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One-pot Synthesis of Some Novel Xanthine Derived Isoxazoles as Potent Antibacterial Agents

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ABSTRACT In search of better antibacterial agents, a series of novel xanthine derived 3,5-disubstituted isoxazole derivatives were synthesized (**3a-3j**) in one-pot using 8-chloro-1,3-dimethyl-7-(prop-2-yn-1-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione and aromatic aldehydes and further evaluated for their antibacterial activity *in vitro*. Among all, the compound **3i** showed two-fold more potent activity against *Bacillus subtilis* and *Staphylococcus aureus*, whereas the compound **3e** showed two-fold more potent activity against *B. subtilis* when compared with standard streptomycin. Besides, the molecular docking studies suggested that the more potent compounds **3i** and **3e** strongly bind to *S. aureus* MurB. It has also been observed that the energy calculations of molecular docking studies were in good contract with the obtained minimum inhibitory concentration values.

KEYWORDS One-pot synthesis, Isoxazole, Xanthine, Antibacterial, Molecular docking.

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INTRODUCTION

The treatment of infectious diseases remains an important problem due to the increase in the number of microbiological pathogens that are resistant to several drugs.[1] Thus, there is a large area for the invention of new antimicrobial agents. Recently, isoxazole and its derivatives have become important target molecules due to their therapeutic and pharmacological properties.[2] For the past few years, the chemist-therapist has paid great attention to the therapeutic interest of isoxazole derivatives in the pharmaceutical and medical fields.[3,4] The presence of two electronegative heteroatoms in the structures of isoxazole is sufficient for donor-acceptor interactions of hydrogen bonds with various enzymes and receptors that contribute to their pharmacological activity.[5] A literature study showed that isoxazole derivatives are known to exhibit antibacterial,[6] antitumor,[7] antidiabetic,[8] and anti-HIV activities.[9] Although a number of synthetic methods are available,[10] the copper(I)-catalyzed union of terminal alkynes and nitrile oxides to give 3,5-disubstituted isoxazole exhibits surprisingly finds wide coverage and exceptional selectivity.[11]

Natural xanthine alkaloids and some of their synthetic derivatives are widely used in medical practice as cardiovascular, bronchodilator, diuretic, analeptic, and lipid-lowering drugs.[12-15] Recently, interest on xanthine derivatives has been increased significantly due to their unique chemical and biological properties.[16-18] Given the importance of the main fragments of xanthine and isoxazole in several pharmacological applications, this paper reports the design and synthesis of new 8-chloro-1,3-dimethyl-7-((3-arylisoxazol-5-yl)methyl)-1*H*-purine-2,6(3*H*,7*H*)-dione hybrids and evaluation of their antibacterial activity along with the *in silico* studies.

RESULTS AND DISCUSSION

The synthetic approach of targeted xanthine-isoxazole derivatives (**3a–3j**) from **2** [**Scheme 1**] is presented in **Scheme 2**. Initially, the starting material

