ISSN: 0974 - 7516 Volume 8 Issue 3

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 8(3), 2012 [89-93]

Samarium nitrate catalyzed synthesis of quinoline Schiff bases and evaluated their DNA photocleavage studies

P.J.Bindu[1]*, K.M.Mahadevan[1], N.T.R.Ravikumar Naik[2]

[1]Department of Studies and Research in Chemistry, Kuvempu University, Shankaraghatta - 577 451, (INDIA)

[2]Department of Organic Chemistry, Indian Institute of Science, Bangalore - 560 012, (INDIA)

Received: 15th June, 2011 ; Accepted: 15th July, 2011

ABSTRACT

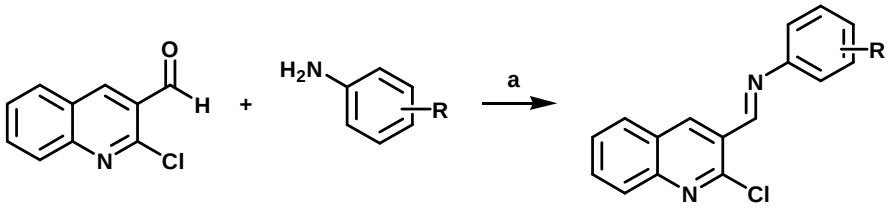
We report the synthesis of Schiff bases of 2-chloro-3-formyl-quinoline with substituted aromatic amines in the presence of acetic acid/ samarium nitrate. The newly synthesized compounds were confirmed ^{1}H NMR and Mass spectral analysis. The new compounds were tested for DNA phtocleavage studies by gel electrophoresis methods. The synthesized compounds were photoirradiated at 365 nm, 2-chloro-3-quinolinyl-methylene-benzenamines were found to promote the photocleavage of plasmid pUC 19 DNA effectively.

INTRODUCTION

Schiff in 1864 discovered the condensation products of primary amines with carbonyl compounds and known as Schiff bases they also know as anils, imines or azomethines[1]. Schiff bases have a wide variety of biological activities such as antifungal, antibacterial, antitumor, anti-inflammatory[2]. Several studies reveals that, the presence of a lone pair of electrons in an sp^2 hybridised orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance. Nowadays, Modern chemists still dealing with Schiff base chemistry, because of synthetic flexibility, the property of C=N group, easy to synthesis. Recent studies showed that, the versatility of Schiff base transition metal complexes have emerged as highly efficient catalysts in various fields of synthesis and other useful reactions[3].

Quinolines are a major class of alkaloids and play an important role in the fields of natural products and medicinal chemistry. Several methods for synthesizing quinoline have been known since the late 1800s. Quinolines and their derivatives are also important constituents of pharmacologically active synthetic compounds such as anti-inflammatory, antimicrobial agents, cytotoxic activity and antibacterial[4].

In particular, quinoline Schiff bases occupy special place because, these ligands developed due to their diverse chelating capability, structural flexibility and pharmacological activities like antibacterial, antifungal,



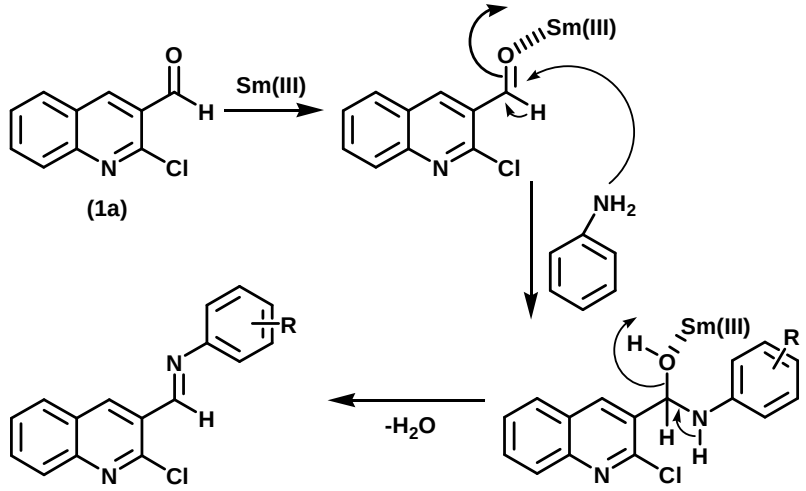
(1a) (2a-k) (3a-k)

