Pharmacological Importance of Bridgenitrogen Containing Heterocycles and Its Different Synthetic Method

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Abstract:
Bridge nitrogen containing fused heterocycles represents important building blocks in both natural and synthetic bioactive compounds which have been shown to possess diverse therapeutic activities.The biological activities of aza-indolizine in all therapeutic targetsand its synthetic method by various groups have been descried in this article.

Keywords: *Aza-indolizine, Heterocyclic chemistry, Medicinal chemistry, Nitrogen containing bridge heterocycle, Synthesis of aza-indolizine*

1. Introduction

Bridge nitrogen containing fused heterocycles represents important building blocks in both natural and synthetic bioactive compounds which have been shown to possess diverse therapeutic activities.[1] Hence they are interesting target for research as therapeutically important heterocyclic entities. Aza-indolizine are of two types, imidazo[1,2-*a*]pyridine and imidazo[1,5-*a*]pyridine (Figure-1).

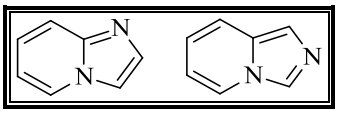


Figure 1

The aza-indolizine containing a phenyl ring fused to a imidazole ring is indicated in the structure, hence it is also known as imidazo[1,2-*a*]pyridine.[2] Several procedure for their synthesis have been extensively studied. Such studies have been stimulated by various promising applications, especially in the case of bridgehead nitrogen containing fused heterocyclic entities. The constitution of imidazo[1,2-*a*]pyridine was reviewed by W. L. Mosby[3] in 1961. imidazo[1,2-*a*]pyridine derivatives not only known for their pharmacological applications, they are also used in disperse dyes.[4]

2. Pharmacology

Imidazo[1,2-*a*]pyridines are potential bioactive agents due to their wide spectrum of therapeutic importance. A large number of substituted imidazo[1,2-*a*]pyridine derivatives are prepared and tested for varieties of biological activities such as,

Table 1. Inhibition of p-38-MAP Kinase by Acetylaminopyridines

1. Anti-inflammatory, analgesic, antipyretic[5,6]	6. Anthelmintic[13]	11. Hypnoselective and anxioselective[21]	16. Cardio tonic agents[26]
2. Antiviral[7,8]	7. Anti bacterials[14,15]	12. β-Amyloid formation inhibitors[22]	17. Anticytomegalo-zoster and antivaricellazoster virus[27-29]
3. Antianxiety[9]	8. Hypnotic[16]	13. Benzodiazepine	18. Long-acting local

		receptor agonists[23]	anesthetic[30]
4. Antiulcer[10,11]	9. Antiherpetie[17,18]	14. Nonsedative anxiolytic[24]	19. Calcium channel blockers[31]
5. Antifungal agents[12]	10. Gastric antisecretory[19,20]	15. Active nonpeptide bradykinin B2 receptor antagonists[24]	

Alexander C. Humphries and *et al*[32] have synthesized 8-fluoro imidazo[1,2-*a*]pyridine derivatives (Figure-2) and evaluated as a bioisosteric replacement for imidazo[1,2-*a*]pyridine in an allosteric modulator ligand of the GABAA receptor. Kristjan S. Gudmundsson and co-workers[33] reported the synthesis and antiviral activity of newer erythrofuranosyl imidazo[1,2-*a*]pyridine C-nucleosides. I. Aramori *et al*.[34] have been synthesized imidazo[1,2-*a*]pyridine derivatives which are highly potent and selective non-peptide bradykinin receptor antagonist (Figure-2).

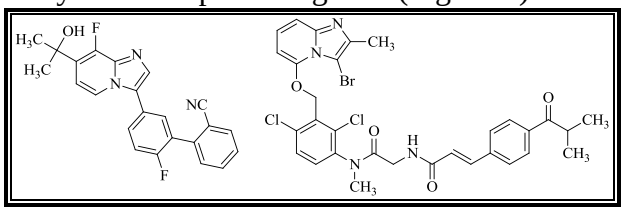


Figure 2

Several imidazo[1,2-*a*]pyridine nucleus already in market which include alpidem[35] [a ligand of both the central benzodiazepine receptors and the peripheral type (Mitochondrial) benzodiazepine receptor] has sedative and anxiolytic properties and zolpidem[35] [a selective ligand for the central benzodiazepine receptor] is a hypnotic drug (Figure-3). Both alpidem and zolpidem have higher affinity for benzodiazepine than for benzodiazepine-2 receptors[36] and their interaction with various receptors has been repoted.[37]

