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RESEARCH ARTICLE

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 5-METHYLPYRAZINE-2-CARBOHYDRAZIDE DERIVATIVES

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ABSTRACT

Here an attempt has been made to synthesize fourteen 5-methylpyrazine-2-carbohydrazide derivatives. The synthesized derivatives were assessed for their in-vitro anti-bacterial activity and minimum inhibitory concentration (MIC) against Gram-positive strains (Staphylococcus aureus and Bacillus subtilis) and Gram-negative strains (Salmonella typhi and Escherichia coli). During the present work, 5-methylpyrazinoic acid was esterified with ethanol to get ethyl-pyrazinoate and it refluxed with hydrazine hydrate to yield the 5-methylpyrazinoic acid hydrazide. The obtained acid hydrazide was then condensed with various substituted aromatic aldehydes to yield various 5-methylpyrazine-2-carbohydrazide derivatives. The structures of newly synthesized compounds so obtained were confirmed by using IR, ^{1}HNMR, MS spectral data. All compounds gave satisfactory elemental analyses. The compounds PM 8-10, (i.e. 2,3 and 4-nitro benzaldehyde derivatives respectively) showed promising activity amongst the compounds tested against both the Gram-positive and Gram-negative strains tested. .

KEY WORDS: *5-methylpyrazine, carbohydrazide, anti-bacterial, synthesis*

INTRODUCTION

There is urgent need in structural modification of existing anti-microbial agents so as to increase microbial intracellular concentration of drug, and thereby to increase anti-microbial activity and also to reduce the microbial resistance. The through literature survey reveals that the molecules having hydrazide and hydrazone skeleton possessing anti-microbial activity viz., anti-TB and anti-bacterial activity[1, 2]. During the present work 5-methylpyrazinoic acid was esterified and reacted with hydrazine hydrate to yield the 5-methylpyrazinoic acid hydrazide. This 5-methylpyrazinoic acid hydrazide was then condensed with various substituted aromatic aldehydes to yield different 5-methylpyrazine carbohydrazide derivatives. These synthesized compounds were evaluated for their *in vitro* anti-bacterial activity.

EXPERIMENTAL

The starting compound 5-methylpyrazionic acid was procured from Sigma-Aldrich Co. All the reagents used were purchased from commercial suppliers. The purity of the synthesized compounds were confirmed by Emerck pre-coated 60 F254 TLC plates and spots were rendered visible by exposing to UV light and iodine fumes. Column chromatographic separations were carried out by gradient elution with chloroform/ methanol/ ethyl acetate mixture and silica gel (60-120 mesh/100- 200 mesh). The compounds were purified by recrystallisation using

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aq.ethanol as a solvent. HPLC was performed on JASCO 2000 SERIES instrument using C-18 reverse phase column and diodearray UV detector.

Melting points were determined in open capillaries using Veego VMP-1 electro-thermal melting point apparatus and were uncorrected. The absorbance (λmax) was taken on JASCO 630V spectrophotometer using methanol as solvent. The IR spectra were recorded on JASCO FTIR 4100 Series spectrometer in KBr pellets and the frequencies are recorded in wave numbers. ^{1}H NMR spectra were recorded on "VARIAN MERCURY YH-300" spectrophotometer at 300 MHz in $CDCl_3$ solutions and their chemical shifts are recorded in δ (parts per million) units with respect to tetramethyl silane (TMS) as an internal standard. The mass spectra were recorded on Waters Q-ToF micro on electron spray ionization (ESI) source. Elemental analyses were done using Elementar CHN analyzer.

General Procedure for synthesis of 5-methylpyrazinoic acid hydrazide [I]

5-Methylpyrazinoic acid was dissolved in ethanol and few drops of conc. H_2SO_4 was added and refluxed for 24 hrs; hydrazine hydrate 100% (3.0 mol) was added to it and further refluxed for a period of 8 hrs. The excess of solvent was distilled off to get the resulting product. The product was crystallized from aq.ethanol [3,4].

General Procedure for synthesis of 5-methylpyrazine-2-carbohydrazide [PM 1-14]

A solution of aromatic/substituted aldehyde (0.05 mol) in ethanol was added to a solution of so obtained 5-methylpyrazinoic acid hydrazide (0.05 mol) in 10 ml ethanol. The mixture was refluxed for 4 hrs. After cooling the mixture, the precipitate was filtered, dried and recrystallised from aq. ethanol [4,5].

