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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME QUINOLINE DERIVATIVES

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ABSTRACT: Cyclocondensation of 5-6 and 7-8 with chloroacetyl chloride in presence of triethylamine give 9-10 and 11-12 respectively. All the synthesized compounds 1-12 have been screened for their antibacterial as well as antifungal activities and compared with reference drugs streptomycin and fusidic acid respectively. These synthesized compounds were screened for their antibacterial activity against *S. aureus* and *B. subtillis* and antifungal activity against *A. niger* and *C. albicans*. The melting points were determined in open glass capillaries tubes. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel G plates and spots were located by using iodine chamber. All the newly synthesized compounds were confirmed by elemental (C, H, N) and spectral IR, ^{1}HNMR analysis. In this series compound 10 showed better antibacterial activity than reference drug streptomycin and compounds 10 and 12 were found to be more potent antifungal agents than reference drug fusidic acid.

INTRODUCTION: Quinoline derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. They are widely used in pharmaceuticals and agrochemicals. Several reports have been published on the biological activity of quinoline derivatives including their antimicrobial [1, 2], antibacterial [3], anti-inflammatory [4], anticancer [5] and anticonvulsant [6] activities. Similarly, various azetidinones have attracted considerable attention as they are also endowed with a wide range of pharmaceutical activities including anticonvulsant[7], antimicrobial [8], anti-inflammatory [9, 10] and antibacterial [11, 12] activities.

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Looking to the medicinal importance of quinolines and azetidinones, we report here the synthesis of new class of heterocyclic molecules in which all of these moieties are present and try to develop potential bioactive molecules.

METERIAL AND METHODS:

All reagents and solvents were of analytical grade and used directly. Reactions were routinely performed in oven-dried borosil glassware. The melting points of compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. The homogeneity of all newly synthesized compounds was routinely checked by thin layer chromatography (TLC) on silica gel G plates and spots were located by using iodine chamber. Elemental analysis (C, H, N) of all the synthesized compounds were determined by Perkin-Elmer 2400 elemental analyzer, and results were found within the ± 0.4% of theoretical values. The IR spectra were recorded on a Beckman Acculab-10

spectrometer (ν_{max} in cm^{-1}) and the ^1H NMR spectra were recorded by Brucker DPX-300 MHz using $CDCl_3$ as solvent.

Pharmacological studies:

All the newly synthesized metal complexes were tested for their antimicrobial activity. The effects of unknown metal complexes were compared with the standard drug streptomycin for bacteria and fusidic acid for fungi. Antibacterial activity was performed against *S. aureus, B. subtillis* and antifungal activity against *A. niger* and *C. albicans*. The antibacterial activity was assayed by cup plate method [13] and antifungal activity was assayed by standard agar disc diffusion method [14].

RESULTS AND DISCUSSION:

The antibacterial activity of compounds 1-12 and the standard drug streptomycin, was carried out against *S. aureus* and *B. substillis*. Results showed the varying degree of antibacterial activity of all the compounds tested (table-1). From the result it is clear that compound 10 showed excellent antibacterial activity, better than the standard drug and good inhibition zones against all the bacterial strains. Compounds 9,11 and 12 showed good antibacterial activity against all the tested organism. The other compounds of this series showed a moderate activity as compared to standard drug. Compounds 1-12 along with the reference drug fusidic acid were also tested for antifungal activity against *A. niger* and *C. albicans* (**Table 1**). The results of the antifungal screening revealed that all the tested compound 1-12 showed moderate to good antifungal properties. Out of these compounds tested, compounds 10 and 12 were found to be more potent antifungal agents against all the fungal strains than the reference drug.

TABLE 1: ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF COMPOUNDS 1-12

Compounds	R	Bacterial inhibition zone/mm		Fungal inhibition zone/mm	
		S. aureus	*B. substillis*	*A. niger*	*C. albicans*
1	H	15	18	-	20
2	CH_3	22	-	20	18
3	H	24	-	25	-
4	CH_3	-	27	-	-
5	H	28	25	28	23
6	CH_3	30	27	29	27
7	H	32	-	32	30
8	CH_3		31	33	-
9	H	35	34	36	35
10	CH_3	42	39	40	39
11	H	39	35	34	36
12	CH_3	38	36	38	40
Streptomycin		39	37		
Fusidic acid				37	38

Preparation of Benzylic azides/2-methyl benzylic azide:

To a solution of benzyl alcohol (1.0 equiv) in Dichloromethane (2.6 ml) was added PBr_3 (0.34 equiv) at room temperature. The reaction mixture was stirred for 1 h and then the solvent was removed under reduce pressure. The crude product was dissolved in DMSO (2.6 ml) and NaN_3 (2.5 equiv) was added at 0^0C. The mixture was stirred 16 h and diluted with water and extracted with EtOAc. The product was dried with Na_2SO_4 and concentrated under reduced pressure to obtain the crude material which was purified on silica gel to yield the benzylic azides.

