Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2014, 6(2):288-293
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and Characterization of Some New Dimeric Imines and Dispiro Bicyclo-γ-Lactam

Nesreen N.Majeed, Ali H.Esaa and Afaq. A. Turki*

** College of Science, University of Basrah, Basrah-Iraq*

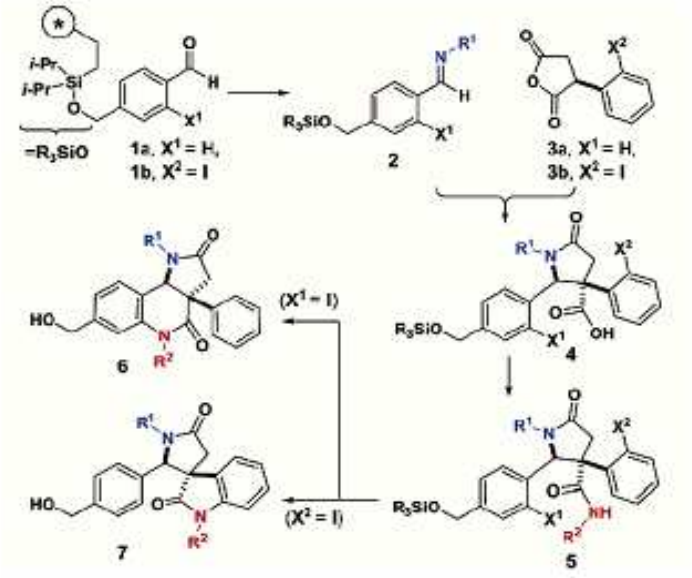
ABSTRACT

The reaction of 1,4-benzoquinone (14) with aniline and its derivatives (15-20) in the presence of a weak acid as a catalyst, afforded the corresponding dimeric imine derivatives (21-26). These compounds were treated with succinc anhydride to yield Dispiro Bicyclo-γ-Lactam compounds(27-32). The structures of these products were characterized by their elemental analysis (C.H.N.),FT-IR, ^{1}H NMR and ^{13}C NMR spectra.

INTRODUCTION

Efficient synthesis of stereo chemically defined, structurally small complex molecules is important for both diversity-oriented synthesis (DOS) and the target- directed synthesis of natural products and other biologically active compounds [1,2]. The success of small molecules libraries for chemical genetics relies on high levels of chemical diversity to elucidate new biological pathways using high-throughput phenotypic screening [3- 11].The synthesis of natural product targets remains an important tool for the elucidation of complex structures [12] and for the preparation of analogues [13] for biological studies. Our investigations strive to advance both goals by developing a methodology which offers a high level of flexibility for the synthesis of small molecules libraries as well as a high level of efficiency for the synthesis of complex targets.

The cycloaddition reaction between imines and cyclic anhydrides was discovered [14,15] and subsequently employed in a variety of natural product syntheses [16- 18]. Cushman's efforts focused mainly on the reactions of homophthalic anhydride and its derivatives, whereas the use of other substrates, substituted succinic anhydrides, was largely unexplored. We initiated a program to fully explore the synthetic potential of the imine anhydride cycloaddition as a mean to develop efficient routes to structurally diverse libraries of small molecules. During the course of these investigations, we made several observations regarding the reactivity and selectivity of this reaction which greatly increased the reaction's utility for the synthesis of small molecules libraries and target-oriented synthesis. In this Report, we disclosed our preliminary results in the development of pathways that are employed in the synthesis of a complex library of polycyclic lactams. We initially envisioned a short synthetic sequence that would produce structurally divergent core structures in a linear synthetic reaction sequence (Scheme 1).