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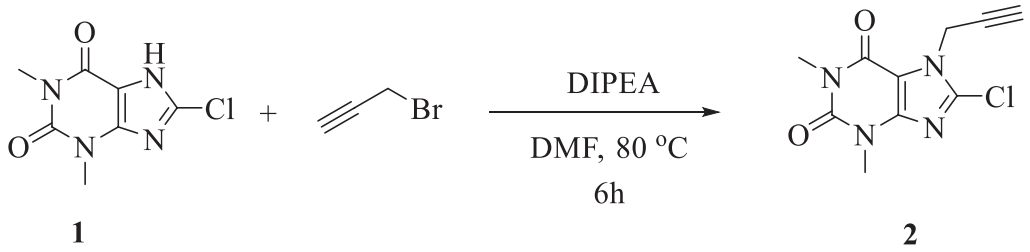
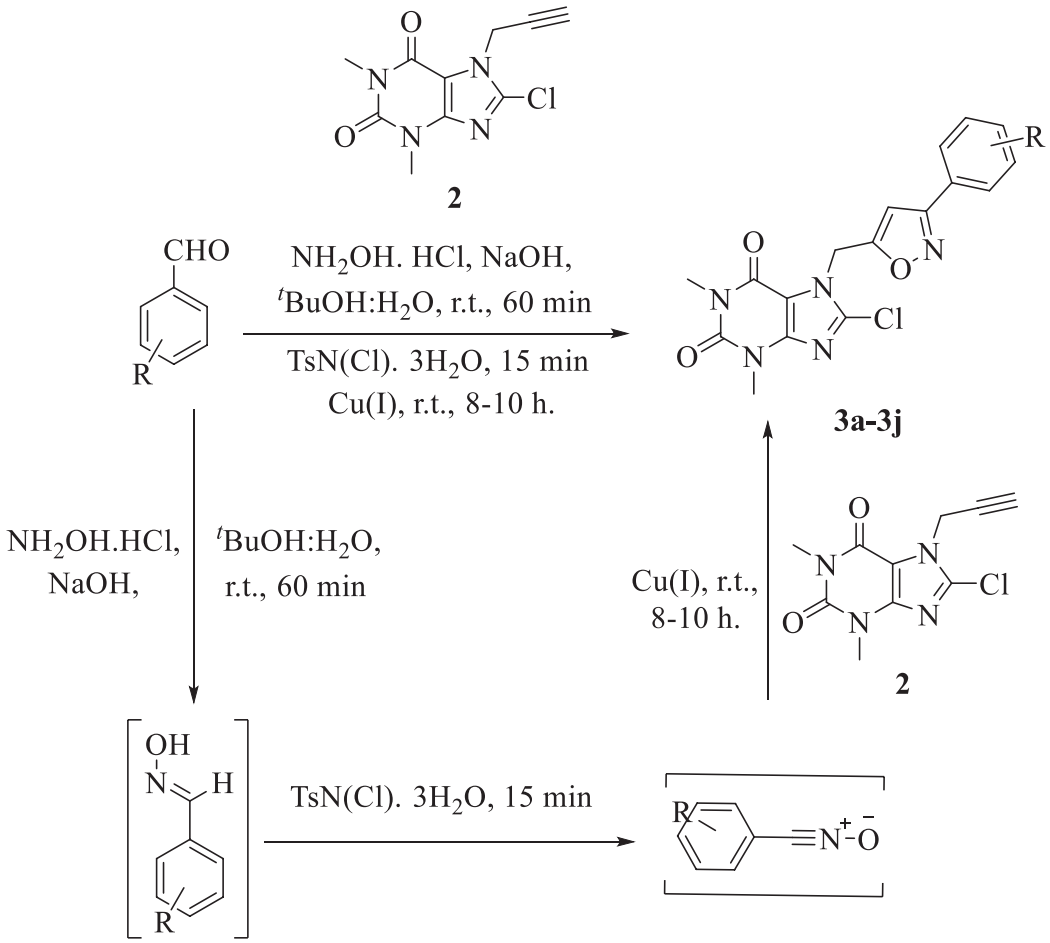


1 **2**

Scheme 1: Synthesis of 8-chloro-1,3-dimethyl-7-(prop-2-yn-1-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione



Scheme 2: One-pot synthesis of isoxazole-xanthine hybrids

8-chloro-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (**1**) was treated with propragyl bromide using N,N-diisopropylethylamine (DIPEA) in dimethylformamide (DMF) solvent at 80°C for 6 h to give 8-chloro-1,3-dimethyl-7-(prop-2-yn-1-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (**2**) in 80%yield [**Scheme 1**].[13,19] Later the aldehydes were converted into the corresponding *in situ* aldoximes using hydroxylammonium chloride and NaOH in t-BuOH:H_2O solvent media at room temperature after 1 h which then consequently converted into corresponding nitrile oxides by the portion-wise addition of chloramine-T trihydrate for 15 min. At the end, the 1,3-dipolar cycloaddition reaction between *in situ* formed nitrile oxides and 8-chloro-1,3-dimethyl-7-(prop-2-yn-1-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (**2**) in the presence of Cu(I) catalyst has provided the corresponding regio selective xanthine-isoxazole derivatives (**3a–3j**) in good yields.[20,21]

