ability to be reused for many times concerning about green solvent. Therefore, ionic liquids have made significant contributions to green chemistry and have been used widely as reaction medium in organic chemistry [8].

As a continuation of our research devoted to the development of new methods for heterocycles in ionic liquid and with iodine as catalyst [9], we would like to report the synthesis of 2,3,3*a*,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione derivatives in ionic liquids by a one-pot reaction catalyzed by iodine.

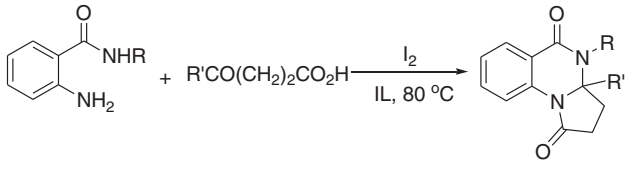
RESULTS AND DISCUSSION

Treatment of 2-aminobenzamides **1** and 4-oxopentanoic acid **2** in ionic liquid of [BMIm]Br in the presence of 5 mol % iodine at 80°C resulted in the corresponding 2,3,3*a*,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione derivatives **3a-u** in high yields (Scheme 1).

By using the conversion of 2-aminobenzamide **1** and 4-oxopentanoic acid **2** as a model, several parameters were explored as shown in Table 1. **3a** was not detected by TLC in the absence of iodine at 80°C (Table 1, Entry 1) and was obtained successfully in the presence of various quantities of the catalyst, reaching a maximum of 89% yield by using 5 mol% iodine as catalyst (Table 1, entries 4, 6, and 7). The yield of **3a** was also dependent on temperature (entries 2~5), proceeding smoothly at 80°C. In addition, different imidazolium ionic liquids were also tested, and [BMIm]Br appeared to be the best medium for this transformation (entry 4 vs 8–12).

After reaction completion as monitored by TLC, the products were isolated by simple filtration after the addition of a small amount of water to the cooled reaction mixture. Water in the filtrate was removed by distillation under reduced pressure, and the [BMIm]Br in the residue could be reused after being evaporated at 80°C for 4 h in vacuum. Successive reuse of the recycled ionic liquid of

Scheme 1. Reaction of **1** and 4-oxopentanoic acid in ionic liquid.



1 **2** **3a-u**

Table 1

Synthetic results of **3a** under different reaction conditions.[a]

Entry	Temp./°C	Ionic liquid[b]	I_2 (mol%)	Yield (%)[c]
1	80	[BMIm]Br	0	0
2	r.t.	[BMIm]Br	5	trace
3	50	[BMIm]Br	5	82
4	80	[BMIm]Br	5	89
5	100	[BMIm]Br	5	88
6	80	[BMIm]Br	10	89
7	80	[BMIm]Br	20	90
8	80	[EMIm]Br	5	83
9	80	[PMIm]Br	5	85
10	80	[EMIm][BF_4]	5	86
11	80	[PMIm][BF_4]	5	86
12	80	[BMIm][BF_4]	5	89

[a]Reaction condition: 2-mL solvent, 2-aminobenzamide (0.272 g, 2 mmol), and 4-oxopentanoic acid (0.244 g, 2.1 mmol).
[b]BMIm = 1-butyl-3-methylimidazolium; EMIm = 1-ethyl-3-methylimidazolium; PMIm = 1-propyl-3-methylimidazolium.
[c]Isolated yields.

[BMIm]Br in the model reaction gave high yields of **3a** (88%) even after the fourth cycle.

The optimized conditions were applied for the conversion of various kinds of 2-aminobenzamides **1** reacting with 4-oxopentanoic acid **2** into the corresponding pyrrolo[1,2-*a*]quinazoline-1,5-dione analogs **3a-k** (Table 2, entries 1–11). In addition, 4-aryl-4-oxo-butanoic acid was also selected as reactant to react with 2-aminobenzamides in the same reaction conditions; the desired reaction proceeded well to give polyhydropyrrolo[1,2-*a*] quinazolines **3l-u** in high yields (Table 2, entries 12–21). From Table 2, we can conclude that this process can tolerate both electron-donating (alkyl and alkoxy) and electron-withdrawing (halogen) substituents on the aromatic aldehydes in **1**(Table 2). In all cases, the reactions proceeded efficiently in ionic liquid at 80°C to afford the desired products in high yields. All the compounds were characterized by ^{1}H NMR, IR, and HRMS, some of them were also characterized by ^{13}C NMR, and they were all in good agreement with their structures.

Consistent with previous suggestions in the literature,[6e] we suggest that iodine catalyzes the reaction as a mild Lewis acid. The proposed mechanism was shown in Scheme 2. The Schiff base **I** is formed by condensation **1** with 4-oxopentanoic acid **2**. Intramolecular attack on the iodine-activated Schiff base **II** then forms the quinazoline **III**, and finally the intermediate **III** gives **3** by an intramolecular dehydration.

