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Synthesis of novel diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonates as antibacterial agent

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Abstract: A novel series of diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonates have been synthesized by the reaction of 2-chloroquinolin-3-carbaldehydes, triethylphosphite and morpholine in high yields. All the novel series of diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonate derivatives have been characterized by IR, 1HNMR and mass spectroscopy. All novel synthesized compounds have been screened for antimicrobial activity against bacterial strains Staphylococcus aureus (NCIM-2654), Bacillus subtilis (NCIM-2635), Escherichia coli (NCIM-2832) and Pseudomonas aeruginosa (NCIM-5032). These novel synthesized compounds show moderate to good antibacterial activity Gram positive and Gram-negative pathogenic strains.

Key-words: 2-chloroquinolin-3-carbaldehydes, triethylphosphite, diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonates, morpholine, antibacterial activity.

Introduction

The current interest in the progress of new antibacterial agent proxies, can be partly attributed to both development of increasing rise of bacterial resistance to antibiotic treatment and to lately emerging new pathogens.[1,2] Over the past decade, we have been primarily engaged in the synthesis of quinoline containing phosphonate for antibacterial evaluations[3]on the premise that quinolines sources is noticed in a large range of naturally occurring compounds. In fact, quinoline has been broadly explored due to their encouraging biologic and pharmacological significance as their analogues have extensive domain of activities such as anti-tuberculosis[4], anticancer[5], antimicrobial[6], antifungal[7] and antimalarial.[8] Among Quinolines the 2-chloroquinoline-3-carbaldehyde signify prominent precursors reactivity and use as building

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blocks in the synthesis of a wide range of heterocyclic systems of influential biological properties as they are crucial intermediates for extended annulation. [9]

Our aim to synergies the antibacterial activity of quinolines phosphonates and other registered heterocycles by synthesising hybrid molecules seeking the characteristics of these scaffolds in an attempt to discover potent antibacterial agents like Morpholine (1-oxa-4- azacyclohexane) is counted as favoured scaffold for medicinal chemistry.[10] encouraging biological activities, on top of, an enhanced metabolic and pharmacokinetic profile to the molecules abiding with it, the most potential synthetic practices containing morpholine moieties along with structure-activity relationship (SAR) evaluated the active pharmacophores accounted for antiviral,[11] anti-inflammatory,[12] anticonvulsant[13](Rivaroxaban), antioxidant,[14] antimicrobial[15] (Linezolid), anticancer[16](Gefitinib), analgesic[17](Phenadoxone) and anti-depressant[18](moclobemide) activity. The biological utility particularly, nitrogen- substituted morpholines are drug contenders with a wide spectrum of activities.

Compounds with C-P bond are renowned in biological systems over and above various phosphonate confining natural molecules are renowned, asα-hydroxyphosphonates[19] are potential sources of bioactivity with applications inmedicines [drug],[20] antibacterial and antifungal.[21] Antibiotic,[22] hPPAR§agonist,[23] agrochemicals,[24] material molecules[catalysis],[25] industrial [anticorrosive and lubricous coating][26] and flame retardant.[27] Although numerous synthetic methods have been developed, our effort to explore new and efficient synthetic routes for the synthesis of these combo pharmacophore.

Thus, the important character exhibited by quinoline, morpholine and phosphonates for numerous therapeutic and biological activities driven us to synthesize certain derivates of relating these three pharmacophores in order to achieve molecules having better drug potential.

