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Synthesis and Antimicrobial Activities of New 3-(Chloromethyl)-2-(Piperazin-1-Yl) Quinolone Derivatives

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ABSTRACT

A novel and practical method was created for the synthesis of 3-(chloromethyl)-2-(piperazin-1-yl)quinoline derivatives, which were obtained from 2-chloroquinolin-3-carbaldehydes. Newly synthesised compounds were characterised by IR, 1HNMR, and mass spectroscopy, and they were tested for their antimicrobial, antibacterial, and antifungal activities. Compounds 4a, 4b, 4c, 4daeruginosa, E. coli, and S.aureus andS. pyogenes in comparison to common antibacterial drugs including Ampicillin, Erythromycin, Chloroamphenicol, Norfloxacin, and Ciprofloxacin.

Compounds 4a, 4b, 4c, 4d, and 4e were discovered to have effective antifungal action against Candida albicans, A. nigeria, and A.Comparing Clavatusas to common forms of Nystatin and Greseofulvin.

Keywords: 2-chloroquinoline-3-carbaldehyde,3-(chloromethyl)-2-(piperazin-1-yl)quinoline, antibacterial, antifungal.

I. INTRODUCTION

Quinoline ring systems, in which the benzene ring is fused with the pyridine heterocyclic ring system, comprise a significant class of heterocyclic compounds. With one nitrogen atom in one benzene ring and none in the other ring or at the ring junction, quinolines are also known as benzo[b]pyridine and 1-azanaphthalene.Nitrogen-containing heterocycles have excellent and intriguing medical and pharmacological effects.[1–4]As an asthma medication, montelukast is utilised.[5]Additionally, many different kinds of natural goods contain quinolines as their primary component.[6-7] drugs.[8–10]Many synthetic heterocyclic compounds contain and to improve their biological and therapeutic characteristics. Quinoline-ringed compounds demonstrated a range of biological, pharmacological, and chemical activities.[11–12]*e.g.* anti-tuberculosis,[13]antiplasmodial,[14] antibacterial,[15-16]antihistamine,[17] antifungal,[18] antimalarial,[19-20] anti-HIV,[21] anticancer,[22] anti-infammatory,[23-24] anti-hypertensive,[25] and antioxidant activities.[26] In addition, the use of quinolines as tyrokinasePDGF-RTKinhibitor,[27] inositol 5-phosphatase (SH_2),[28] DNA gyraseB inhibitors as Mycobacterium tuberculosis,[29] and DNA topoisomerase inhibitors,[30] were reported. Racemic fuoroquinolonenadifoxacin was introduced as a topical antibiotic in Japan in 1993 to treat methicillin-resistant staphylococcal infections and acne. Quinolinic acid has recently been used to research bio-organic

and bio-organometallic processes.[31] Many pharmacologically significant synthetic compounds are designed using the skeleton of the quinoline as a crucial step.[32-33]

A very interesting class of organic compounds, 2-Chloroquinoline-3-carbaldehydes can be used as precursors and building blocks for the synthesis of a variety of heterocyclic systems as well as powerful antibiotics for the treatment of cancer and bacteria.The current study indicates that quinoline derivatives display antibacterial and antifungal activities, continuing our work on the synthesis, characterisation, and activity of compounds containing quinoline[34–39.]

II. MATERIALS AND METHODS

Using the described technique, 2-Chloroquinoline-3-carbaldehydes were produced in the lab.Methanol, sodium hydroxide, sodium borohydride, dichloromethane, and piperazine were purchased from S.D.Fine-chem.At atmospheric pressure, all physical constants were calculated in open capillaries.Using TMS as an internal standard, 1H NMR spectra in CDCl3, DMSO, and 400 MHz were captured on the AVANCE.On a Bruker FTIR, IR spectra were captured using KBr discs. Mass spectra were captured, displaying a molecular ion peak. TLC was used on Merck silica gel plates to determine the product purity and the rate of the reactions.

General procedure:

2-(piperazin-1-yl)quinoline-3-carbaldehyde(2a):1.9 gm of 2-Chloroquinoline-3-carbaldehydes (10 mmol) and 4 gm of piperazine were added gradually while being stirred at room temperature in a 50 mL round-bottom flask. The reaction mixture was heated to 45^{0}C. The progress of reaction was monitored on TLC (8:2 –Hexane: ethyl acetate). After the completion of the reaction (4 hr), the reaction mixture was poured on ice cold water, the solid obtained was filtered off and washed with water to get product 2-(piperazin-1-yl)quinoline-3-carbaldehyde,drywt. 2.10 gm.

