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Synthesis of novel bis (β-Lactams) from bis (ketene) and imines

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Abstract: An efficient synthesis of novel bis-β-lactams via cycloaddition reaction (Staudinger reaction) of imines with bis-ketene derived from adipic acid is reported in this paper. The resulting bis-azetidinones are characterized by IR, ^{1}H NMR and Mass spectral data. The title compounds were screened for their in anti-bacterial activity.
Key words: Imines, ketene, bis-azetidinones, antibacterial activity.

Introduction

β-lactams are widely recognized for their antibiotic activity, in addition to macrolides and fluoroquinolones, research in this area remains indispensable to provide new entries toward azetidin-2-ones with potential biological activity [(1)]. Azetidinones are an interesting and important class of four-membered heterocyclic compounds because of their reactivity [(2)] and biological activity [(3)]. The preparation and chemistry of β-lactams has been the subject of frequent reviews, [(4)] including not only [2+2] cycloadditions of ketenes with imines. It is well-known that bacterial resistance to existing antibiotics is increasing and therefore there is great demand for the creation of a new type of compound bearing a β-lactam motif. Azetidinones are a very important class of compounds possessing a wide range of biological activities such as anti-microbial, anti-tumor [(5)], anti-inflammatory [(6)], anti-convulsant [(7)], antibiotic [(8)], anticancer [(9)], anti-elastase [(10)], anti-viral [(11)] and anti-HCMV [(12)] activities.

The possibility of cooperative effects from two therapeutic functionalities in drug molecules, as well as the possible use of these multifunctional substrates in further synthetic transformations, has prompted interest in the synthesis of bis (β-lactams). Syntheses of bis (β-lactams) [(13)] have most often been carried out from reactions of monoketenes with bis (imines), although there have been recent studies involving reactions of the less accessible bis (ketenes). Many different arrangements of the bis (β-lactam) groups have been produced by different synthetic schemes. Ketenes are usually generated by elimination of an activated carboxylic acid in the presence of a base [(14)]. We wish to report herein our results in the Staudinger [2 + 2] cycloaddition of different substituted imines to bis (ketene) for the synthesis of bis-azetidinones.

Experimental

General: All the chemicals and solvents were obtained from Merck (AR grade) and were used without further purification. Melting points were taken in an open capillary tube. ^{1}H NMR spectra of the titled compounds were recorded on a Bruker-Avance (300 MHz) spectrophotometer using DMSO solvent and TMS as the internal standard. EI-MS spectra were determined on a LCQ ion trap mass spectrometer (Thermo Fisher, San Jose, CA, USA), equipped with an EI source.

Synthesis of Schiff base (1a – 1j): A quantity of 0.008 mol of m-nitrobenzaldehyde, 0.008 mol of aromatic amine and 20 ml of ethanol was refluxed for 1 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was set on one side

to cool. The air which separates was induced to crystallize by rubbing with glass rod. Solid deposit was collected by filtration and the crude product was recrystallized from methanol.

4-methoxy-N-(3-nitrobenzylidene)aniline (1a): Yield 79%; m.p. (^{0}C): 98; IR (KBr, cm^{-1}): 1647 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 3.75 (s, 3H, -OCH_3); 6.9-8.3 (m, 7H, Ar-H); 8.6 (s, 1H, -CH=N-); 8.8 (s, 1H, Ar-H); Mass spectra, m/z = 256 (100%).

4-chloro-N-(3-nitrobenzylidene)aniline (1b): Yield 76%; m.p. (^{0}C): 112; IR (KBr, cm^{-1}): 1647 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.1-8.3 (m, 7H, Ar-H); 8.5 (s, 1H, -CH=N-); 8.7 (s, 1H, Ar-H); Mass spectra, m/z = 260 (100%).

N-(3-nitrobenzylidene)aniline (1c): Yield 72%; m.p. (^{0}C): 103; IR (KBr, cm^{-1}): 1635 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.2-8.2 (m, 8H, Ar-H); 8.7 (s, 1H, -CH=N-); 8.9 (s, 1H, Ar-H); Mass spectra, m/z = 226 (100%).

