Microwave-Assisted Combinatorial Synthesis of Polysubstituent Imidazo[1,2-*a*]quinoline, Pyrimido[1,2-*a*]quinoline and Quinolino[1,2-*a*]quinazoline Derivatives

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A series of unusual fused heterocyclic compound derivatives, consisting of a pyridine and a imidazole or pyrimidine core, with a bridgehead nitrogen, were successfully synthesized by a microwave-assisted, three-component domino reaction of aldehydes, enaminones, and malononnitrile. In this one-pot reaction, up to five new bonds were formed accompanied by generating the lactam group. This method has the advantages of short synthetic route, operational simplicity, increased safety for small-scale high-speed synthesis, and minimal environment impact.

Introduction

At the beginning of the new century, it remains an important challenge to develop concise and effective methodologies for preparing combinatorial libraries of small molecules for drug discovery research. So far, a number of strategies have been developed for meeting such a challenge.[1] Emphasis was initially placed on the development of solution-phase[2–4] and solid-phase[5–9] synthetic methods, as well as deconvolution methods for mixture synthesis.[10] In recent years, there has been a shift in emphasis toward the development of combinatorial synthetic techniques using microwave irradiation (MW).[11] Microwave-assisted organic synthesis has received much attention because of its faster chemistry and formation of cleaner products compared with conventional heating. It is clear that the application of microwave technology to rapid synthesis of biologically significant molecules would be of great value for library generation.[12] This technology has recently been recognized as a useful tool for a drug-discovery program.[13] In conjunction with our continuous interest in developing new protocols in combinatorial synthesis,[14] we explore the use of microwave irradiation as a heating source in conformational rigid heterocycles synthesis.

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity.[15] The interest in bicyclic 5–6 and 6–6 systems with one ring junction and one extra nitrogen atom stems from the saturated and partially saturated imidazo[1,2-*a*]pyridine and pyrido[1,2-*a*]pyrimidine ring systems in many biologically active compounds; some have pharmacological properties such as antiviral,[16] antimalarial,[17] antiulcer,[18] analgesic, antiallergic, antiathmatic, and antipsychotic agents.[19]

Herein, we report a high-speed and one-pot combinatorial method for synthesizing diverse sets of imidazo[1,2-*a*]quinoline, pyrimido[1,2-*a*]quinoline and quinolino[1,2-*a*]quinazoline heterocyclic compounds including imidazo[1,2-*a*]pyridine or pyrido[1,2-*a*]pyrimidine moiety, respectively, from readily available starting materials. To the best of our knowledge, these compounds are scarcely studied and only one product was reported in the literature.[20] Therefore, to obtain the potential pharmacological molecules, the synthesis of imidazo[1,2-*a*]quinoline, pyrimido[1,2-*a*]quinoline and quinolino[1,2-*a*]quinazoline derivatives may be of great significance.

Results and Discussion

Enaminones and related compounds possessing the structural unit are versatile synthetic intermediates in organic chemistry that combine the ambient nucleophilicity of enamine and the electrophilicity of enones.[21] They are frequently applied in the preparation of heterocycles.[22] Our strategy of constructing polysubstituent imidazo[1,2-*a*]quinoline, pyrimido[1,2-*a*]quinoline or quinolino[1,2-*a*]quinazoline derivatives was though one-pot multicomponent reaction of various preformed enaminones (**1a–f**) with structurally diverse aldehydes and malononnitrile. Representing amino acids, that is, 2-aminoacetic acid 2-aminopropanoic acid, 3-aminopropanoic acid as the aliphatic amino acid and 2-aminobenzoic acid, 2-amino-4-chlorobenzoic acid as the aromatic amino acids, were selected for our study. Many methods of synthesizing enaminones (**1a–e**) have been

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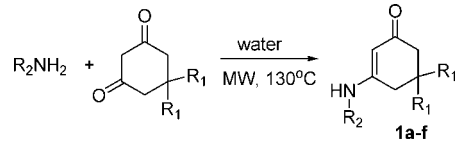
Scheme 1. Preparation of Enaminones **1a–f**