(2-(piperazin-1-yl)quinolin-3-yl)methanol (3a): In a 50 ml round bottom flasktaken 2-(piperazin-1-yl)quinoline-3-carbaldehyde1.95gm (8mmol) and 15 ml methanol was slowly added sodium borohydride (1.0 gm) under stirring at room temperature.TLC was used to track the reaction's development (8:2 – Hexane: ethyl acetate).The reaction mixture was concentrated under decreased pressure to extract residue once the reaction had finished (10 minutes).Ice cold water was then added to this residue, and the resulting solid was filtered out and rinsed with water to achieve the desired product. (2-(piperazin-1-yl)quinolin-3-yl)methanol, dried in oven at 40 ^{0}Cfor 5.0 hr (1.95 gm).

3-(chloromethyl)-2-(piperazin-1-yl)quinoline(4a): To the stirred solution of (2-(piperazin-1-yl)quinolin-3-yl)methanol1.72gm(7mmol) in DCM (10 ml) in a 50 ml round bottom flask was added dropwise a solution of $SOCl_2$ (2 ml) in 5 ml DCM. After the complete addition, stirred it for 1 hr at room temperature. The reaction progress was monitored by the TLC (8:2 -Hexane: ethyl acetate), after complete conversion, distilled out the solvent under reduced pressure to get the product,dried in oven at 50 ^{0}C for 4.0 hr (1.6 gm).

Antibacterial and Antifungal activity:-

Escherichia coli (MTCC-443), Pseudomonas aeruginosa (MTCC-1688), Staphylococcus aureus (MTCC-96), and Streptococcus pyogenes (MTCC-442) were tested for antibacterial activity. Candida albicans (MTCC-227), Aspergillusniger (MTCC-282) and Aspergillusclavatus were tested for anti (MTCC-1323).

The test bacteria were grown and the medication suspension was diluted using Mueller Hinton Broth as a nutrition medium. This agar media was autoclaved at 120 °C for 30 minutes to sanitise it, then it was poured at a uniform depth of 5 mm and left to set.To achieve uniform development of the organisms, themicrobial suspension (105 CFU/mL) was streaked over the surface of media using a sterile cotton swab.The chemicals under test were dissolved in DMSO to produce solutions with concentrations ranging from 3.25 to 1000 g/ml.The solidified nutritional agar medium that has been treated with the appropriate microbe was deposited on sterilised filter paper discs measuring 6.25 mm in diameter. The discs had previously been soaked in a known quantity of the test substance in DMSO (fungi).Without any samples, a control disc impregnated with an equivalent amount of DMSO was also employed, but it did not result in any inhibition.The minimum bacterial inhibitory concentration (MIC) of the substance was measured using the agar streak dilution method. Ampicillin and griseofulvin were utilised as control medicines for antibacterial and antifungalactivity, respectively (Hawkey and Lewis 1994).Graded amounts of the test compounds were added to a defined amount of molten sterile agar for the evaluation of antibacterial and Sabouraud dextrose agar for antifungalactivity, respectively, from a stock solution of the produced compounds in DMSO.A Petri dish was filled to a depth of 4–5 mm with the medium containing the test substance, and aseptic conditions were used to allow the medium to solidify. Asuspension of the respective microorganism of approximately105 CFU/mL was prepared and applied to plateswith serially diluted compounds with concentrations in therange of 3.12–1000 μg/mL in DMSO and incubated at (37± 1)°C for 24 hr (bacteria) and 72 hr(fungi). Test run wastriplicated; the lowest concentration of the substance thatprevents the development of visible growth is considered tobe the MIC value.