Scheme 1 : Reagents and conditions: (a) Samarium nitrate, EtOH, 2-4 hrs at 60-70°C.

antitumoural, antiviral, antimalarial, antituberculosis[5,6].

The design and construction of small molecules to use as structural probes in biological systems has been an active area of research during the last 20 years. The binding of small molecules to DNA is potentially useful in developing design principles to guide the synthesis of new improved drugs which can recognize a specific site or conformation of DNA and to provide a good tool for biotechnology[7]. In recent years much interest has been focused on design and synthesis of biologically active compounds that can cleave DNA with a high affinity and specificity. In addition, compounds which cleave nucleic acids in a sequence specific manner are potentially useful as reagents for accessing structural and genetic information[8].

Recently, we found that, 23.000 articles are reported regarding the synthesis of 2-chloro-3-quinolinyl-methylene-benzenamines **(3a-k)**, their metal complexes and studied their DNA binding and cleavage activity[9-23]. But, in particular, only, few reports are have been published



Scheme 2 : Mechanism for the synthesis of 2-chloro-3-quinolinyl-methylene-benzenamines

on the synthesis of quinoline Schiff complexes and studied their antic cancer activity[24].

In our earlier studies, we have discuss the synthesis of nitrogen containing heterocyclic compound quinolines[25-29], here we wish to report, simple, eco-friendly synthesis of 2-chloro-3-quinolinyl-methylene-benzenamines and evaluated their nucleolytic activities.

RESULTS AND DISCUSSION

Chemistry

The quinoline scaffold having a formyl group adjacent to heterocyclic nitrogen can be easily appended with pharmacophores bearing amino groups to yield Schiff base compounds. In the present study (Scheme 1, TABLE 1), we describe synthesis and characterization of Schiff bases of 2-chloro-3-quinolinyl-methylene-benzenamines. In addition, there has been an intense interest in selection of different catalysts in development of new methods for synthesis of 2-chloro-3-quinolinyl-methylene-benzenamines **(3a-k)**. The utility of acid catalyst for the synthesis of 2-chloro-3-quinolinyl-methylene-benzenamines **(3a-k)** reported in the literature, particularly glacial acetic acid in ethanol or methanol. For the first time we are reporting the synthesis of 2-chloro-3-quinolinyl-methylene-benzenamines **(3a-k)** by samarium nitrate as catalyst (Scheme 1).

We absorbed that, synthetic chemists have used most metals of the periodic table for research and in many cases have shown the importance of metal-mediated organic reactions in simple chemical transformations or even complex organic synthesis. In contrast, samarium metal, which is cheap, has not received much recognition, although the use of Sm(III) is extremely popular in organic synthesis. Sm(III) has been used as an efficient Lewis acid for various transformations such as carbon–carbon bond formation, aldol condensations and β-diketone and α-selenoketone synthesis[30]. Research in this area has substantiated Sm(III) ability to promote reactions that are very difficult to accomplish by many other available reagents. In this letter we report a general and practical route[30], for the synthesis of 2-chloro-3-quinolinyl-methylene-benzenamines using Sm(III) as the catalyst (Scheme 1).

