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Pyrazolone part 3: Antibacterial activity of novel 4-substituted pyrazolone derivatives

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ABSTRACT

In the present research work, the motto was to develop new chemical entities as potential antibacterial agents. Various 4-(2-amino-6-(substituted)pyrimidin-4-yl)-3-methyl-1-(substituted)-1H-pyrazol-5(4H)-one derivatives (5a–5j) screened for their antibacterial activity against Gram positive and Gram negative bacteria.

Keywords Pyrazolne, Antibacterial activity, *E. Coli, B. subtilis.*

INTRODUCTION

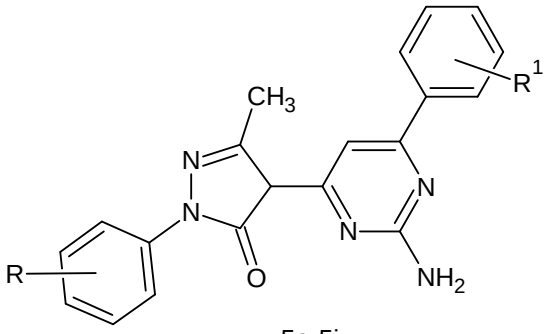
Several antibiotics have been prescribed and found to be effective on various infectious disorders. However, the appearance of multidrug resistant Gram-positive bacteria, in particular, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE) is causing a serious menace. Moreover, the emergence of vancomycinresistant MRSA can be anticipated in foreseeable future. For the treatment of these intractable infections, a new antiinfectious agent is needed. The synthetic antibiotics include the sulfa drugs, nitrofuran derivative, pyridine-carboxylic acid analogues, fluoroquinolones and oxazolidinones. The semi-synthetic antibiotics include the penicillins, cephalosporins, tetracyclines and macrolides. Among them, the sulfa drugs, nitrofuran derivatives, penicillins and tetracyclines are scarcely used in clinical therapy [1].

Antibacterial resistance is now well documented for many pathogens, and studies with a variety of bacteria indicate that resistance can develop within just a few years. Resistance against many members of fluoroquinolones, particularly older ones, such as ciprofloxacin, is increasing. Further advances in quinolone field are likely to provide better compounds capable of dealing with the resistant strains [2].

The importance of sulfa drugs (sulfonamides) is well established in pharmaceutical chemistry and drug design. This class of drugs is well known as antibacterial, carbonic anhydrase inhibitors, anti-cancerous and also as anti-inflammatory agents. Consequent to these physiological activities of sulfa drugs they are used as building blockers for making Mannich bases [3-6].

Therefore, antimicrobial activities of phenolic compounds and their metabolism were one of the most important research fields in phytopathological chemistry many years ago [7-11].

The compounds have had good success against Gram-negative bacteria, but resistance of Gram-positive pathogens, such as *Staphylococcus aureus*, has become a problem [12-16].



5a-5j

Compound code	-R	-R^1
5a	-H	-4-OH-3-OCH_3
5b	-H	4-NO_2
5c	-H	-4-OCH_3
5d	-H	-2-OH
5e	-H	-4-(N,N-$(CH_3)_2$)
5f	-(2,4-NO_2)	-4-OH-3-OCH_3
5g	-(2,4-NO_2)	-3-NO_2
5h	-(2,4-NO_2)	-4-(N,N-$(CH_3)_2$)
5i	-(2,4-NO_2)	-2-NO_2
5j	-(2,4-NO_2)	-4-Cl

Tuberculosis (TB) is an airborne infectious disease caused by Mycobacterium tuberculosis (MTB) and represents one of the leading causes of death worldwide. The dangerous spread of TB is mainly due to its association with HIV infection and to the rapid development of multidrug-resistant (MDR) strains of MTB. This confirms the urgent need to discover new structural classes of antimycobacterial compounds in order to develop agents to replace or supplement the established drugs [17,18]. Mechanisms of action of antibacterial drugs [19]

inhibition of cell wall synthesis, inhibition of protein synthesis, inhibition of nucleic acid synthesis, inhibition of metabolic pathways, interference with cell membrane integrity. In the clinical laboratories antibiotic impregnated disc are commonly used to identify the antibiotic sensitivity of causative organism [20].

