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Potential anti-bacterial agents: Montmorillonite Clay catalyzed synthesis of novel 2-(3, 5-substituted-1*H*-pyrazol-1-yl)-3-substituted quinolones and their in-silico molecular docking studies

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A series of 2-(3,5-substituted-1*H*-pyrazol-1-yl)-3-substituted quinolines **5(a-g)**, were obtained from 2-chloro-3-(1,3-dioxolan-2-yl)quinolines **2(a-c)** and diketones **3(a-c)** in great yields by utilizing Montmorillonite clay K-10 as a catalyst through eco-friendly methodology. All the synthesized compounds were characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectral techniques. Antibacterial screening of the compounds revealed that some of the compounds demonstrate moderate to good results. Amongst all, compound **2c** displayed good inhibitory profile against *P. aeruginosa* and *B. subtilis* while compound **5c** exhibited remarkable activity against *S. aureus, B. subtilis* and *P. aeruginosa* with an MIC value of 25µg/mL and moreover against *E. coli* and *K .pneumonia* the compound **5c** was representing a MIC value of 50µg/mL which was comparable to that of the standard. In addition, the compound **5f** was demonstrating good viability against *S. aureus* and *P. aeruginosa* with a MIC value of 25µg/mL. The compounds **2c** and **5f** however showed relatively moderate inhibition against *S. aureus,* while the later had a moderate acitivity against *B. subtilis* respectively. To further display the antibacterial efficacy of **2c**, **5c** and **5f** molecular docking studies were done which confirmed that compound **5c** possess good binding interaction with that of peptide deformylase protein with a binding energy of -8.1 Kcal/mol which was more prominent than standard Ampicillin (-7.5 Kcal/mol) while the compounds **2c** and **5f** have moderate binding affinity.

1Introduction

Heterocyclic compounds particularly, the functionalized quinolines have exhibited considerable attention owing to their biological properties such as anti-asthmatic, antibacterial, anti-inflammatory and anti-hypertensive properties[1]. The functionalized quinolines are widespread in many natural products[2] and find their applications in the synthesis of pharmaceuticals and biologically active molecules[3]. Subsequently, various procedures have been proposed for developing highly functionalized quinoline frameworks which has always been a fascinating theme to numerous organic and medicinal chemists[4]. In addition, late literature survey on heterocyclic systems either annulated or substituted quinoline frame were signifying different biological activities. For example, the mono triazolyl substituted quinolines possess anti-cancer activity[5], quinoline-based azetidinone and thiazolidinone analogues were promising antimicrobial and antitubercular activity[6], 4-arylchalcogenyl-7-chloroquinolines presented good antioxidant activity[7], isoxazolylpyrimido[4,5-*b*]quinolines and isoxazolylchromeno[2,3-*d*]pyrimidin-4-ones exhibited good antimicrobial, anti-inflammatory and analgesic activity[8]. Particularly, the 2-substituted quinoline ring systems were reported to be possessing diversified therapeutic activities[9-10]. The C-2 pyridinyl and pyridinyl vinyl substituted quinolones were reported to possess very good anti-fungal activity[11] and an introduction of an aryl or indole moiety at C-2 of quinoline ring resulted in potent PDE4 inhibitory properties[12]. Likewise, pyrazoles then again are heterocyclic targets of considerable importance and are available in an extensive number of biologically active molecules relevant to the pharmaceutical and agrochemical sectors. They have shown broad spectrum of pharmacological and biological activities such as anti-microbial[13], anti-tumor[14], anti-fungal [15], anti-tubercular [16], anti-leukemia[17], anti-depressant [18-19], anti-convulsant[20]and anti-hyperglycemic[21]properties.

Compounds incorporating the pyrazolyl structural unit are being developed in a wide variety of therapeutic areas[22]. Pyrazolo [3,4-*b*]quinoline derivatives are significant for their pharmacological activities[23]. Particularly, they display potential antiviral, antimalarial[24]and anti-inflammatory properties[25]. As of late, the utilization of solid supported reagents has gained considerable significance in organic synthesis attributable to their simplicity of handling, reaction rates, greater selectivity, simple work-up and reusability of the catalyst[26]. The effectiveness of Montmorillonite K-10 catalysis in organic synthesis has been demonstrated by their advantages of high atom efficiency, simplified isolation of product, easy recovery and recyclable of the catalysts[27-29]. By considering all the above aspects in continued quinoline research interests[30-34], we were intrigued to synthesize novel molecules having substituted pyrazole ring in the 2nd position of quinoline moiety by green chemistry approach utilizing MK-10 catalyst.

2Results and discussion

2.1 Chemistry

In the present study, synthesis of novel 2-(3, 5-substituted-1*H*-pyrazol-1-yl)-3- quinolines, **4**, **5(a-g)** is reported following the schemes depicted in **Scheme 1**. At first, the 2-chloro-3-(1, 3-dioxolan-2-yl) quinoline derivatives, **1(a-f)** acquired from the corresponding chloroformyl derivatives,[35] were reacted with an

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excess of hydrazine hydrate in ethanolic solution in the presence of catalytic amount of ammonia under reflux condition to offer the 2-hydrazino-3-(1,3-dioxolan-2-yl)quinolines, **2(a-f)** in quantitative yields in a short reaction time (1-2 h) than the reported procedure[36] **(Table 1)**. One of the compounds, **2b** was crystallized, analysed successfully and reported[37].

Compounds **2** were then reacted with diketones, **3(a-c)** in ethanolic medium by utilizing different catalysts to offer the 2-(3,5-substituted-1*H*-pyrazol-1-yl)-3-substituted quinolines, **5(a-g).** The reaction conditions were optimized by conducting the model reaction of **2b** and acetyl acetone, **3a** and by utilizing different catalysts,for example, conc. H_2SO_4, anhydrous $AlCl_3$, $SnCl_2.2H_2O$ and MK-10 under reflux conditions in EtOH. The results are listed in **Table 2**. The reaction did not continue in the absence of catalyst; while, the reaction did proceed with a 57-83% yields in the presence of catalysts. On examining different catalysts, the MK-10 was chosen as the best catalyst for the synthesis of 2-(3, 5-dimethyl-1*H*-pyrazol-yl)-3-(1,3-dioxolan-2yl)-7-methyl quinolones,**5d**. The catalyst loading of MK-10 has been screened from 20 mg to 140 mg and proposed that 100 mg of the catalyst the reaction was essential for the completion of the reaction. The 2-(3, 5-substituted-1*H*-pyrazol-1-yl)-3-substituted quinolines **5(a-g)** were isolated in excellent yields **(Table 3).** It is observed, that in the presence of conc. H_2SO_4, the deprotection of aldehyde protecting group have resulted in the formation of 2-(3, 5-dimethyl-1*H*-pyrazol-1-yl-7-methylquinoline-3-carbaldehyde,**4**. The plausible mechanism of formation of the desired compound, **5d** is delineated in **Fig. 1**.

