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Practical and efficient synthesis of pyrano[3,2-*c*]pyridone, pyrano[4,3-*b*]pyran and their hybrids with nucleoside as potential antiviral and antileishmanial agents

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ABSTRACT

A highly practical and efficient preparation of pyrano[3,2-*c*]pyridone and pyrano[4,3-*b*]pyran derivatives was developed via an ionic liquid mediated and promoted multi-component reaction of aldehyde (**1**), 4-hydroxy-pyridin-2(1*H*)-one or 4-hydroxy-2-pyranone (**2**), and malononitrile (**3**). As an application, a series of pyrimidine nucleoside-pyrano[3,2-*c*]pyridone or pyrano[4,3-*b*]pyran hybrids were efficiently obtained. These hybrid compounds were evaluated as potential antiviral and antileishmanial agents and showed encouraging biological activities.

It is well known that pyridone and pyran structural units occur in various molecules exhibiting diverse biological activities. This can be easily demonstrated by the following examples (Fig. 1). Pyridone L-697,661, was identified as a specific nonnucleoside reverse transcriptase inhibitor of HIV-1.[1,2] Milrinone and Amrinone are well established positive inotropic and vasodilatatory agents, used in the clinic for the treatment of heart failure.[3] Some other 2-pyridone derivatives were reported to show antitumor activity[4] and evaluated as human rhinovirus (HRV) 3C protease (3CP) inhibitors.[5] At the same time, specifically substituted pyran moiety has been reported to show promising anticancer activity exemplified by compounds **A** and **B** (Fig. 1).[6] Therefore, it is not surprising that many compounds containing a 2-pyridone moiety fused with a substituted pyran ring possess very promising biological activities. To wit, YCM1008A[7] was reported as a Ca^{2+} inhibitor, while Zanthosimuline is active against multidrug resistant KB-VI cancer cells and Huajiaosimuline exhibits a selective cytotoxicity profile.[8] Recently, Magedov et al. identified a number of pyrano[3,2-*c*]pyridones displaying low nanomolar antiproliferative activity and inducing apoptosis in human cancer cell lines by structural simplification of bioactive natural products.[9] Their approach to those novel pyrano[3,2-*c*]pyridones was based on a multicomponent reaction of pyrone with malononitrile and various aromatic aldehydes in refluxing ethanol containing a small quantity of Et_3N. Further literature searching revealed that Mekheimer et al.[10a] and Stoyanov et al.[10b] have reported two stepwise versions of this process involving the synthesis of the intermediate Knoevenagel products and their subsequent reactions with 4-hydroxy-6-methyl-2(1*H*)-pyridone in refluxing methanol for hours in the presence of piperidine.[10]

Promoted by the literature precedents, and as part of our continuing interest in the development of new synthetic methods in heterocyclic chemistry,[11] we embarked on the development of a new preparative procedure for this class of heterocyclic scaffolds and related compounds. Our study is guided by the following two objectives: the first is to develop a new procedure without utilizing basic catalysts and volatile organic solvents, which are involved in almost all of the existing procedures and may be incompatible with some structurally precarious substrates; the second is to explore more aldehyde and pyridone substrates to prepare structurally diverse pyrano[3,2-*c*]pyridones and pyrano[4,3-*b*]pyran as a pool for quantitative structure–activity relationship (QSAR) studies.

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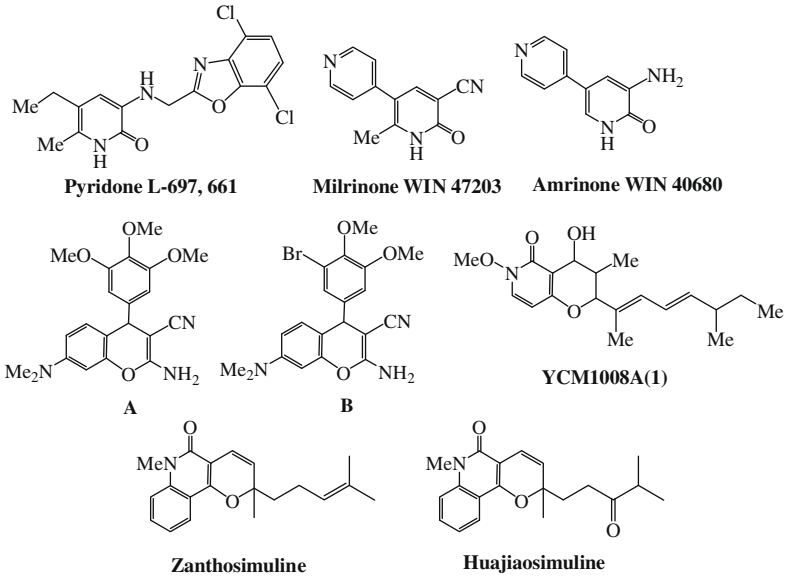