In present work we performed antibacterial activity on substituted pyrazolone derivatives [21] (5a-5j) reported by Antre RV *et al*.

RESULTS AND DISCUSSION

The antibacterial activities of compounds (5a-5j) are reported in (Table No. 1).

Compounds with para nitro, ortho nitro, meta nitro, para chloro substitution on phenyl ring attached to 6th position of aminopyrimidin ring, such as 5b, 5g, 5i, 5j revealed good antimicrobial activity as compared to compounds 5a, 5c, 5d, 5e, 5f, 5h which contain para hydroxy, para methoxy and para N,N-dimethylamino substitution phenyl ring attached to 6th position of aminopyrimidin ring.

Under identical conditions the standard antibiotic amoxicillin (125µg/ml) exhibited a zone of inhibition of 35 and 32 mm against *Escherichia coli* and *Bacillus subtilis* respectively. The antibacterial activity of compound 5b, 5g, 5i 5j is almost identical to that of amoxicillin against *Escherichia coli* and *Bacillus subtilis* (Fig. No. 1).

Table No. 1. Antibacterial activity of compounds[#] (5a-5j)

Cpd code	*E. coli* [1]			*B. subtilis* [2]		
	75 µg/ml ± SD	100 µg/ml ±SD	125 µg/ml ± SD	75 µg/ml ± SD	100 µg/ml ± SD	125 µg/ml ± SD
Amoxicillin	15 ± 0.00	24 ± 0.00	35 ± 0.00	--	22 ± 0.00	32 ± 0.00
5a	7.3 ± 0.14	16.65 ± 0.21	28.55 ± 0.7	13.1 ± 0.14	21.7 ± 0.28	29.35 ± 0.6
5b	13.25 ± 0.07	21.9 ± 0.07	33 ± 0.14	11.85 ± 0.07	22.55 ± 0.07	29.6 ± 0.14
5c	7.21 ± 1.50	11.6 ± 0.30	24.85 ± 1.20	8.3 ± 0.28	14.45 ± 0.21	21.8 ± 0.14
5d	7.05 ± 0.75	13.12 ± 1.01	25.67 ± 0.70	7.85 ± 0.7	13.45 ± 0.07	22.05 ± 0.07
5e	7.01 ± 0.10	11.12 ± 1.11	24.22 ± 0.01	7.45 ± 0.11	12.12 ± 0.54	21.11 ± 0.14
5f	9.35 ± 0.35	19.85 ± 0.07	30.55 ± 0.7	10.7 ± 0.14	21.85 ± 0.07	29.11 ± 0.14
5g	14.4 ± 0.14	23.45 ± 0.21	34.15 ± 0.7	12.55 ± 0.7	20.5 ± 0.42	31.25 ± 0.2
5h	9.75 ± 0.21	13.76 ± 0.66	22.67 ± 0.72	7.45 ± 0.2	14.25 ± 0.07	23.3 ± 0.14
5i	11.8 ± 0.07	22.15 ± 0.77	31.65 ± 0.07	11.4 ± 0.14	20.85 ± 0.07	29 ± 0.70
5j	14.1 ± 0.00	14.25 ± 0.07	34.25 ± 0.21	12.45 ± 0.07	20.15 ± 0.07	30.15 ± 0.7

 # = zone of inhibition in mm, 1 = Escherichia coli, 2 = Bacillus subtilis.
SD= Standard Deviation from 3 comparable concentration

Antibacterial Activity [22,23]

Applying the agar plate diffusion technique all of the newly synthesized compounds were screened in vitro for antibacterial activity against *Escherichia coli* (Gram negative), *Bacillus subtilis* (Gram positive) at 75 µg/ml, 100 µg/ml, 125 µg/ml concentrations, respectively. Under identical conditions, the antibiotics Amoxicillin at 75 µg/ml, 100 µg/ml, 125 µg/ml showed zone

of inhibition 15, 24, 35 mm for Gram negative organism and showed zone of inhibition 22, 32 mm at concentrations 100 µg/ml, 125 µg/ml respectively for Gram positive organism.