TABLE 1 : Synthesis of quinoline Schiff bases via Scheme 1

Entry[a]	R	Acetic acid		Samarium nitrate		M.P (°C)
		Time (hrs)	Yield (%)[b]	Time (hrs)	Yield (%)[c]	
3a	C_6H_5	2-4	85	2-4	90	162-164
3b	4-$CH_3C_6H_4$	2-4	90	2-4	95	187-190
3c	3-$CH_3C_6H_4$	2-4	90	2-4	90	187-190
3d	4-$OCH_3C_6H_4$	2-4	92	2-4	92	217-219
3e	4-ClC_6H_4	2-4	90	2-4	95	150-152
3f	4-BrC_6H_4	2-4	90	2-4	90	186-188
3g	4-$NO_2C_6H_4$	2-4	80	2-4	90	210-212
3h	4-FC_6H_4	2-4	90	2-4	90	149-151
3i	2-FC_6H_4	2-4	90	2-4	90	149-151
3j	2-Cl-4CH_3-C_6H_3	2-4	85	2-4	95	192-194
3k	2-CH_3-4-$NO_2C_6H_3$	2-4	85	2-4	90	211-214

[a]**All the products were characterized by elemental analysis, ^{1}H NMR, and mass spectral data; [b,c]Yields of isolated products**

Samarium nitrate has received considerable attention as an acid catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. However, we carried out the reaction with acetic acid and also in the presence of samarium nitrate catalyst. In both the methods, we got good yields. Also we, explore the interaction of Schiff bases with plasmaid pUC 19 DNA. Varying substitutive group or substituent position in the intercalative Schiff base can create some interesting differences in the space configuration and the electron density, which will result DNA cleavage behaviour, and will be helpful to more clearly understand the cleavage mechanism of Schiff base to DNA. Thus, it is of interest to delineate the effects of the planarity of the intercalative ligand on interaction to DNA.

Photonuclease studies

The 2-chloro-3-quinolinyl-methylene-benzenamines **(3a-k)** were photolysed at 365 nm, figure 1 illustrates that the agorose gel electrophoresis of photolysis compound at different concentration (40, 80 μM) in the presence of pUC-19 DNA. Solutions were irradiated for 2h, in 1:9 DMSO: Trisbuffer (20 μM, pH- 7.2) at l-365 nm. Cleaving ability (%) was determined quantitatively by the effectiveness in converting super coiled plasmid DNA (Form I) to nicked circular (Form II) as shown in figure 2, at the concentration of (80 μM).

The cleavage reaction on plasmid DNA can be monitored by agarose gel electrophoresis. When circular plasmid DNA is subject to electrophoresis, relatively fast migration will be observed for the intact supercoil form

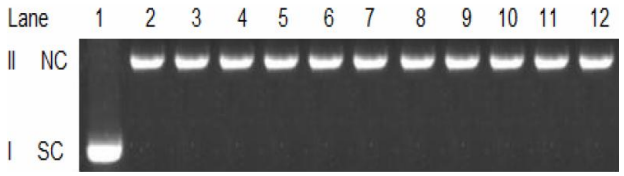


Figure 1 : Photo cleavage of DNA by 2-chloro-3-quinolinyl-methylene-benzenamines were irradiated with UV light at 365 nm. Supercoiled DNA runs at position I (SC) and nicked DNA at position II (NC). Lane; 1: control DNA (with out compound), Lane; 2: 40μM (3a), Lane; 3: 40μM (3b), Lane; 4: 40μM (3c), Lane; 5: 40μM (3d), Lane; 6: 40μM (3e), Lane; 7: 40μM (3f), Lane; 8: 40μM (3g), Lane; 9: 40μM (3h), Lane; 10: 40μM (3i), Lane; 10: 40μM (3j), Lane; 10: 40μM (3k).

