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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF NOVEL HETEROCYCLIC SUBSTITUTED 1,2,3-TRIAZOLES DERIVATIVES

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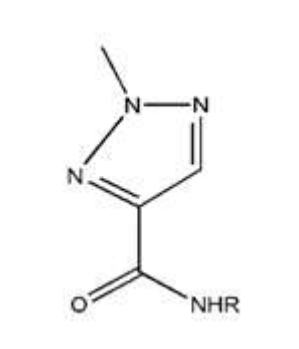
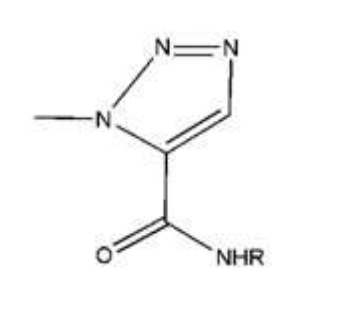
ABSTRACT
1,2,3-Triazoles possess therapeutic value, are synthetic intermediates in the preparation of medicinal compounds and find numerous applications in the chemical industry. In this study, 2-methyl-2H-1,2,3-triazole-4-carboxylic acid and 3-methyl-3H-1,2,3-triazole-4-carboxylic acid were chosen as intermediate for the synthesis of some novel substituted 1,2,3-triazole derivatives. The structures of newly synthesized compounds were established based on analytical and spectral studies. Further these compounds were evaluated for their antioxidant, antifungal and antibacterial activities. Most of the compounds showed good activity when compared with standard.





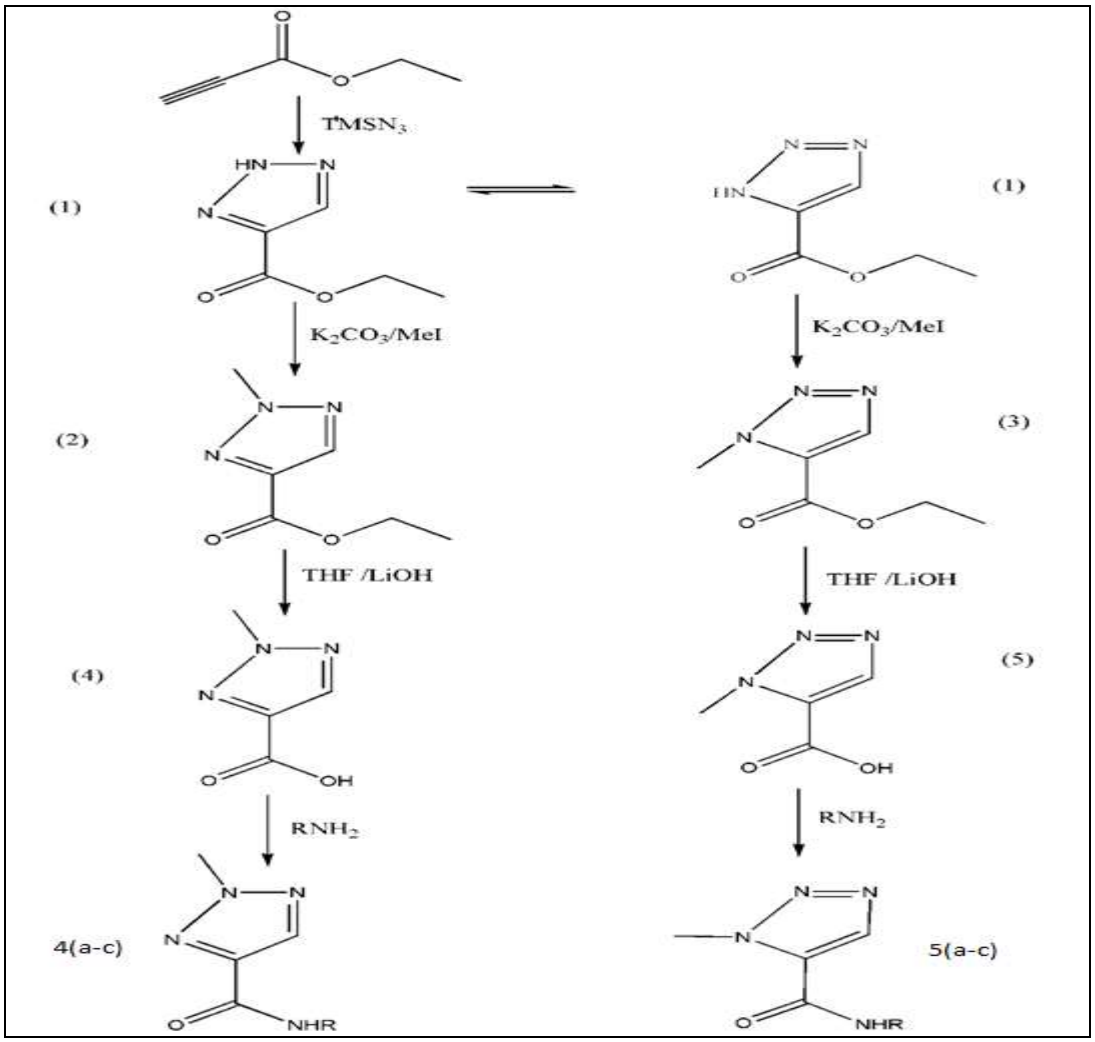
KEYWORDS: Triazole, morpholine, pyrrolidine, biological activity.