PM 1: 5-methyl-N'-[phenylmethylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):307; IR (KBr): 3292 (NH), 2922 (Ar-CH), 1680 (C=O), 1487(C=N), 825, 692 (CH out of plane bending); ^{1}H NMR (300 MHz, $CDCl_3$): 8.28-8.34 (m, 2H, pyrazine), 7.38-7.78 (m, 5H, aromatic), 7.24 (s, 1H, =CH) 10.63 (s, 1H, N-H), 2.68 (s, 3H, CH_3); MS (ESI): *m/z* 263.1699 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_{12}N_4O$:C, 64.99; H, 5.03; N, 23.32. Found: C, 64.95; H, 5.07; N, 23.30.

PM 2: 5-methyl-N'-[3-phenylprop-2-en-1-ylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):271; IR (KBr): 3143 (NH), 3012 (Ar-CH), 1626 (C=O), 1487 (C=N), 785, 680 (CH out of plane bending); ^{1}H NMR (300 MHz, $CDCl_3$): 8.38-9.35(m, 2H, pyrazine), 7.10-7.38 (m, 5H, aromatic), 7.51 (s, 1H, =CH) 6.90-7.09(s, 2H, CH=CH), 10.56 (s, 1H, N-H), 2.68 (s, 3H, CH_3); MS (ESI): *m/z* 289.1128 $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{14}N_4O$:C, 67.65; H, 5.30; N, 21.04. Found: C, 67.61; H, 5.27; N, 21.00.

PM 3: 5-methyl-N'-[furan-3-ylmethylidene]pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):330; IR (KBr): 3302 (NH), 3007 (Ar-CH), 1674 (C=O), 1485 (C=N), 785, 740 (CH out of plane bending); ^{1}H NMR (300 MHz, $CDCl_3$): 8.35-8.44 (m, 2H, pyrazine), 6.47-6.85 (m, 3H, furyl), 7.50 (s, 1H, =CH) 10.54 (s, 1H, N-H), 2.66 (s, 3H, CH_3); MS (ESI): *m/z* 253.1978 $[M+Na]^+$. Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.39; H, 4.38; N, 24.34. Found: C, 57.56; H, 4.32; N, 24.33.

PM 4: 5-methyl-N'-[(4- methoxyphenyl)methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):326; IR (KBr): 3288 (NH), 2926 (Ar-CH), 1678 (C=O), 1508 (C=N), 823 (CH out of plane bending); ^{1}H NMR (300 MHz, $CDCl_3$): 8.17-8.58 (m,2H, pyrazine), 6.87-7.20 (m, 4H, aromatic), 7.69 (s, 1H, =CH), 3.84 (s, 3H, -OCH_3), 10.49 (s, 1H, N-H), 2.56 (s, 3H,

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CH_3); MS (ESI): *m/z* 271.1104 $[M+1]^+$. Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.19; H, 5.27; N, 20.70.

PM 5: 5-methyl-N'-[(2-chlorophenyl) methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):267; IR (KBr): 3287 (NH), 3013 (Ar-CH), 1676 (C=O), 1587 (C=N), 823 (CH out of plane bending), 779 (C-Cl); ^1H NMR (300 MHz, $CDCl_3$): 8.64-9.07 (m, 2H, pyrazine), 7.21-7.38 (m, 4H, aromatic), 7.80 (s, 1H, =CH), 10.75 (s, 1H, N-H), 2.66 (s, 3H, CH_3); MS (ESI): *m/z* 275.1811 $[M+1]^+$. Anal. Calcd. for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40. Found: C, 56.80; H, 4.01; N, 20.43.

PM 6: 5-methyl-N'-[(3-chlorophenyl) methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):272; IR (KBr): 3289 (NH), 2926 (Ar-CH), 1686 (C=O), 1587 (C=N), 835 (CH out of plane bending), 613 (C-Cl); ^1H NMR (300 MHz, $CDCl_3$): 8.72-9.02 (m, 2H, pyrazine), 7.82-8.04 (m, 4H, aromatic), 7.42 (s, 1H, =CH), 10.44 (s, 1H, N-H), 2.86 (s, 3H, CH_3); MS (ESI): *m/z* 275.1498 $[M+1]^+$. Anal. Calcd. for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40. Found: C, 56.88; H, 4.06; N, 20.39.

