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Synthesis and antienteroviral activity of a series of novel, oxime ether-containing pyridyl imidazolidinones

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Abstract—A series of novel, oxime ether-containing pyridyl imidazolidinones were synthesized and their antiviral activity was evaluated in a plaque reduction assay. It is very interesting that this class of compounds is specific for human enteroviruses, in particular, enterovirus 71 (EV71). Some derivatives strongly inhibited enterovirus replication with activities higher or comparable to those of the reference compounds such as $\mathbf{A_1}$ and $\mathbf{A_2}$. Preliminary SAR studies revealed that the chain length of the alkyl linker and the alkyl substituent at the oxime ether group largely influenced the in vitro anti-EV71 activity of this new class of potent antiviral agents. Among this series of compounds synthesized, the pyridyl imidazolidinone with an ethyl oxime ether group located at the *para* position of the phenoxyl ring (**8b**) was identified as the most potent enterovirus 71 inhibitor ($IC_{50} = 0.001\,\mu M$) with no apparent cytotoxic effect toward RD (rhabdomyosarcoma) cell lines ($CC_{50} > 25\,\mu M$). Furthermore, this compound has been shown broad-spectrum activity against most of the serotypes of enteroviruses tested in the nanomolar range.

1. Introduction

Enterovirus 71 (EV71) was first recognized in 1969 in California, USA, when it was isolated from the feces of an infant suffering from encephalitis.[1] EV71 belongs to the human enterovirus A species of the *Enterovirus* genus within the family of Picornaviridae.[2] Virions consist of a nonenveloped capsid surrounding a core of single-stranded, positive-polarity RNA approximately 7.5 kb in size. The viral capsid is icosahedral in symmetry and is composed of 60 identical units each consisting of the four structural proteins VP1–VP4. The complete nucleotide sequence of the EV71 prototype strain BrCr has been determined.[3] Symptoms for EV71 infections range from nonspecific upper respiratory infection and mild fever to central nervous system infections particularly viral meningitis, encephalitis, and severe myocarditis.[4] Children are considered to be relatively immunodeficient, therefore EV71 infections of neonates can be lethal and life threatening, with high risk for morbidity and mortality. Many epidemic outbreaks have been reported from Asian countries.[5] A major outbreak of EV71 infection in Taiwan in 1998 caused many severe cases and 78 deaths.[6] This highlights the urgency and significance for developing anti-EV71 agents.

In 1966, a novel antienteroviral agent, pleconaril (Fig. 1), was made available for treatment of life threatening enteroviral infections, such as meningitis, encephalitis, myocarditis.[7] It is under development by Viropharma, Inc. for the treatment of severe enteroviral infection in phase 2 clinical trials. Unfortunately, pleconaril has been found to have limited activity against EV71 at concentrations tested in vitro.

In our laboratory, many structurally related pyridyl imidazolidinones were recently found to have strong activity against EV71.[8] SAR studies demonstrated that an aryl substituent at the *para* position of the phenoxyl ring and a pyridine-containing imidazolidinone are key structural requirements for anti-EV71 activity. Previously, we reported that the biphenyl analogues $\mathbf{A_1}$ and $\mathbf{A_2}$ (Fig. 1) with either a phenyl or 4-chlorophenyl

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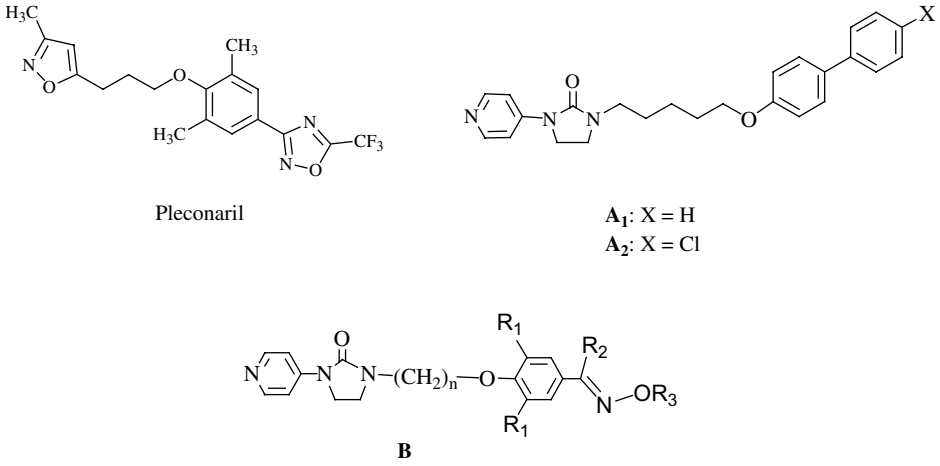


