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Synthesis, characterisation and biological evaluation of some novel Schiff'sbases derived from halovinyl aldehyde and 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol

J. H. Mansoory[a] and S. S. Rajput[*b]

[a]*Department of Chemistry, PSGVPM's Arts, Commerce and Science College, Shahada, Dist. Nandurbar (M.S.)*
[b]*Department of Chemistry, SVS's DadasahebRawal College Dondaicha, Dist. Dhule (M.S.)*

ABSTRACTS

A series of N-substituted phenyl succinimides and their halovinyl aldehydes derivatives (2,5-dichloro-1-(substituted phenyl)-pyrrole-3,4-dicarbaldehyde) have been prepared by using Vilsmeier-Haack reaction. 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol has been synthesized from isoniazidein a series of reactions. Condensation of halovinyl aldehydes and 1,2,4-triazolewith catalytic amount of piperidine in methanolafforded a series of new Schiff's bases.All these compounds were characterised by their spectral analysis.

Keywords: Halovinyl aldehydes, Schiff's bases, Vilsmeier-Haack reaction, 1,2,4-triazole, isoniazide, piperidine.

INTRODUCTION

One of the most fundamental objectives of preparative organic and medicinal chemistry is the design and synthesis of molecules having value as human therapeutic agents. Haloformylation is an important reaction in organic synthesis and results in introduction of halogen and aldehyde group. These groups act as crossroad intermediates. Therefore a number of methods have been developed for haloformylation. Vilsmeier-Haack reaction is one of the important methods used for haloformylation [1].The chemistry of 1,2,4-triazoles and their fused heterocycles have got considerable attention due to their synthetic utility and broad spectrum biological activity.For example, a number of 1,2,4-triazole rings are found into a wide variety of pharmaceutical drugs exhibiting antimicrobial agents [2], antibacterial [3], antifungal [4], anti-mycobacterial [5], anticancer [6], antiviral [7], anti-tubercular [8], anticonvulsants [9], anti-inflammatory and analgesic [10], antioxidant [11], CNS stimulants, antidepressant [12] properties.

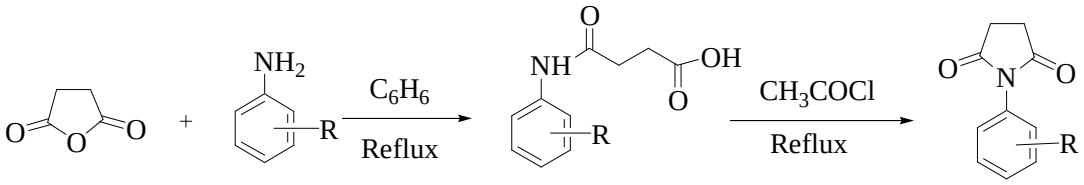
Schiff's bases are the compounds containing an azomethine group (-CH=N-)and are formed by the condensation of a primary amine with a carbonyl compound. Schiff's bases of aliphatic aldehydes are less stable as compared to those of aromatic aldehydes with an effective conjugation system. Schiff's bases, their derivatives and metal complexes are largely studied because of interesting and important biological properties. Many biological important Schiff's bases ligands have been reported which possess antimicrobial [13],antibacterial [14], antifungal [15], antioxidant [16], anti-inflammatory [17, 18], anti-HIV [19] and anti-cancer [20] activities. Schiff's bases are commonly used to prepared metal complexes in co-ordination chemistry because of their ability to form stable complex with different transition metals. Schiff's bases are also used as intermediates to synthesize various heterocyclic compounds by a nucleophilic addition reaction [21].

Keeping in mind above pharmaceutical and biological importance of 1,2,4-triazole and Schiff'sbases, we have decided to synthesize of some novel Schiff's bases by condensation reaction.

MATERIALS AND METHODS

All melting points were determined in opencapillary and are uncorrected.IR spectra were recordedusing KBr discs on a Shimadzu FT-IR PC spectrophotometer.^{1}HNMR spectrum were recorded on Bruker DRX 500MHz NMR spectrometer with DMSO-d_6 as a solvent using TMS as internal reference(chemical shift in δ ppm). The starting compounds were synthesized according to scheme-I.Succinic anhydride**1** reacted with substituted anilineto form N-substituted phenyl succinimide**4a-e** which ondiformylation using Vilsmeier-Haack reaction afforded**5a-e**.

