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Synthesis, Antibacterial And Antifungal Activities Of New 4-(3-(Chloromethyl)Quinolin-2-Yl)Morpholine Derivatives

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Abstract:

A simple and high yielding method was developed for the synthesis of New derivatives of 4-(3-(chloromethyl)quinolin-2-yl)morpholine was obtained from 2-chloroquinolin-3-carbaldehydes, all the synthesized compounds were characterized by IR, ^{1}HNMR, Mass spectroscopy and synthesized compounds were evaluated for their antibacterial as well as antifungal activities. Antibacterial activity of compounds 4a, 4b, 4c, 4d and 4e were found to be good against *E. coli, P. aeruginosa, S. aureus* and *S. pyogenes* as compared to standard Ampicillin, Erythroycin, chloroamphinicol, Norfloxacin and Ciprofloxacin. Antifungal activity of compounds 4a, 4b, 4c, 4dand 4e were found to be good against *C. Albicans, A. Niger,* and *A. Clavatus*as compared to standard Nystatin and Greseofulvin.

Keywords:

2-chloroquinoline-3-carbaldehyde, 4-(3-(chloromethyl)quinolin-2-yl)morpholine, antibacterial, antifungal.

Introduction

Quinoline ring systems represent a major class of heterocyclic compounds in which benzene ring is fused with pyridine heterocyclic ring system. Quinolines are known also as benzo[*b*]pyridine and 1-azanaphthalene with one nitrogen atom in one benzene ring and none in the other ring or at the ring junction. Heterocycles containing a nitrogen atom possess high and interesting medicinal and pharmaceutical properties.[1–4] Montelukast is a drug used as an antiasthma agent.[5] In addition, quinolines are the main core of many types of natural products,[6,7] drugs,[8–10] and were found in many synthetic heterocyclic compounds in order to enhance the biological and medicinal properties. Compounds incorporating quinoline ring

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system exhibited various biological,[11,12] and pharmaceutical activities *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 tyrokinase PDGF-RTK inhibitor,[27] inositol 5^0-phosphatase (SH_2),[28] DNA gyrase B inhibitors as *Mycobacterium tuberculosis*,[29] and DNA topoisomerase inhibitors,[30] were reported. Nadifoxacin is a racemic fuoroquinolone launched as a topical antibiotic in Japan in 1993 to treat acne and methicillin resistant staphylococcal infections. Recently, quinoline has been employed in the study of bio-organic and bio-organometallic processes.[31] The quinoline skeleton is often used as a key intermediate for the design of many pharmacologically important synthetic compounds.[32,33]

2-Chloroquinoline-3-carbaldehydes represent an extremely interesting class of organic compounds that can be exploited as precursors and building blocks for the synthesis of a wide range of heterocyclic systems and potent antibiotics for microbial and cancer treatment. In continuation of our work on synthesis, characterization and activity of quinoline containing compounds[34-39] the present work reports that Quinoline derivatives exhibit antibacterial and antifungal activities

Materials and methods

2-Chloroquinoline-3-carbaldehydes were prepared in the laboratory by the reported method. Dichloromethane, morpholine, sodium borohydride, sodium hydroxide, and methanol were procured from S.D. Fine-chem. All physical constants were determined in open capillaries at atmospheric pressure. ^{1}H NMR spectra were recorded on AVANCE in $CDCl_3$, $CDCl_3$+DMSO at 400 MHz using TMS as an internal standard. IR spectra were recorded on a Bruker FTIR using KBr discs. Mass spectra were recorded using thermo exactive orbitrap methods, showing a molecular ion peak. The test for the purity of products and the progress of the reactions were accomplished by TLC on Merck silica gel plates.

General procedure:

2-morpholinoquinoline-3-carbaldehyde (2a): In a 50 ml round bottom flask taken 2-Chloroquinoline-3-carbaldehydes 1.9 gm (10 mmol) and 10 ml morpholine was slowly added DBU (0.5gm) under stirring at room temperature. The reaction mixture was heated to 100 ^{0}C.

The progress of reaction was monitored on TLC (8:2 – Hexane: ethyl acetate). After the completion of the reaction (6 hr), the reaction mixture was poured on ice cold water, the solid obtained was filtered off and washed with water to get product 2-morpholinoquinoline-3-carbaldehyde, dried in oven at 50 ^{0}C for 6.0 hr (2.20 gm).