Figure 1. Structures of pleconaril, pyridyl imidazolidinones $\mathbf{A_1}$, $\mathbf{A_2}$, and **B**.

moieties at the *para* position bestowed the best potency to this class of compounds.[8]

As part of our continuous efforts toward the identification of more potent broad-spectrum antienteroviral agents, a series of novel, oxime ether-containing pyridyl imidazolidinones **B** (Fig. 1) were synthesized and assayed for antiviral activity against EV71.[9] Some derivatives have shown significant improvement in potency relative to the reference compounds $\mathbf{A_1}$ and $\mathbf{A_2}$ as well as broad-spectrum activity against a variety of enterovirus serotypes. Details of this investigation will be described herein.

2. Results and discussion

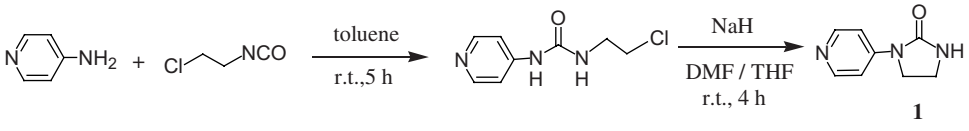
In this paper, we describe the synthesis of the novel antiviral pyridyl imidazolidinones **8a–j** and **11a–d** via the key nucleophilic substitution of 1-(4-pyridyl)-2-imidazolidinone **1**[8] with various oxime ether-containing alkylating agents **7** and **10** (Schemes 1–3). All the resulting compounds were then submitted for anti-EV71 testing as well as cytotoxicity evaluation in the RD cell lines. Preliminary structure–activity relationships against EV71 are reported (Table 1). In all cases examined, the ethyl oxime ether **8b** was selected for further evaluation against a variety of viruses since it appeared to demonstrate excellent activity against EV71. The results of this biological evaluation are illustrated in Table 2.

2.1. Chemistry

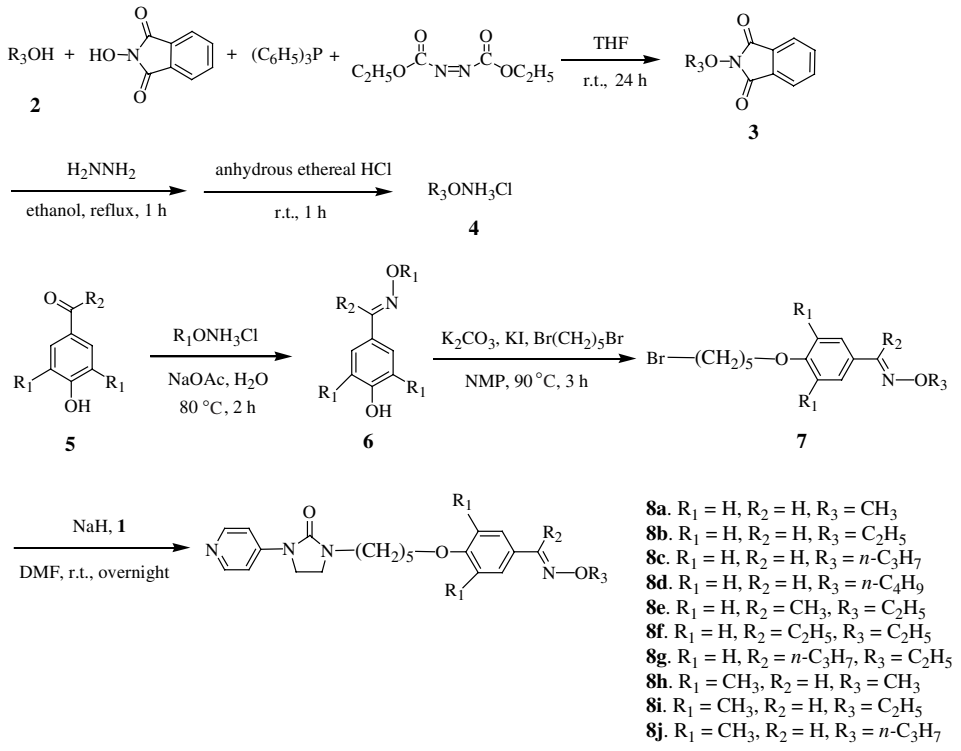
For the preparation of 1-(4-pyridyl)-2-imidazolidinone **1** (Scheme 1), 4-aminopyridine was first coupled with 2-chloroethylisocyanate to give the corresponding urea intermediate in 80% yield. Subsequent intramolecular cyclization of intermediate by treatment with sodium hydride in the THF/DMF (1:1) cosolvent system at room temperature resulted in the formation of cyclic urea **1** in quantitative yield.