Synthesis of 1-(N-substituted phenyl)-pyrrolidine-1,5-dione: To a solution of succinic anhydride **1** (0.01mol) in 40mL of benzene, a solution of substituted aniline **2a-e** (0.01mol) in 10 mL benzene added slowly to obtained N-substituted phenyl succinamic acid **3a-e**. Compound **3a-e** cyclised with acetyl chloride (0.06mol) till complete evaluation of hydrogen chloride gas (scheme I). All the compounds**4a-e**were recrystallized from ethanol.



1 **2a-e** **3a-e** **4a-e**

Where R, a = H, b = -4Me, c = -3Cl, d = -4Cl, e = -3NO_2

Scheme I

1-phenylpyrrolidine-2,5-dione(4a): Yield 92%, M.P. = 150-152 ^{O}C. IR (KBr) cm^{-1}: 2927.52(CH_2), 1699.91(>C=O), 1476.01(ArC=C),1204.87(C-N), 820.35(Cl). ^{1}HNMR (500 MHz, DMSO-d_6, δ ppm): 2.9δ (s, 4H, -CH_2CH_2), 8.1-6.9δ(m,5H,Ar-H).

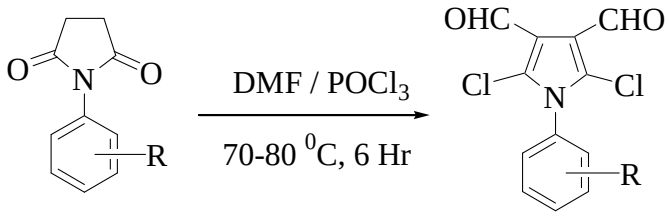
1-(4-methylphenyl)-pyrrolidine-3,4-dione (4b): Yield 85%, M.P. = 110-112 ^{O}C. IR (KBr) cm^{-1}: 2924.55(CH_2), 1702.32(>C=O), 1419.73(ArC=C), 1202.25(C-N). ^{1}HNMR (500 MHz, DMSO-d_6, δ ppm): 2.8- 2.7δ (s, 4H, -CH_2CH_2), 3.16δ (s, 3H, CH_3), 7.5- 6.9δ (m, 4H, Ar-H).

1-(3-chlorophenyl)-pyrrolidine-3, 4-dione(4c): Yield 84%, M.P. = 142-144 ^{O}C. IR (KBr) cm^{-1}: 2936(CH_2), 1703.47(>C=O), 1507.42(ArC=C), 1242.19(C-N). ^{1}HNMR (500 MHz, DMSO-d_6, δppm):2.3δ(s,4H, -CH_2CH_2), 8.5-7.4δ (m,4H, Ar-H),

1-(4-chlorophenyl)-pyrrolidine-3, 4-dione(4d): Yield 89%, M.P. = 162-164 ^{O}C. IR (KBr) cm^{-1}: 2933.94(CH_2), 1706.47(>C=O), 1511.42(ArC=C),1252.19(C-N). ^{1}HNMR (500 MHz, DMSO-d_6, δppm):2.3δ(s,4H, -CH_2CH_2), 7.5-7.1δ (m,4H, Ar-H),

1-(3-nitrophenyl)-pyrrolidine-3, 4-dione(4e): Yield 78%, M.P. = 168-170 ^{O}C IR (KBr) cm^{-1}: 2933.94(CH2), 1706.47(>C=O), 1511.42(ArC=C),1252.19(C-N). ^{1}HNMR (500 MHz, DMSO-d_6, δppm): 2.4δ(s,4H,-CH_2CH_2), 8.4-7.8δ (s, 4H, Ar-H).

Synthesis of 2,5-dichloro-1-(substituted phenyl)-pyrrole-3,4-dicarbaldehyde (5a-e):
Freshly distilled phosphorous oxychloride (0.06mol) was added to a cooled dimethylformamide (0.12mol) in a drop wise manner with constant stirring at 0-5 ^{O}C. Then the substituted N-phenyl succinimides**4a-e** (0.01mol) were added to above cooled Vilsmeier-Haack reagent in small amount at a time with constant stirring using magnetic stirrer (scheme II). This reaction mixture was heated at 60-70 ^{O}C for 6 hours. This mixture was kept overnight and was then work-up with crushed ice and stirred for another 30 minutes. Then the resulting clear coloured solution was neutralised with 40% sodium hydroxide keeping temperature below 50 ^{O}C. Then the reaction mixture was heated at 50-60 ^{O}C for half an hour. After cooling in an ice bath coloured compounds **5a-e**was obtained. These compounds were recrystallized with aqueous ethanol as solvent.