INTRODUCTION
The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry.[1-2] 1,2,3-Triazoles and benzotriazoles are important types of heterocyclic compounds. They find numerous applications in industry, namely as dyestuffs[3], fluorescent whiteners, photo stabilizers[4] of polymers, optical brightening agents[5], corrosion inhibitors[6] and as photographic photoreceptors.[7] Also, due to their extensive biological activities, they find successful application in medicine and as agrochemicals.[8-9] Beyond this, these compounds are intensively studied by many research groups due to their theoretical interest and synthetic usefulness.

In the present study, we have reported the synthesis, characterization and antibacterial, antifungal and antioxidant activities some of substituted 1,2,3-Triazoles. The newly synthesized compounds were characterized by elemental analysis, mass spectrum and FT-IR, ^{1}HNMR and ^{13}C NMR spectral data.

RESULTS AND DISCUSSION
The preliminary studies on spectral data and anti-microbial activity of the new series of (2-methyl-2H-1,2,3-triazol-4-yl)(morpholino)methanone, (2-methyl-2H-1,2,3-triazol-4-yl) (pyrrolidin-1-yl) methanone, (3-methyl-1H-pyrazol-1-yl) (2-methyl-2H-1,2,3-triazol-4-yl) methanone, (3-methyl-3H-1,2,3-triazol-4-yl) (morpholino) methanone, (3- methyl-3H-1,2,3-triazol-4-yl) (pyrrolidin-1-yl) methanone and (3-methyl-1H-pyrazol-1-yl) (3-methyl-3H-1,2,3-triazol-4-yl) methanone have generated some interesting data.[10-14]

SCHEME-1



R= morpholine, pyrrolidine, pyrozoline.

EXPERIMENTAL SECTION

All reagents were purchased from Sigma Aldrich, Nice, and SD fine chemical and used as received. The experimental compounds are synthesized as described below. The synthesized compound was tested initially by visualization of spots on TLC plates illuminated by UV radiation. In addition it is also verified by exposure to iodine vapour and heating the plates dipped in $KMnO_4$ stain.

In order to test the purity of the sample column chromatography technique was employed. Silica gel for column chromatography was purchased from Sigma Aldrich. It was high-purity grade, pore size 60 Å (0.75 cm^3/g pore volume) and 200-400 mesh (40-75 µm particle size). All the synthesized compounds was recrystallised in absolute ethanol.

Melting points were determined by melting point apparatus. The FT-IR spectrum was recorded in the solid state, as KBr dispersion by use of a Perkin- Elmer spectrum 100 series FT-IR spectrometer. All the NMR spectra were recorded using Bruker DPX 500 instrument with 5 mm PABBO BB-1H tubes. ^1H NMR spectra recorded using approximately 0.03 M solutions in $CDCl_3$ or d_6-DMSO at 500 MHz with TMS as internal reference. ^{13}C NMR spectra were recorded using approximately 0.05 M solutions in $CDCl_3$ or d_6-DMSO at 100 MHz with TMS as internal reference. MS EI was obtained using mass spectra recorded on Joel SX-102/ SC/AD/17-005 spectrometer.

Preparation of pure 2-methyl-2H-1,2,3-triazole-4-carboxylic acid (4) and 3-methyl-3H-1,2,3-triazole-4-carboxylic acid (5)[15-20].

