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SYNTHESIS OF POLYNUCLEAR PYRIMIDINE DERIVATIVES AND THEIR PHARMACOLOGICAL ACTIVITIES

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Abstract: A series of 2-(4,5-dihydro-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)-4-aryl-6-(thiophen-2-yl)pyrimidine **5a-e,** ethyl-5-amino-1-[4-aryl-6-(thiophen-2-yl)pyrimidin-2-yl]-1H-pyrazole-4-carboxylate **6a-e** and triazolepyrimidine derivatives **7a-e** starting from thiophene substituted chalcones. Chalcones **1a-e** were cyclised with thiourea in presence of acetic acid to get substituted-pyrimidine-2-thiols **2a-e** which on methylation with methyl iodide to give methylated pyrimidine derivatives **3a-e**. Compounds **3a-e** were refluxed with hydrazine hydrate to afford 4-substituted-2-Hydrazinyl-6-(thiophen-2-yl)pyrimidines **4a-e** which on refluxing with (2*E*)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one in presence of acetic acid produced compounds 2-(4,5-dihydro-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)-4-aryl-6-(thiophen-2-yl)pyrimidine **5a-e**. The compounds **4a-e** on treatment with ethyl-(2*Z*)-2-cyano-3-ethoxyprop-2-enoate yielded ethyl-5-amino-1-[4-aryl-6-(thiophen-2-yl)pyrimidin-2-yl]-1H-pyrazole-4-carboxylate **6a-e.** The compounds **4a-e** on refluxing with acetic anhydride produced triazolepyrimidine derivatives **7a-e**.

Keywords: 2-Acetylthiophene, chalcones, pyrazolopyrimidines, triazolopyrimidines, antibacterial, antioxidant activities.

Introduction:

Combination of two or more heterocyclics has been a greater fashion for organic chemists for the synthesis as well as thinking their biological profile. Many of the drugs are more heterocyclic. Similarly, in recent years pyrazolopyrimidines and related fused heterocyclic have been identified as bioactive molecules as CNS depressants[i], neuroleptics[ii], tuberculostastic[iii] and some pyrazole[3,4-*d*]pyrimidines[iv] have been identified as ligands for adenosine receptor.
Sedereviciute[v] *et al.,* have reported the synthesis and cardiotonic activity of pyrazolylpyrimidines. Apart from the pharmaceutical applications of these molecules, some reports are also available regarding their use in photography. Makino[vi] *et al.,* and Nozawa[vii] *et al.,* of Fuji Photo Film Co. Ltd., have reported that the by incorporation of pyrimidinylpyrazole

into a silver halide emulsion layer has resulted in high gradation and improved preservability of photographs.
The above discussion reveals the importance of pyrazolopyrimidine derivatives as anti-inflammatory[viii], anti-bacterial, anti-neoplastic[ix-xiv], anti- allergic, anti-hypertensive[xv], anti-microbial[xvi-xix], anti-viral, anti-epileptic, sedative-hypnotic[xix,xx], GSK-III inhibitor and Src kinase inhibitor activity in psychological disorders etc. biologically, pharmacologically and industrially important molecules. In view of these facts it was thought worthwhile to synthesize some pyrazolopyrimidine derivatives in the present investigation.

Materials and methods:

All the melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on Bruker alpha FT IR spectrophotometer, ^{1}H NMR spectra were measured on Bruker AV 400MHZ using $CDCl_3$ and DMSO as solvent. Chemical shifts are expressed in ð ppm. Mass spectra were performed on a Joel JMS-D 300 mass spectrometer operating at 70 eV. All the reactions were followed and checked by TLC, and further purification was done by column chromatography. All the reagents used were of AR grade and they were again purified by distillation.

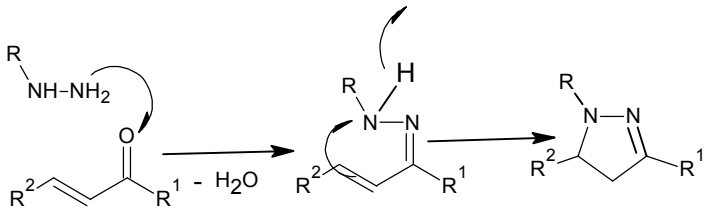
Results and discussion:

Pyrimidines **3a-e** were prepared by the treatment of **2a-e** with methyl iodide in presence of DMF and potassium carbonate. The IR spectrum of **3a** exhibited a absorption band at 1645 cm^{-1} due to C=N group and at 827 cm^{-1} due to C-S-C stretching. The ^{1}H NMR spectrum of compound **3a** showed a singlet at ð 3.85 due to three protons of OCH_3 group and a singlet at ð 2.17 for three protons of S-CH_3 group. Further, it showed a molecular ion peak at m/z 314 in its mass spectrum is in agreement with the structure.

