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SHORT COMMUNICATION

**Synthesis of Biginelli products of thiobarbituric acids
and their antimicrobial activity**

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Abstract: A simple and efficient method has been developed for the synthesis of 2,4,7-tri(substituted)phenyl-2,4,8,10-tetraza-3,9-dithioxo-5-oxobicyclo[4.4.0]dec-1(6)-ene (**4**) and 2,4,7-tri(substituted)phenyl-2,4,8,10-tetraza-3-thioxo-5,9-dioxobicyclo[4.4.0]dec-1(6)-ene (**5**), by a one-pot, three-component cyclocondensation reaction of a 1,3 dicarbonyl compound (thiobarbituric acid), an aromatic aldehyde, and urea/thiourea using catalytic amount of concentrated HCl in refluxing ethanol. Representative samples were screened for their anti-microbial activity against the Gram-negative bacteria, *Escherichia coli* and *Proteus aeruginosa*, and the Gram-positive bacteria, *Staphylococcus aureus* and *Corynebacterium diphtheriae* using the disc diffusion method. The structures of the products were confirmed by IR, ¹H- and ¹³C-NMR spectroscopy, as well as by elemental analysis.

Keywords: aromatic aldehydes; dihydropyrimidine; thiobarbituric acid.

INTRODUCTION

The acid-catalyzed Biginelli reaction, which is a three-component reaction between an aldehyde, a β -ketoester and urea/thiourea, is a rapid and facile method for the synthesis of pyrimidones, which are interesting compounds with potential for pharmaceutical applications.

Pyrimidone products have been reported to possess biological activities such as anti-viral, anti-bacterial, anti-hypertensive and anti-tumor.¹ More recently pyrimidones have emerged as integral backbones of several calcium channel blockers.² Certain substituted 2-thiobarbituric acids have been used as intravenous anesthetics,³ anti-convulsants,⁴ immunotropic and anti-inflammatory compounds.⁵

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons.⁶ In times when premium is put on

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speed, diversity, and efficiency in the drug discovery process,⁷ MCR strategies offer significant advantages over conventional linear-type synthesis. MCR condensations involve three or more compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials. The search and discovery for new MCRs on the one hand,⁸ and the full exploitation of already known multicomponent reactions on the other are therefore of considerable current interest. One such MCR that belongs in the latter category is the venerable Biginelli dihydropyrimidine synthesis.

Over the past decade, dihydropyrimidin-2(1*H*)-ones and their derivatives have attracted considerable attention in organic and medicinal chemistry, as the dihydropyrimidine scaffold displays a fascinating array of pharmacological and therapeutic properties. They have emerged as integral backbones of several calcium channel blockers, antihypertensive agents, α -1 antagonists and neuropeptide Y (NPY) antagonists.⁹ Moreover, several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors. The scope of this pharmacophore has been further increased by the identification of the 4-(3-hydroxyphenyl)-2-thione derivative ($\pm$)-4i, called monastrol,¹⁰ as a novel cell-permeable lead molecule for the development of new anticancer drugs (Fig. 1).

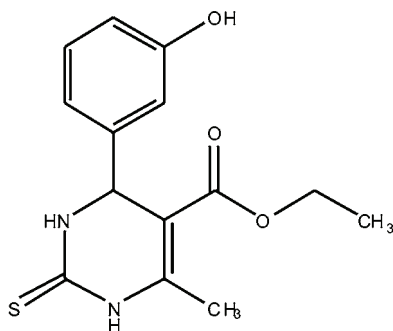


Fig. 1. The structure of monastrol.