Material and methods

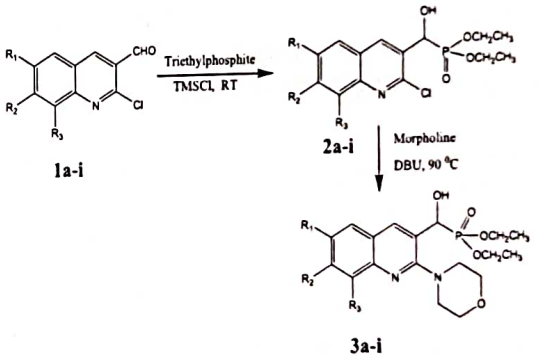
The Chemicals used in experimental work were commercially procured from different companies viz. Sigma Andrich, E. Merck and S.D. Fine Chem. These Solvents and reagents were of LR grade and pure and used directly. The Silica gel G (160-120 mesh) used for analytical chromatography (TLC) was obtained from E. Merck India Ltd. Two solvent system were used, i.e., Ethyl acetate: n- hexane (8:1 and 9:1) Ethyl acetate: n-hexane: methanol (8:1.5:0.5). Vacuum Filtration were carried out on Whatmann no.1 filter paper. Melting points were verified in open capillary using melting point device and uncorrected. The ^1H NMR were recorded on BrukerAvance Neo 500 MHz spectrometer in DMSO using tetramethylsilane [$(CH_3)_4Si$] as internal standard. The Mass spectra were recorded on Waters Q-TOF Micromass (ESI-MS) spectrometer. The IR spectra were in KBR on Bruker FTIR system. The UV lamp were used for Visualisation of TLC spots. The commercially accessible grades of reagents and solvents were observed to be of ample purity. However, to the best of undesirable impurities and others were likely to be used for experimental work was purified.

Results and discussion

The present work involves the synthesis of new diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonates derivatives, starting from 2-chloro-3-formylquinolines were prepared in excellent yield fromthe corresponding acetanilides by treatment with the Vilsmerier reagent generated in situ from $POCl_3$/DMF system by reported method.

[28] The process incorporates the derivatives of diethyl(hydroxy (quinolin-3-yl) phosphonates(2a-i) were prepared from substituted 2-chloroquinoline-3-carbaldehyde on treatment with thylphosphate and trimethylchlorosilane at room temperature with rigorous stirring up to 1 hr,the advance of reaction monitored by TLC by using hexane: ethyl acetate (8:2) as mobile phase.The excess trimethylchlorosilane were removed by adding methanol the solid material obtained after adding ice cold water and after work-up afforded compound(2a-i) in 88-97% yield.

The structure of the compound was determined from the spectroscopic data. The synthesised diethyl (hydroxy(quinolin-3-yl) phosphonates(2a-i) on reaction with Morpholine in the catalytic amount (2 drops) of DBU at 90^{0}C temperature for 10 hr the progress and completion of reaction were supervised by TLC with Ethyl acetate: n-hexane: methanol (8:1.5:0.5). The reaction efficiently under basic condition to afford the corresponding titled diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonates(3a-i) having in high yields (85-88%). The structure elucidations were confirmed by IR, ^{1}H NMR, mass spectroscopic data.The newly synthezed compounds 3a-i were analysed for antibacterial activities for Staphylococcus aureus (NCIM-2654), Bacillus subtilis (NCIM-2635), Escherichia coli (NCIM-2832) and Pseudomonas aeruginosa (NCIM-5032) with standard antibiotic. These novel synthesized compounds shown moderate to good antimicrobial activity Gram positive and Gram-negative pathogenic strains.



Note: R_1, R_2, R_3= -H, -CH_3,-OCH_3, -C_2H_5

Scheme 1: Synthesis of Diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonates

General Procedure

(2a)Diethyl(2-chloro-quinolin-3-yl) (hydroxy) methylphosphonate

To the 2- chloroquinoline-3-carbaldehyde (1.90 gm 10 mmol) triethylphosphite (3.72 ml, 20 mmol), to thischlorotrimethylsilane (1.66 ml, 10 mmol) were added dropwise and stirred at room temperature for 30 min. The reaction advance was monitored by TLC using Hexane: ethyl acetate (8:2) as solvent system. Once completion of the reaction, the reaction mixture was dissolved in methanol for the quenching

of excess TMSCl to remove the residual silyl ester.The methanolic solution was concentrated, further purification was carried out by dissolving the crude compound in dichloromethane and precipitated by hexane. The solid obtained were stirred and filter after 20 min, washed with hexane and dried at 40^0 C. (3.12gm, yield 95% m.p. 120-124 ^{0}C)