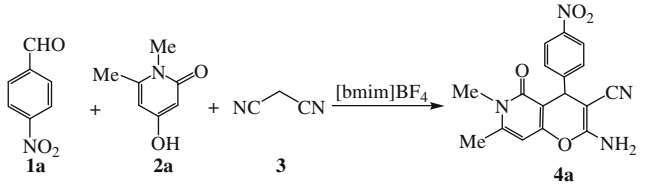
Figure 1. Structures of pyridone L697, 661, Milrinone, Amrinone, A, B, YCM10008A, Zanthosimuline, and Huajiaosimuline.

To achieve these two objectives, we choose ionic liquid as both reaction medium and promoter since the application of ionic liquids as 'green' alternatives to conventional solvents for a wide range of organic transformations has become increasingly important in recent years. Ionic liquids have the potential to show low human toxicities and eco-toxicities.[12] In addition, ionic liquids are nonvolatile, stable, and can be reused.[13] Their high polarity and the ability to solubilize both inorganic and organic compounds can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents.

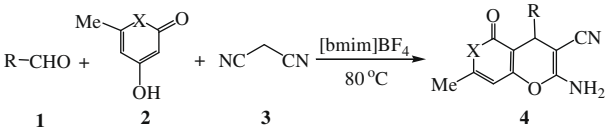
The study was initiated by using 4-nitrobenzaldehyde (**1a**), 4-hydroxy-1,6-dimethylpyridin-2(1*H*)-one (**2a**), and malononitrile (**3**) as model substrates and they were treated with [bmim][BF_4] without any added catalyst (Scheme 1). Encouragingly, after being stirred at rt for 3 h, it gave **4a** with a yield of 85%. The reaction could be further improved by increasing the reaction temperature. When it was run at 80 °C, **4a** was obtained in a yield of 98% in 0.5 h. It is remarkable in that this highly efficient one-pot three component reaction in ionic liquid did not need any basic catalyst and the product was collected by simple filtration thus resulting in a very efficient and easy-going procedure.

The optimized reaction condition was extended to a series of aldehydes to explore its scope and generality (Scheme 2). The results summarized in Table 1 showed that all the aldehyde substrates reacted with **2a** and **3** in [bmim][BF_4] smoothly and efficiently affording **4** in good to excellent yields (Table 1, entries 1–7). It should be noted here that compared with the literature methods, the procedure presented here has such advantages as one-pot reaction from commercially available starting material, no added catalyst, an environmentally beneficial nature, neutral, and simple procedure.

To develop this reaction into a more general method, other pyridin-2-one substrates, 4-hydroxy-6-methyl-pyridin-2(1*H*)-one (**2b**), 4-hydroxy-1-ethyl-6-methyl pyridin-2(1*H*)-one (**2c**), together with 4-hydroxy-6-methyl-2-pyranone (**2d**), were also tried (Scheme 2). They all gave the corresponding products in good to excellent yields (Table 1, entries 8–26). For the three components



Scheme 1. Optimization of reaction conditions with **1a**, **2a**, and **3**.



Scheme 2. Preparation of pyrano[3,2-*c*]pyridone and pyrano[4,3-*b*]pyran.