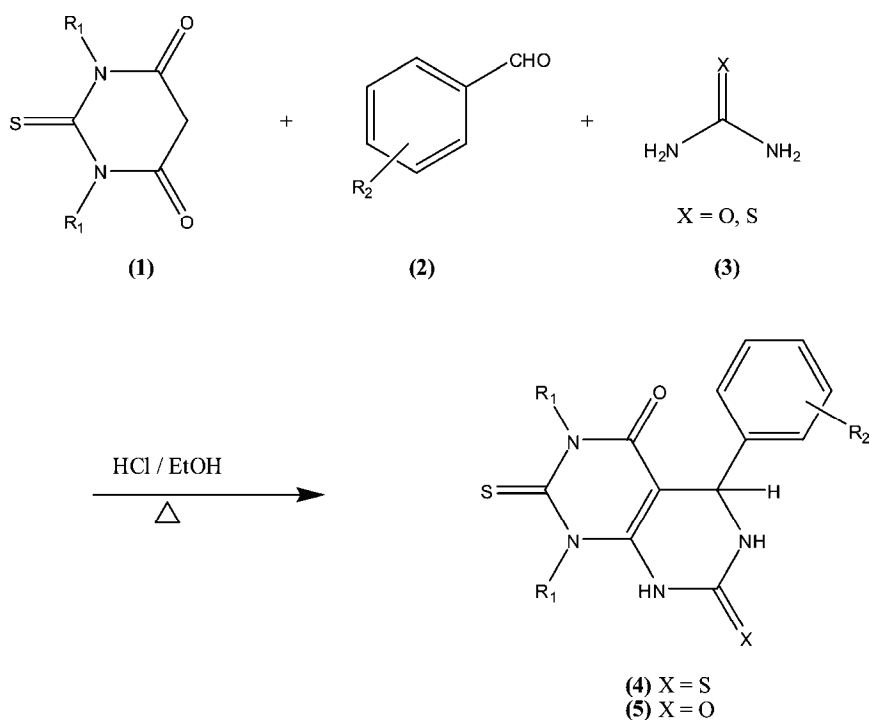
In 1893, the Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea.¹¹ The reaction was performed simply by heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one (DHPM).

Thiobarbituric acid derivatives are known to possess antibacterial activity,¹² some are claimed to be sedatives,¹³ and herbicides,¹⁴ while some are classified as antiviral agents.¹⁵

In addition, it was reported¹⁶ that the insertion of an aryl, amino, or a methyl moiety at 5-position of thiobarbituric acid enhances the antidepressant activities of the resulting compounds.

Bearing in mind the high synthetic utility and pharmacological importance, the synthesis of substituted pyrimidones (DHPMs) is reported herein.

Thus, the pharmacophoric activity of pyrimidones and thiobarbituric acid prompted the design and synthesis of 2,4,7-tri(substituted)phenyl-2,4,8,10-tetraza-3,9-dithioxo-5-oxo-bicyclo [4.4.0] dec-1(6)-ene (**4**) and 2,4,7-tri(substituted)phenyl-2,4,8,10-tetraza-3-thioxo-5,9-dioxo-bicyclo [4.4.0] dec-1(6)-ene (**5**) (Scheme 1).



Scheme 1. The synthesis of the compounds **4** and **5**.

RESULTS AND DISCUSSION

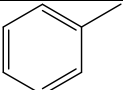
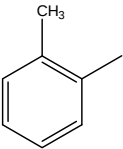
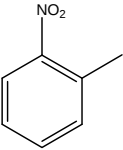
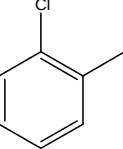
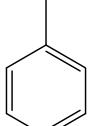
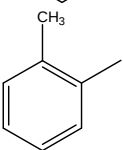
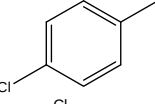
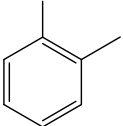
The original Biginelli protocol for the preparation of DHPMs consisted of heating a mixture of the three components thiobarbituric acid (β -keto-ester) (**1**), aromatic aldehyde (**2**), and urea/thiourea (**3**) in ethanol containing a catalytic amount of HCl.¹⁷ This procedure leads in one-step one pot to the desired DHMP.

The target molecules, 2,4,7-tri(substituted)phenyl-2,4,8,10-tetraza-3,9-dithioxo-5-oxobicyclo[4.4.0]dec-1(6)-ene **4(a-d)** and 2,4,7-(substituted)triphenyl-2,4,8,10-tetraza-3-thioxo-5,9-dioxobicyclo[4.4.0]dec-1(6)-ene **5(a-d)** were syn-

thesized in good yield by the one pot reaction of thiobarbituric acid, aromatic aldehydes, and urea/thiourea in refluxing ethanol using few drops of concentrated HCl as the catalyst. Compound **1** was prepared by the solid phase equimolar addition of thiocarbanilide,¹⁸ malonic acid and acetyl chloride.¹⁹

The physical characterization data of the derivatives of **4(a-d)** and **5(a-d)** are reported in Table I.

