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Short Communication

Synthesis and Characterization of Novel Bis-Pyrazole Aldehydes Using Vilsmeier–Haack Reagent

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ABSTRACT

*Synthesis of Ten novel Bis-pyrazole aldehydes **6a-j** from 1-{4-[2-(4-Acetyl-phenoxy)-alkoxy]-phenyl}-ethanone **3a-e**, phenyl hydrazine under Vilsmeier-Haack reaction condition. All the compounds resulted in excellent yields. All the synthesized compounds were analyzed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis and characterized as 3-(4-n-[4-(4-formyl-1-aryl-1H-3-pyrazolyl) phenoxy] alkoxyphenyl)-1-aryl-1H-4-pyrazole carbaldehyde.*

Keywords: Bis-acetophenones, Bis-phenyl hydrazones, Bis-pyrazole aldehydes and Vilsmeier-Haack reaction.

INTRODUCTION

Pyrazole nucleus [1] has drawn the attention of chemists over the years because of it's important biological properties as anti-anxiety [2,3], antipyretic, analgesic, anti-inflammatory [4–6], antitumor [7] and anti-nociceptive drugs [8], as well as its good antimicrobial activities [9–16]. The literature survey reveals the antiparasitic activity in nitro heterocyclic series [17–18] and aryl pyrazoles have also shown neuroprotective activity by blocking sodium channels[19]. Recently, the pyrazoles are reported as inhibitors of P-38 mitogen-activated protein kinase [20]. The large applications of pyrazole heterocycles in pharmaceutical [21] as well as in agrochemical industry [22]. Therefore they are popular synthetic targets [23]. Furthermore bis-heterocyclic compounds with a suitable alkyl spacer constitute an important class of compounds and their various types of activities especially as antitumor [24] and as antimicrobial [25] have been studied. These activities which result in their pharmacological utility have been reported to be enhanced when different functionalities or substitutions are present on the two heterocyclic moieties [26–35]. From the literature survey it is observed that very few reports are available on bis-pyrazole aldehydes. Therefore it is worthwhile to synthesize some new bis-pyrazole aldehydes. The present paper reports the synthesis and characterization of novel bis-pyrazole aldehydes.

MATERIALS AND METHODS

All the chemicals were of LR grade and obtained from Sigma Aldrich, Merck, Avra, Silvery Enterprises. Melting points were determined in open glass capillary tube on a Gallen-Kamp MFB-595 apparatus and

are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR-8400, using samples in KBr pellets. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on BrukerAvance II 400 spectrometer using $CDCl_3$ as solvent and TMS as the internal standard, the chemical shifts are expressed in δ ppm. Mass spectra were recorded on SHIMADZU LCMS 2020 mass spectrometer. The progress of reactions was monitored by TLC (Silica gel, Aluminium sheets 60 F_{254}, Merck).

Synthesis

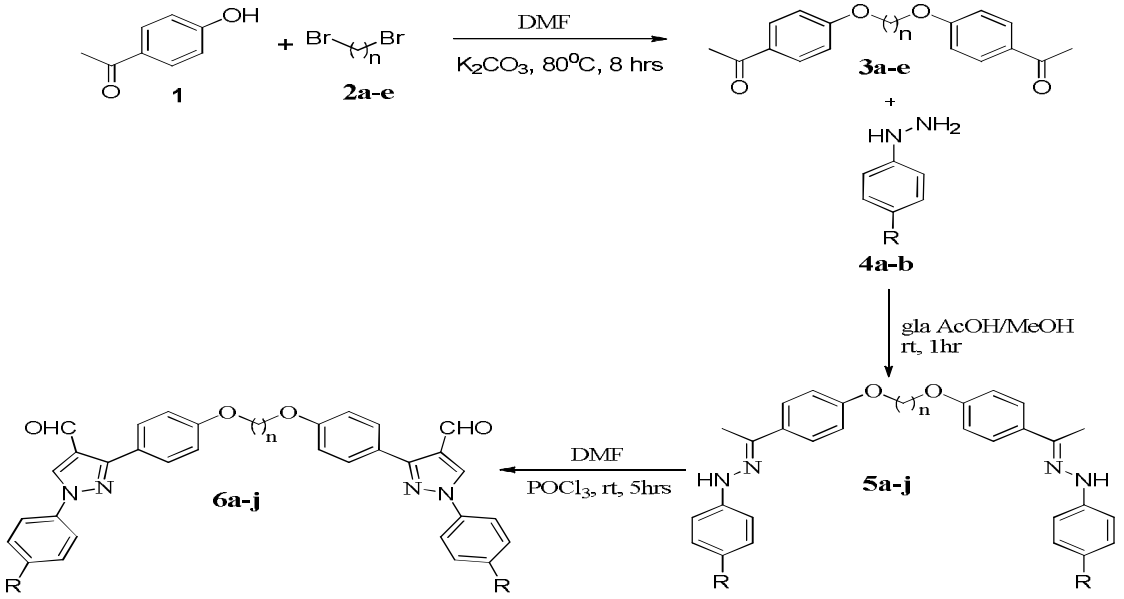
General procedure for the synthesis of bis-acetophenones (3a-e): A mixture of 4-hydroxy acetophenone (1) (2mmol) and dibromoalkane (2) (1mmol) were dissolved in DMF and added K_2CO_3 then the reaction mixture was stirred for 8 hrs at 80^0c temperature. After completion of the reaction the precipitate was filtered and washed with ethanol. All bisacetophenones (3a-e) are prepared by using 1 and 2a-e.