Table 1
Preparation of **4** in [bmim]BF_4[a]

Entry	R	X	Product	Time (h)	Yield[b] (%)
1	4-$NO_2C_6H_4$	N-Me	**4a**	0.5	98
2	C_6H_5	N-Me	**4b**	2	88
3	4-FC_6H_4	N-Me	**4c**	1	94
4	4-ClC_6H_4	N-Me	**4d**	1	91
5	4-BrC_6H_4	N-Me	**4e**	1	88
6	4-$CH_3C_6H_4$	N-Me	**4f**	2	83
7	4-$CH_3OC_6H_4$	N-Me	**4g**	2	81
8	4-$NO_2C_6H_4$	N-H	**4h**	1	85
9	C_6H_5	N-H	**4i**	3	84
10	4-FC_6H_4	N-H	**4j**	2	87
11	4-ClC_6H_4	N-H	**4k**	2	88
12	4-BrC_6H_4	N-H	**4l**	2	86
13	4-$CH_3OC_6H_4$	N-H	**4m**	3	80
14	4-$NO_2C_6H_4$	N-Et	**4n**	1	98
15	C_6H_5	N-Et	**4o**	3	82
16	4-FC_6H_4	N-Et	**4p**	2	92
17	4-ClC_6H_4	N-Et	**4q**	2	85
18	4-BrC_6H_4	N-Et	**4r**	2	81
19	4-$CH_3C_6H_4$	N-Et	**4s**	3	88
20	4-$CH_3OC_6H_4$	N-Et	**4t**	3	82
21	4-$NO_2C_6H_4$	O	**4u**	1	89
22	4-FC_6H_4	O	**4v**	2	88
23	4-BrC_6H_4	O	**4w**	2	88
24	C_6H_5	O	**4x**	3	85
25	4-$CH_3C_6H_4$	O	**4y**	3	86
26	4-$CH_3OC_6H_4$	O	**4z**	3	82

[a] Reaction conditions: 1 mmol of **1**, **2**, **3**, and 1.5 g of [bmim][BF_4], 80 °C.
[b] Isolated yields.

Table 2
Preparation of **4a** in different solvents[a]

Entry	Solvent	Temperature (°C)	Product	Time (h)	Yield[d] (%)
1	[bmim][BF_4][b]	80	**4a**	0.5	98
2	Ethanol[c]	Reflux	**4a**	5	76
3	Toluene[c]	80	**4a**	5	75
4	THF[c]	Reflux	**4a**	5	71
5	[bmim][PF_6][b]	80	**4a**	1	90
6	[bmim][BF_4][e]	80	**4a**	1	90

[a] Reaction conditions: 1 mmol of **1a**, **2a** and **3**, respectively.
[b] 1.5 g of solvent.
[c] 10 mL of solvent.
[d] Isolated yields.
[e] Solvent recovered from the fourth round.

Table 3
Preparation of hybrid **6** in [bmim]BF_4[a]

Entry	R^1	X	Product	Time (h)	Yield[b] (%)
1	Ac	N-Me	**6a**	3	85
2	Ac	N-H	**6b**	3	80
3	Ac	N-Et	**6c**	3	82
4	Ac	O	**6d**	4	79
5	H	N-Me	**6e**	2	86
6	H	N-H	**6f**	3	82
7	H	N-Et	**6g**	3	80
8	H	O	**6h**	4	78

[a] Reaction conditions: 1 mmol of **5**, **2**, **3**, and 1.5 g of [bmim][BF_4], 80 °C.
[b] Isolated yields.

procedure, two constituents in the products can be varied independently of each other, and through this procedure, a library of 26 pyrano[3,2-*c*]pyridone and pyrano[4,3-*b*]pyran derivatives were obtained.

In order to identify the additional advantages ionic liquids possess over conventional organic solvents in addition to their green nature, the reaction of **1a**, **2a**, and **3** was run in different solvents. Of the solvents studied, [bmim][BF_4] gave the best result (Table 2, entry 1). On the other hand, with toluene, ethanol or THF, it usually gave mixtures and **4a** were obtained through column chromatography with lower yields (Table 2, entries 2–4). With another ionic liquid, [bmim][PF_6], the reaction also went efficiently though the yield was somewhat lower (Table 2, entry 5). Further work in relation with the possibility of recovering and reusing of [bmim][BF_4] turned out that the reuse of [bmim][BF_4] conveniently recovered from the fourth round still produced the corresponding product with good yield (Table 2, entry 6).