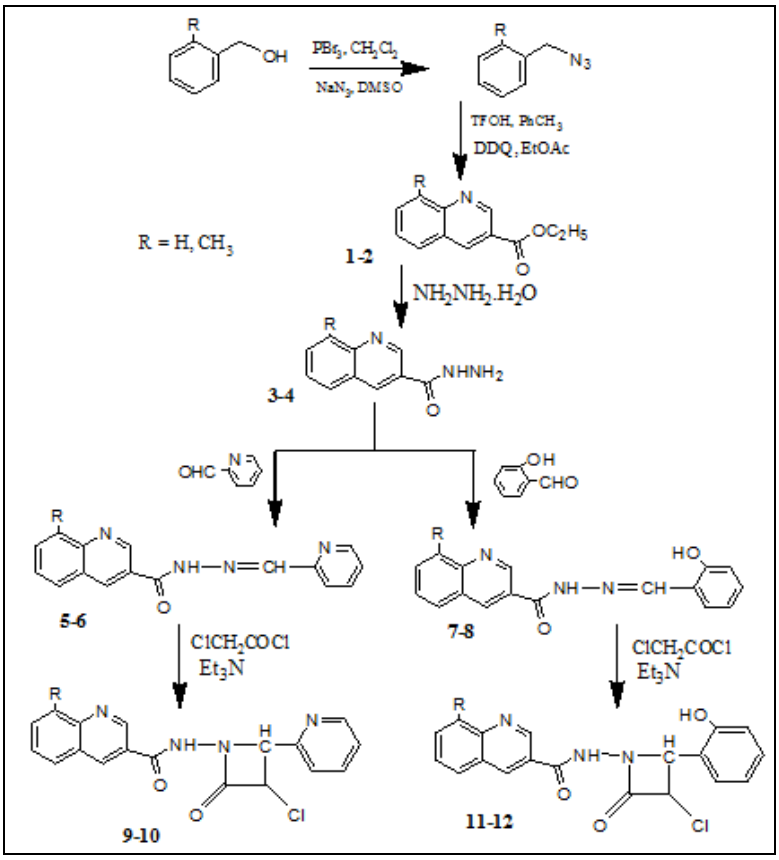
Preparation of Ethyl quinoline-3-carboxylate (1)

To a solution of substituted benzylic azide (1.0 mol) in toluene (20 ml) were added TfOH (1.0 mol) at room temperature respectively. The reaction mixtures were stirred until the evolution of N_2 gas bubbles subsided. The reaction mixtures were stirred for 3h and then added with sat. $NaHCO_3$ to dilute the reaction. The reaction mixtures were extracted with EtOAc (40 ml) and then DDQ was added and stirred for 5 min. The solvent was removed under reduced pressure to obtain the crude material which as purified on silica gel using hexane to yield compounds 1-2.

Yield (67), m.p:156 ^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1296 (C-N), 1575 (-N=CH), 1724 (-C=O), 1784 (COOEt), 3017 (C-H aromatic); ^{1}H-NMR (DMSO-d_6 δ ppm): 3.25 (s, 5H, OC_2H_5), 7.72-8.30 (m, 6H, ArH); Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96: Found: C, 71.66; H, 5.54; N, 6.94%.

Ethyl 8-methylquinoline-3-carboxylate (2):
Yield (61), m.p: 173^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1299 (C-N), 1573 (-N=CH), 1720 (-C=O), 1787 (COOEt), 3015 (C-H aromatic); ^{1}H-NMR (DMSO-d_6 δ ppm): 2.23 (s, 3H, CH_3), 3.27 (s, 5H, OC_2H_5), 7.70-8.31 (m, 5H, ArH); Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51: Found: C, 72.56; H, 6.12; N, 6.54%.

