Tetrahedron 68 (2012) 906–912

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A transition metal-free tandem process to pyrrolopyrazino[2,3-*d*]pyridazine-diones

Aiping Huang [a], Zhi Qiao [a], Xinhai Zhang [a], Wei Yu [a], Qingqing Zheng [a], Ying Ma [a], Chen Ma [a,b,*]

[a] School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, PR China
[b] State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100191, PR China

ARTICLE INFO

Article history:
Received 8 August 2011
Received in revised form 18 October 2011
Accepted 8 November 2011
Available online 15 November 2011

Keywords:
Pyrrolopyrazino[2,3-*d*]pyridazine-dione
Smiles rearrangement
Tandem reaction
Synthesis
X-ray crystallographic analysis

ABSTRACT

A transition metal-free tandem process for the synthesis of pyrrolopyrazino[2,3-*d*]pyridazine-diones is described. The process is an efficient construction of this tricyclic system by a one-pot coupling/Smiles rearrangement/cyclization approach. This methodology has potential applications in the synthesis of biologically and medicinally relevant compounds.

1. Introduction

Pyridazinone moiety is found in various natural products and biologically active compounds. Many pyridazinones exhibit a wide range of activities,[1–4] such as antimicrobial,[5] analgesic,[6] anti-inflammatory,[7] herbicidal,[8] antihypertensive,[9] antitumor[10] properties. Pyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones are known as excellent PARP inhibitors, and inhibitors against proliferation of BRCA deficient cells.[11] Heterocyclic compounds possessing a pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one moiety show important biological activities,[12–20] including anti-HIV,[21] antimalarial,[22] antiviral,[23] and anticancer[24] properties. We envision that pyrrolopyrazino[2,3-*d*]pyridazine-diones would be biologically active molecules and intermediates (Fig. 1).

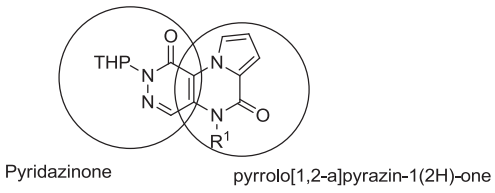


Fig. 1. The structure of pyrrolopyrazino[2,3-*d*]pyridazine-dione.

Tandem reactions now serve as efficient strategies in synthetic organic chemistry,[25–27] because they can complete several chemical processes in one-pot. There are many important advantages of tandem reactions, such as atom economy, higher yield, decrease of the cost of isolating and purifying intermediates. Smiles rearrangement is a direct and facile approach for the formation of many heterocyclic compounds.[28–32]

Herein we report a simple and effective synthesis of pyrrolopyrazino[2,3-*d*]pyridazine-dione derivatives for constructing a tricyclic system via a coupling/Smiles rearrangement/cyclization tandem reaction. We used 2-tetrahydropyranyl-4,5-dichloropyridazin-3-one and pyrrole-2-carboxamides[33–36] as substrates, cesium carbonate as the base, and acetonitrile as the solvent in one-pot.

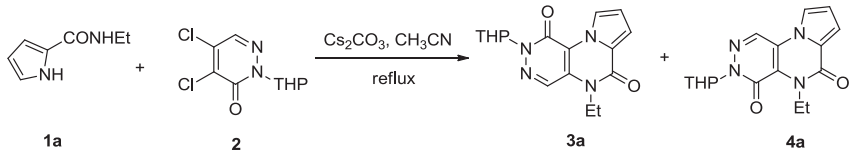
2. Results and discussion

We optimized the reaction conditions using *N*-ethyl-1*H*-pyrrole-2-carboxamide **1a** and **2** as the model substrates, and we found that Cs_2CO_3 in CH_3CN was the most efficient system (Table 1). We started by screening various bases in CH_3CN, and Cs_2CO_3 provided the highest yields (entries 1–3). We then investigated the effect of solvents, and CH_3CN was the most efficient solvent (entries 2, 4–7). The reaction was also investigated by using K_2CO_3 as the base and DMF as the solvent, but yields of the products were much lower. As shown in Table 1, NaH in CH_3CN, K_2CO_3 in DMF could afford **3a** much more than **4a** (entries 3, 8), but yields of them were much lower. Yields of **3a** and **4a** under other conditions were

* Corresponding author. Tel.: +86 531 8836 4464; fax: +86 531 8856 4464; e-mail address: chenma@sdu.edu.cn (C. Ma).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.11.021

Table 1
Effects of base and solvent on the yields of **3a** and **4a**[a]



1a 2 3a 4a

Entry	Base	Solvent	T (°C)	Time (h)	Yield[b] (%) (**3a**+**4a**)		
					3a	**4a**	Total
1	K_2CO_3	CH_3CN	Reflux	—	0	0	0
2	Cs_2CO_3	CH_3CN	Reflux	22	48	30	78
3	NaH	CH_3CN	Reflux	4	22	9	31
4	Cs_2CO_3	DMF	80	9	20	13	33
5	Cs_2CO_3	NMP	80	20	6	4	10
6	Cs_2CO_3	DMSO	80	10	45	32	77
7	Cs_2CO_3	THF	Reflux	23	24	19	43
8	K_2CO_3	DMF	80	20	8	4	12

[a] Reaction conditions: *N*-ethyl-1*H*-pyrrole-2-carboxamide **1a** (1.0 equiv), **2** (1.2 equiv), Cs_2CO_3 (3.5 equiv), reflux.
[b] Isolated yield.

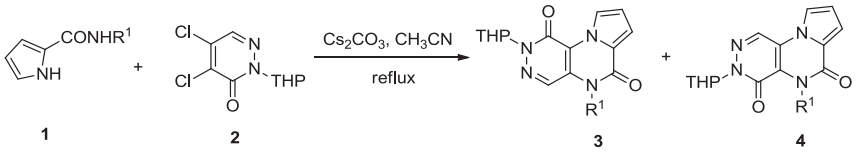
similar (entries 2, 4–7). Consequently, all following reactions were conducted with cesium carbonate in refluxing acetonitrile.

To explore the scope of this methodology, a variety of amines were studied under the reaction conditions, which were optimized above. The experimental results are collected in Table 2. As observed in Table 2, a variety of pyrrole-2-carboxamides ranging from aliphatic to aromatic afforded moderate to good yields of tricyclic products. These all gave a mixture containing **3** and **4** (Table 2).

It is possible that in compound **3a** there was an intramolecular hydrogen bonding between hydrogen atom on the pyrrole ring and oxygen atom on the pyridazinone, and they can form a six-centered structure.

A possible mechanism for the results was proposed in Scheme 1. Nucleophilic substitution of compound **2** by **1** provided compound **5**. Then carboxamide **5** formed carboxamide anion **6**. Subsequently, **6** followed two paths **a** and **b**. Path **b** led to **4** by direct cyclization,

Table 2
Synthesis of pyrrolopyrazino[2,3-*d*]pyridazine-diones[a]



1 2 3 4

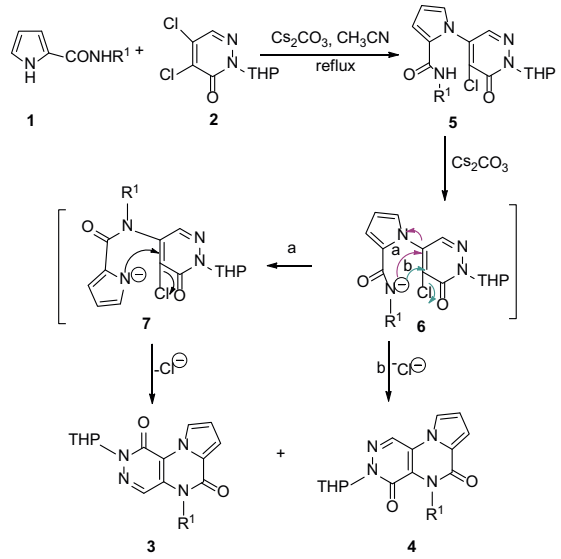
Entry	R^1	Time (h)	Yield[b] (%)				Total (**3**+**4**)
			4		**3**		
1	Et	13	30	**4a**	48	**3a**	78
2	Pr	22	35	**4b**	59	**3b**	94
3	*i*-Pr	19	27	**4c**	54	**3c**	81
4	*c*-Hex	14	38	**4d**	51	**3d**	89
5	Bn	18	31	**4e**	47	**3e**	78
6	3,4-$(MeO)_2$–$C_6H_3(CH_2)_2$	12	23	**4f**	40	**3f**	63
7	Ph	13	36	**4g**	57	**3g**	93
8	4-FC_6H_4	12	29	**4h**	66	**3h**	95
9	4-ClC_6H_4	9	14	**4i**	74	**3i**	88
10	4-BrC_6H_4	7	27	**4j**	64	**3j**	91
11	4-MeC_6H_4	14	28	**4k**	70	**3k**	98
12	4-$MeOC_6H_4$	12	31	**4l**	54	**3l**	85

[a] Reaction conditions: pyrrole-2-carboxamide **1** (1.0 equiv), 2-tetrahydropyranyl-4,5-dichloropyridazin-3-one **2** (1.2 equiv), Cs_2CO_3 (3.5 equiv), reflux.
[b] Isolated yield.