TABLE I. Characterization data of compounds **4** (X = S) and **5** (X = O)

Compound	R1	R2	M.p., °C	Yield, %
4a		<i>p</i> -OCH ₃	160	62
4b		<i>p</i> -Cl	88	67
4c		H	77	57
4d		<i>o</i> -OH	125	67
5a		<i>o</i> -OH	155	72
5b		<i>p</i> -OCH ₃	110	68
5c		<i>p</i> -OCH ₃	128	77
5d		<i>o</i> -OH	108	72

2,4-Diphenyl-7-p-methoxyphenyl-2,4,8,10-tetraza-3,9-dithioxo-5-oxobicyclo[4.4.0]dec-1(6)-ene (4a). Orange crystals; Anal. Calcd. for $C_{25}H_{20}N_4O_2S_2$: C, 63.56; H, 4.24; N, 11.86 %; Found: C, 63.54; H, 4.23; N, 11.84 %. IR (KBr, cm^{-1}): 1680, 1740, 3310. 1H -NMR (500 MHz, DMSO- d_6 , δ / ppm): 3.8 (3H, s, OCH₃), 4.4 (1H, s, CH), 6.8–7.8 (14H, m, Ar–H), 8.6 (1H, s, NH), 8.7 (1H, s, NH). ^{13}C -NMR (500 MHz, DMSO- d_6 , δ / ppm): 52.3 (C–H), 55.1 (OCH₃), 85.2 (C=C), 153.4 (C=C), 172.2 (C=O), 183.4 (C=S), 191.8 (C=S).

2,4-Di-o-methylphenyl-7-p-chlorophenyl-2,4,8,10-tetraza-3,9-dithioxo-5-oxobicyclo[4.4.0]dec-1(6)-ene (4b). Yellow crystals; Anal. Calcd. for $C_{26}H_{21}N_4OS_2Cl$: C, 61.84; H, 4.16; N, 11.10 %; Found: C, 61.82; H, 4.14; N, 11.09 %. IR (KBr, cm^{-1}): 1670, 1730, 3330. 1H -NMR (500 MHz, DMSO- d_6 , δ / ppm): 2.1 (3H, s, CH₃), 2.2 (3H, s, CH₃), 4.5 (1H, s, CH), 6.5–7.9 (12H, m, Ar–H), 8.8 (1H, s, NH), 8.9 (1H, s, NH). ^{13}C -NMR (500 MHz, DMSO- d_6 , δ / ppm): 31.2 (CH₃), 37.8 (CH₃), 54.3 (C–H), 79.2 (C=C), 152.1 (C=C), 162.3 (C=O), 178.4 (C=S), 201.1 (C=S).

2,4-Di-o-nitrophenyl-7-phenyl-2,4,8,10-tetraza-3,9-dithioxo-5-oxobicyclo[4.4.0]dec-1(6)-ene (4c). Brick red crystals, Anal. Calcd. for $C_{24}H_{16}N_6O_5S_2$: C, 54.13; H, 3.01; N, 15.79 %; Found: C, 54.11; H, 3.00; N, 15.78 %. IR (KBr, cm^{-1}): 1680, 1780, 3360. 1H -NMR (500 MHz, DMSO- d_6 , δ / ppm): 4.5 (1H, s, CH), 6.5–7.5 (13H, m, Ar–H), 7.9 (1H, s, NH), 8.1 (1H, s, NH). ^{13}C -NMR (?MHz, DMSO- d_6 , δ / ppm): 55.1 (C–H), 83.2 (C=C), 147 (C=C), 159.2 (C=O), 182.6 (C=S), 199.3 (C=S).

2,4-Di-o-chlorophenyl-7-(o-hydroxyphenyl)-2,4,8,10-tetraza-3,9-dithioxo-5-oxobicyclo[4.4.0]dec-1(6)-ene (4d). Light green crystals; Anal. Calcd. for $C_{24}H_{16}Cl_2N_4O_2S_2$: C, 54.65; H, 3.04; N, 10.63 %; Found: C, 54.63; H, 3.02; N, 10.61 %. IR (KBr, cm^{-1}): 1660, 1730, 3290. 1H -NMR (500 MHz, DMSO- d_6 , δ / ppm): 4.3 (1H, s, CH), 5.6 (1H, s, OH), 6.5–7.8 (12H, m, Ar–H), 8.4 (1H, s, NH), 8.7 (1H, s, NH). ^{13}C -NMR (500 MHz, DMSO- d_6 , δ / ppm): 52.4 (C–H), 82.2 (C=C), 154.3 (C=C), 166.4 (C=O), 182.4 (C=S), 200.5 (C=S).