1a: $R_1 = CH_3$, $R_2 = CH_2COOH$
1b: $R_1 = CH_3$, $R_2 = CH_2CH_2COOH$
1c: $R_1 = CH_3$, $R_2 = CH_3CHCOOH$
1d: $R_1 = H$, $R_2 = CH_2COOH$
1e: $R_1 = CH_3$, $R_2 = 2\text{-}COOHC_6H_4$
1f: $R_1 = CH_3$, $R_2 = 4\text{-}Cl\text{-}2\text{-}COOHC_6H_3$

Table 1. Reaction Times and Yields for Synthesis of Enaminones **1a–1f**

entry	product	time/min	yield[a]/%	Mp/°C
1	**1a**	3	96	232–233
2	**1b**	2	98	163–164
3	**1c**	5	95	225–226
4	**1d**	6	94	213–214
5	**1e**	8	96	188–189
6	**1f**	8	96	224–225

[a] Isolated yields.

Table 2. Solvent Optimization for the Synthesis of **4b** under Microwave Irradiation Conditions at 100 °C

entry	solvent	time/min	yield[a]/%
1	ethylene glycol	6	82
2	DMF	8	58
3	HOAc	7	70
4	EtOH	8	56
5	Water	8	6

[a] Isolated yields.

reported in the literature.[23] We found that enaminones (**1a–f**) were obtained in good to excellent yields in water by microwave-assisted reaction of the corresponding amino acid and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione at 130 °C for 2–8 min (Scheme 1). The reaction times and yields are listed in Table 1.

Choosing an appropriate solvent is of crucial importance for the successful microwave-assisted synthesis. To search for the optimal solvent, the microwave-assisted reaction of 4-fluorophenylaldehyde **2b**, malononitrile **3**, and 2-(5,5-dimethyl-3-oxocyclohex-1-enylamino)acetic acid **1a** was examined using water, ethylene glycol, *N*, *N*-dimethylformamide (DMF), glacial acetic acid (HOAc), and ethanol (EtOH) as solvent at 100 °C, respectively. All the reactions were carried out under microwave irradiation (initial power 100 W and maximum power 200 W) (Table 2).

As shown in Table 2, the reactions using ethylene glycol as the solvent resulted in higher yields and shorter reaction time than those using water, HOAc, DMF, and ethanol as solvents. So, ethylene glycol was used as the solvent for further optimization of reaction conditions, the same reaction was carried out at temperatures ranging from 80 to 140 °C, with an increment of 10 °C each time. The yield of product **4b** was increased, and the reaction time was shortened when the temperature was increased from 80 to 120 °C. The yield levelled off when the temperature was further increased to 130 and 140 °C.

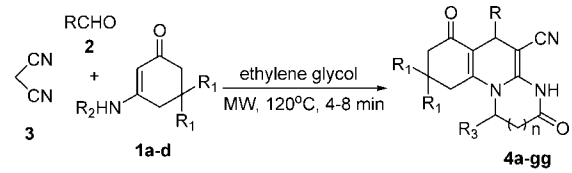
Therefore, the temperature of 120 °C was chosen for all further microwave-assisted reactions (Table 3).

Table 3. Temperature Optimization for the Synthesis of **4b** under Microwave Irradiation

entry	temp/°C	time/min	yield[a]/%
1	80	11	70
2	90	9	79
3	100	6	82
4	110	6	83
5	120	5	87
6	130	5	85
7	140	4	78

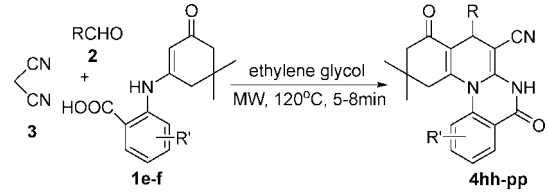
[a] Isolated yields.