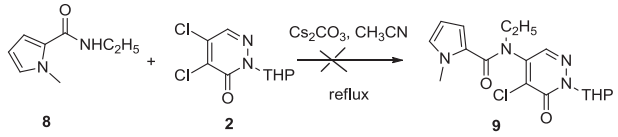
As shown in Table 2, the reactions of 2-tetrahydropyranyl-4,5-dichloropyridazin-3-one **2** with aromatic pyrrole-2-carboxamides (Table 2, entries 7–12) gave higher yields of **3** compared to aliphatic pyrrole-2-carboxamides (Table 2, entries 1–6). However, aromatic amines with an electron-withdrawing group (Table 2, entries 8–10) gave higher yields than the ones with an electron-donating group (Table 2, entry 12).

In the ^1H NMR spectrum of **3** and **4**, the signals of pyrrol protons were different. These signals of the protons on the pyrrole ring in compound **4a** were 6.80, 7.28, 7.57 ppm, and in compound **3a** were 6.74, 7.35, 8.97 ppm. One signal shifted to 8.97 ppm from 7.57 ppm. whereas path **a** led to intermediate **7** via Smiles rearrangement. Finally, intermediate **7** underwent an intramolecular nucleophilic with loss of chlorine atom to yield **3**.

To demonstrate this mechanism, we used *N*-ethyl-1-methyl-1*H*-pyrrole-2-carboxamide **8** and **2** as substrates and cesium carbonate as the base in acetonitrile (Scheme 2). However, there was not any new product **9** even the reaction was refluxed for 8 h. This result suggested that the first step of the reaction of **1** and **2** was the replacement of chlorine anion with pyrrolyl anion and then proceeded through path **a** or **b** to give **3** or **4**, respectively. The configuration of **3b** was determined by X-ray crystallographic analysis (Fig. 2).



Scheme 1. Proposed mechanism for formation of **3** and **4**.



Scheme 2. Reaction of *N*-ethyl-1-methyl-1*H*-pyrrole-2-carboxamide **8** with **2**.

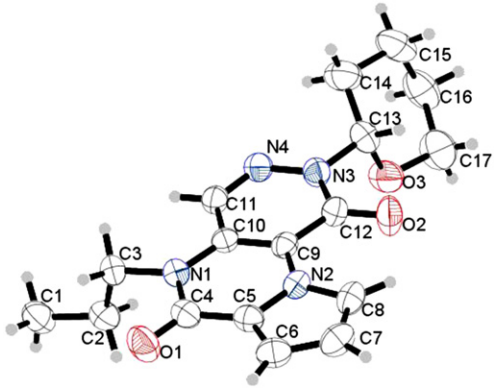


Fig. 2. X-ray structure of compound **3b**.

To expand the scope of this methodology, we studied the reaction of indole-2-carboxamides[37] **10** and **2** under the same conditions. The results are shown in Table 3. The reactions of **2** with different indole-2-carboxamides, 5-fluoro-, and 5-methoxy-indole-2-carboxamides proceeded well to afford the products **11** and **12**.

3. Conclusion

In summary, we have developed a transition metal-free tandem process for the synthesis of pyrrolopyrazino[2,3-*d*]pyridazine-diones. A wide range of pyrrole-2-carboxamides with 2-tetrahydropyranyl-4,5-dichloropyridazin-3-one worked well to afford the tricyclic products. Indole-2-carboxamides were also compatible with this method. Further studies on its application in the synthesis of biologically relevant compounds are currently in progress.

4. Experimental section

4.1. General

Pyrrole-2-carboxamides, *N*-ethyl-1-methyl-1*H*-pyrrole-2-carboxamide,[33–36] and indole-2-carboxamides[37] were prepared according to literature procedures. Acetonitrile was distilled from calcium hydride prior to use. Other reagents were commercially available and were used without further purification. All reactions were monitored by thin-layer chromatography (TLC). ^{1}H NMR spectra were recorded on a Bruker Avance 400 or 300 spectrometer at 400 or 300 MHz, using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were run in the same instrument at 100 or 75 MHz. Melting points were determined on an XD-4 digital micro melting point apparatus. IR spectra were recorded with an IR spectrophotometer VERTEX 70 FTIR (Rruker Optics). HRMS spectra were determined on a Q-TOF6510 spectrograph (Agilent).

4.2. General procedure for the synthesis of compounds 3 and 4

A mixture of pyrrolamide **1** (1.0 mmol), 2-tetrahydropyranyl-4,5-dichloropyridazin-3-one **2** (1.2 mmol), and Cs_2CO_3 (3.5 mmol) in acetonitrile (15 mL) was refluxed, and TLC monitored the end of the reaction. Then the mixture was cooled to room temperature and diluted with brine (60 mL) and extracted with dichloromethane twice (2×30 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuo to afford a residue. The residue was purified by column chromatography on silica gel to afford **3** and **4**.

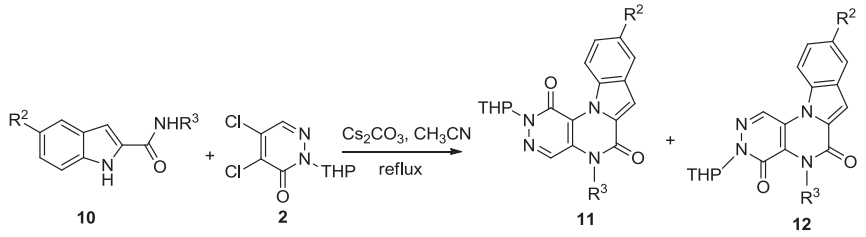
*4.2.1. 5-Ethyl-2-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1,6]pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3a**).* White solid. Mp 206–207 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.97 (1H, q, J=1.5 Hz), 8.15 (1H, s), 7.35 (1H, dd, J=3.9, 1.5 Hz), 6.74 (1H, dd, J=4.2, 3.0 Hz), 6.21 (1H, dd, J=10.8, 2.1 Hz), 4.2–4.4 (2H, m), 4.17 (1H, m), 3.81 (1H, m), 2.03–2.32 (2H, m), 1.57–1.86 (4H, m), 1.39 (3H, t, J=7.2 Hz); ^{13}C NMR (75 M, $CDCl_3$): δ 13.70, 22.88, 24.96, 28.86, 36.69, 68.98, 83.22, 113.96, 114.19, 115.70, 123.20, 123.66, 127.53, 127.62, 154.39, 154.71; IR (KBr, cm^{-1}): 3179, 3147, 3094, 2962, 2843, 1672, 1563, 1209; HRMS calcd for $C_{16}H_{18}N_4O_3$ 314.1379; found: 314.1368.

*4.2.2. 5-Ethyl-3-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1,6]pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4a**).* Orange solid. Mp 180–182 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.30 (1H, s), 7.57 (1H, q, J=1.5 Hz), 7.28 (1H, dd, J=3.9, 1.2 Hz), 6.80 (1H, dd, J=3.9, 3.0 Hz), 6.11 (1H, dd, J=10.5, 1.8 Hz), 4.80 (2H, m), 4.12 (1H, m), 3.75 (1H, m), 2.01–2.17 (2H, m), 1.55–1.80 (4H, m), 1.41 (3H, t, J=6.9 Hz); ^{13}C NMR (75 M, $CDCl_3$): δ 15.66, 22.93, 24.97, 29.06, 39.86, 69.00, 83.81, 113.58, 115.80, 116.00, 120.32, 122.92, 124.17, 127.08, 154.72, 155.68; IR (KBr, cm^{-1}): 3121, 3049, 2933, 2874, 1650, 1241; HRMS calcd for $C_{16}H_{18}N_4O_3$ 314.1379; found: 314.1358.