The structures of all the compounds **4, 5(a-g)** were affirmed by from the FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass and HRMS spectra. The mass spectrum of **5d** demonstrated a molecular ion peak at *m/z* 310 $[M + H]^+$, which indicates the addition reaction of the acetyl acetone, **3a** to the 1-(3-(1,3-dioxolan-2-yl)-7-methylquinolin-2-yl)hydrazine, **2b**. The appearance of three methyl protons at δ 2.32 ppm is attributable to the $-CH_3$ group at 7 position of the quinoline system. The three methyl protons appeared as singlet each at δ 2.43 ppm and δ 2.47 ppm attributable to the two methyl groups in the pyrazole moiety. Likewise, the existence of four methylene protons at δ 4.08 ppm indicates the dioxalanyl moiety and the peaks observed at δ 5.97, δ 6.13, δ 7.45, δ 7.79 and δ 7.82 ppm are attributable to the five aromatic protons in ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum of compound **5d** demonstrated peakscarbons at δ 10.9, δ 17.3, δ 22.7 and δ 66.4 ppm attributable to the aliphatic and peaks from δ 101.6 to δ 160 ppm are attributable to the aromatic carbons.

2.2Anti-bacterial evaluation

The structural activity relationship investigations of 2-hydrazino-3-(1,3-dioxolan-2yl)quinolines, (**2a-c**) and 2-pyrazoloquinolin-3-(1,3-dioxolan-2-yl)quinolones, (**5a-f)** were performed for their antimicrobial activity against five separate bacterial organisms. The antibacterial effect of the compounds was assessedutilizing ampicillin as a standard and reported as minimum inhibitory concentration (MIC) values. Graphical representation of the antibacterial trend followed could be seen in **Fig. 2.** In the 2-hydrazino-3-(1,3-dioxolan-2-yl)quinoline series, from compound **2a** to **2c** the number of methyl groups was found to be increasing at positions 7 and 8 and therefore amongst **2(a-c)** the antibacterial effects was found to be higher for compound **2c**, against all the tested bacteria. The compound **2c** exhibited MIC value of 25µg/mL which is comparable to the standard employed against *P. aeruginosa* and *B. subtilis.* This may be ascribed to the existence of methyl groups at position 7 and 8 of quinoline nucleus which may expect to increase lipophilicity of the molecule.

The same pattern was observed in biological effect for the series **5(a-g**), where, the compounds **5c** and **5f** were found to be better active over all other members of the series. The compound **5c** was found to have same or better MIC values over the standard utilized for the study. In the compounds **5a, 5b** and **5c** the position 7 on quinoline nucleus was unsubstituted while, two methyl groups existed in the 3' and 5' positions of the compound **5a**. Likewise, in the compound **5c** the methyl groups were replaced with aromatic system at 3' and 5' positions. Compound **5c** was found to have potential and exceptional antibacterial character with a MIC value of 25µg/mL against *S. aureus, P. aeruginosa, B. Subtilis* and 50µg/mL against *E. coli* and *K. pneumonia* respectively. The compound **5f**, having methyl groups at position 7 and 8 of quinoline nucleus and further more at 3' and 5' positions in pyrazole moiety has astounding activity against *S. aureus, P. Aeruginosa* with a MIC of 25 µg/mL. Remaining compounds were found to be not signifying any promising antibacterial activity. This indicated that the replacement of methyl to aromatic ring have resulted in compounds with better antibacterial property which makes the compound optimum lipophilic in nature.

The assessment of the docking results were carried out by simultaneously sorting the different complexes concerning the anticipated binding energies **(Table 5), (Fig 3)**. From the results acquired from the docking analysis it was apparent that the compound **5c** have good binding interaction with that of peptide deformylase with binding energy of -8.1 Kcal/mol which was more noteworthy than the standard Ampicillin (-7.5 Kcal/mol). The compounds **2c** and **5f** have moderate binding affinity with receptor possessing binding energies -7.3 and -6.9 Kcal/mol.

3 Experimental

The materials were purchased from Sigma-Aldrich, Merck and were utilized without any additional purification. All reactions were observed by TLC (Thin layer chromatography). Melting points were recorded on an Elchem digital melting point apparatus in open capillaries and are uncorrected. The ^{1}H-NMR spectra was measured on a Bruker Avance-400 MHz instrument at room temperature. Chemical shifts δ are in parts per million (ppm) measured in $CDCl_3$ or DMSO-*d6* as solvent and relative to TMS as the internal standard. Mass spectra were obtained using ESI, LCMS, and HRMS spectrometry.

3.1 General procedure of the synthesis of 2-chloro-3-(1,3-dioxolan-2-yl)quinolines, 1(a-f)

A solution of 2-chloroquinoline-3-carbaldehydes, (10 mmol) in benzene (50 mL) containing ethylene glycol (1.78 g, 1.6 mL, 28.5 mmol) and a crystal of toluene-*p*-sulfonic acid was heated under reflux for 5 h utilizing a Dean-Stark apparatus until no more water collected in the side arm. The cooled solution was treated with saturated aqueous sodium carbonate (50 mL). Benzene layer was separated, dried and evaporated to afford **1(a-f)** which were recrystallized from petroleum ether gave a yellowish solids. The products were characterized by NMR, mass spectral techniques.

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2-Chloro-3-(1,3-dioxolan-2-yl)quinolines,1a Pale yellow powder, 65 % yield, mp 60-62 °C (Lit. 59-60 °C)[36].IR (KBrpellets, cm^{-1}) υ: 2899, 1621, 1567, 1330, 1100, 755. ^1H NMR ($CDCl_3$, ppm, 400 MHz) δ: 4.13 (4H, m, CH_2), 6.24 (1H, s, CH), 7.55 (1H, t, *J* = 8 Hz, CH), 7.73 (1H, t, *J* = 8 Hz, CH), 7.84 (1H, d, *J* = 8 Hz, CH), 8.02 (1H, d, *J* = 8 Hz, CH), 8.40 (1H, s, CH). ^{13}C NMR ($CDCl_3$,ppm, 100 MHz) δ: 2 x 66.2 (CH_2-CH_2), 100.7 (CH-O), 124.8, 126.7, 127.1, 127.8, 128.9, 135.4, 141.7, 148.3, 149.2 (C=N). Mol. formula: $C_{12}H_{10}ClNO_2$ requires 235; ESI-MS *m*/*z*: 235 (M^+).