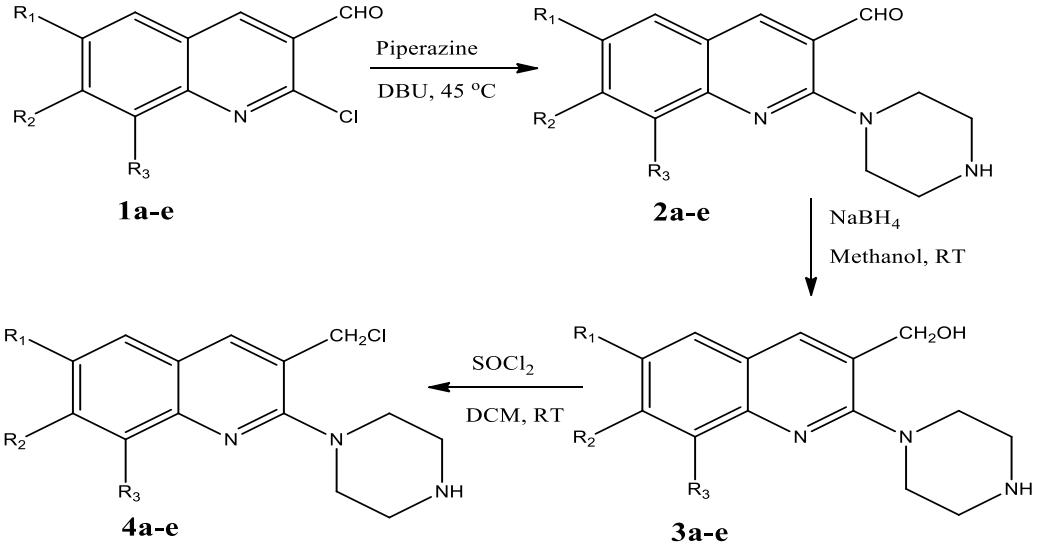
III. RESULTS AND DISCUSSION

Herein, we report a simple method for the synthesis of new3-(chloromethyl)-2-(piperazin-1-yl)quinolone derivatives in excellent yields **(Scheme-I).**The2-chloroquinoline-3-carbaldehyde **1a–e** when reacted with piperazine using DBU base catalyst at 45^{0}Cformed the derivatives of2-(piperazin-1-yl)quinoline-3-carbaldehyde**2a–e** in excellent 90–95% yields (Table 1, entries 1–5).These 2-(piperazin-1-yl)quinoline-3-carbaldehyde2a–e derivatives on reduction with sodium borohydride in methanol at room temperature formed substituted (2-(piperazin-1-yl)quinolin-3-yl)methanol**3a–e**. These (2-(piperazin-1-yl)quinolin-3-yl)methanolreactsthionyl chloride in DCM at room temperature to give the products3-(chloromethyl)-2-(piperazin-1-yl)quinolone**4a-e** in excellent yields (88–93%) (Table-1, entries 11–15).The progress of the reaction was monitored by thin layer chromatography (8:2 - hexane: ethyl acetate solvent system). The reaction proceeded smoothly and completed in 1 hr to afford the corresponding titled compounds in very high yields (88–93%) **(Table-1, entries 11–15)**. The chemical structures of all the new compounds were

confirmed by IR, ^{1}H NMR, mass spectroscopic data, and elemental analysis.

The antibacterial activity of the titled compounds (4a–e) was carried out *against S. pyogenes, P. aeruginosa*, *S. aureus* and *E. coli* using Ampicillin as thestandard. MIC values were obtained by the broth dilutiontechnique. DMSO was used as diluent. MIC values aresummarized in **Table 2**. Most of the synthesized compoundsdisplayed good antibacterialactivity compared with standard drug Ampicillin with Gram +vebacterial strains and Gram –vestrain.

The antifungal activity of the titled compounds (4a–e) was appraised against *A. niger*, *A. clavatus*and*C. albicans* using Griseofulvin as the standard drugwith the broth dilution method **(Table3)**. The synthesizedcompounds were found to be good activity against the standarddrug Griseofulvin against *A. niger*, *A. clavatus*and*C. Albicans,* strains.



