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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL COUMARIN ANALOGUES

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ABSTRACT: The desired target Compounds (4a-e), (5a-e) and (6a-e) were prepared in two steps. Reaction of 3-acetyl-6-bromo-2*H*-chromen-2-one (1) with 3-(Aryl)-1-phenyl-1H-pyrazole-4-carbaldehydes (2a-e) in presence of aqueous KOH solution and the reaction mixture stirred for 2 hours and then filtered, furnished the desired 6-bromo-3-((E)-3-(3-(Aryl)-1-phenyl- 1*H*-pyrazole-4-yl) acryloyl)- 2*H*-chromen-2- ones (3a-e) crystalline solids in 60-70% yield (Scheme-1). Further, compounds (3a-e) reaction with thiourea, urea and hydrazine hydrate in the presence of a base in EtOH yielded the compounds (4a-e), (5a-e) and (6a-e) in 50-85% yield. All the synthesized compounds have been characterized by spectral data's, and they are screened for anti-microbial activity. Among synthesized compounds 3b, 3c, 3d, 5a, and 5d exhibited good activity against bacterial strains *S. aureus*, *P. aeruginosa*, and *E. coli*, respectively. Whereas other compounds showed poor to moderate activity against all bacterial strains and compounds 3a, 3b, 3d, 4c, 5d, and 5c exhibited good antifungal activity against *A. niger*, and *A. flavus* and remaining compounds exhibited moderate antifungal activity. Results were tabulated in Table 2.

INTRODUCTION: A variety of coumarin derivatives with diverse substituents at C-4 have been found to exhibit anticoagulant, [1] cytochrome 450 inhibiting, [2] antimicrobial and antitumour [3] activities. And also pyrimidines are well known nitrogen-containing six-membered heterocyclic compounds found to possess considerable biological activities, such as, antimycobacterial [4], antimicrobial [5], analgesic, antitumor [6] and antiviral activities.

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In addition pyrazole derivatives have a broad spectrum of biological activities being used as antipyretic, antidepressant against rheumatoid arthritis, antibacterial [8, 9], anticonvulsant, [10] antifilarial agents, [11] herbicides, [12, 13] fungicides, pesticides, insecticides, anticancer agents [14] and dyestuffs in sunscreen materials. In view of above potent pharmacological activity, we became interested in synthesis and antimicrobial activity of 6- bromo- 3-((E)-3-(3-(Aryl)-1-phenyl-*1H*-pyrazol-4-yl)acryloyl)- *2H*- chromen- 2- ones (3a-e), 6-bromo-3- (1,2,5,6-tetrahydro-6-(3-(Aryl)-1-phenyl-*1H*-pyrazol-4-yl)- 2- thioxopyrimidin- 4- yl)- *2H*-chhromen-2-ones (4a-e), 4- (6-bromo-2-oxo-*2H*-chromen-3-yl)-5, 6- dihydro-6- (3-(Aryl)-1-phenyl-*1H*-pyrazol-4-yl) pyrimidin-2(*1H*)-ones (5a-e) and 6-bromo-3- (4, 5-dihydro-5-(3-(Aryl)-1-phenyl-*1H*-

pyrazol-4-yl)- *1H*- pyrazol-3-yl)- *2H*- chromen- 2-ones (6a-e).

MATERIAL AND METHODS: Melting points were recorded by using Thomas-Hoover melting point apparatus and were uncorrected. IR spectra in KBr disc were recorded on Perkin-Elmer-Spectrum-one FTIR spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR in DMSO-d_6 and $CDCl_3$ on amx 400 MHz spectrophotometer using TMS as an internal standard. Mass spectra were recorded on a JEOL SX 102 Mass spectrometer using Argon/Xenon (6kv, 10 mA) as the FAB gas. The purity of the compounds was checked by TLC using silica gel 'G' plates obtained from Whatman Inc, and a fluorescent indicator. Elemental analysis was carried out on a Carlo Erba 1108 analyzer. 3-aryl-1-phenyl- *1H*- pyrazole- 4- carbaldehydes were prepared by known literature method [20].