PM 7: 5-methyl-N'-[(4-chlorophenyl) methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):270 IR (KBr): 3287 (NH), 3013 (Ar-CH), 1676 (C=O), 1587 (C=N), 823 (CH out of plane bending), 779 (C-Cl); ^1H NMR (300 MHz, $CDCl_3$): 8.54-8.88 (m, 2H, pyrazine), 7.40-7.98 (m, 4H, aromatic), 7.15 (s, 1H, =CH), 9.85 (s, 1H, N-H), 2.86(s, 3H, CH_3); MS (ESI): *m/z* 275.1271 $[M+1]^+$. Anal. Calcd. for $C_{13}H_{11}ClN_4O$: C, 56.86; H, 4.07; N, 20.43. Found: C, 56.83; H, 4.01; N, 20.43.

PM 8: 5-methyl-N'-[(2-nitrophenyl) methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):263; IR (KBr): 3317 (NH), 2930 (Ar-CH), 1668 (C=O), 1606 (C=N), 1570 (C-NO_2 bending), 700 (CH out of plane bending); ^1H NMR (300 MHz, $CDCl_3$): 8.39-8.80. (m, 2H, pyrazine), 7.55-7.92 (m, 4H, aromatic), 7.20 (s, 1H, =CH), 10.83 (s, 1H, N-H), 2.69(s, 3H, CH_3); MS (ESI): *m/z* 308.1124 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_{11}N_5O_3$: C, 54.74; H, 3.89; N, 24.55. Found: C, 54.72; H, 3.96; N, 24.53.

PM 9: 5-methyl-N'-[(3-nitrophenyl) methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):269; IR (KBr): 3307 (NH), 2910 (Ar-CH), 1658 (C=O), 1606 (C=N), 1521 (C-NO_2 bending), 704 (CH out of plane bending); ^1H NMR (300 MHz, $CDCl_3$): 8.10-8.38 (m, 2H, pyrazine), 7.62-7.90 (m, 4H, aromatic), 7.22 (s, 1H, =CH), 10.38 (s, 1H, N-H), 2.38(s, 3H, CH_3); MS (ESI): *m/z* 308.1467 $[M+1]^+$. Anal. Calcd. for $C_{13}H_{11}N_5O_3$: C, 54.74; H, 3.89; N, 24.55. Found: C, 54.70; H, 3.93; N, 24.51.

PM 10: 5-methyl-N'-[(4-nitrophenyl) methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):236; IR (KBr): 3223 (NH), 3067 (Ar-CH), 1630 (C=0), 1597 (C=N), 1577 (C-NO_2 bending), 694 (CH out of plane bending); ^1H NMR (300 MHz, $CDCl_3$): 8.04-8.20 (m, 2H, pyrazine), 7.66-7.80 (m, 4H, aromatic), 7.20 (s, 1H, =CH), 9.96 (s, 1H, N-H), 2.44(s, 3H, CH_3); MS (ESI): *m/z* 308.1346 $[M+1]^+$. Anal. Calcd. for $C_{13}H_{11}N_5O_3$: C, 54.74; H, 3.89; N, 24.55. Found: C, 54.75; H, 3.90; N, 24.57.

PM 11: 5-methyl-N'-[(2-hydroxyphenyl) methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):370; IR (KBr): 3422 (C-OH), 3322 (NH), 3007 (Ar-CH), 1674 (C=O), 1583 (C=N), 692 (CH out of plane bending); ^1H NMR (300 MHz, $CDCl_3$): 8.42-8.92 (m, 2H, pyrazine), 7.20-7.60 (m, 4H, aromatic), 7.10 (s, 1H, =CH), 10.66 (s, 1H, N-H), 11.36 (s, 1H, OH), 2.80 (s, 3H, CH_3); MS (ESI): *m/z* 257.2192 $[M+1]^+$. Anal.

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Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.90; H, 4.70; N, 21.80.