General procedure for the synthesis of bis-phenylhydrazones (5a-j): A mixture of bis acetophenone (3) (1mmol), phenyl hydrazine (4) (2mmol) dissolved in methanol and glacial acetic acid is added then the reaction mixture was stirred for 1hr at room temperature. The precipitate was filtered and washed with ethanol. All bis phenyl hydrazones (5a-j) are prepared by using 3a-e and 4a-b.

Vilsmeier–Haackreaction (6a-j):

DMF(7mmol) and $POCl_3$(14mmol) were previously cooled separately at 0^0C before being stirred at 0^0c temperature. A solution of 5 (1mmol) in DMF(3 ml) was added drop wise to the reaction mixture. After addition the reaction mixture was stirred at room temperature for 5hrs. Progress of the reaction was monitored by TLC, after completion of the reaction, the reaction mixture was poured in water and basified with a cool saturated NaOH solution. The precipitate was filtered, strongly washed with water and purified by using column chromatography to yield the title compound **6**. All the compounds 6a-j are synthesized by the same method using appropriate 5a-j. All the compounds resulted in good yields (80-85 %).

Scheme 1:



6a: n=2 R=H
6b: n=3 R=H
6c: n=4 R=H
6d: n=5 R=H
6e: n=6 R=H
6f: n=2 R=CH_3
6g: n=3 R=CH_3
6h: n=4 R=CH_3
6i: n=5 R=CH_3
6j: n=6 R=CH_3

4A-B; A,R=H, B,R=CH_3

RESULTS AND DISCUSSION

The reaction of bis-phenylhydrazones (5a-j) with DMF and $POCl_3$ resulted in the formation of bis-pyrazole aldehydes (6a-j) in good yields (80-85%). All the compounds were pale yellow in colour. IR spectra of **6a** compound showed absorption band at 1675 cm^{-1} due to C=O, showed absorption at 1560 cm^{-1} due to C=N and showed absorption bands at 1083 and 1245 cm^{-1} due to C-O-C stretching. ^{1}H NMR spectra of **6a** compound showed a singlet at δ 4.15 due to O-CH_2- CH_2-O, showed another singlet at δ 8.52 due to pyrazolene-H, showed a singlet at δ 10.03 due to aldehyde (CHO), and showed signals in the range of δ 7.02-7.81 due to Aromatic protons(18 H). ^{13}C NMR spectra of **6a** compound showed a signal at δ 66.5 due to O-CH_2-CH_2-O, showed a signal at δ 190.1 due to C=O. The mass spectra of **6a** compound showed [M+H] peak at 555. Therefore the compound is characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral data as 3-(4-2-[4-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)phenoxy]ethoxyphenyl)-1-phenyl-1*H*-4-pyrazole carbaldehyde *(6a)*.