3-chloro-N-(3-nitrobenzylidene)aniline (1d): Yield 69%; m.p. (^{0}C): 109; IR (KBr, cm^{-1}): 1655 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.0-8.2 (m, 7H, Ar-H); 8.4 (s, 1H, -CH=N-); 8.6 (s, 1H, Ar-H); Mass spectra, m/z = 260 (100%).

4-methyl-N-(3-nitrobenzylidene)aniline (1e): Yield 65%; m.p. (^{0}C): 115; IR (KBr, cm^{-1}): 1640 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.6 (s, 3H, -CH_3); 7.0-8.3 (m, 7H, Ar-H); 8.5 (s, 1H, -CH=N-); 8.7 (s, 1H, Ar-H); Mass spectra, m/z = 240 (100%).

4-(3-nitrobenzylideneamino)phenol (1f): Yield 70%; m.p. (^{0}C): 110; IR (KBr, cm^{-1}): 1655 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 6.6-8.2 (m, 7H, Ar-H); 8.4 (s, 1H, -CH=N-); 8.6 (s, 1H, Ar-H); 12.5 (s, 1H, -OH); Mass spectra, m/z = 242 (100%).

3-nitro-N-(3-nitrobenzylidene)aniline (1g): Yield 63%; m.p. (^{0}C): 123; IR (KBr, cm^{-1}): 1648 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.2-8.6 (m, 8H, Ar-H); 8.4 (s, 1H, -CH=N-); Mass spectra, m/z = 271 (100%).

4-nitro-N-(3-nitrobenzylidene)aniline (1h): Yield 60%; m.p. (^{0}C): 126; IR (KBr, cm^{-1}): 1641 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.3-8.6 (m, 8H, Ar-H); 8.3 (s, 1H, -CH=N-); Mass spectra, m/z = 271 (100%).

2-chloro-N-(3-nitrobenzylidene)aniline (1i): Yield 74%; m.p. (^{0}C): 112; IR (KBr, cm^{-1}): 1652 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.0-8.2 (m, 7H, Ar-H); 8.4 (s, 1H, -CH=N-); 8.6 (s, 1H, Ar-H); Mass spectra, m/z = 260 (100%).

2-(3-nitrobenzylideneamino)benzoic acid (1j): Yield 68%; m.p. (^{0}C): 119; IR (KBr, cm^{-1}): 1636 (-CH=N-); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.2-8.3 (m, 7H, Ar-H); 8.4 (s, 1H, -CH=N-); 11.3 (s, 1H, COOH); Mass spectra, m/z = 270 (100%).

Synthesis of bis-azetidinones (2a–2j): A solution of adipoyl chloride (0.01mol) in dry dichloromethane was added dropwise to a well-stirred solution of appropriate Schiff base (0.01mol) and triethylamine (0.02 mol) in anhydrous dichloromethane (50 ml). After the addition had been completed, the solution was stirred for ~14 hr. The completion of the reaction was monitored by TLC. The reaction mixture was washed with water and dried over sodium sulphate. The products that were obtained after removing the solvent were purified from ethyl acetate and n-hexane.

3,3'-(ethane-1,2-diyl)bis(1-(4-methoxyphenyl)-4-(3-nitrophenyl)azetidin-2-one) (2a): Yield 75%; m.p. (^{0}C): 165; IR (KBr, cm^{-1}): 1705 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.7 (t, 4H, -CH_2-CH_2-); 3.3 (q, 2H, -CH-CO); 3.8 (s, 6H, -OCH_3); 4.9 (d, 2H, -CH-N); 6.9-8.7 (m, 16H, Ar-H); Mass spectra, m/z = 622 (100%).