PM 12: 5-methyl-N'-[(3-hydroxyphenyl) methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):345; IR (KBr): 3483 (C-OH), 3308 (NH), 3024 (CH), 1676 (C=O), 1608 (C=N), 827 (CH out of plane bending); ^{1}H NMR (300 MHz, $CDCl_3$): 8.66-8.96 (m, 2H, pyrazine), 7.60-7.88 (m, 4H, aromatic), 7.40 (s, 1H, =CH), 12.36 (s, 1H, OH) 10.36 (s, 1H, N-H) 2.40(s, 3H, CH_3); MS (ESI): *m/z* 257.2889 $[M+1]^+$. Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.91; H, 4.68; N, 21.81.

PM 13: 5-methyl-N'-[(4-hydroxyphenyl) methylidene] pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):345; IR (KBr): 3432 (C-OH), 3261 (NH), 3024 (Ar-CH), 1623 (C=O), 1597 (C=N), 732 (CH out of plane bending); ^{1}H NMR (300 MHz, $CDCl_3$): 8.53-8.64 (m, 2H, pyrazine), 7.52-7.68 (m, 4H, aromatic), 6.85 (s, 1H, =CH), 11.84 (s, 1H, OH) 10.07 (s, 1H, N-H) 2.50(s, 3H, CH_3); MS (ESI): *m/z* 257.2273 $[M+1]^+$. Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.95; H, 4.77; N, 21.87.

PM 14: 5-methyl-*N*'-{[4-dimethylamino)phenyl]methylidene} pyrazine-2-carbohydrazide

UV λ_{max} (CH_3OH):392; IR (KBr): 3300 (NH), 2924 (Ar-CH), 1680 (C=O), 1601 (C=N), 812 (CH out of plane bending); ^{1}H NMR (300 MHz, $CDCl_3$): 8.10-8.20 (m, 2H, pyrazine), 7.38-7.78 (m, 4H, aromatic), 7.12 (s, 1H, =CH), 10.20 (s, 1H, N-H), 3.15(s, 3H, CH_3), 2.40 (s, 3H, CH_3); MS (ESI): *m/z* 284.3162 $[M+1]^+$. Anal. Calcd. for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72. Found: C, 63.60; H, 6.10; N, 24.70.

ANTIBACTERIAL ACTIVITY

The synthesized compounds were screened for their *in vitro* anti-bacterial activity against two Gram-positive strains such as *Staphylococcus aureus* (NCIM 2079) and *Bacillus subtilis* (NCIM 2711),and two Gram-negative strains i.e. *Salmonella typhi* (NCIM 2501) and *Escherichia coli* (NCIM 2685). The *in vitro* antibacterial activities of the compounds were carried out by the agar cup plate method [6,7]. The concentration of compounds (250 µg/ml) were prepared in dimethyl sulfoxide (DMSO). Ofloxacin was used as standard.

The antibacterial activity was evaluated by employing 24 hours cultures of *S. aureus*, *B. subtilis*, *S. typhi* and *E. coli* using Muller Hinton agar medium. The medium was sterilized by autoclaving at 120^0 C (15 lb/in^2) for 30 minutes. About 30 ml of molten nutrient agar medium inoculated with the respective strains of bacteria (6ml of inoculum to 300 ml of nutrient agar medium) was transferred aseptically into each sterilized petri plates (10 cm diameter). The plates were left at room temperature to allow solidification. In each plate 3 wells of 6 mm diameter were made using a sterile borer. Accurately 0.1 ml of the test and standard solution were transferred to cups aseptically by micropipette and labeled accordingly .The plates were then maintained at room temperature for 2 hours to allow the diffusion of the solution in the medium. The petri dishes used for antibacterial screening were incubated at 37 ± 1^0 C for 24 hours. The diameter of zone of inhibition surrounding each of the wells was recorded.

The compounds exhibited antibacterial activity was assayed on a quantitative basis determining the Minimal Inhibitory Concentration (MIC) for those microorganisms [8].

RESULTS AND DISCUSSION

The series of fourteen new compounds of 5-methypyrazine-2-carbohydrazide derivatives were achieved following the steps outlined in Scheme-1. Physical data of the synthesized compounds are shown in Table 1.