Spectral Data and structure elucidation of compounds 6 a-j

3-(4-2-[4-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)phenoxy]ethoxyphenyl)-1-phenyl-1*H*-4-pyrazole carbaldehyde*(6a)*: yield 83%, mp: 196-198^{o}C. IR spectrum, ν, cm^{-1}: 1675 (C=O), 1560 (C=N), 1245, 1083 .^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.15(s,4H, 2x OCH_2), 7.02 (d, J = 8.2 Hz, 4H), 7.37-7.41 (m, 2H), 7.49 (d, J = 8.0 Hz, 4H), 7.77-7.81 (m, 8H), 8.52(s, 2H, pyrazolene-H), 10.03(s, 2H, CHO). ^{13}CNMR spectrum, δ_C, ppm: 66.5, 114.2, 123.9, 127.0, 128.1, 121.2, 128.2, 128.3, 128.4,128.5, 146.2, 158.2,190.1. *m/z*=555$[M+H]^+$, $C_{34}H_{26}N_4O_4$.

3-(4-3-[4-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)phenoxy]propoxyphenyl)-1-phenyl-1*H*-4-pyrazole carbaldehyde*(6b):* Yield 82%,mp: 245-247^{o}C. IR spectrum, ν, cm^{-1}: 1672 (C=O), 1565 (C=N), 1242, 1078.^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20-1.25(m,2H, C-CH_2-C), 4.25 (t, 4H, 2x OCH_2), 7.00(d, J = 8.1 Hz, 4H), 7.37-7.41 (m, 2H), 7.50(d, J = 8.0 Hz, 4H), 7.77-7.82(m, 8H), 8.50(s, 2H, pyrazolene-H), 10.00(s,2H, CHO).^{13}CNMR spectrum, δ_C, ppm: 31.6, 65.9, 114.0, 124.0, 127.0, 127.9, 128.1, 128.2, 128.3, 128.4, 128.6, 146.3, 158.1, 190.0. *m/z*=569 $[M+H]^+$, $C_{35}H_{28}N_4O_4$.

3-(4-4-[4-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)phenoxy]butoxyphenyl)-1-phenyl-1*H*-4-pyrazole carbaldehyde*(6c):* Yield 80%,mp: 240-241^{o}C. IR spectrum, ν, cm^{-1}: 1670 (C=O), 1562 (C=N), 1240, 1075. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.73(t,4H, 2x C-CH_2-C), 4.06(t,4H, 2x OCH_2), 7.00(d, J = 8.0 Hz, 4H), 7.26-7.41 (m, 2H), 7.41(d, J = 8.0 Hz, 4H), 7.76-7.82 (m, 8H), 8.52(s, 2H, pyrazolene-H), 10.00(s, 2H, CHO). ^{13}CNMR spectrum, δ_C, ppm: 32.7, 66.2, 114.0, 123.7, 127.5, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 146.5, 158.0, 190.1.*m/z*=583$[M+H]^+$, $C_{36}H_{30}N_4O_4$.

3-[4-(5-[4-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)phenoxy]pentyloxy)phenyl]-1-phenyl-1*H*-4-pyrazole carbaldehyde*(6d)*:Yield 81%, mp: 208-210^{o}C. IR spectrum, ν, cm^{-1}: 1665 (C=O), 1560 (C=N), 1243, 1073. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.18-1.29(m, 2H, C-CH_2-C), 1.83-1.90 (m, 4H, 2x C-CH_2-C), 4.03 (t, 4H, 2x OCH_2), 7.01 (d, J = 8.2 Hz, 4H),7.25-7.29 (m, 2H), 7.37(d, J = 8.1 Hz, 4H), 7.49-7.80 (m,8H), 8.52 (s,2H, pyrazolene-H), 10.04 (s,2H, CHO).^{13}C NMR spectrum, δ_C, ppm: 21.6, 28.0, 67.5, 114.3, 123.7, 127.0, 128.1, 128.2, 128.3,128.4, 128.6, 128.7, 146.1, 158.2, 190.2.*m/z*=597 $[M+H]^+$, $C_{37}H_{32}N_4O4$.

3-[4-(6-[4-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)phenoxy]hexyloxy)phenyl]-1-phenyl-1*H*-4-pyrazole carbaldehyde*(6e)*:Yield 80%, mp: 225-227^{o}C. IR spectrum, ν, cm^{-1}: 1662 (C=O), 1555 (C=N), 1241, 1071. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.58-1.63 (m,4H, C-CH_2-C), 1.86-1.93 (m, 4H, C-CH_2-C), 4.04(t, 4H, 2x OCH_2), 7.01(d, J = 8.0 Hz, 4H), 7.37-7.39(m, 2H), 7.49(d, J = 8.2 Hz, 4H), 7.76-7.80 (m, 8H), 8.52 (s, 2H, pyrazolene-H), 10.04(s, 2H, CHO).^{13}C NMR spectrum, δ_C, ppm: 21.4, 28.0, 67.8, 114.5, 123.6, 127.2, 128.0, 128.1, 128.2, 128.3, 128.5, 128.7, 146.0, 158.2, 190.0.*m/z*=611 $[M+H]^+$, $C_{38}H_{34}N_4O_4$.