Scheme 2. Synthesis of Polysubstituent Imidazo[1,2-*a*]-quinazolines and Pyrimido[1,2-*a*]quinolines **4a-gg**



$R_1 = CH_3$, $R_2 = CH_2COOH$, $R_3 = H$, $n = 0$
$R_1 = CH_3$, $R_2 = CH_3CHCOOH$, $R_3 = CH_3$, $n = 0$
$R_1 = CH_3$, $R_2 = CH_2CH_2COOH$, $R_3 = H$, $n = 1$
$R_1 = H$, $R_2 = CH_2COOH$, $R_3 = H$, $n = 0$

Scheme 3. Synthesis of Polysubstituent Quinolino[1,2-*a*]quinazolines **4hh-pp**



Furthermore, the volume of ethylene glycol was important as well to the yields of the reactions. The synthesis of **4b** [**2b** (1 mmol), **3** (1 mmol), and **1a** (1 mmol)] was tested in different volumes of ethylene glycol at 120 °C under microwave irradiation conditions. When 2.0 mL of ethylene glycol was used as solvent for the reaction, the yield was the highest.

Under these optimal conditions [ethylene glycol (2.0 mL), 120 °C], the reactions of different aldehydes, various enaminones and malononitrile were performed (Schemes 2 and 3). Initially, to test the scope of aldehyde substrates, enaminone **1a** and malononitrile were used as model substrates (Table 4, entries 1–9), and the results indicated that aromatic aldehydes bearing functional groups such as chloro, bromo, fluoro, nitro, or methoxy are suitable for the reaction. At the same time, we have also observed delicate electronic effects: that is, aldehydes with electron-withdrawing groups (Table 4, entries 1–4) reacted rapidly, while electron-rich groups (Table 4, entries 6–7) decreased the reactivity, requiring longer reaction times. Moreover, the heterocyclic aldehydes such as thiophene-2-carbaldehyde (Table 4, entry 8) and aliphatic aldehydes such as pentanal (Table 4, entry 9) still displayed high reactivity under this standard condition.

To further expand the scope of enaminone substrates, we employed different aldehydes and malononitrile as model substrates and examined various enaminones including **1b**, **1c**, **1d**, **1e**, and **1f**. In all these cases, the reactions proceeded smoothly to give the corresponding new imidazo[1,2-