(Form I). If scission occurs on one strand (nicking), the supercoil will relax to generate a slower-moving open circular form (Form II). If both strands are cleaved, a linear form (Form III) that migrates between Form I and Form II will be generated[31]. Figure 2 shows gel electrophoresis separation of pUC 19 DNA after incubation with 2-chloro-3-quinolinyl-methylene-benzenamines and irradiation at 365 nm. No DNA cleavage was observed for controls in which 2-chloro-3-quinolinyl-methylene-benzenamines was absent (lane 1). With increasing concentration of the 2-chloro-3-quinolinyl-methylene-benzenamines (lanes 1–4 and lanes 6–9), the amount of Form I of pUC 19 DNA diminish gradually, whereas Form II increases. Under comparable experimental conditions, 2-chloro-3-quinolinyl-methylene-benzenamines 2 exhibits more effective DNA cleavage activity than 2-chloro-3-quinolinyl-methylene-benzenamines 1. Further studies in detail are currently underway to clarify the cleavage mechanism.

EXPERIMENTAL

Melting points were recorded on an open capillary tube with a Buchi melting point apparatus and are uncor-

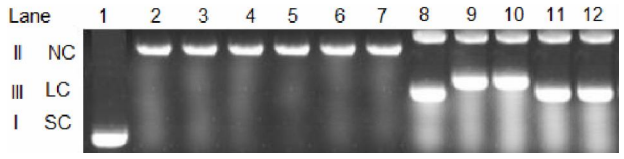


Figure 2 : Photo cleavage of DNA by 2-chloro-3-quinolinyl-methylene-benzenamines were irradiated with UV light at 365 nm. Supercoiled DNA runs at position I (SC) and nicked DNA at position II (NC). Lane; 1: control DNA (with out compound), Lane; 2: 80μM (3a), Lane; 3: 80μM (3b), Lane; 4: 80μM (3c), Lane; 5: 80μM (3d), Lane; 6: 80μM (3e), Lane; 7: 80μM (3f), Lane; 8: 80μM (3g), Lane; 9: 80μM (3h), Lane; 10: 80μM (3i), Lane; 11: 80μM (3j), Lane; 12: 80μM (3k).

rected. Elemental analyses were carried out using Perkin-Elmer 240C CHN-analyzer. IR spectra were recorded on a FT-IR infrared spectrophotometer. ^{1}H- NMR spectra were obtained using a 300 MHz and 400 MHz on a Broker spectrometer (chemical shifts in δ ppm). Mass spectra were recorded on a micro spray Q-TOF MS ES Mass spectrometer.

General procedure for the synthesis of 2-chloro-3-quinolinyl-methylene-benzenamines (3a-k) in presence of acetic acid as catalyst (3a- k)

Equimolar quantity of the 2-chloro-3-formyl quinoline (1, 1mmol) and various aromatic anilines **(2a-k)**, (1mmol) in ethanol acetic acid (20 ml) were stirred for 2-4 hrs. The resulting 2-chloro-3-quinolinyl-methylene-benzenamines **(3a-k)** were cooled and poured into crushed ice. The precipitate thus obtained was filtered washed with cold water and purified by recrystallized from ethanol.

General procedure for the synthesis of 2-chloro-3-quinolinyl-methylene-benzenamines (3a-k) in presence of samarim nitrate as catalyst (3a- k)

An equimolar mixture of the 2-chloro-3-formyl quinoline (1, 1mmol) and substituted anilines **(2a-k)**, (1mmol) in ethanol (20 ml) were refluxed at 60-70 °C on an oil bath for 2-4 hrs. The resulting 2-chloro-3-quinolinyl-methylene-benzenamines **(3a-k)** were cooled and poured into crushed ice. The precipitate thus obtained was filtered washed with cold water and purified by recrystallized from ethanol. The physicochemical and spectral data of the compounds **(3a-k)** is described in TABLE 1.

2-Chloro-3-quinolinyl-methylene-benzenamine (3a): M.p: 162-164 °C; IR (KBr): 3348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 6.68-6.70 (d, 2H), 7.31-7.44 (d, 2H), 7.46-7.55 (t, 1H), 7.59-7.62 (t, 1H), 7.68-7.75 (d, 1H), 7.84.-7.88 (d, 1H), 7.79-8.07(d, 1H), 8.99 (s, 1H) 9.09 (s, CH=N) ppm; MS (m/z): 289 (M+23), Calcd (266), Found (289); Anal. Calcd (%) for $C_{16}H_{11}ClN_2$: C; 72.05, H; 4.16, N; 10.50. Found: C; 72.03, H; 4.13, N; 10.48.