2,4-Diphenyl-7-(o-hydroxyphenyl)-2,4,8,10-tetraza-3-thioxo-5,9-dioxobicyclo[4.4.0]dec-1(6)-ene (5a). Red crystals; Anal. Calcd. for $C_{24}H_{18}N_4O_3S$: C, 70.24; H, 4.39; N, 13.66 %; Found: C, 70.23; H, 4.37; N, 13.64 %. IR (KBr, cm^{-1}): 1660, 1750, 3290. 1H -NMR (500 MHz, DMSO- d_6 , δ / ppm): 4.4 (1H, s, CH), 4.7 (1H, s, OH), 6.5–7.7 (14H, m, Ar–H), 8.6 (1H, s, NH), 8.9 (1H, s, NH). ^{13}C -NMR (500 MHz, DMSO- d_6 , δ / ppm): 59.6 (C–H), 87.1 (C=C), 155.3 (C=C), 163.2 (C=O), 168.3 (C=O), 179.1 (C=S).

2,4-Di-o-methylphenyl-7-(p-methoxyphenyl)-2,4,8,10-tetraza-3-thioxo-5,9-dioxobicyclo[4.4.0]dec-1(6)-ene (5b). Orange crystals, Anal. Calcd. for $C_{27}H_{24}N_4O_3S$: C, 66.94; H, 4.96; N, 11.57 %; Found: C, 66.92; H, 4.95; N, 11.55 %. IR (KBr, cm^{-1}): 1680, 1770, 3330. 1H -NMR (500 MHz, DMSO- d_6 , δ / ppm): 2.1 (3H, s, CH₃), 2.4 (3H, s, CH₃), 3.9 (1H, s, OCH₃), 4.5 (1H, s, C–H), 6.5–7.9 (12H, m,

Ar-H), 9.2 (1H, s, NH), 9.8 (1H, s, NH). ^{13}C -NMR (500 MHz, DMSO- d_6 , δ / ppm): 31.2 (CH_3), 33.1 (CH_3), 56.6 (C-H), 58.3 (OCH_3), 87.4 (C=C), 147.4 (C=C), 171.9 (C=O), 187.7 (C=O), 200.8 (C=S).

2,4-Di-p-chlorophenyl-7-(2'-hydroxy-4'-methoxyphenyl)-2,4,8,10-tetraza-3-thioxo-5,9-dioxobicyclo[4.4.0]dec-1(6)-ene (5c). Orange crystals, Anal. Calcd. for $\text{C}_{25}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_4\text{S}$: C, 55.45; H, 3.33; N, 10.35 %; Found: C, 55.42; H, 3.31; N, 10.33 %. IR (KBr, cm^{-1}): 1650, 1780, 3340. ^1H -NMR (500 MHz, DMSO- d_6 , δ / ppm): 3.9 (1H, s, OCH_3), 4.5 (1H, s, C-H), 6.8–7.8 (11H, m, Ar-H), 8.3 (1H, s, NH), 8.9 (1H, s, NH), 9.8 (1H, s, OH). ^{13}C -NMR (500 MHz, DMSO- d_6 , δ / ppm): 56.3 (C-H), 62.1 (OCH_3), 63.3 (C=C), 152.2 (C=C), 163.7 (C=O), 167.1 (C=O), 187.3 (C=S).

2,4-di-o-chlorophenyl-7-(o-hydroxyphenyl)-2,4,8,10-tetraza-3-thioxo-5,9-dioxobicyclo[4.4.0]dec-1(6)-ene (5d). Purple crystals; Anal. Calcd. for $\text{C}_{24}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_3\text{S}$: C, 56.36; H, 3.13; N, 10.96 %; Found: C, 56.35; H, 3.11; N, 10.94 %. IR (KBr, cm^{-1}): 1680, 1730, 3330. ^1H -NMR (500 MHz, DMSO- d_6 , δ / ppm): 4.6 (1H, s, CH), 6.7–7.9 (12H, m, Ar-H), 8.3 (1H, s, NH), 8.8 (1H, s, NH). ^{13}C -NMR (500 MHz, DMSO- d_6 , δ / ppm): 55.5 (C-H), 83.7 (C=C), 157.2 (C=C), 159.2 (C=O), 164.3 (C=O), 191.3 (C=S).