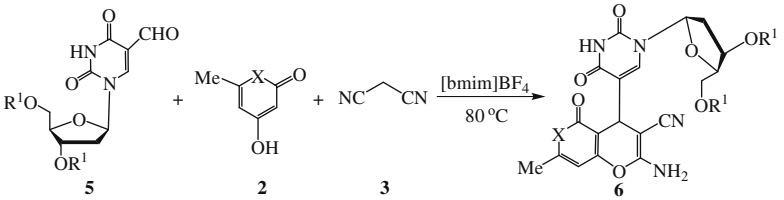
As a further respect, we have pursued a chemistry-driven strategy for the discovery of novel nucleoside molecules with antiviral activity.[14] Since both pyrimidine nucleosides and pyrano[3,2-*c*]pyridones or pyrano[4,3-*b*]pyrans scaffolds are excellent points of departure in the search for new lead compounds with various biological activities, we were interested in applying the methodology developed in this Letter to prepare novel pyrimidine nucleoside-pyrano[3,2-*c*]pyridone or pyrano[4,3-*b*]pyran hybrids with the aim to get new chemical entities with synergistic effects on their biological activities.

Thus, a mixture of 5-formyl-2′-deoxyuridine (**5**), **2**, and **3** was treated with [bmim][BF_4] at 80 °C (Scheme 3). We were pleased to find that the reaction afforded the pyrimidine nucleoside-pyrano[3,2-*c*]pyridone or pyrano[4,3-*b*]pyran chimera **6** with high efficiency (Table 3). It was demonstrated that as an aldehyde substrate, nucleoside **5** reacted with **2a**, **2b**, **2c** or **2d** and **3** with almost equally high efficiency as described above. Upon completion, the hybrid products were in solid state and could be simply collected by suction with high purity. The structure of **6** was fully characterized by their spectra data of NMR and HRMS. Based on NMR data, it was concluded that compound **6** was obtained as a 1:1 diastereomeric mixture arising from the generation of a chiral carbon at position 4 of the newly formed pyran moiety.

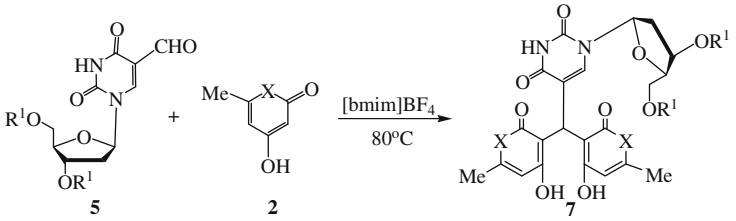
To get more pyridone and pyran derivatives for SAR study, the hybrid compounds of pyrimidine nucleoside with pyridin-2(1*H*)-one or 2-pyranone were also prepared through the reaction of **5** with **2a**, **2b** or **2d** in [bmim][BF_4]. The reactions underwent efficiently and gave compounds **7** in high yields (Scheme 4). The results were summarized in Table 4.

As many 5-substituted pyrimidine nucleoside derivatives are known to exhibit remarkable antiviral activities,[15] the hybrid compounds **6** and **7** were firstly evaluated against varicella-zoster virus (VZV) and cytomegalovirus (CMV) in human embryonic lung (HEL) cells. The results are listed in Tables 5 and 6.

As indicated in Table 5, the hybrid compounds **6e–g** showed moderate anti-VZV activity with a median EC_{50} ranging from 55.7 to 74.6 μM. Their *O*-containing counter-parts **6d**, **6h** exhibited higher antiviral activity, but they showed toxicity to human embryonic lung (HEL) cells, probably by inhibiting cellular DNA synthesis. On the other hand, **7d–f** showed remarkable anti-VZV activity, but were toxic to the cell growth. Further structural elaboration should emphasis on how to alleviate their toxicity while keeping antiviral activity.



Scheme 3. Preparation of pyrano[3,2-*c*]pyridone or pyrano[4,3-*b*]pyran nucleoside hybrids.



Scheme 4. Preparation of pyridinone or pyranone nucleoside hybrids.