Compounds **3a-e** on refluxion with hydrazine hydrate in presence of ethanol produced 4-substituted-2-Hydrazinyl-6-(thiophen-2-yl)pyrimidine **4a-e**. The reactions were monitored by TLC. IR spectrum of **4a** showed absorption band at 3310 cm^{-1} due to NH group. The ^{1}H NMR spectrum showed a singlet at ð 3.66 due to three protons of OCH_3 group and singlets at ð 2.66 and ð 4.39 due to NH_2 and NH group respectively. Its mass spectrum showed a molecular ion peak at m/z 298 which is in agreement with the structure.

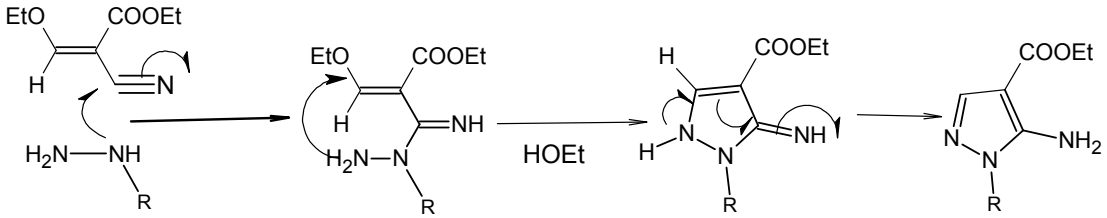
Compounds **4a-e** were refluxed with chalcone, (2*E*)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one in presence of catalytic amount of acetic acid produced 2-(4,5-dihydro-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)-4-aryl-6-(thiophen-2-yl)pyrimidine **5a-e.** The IR spectrum of **5a** showed absorption band at 1030 cm^{-1} due to C-O-C group. The ^{1}H NMR spectrum showed a singlet at ð 3.88 due to three protons of OCH_3 group and triplet at ð 2.19 and doublet at ð 2.78 due to CH and CH_2 group respectively.

Probable reaction mechanism of pyrazole formation



Compounds **4a-e** were treated with ethyl (2*Z*)-2-cyano-3-ethoxyprop-2-enoate in ethanol medium to afford Ethyl-5-amino-1-[4-(4-substituted)-6-(thiophen-2-yl)pyrimidin-2-yl]-1H-pyrazole-4-carboxylate **6a-e**. The IR spectrum of **6a** showed absorption band at 3270 cm^{-1}due to NH group and at 1750 cm^{-1} due to C=O group. The ^{1}H NMR spectrum showed a singlet at ð 3.92 due to three protons of OCH_3 group and triplet at ð 1.33 and a quartet at ð 4.32 due to CH_3 and CH_2 group respectively. Its mass spectrum showed a molecular ion peak at m/z 421 which is in agreement with the structure.

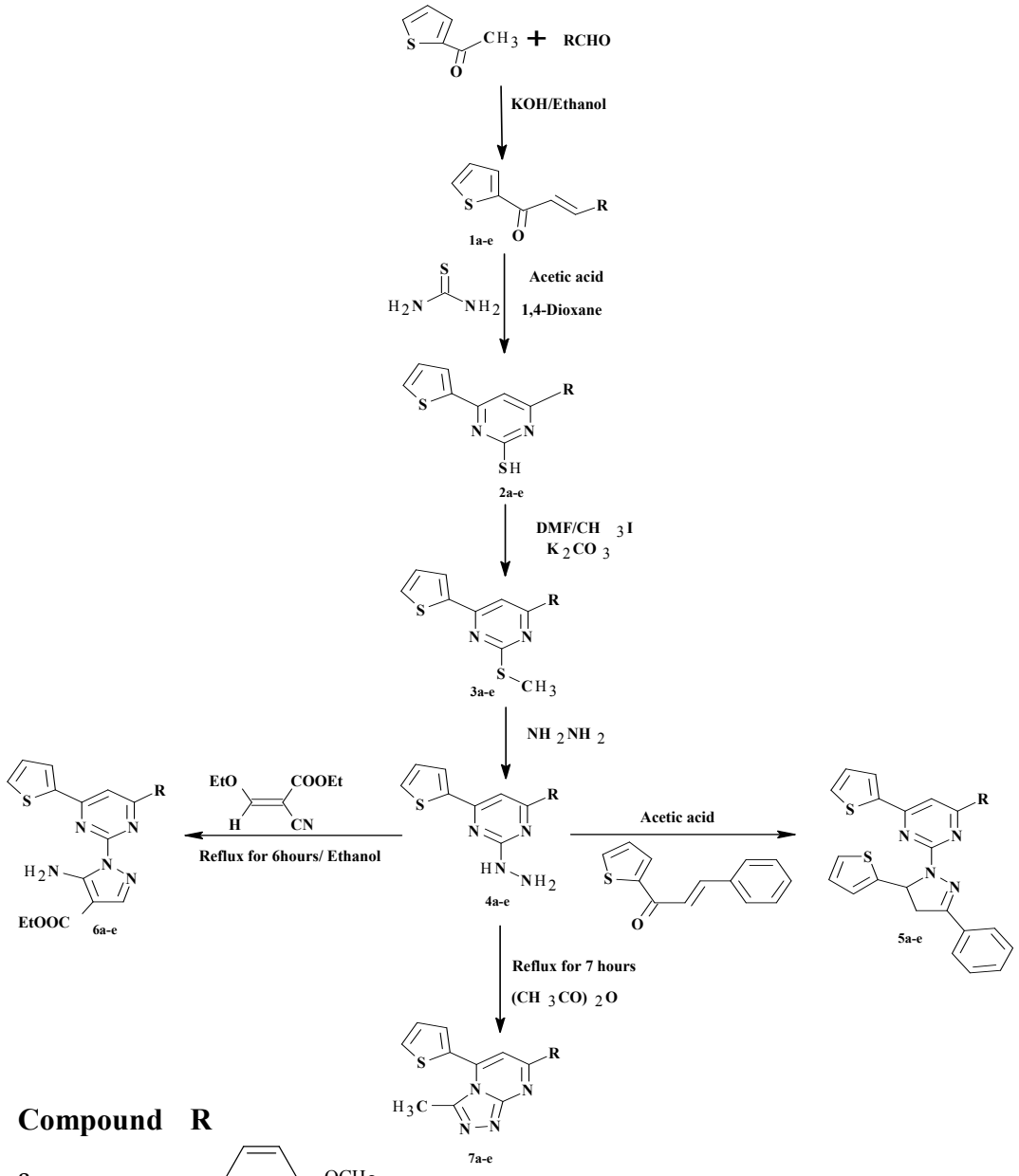
Probable reaction mechanism of pyrazole formation