Scheme1. Synthetic plan for structurally divergent library

We planned to condense aldehydes **1a** and **1b** with a variety of amines, which would be subsequently used in a cycloaddition reaction with succinic anhydrides **3a** and **3**b. The reaction partners would be segregated such that each lactam product possessed only one iodine substituent, originating from either the aldehyde or the anhydride. These substrates would be pooled and splited into amide formation reactions using primary amines. Finally, these iodoaryl amides would be cyclized to form either fused or spirocyclic products, depending on where the iodide was located [19]. Thus, the structural complexity that emerges from this sequence emanates from the strategic placement of key functional groups which undergo a reaction that defines the three-dimensional array of the products, in analogy to another library recently published from our laboratories [20]. This three-step sequence would provide diverse products reminiscent of a variety of bioactive small molecules of natural and unnatural origin (Figure 1)[21- 27].Given on the importance of structural diversity on broad biological activity[28, 29], we anticipate that a library of compounds including these structures will display a wide variety of biological activities

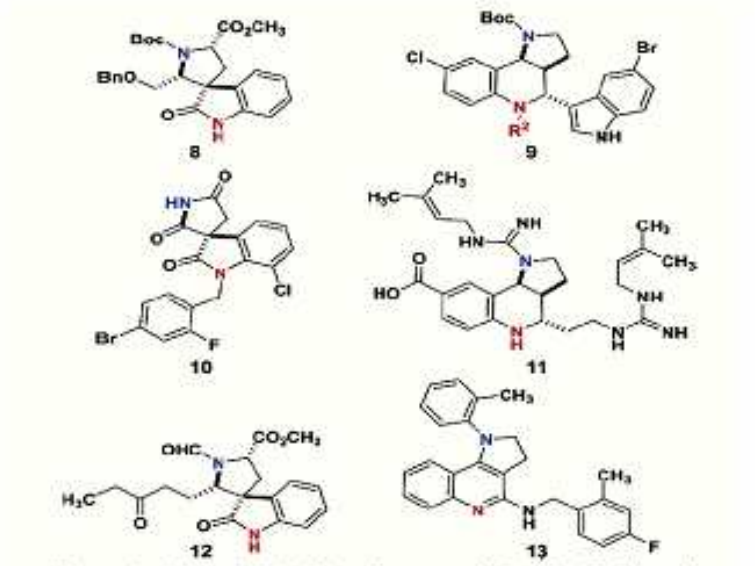


Figure 1. Natural (**11**, **12**) and unnatural (**8**−**10**, **13**) bioactive compounds featuring spirobicyclic and fused tricyclic core structures related to **6** and **7**.

MATERIALS AND METHODS

2.1 General:
Melting points were uncorrected. NMR spectra were acquired with a Bruker Ultra Shield (^{1}H : 300 MHz and ^{13}C : 100 MHz). The chemical shifts were referenced to tetra methyl silane (TMS) as an internal standard.

2.2 Synthesis of dimeric imines:
General procedure:
(0.01 mole) of 1,4-benzoquinone (14) was disolved in absolute ethanol in the presence of p-toluene sulphonic acid. Then, (0.02 mole) of aniline and its derivatives (15-20) were added and heated under reflux for (2-8) hrs. Then, the mixture was cooled in an ice bath for 2 hrs and yielded different coloured crystals. The residue was purified by recrystallization from toluene or benzene. Then, further purified by column of silica gel,using benzene:methanol 8:2 as eluent.

3,6-Bis phenylimino cyclohexa-1,4-diene:
From aniline 15 (1.86 g) with 75% yield ; m.p. (153-155) ^{o}c; CHN analysis for $C_{18}H_{14}N_2$; C 83.72; H 5.426; N 10.852 Found; C 83.710; H 5.423; N 10.650. FT-IR spectra υ $(cm)^{-1}$ (C=N). δ ^{1}H (DMSO) 6.553 ppm (s,4H,cyclo Hexa-2,3,4,5- tetraene); (7.100-7.300) ppm (m,10H,ArH). δ ^{13}C(DMSO) 125.01ppm [(C- cyclohexa- 2,3,4,5-tetraene)]; 142.75ppm (C-1); 116.10ppm (C-2); 136.08ppm (C-3); 126.85ppm (C-4); 156.17ppm(C-5).

3,6-Bis(4-methyl phenylimino)-cyclohexa-1,4-diene:
From 4-methyl aniline 16 (2.14 g) with 77% yield ; m.p. (198-200) ^{o}c; CHN analysis for $C_{20}H_{18}N_2$; C 83.916; H 6.293; N 9.790 Found; C 83.906; H 6.290; N 9.780. FT-IR spectra υ(cm)$^{-1}$ 1633cm^{-1} (C=N). δ ^{1}H(DMSO) 2.290ppm (s,6H, CH_3); (7.217-7.243)ppm (d,4H,H 2 ArH).
δ ^{13}C(DMSO) 21.24ppm (C-CH_3), 125.95ppm [(C- cyclohexa-2,3,4,5-tetraene)]; 130.50ppm (C-1); 116.09ppm (C-2); 128.49ppm (C-3); 130.16ppm (C-4); 150.18ppm (C-5).