Antimicrobial and antifungal activities

The activities of representative compounds are reported in Table II.

TABLE II. Antibacterial activity of compounds 4 and 5

Compound	Zone of inhibition, mm			
	Gram-positive		Gram-negative	
	<i>S. aureus</i>	<i>C. diphtheria</i>	<i>P. aeruginosa</i>	<i>E. coli</i>
4a	22	25	22	27
4b	21	26	25	28
4c	19	20	22	23
4d	21	27	28	32
5a	20	22	30	29
5b	15	17	22	23
5c	13	16	25	25
5d	22	23	20	24
Ampiciline trihydrate	26	28	24	21
DMSO	0	0	0	0

EXPERIMENTAL

The melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as the adsorbent and UV light as the visualizing agent. The ^1H -NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $\text{CDCl}_3/\text{DMSO}-d_6$ as solvent and TMS as an internal standard. The C, H, N estimations were recorded on Carlo Erba 1108 (CHN) elemen-

tal analyzer. ^{13}C -NMR was performed on a Varian 500 MHz spectrophotometer using $\text{DMSO}-d_6$ as solvent and IR was performed on PerkinElmer Spectrum 100 FT-IT using a KBr pellet.

Synthesis of 3,4-dihydropyrimidin-2(1H)-ones

Aromatic aldehydes (0.050 mol), substituted thiobarbituric acid (0.050 mol) and urea/thiourea (0.050 mol) were dissolved in ethanol and the mixture refluxed on a water bath in the presence of a catalytic amount of concentrated HCl. The progress of the reaction was monitored by TLC. After completion of the reaction, the concentrated reaction mixture was cooled and poured onto ice-cold water. The solid that separated was filtered off, dried, and recrystallized from absolute alcohol to obtain the pure compounds **4** and **5**.

Antimicrobial and antifungal activities

The newly synthesized compounds **4(a-d)** and **5(a-d)** were screened for their antibacterial activity against *Staphylococcus aureus* (ATTC-27853), *Corynebacterium diphtheria* (ATTC-11913), *Proteus aeruginosa* (recultured) and *Escherichia coli* (ATTC-25922) bacterial strains by the disc diffusion method.^{20,21} Discs (6 mm) were prepared from Whatman filter paper No. 41 and used after autoclaving at 121 psi for 15 min and drying in a hot air oven. The bacterial inoculums equivalent to the 0.5 McFarland turbidity standard were prepared in normal saline and subsequently diluted. The compounds were dissolved in DMSO and tested at a concentration of $100\text{ }\mu\text{g ml}^{-1}$. The zone of inhibition after 24 h incubation was measured in mm and the potency was compared with standard drug (ampiciline trihydrate).

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ИЗВОД

СИНТЕЗА BIGINELLI-ЈЕВИХ ПРОИЗВОДА ТИОБАРБИТУРНИХ КИСЕЛИНА И ЊИХОВА АНТИМИКРОБНА АКТИВНОСТ

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Развијен је једноставан и ефикасан метод за синтезу 2,4,7-три(супституисаног)фенил-2,4,8,10-тетраза-3,9-дитиоксо-5-оксобицикло[4.4.0]дец-1(6)-ена (**4**) и 2,4,7-три(супституисаног)фенил-2,4,8,10-тетраза-3-тиоксо-5,9-диоксобицикло[4.4.0]дец-1(6)-ена (**5**), једнофазном трикомпонентном циклокондензационом реакцијом 1,3-дикарбонилног једињења (тиобарбитурне киселине), ароматичног алдехида и урее/тиоурее, користећи каталитичку количину концентроване HCl у рефлукујућем етанолу. Одабрани узорци тестирани су на анти-микробну активност према грам-негативним бактеријама, *E. coli* и *P. aeruginosa*, и грам-позитивних бактерија, *S. aureus* и *C. diphtheriae*, применом диск-дифузионог поступка. Структуре производа су потврђене помоћу IR, ^1H , ^{13}C -NMR и елементалне анализе.