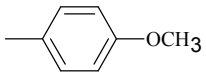
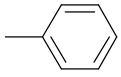
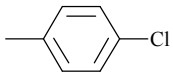
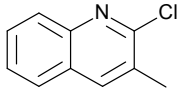
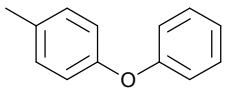


Compounds **4a-e** were refluxed with acetic anhydride in presence of catalytic amount of sulphuric acid afforded **7a-e.** The IR spectrum of **7a** showed absorption band at 1510 cm^{-1} due to C=N group. The ^{1}H NMR spectrum showed a singlet at ð 3.87 due to three protons of OCH_3 group and singlet at ð 2.33 due to CH_3. Its mass spectrum showed a molecular ion peak at m/z 322 which is in agreement with the structure.

The sequence of reactions carried out are depicted in scheme I. Some of the selected compounds were screened for antibacterial activity and antioxidant activity studies, the results are shown in **Table-1** and **Table 2** respectively.

SCHEME I



Compound	R
a	
b	
c	
d	
e	

Experimental:

Preparation of 4-(4-Methoxyphenyl)-6-(thiophen-2-yl)pyrimidine-2-thiol 2a:
A mixture of (2*E*)-3-(4-Methoxyphenyl)-1-(thiophen-2-yl) prop-2-en-1-one **1a** (2.45g, 0.01 mol) and thiourea (0.76g, 0.01 mol) in 1,4-dioxane (10 mL) and a catalytic amount of acetic acid is taken in a round bottomed flask and refluxed for about 24 h. The progress of the reaction is monitored by TLC. The reaction mixture is cooled and poured into ice cold water with stirring. The product is filtered, dried and recrystalised using ethanol. Compounds **2b-e** are prepared analogously.

4-(4-Methoxyphenyl)-6-(thiophen-2-yl)pyrimidine-2-thiol 2a:
Solid; (60%); IR (KBr) ν (cm^{-1}): 2363 (SH), 1250 (C-O-C); ^{1}H NMR(400MH_Z, $CDCl_3$) ð(ppm): 12.50 (b, 1H, SH), 3.86 (s, 3H, OCH_3), 7.17-8.19 (m, 8H, Ar-H); Elemental analysis: Calculated (%) for $C_{15}H_{14}N_2OS_2$: C, 60.00; H, 4.66; N, 9.33; Found: C, 59.32; H, 4.58; N, 9.54; MS: m/z 300.

4-Phenyl-6-(thiophen-2-yl)pyrimidine-2-thiol 2b:
Solid; (45%); IR (KBr) ν (cm^{-1}): 2375 (SH); ^{1}H NMR (400 MH_Z, $CDCl_3$) ð(ppm): 13.10 (b, 1H, SH), 7.02-8.22 (m, 9H, Ar-H); Elemental analysis: Calculated (%) for $C_{14}H_{10}N_2S_2$: C, 62.22; H, 3.70; N, 10.37; Found: C, 62.28; H, 3.63; N, 10.47; MS: m/z 270.