Ethyl propiolate (5 g, 51 mmol) and azidotrimethylsilane (15.3 g, 132.5 mmol), were taken in a 3 neck round bottom flask and heated to 100^0C for 16 hrs. After completion of reaction (monitored by TLC), reaction mixture was cooled to 0^0C, methanol was added and stirred at room temperature for 30 min. Then reaction mixture was concentrated under reduced pressure and hexane was added. The solid precipitate was filtered and dried to get pure ethyl 2H-1, 2, 3-triazole-4-carboxylate (6g, 42.5 mmol, 83%) as a colorless solid.[1]

To a stirred solution of ethyl 2H-1,2,3-triazole-4-carboxylate[1] (6 g, 42.5 mmol) in acetonitrile (80 ml),

potassium carbonate(10.6 g, 76.5mmol) and iodomethane (24.1 g, 170.1 mmol) were added and heated to 60^{0}C for 16 hrs. After completion of reaction, the reaction mixture was cooled to room temperature and filtered. The filterate was concentrated and purified by column chromatography using 20-30% ethyl acetate in hexane, to get pure ethyl 2-methyl-2H-1,2,3-triazole-4-carboxylate (2.5 g ,16 mmol) of isomer[2] and ethyl 3-methyl-3H-1,2,3-triazole-4-carboxylate (2.5 g, 16 mmol) of isomer.[3]

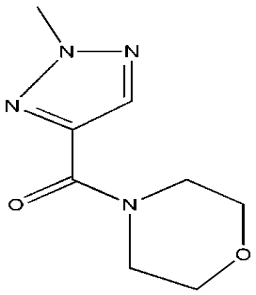
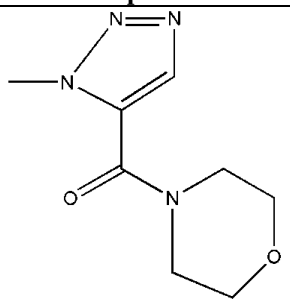
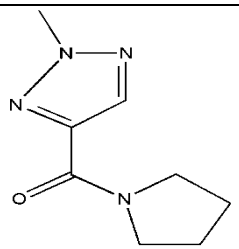
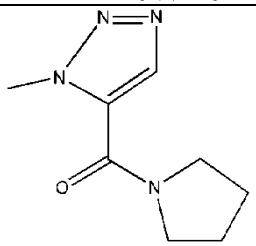
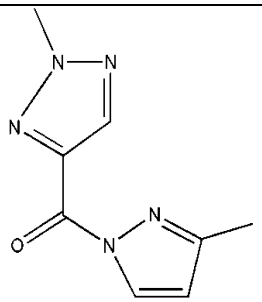
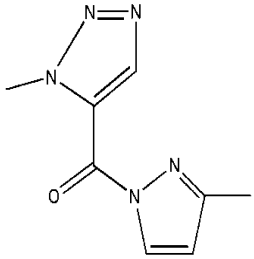
To a stirred solution of ethyl 2-methyl-2H-1,2,3-triazole-4-carboxylate (2) (2 g, 12.9 mmol) or ethyl 3-methyl-2H-1, 2, 3-triazole-4-carboxylate[3] (2 g, 12.9 mmol) in THF (10 ml), were cooled to 0^{0}C. LiOH (1.08 g, 25.8 mmol) in water (5 ml) was added drop wise. Then reaction mixture was stirred for 2 hrs at room temperature. After completion of reaction, acidified with 1.5 N HCl then extracted with dichloromethane (20 ml), the organic layer was separated and dried over sodium sulfate, to get pure 2-methyl-2H-1,2,3-triazole-4-carboxylic acid (1.3 gm, 81% yield)[4] and 3-methyl-3H-1,2,3-triazole-4-carboxylic acid (1.1 gm, 78% yield).[5]

To a stirred solution of 2-methyl-2H-1,2,3-triazole-4-carboxylic acid[4] (2 g, 12.9 mmol) or 3-methyl-3H-1,2,3-triazole-4- carboxylic acid (5) (2 g, 12.9 mmol) and dichloromethane (9 ml) was mixed. Then one equal amount of amine, morpholine or pyrrolidine or pyrozoline and 2 equal amounts of TEA were added and stirred for 16 hrs. After completion of reaction (monitored by TLC) reaction mixture was diluted with water and filtered, to get pure compounds 4(a-c) and 5(a-c).