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REFERENCES

1. a) D. W. McKinstry, E. H. Reading, *J. Frankin Inst.* **237** (1994) 422; b) T. Matsuda, I. Hirao, *Nippon Kagaku Zasshi* **86** (1965) 1195

2. T. Takatani, H. Takasugi, A. Kuno, Z. Inoue, *Chem. Abstr.* **108** (1988)159930
3. W. J. Doran, in *Medicinal Chemistry*, Vol. 4, F. F. Blicke, R. H. Cox, Eds., Wiley, New York, 1959, p. 5
4. A. Dhasmana, J. P. Barthwal, B. R. Pandey, B. Ali, K. P. Bhargava, S. S. Parmer, *J. Heterocyclic Chem.* **18** (1981) 635
5. T. Zawisza, H. Matczak, S. H. Bronisz, T. Jakobiec, *Pol. Arch. Immunol. Ther. Exp.* **29** (1981) 235
6. Passerini three-component and Ugi four-component condensations are the most popular among many other reactions for their wide scope and synthetic utility. For reviews, see: a) H. Bienayme, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **6** (2000) 3321; b) A. Domling, I. Ugi, *Angew. Chem. Int. Ed.* **39** (2000) 3168
7. a) S. L. Schreiber, *Science* **287** (2000) 1964; b) R. E. Dolle, K. H. J. Nelson, *Comb. Chem.* **1** (1999) 235; c) D. Obrecht, J. M. Villalgordo, in *Solid-Supported Combinatorial and Parallel Synthesis of Small – Molecular-Weight Compounds Libraries*, J. E. Baldwin, R. M. Williams, Eds., Pergamon Press, New York, 1998
8. L. Weber, K. Illgen, M. Almstetter, *Synlett.* **3** (1999) 366
9. a) K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie, M. F. Malley, *J. Med. Chem.* **33** (1990) 2629; b) G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. DiMarco, J. Z. Gougoutas, A. Hedberg, M. F. Malley, J. P. Zhang, S. Moreland, *J. Med. Chem.* **38** (1995) 119, and references therein
10. T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber, T. J. Mitchison, *Science* **286** (1999) 971
11. P. Biginelli, *Gazz. Chim. Ital.* **23** (1893) 360
12. a) L. K. Akopyan, A. S. Adzhibekyan, G. A. Porkinyan, E. A. Tumasyan, *Bilzh. Arm.* **29** (1976) 80; b) L. K. Akopyan, A. S. Adzhibekyan, G. A. Porkinyan, E. A. Tumasyan *Chem. Abstr.* **85** (1976) 72068
13. a) S. Senda, H. Fugimura, H. Izumi, Japan Patent 193,6824, 1968; S. Senda, H. Fugimura, H. Izumi, *Chem. Abstr.* **70** (1969) 78001
14. a) S. L. Katz, A. W. Gay, U.S. Patent 352,806, 1982; S. L. Katz, A. W. Gay, *Chem. Abstr.* **98** (1983) 215603
15. a) W. G. Brouwer, E. E. Felauerand, A. R. Bell, U.S. Patent 779,982, 1990; W. G. Brouwer, E. E. Felauerand, A. R. Bell, *Chem. Abstr.* **114** (1991) 185539; c) A. Esanu, BE Patent 902,232, 1985; d) A. Esanu *Chem. Abstr.* **104** (1986) 130223
16. V. Singh, R. Khanna, V. K. Srivastava, G. Palit, K. Shanker, *Arzneim-Forsch.* **42** (1992) 277
17. a) C. O. Kappe, *Tetrahedron* **49** (1993) 6937, and references cited therein; b) C. O. Kappe, *Acc. Chem. Res.* **33** (2000) 879
18. A. I. Vogel, *The Text Book of Practical Organic Chemistry*, 4th ed., ELBS/Longmann, Harlow, 1984, p. 735
19. I. N. D. Dass, S. Dutt, *Proc. Indian. Acad. Sci.* **8A** (1938) 145
20. R. Cruickshank, J. P. Duguid, B. P. Marmion, *Medicinal Microbiology*, Vol. 11, 12th ed., Churchill Livingstone, London, 1975
21. B. A. Arthington-Skaggs, M. Motley, C. J. Morrison, *J Clin Microbiol.* **38** (2000) 2254.

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