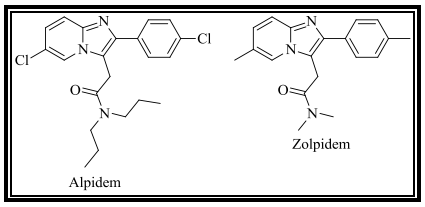


Figure 3

James J. Kaminski *et al*[38] have investigated imidazo[1,2-*a*]pyridine derivative 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (Figure-4) for an antiulcer activity. On the basis of the reported metabolism of zolimidine, they reported that the 3-cyanomethyl and 8-phenylmethoxy group have been established as metabolic sites.

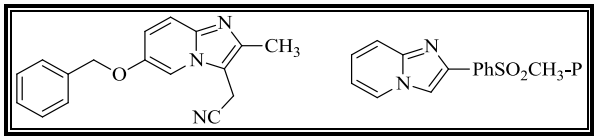


Figure 4

Brian A. Johns *et al*.[39] and Chaouni-Bendallah A. *et al*.[40] synthesized a novel imidazo[1,2-*a*]pyridines (Figure-5) with potent activity against herpes simplex viruses. Sophic Ceard *et al*[41] have synthesized some newer imidazo[1,2-*a*]pyridine derivatives (Figure-5) as bioactive agent. Imidazo[1,2-*a*]pyridine units appear as important building blocks in both natural and synthetic bioactive compounds[42-44] and recognition on DNA binding and to yield different pharmacokinetic profile.

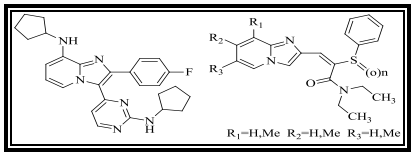


Figure 5

Mohamed A. Ismail *et al*[45] have synthesized some newer diamine imidazo[1,2-*a*]pyridine (Figure-6), 5,6,7,8-tetrahydo imidazo[1,2-*a*]pyridines and their corresponding *N*-hydroxy and *N*-methoxy analogues and evaluated against Trypanosoma B. Rhodesiense (T. B. Rhodesiense) and Plasmodium Falciparum (P. Falciparum). Aromatic diamidines exhibit broad spectrum antimicrobial activity including effectiveness against the protozoan disease caused by Trypanosoma SP and Plasmodium SP.[46]

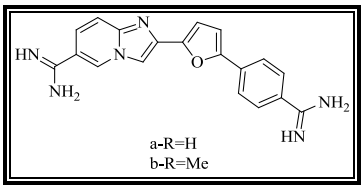


Figure 6

3. p38 MAP (Mitogen-activated protein) kinase

Laufer *et. al.*[47] reported a series of polysubstituted pyridin-4-yl imidazole inhibitors of p38 MAP kinase which was prepared as small molecular anticytokine agents and drug candidates for the treatment of chronic inflammatory diseases. The contribution of substituents at the pyridine and imidazole moiety to selective inhibition of p38 without concomitant cytochrome P450 interaction was evaluated. Placement of a 1-phenylethyl (p38: IC_{50} 0.38 µM) or acetyl substituent at the exocyclic nitrogen of several 2-aminopyridine imidazoles led to the identification of potent p38 inhibitors which exceeded the starting lead ML 3375 (p38: IC_{50} 0.63 µM) in potency (Figure-7).

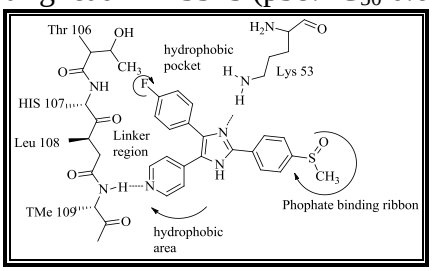


Figure 7. Schematic drawing of important interactions between the prototypicalpyridine-4-yl imidazole inhibitor of SB 203580 and the ATP binding site of p38

A preliminary modeling study related the enhanced bioactivity of 1-phenylethyl substituent to a novel interaction between its 1-phenylethylamino side chain and a hydrophobic pocket close to the linker region of p38. The most active p38 inhibitors in this series maintained their efficacy in functional PBMC (peripheral blood mononuclear cells) and whole blood assays (Figure-8).