*4.2.3. 5-Propyl-2-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1,6]-pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3b**).* White solid. Mp 181–182 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.97 (1H, q, J=1.5 Hz), 8.13 (1H, s), 7.35 (1H, dd, J=3.9, 1.5 Hz), 6.74 (1H, dd, J=3.9, 3.0 Hz), 6.21 (1H, dd, J=10.8, 2.1 Hz), 4.11–4.32 (3H, m), 3.81 (1H, m), 2.04–2.32 (2H, m), 1.57–1.86 (6H, m), 1.04 (3H, t, J=7.2 Hz); ^{13}C NMR (75 M, $CDCl_3$): δ 11.10, 21.90, 22.88, 24.96, 28.86, 42.97, 68.98, 83.19, 114.02, 114.20, 115.70, 123.11, 123.65, 127.72, 127.80, 154.38, 154.95; IR (KBr, cm^{-1}): 3178, 3139, 3090, 2962, 2859, 1673, 1651, 1260; HRMS calcd for $C_{17}H_{20}N_4O_3$ 328.1535; found: 328.1542.

*4.2.4. 5-Propyl-3-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1,6]-pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4b**).* White solid. Mp 169–171 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.30 (1H, s), 7.57 (1H, q,

Table 3
Reactions of indole-2-carboxamides **10** with **2**[a]



Entry	R^2	R^3	Time (h)	Yield[b] (%)				Total (**11**+**12**)
				11		**12**		
1	H	4-MeC_6H_4	16	54	**11a**	43	**12a**	97
2	5-MeO	4-MeC_6H_4	19	45	**11b**	42	**12b**	87
3	5-F	4-MeC_6H_4	13	43	**11c**	34	**12c**	77
4	H	4-FC_6H_4	15	46	**11d**	37	**12d**	83
5	5-MeO	Bn	20	44	**11e**	35	**12e**	79

[a] Reaction conditions: **10** (1.0 equiv), 2-tetrahydropyranyl-4,5-dichloropyridazin-3-one **2** (1.2 equiv), Cs_2CO_3 (3.5 equiv), reflux.
[b] Isolated yield.

J=1.5 Hz), 7.28 (1H, dd, *J*=3.9, 1.5 Hz), 6.80 (1H, dd, *J*=3.9, 3.0 Hz), 6.11 (1H, dd, *J*=10.5, 2.1 Hz), 4.70 (2H, m), 4.19 (1H, m), 3.79 (1H, m), 2.06–2.28 (2H, m), 1.59–1.86 (6H, m), 1.01 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75M, $CDCl_3$): δ 11.16, 22.89, 23.74, 24.96, 29.09, 45.65, 68.96, 83.68, 113.61, 115.77, 115.99, 120.26, 122.93, 124.10, 127.08, 154.73, 155.76; IR (KBr, cm^{-1}): 3119, 3048, 2931, 2854, 1648, 1156; HRMS calcd for $C_{17}H_{20}N_4O_3$ 328.1535, found: 328.1544.

*4.2.5. 5-Isopropyl-2-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1, 6]pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3c**).* White solid. Mp 188–200 °C. ^1H NMR (300 M, $CDCl_3$): δ 8.96 (1H, q, *J*=1.5 Hz), 8.37 (1H, s), 7.32 (1H, dd, *J*=3.9, 1.5 Hz), 6.72 (1H, dd, *J*=4.2, 3.0 Hz), 6.21 (1H, dd, *J*=10.8, 3.0 Hz), 4.15–4.20 (1H, m), 3.81 (1H, m), 2.04–2.32 (2H, m), 1.57–1.86 (4H, m), 1.66 (3H, d, *J*=3.0 Hz), 1.64 (3H, d, *J*=3.0 Hz); ^{13}C NMR (75 M, $CDCl_3$): δ 20.68, 20.71, 22.88, 24.97, 28.88, 69.00, 83.14, 114.01, 114.23, 116.36, 123.41, 123.56, 127.88, 128.44, 154.58, 155.35; IR (KBr, cm^{-1}): 3161, 3135, 2943, 2848, 1667, 1609, 1231; HRMS calcd for $C_{17}H_{20}N_4O_3$ 328.1535; found: 328.1537.

*4.2.6. 5-Isopropyl-3-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1, 6]pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4c**).* White solid. Mp 167–169 °C. ^1H NMR (300 M, $CDCl_3$): δ 8.27 (1H, s), 7.52 (1H, q, *J*=1.5 Hz), 7.23 (1H, d, *J*=3.9 Hz), 6.76 (1H, t, *J*=3.6 Hz), 6.11 (1H, dd, *J*=10.5, 1.8 Hz), 5.74 (1H, m), 4.19 (1H, m), 3.79 (1H, m), 2.06–2.28 (2H, m), 1.65–1.79 (10H, m); ^{13}C NMR (75M, $CDCl_3$): δ 20.60, 20.71, 22.93, 24.94, 29.03, 52.20, 69.02, 83.95, 113.33, 115.71, 115.96, 120.90, 124.14, 125.12, 127.22, 130.21, 155.28; IR (KBr, cm^{-1}): 3128, 3115, 3048, 2922, 2851, 1649, 1269; HRMS calcd for $C_{17}H_{20}N_4O_3$ 328.1535; found: 328.1527.

*4.2.7. 5-Cyclohexyl-2-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1, 6]pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3d**).* White solid. Mp 163–165 °C. ^1H NMR (300 M, $CDCl_3$): δ 8.95 (1H, q, *J*=1.5 Hz), 8.47 (1H, s), 7.31 (1H, dd, *J*=3.9, 1.5 Hz), 6.71 (1H, dd, *J*=3.9, 3.0 Hz), 6.19 (1H, dd, *J*=10.5, 2.1 Hz), 5.65 (1H, d, *J*=15.9 Hz), 5.34 (1H, d, *J*=16.5 Hz), 5.02 (1H, s), 4.15–4.20 (m, 1H), 3.80 (1H m), 1.24–2.38 (16H m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.84, 24.95, 25.22, 26.41, 28.81, 30.04, 30.12, 68.87, 83.04, 113.83, 114.06, 116.17, 123.42, 123.47, 128.17, 128.60, 154.47, 155.39; IR (KBr, cm^{-1}): 3163, 3148, 2935, 2853, 1660, 1610, 1258; HRMS calcd for $C_{20}H_{24}N_4O_3$ 368.1848; found: 368.1843.

*4.2.8. 5-Cyclohexyl-3-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1, 6]pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4d**).* White solid. Mp 159–160 °C. ^1H NMR (300 M, $CDCl_3$): δ 8.27 (1H, s), 7.52 (1H, q, *J*=1.5 Hz), 7.20 (1H, dd, *J*=3.9, 1.2 Hz), 6.75 (1H, dd, *J*=3.6, 3.0 Hz), 6.14 (1H, dd, *J*=10.5, 1.8 Hz), 5.20 (1H, m), 4.15–4.20 (1H, m), 3.80 (1H, m), 2.63 (2H, m), 2.09–2.24 (2H, m), 1.31–1.87 (12H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.89, 24.95, 25.35, 26.60, 26.63, 29.14, 29.95, 30.18, 60.66, 69.01, 83.64, 113.33, 115.67, 115.87, 120.95, 124.40, 125.26, 127.22, 155.27, 156.71; IR (KBr, cm^{-1}): 3233, 3133, 2931, 2851, 1648, 1610, 1196; HRMS calcd for $C_{20}H_{24}N_4O_3$ 368.1848; found: 368.1851.