3,3'-(ethane-1,2-diyl)bis(1-(4-chlorophenyl)-4-(3-nitrophenyl)azetidin-2-one) (2b): Yield 72%; m.p. (^{0}C): 150; IR (KBr, cm^{-1}): 1734 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.6 (t, 4H, -CH_2-CH_2-); 3.5 (q, 2H, -CH-CO); 4.8 (d, 2H, -CH-N); 7.0-8.6 (m, 16H, Ar-H); Mass spectra, m/z = 630 (100%).

3,3'-(ethane-1,2-diyl)bis(4-(3-nitrophenyl)-1-phenylazetidin-2-one) (2c): Yield 68%; m.p. (^{0}C): 124; IR (KBr, cm^{-1}): 1741 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.8 (t, 4H, -CH_2-CH_2-); 3.6 (q, 2H, -CH-CO); 4.7 (d, 2H, -CH-N); 7.1-8.5 (m, 18H, Ar-H); Mass spectra, m/z = 562 (100%).

3,3'-(ethane-1,2-diyl)bis(1-(3-chlorophenyl)-4-(3-nitrophenyl)azetidin-2-one) (2d): Yield 70%; m.p. (^{0}C): 146; IR (KBr, cm^{-1}): 1738 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.5 (t, 4H, -CH_2-CH_2-); 3.4 (q, 2H, -CH-CO); 4.9 (d, 2H, -CH-N); 7.1-8.7 (m, 16H, Ar-H); Mass spectra, m/z = 630 (100%).

3,3'-(ethane-1,2-diyl)bis(4-(3-nitrophenyl)-1-p-tolylazetidin-2-one) (2e): Yield 67%; m.p. (^{0}C): 157; IR (KBr, cm^{-1}): 1715 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.6 (t, 4H, -CH_2-CH_2-); 2.5 (s, 6H, -CH_3); 3.4 (q, 2H, -CH-CO); 4.8 (d, 2H, -CH-N); 6.8-8.6 (m, 16H, Ar-H); Mass spectra, m/z = 590 (100%).

3,3'-(ethane-1,2-diyl)bis(1-(4-hydroxyphenyl)-4-(3-nitrophenyl)azetidin-2-one) (2f): Yield 65%; m.p. (^{0}C): 162; IR (KBr, cm^{-1}): 1751 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.7 (t, 4H, -CH_2-CH_2-); 3.5 (q, 2H, -CH-CO); 4.7 (d, 2H, -CH-N); 6.8-8.4 (m, 16H, Ar-H); 12.2 (s, 2H, -OH); Mass spectra, m/z = 594 (100%).

3,3'-(ethane-1,2-diyl)bis(1,4-bis(3-nitrophenyl)azetidin-2-one) (2g): Yield 69%; m.p. (^{0}C): 174; IR (KBr, cm^{-1}): 1725 (CO, β-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.6 (t, 4H, -CH_2-CH_2-); 3.4 (q, 2H, -CH-CO); 4.9 (d, 2H, -CH-N); 7.4-8.8 (m, 16H, Ar-H); Mass spectra, m/z = 652 (100%).

