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An Efficient Synthetic Approach Towards 4-Cyano-3-(Methylthio)-5-Oxo-2*H*-Pyrazole-1(5*H*)-Carbothioamide And Its Derivatives As Potent Antimicrobial Agents.

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ABSTRACT: *Synthesis of novel heterocyclic 4-cyano -3-(methylthio)-5-oxo-2H-pyrazole-1(5H)-carbothioamide (3) was prepared by condensing ethyl-2-cyano-3,3-bis (methylthio)acrylate (1) with thiosemicarbazide (2) in DMF and catalytic amount of potassium carbonate. Compound (3) has methylthio group at third position, which is replaced by different nucleophiles such as substituted anilines| phenols| hetryl amines| compounds containing active methylene group to afford 3-substituted derivatives of compound (3). All the newly synthesized compounds were screened for their antimicrobial activity.*

KEYWORDS: *DMF, Ethyl-2-cyano-3,3-bis(methylthio)acrylate, Potassium carbonate, Thiosemicarbazide.*

I. INTRODUCTION

Synthesis of heterocyclic compounds is becoming an important field of investigation in organic chemistry due to their wide spread presence in nature and are of great significance to life because its structural subunit exist in many natural products such as vitamins, hormones and antibiotics[1-2]. In drug designing programs an essential component is to develops the new molecules which consist of chemical characteristics that clearly differ from those of existing molecules. Certain small heterocyclic moieties act as highly functionalized scaffolds and are known pharmacophores[3-4]. It is well known that, the heterocyclic compounds are participate in the metabolic pathway of live organism, performing several biochemical functions and are widely used. In the family of heterocycles, compounds containing nitrogen atoms are an important class of compounds having a potent biological activity, hence they attracted considerable attention in the design of biologically active molecules[5-6].

In order to synthesize biologically active heterocycles, one of the best method is reaction of thiosemicarbazides with system containing -C=O, -C=N, -C-SCH_3 groups it gives pyrazole, triazole, oxadiazole etc. Thiosemicarbazides are efficient precursor which have been extensively utilised in heterocyclic synthesis. The derivatives of thiosemicarbazides are useful intermediate and subunit for the development of molecule having a pharmaceutical interest[7].Pyrazoles are important nitrogen containing five membered heterocyclic compounds. Numerous reports shows that pyrazole derivatives have been found to posses promising pharmaceutical activities such as antibacterial[8], antifungal[9], antipyretic[10], analgesic[11], anti-inflammatory[12], antitubercular[13], antidepressant[14], anticonvulsant[15], anticancer activity[16]. More over they also exhibit protein kinases inhibitors activity[17], cytoxic activity[18] and herbicidal activity[19]. By survey of literature it is found that number of synthetic methods are available for the preparation of pyrazoles. Synthesis of pyrazole-1-carbothioamide have been prepared by condensation of α-β unsaturated carbonyl compounds/ 1,3 diketones/ compound containing activated double bonds with thiosemicarbazide[20-26].The aim of present review is devoted exclusively to the synthesize systematically 4-cyano-3-(methylthio)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide and its 3-substituted derivatives with antimicrobial study.

II. MATERIAL AND METHODS

Electrothermal IA 9000 SERIES digital melting point apparatus was used to determine the melting points of synthesized compounds and were uncorrected. Homogeneity of all the compounds were routinely checked on 0.2 mm silica gel-C plates using ethyl acetate:hexane (3:7) as irrigant, the spots were examined under UV light chamber. Infrared spectra were recorded in Nujol or as potassium bromide pallets on infrared spectrophotometer, nuclear magnetic resonance spectra were obtained on Brukner advance spectrophotometer 400 MHz in DMSO-d6 using tetramethylsilane (TMS) as internal reference, Mass spectra were recorded on FT-VC-7070 H Mass spectrometer using the EI technique at 70 eV. All the reactions were carried out under ambient atmosphere. Elemental analysis was performed on a Heraeus CHN-O rapid analyser.

III. GENERAL PROCEDURE

4-Cyano-3-(methylthio)-5-oxo-2*H*-Pyrazole-1(5*H*)-Carbothioamide(3) A mixture ethyl-2-cyano-3,3-bis (methylthio)acrylate (1) (0.01mol) and thiosemicarbazide (2) (0.01mol) in 10 ml of DMF and anhydrous potassium carbonate (10mg) was refluxed for 12 hours. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystalized from DMF-ethanol mixture to give pure compound (3).