*4.2.9. 5-Benzyl-2-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1,6]-pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3e**).* White solid. Mp 207–208 °C. ^1H NMR (300 M, $CDCl_3$): δ 9.01 (1H, q, *J*=1.5 Hz), 8.07 (1H, s), 7.44 (1H, dd, *J*=3.9, 1.5 Hz), 7.24–7.37 (5H, m), 6.78 (1H, dd, *J*=4.2, 3.0 Hz), 6.18 (1H, dd, *J*=10.5, 2.1 Hz,), 5.65 (1H, d, *J*=15.9 Hz), 5.34 (1H, d, *J*=16.5 Hz), 4.10–4.15 (1H, m), 3.80 (1H, m), 2.04–2.23 (2H, m), 1.59–1.82 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.84, 24.91, 28.85, 45.10, 68.97, 83.20, 114.39, 114.77, 115.95, 122.93, 124.08, 126.60, 127.86, 128.10, 129.26, 135.35, 154.30, 155.26; IR (KBr, cm^{-1}): 3173, 3132, 2945, 2864, 1678, 1645, 1210; HRMS calcd for $C_{21}H_{20}N_4O_3$ 376.1535; found: 376.1540.

*4.2.10. 5-Benzyl-3-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1,6]-pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4e**).* Yellow solid. Mp 215–217 °C. ^1H NMR (300 M, $CDCl_3$): δ 8.30 (1H, s), 7.58 (1H, q, *J*=1.5 Hz), 7.19–7.34 (6H, m), 6.84 (1H, dd, *J*=3.9, 2.7 Hz), 6.14 (2H, d, *J*=3.6 Hz), 6.08 (1H, dd, *J*=10.5, 2.1 Hz), 4.12–4.17 (1H, m), 3.76 (1H, m), 2.03–2.23 (2H, m), 1.56–1.81 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.83, 24.94, 29.04, 46.17, 68.91, 83.69, 114.27, 115.91, 116.51, 120.55, 122.41, 123.91, 127.07, 127.48, 128.36, 138.34, 154.71, 155.91; IR (KBr, cm^{-1}): 3123, 3111, 3051, 2928, 2855, 1647, 1233; HRMS calcd for $C_{21}H_{20}N_4O_3$ 376.1535; found: 376.1544.

*4.2.11. 5-(3,4-Dimethoxyphenethyl)-2-(tetrahydro-2H-pyran-2-yl) pyrrolo[1′,2′:1,6]pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3f**).* White solid. Mp 178–180 °C. ^1H NMR (300 M, $CDCl_3$): δ 8.98 (1H, q, *J*=1.5 Hz), 8.12 (1H, s), 7.38 (1H, *J*=3.9, 1.5 Hz), 6.81–6.84 (2H, m), 6.75–6.78 (2H, m), 6.19 (1H, dd, *J*=10.8, 2.1 Hz), 4.32–4.48 (2H, m), 4.19–4.20 (1H, m), 3.86 (6H, d, *J*=1.8 Hz), 3.81 (1H, m), 2.97 (2H, m), 2.08–2.25 (2H, m), 1.61–1.81 (4H, m); ^{13}C NMR (75M, $CDCl_3$): δ 22.85, 24.95, 28.92, 34.34, 43.32, 55.92, 65.53, 68.97, 83.20, 111.55, 111.90, 114.10, 114.28, 115.54, 120.77, 123.07, 127.59, 127.65, 129.59, 148.18, 149.26, 154.24, 154.81; IR (KBr, cm^{-1}): 3193, 2925, 2850,

1727, 1653, 1263; HRMS calcd for $C_{24}H_{26}N_4O_5$ 450.1903; found: 450.1906.

*4.2.12. 5-(3,4-Dimethoxyphenethyl)-3-(tetrahydro-2H-pyran-2-yl) pyrrolo[1′,2′:1,6]pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4f**).* White solid. Mp 191–193 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.28 (1H, s), 7.57 (1H, q, *J*=1.5 Hz), 7.30 (1H, dd, *J*=3.9, 1.5 Hz), 6.91–6.94 (2H, m), 6.77–6.82 (2H, m), 6.13 (1H, dd, *J*=10.5, 2.1 Hz,) 4.86–5.05 (2H, m), 4.16–4.20 (1H, m), 3.85 (6H, d, *J*=6.0 Hz), 3.75 (1H, m), 3.02 (2H, dd, *J*=15.9, 8.4 Hz), 2.08–2.27 (2H, m), 1.57–1.85 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.92, 24.96, 29.06, 35.93, 45.72, 55.83, 55.90, 68.99, 83.61, 111.17, 112.43, 113.72, 115.88, 116.19, 120.15, 121.18, 122.91, 124.05, 127.01, 131.33, 147.57, 148.78, 154.74, 155.83; IR (KBr, cm^{-1}): 3116, 3044, 2927, 2852, 1645, 1236; HRMS calcd for $C_{24}H_{26}N_4O_5$ 450.1903; found: 450.1908.

*4.2.13. 5-Phenyl-2-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1, 6]pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3g**).* White solid. Mp 154–156 °C. ^{1}H NMR (300M, $CDCl_3$): δ 9.04 (1H, q, *J*=1.5 Hz), 8.37 (1H, s), 7.54–7.63 (3H, m), 7.46 (1H, s), 7.42 (2H, dd, *J*=4.2, 1.5 Hz), 7.29–7.35 (2H, m), 6.78 (1H, dd, *J*=3.9, 3.0 Hz), 6.18 (1H, dd, *J*=10.8, 2.1 Hz), 4.09–4.16 (1H, m), 3.81 (1H, m), 2.04–2.20 (2H, m), 1.61–1.78 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.84, 24.94, 28.72, 68.90, 83.19, 114.41, 114.85, 115.17, 123.30, 124.18, 128.82, 128.96, 129.06, 129.90, 130.33, 134.67, 154.41, 154.91; IR (KBr, cm^{-1}): 3170, 3064, 2924, 2855, 1696, 1662, 1207; HRMS calcd for $C_{20}H_{18}N_4O_3$ 362.1379; found:362.1387.

*4.2.14. 5-Phenyl-3-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1, 6]pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4g**).* Orange solid. Mp 204–207 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.37 (1H, s), 7.65 (1H, q, *J*=1.5 Hz), 7.47–7.49 (3H, m), 7.35 (1H, dd, *J*=3.9, 1.5 Hz), 7.24–7.28 (2H, m), 6.84 (1H, dd, *J*=3.6, 2.7 Hz), 5.96 (1H, dd, *J*=10.5, 2.1 Hz), 4.06–4.10 (1H, m), 3.63 (1H, m), 1.96–2.18 (2H, m), 1.50–1.73 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.82, 24.87, 29.12, 29.70, 68.91, 83.13, 114.98, 115.99, 116.99, 120.05, 122.62, 124.06, 127.10, 128.39, 128.56, 138.00, 153.75, 155.58; IR (KBr, cm^{-1}): 3112, 3055, 2923, 2853, 1661, 1278; HRMS calcd for $C_{20}H_{18}N_4O_3$ 362.1379; found: 362.1382.

*4.2.15. 5-(4-Fluorophenyl)-2-(tetrahydro-2H-pyran-2-yl)pyrrolo-[1′,2′:1,6]pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3h**).* White solid. Mp 216–218 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 9.01 (1H, q, *J*=1.5 Hz), 7.46 (1H, s), 7.37 (1H, dd, *J*=3.9, 1.5 Hz), 7.25–7.35 (4H, m), 6.76 (1H, dd, *J*=3.6, 2.7 Hz), 6.18 (1H, dd, *J*=10.5, 2.1 Hz), 4.11–4.16 (1H, m), 3.81 (1H, m), 2.04–2.21 (2H, m), 1.67–1.77 (4H, m); ^{13}C NMR (75 M $CDCl_3$): δ 22.77, 24.91, 28.61, 68.72, 83.14, 114.21, 114.57, 114.94, 117.28 (d, *J*=23.2 Hz), 122.94, 124.07, 128.60, 130.45 (d, *J*=3.7 Hz), 130.95 (q, *J*=5.3 Hz), 154.12, 154.66, 161.23, 164.54; IR (KBr, cm^{-1}): 3166, 3070, 2927, 2856, 1690, 1660, 1222; HRMS calcd for $C_{20}H_{17}FN_4O_3$ 380.1285; found: 380.1263.