3,6-Bis(4-methoxy phenylimino)-cyclohexa-1,4-diene:
From 4-methoxy aniline 17 (2.46 g) with 91% yield ; m.p.(110-112) ^{o}c; CHN
analysis for $C_{20}H_{18}N_2O_2$; C 75.471; H 5.660; N 8.805 Found; C 75.468; H 5.659; N 8.803. FT-IR spectra υ(cm^{-1}) 1637cm^{-1} (C=N). δ ^{1}H(DMSO) 3.615ppm (s,6H, OCH_3); 6.556 ppm (s,4H,cyclohexa-2,3,4,5-tetraene), (6.625-6.654)ppm (d,4H,H_1, ArH), (6.494-6.523)ppm (d,4H,H 2 ArH). δ ^{13}C(DMSO) 55.77ppm (C-OCH_3), 116.12ppm [(C- cyclohexa-2,3,4,5-tetraene)]; 142.76ppm (C-1); 115.43ppm (C-2); 114.98ppm (C-3); 150.21ppm (C-4); 151.15ppm(C-5).

3,6-Bis(4-hydroxy phenylimino)-cyclohexa-1,4-diene:
From 4-hydroxy aniline 18 (2.18 g) with 87% yield ; m.p.(142-144) ^{o}c; CHN
analysis for $C_{18}H_{14}N_2O_2$; C 74.482; H 4.827; N 9.655 Found; C 74.480; H 4.823; N 9.653. FT-IR spectra υ (cm^{-1}) 1571 cm^{-1} (C=N). δ ^{1}H (DMSO) 6.556 ppm (s,4H,cyclohexa-2,3,4,5-tetraene), (7.140-7.169) ppm (d,4H, H1,ArH), (6.801- 6.830)ppm (d,4H,H 2 ArH), 9.166ppm (s,2H,OH). δ ^{13}C(DMSO) 125.98ppm [(C-cyclohexa-2,3,4,5-tetraene)]; 140.77ppm (C-1); 123.21ppm (C-2); 118.75ppm (C-3); 155.65ppm (C-4); 151.92ppm (C-5).

3,6-Bis(4-bromo phenylimino)-cyclohexa-1,4-diene:
From 4-bromo aniline 19 (3.42 g) with 68% yield; m.p. (160-162) ^{o}c; CHN analysis for $C_{18}H_{12}N_2Br_2$; C 52.173; H 2.898; N 6.763 Found; C 52.170; H 2.896; N 6.762. FT-IR spectra υ (cm^{-1}) 1631 cm^{-1} (C=N). δ ^{1}H (DMSO) 6.552 ppm (s,4H,cyclohexa-2,3,4,5-tetraene), (7.172-7.201) ppm (d,4H, H1,ArH), (7.464-7.493)ppm (d,4H,H2, ArH). δ ^{13}C(DMSO) 128.67ppm [(C- cyclohexa-2,3,4,5-tetraene)]; 147.10 ppm (C-1); 124.49 ppm (C-2); 132.44 ppm (C-3); 117.19 ppm (C-4); 154.39 ppm (C-5).

3,6-Bis(4-nitro phenylimino)-cyclohexa-1,4-diene:
From 4-nitro aniline 20 (2.76 g) with 62% yield ; m.p.(130-132) ^{o}c; CHN analysis for $C_{18}H_{12}N_2O_4$; C 62.068; H 3.448; N 16.091 Found; C 62.061; H 3.445; N 16.090. FT-IR spectra υ (cm^{-1}) 1650 cm^{-1} (C=N). δ ^{1}H (DMSO) 6.723 ppm (s,4H,cyclohexa-2,3,4,5-tetraene), (7.560-7.590) ppm (d,4H, H1,ArH), (8.011-8.041)ppm (d,4H,H2, ArH). δ ^{13}C(DMSO) 126.30ppm [(C- cyclohexa-2,3,4,5-tetraene)]; 150.19ppm (C-1); 124.49ppm

(C-2); 126.00ppm (C-3); 149.72ppm (C-4); 154.39ppm (C-5).