4a-e **5a-e**

Where R, a = H, b = -4Me, c = -3Cl, d = -4Cl, e = -3NO_2

Scheme II

2,5-dichloro-1-(phenyl)-1H-pyrrole-3,4-dicarbaldehyde (5a):
Yield 86%, M.P. = 110-112^{O}C. IR (KBr) cm^{-1}:2820(-CHO), 1700.40(>C=O), 1475.11(Ar=C), 1311.14(C-N), 812.81(C-Cl). ^{1}HNMR (500 MHz, DMSO-d_6, δppm): 8.3-7.2δ (m, 3H, Ar), 10.9δ (s, 1H, -CHO)

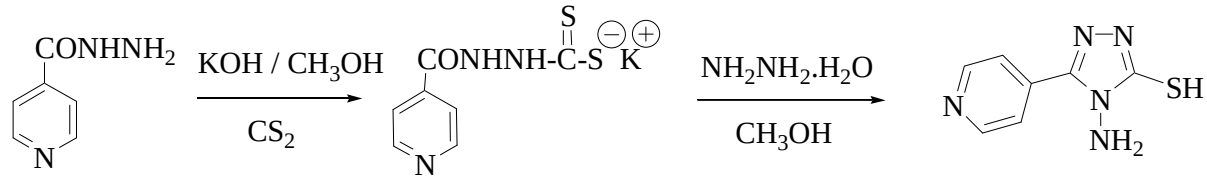
2,5-dichloro-1-(4-methylphenyl)-1*H*-pyrrole-3,4-dicarbaldehyde (5b):
Yield 76%, M.P. = 114-116 ^{O}C. IR (KBr) cm^{-1}:2835(CHO), 1705.93(>C=O), 1507.61(ArC=C), 1187(C-N). ^{1}HNMR (500 MHz, DMSO-d_6, δppm): 3.3δ(s, 3H, -CH_3),7.68-6.9δ (m, 3H, Ar-H), 10.1δ (s, 1H, -CHO).

2,5-dichloro-1-(3-chlorophenyl)-1H-pyrrole-3, 4-dicarbaldehyde (5c):
Yield 75%, M.P. = 148-150 ^{O}C. IR (KBr) cm^{-1}: 2850(CHO), 1700.93(>C=O), 1501.61(ArC=C), 1184(C-N). ^{1}HNMR (500 MHz, DMSO-d_6, δ ppm): 7.6-7.0δ (s, 4H, Ar-H), 9.43δ (s, 1H, -CHO).

2,5-dichloro-1-(4-chlorophenyl)-1H-pyrrole-3, 4-dicarbaldehyde (5d):
Yield 86%, M.P. = 158-160 ^{O}C. IR (KBr) cm^{-1}: 2860(CHO), 1705.93(>C=O), 1507.61(ArC=C), 1187(C-N). ^{1}HNMR (500 MHz, DMSO-d_6, δ ppm): 7.9-7.0δ (s, 4H, Ar-H), 9.64δ (s, 1H, -CHO).

2,5-dichloro-1-(3-nitrophenyl)-1H-pyrrole-3, 4-dicarbaldehyde (5e):
Yield 71%, M.P. = 128-130 ^{O}C. IR (KBr) cm^{-1}:2860(CHO), 1705.93(>C=O), 1507.61(ArC=C), 1187(C-N), ^{1}HNMR (500 MHz, DMSO-d_6, δppm): 8.8-7.2δ (m, 4H, Ar-H), 9.64δ (s, 1H, -CHO).

