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RESEARCH ARTICLE

DESIGN, SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL PYRAZOLYL-DIHYDROPYRIMIDINONES

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ABSTRACT

A series of new pyrazolyl-dihydropyrimidinones 4(a-g) have been synthesized from 3,5-dimethyl-1-aryl-1*H*-4-pyrazolecarbaldehyde 3(a-g). The structures of the synthesized compounds have been confirmed *via* IR, ^{1}H NMR, ^{13}C NMR and MS spectral analyses. Further, all the synthesized new compounds 4(a-g) have been assayed for their antibacterial activity against Gram-positive bacteria *viz*. *Bacillus subtilis*, *Bacillus sphaericus* and *Staphylococcus aureus*, and Gram-negative bacteria *viz*. *Pseudomonas aeruginosa*, *Klobsinella aerogenes* and *Chromobacterium violaceum.* The antibacterial screening data reveal that, compounds 4 which contain 3-flourophenyl (4c), 4-chlorophenyl (4d) and benzyl (4g) moieties on pyrazole ring might be the reason for the significant inhibitory activity. Most of these new compounds showed appreciable activity against test bacteria and emerged as potential molecules for further development.

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INTRODUCTION

Dihydro-2(1*H*)-pyrimidinone esters (DHPMs) represents a heterocyclic system of remarkable pharmacological efficiency (Kappe, 2000). In the last few decades, DHPMs containing natural and non natural compounds gained importance due to their antiviral activity such as Nitracin (i) (Hurst, 1961) antitumor, antibacterial and anti-inflammatory activities has been ascribed to these partly reduced pyrimidine derivatives (Kappe, 2000). Further, appropriately functionalized derivatives have emerged as potent calcium channel modulators (e.g. ii) (Atwal, 1990, George, 1995), orally active antihypertensive agents (e.g. SQ32926, iii) (Karnail, 1991, Grover, 1995), α-1a-adrenoreceptor-selective antagonists (e.g. iv) (James, 2000), anticancer (e.g. Monastrol, v) (Stephen, 2000), neuropeptide Y (NPY) antagonists (Mayer, 1991). Several marine alkaloids containing the DHPMs unit have shown interesting biological properties (Larry, 1995, Snider 1993). Most notably among them are batzelladine alkaloids, which were found to be potent HIVgp-120-CD_4 inhibitors (Snider, 1996) (Fig. 1). The classes of pyrazole and its derivatives possess a broad spectrum of biological effectiveness such as antiviral (Sabbagh, 2009), antibacterial (Yu, 2015, Liu, 2014), antidepressants (Gamal, 2009), inhibitors of protein kinases (Persson, 2007), anticancer (Balbi, 2011), antiarthritic (Nugent, 1993), and herbicidal (Kudo, 1999). Some aryl pyrazoles (Mohd, 2016) were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitors (Genin, 2000), COX-2 inhibitors (Habeeb, 2001, Hashimoto, 2002, Alam, 2016), potent activator of the nitric oxide receptor and soluble guanylate cyclase (David, 2001). Besides, great interest in the pyrazole molecule has been stimulated by some promising pharmacological, agrochemical and analytical applications of its derivatives (Chauhan, 2011, Florence, 2013, Hassan, 2009, Hassan, 2009). Owing to the immense importance and varied bioactivities exhibited by pyrazole and dihydropyrimidinone derivatives and in continuation of our ongoing research on the synthesis of new heterocyclic compounds (Nagaraj, 2015, 2017, 2017, Sanjeeva Reddy, 2015, 2016), it was thought of interest to accommodate pyrazole and dihydropyrimidinone moieties in a single molecular frame and to obtain a new heterocyclic compounds with potential biological activity. In this article, we wish to report the synthesis of a new class of pyrazolyl-dihydropyrimidinones 4(a-g) and evaluation of their *in vitro* antibacterial activity.

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MATARIALS AND METHODS

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography

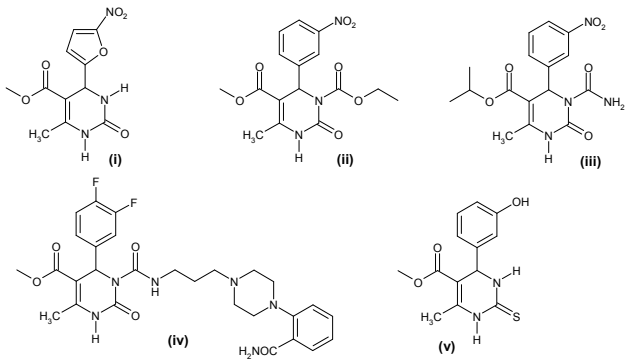


Fig 1. Structures of biological important DHPMs derivatives

(TLC) on pre-coated silica gel F_{254} plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer.