The oxime ether derivatives **8a–j** were prepared by the method summarized in Scheme 2. Mitsunobu reaction[10] of the alcohol **2** with *N*-hydroxyphthalimide in the presence of diethyl azodicarboxylate and triphenylphosphine at room temperature gave *N*-alkoxyphthalimide **3**. Subsequent Ing–Manske reaction[11] of compound **3** with hydrazine followed by acidification with anhydrous ethereal hydrogen chloride afforded the corresponding alkoxyamine hydrochloride **4**.[12] Aldehyde (or ketone) **5** was condensed with the above key intermediate **4** in aqueous solution with the aid of sodium acetate to give compound **6** in moderate yields. Nucleophilic substitution of compound **6** with 1,5-dibromopentane using potassium carbonate as a base in 1-methyl-2-pyrrolidinone (NMP) at refluxing temperature afforded compound **7**. Subsequent N-alkylation of 1-(4-pyridyl)-2-imidazolidinone **1** with compound **7** in the presence of sodium hydride in DMF gave the desired compounds **8a–j** in excellent yields.

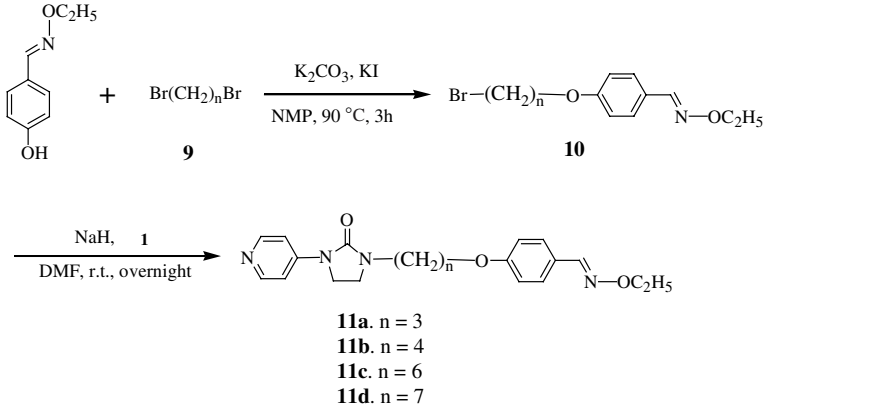
Variation in the length of the connecting chain was accomplished according to Scheme 3. This procedure was used for the preparation of the oxime ethers **11a–d**. The key intermediate, 4-hydroxybenzaldehyde-*O*-ethyloxime, was obtained in 90% yield by treating 4-hydroxybenzaldehyde with ethoxyamine hydrochloride and sodium acetate in aqueous solution. In the presence of potassium carbonate, 4-hydroxybenzaldehyde-*O*-ethyloxime can undergo nucleophilic substitution with dibromo compound **9** to give compound **10**. Subsequent



Scheme 1. Synthesis of 1-{4-pyridyl}-2-imidazolidinone **1**.



Scheme 2. General synthetic route to oxime ethers **8a**–**j**.