Synthesis of 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol:Isoniazide**6** (0.01mol) was added to absolute alcohol (50mL) containing potassium hydroxide (1.8g) at room temperature. Carbon disulphide was added (2.23g, 0.013mol) and the mixture stirred at room temperature for 10 hrs. The mixture was diluted with ether (30mL) and stirred for further 1 hour. The potassium salt was used for the next stage without further purification. 99% hydrazine hydrate (0.02mol) was gradually added to the above potassium salt **7** (0.01mol) dissolved in water (20mL) with stirring and the mixture changed to dark yellow. It was then cooled at 5 ^{O}C and acidified with conc. hydrochloric acid to pH 1.0. A yellow solid separated out which was filtered, wash with water and purified by recrystallization from ethanol to afforded the 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol**8**.

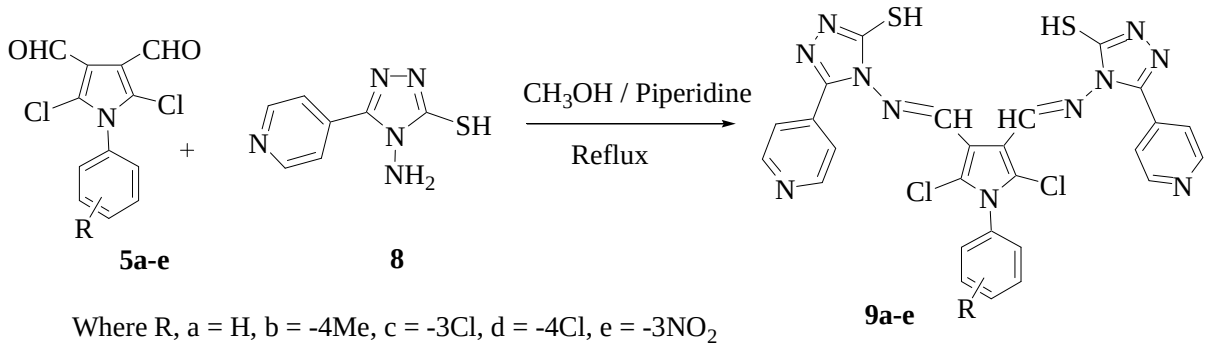


6 **7** **8**

Scheme III

Yield 65.7%, M.P. = 260-262 ^{O}C IR (KBr) cm^{-1}: 3118-3273(broad, -NH_2), 2391(-SH), 920, 997, 1057(Ar C=C), 1548, 1598(C=N), ^{1}HNMR (500 MHz, DMSO-d_6, δppm): 10.0δ (s, 1H, -SH), 9.5δ (s, 2H, -NH_2), 7.8-7.7δ(dd, 2H, pyridine), 8.35-8.2δ(dd, 2H, pyridine)

Synthesis of Schiff's bases 9a-e: A mixture of 2,5-dichloro-1-(substituted phenyl)-pyrrole-3,4-dicarbaldehyde**5a-e** (0.001mol) and4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol**8** (0.002mol) in methanol (10mL) containing a drop of piperidine was refluxed for 2-3 hours. The reaction mixture on cooling was filtered and purified by recrystallization from ethanol to give **9a-e**.



5a-e **8** **9a-e**

Where R, a = H, b = -4Me, c = -3Cl, d = -4Cl, e = -3NO_2

Scheme IV

4,4'-[(2,5-dichloro-1-phenyl-pyrrole-3,4-diyl)bis(methanylylideneazanylylidene)]bis[5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol]9a: Yield 82%, M.P. = 150-152 ^{O}C. IR (KBr) cm^{-1}: 2927.52(CH_2), 1699.91(>C=O), 1476.01(ArC=C),1204.87(C-N), 820.35(Cl). ^{1}HNMR (500 MHz, DMSO-d_6, δ ppm): 7.9-7.5δ (dd, 4H, pyridine), 7.5-7.3δ (m,5H,Ar-H), 8.8δ (s, N=CH), 10.2δ (s, 1H, -SH).

4,4'-[(2,5-dichloro-1-(4-methylphenyl)-pyrrole-3,4-diyl)bis(methanylylideneazanylyli-dene)]bis[5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol]9b :Yield 82%, M.P. 180-182 ^{O}C. IR (KBr) cm^{-1}: 2927.52(CH_2), 1699.91(>C=O), 1476.01(ArC=C),1204.87(C-N), 820.35(Cl). ^{1}HNMR (500 MHz, DMSO-d_6, δ ppm): 7.9-7.6δ (dd, 4H, pyridine), 7.5-7.3δ (m, 4H,Ar-H), 8.8δ (s, 1H, N=CH), 10.2δ (s, 1H, -SH), 2.35δ (s, 3H, -CH_3).