*4.2.16. 5-(4-Fluorophenyl)-3-(tetrahydro-2H-pyran-2-yl)pyrrolo-[1′,2′:1,6]pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4h**).* White solid. Mp 269–271 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.38 (1H, s), 7.66 (1H, q, *J*=1.5 Hz), 7.35 (1H, dd, *J*=3.9, 1.2 Hz), 7.13–7.26 (4H, m), 6.85 (1H, q, *J*=3.9, 2.7 Hz), 5.96 (1H, dd, *J*=10.8, 2.1 Hz), 4.07–4.13 (1H, m), 3.66 (1H, m), 1.98–2.21 (2H, m), 1.55–1.76 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.80, 24.85, 29.11, 68.96, 83.19, 115.21, 115.62 (d, *J*=24.4 Hz), 116.12, 117.10, 120.14, 122.46, 123.91, 127.08, 129.83 (d, *J*=21.8 Hz), 133.75 (d, *J*=3.0 Hz), 153.79, 155.62, 160.58, 163.86; IR (KBr, cm^{-1}): 3120, 3053, 2950, 2873, 1653, 1277; HRMS calcd for $C_{20}H_{17}FN_4O_3$ 380.1285; found: 380.1295.

*4.2.17. 5-(4-Chlorophenyl)-2-(tetrahydro-2H-pyran-2-yl)pyrrolo [1′,2′:1,6]pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3i**).* White solid. Mp 161–163 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 9.03 (1H, q, *J*=2.9 Hz), 7.57–7.76 (2H, m), 7.47 (1H, s), 7.41 (1H, dd, *J*=4.0, 1.5 Hz), 7.24–7.30 (2H, m), 6.78 (1H, dd, *J*=3.9, 3.0 Hz), 6.18 (1H, dd, *J*=10.7, 2.2 Hz), 4.12–4.16 (1H, m), 3.81 (1H, m), 2.04–2.20 (2H, m), 1.57–1.77 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.82, 24.93, 28.67, 68.90, 83.28, 114.54, 115.16, 115.33, 123.06, 124.41, 128.48, 128.62, 130.37, 130.48, 130.60, 133.09, 136.07, 154.34, 154.75; IR (KBr, cm^{-1}): 3165, 3092, 3060, 2926, 2853, 1686, 1657, 1273; HRMS calcd for $C_{20}H_{17}ClN_4O_3$ 396.0989; found: 396.0977.

*4.2.18. 5-(4-Chlorophenyl)-3-(tetrahydro-2H-pyran-2-yl)pyrrolo [1′,2′:1,6]pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4i**).* Orange solid. Mp 184–186 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.38 (1H, s), 7.66 (1H, d, *J*=1.44 Hz), 7.43 (2H, d, *J*=8.44 Hz), 7.36 (1H, d, *J*=3.1 Hz), 7.21 (2H, d, *J*=7.5 Hz), 6.84 (1H, t, *J*=3.32 Hz), 5.96 (1H, dd, *J*=10.5, 1.7 Hz), 4.10 (1H, m), 3.67 (1H, m), 1.98–2.15 (2H, m), 1.53–1.72 (4H, m); ^{13}C NMR (75 M, DMSO-d_6): δ 22.84, 25.11, 28.65, 67.99, 83.19, 114.33, 115.73, 120.02, 120.59, 122.50, 123.85, 128.31, 128.65, 130.75, 132.50, 138.13, 153.75, 155.44; IR (KBr, cm^{-1}): 3115, 3056, 2925, 2855, 1651, 1624, 1278; HRMS calcd for $C_{20}H_{17}ClN_4O_3$ 396.0989; found: 396.0968.

*4.2.19. 5-(4-Bromophenyl)-2-(tetrahydro-2H-pyran-2-yl)pyrrolo [1′,2′:1,6]pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3j**).* White solid. Mp 144–147 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 9.04 (1H, q, *J*=1.5 Hz), 7.72–7.76 (2H, m), 7.47 (1H, s), 7.41 (1H, dd, *J*=3.9, 1.5 Hz), 7.17–7.26 (2H, m), 6.78 (1H, dd, *J*=3.9, 2.7 Hz), 6.18 (1H, dd, *J*=10.5, 2.1 Hz), 4.09–4.16 (1H, m), 3.81 (1H, m), 2.04–2.24 (2H, m), 1.57–1.82 (4H, m); ^{13}C NMR (75M, $CDCl_3$): δ 22.82, 24.93, 28.66, 68.90, 83.28, 114.54, 115.18, 115.33, 123.05, 124.13, 124.41, 128.41, 128.60, 130.65, 130.77, 133.63, 154.34, 154.67; IR (KBr, cm^{-1}): 3164, 3089, 2927, 2852, 1687, 1658, 1209; HRMS calcd for $C_{20}H_{17}BrN_4O_3$ 440.0484; found: 440.0484.

*4.2.20. 5-(4-Bromophenyl)-3-(tetrahydro-2H-pyran-2-yl)pyrrolo [1′,2′:1,6]pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4j**).* White solid. Mp 169–172 °C. ^{1}H NMR (300M, $CDCl_3$): δ 8.38 (1H, s), 7.65 (1H, q, *J*=1.5 Hz), 7.58 (2H, d, *J*=8.7 Hz), 7.36 (1H, dd, *J*=3.9, 1.2 Hz), 7.13 (2H, d, *J*=8.1 Hz), 6.84 (1H, dd, *J*=3.6, 2.7 Hz), 5.96 (1H, dd, *J*=10.5, 1.7 Hz), 4.10 (1H, m), 3.67 (1H, m), 1.98–2.15 (2H, m), 1.53–1.72 (4H, m); ^{13}C NMR (75 M, DMSO-d_6): δ 27.59, 29.87, 33.32, 72.69, 87.87, 119.11, 120.50, 122.27, 124.79, 125.76, 128.58, 130.68, 133.41, 135.90, 137.37, 143.02, 146.85, 160.79; IR (KBr, cm^{-1}): 3112, 3054, 2925, 2854, 1651, 1614, 1276; HRMS calcd for $C_{20}H_{17}BrN_4O_3$ 440.0484, 440.0478.

*4.2.21. 2-(Tetrahydro-2H-pyran-2-yl)-5-(p-tolyl)pyrrolo[1′,2′:1,6] pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3k**).* White solid. Mp 186–188 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 9.02 (1H, q, *J*=1.5 Hz), 7.49 (1H, s), 7.37–7.41 (3H, m), 7.15–7.23 (2H, m), 6.78 (1H, t, *J*=4.0 Hz), 6.18 (1H, dd, *J*=10.5, 2.1 Hz), 4.12–4.16 (1H, m), 3.81 (1H, m), 2.46 (3H, s), 2.04–2.20 (2H, m), 1.57–1.77 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 21.29, 22.82, 24.94, 28.64, 68.80, 83.14, 114.22, 114.54, 114.97, 123.27, 123.97, 128.62, 128.70, 128.92, 129.11, 130.91, 131.92, 139.94, 154.33, 154.94; IR (KBr, cm^{-1}): 3164, 3145, 2922, 2851, 1696, 1658, 1215; HRMS calcd for $C_{21}H_{20}N_4O_3$ 376.1535; found: 376.1534.

*4.2.22. 3-(Tetrahydro-2H-pyran-2-yl)-5-(p-tolyl)pyrrolo[1′,2′:1,6] pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4k**).* White solid. Mp 279–282 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.38 (1H, s), 7.65 (1H, q, *J*=1.2 Hz), 7.33 (1H, dd, *J*=3.9, 1.2 Hz), 7.26–7.29 (2H, m), 7.15 (2H, d, *J*=7.2 Hz), 6.84 (1H, dd, *J*=3.9, 3.0 Hz), 5.96 (1H, dd, *J*=10.8, 2.1 Hz), 4.10 (1H, m), 3.67 (1H, m), 2.43 (3H, s), 1.98–2.15 (2H, m), 1.53–1.72 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 21.46, 22.82, 24.87, 29.15, 68.91, 83.07, 114.89, 115.96, 116.92, 120.01, 122.70, 124.08, 127.15, 127.42, 127.79, 129.37, 135.36, 138.14, 153.79, 155.74; IR (KBr, cm^{-1}): 3112,

3054, 2924, 2870, 1654, 1626, 1276; HRMS calcd for $C_{21}H_{20}N_4O_3$ 376.1535; found: 376.1528.