(2-morpholinoquinolin-3-yl)methanol (3a): In a 50 ml round bottom flask taken 2-morpholinoquinoline-3-carbaldehyde 2.0 gm (8 mmol) and 15 ml methanol was slowly added sodium borohydride (1.0 gm) under stirring at room temperature. The progress of reaction was monitored on TLC (8:2 – Hexane: ethyl acetate). After the completion of the reaction (10 min), the reaction mixture was concentrated under reduced pressure to obtain residue. To this residue, ice cold water was added and the solid obtained was filtered off and washed with water to get product (2-morpholinoquinolin-3-yl)methanol, dried in oven at 40 ^{0}C for 5.0 hr (1.95 gm).

4-(3-(chloromethyl)quinolin-2-yl)morpholine (4a): To the stirred solution of (2-morpholinoquinolin-3-yl)methanol 1.75 gm (7 mmol) 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 (1.7 gm). The obtained product was purified by silica gel (60–120 mesh) column chromatographic technique using Hexane:ethyl acetate (8:3) as an eluent.

Antibacterial and Antifungal activity:-

The antibacterial activity was evaluated against *Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688), *Staphylococcus aureus* (MTCC-96) and *Streptococcus pyogenes* (MTCC-442), and antifungal activity was evaluated against *Candida albicans* (MTCC-227), *Aspergillus niger* (MTCC-282) and *Aspergillus clavatus* (MTCC-1323). These strains were provided by the Institute of Microbial Technology (IMT), Chandigarh. Mueller Hinton Broth was used as nutrient medium to grow and dilute the drug suspension for the test bacteria. This agar media was sterilized (autoclaved at 120 °C for 30 min), poured at a uniform depth of 5

mm and allowed to solidify. The microbial suspension (105 CFU/mL) was streaked over the surface of media using sterile cotton swab to ensure even growth of the organisms. The tested compounds were dissolved in DMSO to give the solutions with concentration 3.25–1000 µg/ml. Sterile filter paper discs measuring 6.25 mm in diameter, previously soaked in a known concentration of the respective test compound in DMSO, were placed on the solidified nutrient agar medium that has been incubated with the respective microorganism and plates were incubated at (37 ± 1)°C for 24 hr (bacteria) and 72 hr (fungi). A control disc impregnated with an equivalent amount of DMSO without any sample was also used and did not produce any inhibition. Ampicillin and Greseofulvin was used as control drugs for antibacterial and antifungal activity respectively. Minimum bacterial inhibitory concentration (MIC) of the compound was determined by the agar streak dilution method (Hawkey and Lewis 1994). A stock solution of the synthesized compounds in DMSO was prepared and graded quantities of the test compounds were incorporated in a specified quantity of molten sterile agar for the evaluation of antibacterial and Sabouraud dextrose agar for antifungal activity respectively. The medium containing the test compound was poured into a Petri dish at a depth of 4–5 mm and allowed to solidify under aseptic conditions. A suspension of the respective microorganism of approximately 105 CFU/mL was prepared and applied to plates with serially diluted compounds with concentrations in the range of 3.12–1000 µg/mL in DMSO and incubated at (37± 1)°C for 24 hr (bacteria) and 72 hr (fungi). Test run was triplicated; the lowest concentration of the substance that prevents the development of visible growth is considered to be the MIC value.