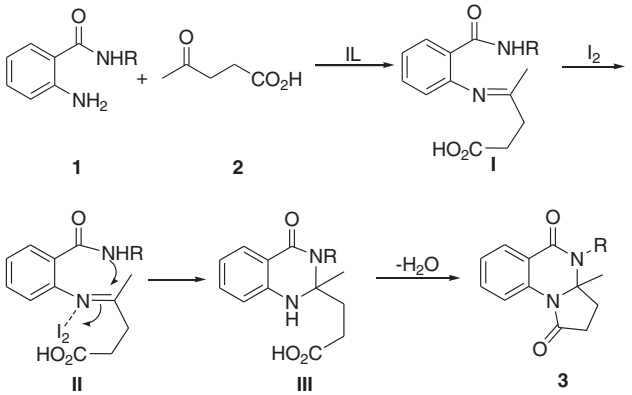
Table 2

Synthetic results of **3a–u** in ionic liquids.[a]

Entry	*R*	*R′*	Products	Time (h)	Yield (%)[b]
1	H	CH_3	**3a**	4	89
2	4-MeC_6H_4	CH_3	**3b**	7	86
3	4-FC_6H_4	CH_3	**3c**	6	90
4	Ph	CH_3	**3d**	5	94
5	4-$MeOC_6H_4$	CH_3	**3e**	5.5	92
6	4-$MeOC_6H_4(CH_2)_2$	CH_3	**3f**	5.5	90
7	4-$MeOC_6H_4CH_2$	CH_3	**3g**	5	91
8	$C_6H_5CH_2$	CH_3	**3h**	4	93
9	$C_6H_5CH_2CH_2$	CH_3	**3i**	4	92
10	(Furan-2-yl)methyl	CH_3	**3j**	6	87
11	3,4-$OCH_2OC_6H_3(CH_2)_2$	CH_3	**3k**	5	92
12	$C_6H_5CH_2$	4-*i*-Pr-C_6H_4	**3l**	8	87
13	$C_6H_5CH_2$	4-MeC_6H_4	**3m**	8	83
14	$C_6H_5CH_2$	4-$MeOC_6H_4$	**3n**	9	87
15	$C_6H_5CH_2$	4-EtC_6H_4	**3o**	8	90
16	$C_6H_5CH_2$	4-ClC_6H_4	**3p**	6	85
17	4-$MeOC_6H_4CH_2$	4-MeC_6H_4	**3q**	6	84
18	4-$MeOC_6H_4CH_2$	4-$MeOC_6H_4$	**3r**	7	87
19	4-$MeOC_6H_4CH_2$	4-*i*-Pr-C_6H_4	**3s**	8	93
20	4-$MeOC_6H_4CH_2$	4-ClC_6H_4	**3t**	6	92
21	4-$MeOC_6H_4CH_2$	4-EtC_6H_4	**3u**	7	89

[a]Reaction condition: 2 mL [BMIm]Br, **1** (2 mmol), **2** (2.1 mmol), and iodine (0.025 g, 0.1 mmol), 80°C.
[b]Isolated yields.

Scheme 2. The possible mechanism for the formation of products **3**.



CONCLUSION

In summary, a mild, facile, and environmentally benign method is developed for the synthesis of pyrrolo[1,2-*a*] quinazoline-1,5-dione derivatives in high yields catalyzed by iodine in ionic liquids. The advantages of this procedure include mild reaction conditions, high yields, one-pot, operational simplicity, and environmentally benign.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer (Bruker Corporation, Karlsruhe, DE) in KBr pellet. ^{1}H NMR spectra were obtained from a solution in DMSO-d_6 with Me_4Si as internal standard by using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

General procedure for the synthesis of 2,3,3a,4-tetrahydropyrrolo[1,2-a]quinazoline-1,5-dione derivatives 3. A dry 50-mL flask was charged with 2-aminobenzamides **1** (2.0 mmol), 4-oxopentanoic acid, or 4-aryl-4-oxo-butanoic acid **2** (2.1 mmol), iodine (0.025 g, 0.1 mmol), and ionic liquid of [BMIm]Br (2 mL). The reaction mixture was stirred at 80°C for 4–9 h, and then a small amount of water (5 mL) was added to the mixture, and the generated yellow solid was filtered off. The water in the filtrate was removed by distillation under reduced pressure, and the ionic liquid in the residue could be reusable by being evaporated at 80°C for 4 h at vacuum. The crude yellow products were washed with water, purified by recrystallization from 95% EtOH, and then dried at 80°C for 2 h under vacuum to give **3**.

***2,3,3a,4-Tetrahydro-3a*-methylpyrrolo[1,2-*a*]quinazoline-1,5-dione (3a).** m.p. 184~186°C, (Lit.[6f] m.p. 181~182°C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.58 (s, 3H, CH_3), 2.36~2.40 (m, 2H, CH_2), 2.69~2.73 (m, 2H, CH_2), 7.29 (t, J = 7.6 Hz, 1H, ArH), 7.58~7.62 (m, 2H, NH + ArH), 8.07 (d, J = 7.6 Hz, 1H, ArH), 8.16 (d, J = 8.4 Hz, 1H, ArH). IR (KBr): 3174, 3057, 2965, 2925, 1719, 1681, 1603, 1492, 1446, 1386, 1352, 1211, 1153, 791, 759, 617 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{12}H_{12}N_2NaO_2$ $[M + Na]^+$ 239.0796, found 239.0790.