Brown powder, Yield 68%, m.p. 177-178 °C. IR (KBr/cm^{-1}) 1696 (CO), 2230 (CN), 3343 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.7 (s, 3H, SCH_3), 3.8 (s, 1H, NH), 7.4 (s, 2H, NH_2): EI-MS(m/z: RA%): 214 (M^+). Anal. Calcd for $C_6H_6N_4OS_2$ C,33.64; H,2.80; N,26.16; found; C,33.56; H,2.67; N,26.10.

3-Substituted derivatives of 4-cyano-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (4a-4d,5a-5d,6a-6d,7a-7d)
A mixture of compound (3) (0.001mol) refluxed independently with substituted anilines/ phenols/ hetryl amines/ compound containing active methylene groups (0.001mol) in 10 ml of DMF and anhydrous potassium carbonate(10mg) for 8 hours. The reaction progress was checked by TLC. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystalized from DMF-ethanol (2:8) mixture to give pure compounds (4a-4d,5a-5d,6a-6d,7a-7d).

4-Cyano-3-(4-methyl anilino)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (4a)
Brown powder, Yield 68.08%, m.p. 164-166 °C. IR (KBr/cm^{-1}) 1685 (CO), 2215 (CN), 3318 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.1 (s, 3H, Ar-CH_3), 3.79 (s, 1H, NH), 5.8-6.7(m, 4H, Ar-H), 7.74 (s, 2H, NH_2): EI-MS(m/z: RA%): 273 (M^+). Anal. Calcd for $C_{12}H_{11}N_5OS$ C,52.74; H,4.02; N,25.64 found;C,52.63; H,3.94; N,25.48.

4-Cyano-3-(4-methoxyanilino)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (4b)
Brown powder, Yield 76.54%, m.p. 152-153°C. IR (KBr/cm^{-1}) 1662 (CO), 2210 (CN), 3331 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 3.6-3.8 (s, 3H, -OCH_3), 4.12 (s, 1H, NH), 5.6-6.8(m, 4H, Ar-H), 7.52 (s, 2H, NH_2): EI-MS(m/z: RA%): 289 (M^+). Anal. Calcd for $C_{12}H_{11}N_5O_2S$ C,49.82; H,3.80; N,24.22 found;C,49.64; H,3.73; N,24.19.

4-Cyano-3-(4-bromoanilino)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (4c)
Brown powder, Yield 59.48%, m.p. 187-189 °C. IR (KBr/cm^{-1}) 1695 (CO), 2208 (CN), 3280 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 4.06 (s, 1H, NH), 6.0-7.1(m, 4H, Ar-H), 6.91 (s, 2H, NH_2): EI-MS(m/z: RA%): 336 (M^+). Anal. Calcd for $C_{11}H_8N_5OSBr$ C,39.28; H,2.38; N,20.83 found;C,39.21; H,2.35; N,20.76. .

4-Cyano-3-(4-nitroanilino)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (4d)
Brown powder, Yield 62.33%, m.p. 206-208°C. IR (KBr/cm^{-1}) 1658 (CO), 2205 (CN), 3315 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 3.92 (s, 1H, NH), 6.2-7.2(m, 4H, Ar-H), 7.14 (s, 2H, NH_2): EI-MS(m/z: RA%): 304 (M^+). Anal. Calcd for $C_{11}H_8N_6O_3S$ C,43.42; H,2.63; N,27.63 found;C,43.28; H,2.59; N,27.54.

4-Cyano-3-(2-methyl phenoxy)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (5a)
Brown powder, Yield 78.53%, m.p. 192-194°C. IR (KBr/cm^{-1}) 1692 (CO), 2218 (CN), 3262 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.2 (s, 3H, Ar-CH_3), 3.97(s, 1H, NH), 6.1-6.8 (m, 4H, Ar-H), 7.81 (s, 2H, NH_2): EI-MS (m/z: RA%): 274 (M^+). Anal. Calcd for $C_{12}H_{10}N_4O_2S$ C,52.55; H,3.64; N,20.43; found; C,52.38; H,3.53; N,20.38.

4-Cyano-3-(4-chloro phenoxy)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (5b)
Yellow powder, Yield 71.89, m.p. 157-159°C. IR (KBr/cm^{-1}) 1682 (CO), 2230 (CN), 3310 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 3.82 (s, 1H, NH), 6.3-7.2 (m, 4H, Ar-H), 7.77 (s, 2H, NH_2): EI-MS (m/z: RA%): 294 (M^+). Anal. Calcd for $C_{11}H_7N_4O_2SCl$ C,44.89; H,2.38; N,19.04; found; C,44.84; H,2.33; N,19.00.