2.3 Synthesis of dispiro bicyclo-γ-lactam:
General procedure:
(0.01 mole) of dimeric imines (21-26) was disolved in dry toluene .Then, (0.02 mole) of sucsinc anhydrid was added and heated under reflux for (24) hrs. Then, the mixture was precipitated by chloroform and yielded different coloured crystals. The residue was purified by recrystallization from absolute ethanol. Then, further purified by column of silica gel,using n-hexane:ethanol ratio 8:2 as eluent.

2,10-dioxo-1,9-diphenyl-1,9-diazodispiro[4-2-4-2]tetradeca-6,13-diene-4,12- dicarboxylicacid:
From 3,6-Bis phenylimino cyclohexa-1,4-diene 21 (1.29g) with 64% yield ; m.p. (158-160)^{O} c; CHN analysis for $C_{26}H_{22}N_2O_6$; Calculated C 68.122; H 4.803; N 6.113 Found; C 68.120; H 4.800; N 6.110. FT-IR spectra υ(cm^{-1}) (3500-3250)cm^{-1} (O-H); 1714cm^{-1} (C=O). δ ^{1}H(DMSO) (4.233-4.269)ppm (t,2H,H $_4$); (3.039-3.022) ppm (d,4H,H5); 9.942 ppm (s,1H,carboxylic acid). δ ^{13}C (DMSO) 65.82 ppm (C-5); 52.95 ppm (C-6); 34.56 ppm (C-7); 170.51 ppm (C-8); 174.08 ppm (C-9).

2,10-dioxo-1,9-Bis(4-methylphenyl)-1,9-diazodispiro[4-2-4-2]tetradeca-6,13- diene-4,12-dicarboxylicacid:
From 3,6-Bis(4-methyl phenylimino)-cyclohexa-1,4-diene 22 (1.31g) with 67% yield ; m.p. (155-157)^{O} c; CHN analysis for $C_{27}H_{26}N_2O_6$; calculated C 69.135; H 5.349; N 5.761 Found; C 69.132; H 5.342; N 5.758. FT-IR spectra υ(cm $^{-1}$) (3500-2500) $^{-1}$ (O-H); 1700cm^{-1} (C=O). δ ^{1}H(DMSO) (4.233-4.269)ppm (t,2H,H $_4$); (2.411- 2.428)ppm (d,4H,H $_5$); 9.872ppm (s,1H,carboxylic acid). δ ^{13}C(DMSO) 65.82ppm(C- 5); 52.95ppm (C-6); 34.56ppm (C-7); 170.25ppm (C-8); 174.10ppm (C-9).

2,10-dioxo-1,9-Bis(4-methoxyphenyl)-1,9-diazodispiro[4-2-4-2]tetradeca-6,13- diene-4,12-dicarboxylicacid:
From 3,6-Bis(4-methoxy phenylimino)-cyclohexa-1,4-diene 23 (1.59g) with 81% yield ; m.p.(130-132)^{o} c; CHN analysis for $C_{27}H_{26}N_2O_8$; Calculated C 64.864; H 5.019; N 5.405 Found; C 64.766; H 5.015; N 5.398. FT-IR spectra υ(cm^{-1}) (3500- 2250) cm^{-1} (O-H); 1700cm (C=O). δ ^{1}H(DMSO) (4.233-4.269)ppm (t,2H,H $_4$); (3.039- 3.022)ppm (d,4H,H); 9.781ppm (s,1H,carboxylic acid). δ ^{13}C (DMSO) 65.82ppm(C- 5); 52.95ppm (C-6); 34.56ppm (C-7); 174.01ppm (C-8); 174.27ppm (C-9).