***2,3,3a,4-Tetrahydro-3a*-methyl-4-*p*-tolylpyrrolo[1,2-*a*]quinazoline-1,5-dione (3b).** m.p. 244~246°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.75 (s, 3H, CH_3), 1.79~1.83 (m, 1H, CH), 2.34~2.40 (m, 4H, CH_3 + CH), 2.60~2.64 (m, 2H, CH_2), 7.13~7.16 (m, 2H, ArH), 7.27~7.32 (m, 3H, ArH), 7.58~7.63 (m, 1H, ArH), 8.13 (dd, J = 8.0 Hz, J' = 1.2 Hz, 1H, ArH), 8.60 (dd, J = 8.4 Hz, J' = 0.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 171.8, 161.1, 137.6, 135.5, 134.4, 133.5, 129.7, 129.6, 128.3, 124.6, 119.7, 119.5, 79.0, 31.2, 29.8, 24.6, 20.6. IR (KBr): 3028, 2974, 2872, 1720, 1650, 1602, 1513, 1484, 1468, 1385, 1346, 1199, 1140, 813, 766, 698 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{18}N_2NaO_2$ $[M + Na]^+$ 329.1266, found 329.1251.

***4-(4-Fluorophenyl)-2,3,3a*,4-tetrahydro-3*a*-methylpyrrolo[1,2-*a*]quinazoline-1,5-dione (3c).** m.p. 225~227°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.75 (s, 3H, CH_3), 1.80~1.86 (m, 1H, CH), 2.29~2.37 (m, 1H, CH), 2.62~2.65 (m, 2H, CH_2), 7.18 (t, J = 8.8 Hz, 2H, ArH), 7.24~7.27 (m, 2H, ArH), 7.29~7.33 (m, 1H, ArH), 7.60~7.64 (m, 1H, ArH), 8.12 (dd, J = 7.6 Hz, J' = 1.2 Hz, 1H, ArH), 8.27 (d, J = 8.4 Hz, 1H, ArH). IR (KBr): 3067, 2976, 2931, 1718, 1656, 1602, 1510, 1486, 1397, 1348, 1222, 1155, 1092, 843, 758, 696 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{15}FN_2NaO_2$ $[M + Na]^+$ 333.1015, found 333.1011.

***2,3,3a*,4-Tetrahydro-3*a*-methyl-4-phenylpyrrolo[1,2-*a*]quinazoline-1,5-dione (3d).** m.p. 224~225°C, (Lit.[6g] m.p. 223~224°C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.77 (s, 3H, CH_3), 1.80~1.84 (m, 1H, CH), 2.30~2.39 (m, 1H, CH), 2.60~2.64 (m, 2H, CH_2), 7.28~7.33 (m, 3H, ArH), 7.41~7.51 (m, 3H, ArH), 7.59~7.64 (m, 1H, ArH), 8.14 (dd, J = 8.0 Hz, J' = 1.2 Hz, 1H, ArH), 8.27 (dd, J = 8.4 Hz, J' = 0.8 Hz, 1H, ArH). IR (KBr): 3083, 2971, 2928, 1718, 1659, 1602, 1488, 1465, 1391, 1342, 1194, 1136, 764, 708, 697 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{18}H_{16}N_2NaO_2$ $[M + Na]^+$ 315.1109, found 315.1093.

***2,3,3a*,4-Tetrahydro-4-(4-methoxyphenyl)-3*a*-methylpyrrolo[1,2-*a*]quinazoline-1,5-dione (3e).** m.p. 202~205°C, (Lit.[6e] m.p. 198~200°C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.74 (s, 3H, CH_3), 1.78~1.84 (m, 1H, CH), 2.33~2.41 (m, 1H, CH), 2.60~2.64 (m, 2H, CH_2), 3.85 (s, 3H, CH_3O), 6.99 (d, J = 9.2 Hz, 2H, ArH), 7.18 (d, J = 8.8 Hz, 2H, ArH), 7.30 (t, J = 7.6 Hz, 1H, ArH), 7.58~7.63 (m, 1H, ArH), 8.13 (d, J = 7.6 Hz, 1H, ArH), 8.26 (d, J = 8.4 Hz, 1H, ArH). IR (KBr): 2970, 2932, 2836, 1717, 1652, 1601, 1514, 1487, 1468, 1398, 1347, 1303, 1251, 1176, 1038, 767, 696 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{18}N_2NaO_3$ $[M + Na]^+$ 345.1215, found 345.1200.