Experimental:

Preparation of 6-bromo-3-((E)-3-(3-(Aryl)-1-phenyl-*1H*-pyrazol-4-yl) acryloyl)- 2*H*-chromen-2-ones (3a-e): 3-Acetyl-6-bromo-2*H*-chromen-2-one (1) (0.01 mol) and 1,3-diphenyl-1H-pyrazole-4-carbaldehydes (2a-e) (0.01 mol) in absolute alcohol (30 ml) added 5 ml of 10% potassium hydroxide with constant shaking maintaining a temperature of 5-10 ºC. The mixture was stirred for 2 hours at room temperature and kept overnight. The solid separated was collected by filtration and crystallized from ethanol gave the desired 6-bromo-3-((E)-3-(3-(Aryl)- 1- phenyl- 1*H*- pyrazol-4 - yl) acryloyl)-2*H*-chromen-2-ones (3a-e).

6-Bromo-3-((E)-3-(1,3-diphenyl- *1H*- pyrazol- 4-yl)acryloyl)-*2H*-chromen-2-one (3a): IR (KBr): 1681, ^1H NMR (DMSO-d6, δ in ppm): δ 10.0 (s, 1H, C_4H), 8.4 (s, 1H, C_5H of pyrazole), 7.8-7.2 (m, 13H ArH, 2H C=CH). Mass (m/z): 496 (M^+, 100%). Elemental analysis: Calcd for $C_{27}H_{17}BrN_2O_3$: C, 65.20; H, 3.45; N, 5.63. Found: C, 65.18; H, 3.42; N, 5.61.

6-Bromo-3-((E)-3-(3-(4-nitrophenyl)- 1- phenyl-*1H*-pyrazol-4-yl) acryloyl)- *2H*-chromen-2-one (3b): IR (KBr): 1691, ^1H NMR (DMSO-d6, δ in ppm): δ 10.1 (s, 1H, C_4H), 8.6 (s, 1H, C_5H of pyrazole), 8.4-7.2 (m, 12H ArH, 2H C=CH). Mass (m/z): 541 (M^+, 10%). Elemental analysis: Calcd for $C_{27}H_{16}BrN_3O_5$: C, 59.79; H, 2.97; N, 7.75. Found: C, 59.77; H, 2.95; N, 7.72.

6- Bromo- 3- ((E)-3- (3- (4- methoxyphenyl)- 1-phenyl-*1H*-pyrazol-4-yl)acryloyl)- *2H*- chromen-2-one (3c): IR (KBr): 1681, ^1H NMR (DMSO-d6, δ in ppm): δ 10.1 (s, 1H, C_4H), 8.6 (s, 1H, C_5H of pyrazole), 7.8-7.0 (m, 12H ArH, 2H C=CH), 3.8 (s, 3H, OCH_3). Mass (m/z): 526 (M^+, 100%). Elemental analysis: Calcd for $C_{28}H_{19}BrN_2O_4$: C, 63.77; H, 3.63; N, 5.31. Found: C, 63.75; H, 3.61; N, 5.29.

6- Bromo- 3- ((E)- 3- (1- phenyl- 3-p-tolyl-*1H*-pyrazol-4-yl)acryloyl)-*2H*-chromen- 2- one (3d): IR (KBr): 1680, ^1H NMR (DMSO-d6, δ in ppm): δ 10.0 (s, 1H, C_4H), 8.6 (s, 1H, C_5H of pyrazole), 7.8-7.2 (m, 12H ArH, 2H C=CH), 2.4 (s, 3H, CH_3). Elemental analysis: Calcd for $C_{28}H_{19}BrN_2O_3$: C, 65.76; H, 3.75; N, 5.48. Found: C, 65.74; H, 3.72; N, 5.46.

3- ((E)-3- (3- (4-aminophenyl)- 1- phenyl- *1H*-pyrazol-4-yl)acryloyl)-6-bromo-*2H*- chromen- 2-one (3e): IR (KBr): 1736, ^1H NMR (DMSO-d6, δ in ppm): δ 10.0 (s, 1H, C_4H), 8.5 (s, 1H, C_5H of pyrazole), 7.8-7.2 (m, 12H ArH, 2H C=CH, 2H NH). Mass (m/z): 512 (M^+, 5%). Elemental analysis: Calcd for $C_{27}H_{18}BrN_3O_3$: C, 63.29; H, 3.54; N, 8.20. Found: C, 63.26; H, 3.50; N, 8.18.