The assigned structures were established from the IR and NMR spectral data. Mass spectra of the compound showed [M+1] peaks in agreement with their molecular weight.

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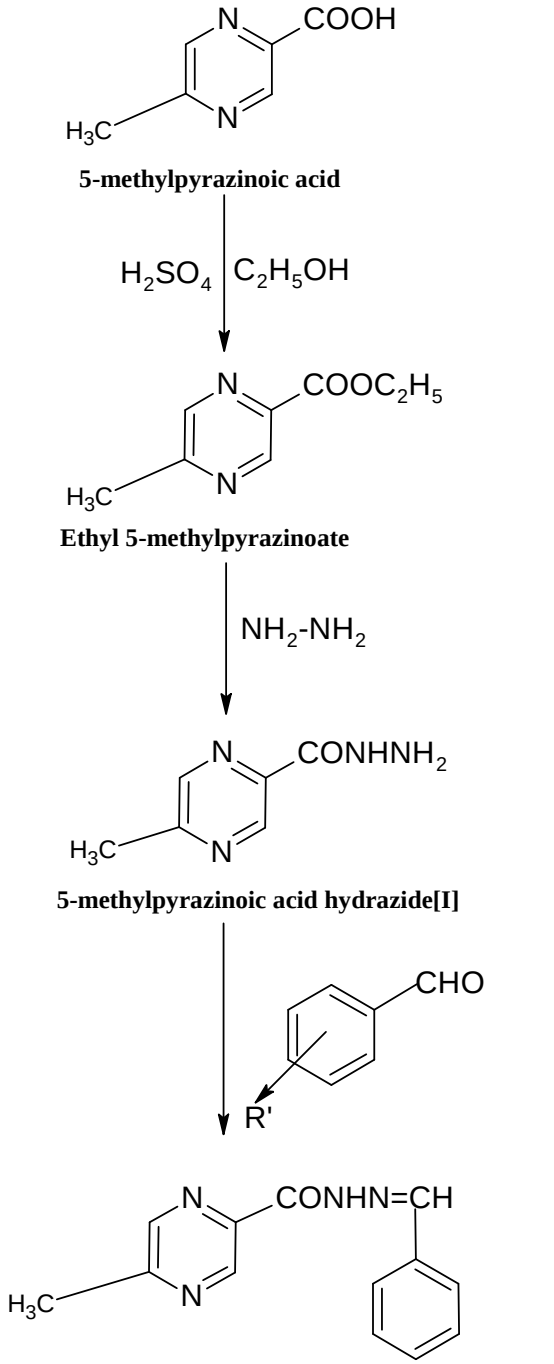
Elemental analyses for all the compounds were found to be within the limits of accuracy.

The compounds PM 8-10, (i.e. 2,3 and 4-nitro benzaldehyde derivatives respectively) showed promising activity amongst the compounds tested against both the Gram-positive and Gram-negative strains tested. Where as the compounds PM 1-4, showed anti-bacterial activity against *S. aureus* and *B. subtilis* and the compounds PM 1-2 were found to be active against *S. typhi* as compared with the standard ofloxacin summarized in Table 2.

From the table no. 3 the MIC values of active anti-bacterial compounds were in the range of 160 to 190 µg/ml concentrations against common bacterial infection causing species. This indicates the synthesized compounds were active against routinely infection causing bacteria. Hence, further studies are going to improve the yield of the compounds by microwave assisted heating technology and to explore these compounds against variety of bacteria causing human infections.



5-methyl pyrazine-2-carbohydrazide [PM 1 - 14]

(R'=-NO_2, -X, -OH, -OCH_3 etc.)

Scheme 1:Synthetic route of the compounds

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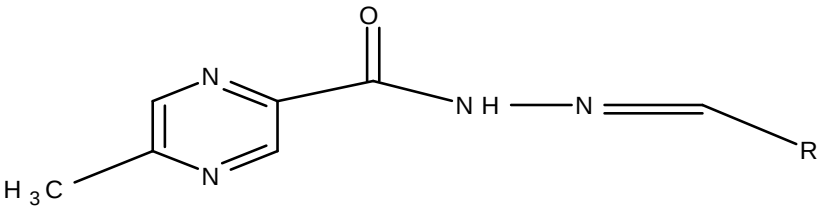
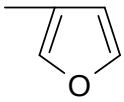
Table 1: Physical data of synthesized Compounds (PM SERIES)