***4-(4-Methoxyphenethyl)-2,3,3a*,4-tetrahydro-3*a*-methylpyrrolo[1,2-*a*]quinazoline-1,5-dione (3f).** m.p. 159~160°C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 1.41 (s, 3H, CH_3), 2.27~2.47 (m, 3H, CH_2 + CH), 2.68~2.96 (m, 3H, CH + CH_2), 3.25~3.33 (m, 1H, CH), 3.71~3.78 (m, 4H, CH_3O + CH), 6.89 (d, J = 8.8 Hz, 2H, ArH), 7.20 (d, J = 8.4 Hz, 2H, ArH), 7.31 (t, J = 7.6 Hz, 1H, ArH), 7.62 (t, J = 7.6 Hz, 1H, ArH), 7.97 (d, J = 7.6 Hz, 1H, ArH), 8.19 (d, J = 8.4 Hz, 1H, ArH). IR (KBr): 2994, 2963, 2929, 2834, 1704, 1646, 1613, 1587, 1512, 1488, 1438, 1402, 1340, 1307, 1247, 1162, 1041, 978, 819, 770, 695 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{21}H_{22}N_2NaO_3$ $[M + Na]^+$ 373.1548, found 373.1539.

***4-(4-Methoxybenzyl)-2,3,3a*,4-tetrahydro-3*a*-methylpyrrolo[1,2-*a*]quinazoline-1,5-dione (3g).** m.p. 139~141°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.45 (s, 3H, CH_3), 2.18~2.23 (m, 1H, CH), 2.44~2.63 (m, 3H, CH_2 + CH), 3.79 (s, 3H, CH_3O), 4.30 (d, J = 15.6 Hz, 1H, CH), 5.14 (d, J = 15.2 Hz, 1H, CH), 6.85 (d, J = 8.8 Hz, 1H, ArH), 7.23~7.31 (m, 3H, ArH), 7.56~7.59 (m, 1H, ArH), 8.15 (d, J = 8.0 Hz, 1H, ArH), 8.26 (d, J = 8.4 Hz,

1H, ArH). IR (KBr): 3074, 2976, 2954, 2835, 1714, 1650, 1601, 1515, 1487, 1469, 1434, 1403, 1362, 1341, 1246, 1200, 1178, 1036, 959, 825, 759, 696 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{20}H_{20}N_2NaO_3$ $[M+Na]^+$ 359.1372, found 359.1373.

***4-Benzyl-2,3,3a*,4-tetrahydro-3*a*-methylpyrrolo[1,2-*a*] quinazoline-1,5-dione (3h).** m.p. 102~103°C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.48 (s, 3H, CH_3), 2.17~2.22 (m, 1H, CH), 2.38~2.65 (m, 3H, CH_2+CH), 4.30 (d, $J=15.6$ Hz, 1H, CH), 5.25 (d, $J=15.6$ Hz, 1H, CH), 7.24~7.34 (m, 6H, ArH), 7.58 (t, $J=8.4$ Hz, 1H, ArH), 8.16 (d, $J=7.6$ Hz, 1H, ArH), 8.27 (d, $J=8.0$ Hz, 1H, ArH). IR (KBr): 3046, 2983, 2934, 1729, 1643, 1600, 1487, 1471, 1410, 1367, 1342, 1220, 1208, 1164, 761, 743, 703, 627 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{19}H_{18}N_2NaO_2$ $[M+Na]^+$ 329.1266, found 329.1248.

***2,3,3a*,4-Tetrahydro-3*a*-methyl-4-phenethylpyrrolo[1,2-*a*] quinazoline-1,5-dione (3i).** m.p. 161~163°C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.44 (s, 3H, CH_3), 2.11~2.19 (m, 2H, CH_2), 2.44~2.57 (m, 2H, CH_2), 2.96~3.00 (m, 1H, CH), 3.10~3.20 (m, 2H, CH_2), 3.99~4.07 (m, 1H, CH), 7.22~7.34 (m, 6H, ArH), 7.55~7.59 (m, 1H, ArH), 8.12 (dd, $J=7.6$ Hz, $J'=1.2$ Hz, 1H, ArH), 8.26 (dd, $J=8.0$ Hz, $J'=0.4$ Hz, 1H, ArH). IR (KBr): 3027, 2973, 2934, 1692, 1651, 1602, 1488, 1471, 1407, 1369, 1346, 1218, 1167, 1121, 1005, 762, 697 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{20}H_{20}N_2NaO_2$ $[M+Na]^+$ 343.1422, found 343.1408.

***4-((Furan-2-yl)methyl)-2,3,3a*,4-tetrahydro-3*a*-methylpyrrolo [1,2-*a*]quinazoline-1,5-dione (3j).** m.p. 187~189°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 1.33 (s, 3H, CH_3), 2.42~2.51 (m, 3H, CH_2+CH), 2.76~2.81 (m, 1H, CH), 4.73 (q, $J=16.0$ Hz, 2H, CH_2), 6.37~6.41 (m, 2H, ArH), 7.31 (t, $J=7.6$ Hz, 1H, ArH), 7.59~7.65 (m, 2H, ArH), 7.96 (d, $J=7.6$ Hz, 1H, ArH), 8.20 (d, $J=8.4$ Hz, 1H, ArH). IR (KBr): 3107, 2973, 2829, 1716, 1657, 1600, 1486, 1468, 1422, 1396, 1360, 1330, 1307, 1218, 1160, 1024, 936, 874, 828, 767, 758 cm^{-1}. HRMS (ESI, *m/z*): calcd for $C_{17}H_{16}N_2NaO_3$ $[M+Na]^+$ 319.1059, found 319.1067.