(3a)Diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonate($C_{18}H_{25}N_2O_5P$)

To the stirred solution of Diethyl(2-chloro-quinolin-3-yl) (hydroxy) methylphosphonate (1.65 gm 5mmol) morpholine (3 mL) were added dropwise a solution and DBU (2 drops). After the complete addition, and stirred it for 8 h at 90^{0}C temperature. The reaction progress was monitored by the TLC (8:1.5:0.5,Hexane: ethyl acetate: methanol), after complete conversion, added acetone and precipitated by cold water. Solid was obtained and filtered through vacuum pump and dried product. dry weight 1.7 gm 90% yield, which was then purified by using acetone/H_2O.

White solid. 90 % yield, mp.164-167 ^{0}C, IR (KBr, cm^{-1}): 3397&1105 (-OH), 1685 (-C=N), 1225 (-P=O), 1005 (-P-O-C)

^{1}H NMR: (500 MHz DMSO, δ ppm):δ2.45-2.52 (m, J=7.25 Hz, 6H, -C$\underline{H}_3$),3.32-3.34 (m, J=7.25 Hz, 4H, -OC$\underline{H}_2$CH$_3$), 3.58(s, 2H, -O$\underline{H}$ & -C$\underline{H}$), 3.58-3.60 (t, J=6.25 Hz, 4H, -C$\underline{H}_2$-N), 3.78-3.81 (t, J=6.25 Hz, 4H, -C$\underline{H}_2$-O), 7.38-7.41(m, 1H, Quin), 7.59-7.63 (m, 1H, Quin), 7.64-7.77(dd, 1H, Quin), 7.84-7.86(dd, 1H, Quin), 8.21(s, 1H, Quin).

ESMS: 397.50 m/z(m+18, NH_4 adduct)

(3b)diethyl (hydroxy(8-methyl-2-morpholinoquinolin-3-yl) methyl) phosphonate($C_{19}H_{27}N_2O_5P$) yellow solid. 92 % yield, mp.169-171^{0}C, IR (KBr, cm^{-1}): 3387&1108 (-OH), 1641 (-C=N), 1229 (-P=O), 1049 (-P-O-C)

^{1}H NMR (500 MHz DMSO, δ ppm): δ 2.44-2.52 (m, J=7.45 Hz, 9H, -OCH$_2$C$\underline{H}_3$ & -C$\underline{H}_3$), 3.28-3.32 (m, J=7.45 Hz, 4H, -OC$\underline{H}_2$CH$_3$), 3.57 (s, 2H, -O$\underline{H}$ & -C$\underline{H}$), 3.58-3.60 (t, J=6.85 Hz, 4H, -C$\underline{H}_2$-N), 3.77-3.79 (t, J=6.85 Hz, 4H, -C$\underline{H}_2$-O), 7.44-7.46(dd, 1H, Quin), 7.61 (s, 1H, Quin), 7.65-7.67(dd, 1H, Quin), 8.12(s, 1H, Quin).

ESMS:411.49 m/z (m+18, NH_4 adduct)

(3c)diethyl (hydroxy(7-methyl-2-morpholinoquinolin-3-yl) methyl) phosphonate($C_{19}H_{27}N_2O_5P$)

Pale yellow solid. 93 % yield, mp.174-176^{0}C, IR (KBr, cm^{-1}): 3379&1106 (-OH), 1642 (-C=N), 1227 (-P=O), 1043 (-P-O-C)

^{1}H NMR (500 MHz DMSO, δ ppm): δ 2.44-2.52 (m, J=7.25 Hz, 9H, -OCH2C$\underline{H}$3 & -C$\underline{H}$3), 3.30-3.32 (m, J=7.25 Hz, 4H, -OC$\underline{H}$2CH3), 3.55 (s, 2H, -OH & -CH), 3.58-3.60 (t, J=7.25 Hz, 4H, -CH2-N), 3.77-3.79 (t, J=6.25 Hz, 4H, -CH2-O), 7.23-7.25(dd, 1H, Quin), 7.56 (s, 1H, Quin), 7.72-7.74(dd, 1H, Quin), 8.14(s, 1H, Quin).