*4.2.23. 5-(4-Methoxyphenyl)-2-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1,6]pyrazino[2,3-d]pyridazine-1,6(2H,5H)-dione (**3l**).* White solid. Mp 186–187 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 9.02 (1H, q, *J*=1.2 Hz), 7.52 (1H, s), 7.40 (1H, dd, *J*=3.9, 1.2 Hz), 7.18–7.25 (2H, m), 7.06–7.11 (2H, m), 6.78 (1H, dd, *J*=3.9, 3.0 Hz), 6.18 (1H, dd, *J*=10.5, 1.8 Hz), 4.10–4.16 (1H, m), 3.89 (3H, s), 3.81 (1H, m), 2.04–2.26 (2H, m), 1.57–1.83 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.84, 24.94, 28.68, 55.61, 68.85, 83.17, 114.29, 114.64, 115.06, 115.45, 115.57, 123.32, 124.04, 126.96, 129.13, 129.18, 129.97, 130.04, 154.38, 155.18, 160.37; IR (KBr, cm^{-1}): 3165, 2923, 2852, 1686, 1658, 1250; HRMS calcd for $C_{21}H_{20}N_4O_4$ 392.1485; found: 392.1479.

*4.2.24. 5-(4-Methoxyphenyl)-3-(tetrahydro-2H-pyran-2-yl)pyrrolo[1′,2′:1,6]pyrazino[2,3-d]pyridazine-4,6(3H,5H)-dione (**4l**).* Brown solid. Mp 206–207 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 8.37 (1H, s), 7.64 (1H, q, *J*=1.2 Hz), 7.33 (1H, dd, *J*=3.9, 1.5 Hz), 7.17 (2H, d, *J*=6.9 Hz), 6.98 (2H, d, *J*=9.0 Hz), 6.83 (1H, dd, *J*=3.9, 3.0 Hz), 5.96 (1H, dd, *J*=10.5, 1.8 Hz), 4.10 (1H, m), 3.86 (3H, s), 3.67 (1H, m), 2.01–2.20 (2H, m), 1.26–1.72 (4H, m); ^{13}C NMR (75 M, $CDCl_3$): δ 22.82, 24.87, 29.16, 55.31, 68.94, 83.11, 113.87, 114.89, 115.97, 116.84, 119.97, 122.77, 124.11, 127.09, 128.63, 129.01, 130.53, 153.83, 155.90, 159.23; IR (KBr, cm^{-1}): 3109, 3059, 2924, 2852, 1727, 1654, 1246; HRMS calcd for $C_{21}H_{20}N_4O_4$ 392.1485; found: 392.1486.

*4.2.25. 2-(Tetrahydro-2H-pyran-3-yl)-5-(p-tolyl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-1,6(2H,5H)-dione (**11a**).* White solid. Mp 289–292 °C. ^{1}H NMR (300 M, DMSO-d_6): δ 12.906 (1H, s), 9.33 (1H, s), 8.58 (1H, d, *J*=7.8 Hz), 7.69 (1H, t, *J*=9.0 Hz), 7.58 (1H, t, *J*=7.8 Hz), 7.39 (1H, t, *J*=7.2 Hz), 7.12–7.25 (4H, m), 5.76 (1H, dd, *J*=9.0, 5.1Hz), 3.92 (1H, d, *J*=11.7 Hz), 3.42–3.58 (1H, m), 2.41 (3H, s), 1.92–2.24 (2H, m), 1.49–1.64 (4H, m); ^{13}C NMR (100 M, DMSO-d_6): δ 21.27, 23.02, 25.25, 28.86, 68.00, 83.06, 113.92, 115.30, 115.85, 122.03, 122.27, 123.34, 127.44, 128.10, 128.31, 128.88, 128.99, 130.78, 133.63, 137.02, 138.02, 140.17, 153.58, 156.33; IR (KBr, cm^{-1}): 3192, 3048, 2919, 2849, 1674, 1653, 1211; HRMS calcd for $C_{25}H_{22}N_4O_3$ 426.1692; found: 426.1682.

*4.2.26. 3-(Tetrahydro-2H-pyran-2-yl)-5-(p-tolyl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-4,6(3H,5H)-dione (**12a**).* White solid. Mp 345–347 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 9.12 (1H, s), 8.10 (1H, d, *J*=8.7 Hz), 7.93 (1H, d, *J*=8.1 Hz), 7.62 (1H, s), 7.60 (1H, t, *J*=8.1 Hz), 7.47 (1H, t, *J*=7.5 Hz), 7.29 (2H, d, *J*=8.1 Hz), 7.19 (2H, d, *J*=8.4 Hz), 6.02 (1H, q, *J*=10.8, 2.1 Hz), 4.10 (1H, d, *J*=11.1 Hz), 3.67 (1H, t, *J*=12.0 Hz), 2.44 (3H, s), 1.99–2.20 (2H, m), 1.26–1.79 (4H, m); ^{13}C NMR (75 M, DMSO-d_6): δ 21.25, 22.88, 25.18, 28.73, 68.04, 83.08, 108.84, 115.79, 123.61, 123.72, 124.15, 126.86, 128.22, 128.60, 128.88, 129.71, 134.12, 136.63, 137.06, 153.85, 156.79; IR (KBr, cm^{-1}): 3181, 2925, 2857, 1656, 1274; HRMS calcd for $C_{25}H_{22}N_4O_3$ 426.1692; found: 426.1680.

*4.2.27. 9-Methoxy-2-(tetrahydro-2H-pyran-3-yl)-5-(p-tolyl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-1,6(2H,5H)-dione (**11b**).* White solid. Mp 288–291 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 11.46 (1H, s), 8.95 (1H, s), 7.53 (1H, d, *J*=2.1 Hz), 7.39 (2H, d, *J*=8.1 Hz), 7.20–7.25 (3H, m), 7.15 (1H, dd, *J*=9.0, 2.1 Hz), 6.08 (1H, dd, *J*=10.5, 1.8 Hz), 4.07–4.18 (1H, m), 3.94 (3H, s), 3.63–3.71 (1H, m), 2.53 (3H, s), 1.99–2.37 (2H, m), 1.51–1.76 (4H, m); ^{13}C NMR (100 M, $CDCl_3$): δ 21.52, 22.95, 25.01, 29.30, 55.79, 68.87, 82.83, 102.87, 114.77, 115.56, 116.72, 118.47, 122.31, 127.14, 127.62, 129.44, 130.42, 133.69, 135.24, 137.19, 138.08, 153.94, 155.69, 157.06; IR (KBr, cm^{-1}): 3231, 2938, 2850, 1652, 1626, 1221; HRMS calcd for $C_{26}H_{24}N_4O_4$ 456.1798; found: 456.1776.

*4.2.28. 9-Methoxy-3-(tetrahydro-2H-pyran-2-yl)-5-(p-tolyl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-4,6(3H,5H)-dione (**12b**).* Brown solid. Mp 313–315 °C. ^{1}H NMR (300 M, $CDCl_3$): 9.04 (1H, s), 7.98 (1H, d, *J*=9.3 Hz), 7.61 (1H, s), 7.26–7.31 (2H, m), 7.17–7.24 (4H, m), 6.01 (1H, dd, *J*=10.5, 1.8 Hz), 4.07–4.11 (1H, m), 3.92 (3H, s), 3.60–3.73 (2H, m), 2.44 (1H, s), 1.99–2.22 (2H, m), 1.51–1.73 (4H, m); ^{13}C NMR (100 M, $CDCl_3$): δ 21.35, 23.04, 25.14, 28.98, 56.02, 68.89, 82.88, 109.09, 112.56, 113.32, 118.80, 119.35, 124.05, 128.56, 129.55, 129.72, 129.80, 130.89, 133.19, 134.15, 134.82, 140.13, 155.10, 158.26; IR (KBr, cm^{-1}): 3157, 2937, 2861, 1653, 1276; HRMS calcd for $C_{26}H_{24}N_4O_4$ 456.1798, 456.1774.