2-Chloro-3-(1,3-dioxolan-2-yl)-7-methylquinolines,1b[35] Pale yellow powder, 85 % yield, mp 72-74 °C (Lit. 75-76 °C) [36]. IR (KBr pellets, cm^{-1}) υ: 2921, 1626, 1541, 1330, 1101, 810. ^1H NMR ($CDCl_3$, ppm, 400 MHz) δ: 2.58 (3H, s, CH_3), 4.13 (4H, m, CH_2), 6.24 (1H, s, CH), 7.42 (1H, d, *J* = 8 Hz, CH), 7.75 (1H, d, *J* = 8 Hz, CH), 7.83 (1H, s, CH), 8.37 (1H, s, CH). ^{13}C NMR ($CDCl_3$, ppm, 100 MHz) δ: 22.0 (CH_3), 2 x 65.5 (CH_2-CH_2), 100.5 (CH-O), 124.8, 127.3, 127.6, 128.4, 129.5, 136.4, 141.7, 148.0, 149.2 (C=N). Mol formula: $C_{13}H_{12}ClNO_2$ requires 249; ESI-MS *m*/*z*: 250 (M+1).

2-Chloro-3-(1,3-dioxolan-2-yl)-7,8-dimethylquinolines,1c. Pale yellow powder, 81 % yield, mp 107-109 °C. IR (KBr pellets, cm^{-1}) υ: 3053, 2887, 1606, 1563, 1360, 1108, 781. ^1H NMR ($CDCl_3$, ppm, 300 MHz) δ: 2.54 (3H, s, CH_3), 2.72 (3H, s, CH_3), 4.10 (4H, m, CH_2), 6.22 (1H, s, CH), 7.44 (1H, d, *J* = 9 Hz, CH), 7.69 (1H, d, *J* = 9 Hz, CH), 8.65 (1H, s, CH). ^{13}C NMR ($CDCl_3$, ppm, 75 MHz) δ: 13.3 (CH_3), 20.7 (CH_3), 2 x 65.4 (CH_2-CH_2), 100.5(CH-O), 124.8, 125.1, 127.8, 129.9, 133.7, 136.6, 138.9, 146.9, 147.9 (C=N). Mol. formula: $C_{14}H_{14}ClNO_2$ requires 263.7; ESI-MS *m*/*z*: 264 (M^+).

2-Chloro-3-(1,3-dioxolan-2-yl)-6-methylquinolines,1d Pale yellow powder, 78 % yield, mp 52-54 °C (Lit. 48-50 °C)[36] IR (KBr pellets, cm^{-1}) υ: 2894, 1598, 1329, 1096, 823. ^1H NMR ($CDCl_3$, ppm, 300 MHz) δ: 2.54 (3H, s, CH_3), 4.20-4.13 (4H, m, CH_2), 6.23 (1H, s, CH), 7.62-7.57 (2H, m, CH), 7.95-7.92 (1H, d, *J* = 8.55 Hz, CH), 8.32 (1H, s, CH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.5, 2 x 65.3 (CH_2-CH_2), 100.3 (CH-O), 126.3, 126.5, 128.3, 135.9, 138.3, 139.5, 148.2, 149.2, 149.7 (C=N). Mol. formula: $C_{13}H_{12}ClNO_2$ requires 249.69: LC-MS *m*/*z*: 250 (M+1).

2-Chloro-3-(1,3-dioxolan-2-yl)-8-methylquinolines,1e Pale yellow powder, 87% yield, mp 86-88 °C (Lit. 88-90 °C)[36]. IR (KBr pellets, cm^{-1}) υ: 2919, 2883, 1614, 1597, 1330, 1101, 765. ^1H NMR ($CDCl_3$, ppm, 400 MHz) δ: 2.78 (3H, s, CH_3), 4.12 (4H, m, CH_2), 6.26 (1H, s, CH), 7.44 (1H, t, *J* = 8 Hz, CH), 7.58 (1H, d, *J* = 8 Hz, CH), 7.68 (1H, d, *J* = 8 Hz, CH), 8.37 (1H, s, CH). ^{13}C NMR ($CDCl_3$, ppm, 100 MHz) δ: 18.0, 2 x 65.0 (CH_2-CH_2), 101.5 (CH-O), 119.1, 121.7, 122.1, 122.6, 126.3, 130.4, 133.2, 135.2, 146.1, 155.4 (C=N). Mol. formula: $C_{13}H_{12}ClNO_2$ requires 249.7; LC-MS *m*/*z*: 250 (M^+).

2-Chloro-3-(1,3-dioxolan-2-yl)-8-methoxyquinolines,1f Pale yellow powder, 82 % yield, mp 119-121 °C. IR (KBr pellets, cm^{-1}) υ: 2923, 1632, 1587, 1330, 1107, 805. ^1H NMR ($CDCl_3$, 300 MHz, ppm) δ: 3.92 (3H, s, OCH_3), 4.10 (4H, m, CH_2), 6.22 (1H, s, CH), 7.10 (1H, d, *J* = 9 Hz, CH), 7.37 (1H, t, *J* = 9 Hz, CH), 7.91 (1H, d, *J* = 9 Hz, CH), 8.30 (1H, s, CH). ^{13}C NMR ($CDCl_3$, ppm, 75 MHz) δ: 55.5, 2 x 65.5 (CH_2-CH_2), 100.4 , 105.5 (CH-O), 2 x 123.5, 127.9, 129.5, 135.3, 143.6, 146.5 (C=N), 158.2 (C-OCH_3). Mol. formula: $C_{13}H_{12}ClNO_3$ requires 265.7; ESI-MS *m*/*z*: 266 (M^+).

3.2 General procedure for the synthesis of compounds 2(a-f)

The 2-hydrazino-3-(1,3-dioxolan-2-yl) quinolines, **2(a-f)** were prepared by refluxing 2-chloro-3-(1,3-dioxolan-2-yl) quinolines[36], **1(a-f)** (0.5 mmol) with excess of hydrazine hydrate (3 ml) in ethanolic solution in the presence of catalytic amount of ammonia for 1-2 h. The completion of the reaction was monitored by TLC, excess solvent was removed and then poured on to crushed ice. The solid separated was filtered and dried. The compounds are pure enough to proceed further without any additional purification.

1-(3-(1,3-Dioxolan-2-yl)quinolin-2-yl)hydrazines,2a Pale brown solid, 68 % yield, mp 68-70 °C (Lit. 68 °C)[36]. IR (KBr pellets, cm^{-1}) υ: 3389, 3290, 2886, 1627. ^1H NMR (DMSO-d_6, ppm, 400 MHz) δ: 4.02 (4H, m, CH_2), 4.47 (2H, s, NH_2), 5.84 (1H, s, CH), 7.20 (1H, t, *J* = 8 Hz, CH), 7.40 (1H, s, CH), 7.53 (2H, m, CH), 7.71 (1H, d, *J* = 8 Hz, CH), 8.01 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 100 MHz) δ: 2 x 65.1 (CH_2-CH_2), 100.0 (CH-O), 120.6, 2 x 122.1, 125.3, 125.9, 127.1, 133.4, 143.6, 156.7(C=N). Mol. formula: $C_{12}H_{13}N_3O_2$ requires 231; LC-MS *m*/*z*: 232 (M+1).