Preparation of Quinoline-3-carbohydrazide (3):
A mixture of compounds1-2 (1.0 mol) and hydrazine hydrate (2.0 mol) in absolute ethanol (80 ml) was refluxed for 20 h respectively. The reaction mixtures were cooled and poured on crushed ice and separated solids were filtered, washed with cold water, dried and recystalliized from ethyl acetate to yield compound 3-4. Yield (56), m.p: 168^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1295 (C-N), 1577 (-N=CH), 1726 (-C=O), 3013 (C-H aromatic), 3324 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 4.65 (hump, 2H, NH_2 exchangeable), 7.46 (br, 1H, NH exchangeable), 7.71-8.30 (m, 6H, ArH); Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45: Found: C, 64.18; H, 4.84; N, 22.44%.



SCHEME: 1

Methylquinoline-3-carbohydrazide (4):
Yield (52), m.p: 185^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1297 (C-N), 1579 (-N=CH), 1723 (-C=O), 3010 (C-H aromatic), 3326 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 2.21 (s, 3H, CH_3), 4.65 (hump, 2H, NH_2 exchangeable), 7.40 (br, 1H, NH exchangeable), 7.72-8.31 (m, 5H, ArH); Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88: Found: C, 65.69; H, 5.54; N, 20.85%.

Preparation of N'-(pyridine-2-ylmethylene) quinoline-3-carbohydrazide (5):
A solution of compounds 3-4 (1.0 mol) in methanol (50 ml) were refluxed with picolinaldehyde (1.0 mol) in the presence of glacial acetic acid (4 ml) for 11h respectively. The reaction mixtures were concentrated, cooled and then poured into ice water. The separated solids were filtered and recrystallized from ethanol to yield compounds 5-6.

Yield (47), m.p: 192^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1295 (C-N), 1512 (N-N), 1573 (-N=CH), 1726 (-C=O), 3013 (C-H aromatic), 3322 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 7.44 (d, 1H, NH), 7.71-8.33 (m, 10H, ArH), 8.63 (s, 1H, -N=CH); Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28: Found: C, 69.56; H, 4.39; N, 20.24%.

8-Methyl - N'- (pyridine - 2 - ylmethylene) quinoline -3-carbohydrazide (6):

Yield (44), m.p: 195^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1294 (C-N), 1507 (N-N), 1577 (-N=CH), 1728 (-C=O), 3016 (C-H aromatic), 3324 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 2.25 (s, 3H, CH_3), 7.43 (d, 1H, NH), 7.73-8.30 (m, 9H, ArH), 8.61 (s, 1H, -N=CH); Anal. Calcd. for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30: Found: C, 70.36; H, 4.84; N, 19.34%.

N'-(Pyridine - 2 - ylmethylene) quinoline-3-carbohydrazide (7):

A mixture of compound 3-4 (1.0 mol) and different substituted benzyldehyde (1.0 mol) in 50 ml of methanol along with glacial acetic acid (2-3 drops) was refluxed for 12 h. The reaction mixtures were cooled. The solids were obtained then filtered, washed with water, dried and recrystallized from appropriate solvents to furnish compounds 7-8.

Yield (), m.p: 214^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1292 (C-N), 1505 (N-N), 1574 (-N=CH), 1723 (-C=O), 3012 (C-H aromatic), 3325 (-C-NH), 3450 (OH); ^{1}H-NMR (DMSO-d_6 δ ppm): 7.41 (d, 1H, NH), 7.70-8.29 (m, 10H, ArH), 8.66 (s, 1H, -N=CH), 12.20 (s, 1H, OH); Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28: Found: C, 69.57; H, 4.34; N, 20.26%.

8-Methyl-N'-(pyridine-2 -ylmethylene) quinoline -3-carbohydrazide (8):

Yield (45), m.p: 221^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1297 (C-N), 1509 (N-N), 1577 (-N=CH), 1726 (-C=O), 3014 (C-H aromatic), 3326 (-C-NH), 3455 (OH); ^{1}H-NMR (DMSO-d_6 δ ppm): 2.23 (s, 3H, CH_3), 7.46 (d, 1H, NH), 7.73-8.31 (m, 9H, ArH), 8.64 (s, 1H, -N=CH), 12.25 (s, 1H, OH); Anal. Calcd. For $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30: Found: C, 70.36; H, 4.84; N, 19.34%.