Comp. Code	Substituents (-R)	M. F.	M.W.	m.p. (^{0}C)	(%) Yield	Rf value
PM 1	-C_6H_5	$C_{13}H_{12}N_4O$	240.260	235-236	65	0.738
PM 2	-CH=CH-C_6H_5	$C_{15}H_{14}N_4O$	266.297	172-174	45	0.857
PM 3		$C_{11}H_{10}N_4O_2$	230.222	224-225	68	0.693
PM 4	-C_6H_4-*p*-OCH_3	$C_{14}H_{14}N_4O_2$	270.286	178-180	54	0.847
PM 5	-C_6H_4-*o*–Cl	$C_{13}H_{11}ClN_4O$	274.705	156-157	55	0.760
PM 6	-C_6H_4-*m*–Cl	$C_{13}H_{11}ClN_4O$	274.705	226-227	50	0.595
PM 7	-C_6H_4-*p*–Cl	$C_{13}H_{11}ClN_4O$	274.705	90-91	46	0.591
PM 8	-C_6H_4-*o*–NO_2	$C_{13}H_{11}N_5O_3$	285.258	89-90	52	0.863
PM 9	-C_6H_4-*m* -NO_2	$C_{13}H_{11}N_5O_3$	285.258	114-115	42	0.627
PM 10	-C_6H_4-*p*–NO_2	$C_{13}H_{11}N_5O_3$	285.258	132-134	56	0.688
PM 11	-C_6H_4-*o*–OH	$C_{13}H_{12}N_4O_2$	256.259	217-218	67	0.904
PM 12	-C_6H_4-*m*–OH	$C_{13}H_{12}N_4O_2$	256.259	248-249	57	0.333
PM 13	-C_6H_4-*p*–OH	$C_{13}H_{12}N_4O_2$	256.259	266-268	66	0.452
PM14	-C_6H_4-N $(CH_3)_2$	$C_{15}H_{17}N_5O$	283.328	268-270	71	0.886

All the compound in Table No.1were crystallized from aqueous ethanol.

Purity of the compounds in Table No. 1 were determined using Chloroform: Methanol: Ethyl acetate (4:1:1).

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Table 2: Anti-bacterial activity of PM Series

Compound code	*S. aureus*	*B.subtilis*	*E. coli*	*S.typhi*
PM 1	9.6 ±0.05	7.8 ±0.05	_	9.8 ±0.1
PM 2	9.7 ±0.07	8.2 ±0.07	_	9.5 ±0.1
PM 3	8.5 ±0.07	8.2 ±0.07	_	_
PM 4	8.6 ±0.05	6.3 ±0.05	_	_
PM 5	_	_	_	_
PM 6	_	_	_	_
PM 7	_	_	_	--
PM 8	9.8 ±0.1	9.5 ±0.1	8.2 ±0.1	7.9 ±0.1
PM 9	8.0 ±0.09	8.4 ±0.09	7.9 ±0.09	8.1 ±0.1
PM 10	8.5 ±0.10	8.1 ±0.10	8.2 ±0.10	7.5 ±0.1
PM 11	_	_	_	_
PM 12	_	_	_	_
PM 13	_	_	_	_
PM 14	_	_	_	_
Control (DMSO)	_	_	_	_
Standard (Ofloxacin)	14.6 ±0.08	15.2 ±0.08	13.8 ±0.08	13.4 ±0.08

Zone of Inhibition in mm at 250µg/ml concentration (n=6, ± standard err

Table 3: MIC of PM Series

Compound code	*S. aureus*	*B.subtilis*	*E. coli*	*S.typhi*
PM 1	180	180	_	180
PM 2	160	180	_	170
PM 3	170	190	_	_
PM 4	170	170	_	_
PM 5	_	_	180	_
PM 6	_	_	190	_
PM 7	_	170	190	_
PM 8	180	180	_	180
PM 9	170	180	_	170
PM 10	160	190	_	170
PM 11	_	_	_	_

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PM 12	_	_	_	_
PM 13	_	_	_	_
PM 14	_	_	_	_

Results are expressed in µg/ml concentration

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