4,4'-[(2,5-dichloro-1-(3-chlorophenyl)-pyrrole-3,4-diyl)bis(methanylylideneazanylyli-dene)]bis[5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol] 9c:Yield 74%, M.P. = 194-196 ^{O}C. IR (KBr) cm^{-1}: 2917.52(CH2), 1695.9(>C=O), 1471.5(ArC=C), 1200.7(C-N), 824.5(Cl). ^{1}HNMR (500 MHz, DMSO-d_6, δ ppm): 7.8-7.5δ (dd, 4H, pyridine), 7.6-7.2δ (m, 4H,Ar-H), 8.9δ (s, 1H, N=CH), 10.2δ (s, 1H, -SH).

4,4'-[(2,5-dichloro-1-(4-chlorophenyl)-pyrrole-3,4-diyl)bis(methanylylideneazanylyli-dene)]bis[5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol] 9d:Yield 82%, M.P. = 210-212 ^{O}C.
IR (KBr) cm^{-1}: 2927.52(CH2), 1699.91(>C=O), 1476.01(ArC=C), 1204.87(C-N), 820.35(Cl).
^{1}HNMR (500 MHz, DMSO-d_6, δ ppm): 7.9-7.6δ (dd, 4H, pyridine), 7.5-7.3δ (m, 4H,Ar-H), 8.9δ (s, 1H, N=CH), 10.3δ (s, 1H, -SH).

4,4'-[(2,5-dichloro-1-(3-nitrophenyl)-pyrrole-3,4-diyl)bis(methanylylideneazanylyli-dene)]bis[5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol]9e:Yield 82%, M.P. = 190-192 ^{O}C. IR (KBr) cm^{-1}: 2927.5(CH_2), 1699.9(>C=O), 1476.0(ArC=C),1204.87(C-N), 820.3(Cl). ^{1}HNMR (500 MHz, DMSO-d_6, δ ppm): 8.1-7.4δ (m, 4H,Ar-H), 7.8-7.6δ (dd, 4H, pyridine), 8.9δ (s, 1H, N=CH), 10.2δ (s, 1H, -SH).

Biological Activity of Synthesized Schiff's bases:
The synthesized compounds **9a-e** were evaluated in-vitrofor antimicrobial activity against *Staphylococusaureus*, *Bacillus sabtilis*, *Escherichia coli*and*Pseudomasaeruginosa*antifungal activity against*Aspergillusniger*and *Candida albicans*at the concentration 1000 microgram/mL by paper diskdiffusion method using DMSO as solvent and nutrient agar wasemployed as culture media, the results were obtained in the form ofclearing zone and were noted after the period of incubation (at 37^{O}Cfor 24-48 hours). The zones of inhibitions were measured in mm andthe data is presented in table-I.

Sr. No.	Compound	***S. aureus***	***B. subtilis***	***E. coli***	***P. aeruginosa***	***C. albicans***	***A. niger***
1.	9a	8.77	-	-	-	8.08	-
2.	9b	7.36	-	-	-	6.76	-
3.	9c	13.26	-	-	-	9.61	-
4.	9d	14.25	-	-	-	11.71	-
5.	9e	9.31	-	-	-	7.93	-
6.	Ciprofloxacin	16.06	16.29	20.05	19.20	NA	NA
7.	Amphotericin-B	NA	NA	NA	NA	12.87	8.93

RESULTS AND DISCUSSION

There have been a number of routes developed for functionalized pyrroles, the Vilsmeier-Haack reaction is found to be the most efficient for achieving useful functional group transformation. Hence we synthesized halovinyl

aldehydes from the reaction of a series of N-substituted phenyl succinimides with Vilsmeier reagent (dimethyl formamide and phosphorous oxychloride).

The required N-substituted phenyl succinimides**4a-e**were prepared from the reaction of corresponding substituted anilines with cyclic succinic anhydride in benzene, followed by cyclisation with acetyl chloride. Halovinyl aldehydes **5a-e**were obtained by treating corresponding succinimides with Vilsmeier reagent. While 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol **8** synthesized in a multiple reactions starting from isoniazide. All the synthesized compounds were assigned by their spectroscopic data (IR and ^{1}H NMR).