4-Cyano-3-(4-bromo phenoxy)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (5c)
Brown powder, Yield 66.21%, m.p. 172-174°C. IR (KBr/cm^{-1}) 1674 (CO), 2206 (CN), 3313 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 3.75 (s, 1H, NH), 6.1-7.0 (m, 4H, Ar-H), 7.36 (s, 2H, NH_2): EI-MS (m/z: RA%): 337 (M^+). Anal. Calcd for $C_{11}H_7N_4O_2SBr$ C,39.16; H,2.07; N,16.61; found; C,39.07; H,2.04; N,16.55.

4-Cyano-3-(4-nitro phenoxy)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (5d)
Brown powder, Yield 58.02%, m.p. 198-200°C. IR (KBr/cm^{-1}) 1680 (CO), 2212 (CN), 3290 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 3.80 (s, 1H, NH), 6-6.9 (m, 4H, Ar-H), 7.22 (s, 2H, NH_2): EI-MS (m/z: RA%): 305 (M^+). Anal. Calcd for $C_{11}H_7N_5O_4S$ C,43.27; H,2.29; N,22.95; found; C,43.18; H,2.16; N,22.88.

4-Cyano-3-(malononitriyl)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (6a)
Brown powder, Yield 64.36%, m.p. 211-213°C. IR (KBr/cm^{-1}) 1696 (CO), 2210 (CN), 3285 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.43 (s, 1H, -CH), 4.20 (s, 1H, NH) 7.80 (s, 2H, NH_2): EI-MS (m/z: RA%): 232 (M^+). Anal. Calcd for $C_8H_4N_6OS$ C,41.37; H,1.72; N,36.20; found; C,41.25; H,1.66; N,36.08.

4-Cyano-3-(ethylcyanoacetyl)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (6b)
Brown powder, Yield 61.74%, m.p.168-170°C. IR (KBr/cm^{-1}) 1684 (CO), 2228 (CN), 3298 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 1.5 (t, 3H, -CH_3), 2.40 (s, 1H, -CH), 3.2 (q, 2H, -OCH_2), 3.68 (s, 1H, NH), 7.18 (s, 2H, NH_2): EI-MS (m/z: RA%): 279 (M^+). Anal. Calcd for $C_{10}H_9N_5O_3S$ C,43.01; H,3.22; N,25.08; found; C,42.94; H,3.14; N,25.02.

4-Cyano-3-(acetylacetonyl)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (6c)
Brown powder, Yield 65.00%, m.p. 178-180°C. IR (KBr/cm^{-1}) 1690 (CO), 2213 (CN), 3346 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.1 (s, 6H, -$2CH_3$), 2.35(s, 1H, -CH), 3.95 (s, 1H, NH), 6.98 (s, 2H, NH_2): EI-MS (m/z: RA%): 266 (M^+). Anal. Calcd for $C_{10}H_{10}N_4O_3S$ C,45.11; H,3.75; N,21.05; found; C,45.08; H,3.69; N,21.00.

4-Cyano-3-(ethylacetoacetyl)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (6d)
Brown powder, Yield 69.65%, m.p. 166-168°C. IR (KBr/cm^{-1}) 1655 (CO), 2216 (CN), 3348 (NH):^{1}HNMR (400 MHz,DMSO-d_6):δ =1.6 (t, 3H, -CH_3), 2.14 (s, 3H, -CH_3),2.31(s, 1H,CH), 3.3 (q, 2H, -OCH_2), 3.89 (s, H, NH), 8.01 (s, 2H, NH_2),: EI-MS (m/z: RA%): 296 (M^+). Anal. Calcd for $C_{11}H_{12}N_4O_4S$ C,44.59; H,4.05; N,18.91; found; C,44.42; H,3.99; N,18.88.

4-Cyano-3-(pyrolidino)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (7a)
Brown powder, Yield 72.15%, m.p. 201-203°C. IR (KBr/cm^{-1}) 1688 (CO), 2208 (CN), 3312 (NH):^{1}HNMR (400 MHz,DMSO-d_6): δ = 1.86 (m, 4H, -pyrolidine H), 2.32 (m, 4H, -pyrolidine H), 4.48 (s, 1H, NH), 7.36 (s, 2H, NH_2),: EI-MS (m/z: RA%): 237 (M^+). Anal. Calcd for $C_9H_{11}N_5OS$ C,45.56; H,4.64; N,29.53; found; C,45.37; H,4.45; N,29.33.