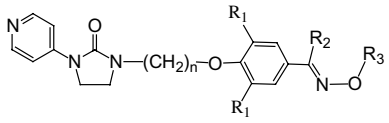
Scheme 3. General synthetic route to oxime ethers **11a**–**d**.

N-alkylation of 1-(4-pyridyl)-2-imidazolidinone **1** with compound **10** in the presence of sodium hydride in DMF provided the desired compounds **11a**–**d** in excellent yields. All the new oxime ether derivatives were characterized by ^{1}H NMR and ES mass spectra.[13] According to previous literature report, we have assigned this series of compounds as the *trans* or *E* stereoisomer forms of the oxime ether by ^{1}H NMR spectra.[14]

3. Bioactivity

The oxime ether derivatives described herein were tested in a plaque reduction assay[9] under a standard procedure. Compounds **8a**–**j** and **11a**–**d** were submitted for anti-EV71 testing as well as cytotoxicity evaluation in the RD cell lines. The results are shown in Table 1 and are compared to the reference compounds $\mathbf{A_1}$ and bf $\mathbf{A_2}$. Replacement of the phenyl group at the *para* position of the phenoxyl ring of $\mathbf{A_1}$ and $\mathbf{A_2}$ with a methyl oxime ether (**8a**) resulted in a sixfold improvement in activity against EV71. It is very interesting to note that compound **8a** exhibited excellent activity against EV71 (IC_{50} = 0.005 μM) with no cytotoxicity up to the concentration of 25 μM. These significant results demonstrated that the *O*-substituted oxime ether moiety of the pyridyl imidazolidinones seem to play a very important role in enhancing the anti-EV71 activity. This effect might be due to their drastically conformational change and steric requirement at the *para* position of the phenoxyl ring.

Table 1. Anti-EV71 activity and cytotoxicity for compounds **8a–j** and **11a–d**



Compound	*n*	R_1	R_2	R_3	IC_{50} (μM)[a] EV71[c]	CC_{50} (μM)[b] RD[d]
8a	5	H	H	CH_3	0.005 ± 0.001	>12.5
8b	5	H	H	C_2H_5	0.001 ± 0.001	>12.5
8c	5	H	H	*n*-C_3H_7	0.021 ± 0.003	>12.5
8d	5	H	H	*n*-C_4H_9	0.079 ± 0.019	>12.5
8e	5	H	CH_3	C_2H_5	16.85 ± 0.65	>12.5
8f	5	H	C_2H_5	C_2H_5	1.08 ± 0.17	>12.5
8g	5	H	*n*-C_3H_7	C_2H_5	0.65 ± 0.03	>12.5
8h	5	CH_3	H	CH_3	0.80 ± 0.11	>12.5
8i	5	CH_3	H	C_2H_5	0.36 ± 0.08	>12.5
8j	5	CH_3	H	*n*-C_3H_7	>25	>6.25
11a	3	H	H	C_2H_5	21.35 ± 1.57	>12.5
11b	4	H	H	C_2H_5	0.24 ± 0.01	>12.5
11c	6	H	H	C_2H_5	0.010 ± 0.004	>12.5
11d	7	H	H	C_2H_5	0.025 ± 0.001	>6.25
A_1	—	—	—	—	0.028 ± 0.005	>12.5
A_2	—	—	—	—	0.032 ± 0.004	>12.5

[a] Mean of triplicate well values. All experiments were performed at least twice. Plaque reduction assay was employed.
[b] Mean of triplicate well values. All experiments were performed at least twice.
[c] EV71: human enterovirus 71 strain 4643.
[d] RD: human rhabdomyosarcoma cells.