The synthesized Schiff's bases **9a-e** were evaluated in-vitro for antimicrobial activity against *Staphylococusaureus, Bacillus sabtilis, Escherichia coli* and *Pseudomasaeruginosa*andantifungal activity against *Aspergillusniger*and *Candida albicans*.Compounds**9a-e** showed moderate to good activity against *S. Aureus*and *C. albicans.*

CONCLUSION

In summary, an entire new series of Schiff's bases containing 1,2,4-triazole nucleus have been synthesized from halovinyl aldehydes and 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol. And halovinyl aldehydes were synthesized from N-substituted phenyl succinimides on haloformylation with DMF/$POCl_3$ in good yields which can be used for preparing different heterocyclic systems. The synthetic strategy is straight forward and much simpler. The synthesized Schiff's bases were tested for anti-bacterial and anti-fungal activity and found to be active against *Staphylococcus aureus*and*Candida albicans.*

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REFERENCES

[1] Rajput, A. P.; Rajput, S. S. *Asian J. of Chem.***2007**, 19(6), 4939.
[2] Al-Omar, M. A.; Al-Abdullah, E. S.; Shehata, I. A.; Habib, E. E.; Ibrahim, T. M.; El-Emam, A. A. *Molecules*.**2010**, 15, 2526.
[3] Rajput, S. S. *Int. J. Pharm. Pharm. Sci.***2012**, 4(2), 164.
[4] Shalini, K.; Kumar, N.; Drabu, S.; Sharma, P. K. *Beilstein J. Org. Chem.***2011**, 7, 668.
[5] Ilkay, K.; Güniz, K.; Sevim, R.; Muammer, K. *Bioorg. Med. Chem. Lett.***2001**, 11, 1703.
[6] Yang, J. G.; Pan, F. Y. *Lett. Org. Chem.***2007**, 4, 137.
[7] Stefania-Felicia, B.; Gabriel, S.; Gabriela, L.; Constantin, D.; Florica, B.; Gabriela, B. *Eur. J. Med. Chem.***2012**, 49, 417.
[8] İlkay, K.; Esra, T.; Güniz, K.; Sevim, R.; Erik, D. *Eur. J. Med. Chem.***2008**, 43, 381.
[9] Siddiqui, N.; Alam, M. S.; Ahsan, W. *Acta. Pharm.***2008**, 58, 445.
[10] Palaska, E.; Sahin, G.; Kelicen, P.; Durlu, N. T.; Altinok, G. *Farmaco.***2002**, 57, 101.
[11] Ayhan-Kilcigil, G.; Kuş, C.; Coban, T.; Can-Eke, B.; Ozbey, S.; Iscan, M. *J. Enzyme Inhib. Med. Chem.***2005**, 20, 503.
[12] Patil, M. M.; Rajput, S. S. *Int. J. Pharm. Pharm. Sci.***2014**, 6, 8-14.
[13] Raman, N.; Kulandaisamy, A.; Thangaraja, C. *J. Trans. Met. Chem.***2003**, 28, 29.
[14] Asiri, A. M.; Khan, S. A. *Molecules*.**2010**, 15(10), 6850.
[15] Sridhar, S. K.; Saravan, M.; Ramesh, A. *Eur. J. Med. Chem.***2001**, 36, 615.
[16] Al-Amiery, A. A.; Al-Majedy, Y. K.; Ibrahim, H. H.; Al-Tamimi, A. A. *J. Org. Med. Chem. Lett.***2012**, 2(4), 1.
[17] Janos, G.; Tamas, L. *J. Curr. Med. Chem.***2009**, 16, 1091.
[18] Geronikaki, A.; Hadjipavlou-Litina, D.; Amourgianou, M. M. *Farmaco.***2003**, 58, 489.
[19] Shah, T. J.; Desai, V. A. *ARKIVOC*.**2007**, xiv, 218.
[20] Singh, P.; Kaur, P.; Luxami, V.; Kaur, S.; Subodh, S. *Bioorg. Med. Chem.***2007**, 15, 2386.
[21] Sriram, D.; Yogeeswari, P.; Myneedu, N. S.; Saraswat, V. *Bioorg. Med. Chem. Lett.***2006**, 16, 2127.