As for the results listed in Table 6, all those compounds except for **6h**, **7d**, **7e**, and **7f** are inactive to CMV. Hybrid **6h**, **7d**, **7e**, and **7f** showed EC_{50} of 54.7, 54.7, 44.7, and 20 μM, respectively, but they were also toxic to HEL. On the other hand, it has been reported recently that a series of 5-heteroaryl-2′-deoxyuridine analogues possessed significant activity against *Leishmania donovani* promastigotes.[16] The nature of the pyrimidine 5-substituents that provided active antileishmanial nucleosides included heterocyclic moiety such as thiazole, thiophene, benzothiazole, benzothiophene, and benzopyran. Therefore, we next examined the ability of hybrid compounds **6** and **7** to inhibit *L. donovani* growth in culture and the results are listed in Table 6. It shows that the hybrid compounds exhibited detectable to good activity. It is encouraging that compound **6f** showed an IC_{50} of 10.6 ± 1.3 μM while the reference compound (pentamidine) showed an IC_{50} of 6.5 ± 0.8 μM. At the same time, it was also shown that acetylation of the sugar hydroxyl groups in **6f** caused a dramatic decrease in bioactivity from 10.6 ± 1.3 μM to 139.69 μM (**6b**). This difference could be ascribed both to the trans-

Table 4
Preparation of hybrid **7** in [bmim]BF_4[a]

Entry	R^1	X	Product	Time (h)	Yield[b] (%)
1	Ac	N-Me	**7a**	2	90
2	Ac	N-H	**7b**	2	88
3	Ac	O	**7c**	2	85
4	H	N-Me	**7d**	2	85
5	H	N-H	**7e**	1	87
6	H	O	**7f**	2	86

[a] Reaction conditions: 1 mmol of **5**, 2 mmol of **2** and 1.5 g of [bmim][BF_4], 80 °C.
[b] Isolated yields.

Table 5
Anti-VZV activities of compounds **6** and **7**

Compd	Antiviral activity EC_{50}[a] (μM)				Cytotoxicity (μM)	
	TK^+ VZV		TK^- VZV		Cell morphology[b] (MCC)	Cell growth[c] (CC_{50})
	YS Strain	OKA Strain	07/1 Strain	YS/R Strain		
6a		>100	>100		>100	>100
6b		100	>100		>100	>100
6c		>100	>100		>100	>100
6d		**48.1**	>100		>100	**8.9**
6e		74.6	>100		>100	>100
6f		55.7	>100		>100	>100
6g		71.2	>100		>100	>100
6h		**1.8**	**5.3**		>100	**3.3**
	2.20	**2.17**	**7.49**	**12.83**	>20	
7a		47.8	>100		>100	20
7b		>100	>100		>100	36.9
7c		40.2	48.6		>100	3.8
7d		**2.2**	**16.7**		>100	**7.7**
	6.95	**4.52**	**18.59**	**35.61**	>50	
7e		**0.32**	**1.66**		>100	**2.1**
	1.48	**1.44**	**9.39**	**10.0**	>20	
7f		**0.60**	**2.62**		>100	**1.8**
	1.14	**3.16**	**3.41**	**5.0**	>50	
Acyclovir		**0.84**	**26.7**		>1778	1778
	2.01	**0.89**	**33.4**	**29.9**		

[a] Effective concentration required to reduce virus plaque formation by 50%. Virus input was 20 plaque forming units (PFU).
[b] Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.
[c] Cytotoxic concentration required to reduce cell growth by 50%.

Table 6
Anti-CMV and antileishmanial activities of compounds **6** and **7**

Compd	Anti-CMV activity EC_{50}[a] (μM)		Cytotoxicity (μM)		*Leishmania donovani* IC_{50}[d] (μM) ± SD
	AD-169 strain	Davis strain	Cell morphology[b] (MCC)	Cell Growth[c] (CC_{50})	
6a	>100	>100	>100	>100	>200
6b	>100	>100	>100	>100	**139.69**
6c	>100	>100	>100	>100	>200
6d	>100	>100	>100	8.9	>200
6e	>100	>100	>100	>100	>200
6f	>100	>100	>100	>100	**10.6 ± 1.3**
6g	>100	>100	>100	>100	>200
6h	54.7	54.7	>100	3.3	>200
7a	>100	>100	>100	20	>200
7b	>100	>100	>100	36.9	>200
7c	>100	>100	>100	3.8	>200
7d	**54.7**	>100	>100	**7.7**	>200
7e	**44.7**	>100	>100	**2.1**	**43.5 ± 3.8**
7f	**20**	20	>100	**1.8**	>200
Cidofovir	**1.0**	**0.9**	**>1270**	**175**	—
Pentamidine	—	—	—	—	**6.5 ± 0.8**