Table 4. Synthesis of **4** under Microwave Irradiation

entry	4	R	1	time/min	yield [a]/%	Mp/°C
1	**4a**	4-$NO_2C_6H_4$	**1a**	5	86	201–202
2	**4b**	4-FC_6H_4	**1a**	5	87	>300
3	**4c**	4-ClC_6H_4	**1a**	4	85	>300
4	**4d**	4-BrC_6H_4	**1a**	4	87	>300
5	**4e**	C_6H_5	**1a**	5	88	>300
6	**4f**	4-$MeOC_6H_4$	**1a**	7	85	>300
7	**4g**	4-$CH_3C_6H_4$	**1a**	8	86	>300
8	**4h**	thiophen-2-yl	**1a**	6	84	>300
9	**4i**	$CH_3(CH_2)_3$	**1a**	4	86	250–251
10	**4j**	4-OH-3-$NO_2C_6H_3$	**1b**	5	88	274–275
11	**4k**	4-FC_6H_4	**1b**	6	87	244–245
12	**4l**	4-ClC_6H_4	**1b**	5	85	266–268
13	**4m**	4-$NO_2C_6H_4$	**1b**	5	86	238–240
14	**4n**	4-BrC_6H_4	**1b**	4	85	256–258
15	**4o**	3-$NO_2C_6H_4$	**1b**	5	86	218–219
16	**4p**	2-ClC_6H_4	**1b**	6	88	295–296
17	**4q**	C_6H_5	**1b**	5	85	286–288
18	**4r**	4-$MeOC_6H_4$	**1b**	7	81	246–247
19	**4s**	4-$CH_3C_6H_4$	**1b**	7	83	270–272
20	**4t**	thiophen-2-yl	**1b**	6	86	220–221
21	**4u**	4-FC_6H_4	**1c**	5	87	290–292
22	**4v**	4-BrC_6H_4	**1c**	5	89	298–299
23	**4w**	C_6H_5	**1c**	5	85	299–300
24	**4x**	4-$MeOC_6H_4$	**1c**	6	84	294–296
25	**4y**	4-$CH_3C_6H_4$	**1c**	8	85	291–292
26	**4z**	4-$NO_2C_6H_4$	**1d**	6	86	208–210
27	**4aa**	4-FC_6H_4	**1d**	5	88	286–287
28	**4bb**	4-ClC_6H_4	**1d**	4	89	290–291
29	**4cc**	2-ClC_6H_4	**1d**	4	87	283–285
30	**4dd**	3-$NO_2C_6H_4$	**1d**	5	86	255–256
31	**4ee**	C_6H_5	**1d**	5	85	274–275
32	**4ff**	4-$MeOC_6H_4$	**1d**	7	83	200–201
33	**4gg**	4-$CH_3C_6H_4$	**1d**	8	84	287–289
34	**4hh**	4-ClC_6H_4	**1e**	6	86	240–242
35	**4ii**	2-ClC_6H_4	**1e**	6	85	277–278
36	**4jj**	C_6H_5	**1e**	5	88	298–299
37	**4kk**	4-$MeOC_6H_4$	**1e**	8	82	293–294
38	**4ll**	4-$CH_3C_6H_4$	**1e**	8	80	298–300
39	**4mm**	thiophen-2-yl	**1e**	7	84	295–296
40	**4nn**	4-BrC_6H_4	**1f**	7	83	>300
41	**4oo**	C_6H_5	**1f**	5	86	297–298
42	**4pp**	thiophen-2-yl	**1f**	6	82	299–300

[a] Isolated yields.

a]quinoline, pyrimido[1,2-*a*]quinoline and quinolino[1,2-*a*]quinazoline derivatives in good to excellent yields. It is worth noting that this result is significant since there is no literature precedent for the synthesis of pyrimido[1,2-*a*]quinoline and quinolino[1,2-*a*]quinazoline derivatives.

In addition, we performed the reactions for synthesizing **4b** under both MW (120 °C) and classical heating conditions in ethylene glycol. We found that the reaction was efficiently promoted by MW irradiation, and the reaction time was strikingly reduced to minutes from hours required under the traditional heating conditions, and the yield was increased to 87% from 56%. Therefore, microwave irradiation exhibited several advantages over conventional heating by significantly reducing the reaction time and dramatically improving the reaction yield.

The structures of all the synthesized compounds were based on their spectroscopic data. The structures of **4aa, 4l**, and **4hh** were established by X-ray crystallographic analysis (Figures 1, 2, and 3, respectively).

The formation of **4** is likely to proceed via initial condensation of aldehydes **2** with malononitrile **3** to afford 2-arylidenemalononitrile **8**. The addition compound **8** to enaminones **1** then furnished the intermediate product **11**,

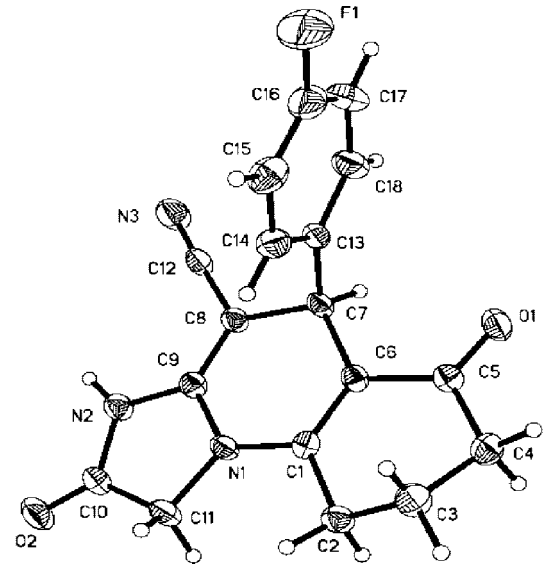


Figure 1. Molecular structure of **4aa**.