Scheme-1: Synthesis of 3-(chloromethyl)-2-(piperazin-1-yl)quinoline

Table-1: Physical data of the synthesized compounds

Entry	Compound	R_1	R_2	R_3	Reaction Time	Yield (%)
1	**2a**	H	H	H	4hr	93
2	**2b**	CH_3	H	H	4hr	94
3	**2c**	H	H	CH_3	4 hr	94
4	**2d**	H	CH_3	H	4 hr	96
5	**2e**	OCH_3	H	H	4hr	93
6	**3a**	H	H	H	10 min	95
7	**3b**	CH_3	H	H	10 min	94
8	**3c**	H	H	CH_3	10 min	94
9	**3d**	H	CH_3	H	10 min	95
10	**3e**	OCH_3	H	H	10 min	94

11	**4a**	H	H	H	60 min	91
12	**4b**	CH_3	H	H	60 min	91
13	**4c**	H	H	CH_3	60 min	90
14	**4d**	H	CH_3	H	60 min	92
15	**4e**	OCH_3	H	H	60 min	91

Table-2: Antibacterial Activity

Sr. No.	Compound	*MINIMAL BACTERICIDAL CONCENTRATION*			
		E.COLI	P.AERUGINOSA	S.AUREUS	S.PYOGENUS
		MTCC 443	MTCC 1688	MTCC 96	MTCC 442
		MICROGRAM/ML			
1	4a	250	250	250	100
2	4b	500	250	500	250
3	4c	250	100	250	125
4	4d	100	250	500	100
5	4e	125	150	250	100

Table-3: Antifungal Activity

Sr. No.	Compound	*MINIMAL FUNGICIDAL CONCENTRATION*		
		C.ALBICANS	A.NIGER	A.CLAVATUS
		MTCC 227	MTCC 282	MTCC 1323
		MICROGRAM/ML		
1	4a	250	500	500
2	4b	500	500	500
3	4c	500	500	500
4	4d	500	1000	500
5	4e	500	500	500

Table-4: Standard Drugs:

MINIMAL BACTERICIDAL CONCENTRATION				
DRUG	E.COLI	P.AERUGINOSA	S.AUREUS	S.PYOGENUS
	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
(MICROGRAM/ML)				
ERYTHROMYCINE	2	5	0.25	0.5
AMPICILLIN	100	100	250	100

CHLORAMPHENICOL	50	50	50	50
CIPROFLOXACIN	25	25	50	50
NORFLOXACIN	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION			
DRUG	C.ALBICANS	A.NIGER	A.CLAVATUS
	MTCC 227	MTCC 282	MTCC 1323
MICROGRAM/ML			
NYSTATIN	100	100	100
GRESEOFULVIN	500	100	100

IV. CONCLUSION

In this study, a series of Newderivatives of 3-(chloromethyl)-2-(piperazin-1-yl)quinolone were prepared from 2-chloroquinolin-3-carbaldehydes and preliminarybiological evaluation of antimicrobial activityof the synthesized compounds showedgood antibacterialactivity with standard drug Ampicillin with Gram +vebacterial strains and Gram –vestrain. The antifungal activity of the titled compounds (4a–e) was evaluted against *A. niger*, *A. clavatus*and *C. albicans* using Griseofulvin as the standard drugwith the broth dilution method (Table 3). The synthesizedcompounds were found to be good activity with the standarddrug Griseofulvin against *A. niger*, *A. clavatus*and*C. albicans* strains.

All the reactions wereperformed under mild reaction conditionsshorter reaction time and in quantitative yields. The methodologydeveloped will be of much use tocombinatorial chemist.

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Spectroscopic data:-

4a) 3-(chloromethyl)-2-(piperazin-1-yl)quinoline

IR (KBr):2897cm^{-1}(-C-H); 1613cm^{-1} (-C=C); 748cm^{-1} (C-Cl);

^{1}H NMR ($CDCl_3$,δppm):3.41(m, 4H, C$\underline{H}_2$);3.88(m, 6H, C$\underline{H}_2$);3.91 (s, 2H, C$\underline{H}_2$);7.36 (t, 1H, Ar-$\underline{H}$); 7.58 (t, 1H, Ar-$\underline{H}$);7.70(d, 1H, Ar-$\underline{H}$); 7.86 (d, 1H, Ar-$\underline{H}$); 8.13 (s, 1H, Ar-$\underline{H}$).