Preparation of compounds (4a-e) and (5a-e): 6-Bromo-3-((E)-3-(3-(Aryl)-1-phenyl-*1H*-pyrazol-4-yl)acryloyl)-*2H*-chromen-2-ones (3a-e) (0.01 mol) was refluxed with thiourea or urea (0.01 mol) in presence of sodium hydroxide (0.04 mol) in ethanol was refluxed for 15 h, then concentrated and cooled. The separated solid was filtered, washed with water and recrystallised from ethanol yielded the 6-bromo- 3- (1,2,5,6-tetrahydro-6-(3-(Aryl)-1-phenyl-*1H*-pyrazol-4-yl)- 2- thioxopyrimidin-4-yl)-*2H*-chhromen-2-ones (4a-e) or 4-(6-bromo-2-oxo-*2H*-chromen-3-yl)-5, 6- dihydro- 6- (3- (Aryl)-1-phenyl-*1H*-pyrazol-4-yl)pyrimidin-2(*1H*)-ones (5a-e) in 50-85% yield.

6- Bromo- 3-(1,2,5,6-tetrahydro-6-(1,3-diphenyl-*1H*- pyrazol-4-yl)- 2-thioxopyrimidin-4-yl)- *2H*-chromen-2-one (4a): IR (KBr): 3225, 1772, ^1H NMR (DMSO-d6, δ in ppm): δ 12.2 (s, 1H, NH), 8.8 (s, 1H, C_4H), 8.2 (s, 1H, C_5H of pyrazole), 7.8-7.0 (m, 13H, ArH). 6.4 (s, 1H, CH), 4.2 (s, 2H, CH_2). Mass (m/z): 554 (M^+, 10%). Elemental analysis: Calcd for $C_{28}H_{19}BrN_4O_2S$: C, 60.55; H, 3.45; N, 10.09. Found: C, 60.55; H, 3.45; N, 10.09.

6- Bromo- 3- (1, 2, 5, 6- tetrahydro-6-(3-(4-nitro-phenyl)- 1- phenyl- *1H*- pyrazol-4-yl)- 2-thioxo-pyrimidin-4-yl)- *2H*- chromen-2-one (4b): IR (KBr): 3126, 1681, ^{1}H NMR (DMSO-d6, δ in ppm): δ 10 (s, 1H, NH), 9.2 (s, 1H, C_4H), 8.5 (s, 1H, C_5H of pyrazole), 8.0-7.4 (m, 12H, ArH), 7.2 (s, 1H, CH), 2.5 (s, 2H, CH_2). Elemental analysis: Calcd for $C_{28}H_{18}BrN_5O_4S$: C, 56.01; H, 3.02; N, 11.66. Found: C, 55.01; H, 3.01; N, 11.62.

6-Bromo-3- (1,2,5,6-tetrahydro-6-(3-(4-methoxy-phenyl)- 1- phenyl- *1H*- pyrazol- 4-yl)- 2-thioxo-pyrimidin-4-yl)- *2H*- chromen-2- one (4c): IR (KBr): 3124, 1674, ^{1}H NMR (DMSO-d6, δ in ppm): δ 10 (s, 1H, NH), 8.6 (s, 1H, C_4H), 7.8 (s, 1H, C_5H of pyrazole), 7.6-7.2 (m, 12H, ArH), 7.0 (s, 1H, CH), 3.8 (s, 3H, OCH_3), 2.2 (s, 2H, CH_2). Elemental analysis: Calcd for $C_{29}H_{21}BrN_4O_3S$: C, 59.49; H, 3.62; N, 9.57. Found: C, 59.46; H, 3.60; N, 9.55.

6-Bromo-3- (1,2,5,6-tetrahydro-6- (1-phenyl-3-p-tolyl- *1H*-pyrazol-4-yl)- 2-thioxopyrimidin-4-yl)- *2H*-chromen-2-one (4d): IR (KBr): 3321, 1699, ^{1}H NMR (DMSO-d6, δ in ppm): δ 10 (s, 1H, NH), 9.4 (s, 1H, C_4H), 8.0 (s, 1H, C_5H of pyrazole), 7.6-7.4 (m, 12H, ArH, 1H, CH), 3.4 (s, 3H, OCH_3), 2.5 (s, 3H, CH_3), 2.2 (s, 2H, CH_2). Mass (m/z): 568 (M^+, 10%). Elemental analysis: Calcd for $C_{29}H_{21}BrN_4O_2S$: C, 61.16; H, 3.72; N, 9.84. Found: C, 61.14; H, 3.70; N, 9.81.