Table 2. Comparative evaluation of compound **8b** and **A_2** against various viruses

	IC_{50} (μM)[a]	
	A_2	**8b**
Enterovirus 71 (2231) genotype C	0.087 ± 0.009	0.019 ± 0.004
Enterovirus 71 (4643) genotype C	0.032 ± 0.004	0.001 ± 0.001
Enterovirus 71 (2086) genotype C	0.071 ± 0.003	0.004 ± 0.001
Enterovirus 71 (BrCr) genotype A	0.054 ± 0.011	0.005 ± 0.001
Enterovirus 71 (1743) genotype B	0.097 ± 0.020	0.009 ± 0.001
Enterovirus 68	>25	6.73 ± 1.30
Coxsackievirus A9	0.049 ± 0.006	0.025 ± 0.004
Coxsackievirus A10	8.61 ± 1.22	0.64 ± 0.06
Coxsackievirus A16	>25	0.36 ± 0.03
Coxsackievirus A24	0.14 ± 0.01	0.031 ± 0.011
Coxsackievirus B1	>25	1.20 ± 0.38
Coxsackievirus B2	>25	>25
Coxsackievirus B3	>25	>25
Coxsackievirus B4	3.14 ± 0.43	1.18 ± 0.16
Coxsackievirus B5	4.18 ± 0.33	4.74 ± 1.09
Coxsackievirus B6	>25	>25
Echovirus 9	0.30 ± 0.01	0.26 ± 0.01
Echovirus 29	0.038 ± 0.004	0.021 ± 0.003

[a] Mean of triplicate well values. All experiments were performed at least twice. Plaque reduction assay was employed.

These encouraging results prompt us to further investigate this class of novel, oxime ether-containing pyridyl imidazolidinones.

Increasing the length of the *O*-substituent (R_3) of the oxime ether group from methyl to *n*-butyl, in the case of the five-carbon homologues **8a–d**, resulted in an interesting pattern in activity against EV71. Chain extension from methyl (**8a**) to ethyl (**8b**) at this position in this series of compounds resulted in a fivefold increase in activity (IC_{50} = 0.001 μM), and a further chain extension to *n*-propyl (**8c**) and *n*-butyl (**8d**) was detrimental to activity. This effect might be due to their distinct differences of hydrophobic properties. On the other hand, when an alkyl substituent (Me, Et, *n*-Pr) was introduced at the oxime carbon (R_2), compounds **8e**, **8f**, and **8g** showed a dramatic decrease in activity against EV71 as compared with the corresponding ethyl oxime ether **8b**. However, it is also very interesting to note that the 3,5-dimethylphenoxyl derivatives (R_1 = Me), such as compounds **8h**, **8i**, and **8j**, were considerably less active than their corresponding 3,5-unsubstituted phenoxyl derivatives **8a**, **8b**,

and **8c**. This unexpected biological result is not fully understood and is worthy of further study.

Several ethyl oxime ethers with various tether lengths (**11a–d**) were synthesized in order to determine the optimal spacing between the imidazolidinone and the phenoxyl ring. Interestingly, the chain length of the alkyl linker was found to be of considerable importance for the activity of the compounds. The results are shown in Table 1 and are compared to the corresponding five-carbon homologue **8b**. However, the six- and seven-carbon homologues, **11c** and **11d**, respectively, showed a 10- and 25-fold loss in activity against EV71, and the three- and four-carbon homologues, **11a** and **11b**, respectively, drastically reduced activity. These significant results demonstrated that the five-carbon homologues in this series were routinely more active against EV71 than their corresponding longer or shorter compounds. These observations provide remarkable evidence that the hydrophobic interaction and conformational flexibility of the alkyl linker largely influence anti-EV71 activity of these novel oxime ether-containing pyridyl imidazolidinones.

In this study, the ethyl oxime ether **8b** was selected for further evaluation since it appeared to demonstrate excellent activity against EV71 ($IC_{50} = 0.001\,\mu M$). A comparison of the activity of **8b** and $\mathbf{A_2}$ against 14 serotypes is illustrated in Table 2. The compounds were individually subjected to evaluation against a variety of human enteroviruses, including coxsackieviruses (10 serotypes), echoviruses (2 serotypes), human enteroviruses 68 and 71. As shown, the ethyl oxime ether **8b** was found, in addition to strongly inhibiting all of the genotypes (A, B, and C) of EV71, to possess antiviral activity against coxsackieviruses A9, A10, A16, A24, B1, B4, and B5, echovirus 9, echovirus 29, and enterovirus 68. However, this compound showed no activity against coxsackieviruses B2, B3, and B6 up to the concentration tested (25 μM). On the basis of these extensive biological evaluation, we observed that compound **8b** is more potent against most of the serotypes of human enteroviruses tested, in particular, enterovirus 71 ($IC_{50} = 0.001$–$0.019\,\mu M$) and also possess a very low cytotoxic effect on the uninfected rhabdomyosarcoma (RD) host cells ($IC_{50} > 25\,\mu M$). Therefore, for our purpose, the ethyl oxime ether **8b** is well qualified to serve as a lead compound for the further development of anti-EV71 agent.