Results and Discussion

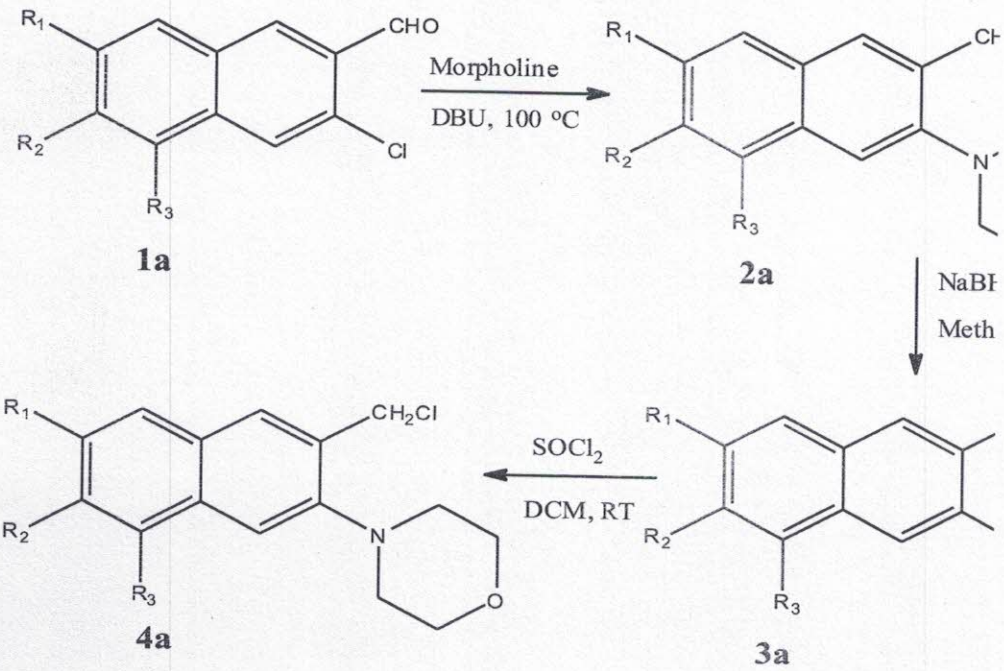
Herein, we report a simple method for the synthesis of new4-(3-(chloromethyl)quinolin-2-yl)morpholine derivatives in excellent yields (**Scheme-I**). The2-chloroquinoline-3-carbaldehyde **1a–e** when reacted with morpholine using DBU base catalyst at 100 ^{0}C formed the derivatives of 2-morpholinoquinoline-3-carbaldehyde **2a–e** in excellent 90–95% yields (Table 1, entries 1–5).These 2-morpholinoquinoline-3-carbaldehyde 2a–e derivatives on reduction with sodium borohydride in methanol at room temperature formed substituted (2-morpholinoquinolin-3-yl)methanol **3a–e**. These (2-morpholinoquinolin-3-yl)methanol reacts thionyl chloride in DCM at room temperature to give the products4-(3-

(chloromethyl)quinolin-2-yl)morpholines **4a–e** in excellent yields (95–98%) (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 (92–98%) **(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–f) was carried out *against S. pyogenes, P.*

aeruginosa, *S. aureus* and *E. coli* using Ampicillin as the standard. MIC values were obtained by the broth dilution technique. DMSO was used as diluent. MIC values are summarized in **Table 2**. Most of the synthesized compounds except the compound with methyl substitution at the eighth position of the quinoline ring 4b, methoxy substitution at the seventh position of the quinoline ring 4e displayed excellent antibacterial activity than standard drug Ampicillin with Gram +ve bacterial strains and Gram –ve strain (*P. aeruginosa*).

The antifungal activity of the titled compounds (4a–f) was appraised against *A. niger*, *A. clavatus* and *C. albicans* using Griseofulvin as the standard drug with the broth dilution method **(Table3)**. The synthesized compounds 4b, 4d and 4f were found to be excellent activity than the standard drug Griseofulvin against *A. niger*, *A. clavatus* and *C. Albicans* strains. On the contrary the compounds 4a, 4c and 4e were found to possess good to moderate activity.



Scheme-1: Synthesis of 4-(3-(chloromethyl)quinolin-2-yl)morpholines

Table-1

Physical data of the synthesized compounds

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

6	**3a**	H	H	H	30 min	96
7	**3b**	CH_3	H	H	30 min	95
8	**3c**	H	H	CH_3	30 min	96
9	**3d**	H	CH_3	H	30 min	97
10	**3e**	OCH_3	H	H	30 min	96
11	**4a**	H	H	H	60 min	89
12	**4b**	CH_3	H	H	60 min	90
13	**4c**	H	H	CH_3	60 min	88
14	**4d**	H	CH_3	H	60 min	90
15	**4e**	OCH_3	H	H	60 min	90

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	500	100	250	100
2	4b	500	500	500	500
3	4c	50	100	125	100
4	4d	100	100	500	100
5	4e	50	150	500	100

Table-3

ANTIFUNGAL ACTIVITY

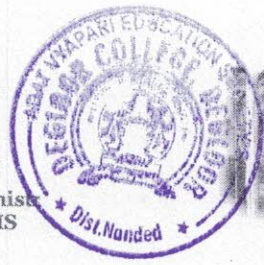
Sr. No.	Compound	*MINIMAL FUNGICIDAL CONCENTRATION*		
		C.ALBICANS	A.NIGER	A.CLAVATUS
		MTCC 227	MTCC 282	MTCC 1323
		MICROGRAM/ML		
1	4a	500	500	1000
2	4b	1000	1000	1000
3	4c	500	500	500
4	4d	1000	1000	1000
5	4e	500	500	500

Table-4

THE 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



Conclusion

In this study, a series of New derivatives of 4-(3-(chloromethyl)quinolin-2-yl)morpholines were prepared from 2-chloroquinolin-3-carbaldehydes and preliminary biological evaluation of antimicrobial activity of the synthesized compounds the compound with methyl substitution at the eighth position of the quinoline ring 4b showed excellent antibacterial activity than standard drug Ampicillin with Gram +ve bacterial strains and Gram –ve strain (*P. aeruginosa*). The antifungal activity of the titled compounds (4a–f) was evaluted against *A. niger*, *A. clavatus* and *C. albicans* using Griseofulvin as the standard drug with the broth dilution method (Table 3). The synthesized compounds 4b and 4d were found to be excellent activity than the standard drug Griseofulvin against *A. niger*, *A. clavatus* and *C. albicans* strains.