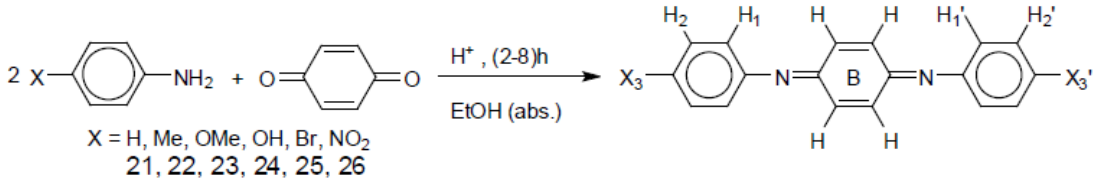
2,10-dioxo-1,9-Bis(4-hydroxyphenyl)-1,9-diazodispiro[4-2-4-2]tetradeca-6,13- diene-4,12-dicarboxylicacid:
From 3,6-Bis(4-hydroxy phenylimino)-cyclohexa-1,4-diene 24 (1.45g) with 77% yield ; m.p. (128-130)^{O} c; CHN analysis for $C_{26}H_{22}N_2O_8$; Calculated C 63.673; H 4.489; N 5.714 Found; C 63.576; H 4.486; N 5.710. FT-IR spectra υ(cm^{-1}) (3500- 2500)cm^{-1} (O-H); 1700cm^{-1} (C=O). δ ^{1}H (DMSO) (2.656-2.704) ppm (t,2H,H $_4$); (2.175- 2.154) ppm (d,4H,H5); 10.092ppm (s,1H,carboxylic acid). δ ^{13}C (DMSO) 65.82ppm(C- 5); 52.95ppm (C-6); 34.56ppm (C-7); 174.08ppm (C-8); 177.68ppm (C-9).

2,10-dioxo-1,9-Bis(4-bromophenyl)-1,9-diazodispiro[4-2-4-2]tetradeca-6,13- diene-4,12-dicarboxylicacid:
From 3,6-Bis(4-bromo phenylimino)-cyclohexa-1,4-diene 25 (2.07g) with 61% yield ; m.p.(134-136) ^{O}c; CHN analysis for $C_{26}H_{20}N_2O_6Br_2$; Calculated C 50.814; H 3.257; N 4.560 Found; C 50.810; H 3.253; N 4.557. FT-IR spectra υ(cm^{-1}) (3500-2250) cm^{-1} (O-H); 1700 cm^{-1} (C=O). δ ^{1}H (DMSO) (2.656-2.704)ppm (t,2H,H $_4$); (1.920-1.940)ppm (d,4H,H5); 10.092ppm (s,1H,carboxylic acid). δ ^{13}C (DMSO) 65.82ppm(C-5); 52.95ppm (C-6); 34.56ppm (C-7); 174.05ppm (C-8); 174.24ppm (C- 9).

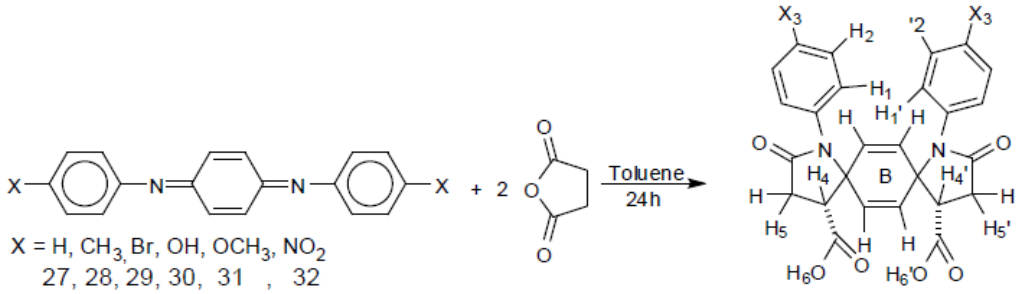
2,10-dioxo-1,9-Bis(4-nitrophenyl)-1,9-diazodispiro[4-2-4-2]tetradeca-6,13-diene- 4,12-dicarboxylicacid:
From 3,6-Bis(4-nitro phenylimino)-cyclohexa-1,4-diene 26 (1.74g) with 56 % yield ; m.p. (168-170) ^{o}c; CHN analysis for C $_{26}$H $_{20}$N $_4$O 10; Calculated C 56.934; H 3.649; N 10.218 Found; C 65.924; H 3.640; N 10.210. FT-IR spectra υ(cm^{-1}) (3250- 2500)cm^{-1} (O-H); 1699 cm^{-1} (C=O). δ ^{1}H (DMSO) (4.233-4.269)ppm (t,2H,H); (3.022- 3.039)ppm (d,4H,H $_5$); 10.649ppm (s,1H,carboxylic acid). δ ^{13}C (DMSO) 65.82ppm(C- 5); 52.95ppm (C-6); 34.56ppm (C-7); 174.17ppm (C-8); 177.68ppm (C-9).