2-Chloro-3-quinolinyl-methylene-4-methyl-benzenamine (3b): M.p: 187-190 °C; IR (KBr): 3348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 2.35 (s, 3H, CH_3), 6.87-6.90 (d, 2H), 7.09-7.19 (d, 2H), 7.59-7.64 (t, 1H), 7.78-7.83 (t, 1H), 7.97-8.00 (d, 1H), 8.04-8.07 (d, 1H), 8.87 (s, 1H), 9.06 (s, CH=N) ppm; MS (m/z): 303 (M+23), Calcd (280), Found (303); Anal. Calcd (%) for $C_{17}H_{13}ClN_2$: C; 72.73, H; 4.67, N; 9.98. Found: C; 72.71, H; 4.65, N; 9.96.

2-Chloro-3-quinolinyl-methylene-4-methoxy-benzenamine (3d): M.p: 217-219 °C; IR (KBr): 3348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 3.87 (s, 3H, OCH_3), 6.97-6.99 (d, 2H), 7.00-7.10 (d, 2H), 7.26-7.28 (t, 1H), 7.35-7.37 (t, 1H), 7.61-7.68 (d, 1H), 7.79-8.03 (d, 1H), 9.00 (s, 1H), 9.03 (s, CH=N) ppm; MS (m/z): 319 (M+23), Calcd (296), Found (319); Anal. Calcd (%) for $C_{17}H_{13}ClON_2$: C; 68.81, H; 4.42, N; 9.44. Found: C; 68.79, H; 4.40, N; 9.42.

2-Chloro-3-quinolinyl-methylene-4-chloro-benzenamine (3e): M.p: 150-152 °C; IR (KBr): 3348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.24-7.26 (d, 2H), 7.40-7.42 (d, 2H), 7.59-7.63 (t, 1H), 7.79-7.83 (t, 1H), 7.94-7.97 (d, 1H), 8.04-8.06 (d, 1H), 8.96 (s, 1H), 9.02 (s, CH=N) ppm; MS (m/z): 323 (M+23), Calcd (300), Found (323); Calcd (%) for $C_{16}H_{10}Cl_2N_2$: C; 63.81, H; 3.35, N; 9.30. Found: C; 63.78, H; 3.33, N; 9.28.

2-Chloro-3-quinolinyl-methylene-4-bromo-benzenamine (3f): M.p: 186-188 °C; IR (KBr): 3348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.28-7.32 (d, 2H), 7.41-7.43 (d, 2H), 7.63-7.65 (t, 1H), 7.71-7.78 (t, 1H), 7.84-7.87 (d, 1H),7.93-8.06 (d, 1H), 8.96 (s, 1H), 9.02 (s, CH=N) ppm; MS (m/z): 368 (M+23), Calcd (345), Found (368); Anal. Calcd (%) for $C_{16}H_{10}BrClN_2$: C; 55.60, H; 2.92, N; 8.11. Found: C; 55.58, H; 2.90, N; 8.08.

2-Chloro-3-quinolinyl-methylene-4-nitro-benzenamine (3g): M.p: 210-212 °C; IR (KBr): 3348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.07-7.13 (d, 2H), 7.32-7.36 (d, 2H), 7.46-7.50 (t, 1H), 7.66-7.68 (t, 1H), 7.79-7.82 (d, 1H),8.10-8.23 (d, 1H), 9.00 (s, 1H), 9.06 (s, CH=N) ppm; MS (m/z): 334 (M+23), Calcd (311), Found (334); Anal. Calcd (%) for $C_{16}H_{10}ClN_3O_2$: C; 61.65, H; 3.23, N;13.48. Found: C; 61.63, H; 3.20, N; 13.46.