3-(6-(3-(4-Aminophenyl)- 1-phenyl- *1H*-pyrazol-4-yl)-1,2,5,6-tetrahydro-2-thioxopyrimidin-4-yl)-6-bromo-*2H*-chromen-2-one (4e): IR (KBr): 3298, 1699, ^{1}H NMR (DMSO-d6, δ in ppm): δ 10.4 (s, 1H, NH), 9.8 (s, 1H, C_4H), 9.4 (s, 1H, C_5H of pyrazole), 7.8-7.4 (m, 12H, ArH), 7.0 (s, 1H, CH), 4.0 (d, 2H, NH), 2.5 (s, 2H, CH_2). Elemental analysis: Calcd for $C_{28}H_{20}BrN_5O_2S$: C, 58.95; H, 3.53; N, 12.28. Found: C, 58.92; H, 3.50; N, 12.25.

4- (6-Bromo- 2-oxo- *2H*-chromen- 3- yl)- 5, 6-dihydro-6-(1,3-diphenyl-*1H*-pyrazol-4-yl) pyrimi din-2(*1H*)-one (5a): IR (KBr): 3107, 1624, ^{1}H NMR (DMSO-d6, δ in ppm): δ 10.0 (s, 1H, NH), 9.4 (s, 1H, C_4H), 8.0 (s, 1H, C_5H of pyrazole), 7.8-7.2 (m, 13H, ArH), 7.0 (s, 1H, CH), 2.5 (s, 2H, CH_2). Mass (m/z): 538 (M^+, 10%). Elemental analysis: Calcd for $C_{28}H_{19}BrN_4O_3$: C, 62.35; H, 3.55; N, 10.39. Found: C, 62.35; H, 3.55; N, 10.39.

4- (6- Bromo-2-oxo-*2H*-chromen-3- yl)-5, 6- dihydro- 6- (3- (4- nitrophenyl)-1-phenyl-*1H*-pyrazol-4-yl) pyrimidin-2(*1H*)-one (5b): IR (KBr): 3045, 1624, ^{1}H NMR (DMSO-d6, δ in ppm): δ 10.4 (s, 1H, NH), 9.6 (s, 1H, C_4H), 9.2 (s, 1H, C_5H of pyrazole), 8.0-7.2 (m, 12H, ArH), 7.0 (s, 1H, CH), 2.5 (s, 2H, CH_2). Elemental analysis: Calcd for $C_{28}H_{19}BrN_4O_3$: C, 57.55; H, 3.10; N, 11.98. Found: C, 57.52; H, 3.08; N, 11.95.

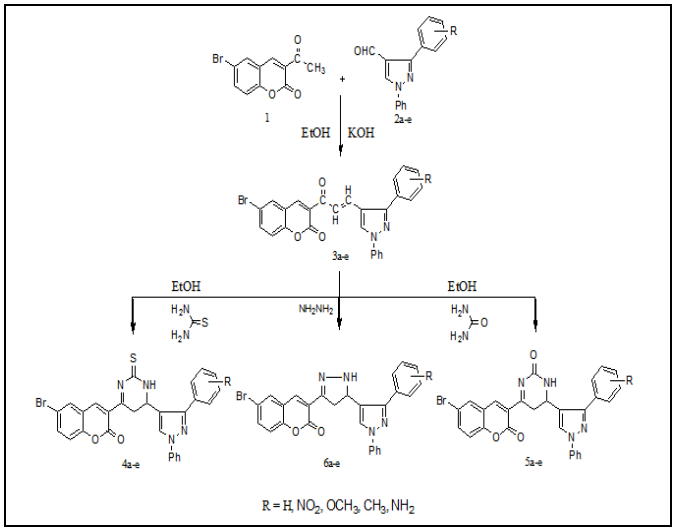
4- (6- Bromo- 2-oxo- *2H*- chromen- 3- yl)- 5, 6-dihydro- 6-(3-(4-methoxyphenyl)- 1- phenyl- *1H*-pyrazol-4-yl)pyrimidin-2(*1H*)-one (5c): IR (KBr): 2920, 1624, ^{1}H NMR (DMSO-d6, δ in ppm): δ 10.0 (s, 1H, NH), 9.4 (s, 1H, C_4H), 8.0 (s, 1H, C_5H of pyrazole), 7.8-7.5 (m, 12H, ArH, 1H, CH), 3.4 (s, 3H, OCH_3), 2.5 (s, 2H, CH_2). Elemental analysis: Calcd for $C_{29}H_{21}BrN_4O_4$: C, 61.17; H, 3.72; N, 9.84. Found: C, 61.15; H, 3.70; N, 9.80.