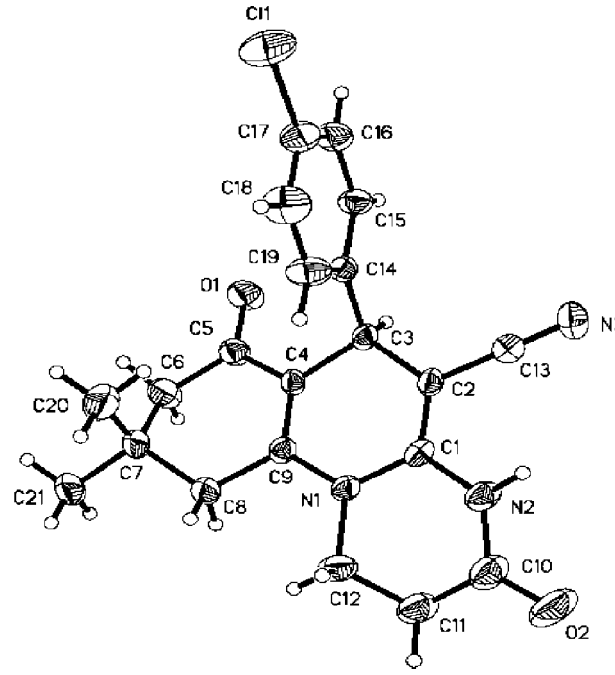


Figure 2. Molecular structure of **4l**.

which upon intermolecular cyclization and dehydration gave rise to **4** (Scheme 4). To support the proposed mechanism, the compound **4b** was prepared independently from 4-fluorophenylaldehyde **2b** and malononitrile **3** and then employed in a two component reaction with enaminone **1a** to afford product **4b**, whose yield is similar to the above one-pot reaction. However, 4-fluorophenylaldehyde **2b** first condensed with **1a** followed by reaction with malononitrile **3** failed to give the target compound **4b**.

Conclusion

In summary, we have successfully combined the advantages of microwave technology with combinatorial chemistry to facilitate the rapid construction of imidazo[1,2-*a*]quinoline, pyrimido[1,2-*a*]-quinoline, and quinolino[1,2-*a*]quinazoline skeletons from readily obtainable and inexpensive materials. Particularly valuable features of this method included the

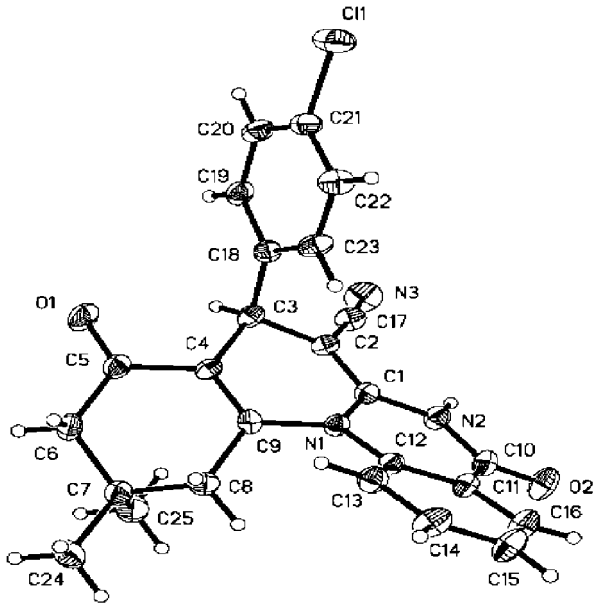
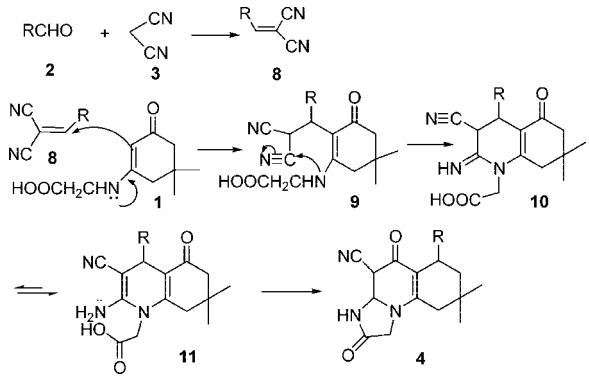


Figure 3. Molecular structure of **4hh**.