Fig. No. 1(a-f): Zone of inhibition of standard and compounds against *E. coli* and *B. subtilis*

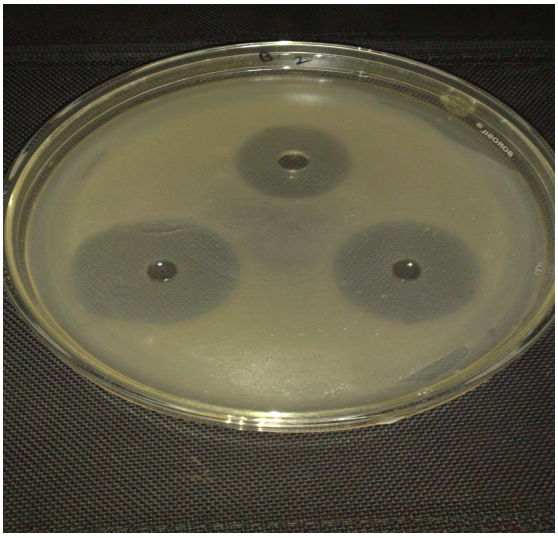


Fig. 1(a): Zone of inhibitions for Ampicillin against *E. coli*

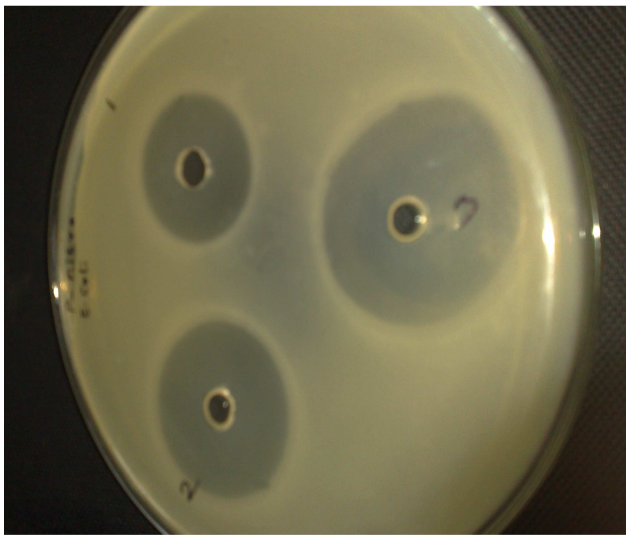


Fig. 1(b): Zone of inhibitions for Ampicillin against *B. subtilis*

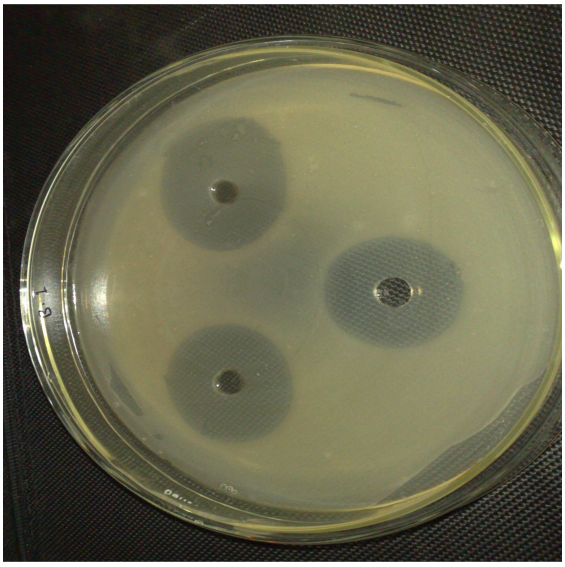