4- (6- Bromo- 2- oxo- *2H*- chromen- 3- yl)- 5, 6-dihydro- 6- (1-phenyl-3-p-tolyl-*1H*-pyrazol-4-yl) pyrimidin-2(*1H*)-one (5d): ^{1}H NMR (DMSO-d6, δ in ppm): δ 11.8 (s, 1H, NH), 9.2 (s, 1H, C_4H), 8.8 (s, 1H, C_5H of pyrazole), 8.2-7.4 (m, 12H, ArH, 1H, CH), 3.5 (s, 3H, CH_3), 2.5 (s, 2H, CH_2). Mass (m/z): 552 (M^+, 10%). Elemental analysis: Calcd for $C_{29}H_{21}BrN_4O_4$: C, 62.94; H, 3.82; N, 10.12. Found: C, 62.91; H, 3.80; N, 10.10.

6- (3-(4-Aminophenyl)- 1- phenyl-*1H*-pyrazol-4-yl)- 4- (6-bromo-2-oxo-*2H*-chromen-3-yl)- 5, 6-dihydropyrimidin- 2(*1H*)-one (5e): ^{1}H NMR (DMSO-d6, δ in ppm): δ 10.4 (s, 1H, NH), 9.8 (s, 1H, C_4H), 9.2 (s, 1H, C_5H of pyrazole), 8.5-6.5 (m, 12H, ArH, 1H, CH , 2H, NH), 2.5 (s, 2H, CH_2). Elemental analysis: Calcd for $C_{28}H_{20}BrN_5O_3$: C, 60.66; H, 3.64; N, 12.63. Found: C, 60.63; H, 3.62; N, 12.60.

Preparation of 6-bromo-3-(4, 5-dihydro-5-(3-(Aryl)-1-phenyl-*1H*-pyrazol-4-yl)-*1H*-pyrazol-3-yl)-*2H*-chromen-2-ones (6a-e): Reaction of compounds (3a-e) (0.01 mol) with hydrazine hydrate (0.01 mol) in ethanol (30 ml). The reaction mixture was refluxed for 5 h and then concentrated and cooled.

The solid separated was filtered, washed several times with water and recrytallised from ethanol yielded the desired compounds (6a-e).



SCHEME 1

6-Bromo-3-(4, 5-dihydro-5-(1, 3-diphenyl-*1H*-pyrazol-4-yl)- *1H*-pyrazol-3-yl)- *2H*-chromen- 2-one (6a): IR (KBr): 3121, 1661, ^{1}H NMR (DMSO-d6, δ in ppm): δ 9.4 (s, 1H, NH), 9.2 (s, 1H, C_4H), 8.8 (s, 1H, C_5H of pyrazole), 8.0-7.2 (m, 12H, ArH, 1H, CH), 2.5 (s, 2H, CH_2). Mass (m/z): 510 (M^+, 10%). Elemental analysis: Calcd for $C_{27}H_{19}BrN_4O_2$: C, 63.42; H, 3.75; N, 10.96. Found: C, 63.40; H, 3.72; N, 10.91.

6-Bromo-3-(4, 5-dihydro-5- (3- (4-nitrophenyl)-1-phenyl-*1H*-pyrazol-4-yl)-*1H*-pyrazol-3-yl)-*2H*-chromen-2-one (6b): IR (KBr): 3128, 1691, ^{1}H NMR (DMSO-d6, δ in ppm): δ 10.2 (s, 1H, NH), 8.4 (s, 1H, C_4H), 8.0 (s, 1H, C_5H of pyrazole), 7.5-7.0 (m, 12H, ArH, 1H, CH), 2.5 (s, 2H, CH_2). Elemental analysis: Calcd for $C_{27}H_{18}BrN_5O_4$: C, 58.29; H, 3.26; N, 12.59. Found: C, 58.27; H, 3.22; N, 12.56.