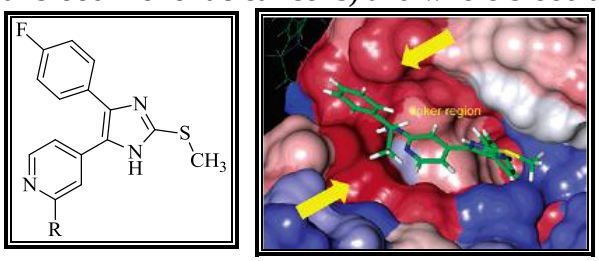


Figure 8. Banzylsulfulfanylimdazoles and modeling of 7g into the ATP cleft of p38 MAP Kinase. The arrows denote the hydrophobic area in close proximity to the linker region which stretches both above and below the pyridine ring

Laufer *et al*[48] then prepared novel 1,2,4,5-tetrasubstituted imidazole derivatives with high anti-inflammatory activity. Systematic optimization of the imidazole *N*-1 substituent resulted in a compound that potently inhibited the mitogen activated protein kinase p38 (p38 IC_{50}) 0.218 μM) as well as the release of the proinflammatory cytokines interleukin-1α (L-1α) and tumor necrosis factor R (TNFR) from human whole blood after stimulation with LPS. Furthermore, this compound exhibited reduced cytochrome P450 interaction in comparison with SB203580. This result is particularly important, since cytochrome P450 interaction is observed for some p38 inhibitors and in

turn can potentially cause drug-drug interaction or lead to other hepatic changes such as P450 enzyme induction (Figure-9).

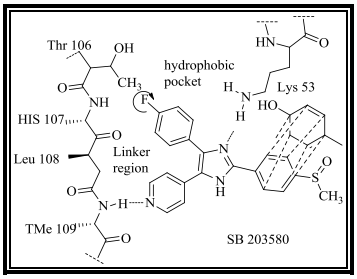


Figure 9. Representation of the active site interactions between SB 203580 and p38-MAPK

A new therapeutic drug target for the treatment of inflammatory disorders is the mitogen-activated protein kinase (MAPK) p38.[49-52] P38 is a serine/threonine kinase that is part of the stress-activated signal transduction cascade that transducers extracellular signals to intracellular response, *e.g.* cytokine production.[53,54] Activated p38 phosphorylates other kinases or transcription factors, leading to mRNA stabilization or expression of certain target genes.[55-57]

Pyridinylimidazoles (*i.e.* SB203580) are potent and selective inhibitors of p38-MAPK7[58,59] by competing with ATP for binding to the ATP pocket.[60-62] This small hydrophobic pocket near the ATP-binding site is responsible for the selectivity of SB203580 for p38 compared to most other kinases.[63,64] The pyridin-4-yl moiety is essential for the inhibitory potency and generates a pivotal hydrogen bond with the amino backbone of Met109 through its pyridinium nitrogen[65] (Figure-10).

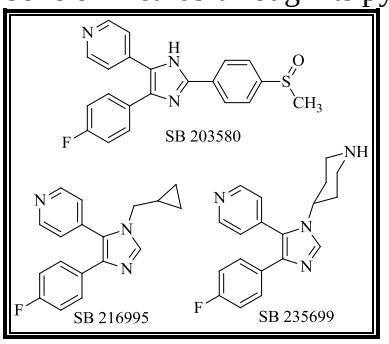
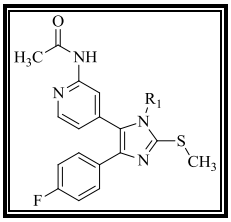


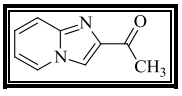
Figure 10. Pyidinylimidazole inhibitors of p-38-MAP kinase



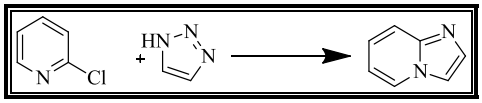
4. Synthetic methods

Classical methods have been reported in the literature for the synthesis of imidazo[1,2-*a*]pyridines. The procedure for synthesizing imidazo[1,2-*a*]pyridines have been described as under. The synthesis of imidazo[1,2-*a*]pyridine from 2-aminopyridine with α-bromoacetophenone was reported by Tschitschibabine.[66]