***4-((3,4-Methylenedioxophenyl)ethyl)-2,3,3a*,4-tetrahydro-3*a*-methylpyrrolo[1,2-*a*]quinazoline-1,5-dione (3k).** m.p. 174~175°C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.44 (s, 3H, CH_3), 2.19~2.29 (m, 2H, CH_2), 2.52~2.64 (m, 2H, CH_2), 2.83~2.91 (m, 1H, CH), 3.06~3.15 (m, 2H, CH_2), 3.91~3.98 (m, 1H, CH), 5.94 (s, 2H, CH_2), 6.69~6.77 (m, 3H, ArH), 7.26~7.30 (m, 1H, ArH), 7.54~7.58 (m, 1H, ArH), 8.11 (d, $J=7.6$ Hz, 1H, ArH), 8.26 (d, $J=8.4$ Hz, 1H, ArH). IR (KBr, *v*, cm^{-1}): 2990, 2962, 2900, 1719, 1639, 1601, 1486, 1471, 1444, 1406, 1347, 1247, 1205, 1188, 1039, 928, 795, 760, 699. HRMS (ESI, *m/z*): Calcd for $C_{21}H_{20}N_2O_4$ $[M+Na]^+$ 387.1321, found 387.1335.

***4-Benzyl-2,3,3a*,4-tetrahydro-3*a*-(4-isopropylphenyl)pyrrolo [1,2-*a*]quinazoline-1,5-dione (3l).** m.p. 199~201°C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 1.18 (d, $J=6.8$ Hz, 6H, $2CH_3$), 2.43~2.55 (m, 2H, CH_2), 2.74~2.87 (m, 3H, CH_2+CH), 4.24 (d, $J=16.0$ Hz, 1H, CH), 5.88 (d, $J=16.0$ Hz, 1H, CH), 7.11~7.16 (m, 4H, ArH), 7.20~7.34 (m, 6H, ArH), 7.49~7.53 (m, 1H, ArH), 8.06~8.10 (m, 2H, ArH). IR (KBr, *v*, cm^{-1}): 2958, 2918, 2867, 1722, 1656, 1602, 1487, 1469, 1426, 1397, 1365, 1343, 1300, 1252, 1223, 1194, 1056, 983, 881, 832, 763, 732, 707, 627. HRMS (ESI, *m/z*): calcd for $C_{27}H_{27}N_2O_2$ $[M+H]^+$ 411.2073, found 411.2065.

***4-Benzyl-2,3,3a*,4-tetrahydro-3*a*-*p*-tolylpyrrolo[1,2-*a*] quinazoline-1,5-dione (3m).** m.p. 236~238°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 2.23 (s, 3H, CH_3), 2.34~2.45 (m, 2H, CH_2), 2.63~2.71 (m, 1H, CH), 2.82~2.91 (m, 1H, CH), 4.54 (d, $J=16.4$ Hz, 1H, CH), 5.58 (d, $J=16.4$ Hz, 1H, CH), 7.15~9.19 (m, 4H, ArH), 7.23~7.27 (m, 2H, ArH), 7.28~7.33 (m, 4H, ArH), 7.56~7.60 (m, 1H, ArH), 7.87 (d, $J=7.6$ Hz, 1H, ArH), 8.00 (d, $J=8.0$ Hz, 1H, ArH). IR (KBr, *v*, cm^{-1}): 3031, 2927, 1720, 1664, 1604, 1489, 1468, 145, 1396, 1377, 1350, 1321, 1311, 1225, 770, 730, 698. HRMS (ESI, *m/z*): calcd for $C_{25}H_{23}N_2O_2$ $[M+H]^+$ 383.1760, found 383.1776.

***4-Benzyl-2,3,3a*,4-tetrahydro-3*a*-(4-methoxyphenyl)pyrrolo [1,2-*a*]quinazoline-1,5-dione (3n).** m.p. 210~212°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 2.37~2.45 (m, 1H, CH), 2.51~2.54 (m, 1H, CH), 2.61~2.67 (m, 1H, CH), 2.81~2.89 (m, 1H, CH), 3.69 (s, 3H, OCH_3), 4.51 (d, $J=16.4$ Hz, 1H, CH), 5.55 (d, $J=16.0$ Hz, 1H, CH), 6.88 (d, $J=8.8$ Hz, 2H, ArH), 7.18 (d, $J=8.8$ Hz, 2H, ArH), 7.24~7.33 (m, 6H, ArH), 7.56~7.60 (m, 1H, ArH), 7.87 (d, $J=7.6$ Hz, 1H, ArH), 7.98 (d, $J=8.4$ Hz, 1H, ArH). IR (KBr, *v*, cm^{-1}): 3065, 2953, 2928, 1733, 1658, 1604, 1581, 1512, 1489, 1468, 1430, 1396, 1371, 1345, 1309, 1254, 1222, 1210, 1180, 1029, 834, 766, 730, 698, 623. HRMS (ESI, *m/z*): calcd for $C_{25}H_{23}N_2O_3$ $[M+H]^+$ 399.1709, found 399.1715.