6- Bromo- 3- (4, 5-dihydro-5- (3- (4- methoxy-phenyl)-1-phenyl-*1H*-pyrazol-4-yl)-*1H*-pyrazol-3-yl)-*2H*-chromen-2-one (6c): IR (KBr): 3203, 1637, ^{1}H NMR (DMSO-d6, δ in ppm): δ 9.0 (s, 1H, NH), 8.4 (s, 1H, C_4H), 8.0 (s, 1H, C_5H of pyrazole), 7.5-7.0 (m, 12H, ArH, 1H, CH), 3.5 (s, 3H, OCH_3), 2.5 (s, 2H, CH_2). Mass (m/z): 540 (M^+, 10%). Elemental analysis: Calcd for $C_{28}H_{21}BrN_4O_3$: C, 62.12; H, 3.91; N, 10.35. Found: C, 62.10; H, 3.88; N, 10.30.

6- Bromo-3- (4, 5-dihydro-5-(1-phenyl-3-p-tolyl-*1H*-pyrazol-4-yl)-*1H*-pyrazol-3-yl)-*2H*-chromen-2-one (6d): IR (KBr): 3367, 1861, ^{1}H NMR (DMSO-d6, δ in ppm): δ 11.0 (s, 1H, NH), 9.0 (s, 1H, C_4H), 8.8 (s, 1H, C_5H of pyrazole), 8.4-7.0 (m, 12H, ArH, 1H, CH), 3.4 (s, 3H, CH_3), 2.5 (s, 2H, CH_2). Mass (m/z): 524 (M^+, 10%). Elemental analysis: Calcd for $C_{28}H_{21}BrN_4O_2$: C, 64.01; H, 4.03; N, 10.66. Found: C, 63.01; H, 4.01; N, 10.63.

3- (5- (3-(4-Aminophenyl)-1-phenyl-*1H*-pyrazol-4-yl)-4,5-dihydro-*1H*-pyrazol-3-yl)-6-bromo-*2H*-chromen-2-one (6e): IR (KBr): 3207, ^{1}H NMR (DMSO-d6, δ in ppm): δ 10.5 (s, 1H, NH), 9.2 (s, 1H, C_4H), 8.6 (s, 1H, C_5H of pyrazole), 8.4-7.0 (m, 12H, ArH, 1H, CH), 3.2 (s, 3H, CH_3), 2.5 (s, 2H, CH_2). Mass (m/z): 525 (M^+, 10%). Elemental analysis: Calcd for $C_{27}H_{20}BrN_5O_2$: C, 61.61; H, 3.83; N, 13.30. Found: C, 61.59; H, 3.80; N, 13.28.

RESULT AND DISCUSSION: The desired target compounds (4a-e), (5a-e) and (6a-e) were prepared in two steps. Reaction of 3-acetyl-6-bromo-2*H*-chromen-2-one (1) with 3-(Aryl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes (2a-e) in presence of aqueous KOH solution and the reaction mixture was stirred for 2 hours and then filtered, furnished the desired 6-bromo-3-((E)-3-(3-(Aryl)-1-phenyl-1*H*-pyrazole-4-yl) acryloyl)- 2*H*- chromen- 2- ones (3a-e) crystalline solids in 60-80% yield (Scheme-1). Its IR spectrum confirmed the formation of compound 3a shows absorption at 1681 cm^{-1} due to C=O. Further compound 3a was confirmed by ^{1}H NMR spectrum shows signals at δ 10.0 (s, 1H, C_4H), 8.4 (s, 1H, C_5H of pyrazole), 7.8-7.2 (m, 13H, ArH, 2H, C=CH). The molecular ion peak of compound 3a was observed at (m/z): 496 (M^+, 100%) in its mass spectrum. Further, compounds (3a-e) reaction with thiourea, urea and hydrazine hydrate in the presence of a base in EtOH yielded the compounds (4a-e), (5a-e) and (6a-e) in 50-85% yield. Its IR spectrum confirmed the formation of compound 4a shows absorption at 3225, 1772 cm^{-1} due to NH and C=O. Further, compound 4a was confirmed by ^{1}H NMR spectrum shows signals at ^{1}H NMR (DMSO-d6, δ in ppm): δ 12.2 (s, 1H, NH), 8.8 (s, 1H, C_4H), 8.2 (s, 1H, C_5H of pyrazole), 7.8-7.0 (m, 13H, ArH). 6.4 (s, 1H, CH), 4.2 (s, 2H, CH_2). The molecular ion peak of compound 4a was observed at m/z = 554 (M^+, 10%) in its mass spectrum. Formation of compound 5a was confirmed by its IR spectrum shows absorption at 3107 and 1624 cm^{-1} due to the presence of NH, C=O stretching.