2-Chloro-3-quinolinyl-methylene-4-floro-benzenamine (3h): M.p: 149-151 °C; IR (KBr): 3348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.14-7.19 (d, 2H), 7.26-7.30 (d, 2H), 7.31-7.34 (t, 1H), 7.59-7.64 (t, 1H), 7.75-7.79 (d, 1H),7.83-7.90 (d, 1H), 8.98 (s, 1H), 9.03 (s, CH=N) ppm; MS (m/z): 307 (M+23), Calcd (284), Found (307); Anal. Calcd (%) for $C_{16}H_{10}FClN_2$: C; 67.50, H; 3.54, N; 9.84. Found: C; 67.48, H; 3.52, N; 9.82.

2-Chloro-3-quinolinyl-methylene-4-methyl-3-cloro-benzenamine (3j): M.p: 192-194 °C; IR (KBr): 3348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d = 2.25 (s, 3H, CH3), 7.00-7.05 (d, 2H), 7.31-7.34 (d, 1H), 7.61-7.66 (t, 1H), 7.81-

7.86 (t, 1H), 8.06-8.09 (d, 1H), 7.98-8.01 (d, 1H), 8.85 (s, 1H), 9.11 (s, CH=N) ppm; MS (m/z): 337 (M+23), Calcd (314), Found (337); Anal. Calcd (%) for $C_{17}H_{12}Cl_2N_2$: C; 64.78, H; 3.84, N; 8.89. Found: C; 64.76, H; 3.82, N; 8.87.

2-Chloro-3-quinolinyl-methylene-3,5-dinitro-benzenamine (3k): M.p: 211-214 °C; IR (KBr): 3348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d = 2.23 (s, 3H, CH_3), 6.87-6.90 (d, 2H), 7.09-7.12 (d, 1H), 7.14-7.17 (t, 2H), 7.19-7.26 (t, 1H), 7.59-7.62 (d, 1H), 7.64-8.07 (d, 1H), 8.87 (s, 1H), 9.06 (s, CH=N) ppm; MS (m/z): 348 (M+23), Calcd (325), Found (348); Anal. Calcd (%) for $C_{17}H_{12}ClN_3O_2$: C; 62.68, H; 3.71, N;12.90. Found: C; 62.66, H; 3.69, N; 12.88.

CONCLUSION

In Conclusion, we have described the synthesis and structural characterization of 2-chloro-3-quinolinyl-methylene-benzenamines. These synthesized 2-chloro-3-quinolinyl-methylene-benzenamines are different with respect to their various functional groups attached to the quinoline ligand. The DNA photoclevage studies are also affected by the nature of the side chains, and our in vitro findings shows that these compounds show an efficient photocleavers of the plasmid DNA.

ACKNOWLEDGEMENTS

One of the authors (bindu) thankful to Kuvempu University, and Indian Institute of science, Bangalore for NMR and mass spectra.