1-(3-(1,3-Dioxolan-2-yl)-7-methylquinolin-2-yl)hydrazines, 2b Reddish brown crystal, 78 % yield, mp 94-96 °C (Lit. 92-94 °C)[36]. IR (KBr pellets, cm^{-1}) υ: 3341, 3211, 2836, 1605. ^1H NMR (DMSO-d_6, ppm, 400 MHz) δ: 2.51 (3H, s, CH_3), 4.07 (4H, m, CH_2), 4.61 (2H, s, NH_2), 5.85 (1H, s, CH), 7.12 (1H, d, *J* = 8 Hz, CH), 7.55 (1H, d, *J* = 8 Hz, CH), 7.59 (1H, s, CH), 7.93 (1H, s, CH), 8.10 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 100 MHz) δ: 21.9, 2 x 65.0 (CH_2-CH_2), 101.8 (CH-O), 117.8, 121.2, 125.0, 125.5, 127.5, 135.0, 140.5, 147.4, 156.5 (C=N). Mol. formula: $C_{13}H_{15}N_3O_2$ requires 245; LC-MS *m*/*z*: 246 (M+1).

1-(3-(1,3-Dioxolan-2-yl)-7,8-dimethylquinolin-2-yl)hydrazines , 2c Reddish brown crystal, 78 % yield, mp 117-119 °C. IR (KBr pellets, cm^{-1}) υ: 3413, 3225, 2841, 1612. ^1H NMR (DMSO-d_6, ppm, 400 MHz) δ: 2.34 (3H, s, CH_3), 2.46 (3H, s, CH_3), 4.07 (4H, m, CH_2), 4.81 (2H, s, NH_2), 6.21 (1H, s, CH), 7.33 (1H, d, *J* = 8 Hz, CH), 7.54 (1H, d, *J* = 8 Hz, CH), 8.27 (1H, s, CH), 8.30 (1H, s, CH), 8.56 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm,100 MHz) δ: 13.3, 20.7, 2 x 65.4 (CH_2-CH_2), 100.5 (CH-O), 124.8, 125.1, 127.8, 129.9, 133.7, 136.6, 138.9, 146.9, 157.4 (C=N). Mol. formula $C_{14}H_{14}ClNO_2$ requires 259; LC-MS *m*/*z*: 260 (M+1).

1-(3-(1,3-Dioxolan-2-yl)-6-methylquinolin-2-yl)hydrazines, 2d Reddish brown solid, 73 % yield, mp 84-86 °C (Lit. 84-86 °C) [36]. IR (KBr pellets, cm^{-1}) υ: 3331, 3221, 2829, 1611. ^1H NMR (DMSO-d_6, ppm, 400 MHz) δ: 2.46 (3H, s, CH_3), 4.07 (4H, m, CH_2), 4.47 (2H, s, NH_2), 5.84 (1H, s, CH), 7.40 (1H, s, CH), 7.42 (1H, d, *J* = 8 Hz, CH), 7.66 (1H, d, *J* = 8 Hz, CH), 7.89 (1H, s, CH), 8.21 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 100 MHz) δ: 21.1, 2 x 64.9 (CH_2-CH_2), 101.7 (CH-O), 118.7, 123.3, 125.8, 127.8, 132.0, 132.5, 134.7, 145.6, 156.0 (C=N). Mol. formula: $C_{13}H_{15}N_3O_2$ requires 245; LC-MS *m*/*z*: 246 (M+1).

1-(3-(1,3-Dioxolan-2-yl)-8-methylquinolin-2-yl)hydrazines, 2e Reddish brown solid, 76 % yield, mp 97-99 °C (Lit. 98-100 °C) [36]. IR (KBr pellets, cm^{-1}) υ: 3374, 3219, 2883, 1619. ^1H NMR (DMSO-d_6, ppm, 300 MHz) δ: 2.48 (3H, s, CH_3), 3.97 (4H, m, CH_2), 4.52 (2H, s, NH_2), 5.86 (1H, s, CH), 7.11 (1H, t, *J* = 9 Hz, CH), 7.40 (1H, d, *J* = 9 Hz, CH), 7.42 (1H, s, CH), 7.55 (1H, d, *J* = 9 Hz, CH), 7.98 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 75 MHz) δ: 18.0, 2 x 65.5 (CH_2-CH_2), 100.5 (CH-O), 119.1, 121.7, 122.1, 122.6, 126.3, 130.4, 133.2, 135.2, 146.1, 155.4 (C=N).

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Mol. formula: $C_{13}H_{15}N_3O_2$ requires 245; ESI *m/z*: 245 (M^+).

1-(3-(1,3-Dioxolan-2-yl)-6-methoxyquinolin-2-yl)hydrazines, 2f Reddish brown solid, 69 % yield, mp 102-104 °C (Lit. 100-102 °C)[36]. IR (KBr pellets, cm^{-1}) υ: 3433, 3219, 2831, 1621.^{1}H NMR (DMSO-d_6, ppm, 400 MHz) δ: 3.90 (3H, s, OCH_3), 4.13 (4H, m, CH_2), 4.52 (2H, s, NH_2), 5.98 (1H, s, CH), 7.42 (1H, s, CH), 7.87 (1H, d, *J* = 8 Hz, CH), 7.93 (1H, d, *J* = 8 Hz, CH), 8.30 (1H, s, CH), 8.76 (1H, s, NH). ^{13}C NMR (DMSO-d_6, ppm, 100 MHz) δ: 55.9, 2 x 65.4 (CH_2-CH_2), 100.3 (CH-O), 109.1, 119.1, 2 x 127.7, 127.9, 136.4, 139.3, 148.3, 159.4 (C=N). Mol. formula $C_{13}H_{12}ClNO_3$ requires 261; ESI-MS *m/z*: 262 (M+1).

3.3 General procedure for the synthesis of compounds 4, 5(a-g)

Equimolar mixture of 2-hydrazino-3-(1, 3-dioxolan-2-yl)quinoline, **2(a-c)** and diketones, **3(a-c)** were taken in ethanol and 100 mg of MK-10 catalyst was added and refluxed on water bath for 2-4 h. On completion of the reaction, the solution was filtered to remove the catalyst, MK-10 and then the excess solvent was extracted using rotary evaporator to yield 2-(3,5-substituted-1*H*-pyrazol-1-yl)-1-(1,3-dioxolan-2-yl), **5(a-g)** in good yields. At the commencement of our work, conventional approach of this synthesis was attempted by reacting compound **2b** with acetyl acetone, **3a** in the presence of conc. H_2SO_4 which resulted in deprotection of aldehyde group and 2-(3, 5-dimethyl-1*H*-pyrazol-1-yl)quinoline-3-carbaldehyde, **4** was formed.