3-[4-(2-4-[4-formyl-1-(4-methylphenyl)-1*H*-3-pyrazolyl]phenoxyethoxy)phenyl]-1-(4-methylphenyl)-1*H*-4-pyrazolecarbaldehyde *(6f)*: Yield 80%, mp: 191-193°C. IR spectrum, ν, cm^{-1}: 1670 (C=O), 1562 (C=N), 1242, 1080. ^{1}H NMR spectrum ($CDCl_3$), *δ*, ppm: 2.32 (s, 6H,2CH_3), 4.12 (s, 4H, 2x OCH_2), 7.00 (d, *J* = 8.0 Hz, 4H), 7.47 (d, *J* = 8.0 Hz, 4H), 7.60-7.73 (m, 8H), 8.51 (s, 2H, pyrazolene-H), 10.04(s, 2H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 20.9, 66.1, 114.6, 123.8, 127.2, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.7, 146.1, 158.6, 190.3.*m/z*=583$[M+H]^+$, $C_{36}H_{30}N_4O_4$.

3-[4-(3-4-[4-formyl-1-(4-methylphenyl)-1*H*-3-pyrazolyl]phenoxypropoxy)phenyl]-1-(4-methyl phenyl)-1*H*-4-pyrazolecarbaldehyde*(6g)*: Yield 79%, mp: 232-236°C. IR spectrum, ν, cm^{-1}: 1667 (C=O), 1558 (C=N) , 1238, 1074. ^{1}H NMR spectrum ($CDCl_3$), *δ*, ppm: 1.22-1.25 (m, 2H, C-CH_2-C), 2.33 (s, 6H,2CH_3), 4.24 (t, 4H, 2x OCH_2), 7.05 (d, *J* = 8.1 Hz, 4H), 7.52 (d, *J* = 8.0 Hz, 4H), 7.62-7.70 (m, 8H), 8.53 (s, 2H, pyrazolene-H), 10.01(s, 2H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 20.5, 31.9, 66.3, 114.5, 123.7, 127.2, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 146.0, 158.6, 190.2. *m/z*=597 $[M+H]^+$, $C_{37}H_{32}N_4O_4$.

3-[4-(4-4-[4-formyl-1-(4-methylphenyl)-1*H*-3-pyrazolyl]phenoxybutoxy)phenyl]-1-(4-methylphenyl)-1*H*-4-pyrazolecarbaldehyde*(6h)*: Yield 81%,mp: 232-234°C. IR spectrum, ν, cm^{-1}: 1665 (C=O), 1560 (C=N), 1244, 1072. ^{1}H NMR spectrum ($CDCl_3$), *δ*, ppm: 2.30(s, 6H,2CH_3), 1.71 (t,4H, 2x C-CH_2-C), 4.20 (t, 4H, 2x OCH_2), 7.01(d, *J* = 8.0 Hz, 4H), 7.40 (d, *J* = 8.0 Hz, 4H), 7.75-7.80 (m, 8H), 8.52(s, 2H, pyazolene-H), 10.04(s, 2H, CHO). ^{13}CNMR spectrum, δ_C, ppm: 21.5, 33.1, 66.8, 114.8, 123.5, 127.2, 127.8, 128.1, 128.2 128.4, 128.5, 128.6, 128.8, 146.1, 158.2, 190.1.*m/z*=611$[M+H]^+$, $C_{38}H_{34}N_4O_4$.

3-[4-(5-4-[4-formyl-1-(4-methylphenyl)-1*H*-3-pyrazolyl]phenoxypentyloxy)phenyl]-1-(4-methyl phenyl)-1*H*-4-pyrazolecarbaldehyde*(6i)*: Yield 79%,mp: 201-203°C. IR spectrum, ν, cm^{-1}: 1671 (C=O), 1562 (C=N), 1248, 1076. ^{1}H NMR spectrum ($CDCl_3$), *δ*, ppm: 1.15-1.24(m, 2H, C-CH_2-C), 1.78-1.84 (m, 4H, 2x C-CH_2-C), 2.28 (s, 6H, 2CH_3), 4.03 (t, 4H, 2x OCH_2), 7.01 (d, *J* = 8.2 Hz, 4H), 7.40 (d, *J* = 8.0 Hz, 4H), 7.75-7.80 (m, 8H), 8.52 (s, 2H, pyrazolene-H), 10.04 (s, 2H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 20.2, 21.3, 32.5, 66.1, 114.6, 123.4, 127.1, 127.7, 128, 128.1, 128.2, 128.3, 128.4, 128.5, 146.0, 158.2, 190.4. *m/z*= 625 $[M+H]^+$, $C_{39}H_{36}N_4O_4$.