REFERENCES

[1] H.Schiff; Annls.Chem., **131**, 118 **(1864)**.
[2] J.Aliasghar, D.Khalili, E.D.Clercq, C.Salmi, J.M.Brunel; Molecules, **12**, 1720 **(2007)**.
[3] A.Echevarria, M.G.Nascimento, V.Geronimo, J.Miller, A.Giesbrecht; J.Braz.Chem.Soc., **10**, 60 **(1999)**.
[4] V.V.Kouznetsov, L.Y.V.Mendez, C.M.Gomez; Curr. Org.Chem., **9**, 141 **(2005)**.
[5] A.Saylam, Z.Seferoglu, N.Ertan; Dyes Pigments, **76**, 470 **(2008)**.
[6] G.S.Kurdekar, S.M.Puttanagouda, N.V.Kulkarni, S.Budagumpi, V.K.Revankar; Med.Chem.Res., 19 **(2010)**.
[7] J.K.Barton; Science, **233**, 727 **(1986)**.
[8] D.E.Brash, A.Ziegler, A.S.Jonason, J.A.Simon, S.Kunala, D.J.Leffell; J.Invest.Dermatol.Symp. Proc., **1**, 136 **(1996)**.
[9] S.Arturo, B.Giampaolo, R.Giuseppe, L.G.Maria, T.Salvatore; J.Inorg.Biochem., **98**, 589 **(2004)**.
[10] N.Maribel, C.F.Efre´n Jose´, S.Anibal, F.M.Mercedes, S.Pedro, A.Dwight, M.Edgar; J.Biol.Inorg.Chem., **8**, 401 **(2003)**.
[11] H.Catherine, P.Marguerite, R.Michael, G.S.Heinz Ste´phanie, M.Bernard; J.Biol.Inorg.Chem., **6**, 14 **(2001)**.
[12] C.V.Kumar, J.K.Barton, N.J.Turro; J.Am.Chem. Soc., **107**, 5518 **(1985)**.
[13] H.Xu, K.C.Zheng, H.Deng, L.J.Lin, Q.L.Zhang, L.N.Ji; Dalton.Trans, **3**, 2260 **(2003)**.
[14] S.Mahadevan, M.Palaniandavar; Inorg.Chim.Acta, **254**, 291 **(1997)**.
[15] H.Xu, K.C.Zheng, H.Deng, L.J.Lin, Q.L.Zhang, L.N.Ji; New J.Chem., **27**, 1255 **(2003)**.
[16] A.Mozaar, S.Elham, R.Bijan, H.Leila; New J.Chem., **28**, 1227 **(2004)**.
[17] J.B.Chaires; Biopolymers, **44**, 201 **(1998)**.
[18] J.K.Barton; Comments Inorg.Chem., **3**, 321 **(1985)**.
[19] P.G.Schultz, J.S.Taylor, P.B.Dervan; J.Am.Chem. Soc., **104**, 6861 **(1982)**.
[20] H.M.Berman, P.R.Young; Annu.Rev.Biophys. Bioeng., **10**, 87 **(1981)**.
[21] S.J.Lippard; Science, **218**, 1075 **(1982)**.
[22] M.Waring; Annu.Rev.Biochem., **50**, 159 **(1981)**.
[23] A.M.Pyle, J.K.Barton; Prog.Inorg.Chem., **38**, 413 **(1990)**.
[24] D.S.Lamani, K.R.Venugopala Reddy, H.S.Bhojya Naik, A.Savyasachi, H.Raja Naik; Nucleosides Nucleotides Nucleic Acids, **27(10)**, 1197 **(2008)**.
[25] B.P.Nandeshwarappa, D.B.Aruna Kumar, H.S.Bhojya Naik, K.M.Mahadevan; Phosphorus Sulfur and Silicon, **181**, 1997 **(2006)**.
[26] A.Srinivasa, K.M.Mahadevan, V.Hulikal; Synth. Commu., **39**, 93 **(2009)**.
[27] M.A.Goudar, H.Jayadevappa, A.Sudhakara, K.M.Mahadevan; Lett.Org.Chem., **5**, 8 **(2008)**.
[28] A.Srinivasa, K.M.Mahadevan, K.M.Hosamani, V.Hulikal; Mona.Fur.Chemie, **139**, 141 **(2008)**.
[29] A.Srinivasa, K.M.Mahadevan, V.Hulikal; Mona. Fur.Chemie, **139**, 255 **(2008)**.
[30] Y.Yu, R.Lin, Y.Zhang; Tetrahedron Lett., **34**, 4547 **(1993)**.
[31] T.R.Ravikumar Naik, H.S.Bhojya Naik, H.R.Prakash Naik, P.J.Bindu, B.G.Harish, V.Krishna; Med. Chem., **5**, 411 **(2009)**.