2-(3,5-dimethyl-1H-pyrazol-1-yl)-7-methylquinoline-3-carbaldehyde, 4 mp 227-229 °C, FTIR, $\tilde{\nu}$ /cm^{-1}:2918, 2850, 1690, 1593, 1498. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm), *δ*: 2.32 (s, 3H, CH_3), 2.61 (s, 3H,CH_3), 2.66 (s, 3H, CH_3), 6.15 (s, 1H, CH), 7.45-7.47 (d, 1H, *J* = 6 Hz, CH), 7.85 (m, 2H, CH), 8.75 (s, 1H, CH), 10.20 (s, 1H, -CHO). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm), *δ*: 13.4, 22.1, 29.6, 108.9 (CH-O), 124.2, 124.3, 127.8, 2 x 128.9, 2 x 129.7, 139.3, 142.3, 142.6, 148.1 (C=N), 163.2 (C=O). GC-MS *m/z*: 265 (M^+).Mol. formula: $C_{16}H_{15}N_3O$ requires 245.12.

2-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-(1,3-dioxolan-2-yl)quinoline, **5a** mp >300 °C, FTIR, $\tilde{\nu}$ /cm^{-1}:2917, 2845, 1689, 1624. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm), *δ*: 2.20 (s, 3H, CH_3), 2.30 (s, 3H,CH_3), 4.00-4.06 (m, 4H, CH_2), 6.10 (s, 1H, CH), 6.24 (s, 1H, CH), 7.70-7.715 (d, 1H, *J* = 7.5 Hz, CH), 7.96-8.11(d, 1H, *J* = 7.5, CH), 8.16-8.26 (m, 2H, CH), 8.72 (s, 1H, CH). ^{13}C NMR (DMSO-d_6, 125 MHz, ppm), *δ*: 11.4, 17.0, 2 x 66.6 (CH_2-CH_2), 103.5(CH-O), 107.2, 116.8, 2 x 125.0, 2 x 127.3, 2 x 129.7, 135.8, 141.3, 143.1, 156.5, 167.8 (C=N). Mol. formula: $C_{17}H_{17}N_3O_2$ HRMS [EI^+] calcd for $C_{17}H_{17}N_3O_2$m/z 295.1321 [M^+], found 295.1312.

3-(1,3-Dioxolan-2-yl)-2-(3-methyl-5-phenyl-1H-pyrazol-1-yl)quinoline, 5b mp >300 °C, FTIR, $\tilde{\nu}$ /cm^{-1}:2909, 2834, 1676, 1612. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm), *δ*: 2.81 (s, 3H, CH_3), 4.08 (m, 4H, CH_2), 6.19 (s, 1H, CH), 6.41 (s, 1H, CH), 7.39-7.42 (m, 3H, CH), 7.51-7.56 (m, 3H, CH), 7.70-7.78 (m, 3H, CH), 8.22-8.26 (d, 1H, *J* = 8, CH). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm), *δ*: 18.9, 2 x 66.7 (CH_2-CH_2), 101.1(CH-O), 105.6, 120.5, 126.1, 3 x 126.9, 3 x 128.2, 2 x 129.0, 129.5, 2 x 133.4, 135.7, 143.1, 145.2, 151.6, 159.9 (C=N). LC-MS *m/z*: 358 (M+1).Mol. formula: $C_{22}H_{19}N_3O_2$ requires 357.14. HRMS [EI^+] calcd for $C_{22}H_{19}N_3O_2$m/z 357.1477 [M^+], found 357.1469.

3-(1,3-dioxolan-2-yl)-2-(3,5-diphenyl-1H-pyrazol-1-yl)quinoline, 5c mp 246 °C, FTIR, $\tilde{\nu}$ /cm^{-1}:2912, 2852, 1668, 1612. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm), *δ*:4.02 (m, 4H, CH_2), 6.12 (s, 1H, CH), 6.71 (s, 1H, CH), 7.31 (m, 2H, CH), 7.41 (m, 5H, CH), 7.52 (m, 4H, CH), 7.56 (t, 1H, CH), 7.71 (m, 2H, CH), 8.03-8.05 (d, 1H, *J* = 8 Hz, CH). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm), *δ*: 2 x 66.3 (CH_2-CH_2), 100.9 (CH-O), 103.6, 119.8, 124.9, 125.8, 2 x 126.7, 2 x 127.5, 127.8, 2 x 128.3, 2 x 128.9, 2 x 132.8, 133.4, 144.5, 145.7, 150.8, 161.4 (C=N). LC-MS *m/z*: 420 (M+1).Mol. formula: $C_{27}H_{21}N_3O_2$ requires 419.16.HRMS [EI^+] calcd for $C_{27}H_{21}N_3O_2$m/z 419.1634 [M^+], found 419.1643.

2-(3,5-dimethyl-1H-pyrazol-1-yl)-3-(1,3-dioxolan-2-yl)-7-methylquinoline, 5d mp >300 °C, FTIR, $\tilde{\nu}$ /cm^{-1}:2920, 2850, 1690, 1628. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm), *δ*: 2.32 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.08 (m, 4H, CH_2), 5.97 (s, 1H, CH), 6.13 (s, 1H, CH), 7.45-7.51 (m, 2H, CH), 7.79 (s, 1H, CH), 7.82 (s, 1H, CH). ^{13}C NMR (DMSO-d_6, 125 MHz, ppm), *δ*: 10.9, 17.3, 22.7, 2 x 66.4 (CH_2-CH_2), 101.6 (CH-O), 105.4, 119.7, 2 x 122.9, 127.1, 2 x 127.9, 133.8, 137.8, 143.6, 144.7, 149.0, 160.1 (C=N). EI-MS*m/z*: 310 (M+1). Mol.formula: $C_{18}H_{19}N_3O_2$ requires 309.14. HRMS [EI^+] calcd for $C_{18}H_{19}N_3O_2$m/z 309.1477 [M^+], found 309.1473.

3-(1,3-dioxolan-2-yl)-7-methyl-2-(3-methyl-5-phenyl-1H-pyrazol-1-yl)quinoline, 5e- mp >300 °C, FTIR, $\tilde{\nu}$ /cm^{-1}:2923,2849, 1687, 1621. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm), *δ*: 2.43 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.10 (m, 4H, CH_2), 6.11 (s, 1H, CH), 6.23 (s, 1H, CH), 7.25-7.33 (m, 4H, CH), 7.51 (m, 2H, CH), 7.70-7.72 (d, 1H, *J* = 8, CH), 7.90 (m, 2H, CH). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm), *δ*: 12.8, 21.3, 2 x 65.8 (CH_2-CH_2), 101.1 (CH-O), 103.4, 118.6, 122.3, 125.9, 2 x 126.7, 127.8, 2 x 128.4, 2 x 129.1, 132.3, 133.7, 137.8, 145.1, 145.9, 147.1, 162.1 (C=N). LC-MS *m/z*: 372 (M+1).Mol. formula: $C_{23}H_{21}N_3O_2$ requires 371.16. HRMS [EI^+] calcd for $C_{23}H_{21}N_3O_2$m/z 371.1634 [M^+], found 371.1626.