***4-Benzyl-3a*-(4-ethylphenyl)-2,3,3*a*,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (3o).** m.p. 128~129°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 1.10 (t, $J=7.6$ Hz, 3H, CH_3), 2.38~2.56 (m, 4H, $2CH_2$), 2.64~2.67 (m, 1H, CH), 2.82~2.91 (m, 1H, CH), 4.54 (d, $J=16.4$ Hz, 1H, CH), 5.57 (d, $J=16.4$ Hz, 1H, CH), 7.15~7.37 (m, 10H, ArH), 7.56~7.60 (m, 1H, ArH), 7.70 (d, $J=7.6$ Hz, 1H, ArH), 7.99 (d, $J=7.6$ Hz, 1H, ArH). IR (KBr, *v*, cm^{-1}): 2964, 2931, 1712, 1655, 1604, 1487, 1470, 1430, 1397, 1365, 1338, 1315, 1221, 1209, 1192, 835, 759, 708. HRMS (ESI, *m/z*): calcd for $C_{26}H_{25}N_2O_2$ $[M+H]^+$ 397.1916, found 397.1915.

***4-Benzyl-3a*-(4-chlorophenyl)-2,3,3*a*,4-tetrahydropyrrolo [1,2-*a*]quinazoline-1,5-dione (3p).** m.p. 200~202°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 2.37~2.45 (m, 1H, CH), 2.54~2.57 (m, 1H, CH), 2.64~2.69 (m, 1H, CH), 2.83~2.87 (m, 1H, CH), 4.57 (d, $J=16.4$ Hz, 1H, CH), 5.80 (d, $J=16.0$ Hz, 1H, CH), 7.25~7.38 (m, 8H, ArH), 7.41 (d, $J=8.4$ Hz, 2H, ArH), 7.58~7.62 (m, 1H, ArH), 7.87 (d, $J=7.6$ Hz, 1H, ArH), 7.97 (d, $J=8.0$ Hz, 1H, ArH). IR (KBr, *v*, cm^{-1}): 3063, 2983, 2954, 2913, 1722, 1652, 1602, 1487, 1470, 1454, 1433, 1393, 1364, 1311, 1250, 1210, 1096, 1009, 878, 839, 762, 731, 711, 685. HRMS (ESI, *m/z*): calcd for $C_{24}H_{19}ClN_2O_2Na$ $[M+Na]^+$ 425.1033, found 425.1060.

***4-(4-Methoxybenzyl)-2,3,3a*,4-tetrahydro-3*a*-*p*-tolylpyrrolo [1,2-*a*]quinazoline-1,5-dione (3q).** m.p. 167~169°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 2.21 (s, 3H, CH_3), 2.36~2.43 (m, 1H, CH), 2.47~2.54 (m, 1H, CH), 2.67~2.73 (m, 1H, CH), 2.81~2.89 (m, 1H, CH), 3.72 (s, 3H, OCH_3), 4.42 (d, $J=16.0$ Hz, 1H, CH), 5.52 (d, $J=16.0$ Hz, 1H, CH), 6.91 (d, $J=8.4$ Hz, 2H, ArH), 7.12~7.15 (m, 4H, ArH), 7.23~7.26 (m, 3H, ArH), 7.55~7.58 (m, 1H, ArH), 7.86 (d, $J=7.6$ Hz, 1H, ArH), 7.95 (d, $J=8.0$ Hz, 1H, ArH). IR (KBr, *v*, cm^{-1}): 3029, 3001, 2921, 1707, 1650, 1603, 1514, 1486, 1469, 1396, 1362, 1338, 1293, 1250, 1216, 1206, 1181, 1135, 1033, 809, 762. HRMS (ESI, *m/z*): calcd for $C_{26}H_{25}N_2O_3$ $[M+H]^+$ 413.1865, found 413.1875.