General procedure for the synthesis of 3,5-dimethyl-1-aryl-1*H*-pyrazole (2a-g): A mixture of acetyl acetone **1** (0.02 mol), and corresponding aryl hydrazine hydrochloride (0.02 mol) in ethanol (20 ml) was heated under reflux for 3 h on a water bath. After completion of the reaction ethanol was evaporated, the residue was dissolved in water, neutralized with sodium bicarbonate and extracted with ether. The solvent was evaporated under reduced pressure to get the compound **2** as yellow-brown liquid.

3,5-Dimethyl-1-phenyl-1H-pyrazole (2a): Yield 90%; b.p. 270-272 ^{o}C; IR (KBr) ν_{max}: 3010, 2962, 1516, 1510 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.21 (s, 1H, Ar-H), 7.10-7.20 (m, 5H, Ar-H); MS: *m/z* 172 (M^+).

General procedure for the synthesis of 3,5-dimethyl-1-aryl-1*H*-4-pyrazolecarbaldehyde (3a-g): To a cold solution of *N*,*N*-dimethylformamide (0.02 mol), freshly distilled phosphorous oxychloride (0.01 mol) was added with stirring over a period of 30 minutes. When formylation solution was obtained, a solution of compound **2(a-g)** (0.01 mol) in *N,N*-dimethylformamide (5 ml) was added drop wise while maintaining the temperature 0-5 ^{o}C. The resulting mixture was heated under reflux for 1 h, cooled and poured with continuous stirring onto crushed ice and the formed yellow precipitate was filtered, crystallized from aqueous ethanol to get the pure compounds.

3,5-Dimethyl-1-aryl-1*H*-4-pyrazolecarbaldehyde (3a): Yield 86%, mp 124-126 ^{o}C; IR (KBr) ν_{max}: 3012, 2961, 2854, 1700, 1516, 1505 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.64 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 7.15-7.25 (m, 5H, Ar-H), 9.98 (s, 1H, CHO); MS: *m/z* 200 (M^+).

General procedure for the synthesis of pyrazolyl-dihydropyrimidinones 4(a-g): A mixture of ethylacetoacetate (1.1 mmol), compounds **3(a-g)** (1 mmol) and urea (2 mmol) was mixed with $ZrOCl_2$ (0.21 mmol, ~5 mol%). The mixture was taken in a glass beaker and the beaker was placed in an alumina bath inside an unmodified house hold microwave oven and subjected to microwave irradiation for 20-80 sec at 360 W, with mechanical stirring to avoid macroscopic hot spots. On completion of the reaction (as determined by TLC), the reaction mixture was cooled and stirred with water to dissolve $ZrOCl_2$ and excess urea. The solid product separated was filtered and recrystallized from ethanol to afford pure **4(a-g)**.

Ethyl4-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate(4a): Yield 67%; IR (KBr) ν_{max}: 3449, 2977, 1897, 1660, 1602, 1172 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.20 (t, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.10 (q, 2H, CH_2), 5.20 (s, 1H, Ar-CH), 5.70 (s, 1H, NH), 7.10-7.20 (m, 5H, ArH), 8.1 (s, 1H, NH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 12.5, 13.7, 15.2, 18.8, 50.7, 52.8, 102.0, 116.5, 122.9, 127.6, 129.0, 134.0, 136.9, 141.7, 143.7, 152.1, 167.8; MS: *m/z* 354 (M^+).

Ethyl 4-[1-(4-methoxyphenyl)-3,5-dimethyl-1*H*-4-pyrazolyl] -6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (4b): Yield 71%; IR (KBr) ν_{max}: 3442, 2976, 1892, 1662, 1602, 1172, 1030 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.22 (t, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.02 (q, 2H, CH_2), 5.21 (s, 1H, Ar-CH), 5.70 (s, 1H, NH), 6.89 (d, *J*=8.4 Hz, 2H, ArH), 7.12 (d, *J*=8.4 Hz, 2H, ArH), 8.14 (s, 1H, NH); MS: *m/z* 384 (M^+).

Ethyl 4-[1-(3-fluorophenyl)-3,5-dimethyl-1*H*-4-pyrazolyl]-6 -methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (4c): Yield 64%; IR (KBr) ν_{max}: 3444, 2977, 1891, 1663, 1602, 1278, 1172 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.22 (t, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.04 (q, 2H, CH_2), 5.21 (s, 1H, Ar-CH), 5.70 (s, 1H, NH), 6.90-7.10 (m, 4H, ArH), 8.17 (s, 1H, NH); MS: *m/z* 372 (M^+).