RESULTS AND DISCUSSION

Treatment of 1,4-benzoquinone (14) with aniline and its derivatives (15-20) in the presence of p-toluene sulphonic acid as catalyst in boiling ethanol , after purification by recrystallization or short column of silica gel, gave pure dimer imino derivatives (21-26) in 62-91% yield,as crystalline compounds, as shown in (scheme 2).The structures of these products were established from their elemental analysis,FT- IR, H NMR and C NMR spectra.All the IR spectra of dimeric imine showed a peak at (1571-1650) cm^{-1} which appeared due to (C=N) stretching. All the H NMR spectra of dimeric imine were characterized [30- 32] by the presence of protons of cyclohexa-2,3,4,5-tetraene ring at δ = (6.551-6.723) ppm, since the CH_3 protons appeared at δ= 2.290 ppm. The OCH_3 protons appeared at δ = 3.615 ppm while the OH protons appeared at δ = 9.166 ppm. The aromatic protons signals appeared in the region δ= (6.494-8.041) ppm. All the ^{13}C NMR spectra of dimeric imine were characterized [30-32] by the presence of imino group (C=N) at δ = (142.57-156.17) ppm, since the signals appeared at δ= (114.98-155.65) ppm which attributed to the carbons of aromatic rings. In addition, signals appeared at(116.12-128.67) ppm which attributed to the carbon of cyclohexa-2,3,4,5-tetraene ring. While, the dispiro bicyclo-γ-lactam synthesis from the treatment of dimeric imine (21-26) with succinic anhydride in boiling toluene , after purification by recrystallization or short column of silica gel, gave pure dispiro bicyclo-γ-lactam in 56-81% yield,as crystalline compounds, as shown in scheme 3.The structures of these products were established from their elemental analysis,FT-IR, ^1H NMR and ^{13}C NMR spectra.All the IR spectra of dispiro bicyclo-γ-lactam showed a peak at (3500-2250) cm^{-1} which appeared due to (O-H) stretching, and showed a peak at (1699-1714) cm^{-1} which appeared due to (C=O) stretching. All the H NMR spectra of dispiro bicyclo- γ-lactam were characterized [30-32] by the presence of protons of H_4 at δ= (2.704-4.269) ppm, since the H5 protons appeared at δ= (1.920-1.940) ppm. The protons of carboxylic acid appeared at δ= (9.781-10.649) ppm. All the ^{13}C NMR spectra of dispiro bicyclo-γ- lactam were characterized [30-32] by the presence of C-5 at δ= 65.82 ppm, since the signals appeared at δ= 52.95 ppm which attributed to the C-6. In addition, signals appeared at 34.56 ppm which attributed to the C-7.The signal of C-8 appeared at(170.25-174.17) ppm, and showed a signal at (174.08-177.68) which attributed to C-9.