***4-(4-Methoxybenzyl)-2,3,3a*,4-tetrahydro-3*a*-(4-methoxyphenyl) pyrrolo[1,2-*a*]quinazoline-1,5-dione (3r).** m.p. 183~184°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 2.35~2.42 (m, 1H, CH), 2.48~2.55 (m, 1H, CH), 2.65~2.73 (m, 1H, CH), 2.80~2.89 (m, 1H, CH), 3.68 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.41 (d, $J=16.0$ Hz, 1H, CH), 5.49 (d, $J=16.0$ Hz, 1H, CH), 6.87 (d, $J=8.8$ Hz, 2H, ArH), 6.91 (d, $J=8.4$ Hz, 2H, ArH), 7.16 (d, $J=8.8$ Hz, 2H, ArH), 7.23~7.27 (m, 3H, ArH), 7.55~7.59 (m, 1H, ArH), 7.87 (d, $J=7.6$ Hz, 1H, ArH), 7.95 (d, $J=8.0$ Hz, 1H,

ArH). IR (KBr, *v*, cm^{-1}): 3063, 2949, 2930, 1725, 1664, 1605, 1584, 1513, 1489, 1467, 1395, 1370, 1349, 1303, 1253, 1221, 1178, 1123, 1035, 828, 812, 773, 699. HRMS (ESI, *m/z*): calcd for $C_{26}H_{25}N_2O_4$ $[M+H]^+$ 429.1814, found 429.1811.

***4-(4-Methoxybenzyl)-2,3,3a*,4-tetrahydro-3*a*-(4-isopropylphenyl) pyrrolo[1,2-*a*]quinazoline-1,5-dione (3s).** m.p. 188~190°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 1.20 (d, $J = 6.8$ Hz, 6H, $2CH_3$), 2.37~2.44 (m, 1H, CH), 2.53~2.55 (m, 1H, CH), 2.66~2.71 (m, 1H, CH), 2.79~2.86 (m, 2H, 2CH), 3.72 (s, 3H, OCH_3), 4.43 (d, $J = 16.0$ Hz, 1H, CH), 5.51 (d, $J = 16.0$ Hz, 1H, CH), 6.90 (d, $J = 8.8$ Hz, 2H, ArH), 7.16~7.27 (m, 7H, ArH), 7.56~7.59 (m, 1H, ArH), 7.88 (d, $J = 7.6$ Hz, 1H, ArH), 7.98 (d, $J = 8.0$ Hz, 1H, ArH),. ^{13}C NMR (DMSO-d_6, 100 MHz): 23.5, 29.7, 31.9, 32.8, 46.7, 55.0, 82.2, 112.7, 113.9, 120.4, 120.5, 125.0, 126.8, 127.8, 127.9, 130.4, 133.3, 135.6, 139.6, 148.7, 158.2, 162.7, 172.4. IR (KBr, *v*, cm^{-1}): 2960,2916, 1722, 1652, 1604, 1512, 1487, 1468, 1430, 1395, 1662, 1341, 1292, 1248, 1217, 1180, 1031, 836, 807, 764. HRMS (ESI, *m/z*): calcd for $C_{28}H_{28}N_2O_3Na$ $[M+Na]^+$ 463.1998, found 468.2001.

***4-(4-Methoxybenzyl)-3a*-(4-chlorophenyl)-2,3,3*a*,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (3t).** m.p. 182~184°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 2.34~2.42 (m, 1H, CH), 2.53~2.57 (m, 1H, CH), 2.69~2.77 (m, 1H, CH), 2.82~2.88 (m, 1H, CH), 3.72 (s, 3H, OCH_3), 4.47 (d, $J = 16.0$ Hz, 1H, CH), 5.52 (d, $J = 16.0$ Hz, 1H, CH), 6.91 (d, $J = 8.8$ Hz, 2H, ArH), 7.23~7.30 (m, 5H, ArH), 7.40 (d, $J = 8.4$ Hz, 2H, ArH), 7.59 (t, $J = 7.6$ Hz, 1H, ArH), 7.88 (d, $J = 7.6$ Hz, 1H, ArH), 7.94 (d, $J = 8.0$ Hz, 1H, ArH). IR (KBr, *v*, cm^{-1}): 3074, 2963, 2921, 1720, 1658, 1604, 1514, 1487, 1470, 1432, 1327, 1307, 1289, 1249, 1220, 1177, 1094, 1010, 879, 841, 824, 800, 758, 683. HRMS (ESI, *m/z*): calcd for $C_{25}H_{22}ClN_2O_3$ $[M+H]^+$ 433.1319, found 433.1339.

***4-(4-Methoxybenzyl)-3a*-(4-ethylphenyl)-2,3,3*a*,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (3u).** m.p. 160~162°C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 1.09 (t, $J = 7.2$ Hz, 3H, CH_3), 2.38~2.44 (m, 1H, CH), 2.49~2.55 (m, 3H, CH_2 + CH), 2.66~2.72 (m, 1H, CH), 2.82~2.86 (m, 1H, CH), 3.72 (s, 3H, OCH_3), 4.43 (d, $J = 16.0$ Hz, 1H, CH), 5.20 (d, $J = 16.0$ Hz, 1H, CH), 6.91 (d, $J = 8.4$ Hz, 2H, ArH), 7.14~7.19 (m, 4H, ArH), 7.23~7.26 (m, 3H, ArH), 7.57 (t, $J = 7.6$ Hz, 1H, ArH), 7.87 (d, $J = 8.0$ Hz, 1H, ArH), 7.97 (d, $J = 8.0$ Hz, 1H, ArH). IR (KBr, *v*, cm^{-1}): 2965, 2929, 2906, 1725, 1655, 1605, 1513, 1487, 1467, 1391, 1362, 1339, 1316, 1293, 1246, 1218, 1181, 1025, 987, 908, 840, 830, 809, 761, 704. HRMS (ESI, *m/z*): calcd for $C_{27}H_{27}N_2O_3$ $[M+H]^+$ 427.2022, found 427.2031.