ESMS: 411.46 m/z (m+18, NH_4 adduct)

(3d)diethyl (hydroxy(6-methyl-2-

morpholinoquinolin-3-yl) methyl) phosphonate($C_{19}H_{27}N_2O_5P$)

White solid. 92 % yield, mp.165-167 ^{0}C, IR (KBr, cm^{-1}): 3378&1107 (-OH), 1655 (-C=N), 1230 (-P=O), 1013 (-P-O-C)

^{1}H NMR (500 MHz DMSO, δ ppm): 2.44-2.52 (m, J=7.25 Hz, 9H, -OCH$_2$CH$_3$& -CH$_3$), 3.27-3.32 (m, J=7.25 Hz, 4H, -OCH$_2$CH$_3$), 3.57(s, 2H, -OH & -CH), 3.58-3.60 (t, J=7.25 Hz, 4H, -CH$_2$-N), 3.77-3.79 (t, J=6.25 Hz, 4H, -CH$_2$-O), 7.44-7.46(dd, 1H, Quin), 7.61 (s, 1H, Quin), 7.65-7.67(dd, 1H, Quin), 8.12(s, 1H, Quin).

ESMS:411.48m/z (m+18, NH$_4$ adduct)

(3e) diethyl (hydroxy(8-methoxy-2-morpholinoquinolin-3-yl) methyl) phosphonate($C_{19}H_{27}N_2O_6P$)

brown solid. 88 % yield, mp.184-186 ^{0}C,IR (KBr, cm^{-1}):3370&1115 (-OH), 1655 (-C=N), 1228 (-P=O), 1012 (-P-O-C)

^{1}H NMR (500 MHz DMSO, δ ppm): δ 2.36-2.48 (m, J=7.25 Hz, 6H, -OCH$_2$CH$_3$), 3.35 (m, J=7.25 Hz, 4H, -OCH$_2$CH$_3$), 3.52 (s, 2H, -OH & -CH), 3.58 (t, J=7.25 Hz, 4H, -CH$_2$-N), 3.77-3.82 (t, J=6.25 Hz, 4H, -CH$_2$-O),3.89(-OCH$_3$) 7.04-7.06(dd, 1H, Quin), 7.16 (d, 1H, Quin), 7.76-7.79(dd, 1H, Quin), 8.14 (s, 1H, Quin).

ESMS:428.22 m/z (m+18, NH$_4$ adduct)

(3f)diethyl (hydroxy(7-methoxy-2-morpholinoquinolin-3-yl) methyl) phosphonate($C_{19}H_{27}N_2O_6P$)

yellow solid, 93 % yield, mp.177-179^{0}C, IR (KBr, cm^{-1}): 3472&1109 (-OH), 1609 (-C=N), 1220 (-P=O), 1021 (-P-O-C)

^{1}H NMR (500 MHz DMSO, δ ppm): δ 2.36-2.50 (m, J=7.25 Hz, 6H, -OCH$_2$CH$_3$), 3.32 (m, J=7.25 Hz, 4H, -OCH$_2$CH$_3$), 3.52 (s, 2H, -OH & -CH), 3.58 (t, J=7.25 Hz, 4H, -CH$_2$-N), 3.77-3.82 (t, J=6.25 Hz, 4H, -CH$_2$-O),3.87(-OCH$_3$) 7.02-7.04(dd, 1H, Quin), 7.14 (d, 1H, Quin), 7.73-7.74(dd, 1H, Quin), 8.10 (s, 1H, Quin).