2-(3,5-dimethyl-1H-pyrazol-1-yl)-3-(1,3-dioxolan-2-yl)-7,8-dimethylquinoline, 5f- mp >300 °C, FTIR, $\tilde{\nu}$ /cm^{-1}:2927, 2841, 1691, 1634. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm), *δ*: 2.24 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 4.08 (m, 4H, CH_2), 6.01 (s, 1H, CH), 6.16 (s, 1H, CH), 7.36-7.41 (m, 2H, CH), 7.79 (s, 1H, CH). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm), *δ*: 11.3, 12.8, 16.9, 17.7, 2 x 65.8 (CH_2-CH_2), 101.2 (CH-O), 104.8, 117.8, 121.3, 124.7, 127.2, 133.3, 135.6, 136.5, 143.4, 147.3, 152.8, 160.1 (C=N). LC-MS *m/z*: 324 (M+1).Mol. formula: $C_{19}H_{21}N_3O_2$ requires 323.16. HRMS [EI^+] calcd for $C_{19}H_{21}N_3O_2$m/z 323.1634 [M^+], found 323.1647.

3-(1,3-dioxolan-2-yl)-7,8-dimethyl-2-(3-methyl-5-phenyl-1H-pyrazol-1-yl)quinoline, 5g- mp 243 °C, FTIR, $\tilde{\nu}$ /cm^{-1}:2929, 2845, 1689, 1632. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm), *δ*: 2.26 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.10 (m, 4H, CH_2), 5.96 (s, 1H, CH), 6.42 (s, 1H, CH), 7.10-7.19 (m, 2H, CH), 7.30 (s, 1H, CH), 7.44-7.84 (m, 3H, CH), 8.30 (s, 1H, CH), 8.59 (s, 1H, CH). ^{13}C NMR (DMSO-d_6, 100 MHz, ppm), *δ*: 13.6, 18.8, 19.3, 2 x 66.7 (CH_2-CH_2), 101.4 (CH-O), 106.2, 119.1, 2 x 124.3, 125.7, 3 x 127.9, 2 x 128.3, 2 x 129.9, 134.1, 2 x 135.7, 136.8, 143.2, 151.9, 159.6 (C=N). HRMS [EI^+] calcd for $C_{24}H_{23}N_3O_2$m/z 385.1790 [M^+], found 385.1781.

4 Antibacterial activity

Cultures of bacteria were grown on nutrient broth (Hi Media) at 37 °C for 12–14 h and were maintained on respective agar slants at 4 °C. All the compounds **2(a–c)** and **5(a–g)** were tested for

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their minimum inhibition concentrations (MIC) by dissolving in 100% DMSO to obtain a concentration range of 25, 50, 75, 100 μg/cm^3 and screened for their antibacterial activities against Gram-positive *S. aureus* ATCC 700699, *B. subtilis* MTCC 430, and Gram-negative *E. coli* ATCC 11105, *Klebsiella* ATCC 10273 and *P. aeruginosa* ATCC 27853 by agar well technique[38]. The standard antibacterial ampicillin was also tested under similar conditions for comparison.

4.1 Determination of minimum inhibitory concentration (MIC)

The concentration of test cultures was adjusted to 0.5 McFarland standards by using a spectrophotometer Test organisms were lawn cultured on the MHA plates. Agar surface was bored by using a sterilized cork borer and 100 mm^3 of each dilution was poured in the wells. All test plates were incubated at 37 °C for 24 h. The minimum concentration of each compound showing a clear zone of inhibition was considered to be MIC. The experiments were performed in triplicate [39-40] (Table 4).

4.2 Molecular docking analysis for antibacterial efficacy

The binding affinity of compounds 1-(3-(1,3-Dioxolan-2-yl)-7,8-dimethyl quinolin-2-yl) hydrazine **2c**, 3-(1,3-dioxolan-2-yl)-2-(3,5-diphenyl-1H-pyrazol-1-yl)quinoline **5c**, 2-(3,5-dimethyl-1H-pyrazol-1-yl)-3-(1,3 dioxo lan-2-yl)-7,8-dimethylquinoline,**5f** with peptide deformylase were calculated by using Autodock .v.1.5.6. The peptide deformylase was taken from protein data bank (ID: 1BS6). Rapid energy evaluation was achieved by pre calculating atomic affinity potential for each ligand seperately and the energy of interaction of each atom in the ligand was encounteredFinally grid maps were calculated for each ligand seperately and docking analysis were carried out by using Lamarckian Genetic Algorithm. Autodock was run several times to get various docked confirmations which were used further for predicting docking energy. For each ligand 5 best poses were generated and scored by using Autodock 4.2 scoring functions[41]. Peptide deformylase is an enzyme which involves in the deformylation of mitrochondrial proteins in bacteria. Inhibition of peptide deformylase results in membrane delocalization which subsequently leads to bacterial death.

Conclusions

A facile and efficient method has been developed for the synthesis of 2-(3, 5-disubstituted-1*H*-pyrazol-yl)-3-(1,3-dioxolan-2yl)quinolines **5(a-g)** by refluxing equimolar mixture of 2-hydrazino-3-(1,3-dioxolan-2-yl)quinolines, **2(a-c)** and diketones, **3(a-c)** in ethanol using Montmorillonite clay 10 as an efficient catalyst. Also the synthesis of 2-hydrazino-3-(1,3-dioxolan-2-yl) quinolines, **2(a-c)** has been succeeded within lesser time using NH_3. The synthesized compounds were evaluated for in vitro antibacterial activity out of which **2c, 5c, 5f** showed good to moderate efficacy against the tested strains when compared to that of standard ampicillin and in addition to this SAR analysis and docking studies were also in good agreement with the above results.

Notes and references

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FIGURE CAPTIONS

Scheme 1: Scheme 1. Synthesis of 2-hydrazino-3-(1,3-dioxolan-2-yl)quinolines, **2(a-f)**

Scheme 2: Synthesis of 2-(3, 5-substituted-1H-pyrazol-1-yl)-3-substituted quinolines**4** and **5(a-g)**

Fig. 1: Plausible mechanism for the synthesis of 3-(1, 3-dioxolan-2-yl)-2-(3, 5-di methyl-1H-pyrazol-1-yl)-7-methyl quinoline, **5d**

Fig. 2: Antibacterial activity of compounds **2(a-c), 5(a-g)** and S-Ampicillin (standard)

Fig3: The binding interactions of various ligands with peptide deformylase. [A] The binding affinity of **2c** with receptor in ribbon view. [B] Interaction of **2c** with the molecular surface of the receptor. [C] The binding affinity of **5c** with receptor in ribbon view. [D] Interaction of **5c** with the molecular surface of the receptor. [E] The binding affinity of **5f** with receptor in ribbon view. [F] Interaction of **5f** with the molecular surface of the receptor. [G] The binding affinity of Ampicillin with receptor in ribbon view. [H] Interaction of Ampicillin with the molecular surface of the receptor.