4-(4-Chlorophenyl)-6-(thiophen-2-yl)pyrimidine-2-thiol 2c:
Solid; (53%); IR (KBr) ν(cm^{-1}): 2380 (SH), 790 (CCl); ^{1}H NMR (400 MH_Z, $CDCl_3$) ð(ppm): 12.87 (b, 1H, SH), 7.10-8.12 (m, 8H, Ar H); Elemental analysis: Calculated (%) for $C_{14}H_9ClN_2S_2$: C, 55.08; H, 2.95; N, 9.18; Found: C, 55.02; H, 2.79; N, 9.11; MS: m/z 305.

4-(2-Chloroquinolin-3-yl)-6-(thiophen-2-yl)pyrimidine-2-thiol 2d:
Solid; (42%); IR (KBr) ν(cm^{-1}): 2365 (S-H, SH), 790 (CCl); ^{1}H NMR (400 MH_Z, $CDCl_3$) ð (ppm): 12.95 (b, 1H, SH), 7.17-8.10 (m, 8H, Ar H); Elemental analysis: Calculated (%) for $C_{17}H_{10}ClN_3S_2$: C, 57.30; H, 2.80; N, 11.79; Found: C, 57.15; H, 2.85; N, 11.78; MS: m/z 356.

4-(4-Phenoxyphenyl)-6-(thiophen-2-yl)pyrimidine-2-thiol 2e:
Solid; (47%); IR (KBr) ν (cm^{-1}): 2360 (SH); ^{1}H NMR (400 MH_Z, $CDCl_3$) ð(ppm): 13.04 (b, 1H, SH), 7.16-8.24 (m, 13H, Ar H); Elemental analysis: Calculated (%) for $C_{20}H_{14}N_2OS_2$: C, 66.29; H, 3.86; N, 7.73; Found: C, 66.50; H, 3.82; N, 7.83; MS: m/z 362.

Preparation of 4-(4-Methoxyphenyl)-2-(methylsulfanyl)-6-(thiophen-2-yl) pyrimidine 3a:
To a solution of 4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyrimidine-2-thiol **2a** (3.01 g, 0.01 mol) in dimethyl formamide (20 mL), potassium carbonate (2.76 g, 0.02 mol) and methyl iodide (2.84 g, 0.02 mol) is added and stirred for 4 h. Reaction time and completion of reaction is monitored by TLC. Then reaction mixture is diluted with cold water and neutralised by glacial acetic acid. The product is filtered off, dried and recrystalised from ethanol. Compounds **3b-e** are prepared analogously.

4-(4-Methoxyphenyl)-2-(methylsulfanyl)-6-(thiophen-2-yl)pyrimidine 3a:
Solid; (75%); IR (KBr) ν(cm^{-1}): 827 (C-S-C), 1297 (C-O-C), 1645 (C=N); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð (ppm): 2.17 (s, 3H, SCH_3), 6.64-7.70 (m, 8H, Ar H), 3.85 (s, 3H, OCH_3); Elemental analysis: Calculated (%) for $C_{16}H_{14}N_2OS_2$: C, 61.14; H, 4.45; N, 8.91; Found: C, 61.71; H, 4.40; N, 8.85; MS: m/z 314.

2-(Methylsulfanyl)-4-phenyl-6-(thiophen-2-yl)pyrimidine 3b:
Solid; (60%); IR (KBr) ν (cm^{-1}): 780 (C-S-C), 1630 (C=N); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð (ppm): 2.20 (s, 3H, SCH_3), 6.80-7.88 (m, 9H, Ar H); Elemental analysis: Calculated (%) for $C_{15}H_{12}N_2S_2$: C, 63.38; H, 4.22; N, 9.85; Found: C, 63.77; H, 4.26; N, 9.70; MS: m/z 284.

4-(4-Chlorophenyl)-2-(methylsulfanyl)-6-(thiophen-2-yl)pyrimidine 3c:
Solid; (47%); IR (KBr) ν (cm^{-1}): 815 (C-S-C), 752 (C-Cl), 1644 (C=N); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð (ppm): 2.04 (s, 3H, SCH_3), 7.02-7.12 (m, 8H, Ar H); Elemental analysis: Calculated (%) for $C_{15}H_{11}ClN_2S_2$: C, 56.42; H, 3.44; N, 8.77; Found: C, 56.15; H, 3.38; N, 8.66; MS: m/z 319.

2-Chloro-3-[2-(methylsulfanyl)-6-(thiophen-2-yl)pyrimidin-4-yl]quinoline 3d:
Solid; (58%); IR (KBr) ν (cm^{-1}): 825 (C-S-C), 1644 (C=N); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð (ppm): 2.44 (s, 3H, SCH_3), 6.68-8.11 (m, 9H, Ar H); Elemental analysis: Calculated (%) for $C_{18}H_{12}ClN_3S_2$: C, 58.37; H, 3.24; N, 11.35; Found: C, 58.19; H, 3.20; N, 11.28; MS: m/z 370.