Scheme 2



Scheme 3

REFERENCES

[1] D. S. Tan, *Nat. Chem. Biol.*, **2005**,1,74-84.
[2] S. Shang, D. S. Tan, *Curr. Opin. Chem. Biol*., **2005** , 9, 248-258.
[3] S. L. Schreiber, *Nat. Chem. Biol.***, 2005**,1, 64-66.
[4] C. A. Lipinski, *Drug DiscoVery Today: Technol.* **2004**, 1, 337-341.
[5] B. A. Bunin, J. A.Ellman, *J. Am. Chem. Soc.*, **1992**, 114, 10997.
[6] L. A.Thompson,J.A. Ellman, *J. A., Chem. Rev*.**, 1996**, 96, 555-600.
[7] H. E. Blackwell, L.Perez, R. A. Stavenger, J. A. Tallarico, , E.Cope Eatough, , M. A.,Foley, S. L. Schreiber, *Chem. Biol.*, **2001**, 8, 1167-1182.
[8] P. A Clemons, A. N. Koehler, B. K.Wagner, T. G. Sprigings, D. R. Spring, , R. W. King, S. L. Schreiber, M. A.Foley, *Chem. Biol*.**, 2001**, 8, 1183-1195.
[9] D. G. Hall, S. Manku, , F.Wang, *J. Comb. Chem.*,**2001**,3, 125-150.
[10] L. Burdine, T. Kodadek, *Chem. Biol*.**,2004**,11, 593-597.
[11] D. R. Spring, *Chem. Soc. Rev.*,**2005**,34, 472-482.
[12] K. C. Nicolaou, S. A.Snyder, *Angew. Chem., Int. Ed.*,**2005**,44, 1012-1044.
[13] A. Rivkin,T.C. Chou, , S. J.Danishefsky, *Angew. Chem., Int. Ed*.**, 2005**, 44, 2838-2850.
[14] N. J.Castagnoli, M.Cushman, *J. Org. Chem.*,**1971**, 36, 3404-3406.
[15] M.Cushman, E. J. Madaj, *J. Org. Chem*.**, 1987**, 52, 907-915.
[16] M.Cushman, A. Abbaspour, Y. P.Gupta, *J. Am. Chem. Soc.*,**1983**, 105, 2873-2879.
[17] M.Cushman, T. C.Choong, J. T.Valko, M. P.Koleck, *J. Org. Chem.*, **1980**,45, 5067-5073.
[18] M.Cushman, L.Cheng, *J. Org. Chem*.**,1978**,43, 286-288.
[19] G.Cuny, M. Bois-Choussy, J. Zhu , *J. Am. Chem. Soc.*, **2004**,126, 14475-14484.
[20] J. M. Mitchell, J. T.Shaw, *Angew. Chem., Int. Ed.*, **2006**,45, 1722-1726.
[21] S.Edmondson, S. J.Danishefsky, L.Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.*,**1999**, 121, 2147-2155.
[22] D.Ponglux, S. Wongseripipatana, N. Aimi, M. Nishimura, M. Ishikawa, H. Sada, , J.Haginiwa, S. Sakai, *Chem. Pharm. Bull.*,**1990**, 38, 573-575.
[23] J. Wrobel, A. Dietrich, S. A.Woolson, J. Millen, M. McCaleb, M. C. Harrison, T. C.Hohman, J. Sredy, D. Sullivan, *J. Med. Chem*.**,1992**,35, 4613-4627.
[24] C. Marti, E. M. Carreira, *Eur. J. Org. Chem.*,**2003**,2209-2219.
[25] M. Z. Hoemann, R. L. Xie, R. F. Rossi, S. Meyer, A. Sidhu, G. D. Cuny, J. R. Hauske, *Bioorg. Med. Chem. Lett.*,**2002**,2, 129-132.
[26] K. M. Witherup, R. W. Ransom, A. C. Graham, A. M. Bernard, M. J. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzenberger, S. L.Varga, *J. Am. Chem. Soc.*,**1995**, 117, 6682-6685.
[27] R. J.Ife, T. H. Brown, P. Blurton, D. J. Keeling, C. A. Leach, M. L. Meeson, M. E. Parsons, C. J. Theobald, *J. Med. Chem.*, **1995**,38, 2763-2773.
[28] P. A. Clemons, S. L. Schreiber, *J. Am. Chem. Soc.*, **2004**,126, 14740-14745.
[29] W. H. B.Sauer, M. K. Schwarz, *J. Chem. Inf. Comput. Sci.*, **2003**,43, 987-1003.
[30] R.M. Silverstien, F.X. Webster, D.J. Kiemle, "Spectrometric Identification of Organic Compounds", sixth ed., John Wiley and Sons, **2005**, New Yourk, USA.
[31] J.W.Cooper, "Spectroscopic Techniques for Organic Chemistry", John Wiley and Sons, **1980,** New Yourk, USA.
[32] R.L. Shriner, C.K. Hermann, "Spectroscopic Techniques for Organic Chemistry", John Wiley and Sons, **2004**, New Yourk, USA.