The structures of all the newly synthesized compounds (**3a–3j**) were confirmed by Proton nuclear magnetic resonance (^{1}H-NMR), electrospray ionization mass spectrum (ESI-MS), and elemental (CHN) analysis data. All the spectral and analytical data of the synthesized compounds were in full agreement with the proposed structures. For a representative compound **3a**, in the ^{1}H-NMR spectrum, the presence of the singlet signal that appeared at δ value 6.69 ppm, confirmed the presence of isoxazole ring proton. Besides, the presence of $[M+H]^+$ ion peak at m/z 402 in ESI-MS as well as the elemental analysis (CHN) data (C, 53.77; H, 3.95; N, 17.37) also confirmed the formation of isoxazole ring.

Antibacterial activity

All the newly synthesized compounds **3a-3j** were further investigated for their *in vitro* antibacterial activity against

Table 1: *In vitro* antibacterial activity data of compounds 3a-3j

Entry	R	MIC, μg/mL[a]			
		Bacillus subtilis	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Escherichia coli*
3a	4-OMe	12.5±0.32	50±0.98	50±0.87	50±0.82
3b	4-Me	-	-	-	-
3c	3-Me	50±0.84	25±0.65	50±0.56	-
3d	4-NO_2	25±0.78	-	-	50±0.91
3e	4-Cl	3.12±0.33	6.25±0.88	50±0.98	12.5±0.16
3f	4-Br	-	-	-	25±1.14
3g	3-NO_2	25±0.49	50±0.45	50±0.43	25±0.39
3h	3, 5-diMe	50±0.29	50±0.69	50±0.71	25±0.45
3i	3,5-diCl	3.12±0.76	3.12±0.34	25±0.62	6.25±0.61
3j	3,5-diOMe, 4-Cl	6.25±0.33	6.25±0.54	12.5±0.62	12.5±0.42
Standard-1	Penicillin	1.56±0.13	1.56±0.21	3.12±0.14	12.5±0.31
Standard-2	Streptomycin	6.25±0.22	6.25±0.24	3.12±0.16	6.25±0.28

"-" indicates concentration > 50 µg/mL. Abbreviations: MIC: Minimum inhibitory concentration; [a]Minimum inhibitory concentration (MIC) (µg/mL), that is, the lowest concentration of the test compound to inhibit the growth of bacteria completely

various Gram-positive microorganisms, that is, *Bacillus subtilis*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*, and Gram-negative microorganism *Escherichia coli* using the broth dilution method using penicillin and streptomycin are standard drugs for the comparison.[22,23] The minimum inhibitory concentrations (MICs) for all the synthesized compounds were reported in μg/mL and the results are illustrated in **Table 1**. It is evident from **Table 1** that the majority of the tested compounds exerted significant *in vitro* antibacterial activity against almost all the tested bacterial strains with MICs ranging from 3.12 to 12.5 µg/mL.

The structure-activity relationship (SAR) studies revealed that the compound **3i** containing two chlorine substituents on the meta positions of phenyl ring attached to third position of isoxazole ring displayed twofold more potent activity against *B. subtilis* and *S. aureus* (MIC = 3.12 ± 0.76 and 3.12 ± 0.34 μg/mL) compared with standard streptomycin (MIC = 6.25 ± 0.22 and 6.25 ± 0.24 µg/mL) and equipotent activity against *E. coli* (MIC = 6.25 ± 0.61 µg/mL) compared with standard streptomycin (MIC = 6.25 ± 0.28 µg/mL). On the other hand, the compound **3e** containing 4-chloro group on phenyl ring at the third position of isoxazole ring also effectively inhibited the *B. subtilis* (MIC = 3.12 ± 0.33 µg/mL; twofold more potent to streptomycin) and equipotent activity against *S. aureus* (MIC = 6.25 ± 0.88 µg/mL) and good activity against *E. coli* (MIC = 12.5 ± 0.16 µg/mL); however, this compound has shown slightly lesser activity against all the microorganisms than the compounds **3i**. Replacement of 4-Cl group by 4-Br and 4-NO_2 substituents (compounds **3f** and **3d**) on phenyl ring has led to give very poorer *in vitro* antibacterial activity against the corresponding microorganisms as compared to standards and compound **3e**. Whereas, the compound **3g** containing NO_2 group on third of position of phenyl ring was displayed very low activity against all the cell lines as compared to standards and compound **3i.** In the case of electron releasing groups, all the compounds containing strong and weak electron releasing groups irrespective of their positions on phenyl ring were not found to be effective in the present *in vitro* antibacterial activities as compared to standards. However, the *in vitro* activity has been improved dramatically in the case of compound containing both strong electron releasing groups and chlorine which was also suggested that the presence of chloro group is crucial in the present antibacterial activity studies