Fig. 1(c): Zone of inhibitions for 5i against *E. coli*

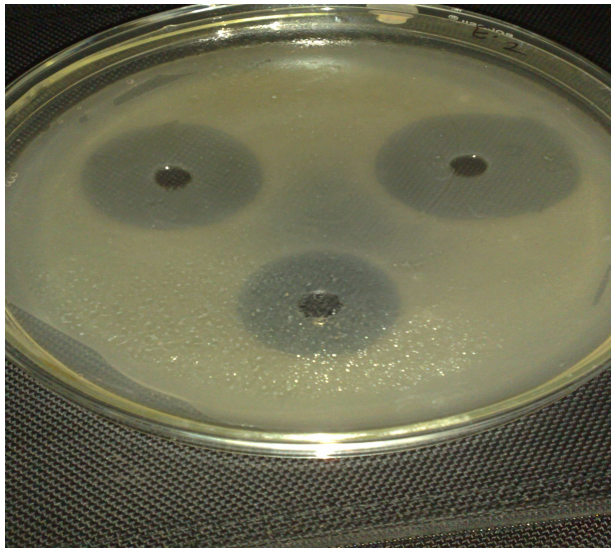


Fig. 1(d): Zone of inhibitions for 5b against *B. subtilis*

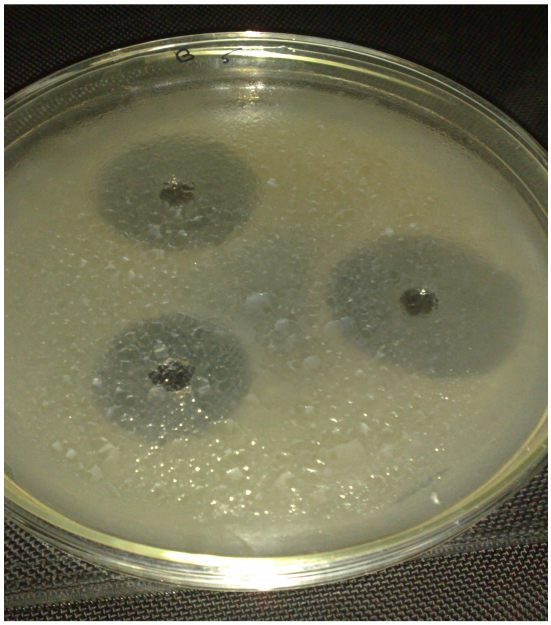


Fig. 1(e): Zone of inhibitions for 5g against *B. subtilis*

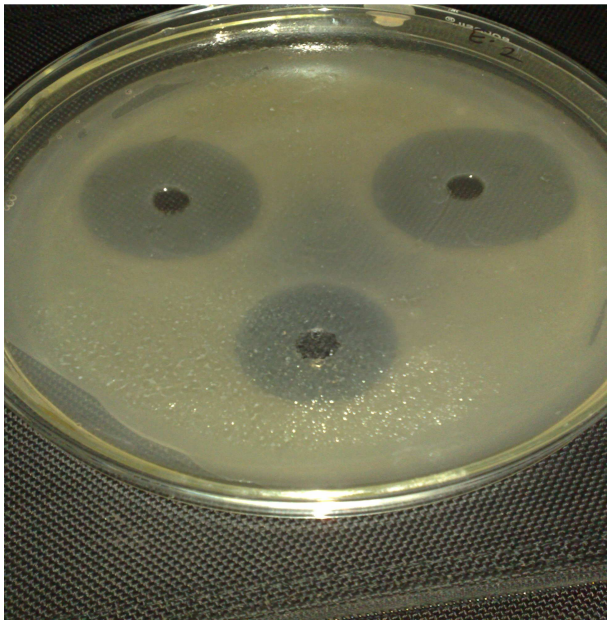


Fig. 1(f): Zone of inhibitions for 5j against *E. coli*

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