4. Conclusion

In summary, we have developed an efficient synthesis of this series of novel, oxime ether-containing pyridyl imidazolidinones in an attempt to evaluate their anti-EV71 activity in a plaque reduction assay. According to our SAR investigation, the alkyl substituent at the oxime ether group and the phenoxyl ring largely influenced the in vitro anti-EV71 activity of this new class of potent antiviral agents. On the other hand, it is also very interesting to note that the activities of this series of compounds were very sensitive to the variation in the chain length of the alkyl linker. On the basis of these biological results, the ethyl oxime ether **8b** was found to exhibit the most potent antiviral activity against EV71 ($IC_{50} = 0.001\,\mu M$) with no apparent cytotoxic effect toward RD (rhabdomyosarcoma) cell lines ($CC_{50} > 25\,\mu M$). Additionally, we observed that this compound has been shown to have a broad-spectrum activity against most of the serotypes of enteroviruses tested in the nanomolar range. Further SAR studies and mechanistic studies on this new class of antiviral compounds are currently under active investigation and will be reported in due course.

Acknowledgements

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References and notes

1. (a) Schmidt, N. J.; Lennette, E. H.; Ho, H. H. *J. Infect. Dis.* **1974**, *129*, 304–309; (b) Melnick, J. L. *Rev. Infect. Dis.* **1984**, *6*(Suppl. 2), S387–S390; (c) Melnick, J. L.; Tagaya, I.; von Magnus, H. *Intervirology* **1974**, *4*, 369–370.
2. King, A. M. Q.; Brown, F.; Christian, P.; Hovi, T.; Hyypia, T., et al. Picornaviridae. In *Virus Taxonomy. Seventh Report of the International Committee for the Taxonomy of Viruses*; Van Regenmortel, M. H. V., Fauquet, C. M., Bishop, D. H. L., Calisher, C. H., et al., Eds.; Academic: New York, 2000; pp 657–673.
3. Brown, B. A.; Pallansch, M. A. *Virus Res.* **1995**, *39*, 195–205.
4. Melnick, J. L. Enteroviruses: Polioviruses, Coxsackieviruses, Echoviruses, and Newer Enteroviruses. In *Virology*; Fields, B. N., Knipe, D. M., Howley, P. M., Chanock, R. M., Melnick, J. L., Monath, T. P., Roizman, B., Straus, S. E., Eds.; Lippincott–Raven: Philadelphia, PA, 1996; pp 655–712.
5. (a) Chonmaitree, T.; Menegus, M. A., et al. *Pediatrics* **1981**, *67*, 489–493; (b) Ishimaru, Y.; Nakano, S.; Yamaoka, K.; Takami, S. *Arch. Dis. Child* **1980**, *55*, 583–588; (c) Amuda, G. M.; Chang, W. K.; Yeung, C. Y.; Tang, P. S. *Pediatr. Infect. Dis. J.* **1987**, *6*, 206–208; (d) Hayward, J. C.; Gillespie, S. M.; Kaplan, K. M.; Packer, R.; Pallansch, M.; Plotkin, S.; Schonberger, L. B. *Pediatr. Infect. Dis. J.* **1989**, *8*, 611–616; (e) Gilbert, G. L.; Dickson, K. E.; Waters, M. J.; Kennett, M. L.; Land, S. A.; Sneddon, M. *Pediatr. Infect. Dis. J.* **1988**, *7*, 484–488.
6. Ho, M.; Chen, E. R.; Hsu, K. H.; Twu, S. J.; Chen, K. T.; Tsai, S. F.; Wang, J. R.; Shih, S. R. *N. Engl. J. Med.* **1999**, *341*, 929–935.
7. (a) Pevear, D. C.; Tull, T. M.; Seipel, M. E.; Groarke, J. M. *Antimicrob. Agents Chemother.* **1999**, *43*, 2109–2115; (b) Kaiser, L.; Crump, C. E.; Hayden, F. G. *Antiviral Res.* **2000**, *47*, 215–220.
8. Shia, K. S.; Li, W. T.; Chang, C. M.; Hsu, M. C.; Chern, J. H., M. K.; Leong, M. K.; Tseng, S. N.; Lee, C. C.; Lee, Y. C.; Chen, S. J.; Peng, K. C.; Tseng, H. Y.; Chang, Y. L.; Tai, C. L.; Shih, S. R. *J. Med. Chem.* **2002**, *45*, 1644–1655.
9. Otto, M. J.; Fox, M. P.; Fancher, M. J.; Kuhrt, M. F.; Diana, G. D.; McKinlay, M. A. *Antimicrob. Agents Chemother.* **1985**, *27*, 883–886.
10. (a) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427; (b) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