Molecular docking studies

The two potent compounds **3i** and **3e** were docked in the active site of ABC transporter-substrate-binding domain using the AUTODOCK 4.2 version and the images are being rendered using Schrodinger's maestro v9.5 visualizer interface docking values for antimicrobial studies.[24] The crystal structure of *S. aureus* MURB was taken from protein data bank (PDB ID: 1HSK) and binding site has been recognized inside 2.3 A° distance from co-crystal ligand. The active compounds **3i** and **3e** were selected by means of 2D-sketcher and prepared for docking with LigPrep, module of Schrodinger. A total of 10 conformations were generated for two compounds. From **Table 2**, it has been found that the compound **3i** shown binding energy (**−11.04** kcal/mol) than the compound **3e** (**−10.57** kcal/mol). The 2D and 3D interaction diagrams of the ligand **3i** and **3e** with the complex protein is shown in **Figures 1 and 2**.

EXPERIMENTAL

All the reagents were of analytical grade or chemically pure. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates. ^{1}H NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethylsilane as an internal standard. Mass spectral measurements were carried out by EI method. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

Table 2: Molecular docking values of compounds 3e and 3i

Compound	Binding energy (kcal/mol)	Inhibition constant	No. of hydrogen bonds	Residues involved in hydrogen bonding	Run
3e	−10.57	18.00 nM	3	Val A: 199, SER A: 143, ASN A: 80	3
3i	−11.04	8.03 nM	3	Val A: 199, SER A: 143, SER A: 143	5

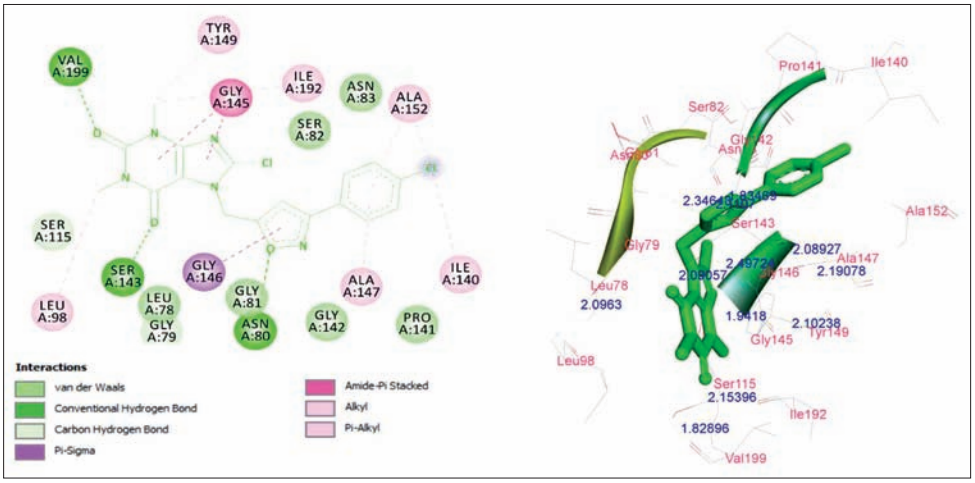


Figure 1: 2D and 3D interaction diagram for the ligand 3e with *Staphylococcus aureus* MurB