TABLE 1: PHYSICAL CONSTANT AND YIELD OF THE SYNTHESIZED COMPOUNDS

Compound no.	R	Yield (%)	M.P. (ºC)
3a	H	60	148-150
3b	OCH_3	70	124-126
3c	NO_2	55	118-120
3d	CH_3	60	140-142
3e	NH_2	65	150-152
4a	H	75	230-232
4b	OCH_3	70	218-220
4c	NO_2	60	234-236
4d	CH_3	65	248-250
4e	NH_2	55	260-262
5a	H	50	230-233
5b	OCH_3	80	250-253
5c	NO_2	65	266-268
5d	CH_3	50	184-187
5e	NH_2	60	258-261
6a	H	70	290-292
6b	OCH_3	55	255-257
6c	NO_2	60	282-285
6d	CH_3	85	238-240
6e	NH_2	50	244-247

Further, compound 5a was confirmed by ^{1}H NMR spectrum shows signals at δ 10.0 (s, 1H, NH), 9.4 (s, 1H, C_4H), 8.0 (s, 1H, C_5H of pyrazole), 7.8-7.2 (m, 13H, ArH), 7.0 (s, 1H, CH), 2.5 (s, 2H, CH_2). The molecular ion peak of compound 5a was observed at m/z = 538 (M^+, 10%) in its mass spectrum. Its IR spectrum confirmed the formation of compound 6a shows absorption at 3121 and 1661 cm^{-1} due to the presence of NH and C=O stretching. Further, compound 6a was confirmed by ^{1}H NMR spectrum shows signals at δ 9.4 (s, 1H, NH), 9.2 (s, 1H, C_4H), 8.8 (s, 1H, C_5H of pyrazole), 8.0-7.2 (m, 12H, ArH, 1H, CH), 2.5 (s, 2H, CH_2). The molecular ion peak of compound 6a was observed at m/z = 510 (M^+, 10%) in its mass spectrum. Physical constants and yield of all the synthesized compounds are tabulated in **Table 1**.

Antimicrobial Activity: The antimicrobial activities were performed by the cup plate method. The synthesized compounds, gentamycin and fluconazole was dissolved in DMF at the concentration of 1000 µg/ml. Antibacterial activity screened against, *S. aureus*, *E-coli a*nd, *P. aeruginosa.* Antifungal activity was carried out against *A. niger* and *A. flavus* under aseptic conditions. Gentamycin and fluconazole were used as a standard drug for antibacterial and antifungal activities. The zone of inhibition was compared with standard drug after 24 h of incubation at 25 ºC for antibacterial activity and 48 hours at 30 ºC for antifungal activity. Among synthesized compounds 3b, 3c, 3d, 5a, and 5d exhibited good activity against bacterial strains *S. aureus*, *P. aeruginosa* and *E. coli*, respectively. Whereas other compounds showed poor to moderate activity against all bacterial strains and 3a, 3b, 3d, 4c 5d, and 5c exhibited good antifungal activity against *A. niger* and *A. flavus* and remaining compounds exhibited moderate antifungal activity. Results were tabulated in **Table 2**.

TABLE 2: ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Compound no.	Dose (µg/ml)	Antibacterial Activity			Antifungal Activity	
		Zone of Inhibition (mm)			Zone of Inhibition (mm)	
		S. aureus	*E. coli*	*P. aeruginosa*	*A. niger*	*A. flavus*
3a	1000	12	10	16	13	10
3b	1000	14	09	12	16	13
3c	1000	18	15	10	08	12
3d	1000	20	12	08	10	18
3e	1000	12	12	12	12	13
4a	1000	12	06	12	10	06
4b	1000	08	12	10	12	12
4c	1000	06	10	06	06	14
4d	1000	14	12	14	08	10
4e	1000	16	10	16	06	06
5a	1000	12	14	10	12	10
5b	1000	10	10	12	10	12
5c	1000	06	08	14	10	14
5d	1000	08	14	18	14	10
5e	1000	08	10	14	16	08
6a	1000	14	08	06	12	06
6b	1000	10	16	10	06	10
6c	1000	12	12	08	12	12
6d	1000	10	08	10	08	08
6e	1000	08	12	08	10	12
Control (DMF)	-	-	-	-	-	-
Standard	1000	16	14	18	14	15

CONCLUSION: Among synthesized compounds 3b, 3c, 3d, 5a, and 5d exhibited good activity against bacterial strains *S. aureus*, *P. aeruginosa* and *E. coli*, respectively. Whereas other compounds showed poor to moderate activity against all bacterial strains and compounds 3a, 3b, 3d, 4c, 5d, and 5c exhibited good antifungal activity against *A. niger*, and *A. flavus* and remaining compounds exhibited moderate antifungal activity.