ESMS: m/z 262.05(m+1)

4b) 3-(chloromethyl)-6-methyl-2-(piperazin-1-yl)quinoline

IR (KBr):2975 cm^{-1}(-C-H), 1615 cm^{-1}(-C=C), 752 cm^{-1}(-C-Cl)

^{1}H NMR ($CDCl_3$, δ ppm):2.50(s, 3H, Ar-C$\underline{H}_3$);3.33(m, 4H, C$\underline{H}_2$); 3.70(m, 6H, C$\underline{H}_2$); 3.88(s, 2H, C$\underline{H}_2$); 7.19 (d, 1H, Ar-$\underline{H}$); 7.26 (s, 1H, Ar-$\underline{H}$); 7.58 (d, 1H, Ar-$\underline{H}$); 8.03(s, 1H, Ar-$\underline{H}$).

ESMS:m/z 276.06 (m+1)

4c) 3-(chloromethyl)-7-methyl-2-(piperazin-1-yl)quinoline

IR (KBr): 2930 cm^{-1}(-C-H), 1608cm^{-1} (-C=C), 748 cm^{-1}(-C-Cl)

^{1}H NMR ($CDCl_3$, δ ppm):2.50(s, 3H, Ar-CH_3);3.33- 3.70 (m, 10H, CH_2); 3.92(s, 2H, CH_2); 7.21(d, 1H, Ar-H); 7.26 (s, 1H, Ar-H); 7.58 (d, 1H, Ar-H); 8.03(s, 1H, Ar-H).

ESMS:m/z 276.06 (m+1)

4d) 3-(chloromethyl)-8-methyl-2-(piperazin-1-yl)quinoline

IR (KBr):2919 cm^{-1} (C-H); 1594 cm^{-1} (C=C); 745cm^{-1} (C-Cl)

^{1}H NMR ($CDCl_3$, δ ppm): 2.50(s, 3H, Ar-CH_3);3.33 – 3.70 (m, 10H, CH_2); 3.88(s, 2H, CH_2); 7.15 (d, 1H, Ar-H); 7.26 (s, 1H, Ar-H); 7.58 (d, 1H, Ar-H); 8.03(s, 1H, Ar-H).

ESMS:m/z 276.02 (m+1)

4e) 3-(chloromethyl)-6-methoxy-2-(piperazin-1-yl)quinoline

IR (KBr):2973 cm^{-1}(-C-H), 1621 cm^{-1}(-C=C), 737cm^{-1} (-C-Cl)

^{1}H NMR ($CDCl_3$, δ ppm): 3.30 - 3.70(s, 10H, CH_2); 3.83(s, 3H, Ar-OCH_3); 3.90(s, 2H, CH_2); 7.02 (d, 1H, Ar-H); 7.26 (s, 1H, Ar-H); 7.76 (d, 1H, Ar-H); 8.03(s, 1H, Ar-H).

ESMS:m/z 292.02 (m+1)

V. REFERENCES

[1]. B. Nammalwar and R. A. Bunce, Molecules, 2014, 19, 204–232.

[2]. M. J. Mphahlele and A. O. Adeloye, Molecules, 2013, 18, 15769–15787.

[3]. N. H. Al-Shaalan, Molecules, 2007, 12, 1080–1091.

[4]. O. Afzal, S. Bawa, S. Kumar and R. K. Tonk, Molbank, 2012, M748.

[5]. J. Jaware and S. Borhade, Indo Am. J. Pharm. Res., 2014, 4(5),2496–2502.

[6]. J. P. Michael, Nat. Prod. Rep., 2004, 650–668.

[7]. J. P. Michael, Nat. Prod. Rep., 2003, 476–493.

[8]. A. A. Alhaider, M. A. Abdelkader and E. J. Lien, J. Med. Chem., 1985, 28, 1394–1398.

[9]. S. F. Campbell, J. D. Hardstone and M. J. Palmer, J. Med. Chem., 1988, 31, 1031–1035.

[10].D. Wu, Tetrahedron, 2003, 59, 8649–8687.

[11].N. J. P. Subhashini, J. Amanaganti, L. BodduandP. A. Nagarjuna, J. Chem. Pharm. Res., 2013, 5(1), 140–147.

[12].W. Gao, J. Liu, Y. Jiang and Y. Li, Beilstein J. Org. Chem.,2011, 7, 210–217.

[13].R. S. Keri and S. A. Patil, Biomed. Pharmacother, 2014, 68, 1161–1175.

[14].S. Vandekerckhove, S. V. Herreweghe, J. Willems,B. Danneels, T. Desmet, C. de Kock, P. J. Smith,K. Chibale and M. D'hooghe, Eur. J. Med. Chem., 2015, 92, 91–102.