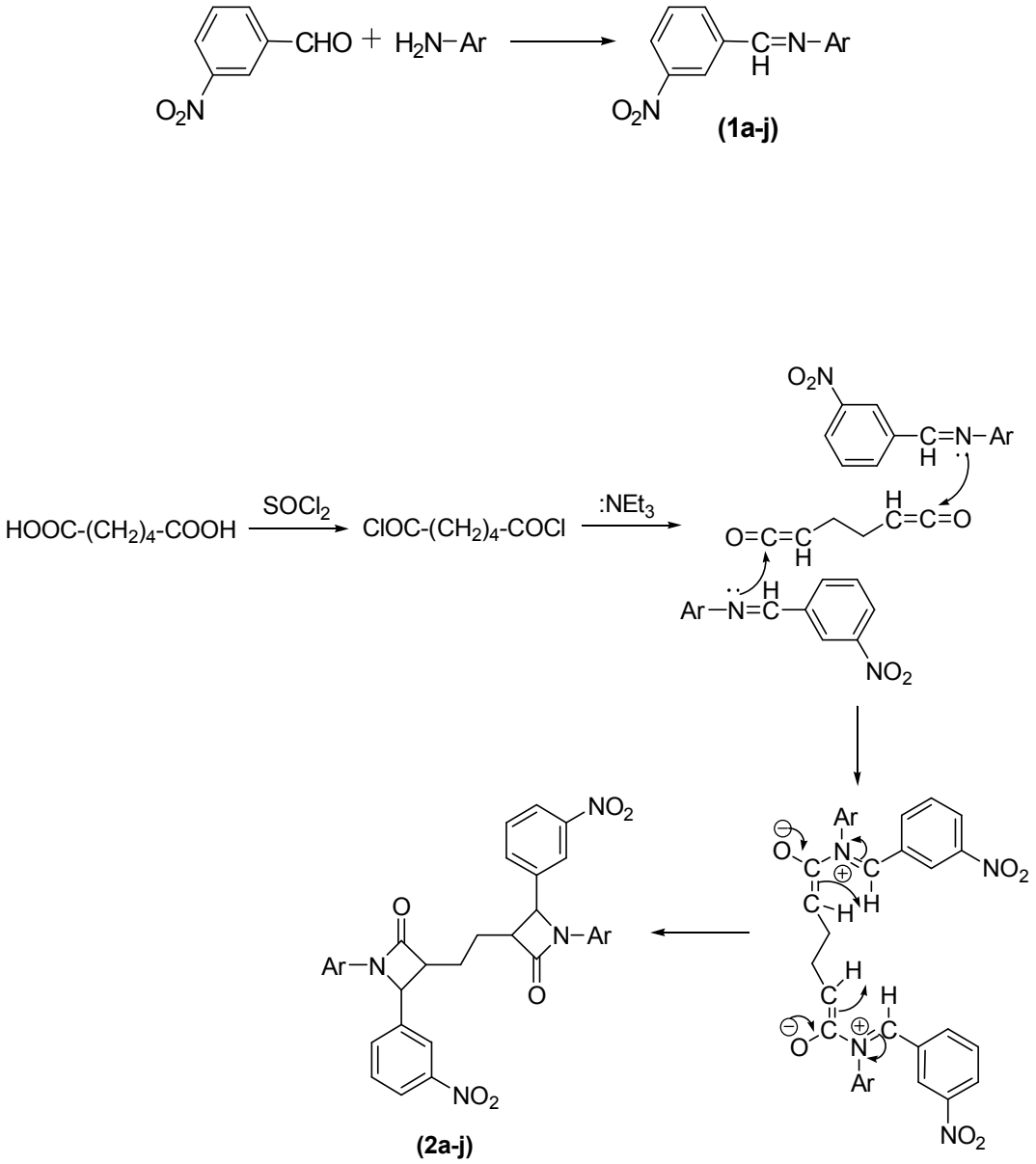
3,3'-(ethane-1,2-diyl)bis(4-(3-nitrophenyl)-1-(4-nitrophenyl)azetidin-2-one) (2h): Yield 63%; m.p. (^{0}C): 169; IR (KBr, cm^{-1}): 1736 (CO, *β*-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.6 (t, 4H, -CH_2-CH_2-); 3.5 (q, 2H, -CH-CO); 4.8 (d, 2H, -CH-N); 7.2-8.7 (m, 16H, Ar-H); Mass spectra, m/z = 652 (100%).

3,3'-(ethane-1,2-diyl)bis(1-(2-chlorophenyl)-4-(3-nitrophenyl)azetidin-2-one) (2i): Yield 71%; m.p. (^{0}C): 152; IR (KBr, cm^{-1}): 1720 (CO, *β*-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.5 (t, 4H, -CH_2-CH_2-); 3.4 (q, 2H, -CH-CO); 4.9 (d, 2H, -CH-N); 6.9-8.4 (m, 16H, Ar-H); Mass spectra, m/z = 630 (100%).