2-(Methylsulfanyl)-4-(4-phenoxyphenyl)-6-(thiophen-2-yl)pyrimidine 3e:
Solid; (67%); IR (KBr) ν (cm^{-1}): 821 (C-S-C), 1634 (C=N); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð (ppm): 2.15 (s, 3H, SCH_3), 6.66-8.25 (m, 13H, Ar H); Elemental analysis: Calculated (%) for $C_{21}H_{16}N_2OS_2$: C, 67.02; H, 4.25; N, 7.44; Found: C, 66.98; H, 4.27; N, 7.33; MS: m/z 376.

Preparation of 2-Hydrazinyl-4-(4-methoxyphenyl)-6-(thiophen-2-yl) pyrimidine 4a:
A mixture of compound 4-(4-methoxyphenyl)-2-(methylsulfanyl)-6-(thiophen-2-yl) pyrimidine **3a** (3.14 g, 0.01 mol) and hydrazine hydrate (0.96 g, 0.03 mol) in absolute ethanol (15 mL) is refluxed for 6 h. After completion of the reaction, the mixture is poured into crushed ice. The separated solid filtered, dried and recrystalised from ethanol. Similarly, the compounds **4b-e** are prepared.

2-Hydrazinyl-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyrimidine 4a:
Solid; (75%); IR (KBr) ν(cm^{-1}): 3310 (N-H), 1280-1165 (C-O-C); 1611 (C=N); ^{1}H NMR (400 MH_Z, $CDCl_3$) ð (ppm): 2.66 (s, 2H, NH_2), 4.39 (s, 1H, NH), 6.93-8.40 (m, 8H, Ar-H), 3.66 (s, 3H, OCH_3); Elemental analysis: Calculated (%) for $C_{15}H_{14}N_4OS$: C, 60.40; H, 4.69; N, 18.79; Found: C, 60.49; H, 4.59; N, 18.85; MS: m/z 298.

2-Hydrazinyl-4-phenyl-6-(thiophen-2-yl)pyrimidine 4b:
Solid; (81%); IR (KBr) ν(cm^{-1}): 3310 (N-H), 1624 (C=N); ^{1}H NMR (400 MH_Z, $CDCl_3$) ð (ppm): 2.07 (s, 2H, NH_2), 4.41 (s, 1H, NH), 6.85-8.21 (m, 9H, Ar H); Elemental analysis: Calculated (%) for $C_{14}H_{12}N_4S$: C, 62.68; H, 4.47; N, 20.89; Found: C, 62.55; H, 4.49; N, 20.85; MS: m/z 268.

4-(4-Chlorophenyl)-2-hydrazinyl-6-(thiophen-2-yl)pyrimidine 4c:
Solid; (66%); IR (KBr) ν (cm^{-1}): 3325 (N-H), 754 (C-Cl), 1644 (C=N); ^{1}H NMR (400 MH_Z, $CDCl_3$) δ (ppm): 2.02 (s, 2H, NH_2), 4.43 (s, 1H, NH), 7.10-8.05 (m, 8H, Ar H); Elemental analysis: Calculated (%) for $C_{14}H_{11}ClN_4S$: C, 55.44; H, 3.63; N, 18.48; Found: C, 55.18; H, 3.57; N, 18.47; MS: m/z 303.

2-Chloro-3-[2-hydrazinyl-6-(thiophen-2-yl)pyrimidin-4-yl]quinoline 4d:
Solid; (64%); IR (KBr) ν(cm^{-1}): 3330 (N-H), 1630 (C=N); ^{1}H NMR (400 MH_Z, $CDCl_3$) δ(ppm): 2.27 (s, 2H, NH_2), 4.22 (s, 1H, NH), 7.01-8.08 (m, 9H, Ar H); Elemental analysis: Calculated (%) for $C_{17}H_{12}ClN_5S$: C, 57.62; H, 3.38; N, 19.77; Found: C, 57.36; H, 3.35; N, 19.67; MS: m/z 354.

2-Hydrazinyl-4-(4-phenoxyphenyl)-6-(thiophen-2-yl)pyrimidine 4e:
Solid; (70%); IR (KBr) ν (cm^{-1}): 3310 (N-H), 1617 (C=N); ^{1}H NMR (400 MH_Z, $CDCl_3$) δ(ppm): 2.35 (s, 2H, NH_2), 4.34 (s, 1H, NH), 7.12-8.45 (m, 13H, Ar H); Elemental analysis: Calculated (%) for $C_{20}H_{16}N_4OS$: C, 66.66; H, 4.44; N, 15.55; Found: C, 66.22; H, 4.40; N, 15.52; MS: m/z 360.

Preparation of 2-(4,5-Dihydro-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyrimidine 5a:
A mixture of compound 2-hydrazinyl-4-(4-methoxyphenyl)-6-(thiophen-2-yl) pyrimidine **4a** (2.98 g, 0.01 mol) and (2*E*)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one (2.14 g, 0.01 mol) in acetic acid (20 mL) is refluxed for 7 h. The reaction mixture is cooled and poured into crushed ice. The separated product is filtered, dried and recrystalised using ethanol. Similarly, the compounds **5b-e** are prepared.