4-Cyano-3-(pipyridino)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (7b)
Brown powder, Yield 77.13%, m.p. 195-197°C. IR (KBr/cm^{-1}) 1660 (CO), 2214 (CN), 3324 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ =1.6 (m, 6H, pi-pyridine H), 2.36 (m, 4H, pi-pyridine H), 4.09 (s, 1H, NH), 7.42 (s, 2H, NH_2),: EI-MS (m/z: RA%): 251 (M^+). Anal. Calcd for $C_{10}H_{13}N_5OS$ C,47.80; H,5.17; N,27.88; found; C,47.55; H,5.09; N,27.76.

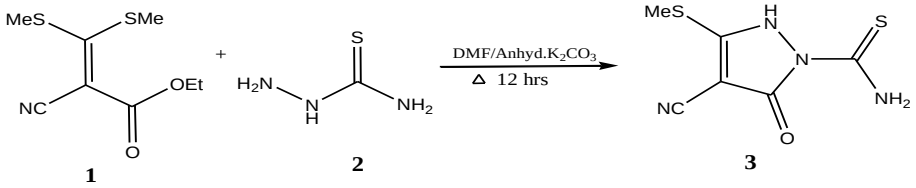
4-Cyano-3-(piperazino)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (7c)
Brown powder, Yield 72.28%, m.p. 190-192°C. IR (KBr/cm^{-1}) 1678 (CO), 2219 (CN), 3315 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.58 (m, 4H, pi-perazine H), 2.62 (m, 4H, pi-perazine H), 3.91 (s, 1H, NH), 7.12 (s, 2H, NH_2),: EI-MS (m/z: RA%): 252 (M^+). Anal. Calcd for $C_9H_{12}N_6OS$ C,42.85; H,4.76; N,33.33; found; C,42.79; H,4.64; N,33.19.

4-Cyano-3-(morpholino)-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (7d)
Brown powder, Yield 68.16%, m.p. 185-187°C. IR (KBr/cm^{-1}) 1665 (CO), 2207 (CN), 3328 (NH): ^{1}HNMR (400 MHz,DMSO-d_6): δ = 2.43 (m, 4H, morpholine H), 3.72 (m, 4H, morpholine H), 3.95 (s, 1H, NH), 7.28 (s, 2H, NH_2),: EI-MS (m/z: RA%): 253 (M^+). Anal. Calcd for $C_9H_{11}N_5O_2S$ C,42.68; H,4.34; N,27.66; found; C,42.50; H,4.21; N,27.49.

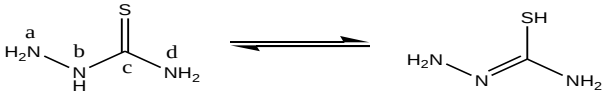
IV. RESULT AND DISCUSSION

In continuing our interest to synthesize heterocyclic compounds, herein we wish to report new, simple and cheap method for synthesis of pyrazole-1-carbothioamides and its 3-substituted derivatives. In our first scheme we condensed ethyl-2-cyano-3,3-bis (methylthio)acrylate (1) and thiosemicarbazide (2) in DMF and catalytic amount of anhydrous K_2CO_3 to afford (3) **Scheme-1** The compound (3) posseses replaceable active methyl thio group which is activated by nitrogen atom, electron withdrawing cyano group. When compound (3) (1mole) was condensed independently with substituted anilines/ phenols/ hetryl amines/ compound containing active methylene groups in DMF and catalytic amount of anhydrous K_2CO_3 to afford 3-substituted derivatives