*4.2.29. 9-Fluoro-2-(tetrahydro-2H-pyran-3-yl)-5-(p-tolyl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-1,6(2H,5H)-dione (**11c**).* Brown solid. Mp 296–298 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 11.13 (1H, s), 8.86 (1H, s), 7.83 (1H, d, *J*=8.1 Hz), 7.38 (3H, d, *J*=7.8 Hz), 7.22 (3H, d, *J*=6.9 Hz), 5.99 (1H, d, *J*=9.6 Hz), 4.08–4.18 (1H, m), 3.38–3.81 (1H, m), 2.52 (1H, s), 2.01–2.25 (2H, m), 1.52–1.75 (4H, m); ^{13}C NMR (100 M, $CDCl_3$): δ 22.35, 24.64, 28.04, 29.91, 67.53, 82.39, 111.49, 113.86, 114.83 (d, *J*=5.0 Hz), 116.79, 120.26, 122.64 (d, *J*=3.0 Hz), 128.72 (q, *J*=15.0 Hz), 130.53 (d, *J*=24.5 Hz), 131.51 (d, *J*=21.0 Hz), 133.27, 134.30, 136.49, 139.13, 154.92, 157.55, 166.85; IR (KBr, cm^{-1}): 3135, 3080, 2927, 2855, 1673, 1655, 1270; HRMS calcd for $C_{25}H_{21}FN_4O_3$ 444.1589; found: 444.1592.

*4.2.30. 9-Fluoro-3-(tetrahydro-2H-pyran-2-yl)-5-(p-tolyl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-4,6(3H,5H)-dione (**12c**).* White solid. Mp 367–369 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 9.04 (1H, s), 8.07 (1H, dd, *J*=9.6, 4.2 Hz), 7.66 (1H, s), 7.55 (1H, dd, *J*=8.4, 2.4 Hz), 7.38 (1H, d, *J*=2.7 Hz), 7.35 (1H, d, *J*=2.4 Hz), 7.30 (1H, d, *J*=8.7 Hz), 7.18 (2H, d, *J*=8.4 Hz), 6.01 (1H, dd, *J*=10.5, 1.8 Hz), 4.08–4.11 (1H, m), 3.62–3.69 (1H, m), 2.44 (3H, s), 2.00–2.23 (1H, m), 1.50–1.74 (4H, m); ^{13}C NMR (100 M, $CDCl_3$): δ 21.46, 22.83, 24.93, 29.16, 68.95, 83.08, 108.34, 108.58, 109.38 (d, *J*=4.0 Hz), 115.14 (d, *J*=9.0 Hz), 115.48, 115.74, 121.71, 123.12, 127.27 (d, *J*=7.0 Hz), 129.46 (d, *J*=8.0 Hz), 130.66, 131.02 (d, *J*=10.0 Hz), 135.34, 138.25, 153.89, 156.53, 160.68; IR (KBr, cm^{-1}): 3122, 2927, 2849, 1644, 1257; HRMS calcd for $C_{25}H_{21}FN_4O_3$ 444.1589; found: 444.1584.

*4.2.31. 5-(4-Fluorophenyl)-2-(tetrahydro-2H-pyran-3-yl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-1,6(2H,5H)-dione (**11d**).* White solid. Mp 276–278 °C. ^{1}H NMR (400 M, $CDCl_3$): δ 11.05 (1H, s), 9.00 (1H, s), 8.21 (1H, d, *J*=8.12 Hz), 7.56 (1H, t, *J*=7.60 Hz), 7.41–7.46 (2H, m), 7.24–7.34 (4H, m), 6.04 (1H, dd, *J*=10.52, 1.56 Hz), 4.12 (1H, d, *J*=11.04 Hz), 3.68 (1H, t, *J*=11.40 Hz), 2.01–2.30 (2H, m), 1.53–1.75 (4H, m); ^{13}C NMR (100 M, DMSO-d_6): δ 22.98, 25.25, 28.86, 68.00, 83.07, 113.94, 115.10 (d, *J*=5.0 Hz), 115.28, 115.36 (d, *J*=7.0 Hz), 115.92, 122.03, 122.33, 127.50, 128.31, 130.44 (q, *J*=8.0 Hz), 130.72, 133.69, 136.81 (d, *J*=3.0 Hz), 140.19, 153.66, 156.32, 160.61, 163.02; IR (KBr, cm^{-1}): 3222, 3145, 2920, 2850, 1673, 1656, 1208; HRMS calcd for $C_{24}H_{19}FN_4O_3$ 430.1441; found: 430.1444.

*4.2.32. 5-(4-Fluorophenyl)-3-(tetrahydro-2H-pyran-2-yl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-4,6(3H,5H)-dione (**12d**).* Brown solid. Mp 324–327 °C. ^{1}H NMR (400 M, $CDCl_3$): δ 9.87 (1H, s), 9.55 (1H, d, *J*=8.48 Hz), 7.53 (3H, d, *J*=6.64 Hz), 7.27–7.41 (5H, m), 6.32 (1H, d, *J*=10.48 Hz), 4.17 (1H, d, *J*=11.44 Hz), 3.85 (1H, t, *J*=11.48 Hz), 2.01–2.22 (2H, m), 1.59–1.81 (4H, m); ^{13}C NMR (100 M, $CDCl_3$): δ 23.05, 25.11, 29.04, 68.99, 83.16, 111.88, 113.65, 117.35 (d, *J*=22.0 Hz), 119.09, 121.91, 123.41, 128.01, 128.71 (q, *J*=7.0 Hz), 129.07, 129.30, 130.76 (d, *J*=3.0 Hz), 136.57, 139.59, 155.62, 158.09, 163.58, 164.79; IR (KBr, cm^{-1}): 3196, 3087, 2935, 2847, 1676, 1235; HRMS calcd for $C_{24}H_{19}FN_4O_3$ 430.1441; found: 430.1434.

*4.2.33. 5-Benzyl-2-(tetrahydro-2H-pyran-3-yl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-1,6(2H,5H)-dione (**11e**).* White solid. Mp 264–267 °C. ^{1}H NMR (400 M, $CDCl_3$): δ 10.97 (1H, s), 8.93 (1H, s), 7.53 (1H, d, *J*=1.60 Hz), 7.29 (4H, d, *J*=4.24 Hz), 7.22–7.24 (2H, m), 7.12 (1H,

dd, J=9.00, 2.04 Hz), 6.50 (2H, d, J=15.76 Hz), 6.18 (1H, d, J=9.00 Hz), 4.16 (1H, d, J=11.04 Hz), 3.93 (3H, s), 3.79 (1H, t, J=11.32 Hz), 2.07–2.28 (2H, m), 1.56–1.82 (4H, m); ^{13}C NMR (100 M, $CDCl_3$) 23.03, 25.12, 29.28, 48.61, 55.83, 68.94, 83.53, 103.12, 114.60, 115.41, 117.31, 118.56, 122.28, 126.66, 126.95, 127.68, 128.54, 130.54, 133.67, 135.13, 138.52, 154.87, 155.74, 156.95; IR (KBr, cm^{-1}): 3140, 3006, 2934, 2853, 1689, 1644, 1215; HRMS calcd for $C_{26}H_{24}N_4O_4$ 456.1798, 456.1772.

*4.2.34. 5-Benzyl-9-methoxy-3-(tetrahydro-2H-pyran-2-yl)pyridazino[4′,5′:5,6]pyrazino[1,2-a]indole-4,6(3H,5H)-dione (**12e**).* Brown solid. Mp 339–342 °C. ^{1}H NMR (400 M, $CDCl_3$): δ 8.62 (1H, d, J=9.48 Hz), 8.04 (1H, s), 7.73 (1H, s), 7.24–7.36 (5H, m), 7.16 (1H, d, J=2.56 Hz), 7.12 (1H, dd, J=9.52, 2.64 Hz), 6.22 (1H, dd, J=10.56, 1.96 Hz), 5.65 (1H, d, J=16.20 Hz), 5.37 (1H, d, J=16.12 Hz), 4.13–4.16 (1H, m), 3.91 (3H, s), 3.77–3.84 (1H, m), 2.04–2.16 (2H, m), 1.55–1.79 (4H, m); ^{13}C NMR (100 M, $CDCl_3$): δ 22.91, 24.98, 29.16, 45.49, 55.62, 69.03, 83.55, 101.75, 110.53, 116.54, 119.19, 121.46, 126.59, 127.20, 128.13, 128.18, 128.31, 128.44, 129.34, 130.41, 131.14, 135.16, 153.94, 156.39; IR (KBr, cm^{-1}): 3192, 3077, 2935, 2870, 1653, 1222; HRMS calcd for $C_{26}H_{24}N_4O_4$ 456.1798; found: 456.1746.