2-(4,5-Dihydro-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)-4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyrimidine 5a:
Solid; (55%); IR (KBr) ν (cm^{-1}): 1030 (C-O-C), 2923 (CH); ^{1}H NMR (400 MH_Z, $CDCl_3$) δ (ppm): 2.19 (t, 1H, CH), 2.78 (d, 2H, CH_2), 6.92-7.94 (m, 16H, Ar H), 3.88 (s, 3H, OCH_3); Elemental analysis: Calculated (%) for $C_{28}H_{22}N_4OS_2$: C, 67.87; H, 4.44; N, 11.31; Found: C, 67.53; H, 4.59; N, 11.42; MS: m/z 495.

2-(4,5-Dihydro-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)-4-phenyl-6-(thiophen-2-yl) pyrimidine 5b:
Solid; (46%); IR (KBr) ν(cm^{-1}): 2890 (CH); ^{1}H NMR (400 MH_Z, $CDCl_3$) δ (ppm): 2.19 (t, 1H, CH), 2.78 (d, 2H, CH_2), 6.90-8.10 (m, 17H, Ar H); Elemental analysis: Calculated (%) for $C_{27}H_{20}N_4S_2$: C, 69.67; H, 4.30; N, 12.04; Found: C, 69.46; H, 4.32; N, 12.41; MS: m/z 465.

4-(4-Chlorophenyl)-2-(4,5-dihydro-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)-6-(thiophene-2-yl)pyrimidine 5c:
Solid; (69%); IR (KBr) ν(cm^{-1}): 790 (C-Cl), 2923 (CH); ^{1}H NMR (400 MH_Z, $CDCl_3$) δ(ppm): 2.19 (t, 1H, CH), 2.78 (d, 2H, CH_2), 6.81-7.85 (m, 16H, Ar H); Elemental analysis: Calculated (%) for $C_{27}H_{29}ClN_4S_2$: C, 64.92; H, 5.81; N, 11.22; Found: C, 64.75; H, 5.74; N, 11.20; MS: m/z 499.

2-Chloro-3-(2-(4,5-dihydro-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)-6-(thiophene-2-yl) pyrimidine-4-yl)quinoline 5d:
Solid; (64%); IR (KBr) ν(cm^{-1}): 787 (C-Cl), 1605 (C=N); ^{1}H NMR (400 MH_Z, $CDCl_3$) ð (ppm): 2.19 (t, 1H, CH), 2.78 (d, 2H, CH_2), 7.11-8.20 (m, 17H, Ar H); Elemental analysis: Calculated (%) for $C_{30}H_{20}ClN_5S_2$: C, 65.45; H, 3.63; N, 12.72; Found: C, 65.36; H, 3.35; N, 12.67; MS: m/z 550.

2-(4,5-Dihydro-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)-4-(4-phenoxyphenyl)-6-(thiophen-2-yl)pyrimidine 5e:
Solid; (68%); IR (KBr) ν (cm^{-1}): 1623 (C=N); ^{1}H NMR (400 MH_Z, $CDCl_3$) ð (ppm): 2.19 (t, 1H, CH), 2.78 (d, 2H, CH_2), 6.90-8.42 (m, 21H, Ar H); Elemental analysis: Calculated (%) for $C_{33}H_{24}N_4OS_2$: C, 71.09; H, 4.30; N, 10.05; Found: C, 71.22; H, 4.40; N, 10.52; MS: m/z 557.

Preparation of Ethyl-5-amino-1-[4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyrimidin-2-yl]-1H-pyrazole-4-carboxylate 6a:
A mixture of 2-hydrazinyl-4-(4-methoxyphenyl)-6-(thiophen-2-yl) pyrimidine **4a** (2.98 g, 0.01 mol) and ethyl (2*Z*)-2-cyano-3-ethoxyprop-2-enoate (1.7 g, 0.01 mol) in ethanol (15 mL) is refluxed for 6 h. The completion of the mixture is monitored by TLC. The excess of solvent is removed through distillation under reduced pressure and the reaction mixture was added to crushed ice with stirring. The product that separated is filtered, washed with water, dried and recrystalised from DMF. Similarly, the compounds **6b-e** are prepared.

Ethyl-5-amino-1-[4-(4-methoxyphenyl)-6-(thiophen-2-yl)pyrimidin-2-yl]-1*H*-pyrazole-4-carboxylate 6a:
Solid; (72%); IR (KBr) ν (cm^{-1}): 3309 (NH), 1090 (C-O-C), 1725 (C=O); ^{1}H NMR (500 MH_Z, $CDCl_3$) ð(ppm): 1.33 (t, 3H, CH_3), 4.32 (q, 2H, CH_2), 4.92 (s, 2H, NH_2), 7.19-7.95 (m, 9H, Ar H), 3.92 (s, 3H, OCH_3); Elemental analysis: Calculated (%) for $C_{20}H_{19}N_5O_3S$: C, 57.07; H, 4.51; N, 16.62; Found: C, 57.23; H, 4.59; N, 16.85; MS: m/z 421.