[a] Effective concentration required to reduce virus plaque formation by 50%. Virus input was 20 plaque forming units (PFU).
[b] Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.
[c] Cytotoxic concentration required to reduce cell growth by 50%.
[d] IC_{50} defined as inhibitory concentration 50%.

porter recognition since the *Leishmania* promastigotes are known to possess a pyrimidine/purine transporter as mentioned in our previous Letter[16] and to the affinity of the compounds towards their intracellular target. It was also observed from these preliminary results that keeping the –NH moiety on the 2-pyridone ring intact is crucial to maintain activity since the replacement of –NH in **6f** with either –NMe (**6e**), –NEt (**6g**) or –O (**6h**) resulted in significant decrease of activity. In addition, hybrid **7e** also showed moderate activity with an IC_{50} of 43.5 ± 3.8 μM. It further demonstrates the free –NH moiety is crucial to the antileishmanial activity. Based on the above results, it is concluded that 5-substituted pyrimidine nucleosides, including those with substantial steric size and bearing polar substituents, are a rich depot for further exploration as antileishmanial agents.

In conclusion, a novel, green and efficient preparation of pyrano[3,2-*c*]pyridone and pyrano[4,3-*b*]pyran derivatives from a one-pot three components reaction was described. Compared with the literature methods, this new procedure has the advantages of high yield, simple experimental and product isolation procedure combined with ease of recovery and reuse of reaction medium. By using this method, several hybrids of pyrimidine nucleoside-pyrano[3,2-*c*]pyridone or pyrano[4,3-*b*]pyran were efficiently prepared. As a further respect, the hybrid compounds of pyrimidine nucleoside with pyridin-2(1*H*)-one or 2-pyranone were also prepared. Evaluation of these hybrids against *L. donovani* promastigotes disclosed a new lead compound with good antileishmania activity probably acting by inhibition of deoxyribonuclease, an enzyme essential for the viability of the organism.[17]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.12.102.