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REFERENCES:

1. Koshihara NT and Murota Y: Inhibitory effect of esculetin on 5-lipoxygenase and leukotriene. Biochem Biophys Acta 1983; 753: 130-132.
2. Fylaktakidou KC, Hadjipavlou-Litina D, Litinas KE and Nicolaides DN: Natural and synthetic coumarin derivatives with anti-inflammatory/antioxidant activities. Curr Pharm Design 2004; 10: 3813-33.
3. Rao S, Aoyama R, Schrag M, Trager WF, Rettie A and Jones JP: A Refined 3-Dimensional QSAR of Cytochrome P450 2C9: Computational Predictions of Drug Interactions. J Med Chem 2000; 43: 2789-2796.
4. Kumar A, Sinha S and Chauhan MS: Synthesis and anti-angiogenic activity of 6-(1,2,4-Thiadiazol-5-yl)-3-amino. Bioorg Med Chem Lett 2002; 12: 667-669.
5. Kumar N, Singh G and Yadav AK: Synthesis of some new pyrido[2,3-d]pyrimidines and their ribofuranosides as possible antimicrobial agents. Heteroatom Chem 2001; 12: 52-56.
6. Sondhi SM, Johar M, Rajvanshi S, Dastidar SG, Shukla R, Raghubir R and Lown JW: Anticancer, anti-inflammatory and analgesic activity evaluation of heterocyclic compounds synthesized by the reaction of 4-Isothicyanato-4- methylpentan-2-one with substituted o-Phenylenediamine, oDiaminopyridine and (un)substituted o-Diaminopyrimidines. Aust J Chem 2001; 54: 69-74.
7. Nasr MN and Gineinah MM: Pyrido[2, 3-d]pyrimidines and pyrimido[5',4':5, 6]pyrido[2, 3-d]pyrimidines as new antiviral agents: synthesis and biological activity. Arch Pharm 2002; 335: 289-235.
8. Genin MJ, Biles C, Keiser BJ, Poppe SM, Swaney SM, Tarpley WG, Yagi Y and Romero DL: Novel 1,5-diphenylpyrazole nonnucleoside HIV-1 reverse transcriptase inhibitors with enhanced activity versus the delavirdine-resistant P236L mutant: lead identification and SAR of 3- and 4-substituted derivatives. J Med Chem 2000; 43: 1034-40.
9. Chauhan PMS, Singh S and Chatterjee RK: synthesis and *in-vitro* antimicrobial studies of some new pyrazolones. Indian J Chem 1993; 32: 858.
10. Natsume B, Kyomura N, Kikutake K and Fukuch T: An efficient catalyst for the synthesis of 1,3,5-trisubstituted Pyrazoles. Eur Pat Appl EP 1992; 116: 128.
11. Londershausen M: Review: approaches to new parasiticides. Pestic Sci 1996; 48: 269-407.
12. Garcia H, Iborra S, Miranda MA and Morera IM: Primo: Zinc mediated reduction of bromohydrins in azetidinones and penems. Application to the synthesis of FCE 22891. J. heterocycles 1991; 32: 1671-1679.
13. Uzoukwu AB: 4-[(Z)-(2-Furyl)(2-naphthylamino) methylene)]-3-methyl-1-phenyl-1 H -pyrazol-5(4 H)- one. Polyhedron 1993; 12: 2719-2724.
14. Daidone G, Maggio B, Plescia S, Raffa D, Musiu C, Milia C, Perra G and Marongiu ME: Synthesis of 3-amino 1H-pyrazoles catalyzed by p-toluene sulphonic acid using polyethylene glycol-400 as an efficient and recyclable reaction medium. Eur J Med Chem 1998; 33: 375.
15. Reddy Gj, Latha D and Rao KS: Synthesis of some new Ethyl-4-(1, 3- Diarylpyrazol-4-yl)-6-Methyl-2- thioxo-1, 3, 4-trihydropyrimidine- 5- carboxylates Heterocyclic Communications 2004; 10: 331.

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