Ethyl-5-amino-1-[4-phenyl-6-(thiophen-2-yl)pyrimidin-2-yl]-1*H*-pyrazole-4-carboxylate 6b:
Solid; (61%); IR (KBr) ν (cm^{-1}): 3320 (NH), 1765 (C=O); ^{1}H NMR (500 MH_Z, $CDCl_3$) ð (ppm): 1.38 (t, 3H, CH_3), 4.30 (q, 2H, CH_2), 4.98 (s, 2H, NH_2), 6.94-7.90 (m, 10H, Ar H); Elemental analysis: Calculated (%) for $C_{20}H_{17}N_5O_2S$: C, 61.38; H, 4.34; N, 17.90; Found: C, 61.55; H, 4.49; N, 17.54; MS: m/z 391.

Ethyl-5-amino-1-[4-(4-chlorophenyl)-6-(thiophen-2-yl)pyrimidin-2-yl]-1*H*-pyrazole-4-carboxylate 6c:
Solid; (65%); IR (KBr) ν (cm^{-1}): 3295 (NH), 775 (C-Cl), 1760 (C=O); ^{1}H NMR (500 MH_Z, $CDCl_3$) ð (ppm): 1.30 (t, 3H, CH_3), 4.39 (q, 2H, CH_2), 5.02 (s, 2H, NH_2), 6.95-7.77 (m, 9H, Ar H); Elemental analysis: Calculated (%) for $C_{20}H_{16}ClN_5O_2S$: C, 56.33; H, 3.75; N, 16.43; Found: C, 56.18; H, 3.57; N, 16.44; MS: m/z 426.
Ethyl-5-amino-1-[4-(2-chloroquinolin-3-yl)-6-(thiophen-2-yl)pyrimidin-2-yl]-1*H*-pyrazole-4-carboxylate 6d:
Solid; (63%); IR (KBr) ν (cm^{-1}): 3270 (NH), 1750 (C=O); ^{1}H NMR (500 MH_Z, $CDCl_3$) ð(ppm): 1.36 (t, 3H, CH_3), 4.33 (q, 2H, CH_2), 4.95 (s, 2H, NH_2), 7.21-8.38 (m, 10H, Ar H), 3.78 (s, 3H,

OCH_3); Elemental analysis: Calculated (%) for $C_{23}H_{17}ClN_2O_2S$: C, 57.86; H, 3.56; N, 5.87; Found: C, 57.30; H, 3.34; N, 5.60; MS: m/z 477.

Ethyl-5-amino-1-(4-(4-phenoxyphenyl)-6-(thiophen-2-yl)pyrimidin-2-yl)-1*H*-pyrazole-4-carboxylate 6e:
Solid; (80%); IR (KBr) ν (cm^{-1}): 3180 (NH), 1775 (C=O); ^{1}H NMR (500 MH_Z, $CDCl_3$) ð (ppm): 1.39 (t, 3H, CH_3), 4.42 (q, 2H, CH_2), 4.83 (s, 2H, NH_2), 6.90-7.75 (m, 14H, Ar H); Elemental analysis: Calculated (%) for $C_{26}H_{21}N_5O_3S$: C, 64.59; H, 4.34; N, 14.49; Found: C, 64.22; H, 4.40; N, 14.52; MS: m/z 483.

Preparation of 7-(4-methoxyphenyl)-3-methyl-5-(thiophen-2-yl)[1,2,4]triazolo[4,3-*a*]pyrimidine 7a:
A mixture of 2-hydrazinyl-4-(4-methoxyphenyl)-6-(thiophen-2-yl) pyrimidine **4a** (2.98 g, 0.01 mol) and acetic anhydride 3 mL in catalytic amount of concentrated sulphuric acid is refluxed for 7 h. The completion of the mixture is monitored by TLC. The reaction mixture is added to crushed ice with stirring. The product that separated is filtered, washed with water, dried and recrystalised from DMF. Similarly, the compounds **7b-e** are prepared.

7-(4-Methoxyphenyl)-3-methyl-5-(thiophen-2-yl)[1,2,4]triazolo[4,3-*a*]pyrimidine 7a:
Solid; (64%); IR (KBr) ν (cm^{-1}): 1510(C=N), 1046 (C-O-C); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð (ppm): 2.33 (s, 3H, CH_3), 7.25-8.28 (m, 8H, Ar H), 3.87 (s, 3H, OCH_3); Elemental analysis: Calculated (%) for $C_{17}H_{14}N_4OS$: C, 63.35; H, 4.34; N, 17.39; Found: C, 63.20; H, 4.37; N, 17.28; MS: m/z 322.