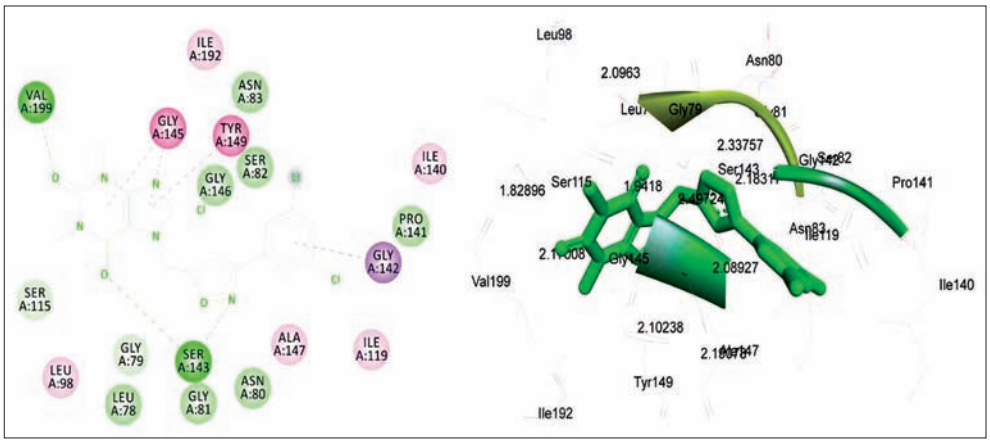


Figure 2: 2D and 3D interaction diagram for the ligand 3i with *Staphylococcus aureus* MurB

8-Chloro-1,3-dimethyl-7-(prop-2-yn-1-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (2)

To a mixture of 8-chloro-1,3-dimethyl-1*H*-purine-2,6(3*H*, 7*H*)-dione(**1**) (0.023 mol) and DIPEA (0.034 mol) in DMF (50 mL) was added propargyl bromide (0.030 mol) at 80°C and stirred at this temperature for 6 h. After completion of the reaction by TLC analysis, the resulting mixture was concentrated under vacuum to afford crude product. The crude was diluted with cold water (50 mL) and stirred for 1 h. The resulting precipitate was collected and crude product was purified by silica gel chromatography using an eluent (15% ethyl acetate in hexane). Yellow solid (Yield 80%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.77 (d, 2H, *J* = 4.0 Hz, N-CH_2), 3.55 (s, 3H, N-CH_3), 3.27 (s, 3H, N-CH_3), 2.18 (t, 1H, *J* = 2.2 Hz, CH); MS (ESI) m/z: 253 [M+H].

General procedure for the synthesis of 8-chloro-1,3-dimethyl-7-((3-arylisoxazol-5-yl) methyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (3a-3j)

Aldehyde (3.67 mmol) was added to a solution of hydroxylamine hydrochloride (5.51 mmol) in 10 mL of 1:1 t-BuOH:H_2O. To this was added NaOH (5.51 mmol), and after stirring for 60 min at ambient temperature, TLC analysis indicated that the oxime formation was complete. Chloramine-T trihydrate (5.51 mmol) was added in small portions over 15 min, followed by CuI (0.23 mmol). Compound **2** (5.14 mmol) was added, the pH was adjusted to 6 by the addition of a few drops of 1 M NaOH, and stirring was continued for a further 8-10 h. The reaction mixture was poured into cold water (50 mL), and 5 mL of dilute NH_4OH was added to remove all copper salts. Isoxazole(**3**) was collected by filtration, redissolved, and passed through

a short plug of silica gel (ethyl acetate: hexanes) to afford the title compounds in good yields.

8-Chloro-7-((3-(4-methoxyphenyl)isoxazol-5-yl) methyl)-1,3-dimethyl-*1H*-purine-2,6(3*H*,7*H*)-dione(3a)

Pale yellow solid (Yield 75%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.64-7.57 (m, 2H, Ar-H), 7.04-6.97 (m, 2H, Ar-H), 6.69 (s, 1H, isoxazole-CH), 5.41 (s, 2H, N-CH_2), 3.85 (s, 3H, O-CH_3), 3.57 (s, 3H, N-CH_3), 3.28 (s, 3H, N-CH_3).^{13}C-NMR (100 MHz, $CDCl_3$): 168.62, 161.96, 159.85, 153.76, 150.96, 148.26, 127.85, 122.36, 121.74, 114.69, 108.60, 100.99, 55.63, 42.81, 31.05, 29.93; MS (ESI) m/z: 402 [M+H]; Anal. Calcd for $C_{18}H_{16}ClN_5O_4$: C, 53.81; H, 4.01; N, 17.43. Found: C, 53.77; H, 3.95; N, 17.37.