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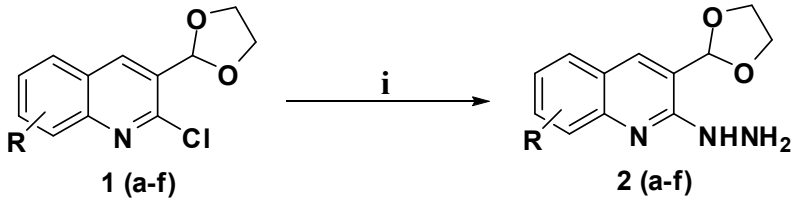

1 (a-f) 2 (a-f)

Reagents and Conditions: (i) $NH_2NH_2.H_2O$, EtOH/NH_3EtOH, reflux, 80 °C

Scheme 1. Synthesis of 2-hydrazino-3-(1, 3-dioxolan-2-yl)quinolines, 2(a-f)

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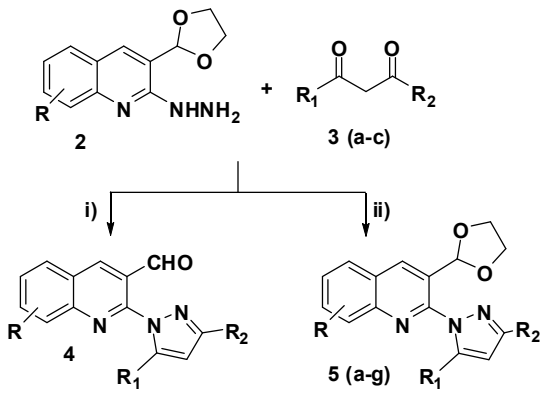

	R	R_1	R_2
4	7-CH_3	-CH_3	-CH_3
5a	H	-CH_3	-CH_3
5b	H	-C_6H_5	-CH_3
5c	H	-C_6H_5	-C_6H_5
5d	7-CH_3	-CH_3	-CH_3
5e	7-CH_3	-C_6H_5	-CH_3
5f	7,8-CH_3	-CH_3	-CH_3
5g	7,8-CH_3	-C_6H_5	-CH_3

Reagents and Conditions: (i) Conc. H_2SO_4, EtOH, reflux, 80 °C (ii) MK-10, EtOH, reflux, 80 °C

Scheme 2. Synthesis of 2-(3,5-substituted-1H-pyrazol-1-yl)-3-substituted quinolines 4 and 5(a-g)

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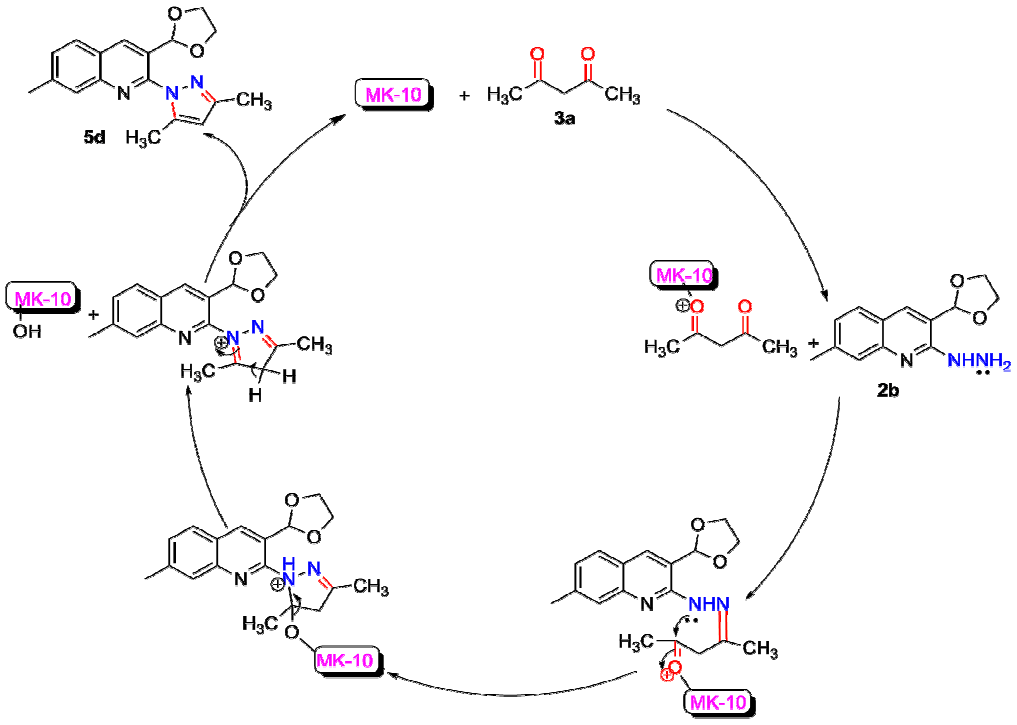

Fig. 1 Plausible mechanism for the synthesis of 3-(1, 3-dioxolan-2-yl)-2-(3, 5-di methyl-1H-pyrazol-1-yl)-7-methyl quinoline**, 5d**

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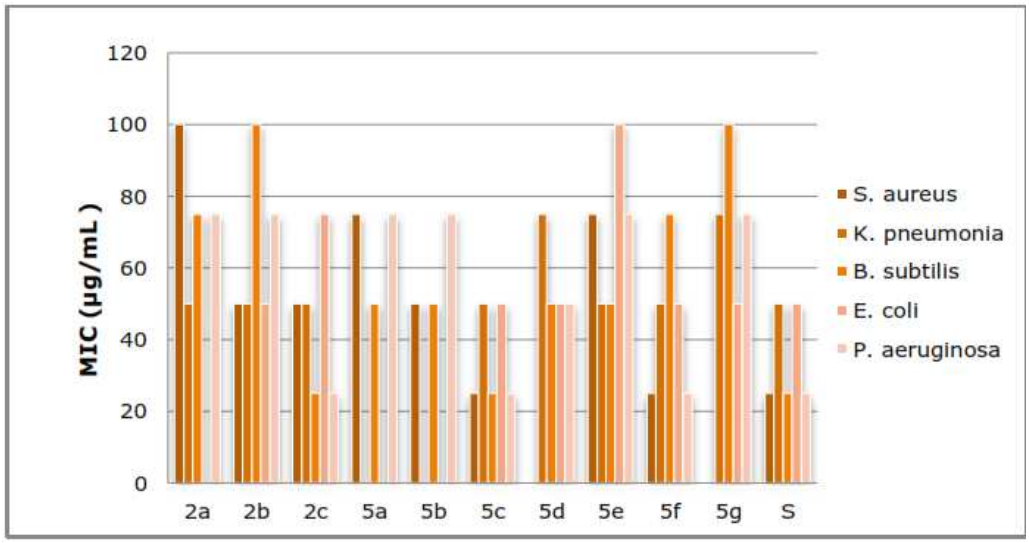

Fig. 2 Antibacterial activity of compounds **2(a-c), 5(a-g)** and S-Ampicillin (standard)