Acknowledgements

We are grateful to National Science Foundation of China (No. 20872079), the Natural Science Foundation of Shandong Province (2009ZRB019YA), IIFSDU (No. 2010TS052) and State Key Laboratory of Natural and Biomimetic Drugs of Peking University (K20090205) for financial support of this research.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.11.021. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Mátyus, P.; Kosáry, J.; Kasztreiner, E.; Makk, N.; Diesler, E.; Czakó, K.; Rabloczky, G.; Jaszlits, L.; Horváth, E.; Tömösközi, Z.; Cseh, G.; Horváth, E.; Arányi, P. *Eur. J. Med. Chem.* **1992**, *27*, 107; (b) Mátyus, P.; Varga, I.; Zára, E.; Mezei, A.; Simay, A.; Haider, N.; Boros, S.; Bakonyi, A.; Horváth, E.; Horváth, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2857; (c) Pankucsi, C.; Magyar, J.; Bányász, T.; Mátyus, P.; Nánási, P. P. *IDrugs* **1998**, *1*, 554; (d) Mátyus, P. *Pharmazie* **2001**, *56*, 50.
2. (a) Timári, G.; Soós, T.; Hajós, G.; Messmer, A.; Nacsa, J.; Molnár, J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2381; (b) Timári, G.; Soós, T.; Hajós, G. *Synlett* **1997**, 1067; (c) Csányi, D.; Timári, G.; Hajós, G. *Synth. Commun.* **1999**, *29*, 3959; (d) Soós, T.; Timári, G.; Hajós, G. *Tetrahedron Lett.* **1999**, *40*, 8607; (e) Csányi, D.; Hajós, G.; Riedl, Z.; Timári, G.; Bajor, Z.; Cochard, F.; Sapi, J.; Laronze, J. Y. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1767; (f) Béres, M.; Timári, G.; Hajós, G. *Tetrahedron Lett.* **2002**, *43*, 6035.
3. (a) Russell, R. K.; Press, J. B.; Rampulla, R. A.; McNally, J. J.; Falotico, R. J.; Keiser, A.; Bright, D. A.; Tobia, A. *J. Med. Chem.* **1988**, *31*, 1786; (b) Chern, J.-W.; Tao, P.-L.; Yen, M.-H.; Lu, G.-Y.; Shiau, C.-Y.; Lai, Y.-J.; Chien, S.-L.; Chan, C.-H. *J. Med. Chem.* **1993**, *36*, 2196; (c) Chern, J.-W.; Tao, P.-L.; Wang, K.-C.; Gutcait, A.; Liu, S.-W.; Yen, M.-H.; Chien, S.-L.; Rong, J.-K. *J. Med. Chem.* **1998**, *41*, 3128.
4. Kenny, B.; Ballard, S.; Blagg, J.; Fox, D. *J. Med. Chem.* **1997**, *40*, 1293.
5. Sayed, G. H.; Sayed, M. A.; Mahmoud, M. R.; Shaaban, S. S. *Egypt. J. Chem.* **2002**, *45*, 767.
6. Katrusiak, B.; Unlu, S.; Banoglu, E.; Kupeli, E.; Yesilada, E.; Sahin, M. F. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 406.
7. Frolov, E. B.; Lakner, F. J.; Khvat, A. V.; Ivachtchenko, A. V. *Tetrahedron Lett.* **2004**, *45*, 4693.
8. Piaz, V. D.; Ciciani, G.; Giovannoni, M. P. *Synthesis* **1994**, 669.
9. Barbaro, R.; Betti, L.; Botta, M.; Corelli, F.; Giannaccini, G.; Maccari, L.; Manetti, F.; Strappaghetti, G.; Corsano, S. *J. Med. Chem.* **2001**, *44*, 2118.
10. Svete, J. *J. Heterocycl. Chem.* **2005**, *42*, 361.
11. Pescatore, G.; Branca, D.; Fiore, F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1094.
12. Miyashiro, J.; Woods, K. W.; Park, C. H.; Liu, X.; Shi, Y.; Johnson, E. F.; Bouska, J. J.; Olson, A. M.; Luo, Y.; Fry, E. H.; Giranda, V. L.; Penning, T. D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4050.
13. Szabó, G.; Kiss, R.; Páyer-Lengyel, D.; Vukics, K.; Szikra, J.; Baki, A.; Molnár, L.; Fischer, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3471.
14. Grande, F.; Aiello, F.; De Grazia, O.; Brizzi, A.; Garofalo, A.; Neamati, N. *Bioorg. Med. Chem.* **2007**, *15*, 288.
15. Milne, J.; Normington, K. D.; Milburn, M. WO2006094210.
16. Guillon, J.; Reynolds, R. C.; Leger, J.-M.; Guie, M. A.; Massip, S.; Dallemagne, P.; Jarry, C. *J. Enzyme Inhib. Med. Chem.* **2004**, *19*, 489.
17. Glennon, R. A.; Daoud, M. K.; Dukat, M.; Teitler, M.; Herrick-Davis, K.; Purohit, A.; Syed, H. *Bioorg. Med. Chem.* **2003**, *11*, 4449.
18. Parihar, H. S.; Kirschbaum, K. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2743.
19. Campiani, G.; Morelli, E.; Gemma, S.; Nacci, V.; Butini, S.; Hamon, M.; Novellino, E.; Greco, G.; Cagnotto, A.; Goegan, M.; Cervo, L.; Valle, F. D.; Fracasso, C.; Caccia, S.; Mennini, T. *J. Med. Chem.* **1999**, *42*, 4362.
20. Katounina, T.; Besret, L.; Dhilly, M.; Petit-Taboué, M.-C.; Barbelivien, A.; Baron, J.-C.; Dauphin, F. *Bioorg. Med. Chem.* **1998**, *6*, 789.
21. Maga, G.; Gemma, S.; Fattorusso, C.; Locatelli, G. A.; Persico, M.; Campiani, G. *Biochemistry* **2005**, *44*, 9637.
22. Guillon, J.; Grellier, P.; Labaied, M.; Sonnet, P.; Jarry, C. *J. Med. Chem.* **2004**, *47*, 1997.
23. Campiani, G.; Fabbrini, F.; Morelli, E.; Ramunno, A.; Armaroli, S.; Nacci, V.; Bergamini, A.; Ventura, L.; Guiso, G.; Caccia, S. *J. Med. Chem.* **2001**, *44*, 305.
24. Desplat, V.; Geneste, A.; Begorre, M.-A.; Guillon, J. *J. Enz. Inh. Med. Chem.* **2008**, *23*, 648.
25. Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.
26. Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551.
27. Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933.
28. Sun, H.; Li, J.; Zhang, D.; Ma, C.; Liu, C. *J. Phys. Org. Chem.* **2008**, *21*, 215.
29. Kaim, L. E.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019.
30. Xiang, J. B.; Zheng, L. Y.; Chen, F.; Dang, Q.; Bai, X. *Org. Lett.* **2007**, *9*, 765.
31. Brauch, S.; Gabriel, L.; Westermann, B. *Chem. Commun.* **2010**, 3387.
32. Nielsen, M.; Jacobsen, C. B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 10581.
33. Harbuck, J. W.; Rapoport, H. *J. Org. Chem.* **1972**, *37*, 3618.
34. Schmuck, C.; Bickert, V.; Merschky, M.; Geiger, L.; Machon, U. *Eur. J. Org. Chem.* **2008**, 324.
35. Thoi, V. S.; Stork, J. R.; Niles, E. T.; Depperman, E. C.; Tierney, D. L.; Cohen, S. M. *Inorg. Chem.* **2008**, *47*, 10533.
36. Regina, G. L.; Silvestri, R.; Artico, M.; Lavecchia, A.; Novellino, E. *Eur. J. Med. Chem.* **2007**, *50*, 922.
37. Koeller, S.; Kadota, J.; Peruch, F.; Deffieux, A.; Pinaud, N.; Desvergne, J.-P.; Bibal, B. *Chem.—Eur. J.* **2010**, *16*, 4196.