8-Chloro-1,3-dimethyl-7-((3-(*p*-tolyl)isoxazol-5-yl) methyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (3b)

Pale yellow solid (Yield 69%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.71-7.64 (m, 2H, Ar-H), 7.23-7.14 (m, 2H, Ar-H), 6.80 (s, 1H, isoxazole-CH), 5.39 (s, 2H, N-CH_2), 3.53(s, 3H, N-CH_3), 3.33 (s, 3H, N-CH_3), 2.28 (s, 3H, Ar-CH_3). MS (ESI) m/z: 386 [M+H]; Anal. Calcd for $C_{18}H_{16}ClN_5O_3$: C, 56.04; H, 4.18; N, 18.15. Found: C, 56.09; H, 4.22; N, 18.10.

8-Chloro-1,3-dimethyl-7-((3-(*m*-tolyl)isoxazol-5-yl) methyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (3c)

Pale yellow solid (Yield 63%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.72 (s, 1H, Ar-H), 7.32-7.08 (m, 3H, Ar-H), 6.78 (s, 1H, isoxazole-CH), 5.42 (s, 2H, N-CH_2), 3.56 (s, 3H, N-CH_3), 3.25 (s, 3H, N-CH_3), 2.33 (s, 3H, Ar-CH_3). MS (ESI) m/z: 386 [M+H]; Anal. Calcd for $C_{18}H_{16}ClN_5O_3$: C, 56.04; H, 4.18; N, 18.15. Found: C, 56.09; H, 4.13; N, 18.11.

8-Chloro-1,3-dimethyl-7-((3-(4-nitrophenyl)isoxazol-5-yl)methyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (3d)

Yellow solid (Yield 77%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.15-8.10 (m, 2H, Ar-H), 7.97–9.91 (m, 2H, Ar-H), 6.87 (s, 1H, isoxazole-CH), 5.44 (s, 2H, N-CH_2), 3.57 (s, 3H, N-CH_3), 3.31 (s, 3H, N-CH_3). MS (ESI) m/z: 417 [M+H]; Anal. Calcd for $C_{17}H_{13}ClN_6O_5$: C, 48.99; H, 3.14; N, 20.16. Found: C, 48.93; H, 3.08; N, 20.12.

8-Chloro-7-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (3e)

Yellow solid (Yield 74 %); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.48 (d, 2H, *J* = 8.0 Hz, Ar-H), 6.82 (s, 1H, isoxazole-CH), 5.40 (s, 2H, N-CH_2), 3.56 (s, 3H, N-CH_3), 3.30 (s, 3H, N-CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$):168.39, 161.05, 155.56, 153.68, 151.53, 147.82, 132.88, 129.96, 125.32, 123.53, 108.53, 100.13, 42.13, 30.26, 29.79;MS (ESI) m/z: 405 [M+H]; Anal. Calcd for $C_{17}H_{13}Cl_2N_5O_3$: C, 50.26; H, 3.23; N, 17.24. Found: C, 50.23; H, 3.18; N, 17.19.

7-((3-(4-Bromophenyl)isoxazol-5-yl)methyl)-8-chloro-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (3f)

Yellow solid (Yield 67 %); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66-7.57 (m, 4H, Ar-H), 6.80 (s, 1H, isoxazole-CH), 5.40 (s, 2H, N-CH_2), 3.57 (s, 3H, N-CH_3), 3.26 (s, 3H, N-CH_3). MS (ESI) m/z: 449 [M+H] and 451 [M+3H]; Anal. Calcd for $C_{17}H_{13}BrClN_5O_3$: C, 45.31; H, 2.91; N, 15.54. Found: C, 45.28; H, 2.86; N, 15.49.