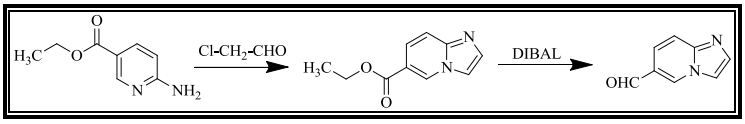
2-Acetylimidazo[1,2-*a*]pyridine[67] can be constructed by the cyclocodensation of 2-aminopyridine with bromo butanedione.



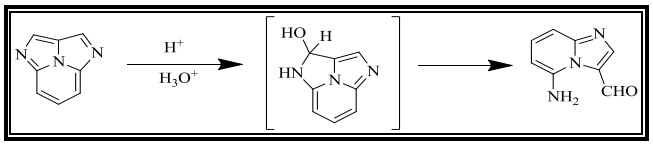
Reaction of 2-chloropyridine with 1,2,3-triazoles and subsequent elimination of nitrogens give the imidazo[1,2-*a*]pyridine.[68]



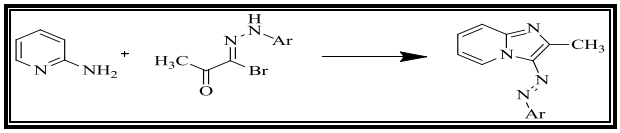
Condensation of ethyl-6-aminonicotinate with chloroacetaldehyde according to Hand's procedure gave imidazo[1,2-*a*]pyridine-6-carbaldehyde.[69]



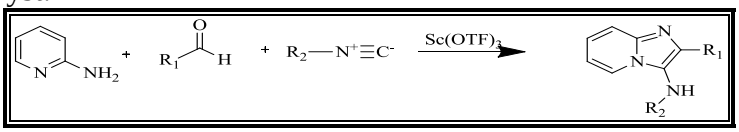
Paudler *et al.*[70] have synthesized 5-amino-3-formylimidazo[1,2-*a*]pyridine from acid catalyzed hydrolysis of 1,4-diazacycl[3,2,2]azine.



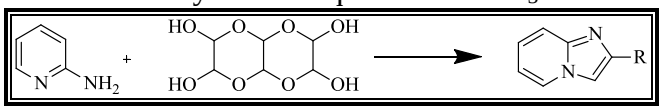
Imidazo[1,2-*a*]pyridine[71] nucleus can be also synthesized by the reaction of α-ketohydrazidoyl halide with heterocyclic amines.



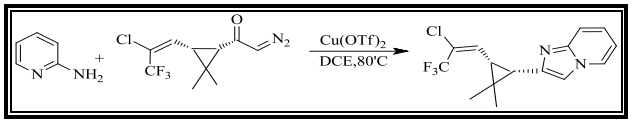
Tsai *et al.*[72] have been prepared 3-amino imidazo[1,2-*a*]pyridine derivatives by a three component condensation reaction between 2-aminopyridine, aldehyde and isonitrile in the presence of scandiumtriflate as a catalyst.



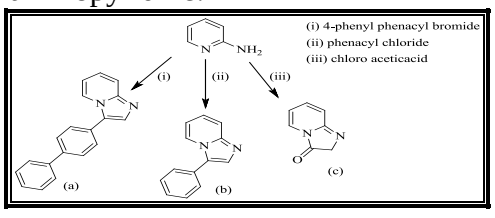
Groziak *et al.*[73] have synthesized substituted imidazo[1,2-*a*]pyridine derivatives by the condensation of 2-aminopyridine with glyoxal trimer dehydrate in aqueous $NaHSO_3$.



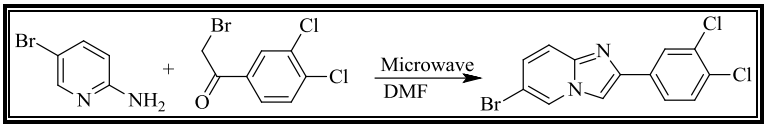
Synthesis of $Cu(OTf)_2$-catalyzed imidazo[1,2-*a*]pyridines from α-diazoketones and 2-aminopyridines by J. S. Yadav.[74]



Jumat Salimon et al.[75] synthesized imidazo[1,2-*a*]pyridine-3(2*H*)-one & 3-substituted-4-yl imidazo[1,2-*a*] pyridine from 2-aminopyridine.