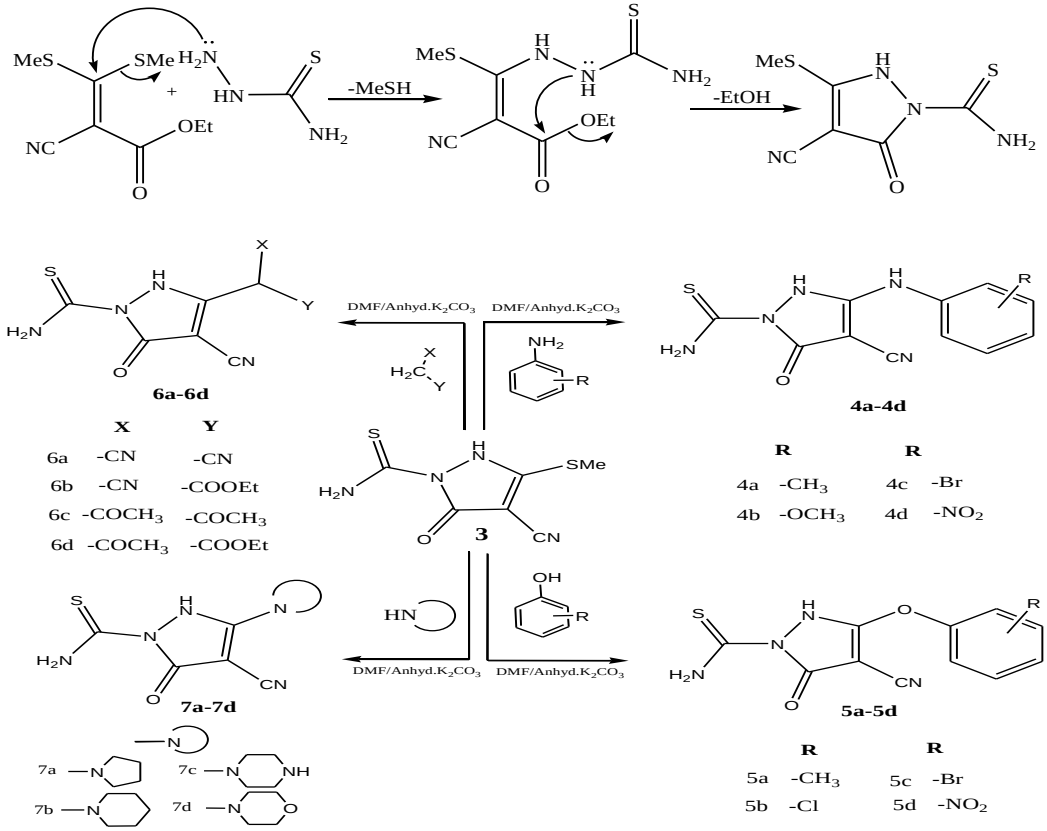
of 4-cyano-5-oxo-2*H*-pyrazole-1(5*H*)-carbothioamide (4a-4d,5a-5d,6a-6d,7a-7d) **Scheme-2.** In order to show generality and scope of this new protocol we used various substituted nucleophiles such as anilines/phenols/hetryl amines/active methylene compounds and checked for their product yield as well as antimicrobial activity. We have been found that various substituent's on nucleophiles affect the yield of product as well as antimicrobial activity. When electron donor groups present on nucleophile, the yield of product was comparatively higher than other product.The structure of newly synthesized compounds were elucidate on the basis of elemental analysis, IR,^{1}HNMR, Mass spectral data. In IR spectrum of compound absorption band appear in the region 2240-2190 cm^{-1}for (CN). ^{1}HNMR spectra of compound shows singlet peak in the region of 7-9 ppm due to (S=C-NH_2) proton. The MASS spectra shows molecular ion peak which is corresponds to the molecular weight of respective compounds. Spectral studies of all compounds shows that compounds were stable and do not exhibit any tautomerism. The elemental analysis values are in good agreement with theoretical data. All the compounds were screened for their antibacterial activities.



Scheme-1. Formation of pyrazole-1-carbothioamide



Thiosemicarbazides are polyfunctional compounds, which possess three possible nucleophilic positions such as NH_2-a, NH-b and NH_2-d having reactivity order NH_2-a > NH-b > NH_2-d. Hence, thiosemicarbazide react with ethyl 2-cyano-3,3-bis (methylthio)acrylate to form pyrazole-1-carbothioamide (3). The mechanism of formation compound (3) deduced as follows.



Scheme-2. Formation of 3-substituted derivatives of pyrazole-1-carbothioamide.