CHARACTERIZATION DATA OF THE SYNTHESIZED COMPOUNDS

Characterization data of (2-methyl-2H-1,2,3-triazol-4-yl)(morpholino)methanone (4a)

Yield: 83% m.p˚C.110-115, LC-MS: m/z 197.4 (M+1), Anal. Calcd. (%) for $C_8H_{12}N_4O_2$: C,48.17; H,6.16; N,28.56;O,16.31; Found: C,48.00; H,6.00;N,28.41;O,16.20. IR (%T, cm^{-1}): 2830(N-CH_3), 3390(N-H), 1730(C=O), 1190(C-N), 1690(C-N), 3140(C-H). ^{1}HNMR (DMSO, 500 MHz, δ ppm): 8.55(s,1H,Ar-H), 3.47(m,2H,CH^2), 3.47(m,2H,CH_2), 3.67(m,2H,CH_2), 3.67(m,2H,CH_2) 3.63(t,3H,CH_3). ^{13}CNMR (DMSO, 100 MHz, δ ppm): 39.7(C1), 144.2(C2), 143.1(C3), 161.8(C4), 45.3(C5), 66.3(C6), 66.3(C7), 45.3(C8).

No	compounds	No	compounds
4a	 (2-methyl-2*H*-1,2,3-triazol-4-yl)(morpholino)methanone	5a	 (3-methyl-3*H*-1,2,3-triazol-4-yl)(morpholino)methanone
4b	 (2-methyl-2*H*-1,2,3-triazol-4-yl)(pyrrolidin-1-yl)methanone	5b	 (3-methyl-3*H*-1,2,3-triazol-4-yl)(pyrrolidin-1-yl)methanone
4c	 (3-methyl-1*H*-pyrazol-1-yl)(2-methyl-2*H*-1,2,3-triazol-4-yl)methanone	5c	 (3-methyl-1*H*-pyrazol-1-yl)(3-methyl-3*H*-1,2,3-triazol-4-yl)methanone

Characterization data of (2-methyl-2H-1,2,3-triazol-4-yl) (pyrrolidin-1-yl) methanone (4b)
Yield: 50% m.p˚C.117-119, LC-MS: m/z 181.4 (M+1), Anal. Calcd. (%) for $C_8H_{12}N_4O$: C,53.32; H,6.17; N,31.09;O,8.88; Found: C,53.33;H,6.17;N,31.00;O,8.89. IR (%T, cm^{-1}): 2820(N-CH_3), 3350(N-H), 1705(C=O), 1698(C=N). ^{1}HNMR (DMSO, 500 MHz, δ ppm): 8.55(m,1H,Ar-H), 3.35(m,2H,CH_2), 3.36(m,2H,CH_2), 3.63(t,3H,CH_3), 1.59(m,2H,CH_2). ^{13}CNMR (DMSO, 100 MHz, δ ppm): 39.7(C1), 144.2(C2), 143.1(C3), 165.4(C4), 48.5(C5), 25.4(C6), 25.4(C7).

Characterization data of (3-methyl-1H-pyrazol-1-yl)(2-methyl-2H-1,2,3-triazol-4-yl) methanone (4c)
Yield: 57% m.p˚C.130-131, LC-MS: m/z 192.4 (M+1), Anal. Calcd. (%) for $C_8H_9N_5O$: C,50.26; H,4.74;N,36.63;O,8.37; Found: C,50.25; H,4.61;N,36.52;O,8.25. IR (%T, cm^{-1}): 2700(N-CH_3), 3450(N-H), 1710(C=O), 1625(C=C). ^{1}HNMR (DMSO, 500 MHz, δ ppm): 8.45(s, 1H, Ar-H), 3.64(t, 3H, CH3), 7.5(m, 1H, Ar-H), 6.1(m, 1H, Ar-H), 2.7(t, 3H, CH_3). ^{13}CNMR (DMSO, 100 MHz, δ ppm): 39.7(C1), 144.2(C2), 154.1(C3), 190(C4), 141.8(C5), 17.4(C6), 105.3(C7), 132.9(C8).

Characterization data of (3-methyl-3H-1,2,3-triazol-4-yl) (morpholino) methanone (5a)
Yield: 56% m.p˚C.110-112, LC-MS: m/z 197.4 (M+1), Anal. Calcd. (%) for $C_8H_{12}N_4O_2$: C,48.17; H,6.16;N,28.56;O,16.31; Found: C,48.14; H,6.00;N,28.50;O,16.30. IR (%T, cm^{-1}): 2830(N-CH_3), 3390(N-H), 1730(C=O), 1190(C-N), 1690(C-N), 3140(C-H). ^{1}HNMR (DMSO, 500 MHz, δ ppm): 8.55(s,1H,Ar-H), 3.47(m,2H,CH^2), 3.47(m,2H,CH_2), 3.67(m,2H,CH_2), 3.67(m,2H,CH_2) 3.63(t,3H,CH_3). ^{13}CNMR (DMSO, 100 MHz, δ ppm): 39.7(C1), 144.2(C2), 143.1(C3), 161.8(C4), 45.3(C5), 66.3(C6), 66.3(C7), 45.3(C8).