3-[4-(6-4-[4-formyl-1-(4-methylphenyl)-1*H*-3-pyrazolyl]phenoxyhexyloxy)phenyl]-1-(4-methyl phenyl)-1*H*-4-pyrazolecarbaldehyde*(6j)*: Yield 81%,mp: 219-221°C. IR spectrum, ν, cm^{-1}: 1665 (C=O), 1560 (C=NC), 1246, 1072. ^{1}H NMR spectrum ($CDCl_3$), *δ*, ppm: 1.56-1.60 (m, 4H, C-CH_2-C), 1.88-1.95 (m, 4H, C-CH_2-C), 2.30 (s, 6H), 4.00 (t, 4H, 2x OCH_2), 7.00(d, *J* = 8.0 Hz, 4H), 7.42 (d, *J* = 8.0 Hz, 4H), 7.74-7.81 (m, 8H), 8.51(s, 2H, pyrazolene-H), 10.03(s, 2H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 20.1, 21.4, 32.3, 66.2, 114.6, 123.5, 127.2, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 146.1, 158.1, 190.0.*m/z*=639$[M+H]^+$, $C_{40}H_{38}N_4O_4$.

CONCLUSIONS

Ten novel bis-pyrazole aldehydes **6a-j** are synthesized by using Vilsmeier–Haack reagent. All the compounds resulted in good yields. All the compounds obtained were stable at room temperature.

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REFERENCES

[1] K. Kirschke, E. Schaumann, Hetarene, GeorgThiemeVerlag, Stuttgart, **1994**, Houben-Weyl Vol. E8b, pp.399–763.

[2] J.Haufel, E.Breitmaier, *Angew. Chem.* **1974**, 13, 604.

[3] D.J. Wustrow, T. Capiris, R.Rubin, J.A.Knobelsdorf, H. Akunne, M.D. Davis, R.MacKenzie, T.A. Pugsley, K.T.Zoski, T.G.Heffner, L.D.Wise, *Bioorg. Med.Chem. Lett,* **1998**, 8, 2067.

[4] A.I.Eid, M.A.Kira, H.H.Fahmy, *J. Pharm. Belg.* **1978**, 33, 303.

[5] G.Menozzi, L. Mosti, P. Fossa, F. Mattioli, M. Ghia, *J.Heterocyclic Chem.* **1997**, 34, 963.

[6] T.D.Penning, J.J.Talley, S.R. Bertenshaw, J.S.Carter, P.W. Collins, S.Docter, M.J. Graneto, L.F.Lee, J.W.Malecha, J.M.Miyashiro, R.S. Rogers, D.J. Rogier, S.S.Yu et.al, *J. Med. Chem*, **1997**, 40,1347.

[7] P.Manojkumar, T.K. Ravi, G. Subbuchettiar, *Acta Pharm*, **2009**, 59, 159.

[8] P.D. Sauzem, S. Sant'AnnaGda, P. Machado, M.M.Duarte, J. Ferreira, C.F. Mello, P. Beck, H.G. Bonacorso, N.Zanatta, M.A. Martins, M.A. Rubin, *Eur. J.Pharmacol*, **2009,** 616, 91.

[9] R.B. Pathak, S.C. Bahel, *J. Indian Chem. Soc*, **1980,** 57, 1108–1111.

[10] S. Devi, P. Mitro, S.B. Mishra, A.S. Mittra, *J. Indian Chem.Soc*, **1983,** 60, 679–681.

[11] G. Daidone, B. Maggio, S. Plescia, D. Raffa, C. Musiu, C.Milia, G. Perra, M.E. Marongiu, *Eur. J. Med. Chem*, **1998,** 33, 375–382.

[12] K. E. Manojkumar, C. G. Darsha. Sreenivasa, N. R. Mohan, P. A. Suchetann Raj and H. Raja Naika, *Journal of Applicable Chemistry*, **2014**, 3 (1), 64-73.