Shankarappa A Biradar[76] have synthesized 6-bromo-2-(3,4-dichlorophenyl) imidazo[1,2-*a*]pyridine using microwave irradiation from 5-bromo-2-aminopyridine and 2-bromo-1-(3,4-dichlorophenyl) ethanone.



Reference

1. A. Abdelhamid, H. Hassaneen, A. Shawli., J. Heterocyclic Chem., 1983, 20, 639.
2. A. Chaouni, C. Galtier, H. Allouchi, C. Teulade., Chem. Pharma. Bull., 2001, 49, 1631.

3. A. Elhakmaoui, A. Gueiffier, C. Milhavet, E. Declercq., Bioorg. Med. Chem. Lett., 1994, 4, 1937.
4. A. Hubert, H. Reimlinger., Chem. Ber., 1970, 103, 3811.
5. A. Humphries, E. Ganeia, M. Gilligan., Bioorg. & Med. Chem. Lett, 2006, 16(6), 1518.
6. A. Laufer, K. Wagner, A. Kotschenreuther, W. Albrecht., J. Med. Chem. 2003, 46, 3230.
7. A. Laufer, W. Zimmermann, J. Ruff., J. Med. Chem. 2004, 47, 6311.
8. A. Montgomery, A. Secrist., Comprehensive Heterocyclic Chemistry; R. Katrisky, W. Rees, T. Potts, Eds; Pergamon; Oxford, 1984, 5, 607.
9. A. Wafford, J. Whitting, A. Kemp., Mol. Pharmocol., 1993, 43, 240; Chem. Abstr., 1996, 118, 77084.
10. B. Dubinsky, A. Shriver, E. Rosenthale., Drug. Dev. Res., 1990, 21, 277.
11. B. Townsend, C. Drach., WO, 27, 205 (1997); Chem. Abstr., 1997, 127, 190983j.
12. C. Bendallah, C. Galtier, C. Teulade., Chem. Pharm. Bull., 2001, 49, 1631.
13. C. Blackburn, B. Guan, S. Tsai., Tet. Lett, 1998, 39(22), 3655.
14. C. Boehm, L. Adams., Expert Opin. Ther. Patents 2000, 10, 25.
15. C. Faure-Hally, D. Graham, S. Arbilla, Z. Langer., Eur. J. Pharmocol. ol. Pharmacol. Sect., 1993, 246, 283.
16. C. Hamdouchi, J. Blass, M. Prade, L. Vance., J. Med. Chem., 1999, 42, 50.
17. C. Jean-Michel, J. Paeshuyse, G. Vincent, C. Damien, M. Aurelie, L. Claire, G. Alain, M. Emmanuel., European Journal of Medicinal Chemistry, 2010, 45(5), 2044.
18. C. Lee, S. Kassis, S. Kumar, A. Badger, L. Adams., Pharmacol. Ther. 1999, 82, 389.
19. C. Lee, S. Kumar, E. Griswold, C. Underwood, J. Votta, L. Adams., Immunopharmacology, 2000, 47, 185.
20. C. Teulade, G. Grassy, P. Girard, P. Chapat., Eur. J. Med. Chem., 1978, 13, 271.
21. D. Dvey, W. Erhardt, W. Lumma, E. Cantor., J. Med. Chem., 1987, 30(8), 1337.
22. E. Abignente, F. Arena, E. Luraschi, C. Saturnino, F. Rossi., Rend. Atti. Accad. Sci. Med. Chir., 1985, 139, 313; Chem. Abstr., 1986, 105, 126822z.
23. E. Abignente., Actual. Chim. Ther., 1991, 18, 193; Chem. Abstr., 1991, 115, 256028n.
24. E. Starrett, A. Montzka, L. Cavanagh., J. Med. Chem., 1989, 32, 2204 .
25. E. Tschitschibabine; Ber., 1925, 58, 1704.
26. F. Karci, A. Demircali., Dyes and Pigments, 2006, 71(2), 97.
27. G. Bartholini., L. Monogr. Ser., 1993, 8, 1; Chem. Abstr., 1996, 124, 164079n.
28. G. Pearson, F. Robinson, B. Gibson, E. Xu, M. Karandikar, K. Berman, H. Cobb., Endocr. Rev. 2001, 22, 153.