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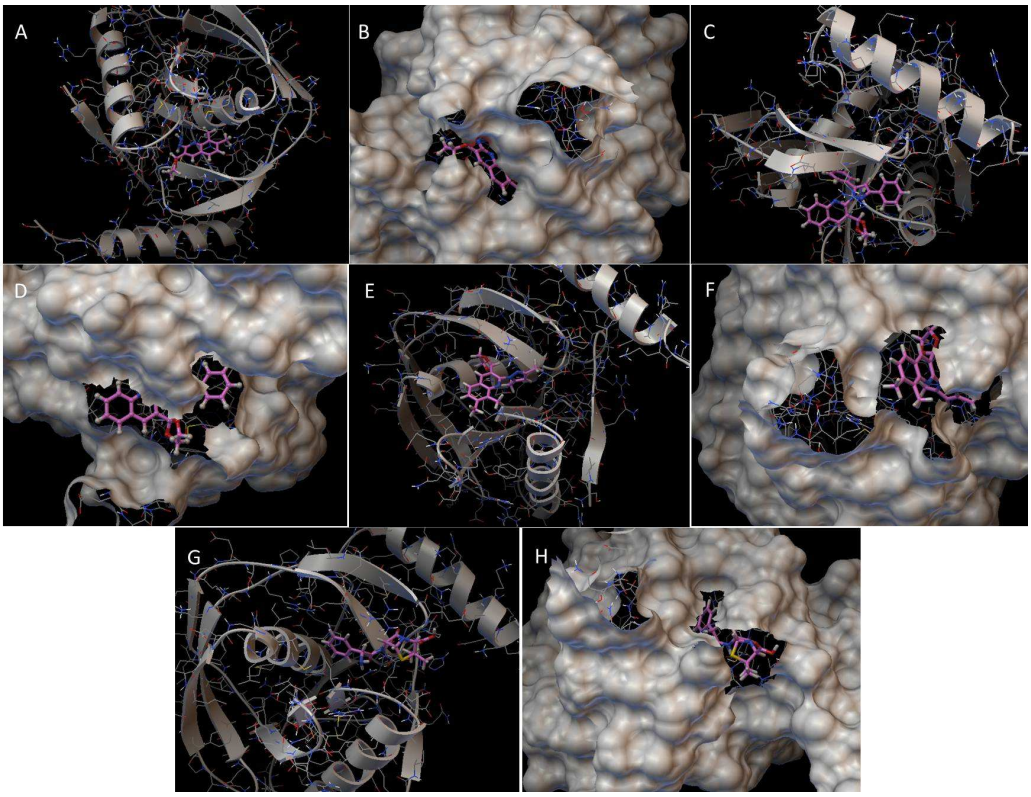

Fig. 3: The binding interactions of various ligands with peptide deformylase. [A] The binding affinity of 2c with receptor in ribbon view. [B] Interaction of 2c with the molecular surface of the receptor. [C] The binding affinity of 5c with receptor in ribbon view. [D] Interaction of 5c with the molecular surface of the receptor. [E] The binding affinity of 5f with receptor in ribbon view. [F] Interaction of 5f with the molecular surface of the receptor. [G] The binding affinity of Ampicillin with receptor in ribbon view. [H] Interaction of Ampicillin with the molecular surface of the receptor.

Table 1.Synthesis of 2-hydrazino-3-(1,3-dioxolan-2-yl)quinolines**2(a-f)**[a]

S. No.	R	Product	Time / h	Reported Yield %	Experimental Yield[b] %
1	H	2a	1.5	80	85
2	7-CH_3	2b	2	85	89.3
3	7,8-CH_3	2c	2	-	81.2
4	6-CH_3	2d	1.5	80	85.2
5	8-CH_3	2e	1	80	84
6	6-OCH_3	2f	2	85	89

Reagents[a]:1(a-f)-1 mmole, $NH_2NH_2.H_2O$ (excess), EtOH, 2-3 drops ofNH_3,80 ºC; [b]isolated yield

Table 2. Screening of the catalyst and its amount of the cyclization reaction[a]

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S. No.	Catalyst	Product	Yield[b]/%	S. No.	MK-10 (mg)	Time/ h	Yield[b]/ %
1	No catalyst	**5d**	-	1	Nil	48	-
				2	20	24	36
2	Conc.H_2SO_4	**4**	57	3	40	18	40
				4	60	10	55
3	$AlCl_3$	**5d**	64	5	80	6	62
				6	100	3	83
4	$SnCl_2.2H_2O$	**5d**	61	7	120	3	84
				8	140	3	85
5	MK-10	**5d**	83				

Reagents[a]: MK-10, EtOH, reflux; [b]isolated yield

Table 3.Synthesis of 2-(3,5-substituted-1*H*-pyrazol-1-yl)-3-substituted quinolines, **5(a-g)**[a]

S. No.	R	R_1	R_2	Product	Time / h	Yield[b] / %
1	H	CH_3	CH_3	**5a**	2.5	85
2	H	C_6H_5	CH_3	**5b**	3	79
3	H	C_6H_5	C_6H_5	**5c**	3.5	75.5
4	7-CH_3	CH_3	CH_3	**5d**	3	83
5	7-CH_3	C_6H_5	CH_3	**5e**	3.5	81
6	7,8-CH_3	CH_3	CH_3	**5f**	2.5	82.6
7	7,8-CH_3	C_6H_5	CH_3	**5g**	3	79

Reagents[a]: 2(a-c) (1 mmole), 3(a-c) (1 mmole), MK-10 (100 mg), EtOH, 80 °C; [b]isolated yield

Table 4. Determination of minimum inhibitory concentration

Test strains	MIC (μg cm^{-3})											
	2a	**2b**	**2c**	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**S**	**N**
S. aureus	100	50	50	75	50	25	-	75	25	-	25	-
K. pneumonia	50	50	50	-	-	50	75	50	50	75	50	-
B. subtilis	75	100	25	50	50	25	50	50	75	100	25	-
E. coli	-	50	75	-	-	50	50	100	50	50	50	-
P. aeruginosa	75	75	25	75	75	25	50	75	25	75	25	-

S-Standard (Ampicillin), N-Negative Control (DMSO)

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Table 5.Binding affinity of synthesized ligands 2c, 5c and 5f and standard Ampicillin with peptide deformylase.

Ligand	Binding Energies (kcal/mol)				
	Conformations				
	1	2	3	4	5
2c	-6.8	-6.4	-7.0	-6.6	-7.3
5c	-7.3	-6.9	-7.8	-7.5	-8.1
5f	-6.4	-6.2	-6.9	-6.0	-6.7
Standard[a]	-6.7	-6.5	-7.5	-6.2	-7.0

[a]Ampicillin

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Potential anti-bacterial agents: Montmorillonite Clay catalyzed synthesis of novel 2-(3, 5-substituted-1H-pyrazol-1-yl)-3-substituted quinolones and their in-silico molecular docking studies

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Graphical Abstract