2,2'-(3,3'-(ethane-1,2-diyl)bis(2-(3-nitrophenyl)-4-oxoazetidine-3,1-diyl))dibenzoic acid (2j): Yield 64%; m.p. (^{0}C): 174; IR (KBr, cm^{-1}): 1746 (CO, *β*-lactam); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.6 (t, 4H, -CH_2-CH_2-); 3.5 (q, 2H, -CH-CO); 4.9 (d, 2H, -CH-N); 7.1-8.6 (m, 16H, Ar-H); 11.4 (s, 2H, COOH); Mass spectra, m/z = 650 (100%).

Results and discussion:

Bis (azetidin-2-ones) (**2a-j**) were prepared by [2+2] cycloaddition (Staudinger reaction) reaction of ketenes, generated *in situ* from adipoyl chloride using tertiary amines and imines derived from reaction of 3-nitrobenzaldehyde with various amines. The synthetic route for novel bis-azetidinone derivatives is presented in **Scheme 1**.



Scheme 1: Synthesis of bis-azetidinone (2a-j)

All the compounds synthesized were adequately characterized by their IR, ^{1}H NMR and Mass spectra. The substituents of the compounds are given in **Table 1**.

Antibacterial activities of all the compounds were tested against Gram positive bacteria (*Bacillus subtilis and Staphylococcus aureus*) and Gram negative bacteria (*E. coli* and *Klebsiella pneumoniae*) by measuring the zone of inhibition on agar plates [15]. The compounds possess moderate to good activity against all strains in comparison with standard drug (Ampicillin). The test results, presented in Table 2, suggest that compounds **2g**, **2h**, **2j** and **2b**, **2h**, **2j** are highly active against *S. aureus* and *E. coli* respectively. The rest of the compounds were found to be either moderately active, slightly active or inactive against the tested microorganisms.

Table 1. Substituents of compounds 1a-j and 2a-j.

Compd.	Substituent Ar
1a, 2a	*p*-$OCH_3C_6H_4$
1b, 2b	*p*-ClC_6H_4
1c, 2c	C_6H_5
1d, 2d	*m*-ClC_6H_4
1e, 2e	*p*-MeC_6H_4
1f, 2f	*p*-OHC_6H_4
1g, 2g	*m*-$NO_2C_6H_4$
1h, 2h	*p*-$NO_2C_6H_4$
1i, 2i	*o*-ClC_6H_4
1j, 2j	o-CO_2HC6H4

Table 2. Antimicrobial activities of Synthesized Compounds.

Compd	Zone of Inhibition (mm)			
	Gram Positive		Gram Negative	
	S. aureus	***B. subtilis***	***K. pneumoniae***	***E. Coli***
2a	+ +	+	+	+ +
2b	+	-	-	+ + +
2c	+ +	+ +	+ +	+ +
2d	+	+	+ +	+
2e	-	-	-	+
2f	-	-	-	+ +
2g	+ + +	+ +	+	+ +
2h	+ + +	+ +	+ +	+ + +
2i	+ +	-	-	+
2j	+ + +	+ +	+ +	+ + +
Ampicillin	+ + +	+ + +	+ + +	+ + +

Key to symbols: Inactive = - (inhibition zone < 6 mm); Slightly active = + (inhibition zone 6-9 mm); Moderately active = + + (inhibition zone 9-12 mm); Highly active = + + + (inhibition zone > 12 mm).

Conclusion:

In summary, we have described here a new approach for the preparation of biologically promising bis (β-lactam) derivatives. This methodology is based on the Staudinger reaction between a bis (ketene) and different substituted imines. From data of antimicrobial activity, it could be observed that compounds of the series, **2a-j** showing good comparable activity against standard drug.