3-Methyl-7-phenyl-5-(thiophen-2-yl)[1,2,4]triazolo[4,3-*a*]pyrimidine 7b:
Solid; (47%); IR (KBr) ν (cm^{-1}): 1605 (C=N); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð (ppm): 2.49 (s, 3H, CH_3), 7.73-9.05 (m, 9H, Ar H); Elemental analysis: Calculated (%) for $C_{18}H_{12}N_4S$: C, 73.97; H, 4.10; N, 19.17; Found: C, 73.93; H, 4.09; N, 19.19; MS: m/z 292.

7-(4-Chlorophenyl)-3-methyl-5-(thiophen-2-yl)[1,2,4]triazolo[4,3-*a*]pyrimidine 7c:
Solid; (53%); IR (KBr) ν (cm^{-1}): 1524 (C=N), 780 (C-Cl); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð(ppm): 2.88 (s, 3H, CH_3), 7.02-8.15 (m, 8H, Ar H); Elemental analysis: Calculated (%) for $C_{16}H_{11}ClN_4S$: C, 58.71; H, 3.36; N, 17.12; Found: C, 58.75; H, 3.39; N, 17.20; MS: m/z 327.

2-Chloro-3-[3-methyl-5-(thiophen-2-yl)[1,2,4]triazolo[4,3-*a*]pyrimidin-7-yl]quinoline 7d:
Solid; (42%); IR (KBr) ν (cm^{-1}): 1645 (C=N); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð (ppm): 2.33 (s, 3H, CH_3) 7.10-8.25 (m, 9H, Ar H); Elemental analysis: Calculated (%) for $C_{19}H_{12}ClN_5S$: C, 60.31; H, 3.17; N, 18.51; Found: C, 60.38; H, 3.50; N, 18.69; MS: m/z 378.

3-Methyl-7-(4-phenoxyphenyl)-5-(thiophen-2-yl)[1,2,4]triazolo[4,3-*a*]pyrimidine 7e:
Solid; (60%); IR (KBr) ν (cm^{-1}): 1620 (C=N); ^{1}H NMR (400 MH_Z, DMSO-D_6) ð (ppm): 2.62 (s, 3H, CH_3), 6.62-8.25 (m, 13H, Ar H); Elemental analysis: Calculated (%) for $C_{22}H_{16}N_4OS$: C, 68.75; H, 4.16; N, 14.58; Found: C, 68.73; H, 4.24; N, 14.50; MS: m/z 384.

Biological activities:

Antibacterial activity:

The antibacterial activity of selected synthesised compounds was studied by cup-plate method[xxi] and the results are compared with of standard antibiotics, Chloramphenicol using two Gram +ve organisms - *Staphylococcus aureus* and *Bacillus subtilis* and two Gram -ve organisms namely, *Escherichia coli* and *S. Paratyphi-A*. The compounds were tested at 40 μg/mL concentration. Some of the compounds were found to show potent activity against bacteria. The zone of inhibition was presented in table-1.

Antioxidant activity:

The antioxidant activity of selected synthesised compounds was tested by DPPH scavenging method[xxii]. DPPH 0.002% in methanol was used as the free radical. The optical density was measured at 517 nm using UV-Visible spectrophotometer. The absorbance of the DPPH control was also noted. The scavenging activity of the compounds against the stable DPPH was calculated using the equation: Scavenging activity (%) = (A – B) /A X 100, where 'A' was the absorbance of DPPH solution and 'B' was the absorbance of DPPH solution with compounds. The results were shown in table-2.

Table-1 Antibacterial activity of the synthesised compounds

Compound	Diameter of zone of inhibition (mm)			
	Staphylococcus aureus	***Escherichia coli***	***S. Paratyphi-A***	***Bacillus Subtilis***
5a	12	11	15	14
5b	15	13	17	20
5c	10	12	16	20
6a	13	15	15	18
6b	14	11	16	17
6c	11	12	18	18
7a	12	14	12	15
7b	16	15	17	19
7c	14	16	16	18
DMF	00	00	00	00
Chloramphenicol	24	20	20	24

Table-2 Antioxidant activity of synthesised compounds

Compound	Scavenging activity of different concentrations (µg/mL) of compounds %				
	25	**50**	**100**	**200**	**400**
5a	50.33	53.64	58.03	63.13	68.31
5b	51.13	53.11	57.77	62.50	66.36
5c	50.67	54.60	58.93	64.36	67.31
6a	53.40	57.30	60.13	66.90	70.23
6b	53.29	58.05	62.56	68.23	73.14
6c	54.08	58.78	63.37	67.30	71.58
7a	52.47	56.30	60.20	65.55	70.22
7b	53.76	56.73	61.43	66.90	71.67
7c	51.86	55.45	62.33	67.64	73.44
Ascorbic acid	80.30	82.19	88.04	93.70	96.11

Conclusion:
The research work is focussed on the synthesis of polynuclear pyrimidines with good yield and potent activity. The reactions performed are eco-friendly. The publication of these facts would be of significant use for the scientific community.

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