V. ANTIMICROBIAL ACTIVITY

All synthesized compounds were subjected to antimicrobial screening against several pathogenic gram positive and gram negative micro-organisms such as *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhi* by paper disk diffusion method. Streptomycin and penicillin were used as standard drugs for studying the activities of these compounds. All the compounds were dissolved in dimethyl sulphoxide (50µg/ml in DMSO). The incubation period for bacteria was 24 hours at 37°c. Activity of compounds was determined by measuring the diameter of zone of inhibition, values obtained was compared with the values produced from standard drugs like streptomycin and penicillin. The newly synthesized compounds show zone of inhibition 5-23 mm in diameter where as standard streptomycin exhibit zone of inhibition 20-24 mm in diameter. Investigation of antimicrobial activity it was found that pyrazole-1-carbothioamide derivatives (4d), (5b), (5d) and (7c) showed higher activity against all the micro-organisms employed for antimicrobial screening. All the synthesized compounds exhibit comparatively less antimicrobial activity against *Escherichia coli* than other micro-organisms. These results suggest that electron withdrawing groups -NO_2 and –Cl groups plays an important role in enhancing antimicrobial activity.

In summary, most of our synthesized compounds showed high and moderate activity against *Staphylococcus aureus, Bacillus subtilis* and *Salmonella typhi*.

Table 1.Antimicrobial activity of compound (4a-7d)

Compounds	Gram positive		Gram negative	
	S.aureus	***B.subtilis***	***E.Coli***	***S.typhi***
4a	++	+++	++	++
4b	+++	++	-	++
4c	+++	++	+	+++
4d	+++	++++	+++	++++
5a	++	+++	++	+++
5b	++++	+++	+++	++++
5c	+++	+++	++	+++
5d	++++	++++	+++	+++
6a	+	++	-	++
6b	+++	++	+	++
6c	++	++	++	+++
6d	+++	++	+	++
7a	++	+	-	++
7b	+++	+++	++	++++
7c	++++	++++	+++	+++
7d	++	++	++	+++
Streptomycin	-	++++	++++	-
Penicillin	++++	-	-	++++

Note: (-) indicate no activity, (+) weak activity with inhibition 01-06 mm, (++) slight activity with inhibition 07-12 mm, (+++) moderate activity with inhibition 13-18 mm and (++++) high activity with inhibition 19-24 mm.

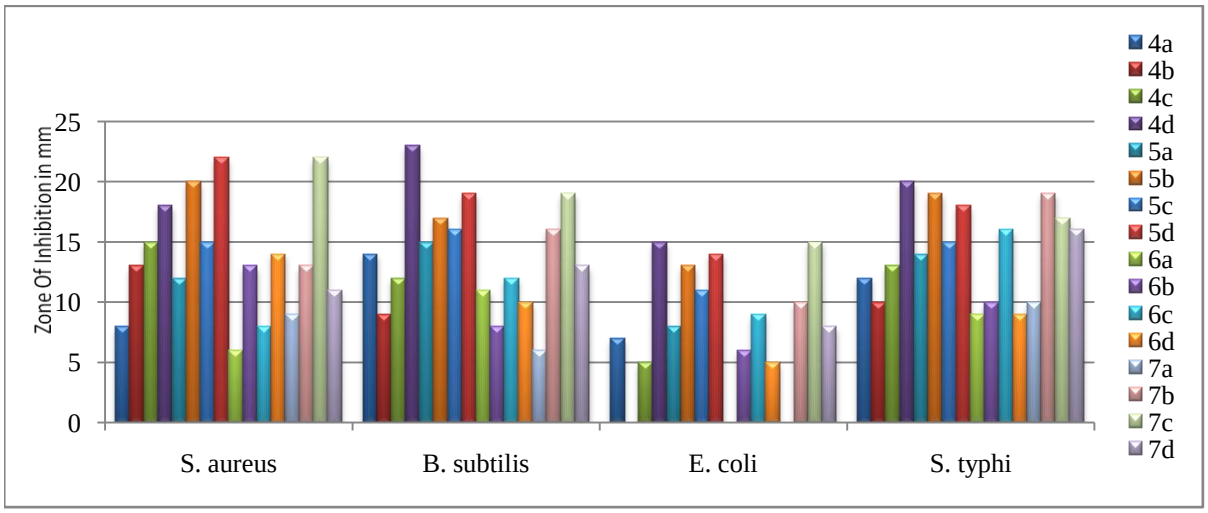


Fig.1: Comparative Antimicrobial activity of compounds 4a-7d.

VI. CONCLUSION

In conclusion, we have reported a simple and efficient method for the synthesis of pyrazole-1-carbothioamide and its 3-substituted derivatives which shows promising antibacterial activity. It has carbothioamide group at first position which is ready to cyclise with another reagent. Hence it has enough scope for further study in developing these as potent biologically active compounds. The elemental and spectroscopy analysis were good agreement with the proposed structures

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