ESMS:428.50 m/z (m+18, NH$_4$ adduct)

(3g)diethyl (hydroxy(6-methoxy-2-morpholinoquinolin-3-yl) methyl) phosphonate($C_{19}H_{27}N_2O_6P$)

White solid. 92 % yield, mp.164-166^{0}C, IR (KBr, cm^{-1}):3379&1106 (-OH), 1640 (-C=N), 1228 (-P=O), 1044 (-P-O-C)

^{1}H NMR (500 MHz DMSO, δ ppm): δ 2.44-2.52 (m, J=7.25 Hz, 6H, -OCH$_2$CH$_3$), 3.27-3.29 (m, J=7.25 Hz, 4H, -OCH$_2$CH$_3$), 3.57 (s, 2H, -OH & -CH), 3.58-3.60 (t, J=7.25 Hz, 4H, -CH$_2$-N), 3.77-3.79 (t, J=6.25 Hz, 4H, -CH$_2$-O),3.85(-OCH$_3$) 7.44-7.46(dd, 1H, Quin), 7.61 (s, 1H, Quin), 7.65-7.67(dd, 1H, Quin), 8.12 (s, 1H, Quin).

ESMS: 428.77 m/z(m+18, NH$_4$ adduct)

(3h)diethyl ((6-ethyl-2-morpholinoquinolin-3-yl) (hydroxy) methyl) phosphonate($C_{20}H_{29}N_2O_5P$)

light yellow solid. 85 % yield, mp.154-156 ^{0}C, IR (KBr, cm^{-1}):3381&1132 (-OH), 1668 (-C=N), 1235 (-P=O), 1025 (-P-O-C)

^{1}H NMR (500 MHz DMSO, δ ppm):

δ 2.43-2.52 (t, J=7.25 Hz, 6H, -CH3), 3.1-3.2 (t, J=6.25 Hz, 4H, -CH2-N), 3.4 (s, 1H, OH), 3.58 (s, 1H), 3.62-3.63(q, J=7.25 Hz, 4H, -CH2-O), 3.82-3.78 (t, J=6.25 Hz, 4H, -CH2-), 7.38-7.42(dd, 1H, Quin), 7.60-7.62(dd, 1H, Quin), 7.752-7.754(dd, 1H, Quin), 7.84-7.86(dd, 1H, Quin), 8.21-8.23(dd, 1H, Quin).

ESMS: 426.3 m/z (m+18, NH_4 adduct)

(3i)diethyl ((7-ethyl-2-morpholinoquinolin-3-yl) (hydroxy) methyl)phosphonate($C_{20}H_{29}N_2O_5P$)

White solid.91 % yield, mp.171-173 ^{0}C, IR (KBr, cm^{-1}):3390&1131 (-OH), 1672 (-C=N), 1229 (-P=O), 1014 (-P-O-C)

^{1}H NMR (500 MHz DMSO, δ ppm): δ 2.43-2.52 (t, J=7.25 Hz, 6H, -CH3), 3.1-3.2 (t, J=6.25 Hz, 4H, -CH2-N), 3.4 (s, 1H, OH), 3.58 (s, 1H), 3.62-3.63(q, J=7.25 Hz, 4H, -CH2-O), 3.82-3.78 (t, J=6.25 Hz, 4H, -CH2-), 7.38-7.42(dd, 1H, Quin), 7.60-7.62(dd, 1H, Quin), 7.752-7.754(dd, 1H, Quin), 7.84-7.86(dd, 1H, Quin), 8.21-8.23(dd, 1H, Quin).

ESMS:426.8 m/z (m+18) and 343.5 m/z

Antibacterial activity:

The synthesized materials were screened for antimicrobial activity against bacterial strains Staphylococcus aureus (NCIM-2654), Bacillus subtilis (NCIM-2635), Escherichia coli (NCIM-2832) and Pseudomonas aeruginosa (NCIM-5032). Chemically synthesized materials exhibit excellent antimicrobial activity against one Gram positive and one Gram negative pathogenic strains. The microbial cultures inoculums were prepared into sterile saline water. The nutrient agar plates were used as a medium for the bacterial growth. The S. aureus, B. subtilis, E. coli and P. aeruginosa cultures were spread on a sterile nutrient agar plate, wells are prepared in these plates using sterile corkborer having size 5mm. 100ug/ml synthesized material were dispersed in the sterile Dimethyl sulfoxide (DMSO) with the help of micropipette. The plates were incubated at 37^{0}C for 24 hr. to test antibacterial activity.