Scheme 4. Investigation of a Possible Reaction Mechanism



broader substrate scope and operational simplicity as well as increased safety for small-scale high-speed synthesis. In addition this series of imidazo[1,2-*a*]quinoline, pyrimido[1,2-*a*]quinoline and quinolino[1,2-*a*]quinazoline derivatives may prove new classes of biological active compound derivatives for biomedical screening, which is in progress in our laboratories.

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Supporting Information Available. Representative experimental procedures, spectral data of compounds **4a-pp**, and crystallographic information files (CIF) of **4aa**, **4l**, and **4hh**. Comparison of microwave and thermal conditions for the above reactions are also included. This material is available free charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
(2) Janda, K. D.; Han, H. *Methods Enzymol.* **1996**, *267*, 234–247.
(3) Blondelle, S. E.; Perez-Paya, E.; Dooley, C. T.; Pinilla, C.; Houghten, R. A. *Trends Anal. Chem.* **1995**, *14*, 83–92.
(4) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567–2573.
(5) Eichler, J.; Houghten, R. A. *Mol. Med. Today* **1995**, 174–180.
(6) Choong, I. C.; Ellman, J. A. *Annu. Rep. Med. Chem.* **1996**, 309–318.
(7) Tietze, L. F.; Hippe, T.; Steinmetz, A. *Synlett* **1996**, 1043–1044.
(8) Wang, G. T.; Li, S.; Wideburg, N.; Krafft, G. A.; Kempf, D. J. *J. Med. Chem.* **1995**, *38*, 2995–3002.
(9) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527–4554.
(10) (a) Baldwin, J. J.; Dolle, R. Deconvolution Tools for Solid-Phase Synthesis. In *A Practical Guide to Combinatorial Chemistry*; Czarnik, A. W., DeWitt, S. H., Eds.; American Chemical Society: Washington, DC, 1997; pp 153–176. (b) Williard, X.; Tartar, A. Deconvolution Tools in Solution-Phase Synthesis. In *A Practical Guide to Combinatorial Chemistry*; Czarnik, A. W., DeWitt, S. H., Eds.; American Chemical Society: Washington, DC, 1997; pp 249–280.
(11) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105.
(12) (a) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591. (b) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233–238. (c) Alcazar, J. *J. Comb. Chem.* **2005**, *7*, 353–355. (d) Varma, R. S. *Green Chem.* **1999**, *1*, 43–55. (e) Takvorian, A. G.; Combs, A. P. *J. Comb. Chem.* **2004**, *6*, 171–174. (f) Bremner, W. S.; Organ, M. G. *J. Comb. Chem.* **2007**, *9*, 14–16.
(13) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406–416.
(14) Tu, S. J.; Jiang, B.; Zhang, J. Y.; Zhang, Y.; Jia, R. H.; Li, C. M.; Zhou, D. X.; Cao, L. J.; Shao, Q. Q. *Synlett* **2007**, 480–484.
(15) Hermecz, I.; Vasvari-Debreczy, L.; Matyus, P. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. V. F., Eds.; Pergamon: London, 1996; Chapter 8.23, pp 563–595, and references cited therein.
(16) (a) Elhakmaoui, A.; Gueiffier, A.; Milhavet, J. C.; Blache, Y.; Chapat, J. P.; Chavignon, O.; Teulade, J. C.; Snoeck, R.; Andrei, De.; Clercq, E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1937–1940. (b) Gueiffier, A.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teluade, J. C.; Kerbal, A.; Essassi, M.; Debouzy, J. C.; Witvrouw, M.; Blache, Y.; Balzarini, J.; De Clercq, E.; Chapat, J. P. *J. Med. Chem.* **1996**, *39*, 2856–2859. (c) Lhassani, M.; Chavignon, O.; Chezal, J. M.; Teluade, J. C.; Chapat, J. P.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271–274. (d) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **1997**, *62*, 3453–3459. (e) Pan, S.; Wang, G.; Shinazi, R. F.; Zhao, K. *Tetrahedron Lett.* **1998**, *39*, 8191–8194.
(17) Srivastava, P.; Pandey, V. C.; Misra, A. P.; Gupta, P.; Raj, K.; Bhaduri, A. P. *Bioorg. Med. Chem.* **1998**, *6*, 181–187.
(18) (a) Adelstein, G. W.; Moormann, A. E.; Yen, C. H. *Chem. Abstr.* **1987**, *108*, 167474t. US 4,721,718, 1988;. (b) Kaminski, J. J.; Puchalski, C.; Solomon, D. M.; Rizvi, R. K.; Conn, D. J.; Elliott, A. J.; Lovey, R. G.; Guzik, H.; Chiu, P. J. S.; Long, J. F.; McPhail, A. T. *J. Med. Chem.* **1989**, *32*, 1686–1700. (c) Kaminski, J. J.; Doweyko, A. M. *J. Med. Chem.* **1997**, *40*, 427–436.
(19) Adib, M.; Yavari, H.; Mollahosseini, M. *Tetrahedron lett.* **2004**, *45*, 1083–1085.
(20) Lichitsky, B. V.; Dudinov, A. A.; Krayushkin, M. M. *ARKIVOC.* **2001**, 73–79.
(21) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277–294.
(22) (a) Tu, S. J.; Zhang, Y.; Jiang, B.; Jia, H. R.; Zhang, J. Y.; Zhang, J. P.; Ji, S. J. *Synthesis* **2006**, 3874–3882. (b) Valla, A.; Valla, B.; Cartier, D.; Guillou, R. L.; Labia, R.; Potier, P. *Tetrahedron Lett.* **2005**, *46*, 6671. (c) Tu, S. J.; Jiang, B.; Jia, R. H.; Zhang, J. Y.; Zhang, Y.; Yao, C. S.; Shi, F. *Org. Biomol. Chem.* **2006**, *4*, 3664–3668.