Acknowledgment. We are grateful to the National Natural Science foundation of China (20802061), a project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions, and the Qing Lan Project (08QLT001, 10QLD008) of Jiangsu Education Committee for financial support.

REFERENCES AND NOTES

[1] (a) Harayama, T.; Morikami, Y.; Shigeta, Y.; Abe, H.; Takeuchi, Y. Synlett 2003, 847. (b) Jolivet-Fouchet, S.; Fabis, F.; Bovy, P.; Ochsenbein, P.; Rault, S. Heterocycles 1999, 51, 1257.

[2] (a) Barraja, P.; Spano, V.; Diana, P.; Carbone, A.; Cirrincione, G. Tetrahedron Lett 2009, 50, 5389. (b) Baek, D.-J. Yakhak Hoechi, 2006, 50, 278. (c) Sarno, S.; Ruzzene, M.; Frascella, P.; Pagano, M. A.; Meggio, F.; Zambon, A.; Mazzorana, M.; Di Maira, G.; Lucchini, V.; Pinna, L. A. Mol Cell Biochem 2005, 274, 69–76.

[3] Anderskewitz, R.; Dollinger, H.; Heine, C.; Pouzet, P. A. J.; Birke, F.; Bouyssou, T. Preparation of pyrroloquinazolines as modulators of chemokine activity. PCT Int. Appl. WO 2004072074 A1 26 Aug 2004, Chem Abstr 141, 225527.

[4] Rioja, I.; Terencio, M. C.; Ubeda, A.; Molina, P.; Tarraga, A.; Gonzalez-Tejero, A.; Alcaraz, M. J. Eur J Pharm 2002, 434, 177.

[5] (a) Dixit, A.; Kashaw, S. K.; Gaur, S.; Saxena, A. K. Bioorg Med Chem 2004, 12, 3591. (b) Maryanoff, B. E.; Zhang, H.-C.; McComsey, D. F. Aminomethyl-pyrroloquinazoline compounds as thrombin receptor antagonists. PCT Int. Appl. WO 2002068425 A1 6 Sep 2002, Chem Abstr 137, 216956. (c) Ahn, H.-S.; Foster, C.; Boykow, G.; Stamford, A.; Manna, M.; Graziano, M. Biochem. Pharm 2000, 60, 1425.

[6] (a) Georgescu, E.; Georgescu, F.; Roibu, C.; Iuhas, P. C.; Draghici, C.; Filip, P. I. ARKIVOC 2008, 60. (b) Abdelrazek, F.; Metwally, N. Synth Commun 2006, 36, 83. (c) Eldin, A. M. S. Heteroatom Chem 2003, 14, 612. (d) Volovenko, Y. M.; Resnyanskaya, E. V. Mendeleev Commun 2002, 119. (e) Wang, M.; Dou, G.; Shi, D. J Comb Chem 2010, 12, 582. (f) Yamato, M.; Takeuchi, Y.; Chem Pharm Bull 1982, 30, 1036. (g) Feng, E.; Zhou, Y.; Zhang, D. Y.; Zhang, L.; Sun, H. F.; Jiang, H. L.; Liu, H. J Org Chem 2010, 75, 3274.

[7] (a) Welton, T. Chem Rev 1999, 99, 2071. (b) Wasser-scheid, P.; Keim, W. Angew Chem Int Ed 2000, 42, 3772.

[8] (a) Fang, D.; Zhang, H. B.; Liu, Z. L. J Heterocycl Chem 2010, 47, 63. (b) Yeung, K. S.; Farkas, M. E.; Qiu, Z.; Yang, Z. Tetrahendron Lett 2002, 43, 5793. (c) Fraga-Dubreuil, J.; Bazureau, J. P. Tetrahendron 2003, 59, 6121. (d) Wang, X. S.; Wu, J. R.; Li, Q.; Zhang, M. M. J Heterocyclic Chem 2009, 46, 1355. (e) Su, C.; Chen, Z. C.; Zheng, Q. G. Synthesis 2003, 555. (f) Wen, L. R.; Xie, H. Y.; Li, M. J Heterocycl Chem 2009, 46, 954.

[9] (a) Wang, X. S.; Wu J. R.; Zhou J.; Tu S. J. J Comb Chem 2009, 11, 1011. (b) Wang, X. S.; Yang, K.; Zhou, J.; Tu, S. J. J Comb Chem 2010, 12, 417. (c) Wang, X. S.; Wu, J. R.; Li, Q.; Yao, C. S.; Tu, S. J. Synlett 2008, 1185. (d) Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. J Heterocycl Chem 2008, 45, 71.