Characterization data of (3- methyl-3H-1,2,3-triazol-4-yl) (pyrrolidin-1--yl) methanone (5b)
Yield: 54% m.p˚C.116-118, LC-MS: m/z 181.4 (M+1), Anal. Calcd. (%) for $C_8H_{12}N_4O$: C,53.32; H,6.17; N,31.09;O,8.88; Found: C,53.32;H,6.18;N,31.05;O,8.78. IR (%T, cm^{-1}): 2820(N-CH_3), 3350(N-H), 1705(C=O), 1698(C=N). ^{1}HNMR (DMSO, 500 MHz, δ ppm): 8.55(m,1H,Ar-H), 3.35(m,2H,CH_2), 3.36(m,2H,CH_2), 3.63(t,3H,CH_3), 1.59(m,2H,CH_2). ^{13}CNMR (DMSO, 100 MHz, δ ppm): 39.7(C1), 144.2(C2), 143.1(C3), 165.4(C4), 48.5(C5), 25.4(C6), 25.4(C7).

Characterization data of (3-methyl-1H-pyrazol-1-yl) (3-methyl-3H-1,2,3-triazol-4-yl) methanone (5c)
Yield: 59% m.p˚C.129-133, LC-MS: m/z 192.4 (M+1), Anal. Calcd. (%) for $C_8H_9N_5O$: C,50.26; H,4.74; N,36.63;O,8.37; Found: C,5.26;H,4.61;N,36.61;O,8.25. IR (%T, cm^{-1}): 2700(N-CH_3), 3450(N-H), 1710(C=O), 1625(C=C). ^{1}HNMR (DMSO, 500 MHz, δ ppm): 8.45(s, 1H, Ar-H), 3.64(t, 3H, CH3), 7.5(m, 1H, Ar-H), 6.1(m, 1H, Ar-H), 2.7(t, 3H, CH_3). ^{13}CNMR (DMSO, 100 MHz, δ ppm): 39.7(C1), 144.2(C2), 154.1(C3), 190(C4), 141.8(C5), 17.4(C6), 105.3(C7), 132.9(C8).

BIOLOGICAL ACTIVITY

Microorganisms tested

1. *Staphylococcus aureus* MTCC3381
2. *Escherichia coli* MTCC739
3. *Pseudomonas aeruginosa* MTCC424
4. *Klebsiella pneumoniae* MTCC432

ANTIBACTERIAL ACTIVITY OF 1, 2, 3-TRIAZOLES DERIVATIVES

We have investigated newly synthesized pyrazolines bearing piperonal for their antibacterial activity against *Staphylococcus aureus* MTCC3381, *Klebsiella pneumonia* MTCC432, *Escherichia coli* MTCC739, *Pseudomonas aeruginosa* MTCC424 bacterial strains by the disc diffusion method.

Results of these studies are given in compounds 4(a-c) and 5(a-c) compared with the standard gentamicin. Interestingly most of them showed the good antibacterial activity. Among the compounds **5b** and **4b** showed good inhibition towards all the four bacteria tested. Compounds **5c, 4c showed** good activity in *Staphylococcus aureus*. Compound **5a** shows good activity against *Escherichia coli.* Compounds **5c, 4b** shows good activity in *Pseudomonas aeruginosa*. Compounds **4a** shows good activity against *Klebsiella pneumonia.*

The structure activity relationship studies revealed that the compounds with fluoro substituent (**5d** and **5d**) are very much active. By the same time bromo phenyl substitution decreases the activity. Almost all these compounds are effective against the tested organisms.

Microorganisms tested

1. *Candida albicans* MTCC227.
2. *Aspergillus niger* MTCC1344.

ANTIFUNGAL ACTIVITY OF 1, 2, 3-TRIAZOLES DERIVATIVES

We have investigated newly synthesized pyrazolines by screening for their antifungal activity against *Aspergillus niger* (MTCC1344), *Candida albicans* (MTCC 227).