References and notes

1. De Clercq, E. *Il Farmaco* **1999**, *54*, 26.
2. Parreira, R. L. T.; Abrahão, O.; Galembeck, S. E. *Tetrahedron* **2001**, *57*, 3243.
3. Presti, E. L.; Boggia, R.; Feltrin, A.; Menozzi, G.; Dorigo, P.; Mosti, L. *Il Farmaco* **1999**, *54*, 465.
4. Anderson, W. K.; Dean, D. C.; Endo, T. *J. Med. Chem.* **1990**, *33*, 1667.
5. Dragovich, P. S.; Prins, T. J.; Zhou, R.; Brown, E. L.; Maldonado, F. C.; Fuhrman, S. A.; Zalman, L. S.; Tuntland, T.; Lee, C. A.; Patick, A. K.; Matthews, D. A.; Hendrickson, T. F.; Kosa, M. B.; Liu, B.; Batugo, M. R.; Gleeson, J.-P. R.; Sakata, S. K.; Chen, L.; Guzman, M. C.; Meador, J. W.; Ferre, R. A.; Worland, S. T. *J. Med. Chem.* **2002**, *45*, 1607.
6. (a) Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Jia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; Vaillancourt, L.; Charron, S.; Dodd, J.; Attardo, G.; Labrecque, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4745; (b) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zhao, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2004**, *47*, 6299; (c) Kemnitzer, W.; Drewe, J.; Jiang, S. C.; Zhang, H.; Zhao, J. H.; Crogan-Grundy, C.; Xu, L. F.; Lamothe, S.; Gourdeau, H.; Denis, R.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2007**, *50*, 2858.
7. Tatsuta, K.; Yamaguchi, T.; Tsuda, Y.; Yamaguchi, Y.; Hattori, N.; Nagai, H.; Hosokawa, S. *Tetrahedron Lett.* **2007**, *48*, 4187.
8. Chen, I. S.; Wu, S. J.; Tsai, I. L.; Wu, T. S.; Pezzuto, J. M.; Lu, M. C.; Chai, H.; Suh, N.; Teng, C. M. *J. Nat. Prod.* **1994**, *57*, 1206.
9. (a) Magedov, I. V.; Manpadi, M.; Rozhkova, E.; Przheval'skii, N. M.; Rogelj, S.; Shors, S. T.; Steelant, W. F. A.; Van Slambrouck, S.; Kornienko *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1381; (b) Magedov, I. V.; Manpadi, M.; Ogasawara, M. A.; Dhawan, A. S.; Rogelj, S.; Van slambrouck, S.; Steelant, W. F. A.; Evdokimov, N. M.; Uglinskii, P. Y.; Elias, E. M.; Knee, E. J.; Tongwa, P.; Antipin, M. Yu.; Kornienko, A. *J. Med. Chem.* **2008**, *51*, 2561.
10. (a) Mekheimer, R. A.; Mohamed, N. H.; Sadek, K. U. *Bull. Chem. Soc. Jpn.* **1997**, *38*, 5301; (b) Stoyanov, E. V.; Ivanov, I. C.; Heber, D. *Molecules* **2000**, *5*, 19.
11. (a) Fan, X.; Hu, X.; Zhang, X.; Wang, J. *Aust. J. Chem.* **2004**, *57*, 1067; (b) Fan, X.; Hu, X.; Zhang, X.; Wang, J. *Can. J. Chem.* **2005**, *83*, 16; (c) Fan, X.; Li, Y.; Zhang, X.; Wang, J. *Can. J. Chem.* **2006**, *84*, 794; (d) Zhang, X.; Fan, X.; Niu, H.; Wang, J. *Green Chem.* **2003**, *5*, 267.
12. (a) Ranke, J.; Stolte, S.; Strörmann, R.; Arning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107*, 2183; (b) Stolte, S.; Matzke, M.; Arning, J.; Böschen, A.; Pitner, W. R.; Welz-Biermann, U.; Jastorff, B.; Ranke, R. *Green Chem.* **2007**, *9*, 1170.
13. (a) Afonso, C. A. M.; Branco, L. C.; Candeias, N. R.; Gois, P. M. P.; Lourenco, N. M. T.; Mateus, N. M. M.; Rosa, J. N. *Chem. Commun.* **2007**, 2669; (b) Pârvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615.
14. (a) Fan, X.; Zhang, X.; Zhou, L.; Keith, K. A.; Prichard, M. N.; Kern, E. R.; Torrence, P. F. *J. Med. Chem.* **2006**, *49*, 4052; (b) Fan, X.; Zhang, X.; Zhou, L.; Keith, K. A.; Prichard, M. N.; Kern, E. R.; Torrence, P. F. *J. Med. Chem.* **2006**, *49*, 3377; (c) Fan, X.; Zhang, X.; Zhou, L.; Keith, K. A.; Prichard, M. N.; Kern, E. R.; Torrence, P. F. *Antiviral Res.* **2006**, *71*, 201; (d) Fan, X.; Zhang, X.; Zhou, L.; Keith, K. A.; Prichard, M. N.; Kern, E. R.; Torrence, P. F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3224.
15. (a) Agrofoglio, L. A. *Curr. Org. Chem.* **2006**, *10*, 333; (b) De Clercq, E. *Antiviral Res.* **2005**, *67*, 56; (c) De Clercq, E. *Curr. Opin. Microbiol.* **2005**, *8*, 552; (d) Mathe, C.; Gosselin, G. *Antiviral Res.* **2006**, *71*, 276.
16. (a) Torrence, P. F.; Fan, X.; Zhang, X.; Loiseau, P. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5047; (b) Peyron, C.; Benhida, R.; Bories, C.; Loiseau, P. M. *Bioorg. Chem.* **2005**, *33*, 439.
17. Dong, Z.; Zhu, B.; Jeffrey, A. *Exp. Parasitol.* **1992**, *75*, 257.