11. Ing, H. R.; Manske, R. H. F. *J. Chem. Soc.* **1926**, 2349.
12. Grochowski, E.; Jurczak, J. *Synthesis* **1976**, 682–684.
13. All the new compounds gave satisfactory spectral data consistent with their proposed structures. Selected spectral data for compounds **8a**, **8b**, **11a**, and **11b**. Compound **8a**: mp 116–118 °C; IR ($CHCl_3$) ν_{max} 1714, 1592, 1506, 1481, 1428, 1257, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 6.3 Hz, 2H), 7.99 (s, 1H), 7.49–7.45 (m, 4H), 6.85 (d, J = 8.7 Hz, 2H), 3.98 (t, J = 6.3 Hz, 2H), 3.94 (s, 3H), 3.81 (dd, J = 10.5 Hz, J = 6.9 Hz, 2H), 3.54 (dd, J = 8.7 Hz, J = 6.0 Hz, 2H), 3.34 (t, J = 6.9 Hz, 2H), 1.86–1.79 (m, 2H), 1.65–1.49 (m, 4H); ESMS 383.2 (M + 1). Compound **8b**: mp 109–111 °C; IR ($CHCl_3$) ν_{max} 1711, 1594, 1511, 1480, 1425, 1250, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 6.0 Hz, 2H), 7.99 (s, 1H), 7.49–7.44 (m, 4H), 6.84 (d, J = 8.7 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.96 (t, J = 6.3 Hz, 2H), 3.79 (dd, J = 10.2 Hz, J = 6.9 Hz, 2H), 3.52 (dd, J = 9.0 Hz, J = 6.0 Hz, 2H), 3.33 (t, J = 6.9 Hz, 2H), 1.87–1.78 (m, 2H), 1.67–1.48 (m, 4H), 1.30 (t, J = 7.2 Hz, 3H); ESMS 397.2 (M + 1). Compound **11a**: mp 97–99 °C; IR ($CHCl_3$) ν_{max} 1710, 1594, 1509, 1479, 1424, 1248, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 5.7 Hz, 2H), 7.99 (s, 1H), 7.49–7.43 (m, 4H), 6.85 (d, J = 8.7 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 4.05 (t, J = 6.0 Hz, 2H), 3.80 (dd, J = 10.5 Hz, J = 7.2 Hz, 2H), 3.59–3.48 (m, 4H), 2.12–2.04 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H); ESMS 369.1 (M + 1). Compound **11b**: mp 144–146 °C; IR ($CHCl_3$) ν_{max} 1701, 1603, 1508, 1489, 1420, 1243, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 5.1 Hz, 2H), 7.98 (s, 1H), 7.48–7.43 (m, 4H), 6.84 (d, J = 8.7 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 4.01 (t, J = 5.7 Hz, 2H), 3.77 (dd, J = 9.9 Hz, J = 6.6 Hz, 2H), 3.53 (dd, J = 9.0 Hz, J = 5.7 Hz, 2H), 3.38 (t, J = 6.9 Hz, 2H), 1.83–1.76 (m, 4H), 1.30 (t, J = 7.2 Hz, 3H); ESMS 383.3 (M + 1).
14. Karabatsos, G. J.; Hsi, N. *Tetrahedron* **1967**, *23*, 1079.