Preparation of N-(3-Chloro-2-oxo-4-(pyridine-2-yl)azetidin-1-yl)quinoline-3-carboxamide (9):

Take the solution of chloroacetyl chloride (1.0 mol) in dry dioxane (50 ml), was added drop wise during 2h to a well stirred solution of compounds 5-6 (1.0 mol) and compounds 7-8 (1.0 mol) respectively. The reaction mixtures were stirred continuously 4h, cooled and poured it into water. A solids were obtained, filtered and washed with water and recystallized from acetone to yield compounds 9-10 and compounds 11-12.

Yield (43), m.p: 231^{0}C; IR (KBr) $_{max}$ in cm^{-1} 661 (C-Cl), 1299 (C-N), 1513 (N-N), 1571 (-N=CH), 1729 (-C=O), 3012 (C-H aromatic), 3324 (-C-NH), 3458 (OH); ^{1}H-NMR (DMSO-d_6 δ ppm): 7.43 (d, 1H, NH), 7.70-8.31 (m, 10H, ArH), 8.65 (s, 1H, -N-CH-pyridine), 8.84 (s, 1H, N-CH of azetidinone); Anal. Calcd. for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88: Found: C, 61.26; H, 3.74; N, 15.87%.

N-(3-Chloro-2-oxo-4-(pyridine-2-yl) azetidin - 1-yl)-8-methylquinoline-3-carboxamide (10):

Yield (39), m.p: 237^{0}C; IR (KBr) $_{max}$ in cm^{-1} 665 (C-Cl), 1292 (C-N), 1509 (N-N), 1577 (-N=CH), 1722 (-C=O), 3014 (C-H aromatic), 3320 (-C-NH), 3452 (OH); ^{1}H-NMR (DMSO-d_6 δ ppm): 2.21 (s, 3H, CH_3), 7.40 (d, 1H, NH), 7.72-8.30 (m, 9H, ArH), 8.60 (s, 1H, -N-CH-pyridine), 8.80 (s, 1H, N-CH of azetidinone); Anal. Calcd. for $C_{19}H_{15}ClN_4O_2$: C, 62.21; H, 4.12; N, 15.27: Found: C, 62.24; H, 4.14; N, 15.24%.

N-(3-Chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)-8-methylquinoline-3-carboxamide (11):

Yield (40), m.p: 245^{0}C; IR (KBr) $_{max}$ in cm^{-1} 660 (C-Cl), 1297 (C-N), 1507 (N-N), 1575 (-N=CH), 1729 (-C=O), 3013 (C-H aromatic), 3326 (-C-NH), 3455 (OH), 3324 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 7.42 (d, 1H, NH), 7.70-8.32 (m, 10H, ArH), 8.61 (s, 1H, -N-CH-pyridine), 8.82 (s, 1H, N-CH of azetidinone), 12.21 (s, 1H, OH); Anal. Calcd. for $C_{19}H_{14}ClN_3O_3$: C, 62.05; H, 3.84; N, 11.43: Found: C, 62.04; H, 3.82; N, 11.44%.

N-(3-Chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)-8-methylquinoline-3-carboxamide (12):

Yield (38), m.p: 265^{0}C; IR (KBr) $_{max}$ in cm^{-1} 667 (C-Cl), 1298 (C-N), 1505 (N-N), 1573 (-N=CH),

1721 (-C=O), 3018 (C-H aromatic), 3329 (-C-NH), 3453 (OH); ^{1}H-NMR (DMSO-d_6 δ ppm): 2.23 (s, 3H, CH_3), 7.46 (d, 1H, NH), 7.71-8.30 (m, 9H, ArH), 8.63 (s, 1H, -N-CH-pyridine), 8.83 (s, 1H, N-CH of azetidinone), 12.21 (s, 1H, OH); Anal. Calcd. for $C_{20}H_{16}ClN_3O_3$: C, 62.91; H, 4.22; N, 11.01: Found: C, 62.94; H, 4.24; N, 11.04%.

CONCLUSION: Compounds 1-8 exhibited mild to moderate antibacterial and antifungal activities. Cyclization of compounds 5-8 into their corresponding azetidinone congeners 9-12 markedly enhanced the antibacterial as well as antifungal activities.

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