[13] N. J. P. Subhashini, Jampaiah Amanaganti and P. Acharya Nagarjuna, *Journal of Applicable Chemistry,* **2014**, 3(6), 2358-2364.

[14] SandeepTalari ,R.Govindarajan , Divya Karunakaram , Srikanth Jupudi S.Udhayavani, *Journal of Applicable Chemistry*, **2013**, 2(2), 236-245.

[15] R. SaundaneAnand, Kirankumar NandibeoorMathada, Annapurna Halu And Prabhaker Walmik, *Journal of Applicable Chemistry*, **2014**, 3(1), 117-128.

[16] Manisha Shukla, D.S. Seth and Hemant Kulshreshtha, *Journal Of Applicable Chemistry*, **2013**, 2 (6), 1484-1488.

[17] F. Tedlaouti, M. Gasquet, F. Delmas, P. Timon-David, E.Madadi, P. Vanelle, J. Maldonado, *J. Pharm. Belg.* **1990,** 45, 306–310.

[18] F.Tedlaouti, M. Gasquet, F. Delmas, B. Majester, P. Timon-David, E. Madadi, P. Vanelle, J. Maldonado, *Farmaco,* **1991,** 46, 1195–1201.

[19] H.M.Gao, J.S. Hong, *Trends Immunol.* **2008**, 29, 357.

[20] M.J.Graneto, R.G. Kurumbail, M.L. Vazquer, H.S. Shieh, J.L. Pawlitz, J.M. Williams, W.C.Stallings, L. Geng, A.S. Narain, F.J.Koszyk, M.A.Stealey, X.D.Xu, R.M. Weier, G.J. Hanson, R.J. Mourey, R.P. Compton, S.J. Mnich, G. D.Anderson, J.B.Monahan, R. Devraj, *J Med Chem*, **2007**, 50, 5712.

[21] S.Tobiishi, T. Sasada, Y. Nojiri, F. Yamamoto, T. Mukai, K.Ishiwata, M. Maeda, *Chem Pharm Bull***, 2007**, 55, 1213.

[22] K.Y. Lee, J.M. Kim, J.N.Kim, *Tetrahedron Lett*, **2003,** 44, 6737.

[23] J.P.Vors, V. Gerbaud,N. Gabas, J.P. Canselier, N. Jagerovic, M.L. Jimenoc, J. Elguero, *Tetrahedron*, **2003**, 59, 555.

[24] D.E. Thurston, D.S. Bose, A.S. Thompson, P.W. Howard, A. Leoni, S.J. Croker, T.C. Jenkins, S. Neidle, J.A. Hartley, L.H.Hurley, *J Org Chem* ,**1996**, 61, 8141.

[25] R.M.Shaker, *Phosphorus Sulfur Silicon Relat Elem.,* **1999**, 149, 7.

[26] A. Kamal, N. Laxman, G. Ramesh, K. Neelima, K.K. Anand, *ChemCommun,* **2001**, 437.
[27] A.Raasch, O. Scharfenstein,C. Trankle, U. Holzgrabe, K.Mohr, *J Med Chem* **2002**, 45,3809.
[28] M.Jain, P. Khanna, A. Saxena, S. Bhagat, C.E. Olsen, S.C.Jain, *Synth Commun* **2006**, 38,1863
[29] M.Jain, R. Sakhuja, P. Khanna, S. Bhagat, S.C. Jain, *Arkivoc,* **2008,** 15, 54.
[30] G.Y.Yang, K.A. Oh, N.J.Park, Y.S. Jung, *BioorgMedChem*, **2007**, 104.
[31] B.D.Giacomo, A. Bedini, G. Spadoni, G. Tarzia, F. Fraschini, M. Pannaccib, V. Lucinib, *Bioorg Med Chem,* **2007**, 15, 4643.
[32] B.S.Holla, R. Gonsalves, S. Shenoy, *Eur J Med Chem*, **2000**, 35, 267.
[33] B.S. Holla, R. Gonsalves, B.S. Rao, S. Shenoy, H.N.Gopalakrishna, *Il Farmaco*, 2001, 56, 899.
[34] B.S.Holla, K.N. Poojary, B.S. Rao, M.K. Shivananda, *Eur J Med Chem*, **2002**, 3, 511.
[35] W.R.Turner, L.M. Werbel, *J Med Chem*, **1985**, 28, 1728.