Antifungal activity was determined by measuring the inhibition zone. The results of these studies were given in compounds **4(a-c)** and **5(a-c)** compared with the standard Ketaconazole. Most of the compounds synthesized showed good activity against all the fungi tested. Particularly compounds **5b** were active against *Aspergillus niger*. Compounds **5a** exhibited good activity against *Candida albicans.* Compounds **5(a-c)** and **4(a-c)** have exhibited the good to moderate antifungal activity.

CONCLUSION

In this study we have successfully synthesized 1,2,3-triazole derivatives and found that they are more active

compounds. The structure of the newly synthesized compounds was elucidated by their FT-IR, ^{1}HNMR, ^{13}CNMR and MS (EI). The melting points of these compounds for medicinal applications were determined by melting point analysis. Some of the compounds contain bio active heterocyclic moiety. Also these compounds were undergone the biological activity tests and results indicate that interestingly most of them showed good anti bacterial and antifungal activity.

Among the compounds **4b, 4c, 5c** were showed good inhibition towards all bacteria tested. Compounds **5a, 5b** shows moderate to low active against all the strains tested. Compounds which showed low activity where tested for higher concentration. All the higher concentration synthesized compounds showed moderate activity. The antimicrobial screening suggests that all the newly synthesized compounds showed moderate to good activity against the tested organism.

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REFERENCES

1. Ykman, p.; Labbe, G.; Smets, G. *Tetrahedron*., 1971; 27: 5623-5629.
2. Gilchrist, T.L.; Gymer, G.E. *Advance in Heterocyclic Chemistry*. 1974; 16: 33-85.
3. Pankaja, K.; Kadaba,; Stanovnik, B. *Advance in Heterocyclic Chemistry*. 1984; 37: 217-349.
4. Nunno, L.D.; Scilimati,A. *Tetrahedron*., 1986; 42: 3913-3920.
5. Williams, E.L. *Tetrahedron letters*., 1992; 33: 1033-1036.
6. Carugo, O.; Clerici, F.; Pocarb, D. *Tetrahedron letters.*, 1993; 49: 9117-9126.
7. Augusti, R.; Kascheres, C. *Tetrahedro.*, 1994; 50: 6723-6726.
8. Romeiro, G.A.; Pereira, L.O.R.; de Souza, B.V.; Ferreira, V.F.; Cunha, A.C. *Tetrahedron letters.*, 1997; 38: 5103-5106.
9. Abarca, B.; Ballesteros, R.; Rodrigo, G.; Jones, G.; Veciana, J.; Gancedo, J.V. *Tetrahedron.* 1998; 54: 9785-9790.
10. Dong, H.S.; Quan, B. *Journal of Molecular Structure*., 2000; 553: 31-36.
11. Kaiya, T.; Aoyama, S.; Kohda, K. *Bioorganic & Medicinal Chemistry Letters*., 1999; 9: 961-964.
12. Holla, B.S.; Mahalinga, M.; Karthikeyan, M.S.; Poojary, B.; Akberali, P.M.; Kumari, N.S. *European journal of medicinal chemistry*., 2005; 40: 1173-1178.
13. Lee, B.Y.; Park, S.R.; Jeon, H.B.; Kim, K.S. *Tetrahedron letters.*, 2006; 47: 5105-5109.
14. Toumi, B.; Harizi, A. *Tetrahedron letters.*, 2006; 47: 6685-6687.
15. Cheng, Z.Y.; Li, W.J.; He, F.; Zhou, J.M.; Zhu, X.F. *Bioorganic & Medicinal Chemistry*., 2007; 15: 1533-1538.
16. Darandale, S.N.; Mulla, N.A.; Pansare, D.N.; Sangshetti, J.N.; Shinde, D.B. *European journal of medicinal chemistry*., 2013; 69: 99-114.
17. Kushwaha, K.; Kaushik, N.; Lata.; Jain, S.C. *Bioorganic & Medicinal Chemistry Letters*. 2014; 24: 1795-1801.
18. Fiandanese, V.; Marchese, G.; Punzi, A.; Iannone, F.; Rafaschieri, G.G. *Tetrahedron.,* 2010; 66: 8846-8853.
19. Sallam, M.A.E. *Carbohydrate Research.,* 2010; 345: 341-345.
20. Tornoe, C.W.; Christensen, C.; Meldal, M. *J. Org. Chem.* 2002; 67: 3057-3064.
21. Abu-Orabi, S.T.; Abu-Naajb, N.A.; Klaiba, S.; Al-Momania, L.; Jibrilb, I. *Jordan Journal of Chemistry*., 2008; 3(4): 337-347.