29. G. Salituro, A. Germann, P. Wilson, W. Bemis, T. Fox, M. Su., Curr. Med. Chem. 1999, 6, 807.
30. H. Fischer, A. Lusi., J. Med. Chem., 1972, 15, 982.
31. H. Taleb, R. Al-Qawasmeh., European journal of medicinal chemistry, 2010, 45(12), 5848.
32. I. Aramori, J. Zenkoh, N. Morikawa, Y. Notsu., Mol. Pharmacol., 1997, 51, 171.
33. J. Gum, M. McLaughlin, S. Kumar, Z. Wang, J. Bower, C. Lee, L. Adams, P. Livi, J. Goldsmith, R. Young., J. Biol. Chem. 1998, 273, 15605.
34. J. Joule, K. Mills., Heterocyclic Chemistry 4th Ed.492.
35. J. Kaminnski, A. Bristol, T. Mcphail., J. Med. Chem., 1985, 28, 876.
36. J. Kaminnski, M. Doweyko., J. Med. Chem., 1997, 40, 427.
37. J. Kaminski, G. Perkins, D. Frantz, J. Long., J. Med. Chem., 1987, 30, 2047.
38. J. Lisnock, A. Tebben, B. Frantz, A. O'Neill, G. Croft, J. O'Keefe, B. Li, C. Hacker, S. Laszlo, A. Smith, B. Libby, N. Liverton, J. Hermes, P. LoGrasso., Biochemistry, 1998, 37, 16573.
39. J. Raingeaud, S. Gupta, S. Rogers, M. Dickens, J. Han, J. Ulevitch, R. Davis., J. Biol. Chem. 1995, 270, 7420.
40. J. Salimon, N. Salih, H. Hussien, E. Yousif., Eur. J. Sci. Research, 2009, 31(2), 256.
41. J. Sanfilippo, M. Urbanski, B. Moore., J. Med. Chem. , 1998, 31, 2221.
42. J. Silvestre, P. Leeson, J. Castaner., Drugs Fut., 1998, 23, 598.
43. J. Sundberg, S. Biswas, K. Murthi, D. Rowe., J. Med. Chem., 1998, 41, 4317.
44. J. Yadav, B. Subba Reddy, Y. Gopal Rao, M. Srinivas, A. Narsaiah., Tet. Lett., 2007, 48, 7717.
45. K. Fuchs, M. Romig, K. Mendla, H. Briem, K. Fechteler; WO, 2002, 14 313,; Chem. Abstr., 2002, 136, 183824r.
46. K. Gudmundsson, B. Johns., Org. Lett., 2003, 5(8), 1369.
47. K. Gudmundsson, J. Williams, L. Townsend., J. Med. Chem., 2003, 46, 1449.
48. K. Wilson, G. McCaffrey, K. Hsiao, S. Pazhinisamy, V. Galullo, G. Bemis, M. Fitzgibbon, P. Caron, M. Murcko, S. Su., Chem. Biol. 1997, 4, 423.
49. L. Tong, S. Pav, M. White, S. Rogers, M. Crane, L. Cywin, L. Brown, A. Pargellis., Nat. Struct. Biol. 1997, 4, 311.
50. Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heyes., J. R. Nature (London) 1994, 372, 739.
51. M. Groziak, S. Wilson, G. Clauson., J. Am. Chem. Soc., 1986, 108, 8002.
52. M. Ismail, R. Burn, D. Boykin., J. Med. Chem., 2004, 47, 3658.
53. M. Lhassani, O. Chavignon, A. Gueiffier., Eur. J. Med. Chem., 1999, 34, 271.
54. M. Mclay, F. Halley, E. Souness, J. McKenna, V. Benning, M. Birrell, B. Burton, M. Belvisi, A. Collis, A. Constan, M. Foster, D. Hele, Z. Jayyosi, M. Kelley., Bioorg. Med. Chem. 2001, 9, 537.
55. P. George, G. Rossey, B. Zivkovic; Eds., Raven Press Ltd.; New York, 1993, 49.
56. P. Kaplan, P. George., Eur. Patent 1982, 0050563; Chem. Abstr., 2002, 97, 149531a.