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References

1. Fisher, J. F.; Meroueh, S. O.; Mobashery, S. Chem. Rev. 2005, 105, 395.
2. (a) N. H. Cromwell and B. Phillips, Chem. Rev. 1979, 79, 331.
3. (a) T. Okutani, T. Kaneko and K. Masuda, Chem. Pharm. Bull. 1974, 22, 1490; (b) J. Kobayashi, J. Cheng, M. Ishibashi, M. P. Walchli, S. Yamamura, Y. Ohizumi, J. Chem. Soc. Perkin Trans. 1, 1991, 1135. (c) J. Frigola, A. Torrens, J. A. Castrillo, J. Mas, D. Vano, J. M. Berrocal, C. Calvet, L. Salgado, J. Redondo, S. Garcra-Granda, E. Valenti and J. R. Quintana, J. Med. Chem. 1994, 37, 4195. (d) A. W. Bannon, M. W. Decker, M. W. Holladay, P. Curzon, D. Donnelly-Roberts, P. S. Puttfarcken, R. S. Bitner, A. Diaz, A. H. Dickenson, R. D. Porsolt, M. Williams, S. P. Arneric, Science 1998, 279, 77. (e) J. W. Daly, H. M. Garraffo, T. F. Spande, M. W. Decker, J. P. Sullivan and M. Williams, Nat. Prod. Rep. 2000, 17, 131. (f) A. K. Bose, M. S. Manhas, J. C. Kapur, S. D. Sharma, S. G. Amine, J. Med. Chem. 1974, 17, 54.
4. (a) Baldwin, J. Tetrahedron, 1983, 39, 2445; (b) van der Steen, F. H.; Van Koten, G. Tetrahedron, 1991, 47, 7503; (c) Miller, M. J. Tetrahedron 2000, 56, 5553; (d) Singh, G. S. Tetrahedron, 2003, 59, 7631; (e) Georg, G. I. Bioorg. Med. Chem. Lett. 1993, 3, 2157; (f) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Eur. J. Org. Chem. 1999, 3223; (g) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Curr. Med. Chem. 2004, 11, 1837; (h) Ojima, I. Acc. Chem. Res. 1995, 28, 383; (i) Mukerjee, A. K.; Srivastava, R. C. Synthesis 1973, 327; (j) Alcaide, B.; Almendros, P.; Aragoncillo, C. Chem. Rev. 2007, 107, 4437.
5. G. S. Singh, B.J. Mmolotsi, IL Farmaco, 2005, 60 (9), 727.
6. Ashok Kumar, C.S. Rajput, S.K. Bhati, Bioorg. Med. Chem. 2007, 15, 3089.
7. J. S. Biradar, S.Y. Manjunath, Indian J. Chem. 2004, 43B, 141.
8. J. M. Desai, V.H. Shah, Indian J. Chem. 2003, 42B, 631.
9. B. K. Banik, F.F. Becker, I. Banik, Bioorg. Med. Chem. 2004, 12 (10), 2523.
10. J. Anaya, D. S. Gero, M. Grande, J. I. M. Hernando, N. M. Laso, Bioorg. Med. Chem. 1999, 7 (5), 837.
11. G. Gerona-Navarro, M. J. Perez de Vega, M. T. Garcia-Lopez, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, R. Gonzalez-Muniz, J. Med. Chem. 2005, 48 (7), 2612.
12. C. Yoakim, W.W. Ogilvie, D. R. Cameron, C. Chabot, I. Guse, B. Hache , J. Naud, J.A. O'Meara, R. Plante, R. Deziel, J. Med. Chem. 1998, 41, 2882.
13. (a) K. Karupaiyan, V. G. Puranik, A. R. A. S. Deshmukh, B. M. Bhawal, Tetrahedron, 2000, 56, 8555. (b) Aarif L. Shaikh, Vedavati G. Puranik, A. R. A. S. Deshmukh, Tetrahedron, 2005, 61, 2441. (c) Natarajan Arumugam, Raghavachary Raghunathan, Tetrahedron Lett. 2006, 47, 8855.
14. Krishnaswamy, D.; Bhawal, B. M.; Deshmukh, A. R. A. S. Tetrahedron Lett. 2000, 41, 417.
15. Weber, A. D. and Sanders, C. S. Antimicrob Agents Chemother 1990, 34, 156.

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