8-Chloro-1,3-dimethyl-7-((3-(3-nitrophenyl)isoxazol-5-yl)methyl)-*1H*-purine-2,6(3*H*,7*H*)-dione (3g)

Yellow solid (Yield 71%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.32–8.26 (m, 1H, Ar-H), 8.20-8.14 (m, 2H, Ar-H), 7.76-7.69 (m, 1H, Ar-H), 6.91 (s, 1H, isoxazole-CH), 5.42 (s, 2H, N-CH_2), 3.58 (s, 3H, N-CH_3), 3.28 (s, 3H, N-CH_3). MS (ESI) m/z: 417 [M+H]; Anal. Calcd for $C_{17}H_{13}ClN_6O_5$: C, 48.99; H, 3.14; N, 20.16. Found: C, 48.91; H, 3.09; N, 20.14.

8-Chloro-7-((3-(3,5-dimethylphenyl)isoxazol-5-yl) methyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (3h)

Pale yellow solid (Yield 68 %); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31 (s, 2H, Ar-H), 7.03 (s, 1H, Ar-H), 7.69-7.61 (m, 2H, Ar-H), 6.84 (s, 1H, isoxazole-CH), 5.39 (s, 2H, N-CH_2), 3.57 (s, 3H, N-CH_3), 3.24 (s, 3H, N-CH_3), 2.38 (s, 6H, 2Ar-CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.68, 161.19, 155.45, 153.96, 151.53, 147.74, 139.05, 130.26, 121.76, 118.26, 108.27, 100.57, 42.09, 30.03, 29.77, 21.31;MS (ESI) m/z: 400 [M+H]; Anal. Calcd for $C_{19}H_{18}ClN_5O_3$: C, 57.07; H, 4.54; N, 17.52. Found: C, 57.13; H, 4.59; N, 17.46.

8-Chloro-7-((3-(3,5-dichlorophenyl)isoxazol-5-yl) methyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (3i)

Yellow solid (Yield 71%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.41 (t, 1H, *J* = 4.0 Hz, Ar-H), 6.82 (s, 1H, isoxazole-CH), 5.40 (s, 2H, N-CH_2), 3.57 (s, 3H, N-CH_3), 3.27 (s, 3H, N-CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.42, 161.23, 153.63, 150.80, 148.31, 134.52, 124.72, 123.07, 122.07, 120.18, 120.13, 108.42, 100.23, 42.65, 31.06, 29.72; MS (ESI) m/z: 440 [M+H]; Anal. Calcd for $C_{17}H_{12}Cl_3N_5O_3$: C, 46.33; H, 2.74; N, 15.89. Found: C, 46.28; H, 2.69; N, 15.81.

8-Chloro-7-((3-(4-chloro-3,5-dimethoxyphenyl) isoxazol-5-yl)methyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (3j)

Pale red solid (Yield 66%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.61 (s, 2H, Ar-H), 6.83 (s, 1H, isoxazole-CH), 5.39 (s, 2H, N-CH_2), 3.25 (t, 4H, *J* = 4.0 Hz, $2SO_2$-CH_2), 3.87 (s, 3H, O-CH_3), 3.84 (s, 3H, O-CH_3), 3.53 (s, 3H, N-CH_3), 3.27 (s, 3H, N-CH_3). MS (ESI) m/z: 466 [M+H]; Anal. Calcd for $C_{19}H_{17}Cl_2N_5O_5$: C, 48.94; H, 3.67; N, 15.02. Found: C, 48.87; H, 3.60; N, 14.96.

CONCLUSION

The synthesis of new 3,5-disusbstituted isoxazole-xanthine hybrids based on 1,3-dipolar cycloaddition of 8-chloro-1,3-dimethyl-7-(prop-2-yn-1-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione through *in situ* generated nitrile oxides catalyzed by Cu(I) has been reported. The newly synthesized hybrids (3a-3j) were evaluated for *in vitro* antibacterial

activity and results revealed that the compounds containing chloro groups i.e. 3i and 3e were found to be most active in the present antibacterial activity studies. The SAR results of this work suggested that by performing a simple structural modification leads to the generation of powerful new antibacterial drugs with good activity. Furthermore, the *in silico* molecular docking *S. aureus MurB* designated that the binding interactions of compounds **3i** and **3e** were intensely related to *in vitro* antibacterial activity.

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