The antimicrobial activity of chemically synthesized materials was checked along with blank Dimethyl sulfoxide (DMSO) as negative control. The antimicrobial potential of synthesized material was studied using agar well gel diffusion method against bacterial strains S. aureus, B. subtilis gram-positive, E. coli, P. aeruginosa gram-negative bacteria using streptomycin as the standard drug. These antibacterial studies revealed synthesized materials present in the well which inhibits the growth of S. aureus, B. subtilis, E. coli and P. aeruginosa bacterial strains, indicates that has been use for antimicrobial activity. The above data represent the mean ± standard error of three replicates in Table 1 material.

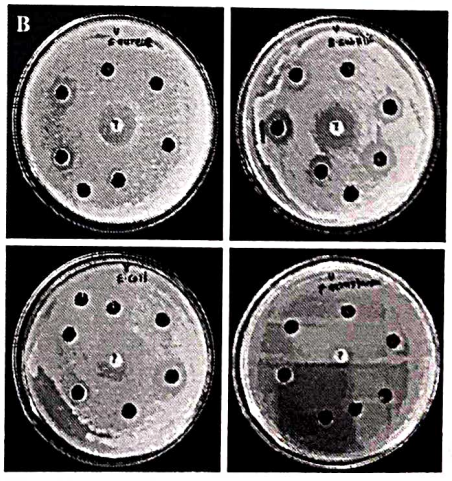


Table 1: Antibacterial activity

Entry	Antibacterial activity			
	Gram + Ve		Gram - Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
1-3a	11.00 ± 1.00	11.66 ± 0.57	11.66 ± 0.57	10.33 ± 0.57
2-3b	11.33 ± 1.15	14.00 ± 1.00	11.00 ± 1.00	10.00 ± 1.00
3-3c	11.33 ± 0.57	13.66 ± 0.57	13.33 ± 1.15	12.00 ± 1.00
4-3d	11.66 ± 0.57	13.33 ± 1.15	11.66 ± 0.57	11.66 ± 0.57
5-3e	9.66 ± 0.57	11.66 ± 0.57	11.00 ± 1.00	7.66 ± 0.57
6-3f	13.66 ± 0.57	15.33 ± 1.15	13.66 ± 0.57	9.66 ± 1.15
g	17.33 ± 1.15	23.00 ± 1.00	21.00 ± 1.52	11.00 ± 1.00

Table 1- Zone of inhibition of sample code- 1-3a, 2-3b, 3-3c, 4-3d, 5-3e, 6-3f, B) Antibiotic code- 7-g antimicrobial activity against human pathogens

Fig. 1(b) Antimicrobial activity on the Staphylococcus aureus (NCIM -2654), Bacillus subtilis (NCIM 2635), Escherichia coli (NCIM-2832) and Pseudomonas aeruginosa (NCIM - 5032) zone of inhibition for material

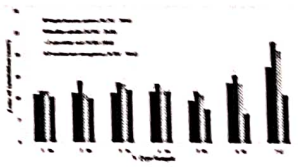


Fig. 1(c) The statistical analysis of material against bacterial human pathogens

Conclusion

A novel series of diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonates developed from the reaction of 2-chloroquinolin-3-carbaldehydes, triethylphosphite and followed by morpholine in high yields. All the innovative series of diethyl (hydroxy(2-morpholinoquinolin-3-yl) methyl) phosphonate derivatives have been illustrated by IR, ^{1}HNMR and mass spectroscopy. All the synthesized compounds have been screened for antibacterial activity against bacterial strains S. aureus, B. subtilis, E. coli and P. aeruginosa. These novel synthesized compounds show moderate to good antimicrobial activity Gram positive and Gram-negative pathogenic strains. The Morpholine is a versatile and accessible synthetic building block with quinoline, and phosphonate enhance the activity of pharmacophore. The phosphonate scientific research community is still striding for suitable quantification, identification, and exploitation of new phosphonate-basedantiviral,antibacterial and antiparasitic compounds.

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