[15].N. C. Desai, G. M. Kotadiya and A. R. Trivedi, Bioorg. Med.Chem. Lett., 2014, 24, 3126–3130.

[16].R. Vlahov, J. Parushev, P. Nickel and G. Snatzke, J. Pure Appl.Chem. Res., 1990, 7, 1303–1306.

[17].A. Srivastava, M. K. Singh and R. M. Singh, Indian J. Chem., 2005, 45B, 292–296.

[18].S. Pramilla, S. P. Garg and S. R. Nautiyal, Indian J. Heterocycl. Chem., 1998, 7, 201–204.

[19].S. Vandekerckhove and M. D'hooghe, Bioorg. Med. Chem., 2015, 23, 5098–5119.
[20].M. A. Lyon, S. Lawrence, D. J. William and Y. A. Jackson, J. Chem. Soc., Perkin Trans. 1, 1999, 437–442.
[21].N. Ahmed, K. G. Brahmbhatt, S. Sabde, D. Mitra, I. P. Singh and K. K. Bhutani, Bioorg. Med. Chem., 2010, 18, 2872–2879.
[22].V. Spano, B. Parrino, A. Carbone, A. Montalbano,Salvador, P. Brun, D. Vedaldi, P. Diana, G. Cirrincione and P. Barraja, Eur. J. Med. Chem., 2015, 102, 334–351.
[23].S. A. El-Feky, Z. K. Abd El-Samii, N. A. Osman, J. Lashine,M. A. Kamel and H. Kh. Thabet, Bioorg. Chem., 2015, 58, 104–116.
[24].M. A. Kerry, G. W. Boyd, S. P. Mackay, O. Meth-cohnandL. Platt, J. Chem. Soc., Perkin Trans. 1, 1999, 2315.
[25].H. P. Heinz, H. C. Milhahn and E. Eckart, J. Med. Chem., 1999, 42, 659–668.
[26].B. Vivekanand, K. M. Raj and B. H. M. Mruthyunjayaswamy,J. Mol. Struct., 2015, 1079, 214–224.
[27].M. P. Maguire, K. R. Sheets, K. McVety, A. P. Spada and A. Zilberstein, J. Med. Chem., 1994, 37, 2129–2137.
[28].C. M. Russo, A. A. Adhikari, D. R. Wallach, S. Fernandes,N. Balch, W. G. Kerr and J. D. Chisholm, Bioorg. Med. Chem. Lett., 2015, 25, 5344–5348.
[29].B. Medapi, J. Renuka, S. Saxena, J. P. Sridevi, R. Medishetti,P. Kulkarni, P. Yogeeswari and D. Sriram, Bioorg. Med. Chem., 2015, 23, 2062–2078.
[30].J. A. Spicer, S. A. Gamage, G. J. Finlay and W. A. Denny, J. Med. Chem., 1997, 42, 2383–2393.
[31].Saito, I.; Sando, S.; Nakatani, K. Bio Org Med Chem. 2001, 9, 2381.
[32].O. Meth-Cohn, B. Narine and B. A. Tarnowski, J. Chem. Soc.,Perkin Trans. 1, 1981, 1520–1530.
[33].Bhaduri, A. P. Synlett1990, 557.
[34].R.U.Pokalwar,R.V.Hangarge,P.V. Maske, M.S. Shingare, Arkivoc2006, xi 196-204.
[35].R.U.Pokalwar, R.V.Hangarge, B.R.Madje, M.N.Ware,M.S.Shingare, Phosphorus, Sulfur, Silicon Relat. Elem. 2008, 183, 1461-1470.
[36].R.U.Pokalwar, R.V. Hangarge, A.H. Kategaonkar,M.S. Shingare, Russian Journal of Organic Chemistry, 2009, 45, 3, 430–433.
[37].R.U.Pokalwar,S. A. Sadaphal, A.H.Kategaonkar,M.S.Shingare, Green Chemistry letters and reviews2010, 1-6.
[38].R.U.Pokalwar, P.V. Shinde, A.B. Chidrawar, M.S. Shingare, Chemistry and biology interface 2012,2,1,31-37.
[39].R.U.Pokalwar, A.B. Chidrawar, Chemistry and biology interface 2013,3,5,339-345.