(23) (a) Murugova, E. Y.; Romanova, O. B.; Alekseeva, L. M.; Rumyantsev, E. A.; Faermark, I. F.; Shvarts, G. Y.; Granik, V. G. *Khim.-Farm. Zh.* **1990**, *24*, 32–35. (b) Vitolina, R.; Stankevich, E. I.; Grinsteins, E.; Dreimane, A. *Khim.-Farm. Zh.* **1981**, *15*, 39–42. (c) Halpern, B. *Aust. J. Chem.* **1965**, *18*, 417–421. (d) Halpern, B.; James, L. B. *Aust. J. Chem.* **1964**, *17*, 1282–1287. (e) Nemeryuk, M. P.; Tolokontseva, L. A.; Yadrovskaya, V. A.; Polezhaeva, A. I.; Petrova, G. A.; Safonova, T. S.; Mashkovskii, M. D. *Khim.-Farm. Zh.* **1985**, *19*, 810–814. (f) Crabbe, P.; Halpern, B.; Santos, E. *Tetrahedron* **1968**, *24*, 4315–4326. (g) Xiao, J.; Yang, M.; Lauher, J. W.; Fowler, F. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2132–2135. (h) Kikelj, D. *Sci. Syn.* **2004**, *16*, 573–749. (i) Al-Sabbagh, O. I.; El-Bermawy, M. A.; El-Sadek, M. A.; Al-Ashmawi, M. I. *Zagazig J. Pharm. Sci.* **1994**, *3*, 131–135. (j) Lessel, J. *Arch. Pharm. (Weinheim, Ger.)* **1994**, *327*, 329–336.

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