All the reactions were performed under mild reaction conditions, shorter reaction time and in quantitative yields. The methodology developed will be of much use to combinatorial chemist.

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Spectroscopic data:-

4a) 4-(3-(chloromethyl)quinolin-2-yl)morpholines

IR (KBr): 2919 cm^{-1} (C-H); 1594 cm^{-1} (C=C); 762 cm^{-1} (C-Cl);

^{1}H NMR ($CDCl_3$+ DMSO, δppm): 3.41(s, 4H, $C\underline{H_2}$);3.88(s, 4H, $C\underline{H_2}$);3.91 (s, 2H, $C\underline{H_2}$);7.36 (t, 1H, Ar-H); 7.58 (t, 1H, Ar-H);7.70(d, 1H, Ar-H); 7.86 (d, 1H, Ar-H); 8.13 (s, 1H, Ar-H).

FTMS: m/z 263.05(m+1)

4b) 4-(3-(chloromethyl)-6-methylquinolin-2-yl)morpholine

IR (KBr):2960 cm^{-1} (C-H); 1608 cm^{-1} (C=C); 734 cm^{-1} (C-Cl);

^{1}H NMR ($CDCl_3$, δ ppm):2.50(s, 3H, Ar-$C\underline{H_3}$);3.33(s, 4H, $C\underline{H_2}$); 3.70(s, 4H, $C\underline{H_2}$); 3.88(s, 2H, $C\underline{H_2}$); 7.19 (d, 1H, Ar-H); 7.26 (s, 1H, Ar-H); 7.58 (d, 1H, Ar-H); 8.03(s, 1H, Ar-H).

FTMS: m/z 277.06 (m+1)

4c) 4-(3-(chloromethyl)-7-methylquinolin-2-yl)morpholine

IR (KBr): 2919 cm^{-1} (C-H); 1602 cm^{-1} (C=C); 739cm^{-1} (C-Cl);

^{1}H NMR ($CDCl_3$, δ ppm): 2.50(s, 3H, Ar-C$\underline{H}_3$);3.33(s, 4H, C$\underline{H}_2$); 3.70(s, 4H, C$\underline{H}_2$); 3.92(s, 2H, C$\underline{H}_2$); 7.21(d, 1H, Ar-$\underline{H}$); 7.26 (s, 1H, Ar-$\underline{H}$); 7.58 (d, 1H, Ar-$\underline{H}$); 8.03(s, 1H, Ar-$\underline{H}$).

FTMS: m/z 277.06 (m+1)

4d) 4-(3-(chloromethyl)-8-methylquinolin-2-yl)morpholine

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-C$\underline{H}_3$);3.33(s, 4H, C$\underline{H}_2$); 3.70(s, 4H, C$\underline{H}_2$); 3.88(s, 2H, C$\underline{H}_2$); 7.15 (d, 1H, Ar-$\underline{H}$); 7.26 (s, 1H, Ar-$\underline{H}$); 7.58 (d, 1H, Ar-$\underline{H}$); 8.03(s, 1H, Ar-$\underline{H}$).

FTMS: m/z 277.02 (m+1)

4e) 4-(3-(chloromethyl)-6-methoxyquinolin-2-yl)morpholine

IR (KBr): 2915 cm^{-1} (C-H); 1601 cm^{-1} (C=C); 739cm^{-1} (C-Cl);

^{1}H NMR ($CDCl_3$, δ ppm): 3.30(s, 4H, C$\underline{H}_2$); 3.70(s, 4H, C$\underline{H}_2$);3.83(s, 3H, Ar-OC$\underline{H}_3$); 3.90(s, 2H, C$\underline{H}_2$); 7.02 (d, 1H, Ar-$\underline{H}$); 7.26 (s, 1H, Ar-$\underline{H}$); 7.76 (d, 1H, Ar-$\underline{H}$); 8.03(s, 1H, Ar-$\underline{H}$).

FTMS: m/z 293.02 (m+1)

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