Ethyl 4-[1-(4-chlorophenyl)-3,5-dimethyl-1*H*-4-pyrazolyl]-6 -methyl-2-oxo-1,2,3,4-tetrahy-dro-5-pyrimidinecarboxylate (4d): Yield 79%; IR (KBr) ν_{max}: 3439, 2974, 1891, 1667, 1601, 1174, 686 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.23 (t, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.02 (q, 2H, CH_2), 5.21 (s, 1H, Ar-CH), 5.70 (s, 1H, NH), 7.22 (d, *J*=8.2 Hz, 2H, ArH), 7.38 (d, *J*=8.2 Hz, 2H, ArH), 8.16 (s, 1H, NH); MS: *m/z* 388 (M^+).

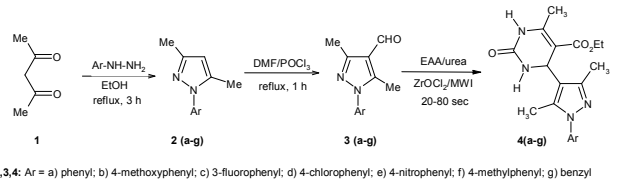
Ethyl 4-[3,5-dimethyl-1-(4-nitrophenyl)-1*H*-4-pyrazolyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (4e): Yield 72%; IR (KBr) ν_{max}: 3442, 2975, 1893, 1664, 1610, 1567, 1370, 1174 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.24 (t, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.02 (q, 2H, CH_2), 5.21 (s, 1H, Ar-CH), 5.70 (s, 1H, NH), 7.32 (d, *J*=8.6 Hz, 2H, ArH), 7.92 (d, *J*=8.6 Hz, 2H, ArH), 8.18 (s, 1H, NH); MS: *m/z* 399 (M^+).

Ethyl4-[3,5-dimethyl-1-(4-methylphenyl)-1*H*-4-pyrazolyl]-6-methyl-2-oxo-1,2,3,4-tetrahy-dro-5-pyrimidinecarboxylate (4f): Yield 63%; IR (KBr) ν_{max}: 3435, 2971, 1889, 1668, 1601, 1178 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.25 (t, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.07 (q, 2H, CH_2), 5.24 (s, 1H, Ar-CH), 5.74 (s, 1H, NH), 7.10 (d, *J*=8.1 Hz, 2H, ArH), 7.20 (d, *J*=8.1 Hz, 2H, ArH), 8.17 (s, 1H, NH); MS: *m/z* 368 (M^+).

Ethyl4-(1-benzyl-3,5-dimethyl-1*H*-4-pyrazolyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (4g): Yield 61%; IR (KBr) ν_{max}: 3445, 2973, 1896, 1661, 1602, 1172 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.22 (t, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.11 (q, 2H, CH_2), 5.08 (s, 2H, CH_2), 5.22 (s, 1H, Ar-CH), 5.74 (s, 1H, NH), 7.10-7.20 (m, 5H, ArH), 8.14 (s, 1H, NH); MS: *m/z* 368 (M^+).

RESULTS AND DISCUSSION

The cyclo-condensation of ethylacetoacetate 1 with corresponding arylhydrazine in ethanol at reflux temperature for 3 h gave the 3,5-dimethyl-1-aryl-1*H*-pyrazole 2 in good yields. Formylation of 2 with DMF in phosphorous oxychloride, at reflux for 1 h, gave the 3,5-dimethyl-1-aryl-1*H*-4-pyrazolecarbaldehyde 3. The cyclo-condensation of 3 with ethylaceto- acetate and urea in the presence of $ZrOCl_2$ (~5 mol%) as a reaction mediator under microwave irradiation in an unmodified house hold microwave oven at 360 W for 20-80 sec, gave pyrazolyl-dihydropyrimidinones 4(a-g) in good to excellent yields (Scheme-1). The structures of the synthesized compounds were elucidated by IR, ^{1}H, ^{13}C NMR and MS spectral analysis.



2,3,4: Ar = a) phenyl; b) 4-methoxyphenyl; c) 3-fluorophenyl; d) 4-chlorophenyl; e) 4-nitrophenyl; f) 4-methylphenyl; g) benzyl

Scheme 1. Schematic route for the synthesis of compounds 7(a-j)

The IR spectrum of compound 4a disappearance of formyl (C=O) absorption band at 1700 cm^{-1}, which was present in compound 3a, confirmed the cyclization or involvement of formyl carbonyl group.

The C=O, N-H bands of the pyrimidinone ring were observed at 1897 and 3449 cm^{-1} respectively. Its ^{1}H NMR spectra, the CH-Ar proton of pyrimidinone ring at 5.20 ppm, NH protons at 5.70 and 8.1 as a singlet. All the other aromatic and aliphatic protons of 4a were observed at the expected regions. In the ^{13}C NMR spectrum, the prominent signals corresponding to the C-3, C-4 and C-5 carbons of pyrazole ring is observed at 143.7, 116.5 and 136.9 ppm, the C-2', C-4', C-5' and C-6' carbons of pyrimidinone ring is observed at 152.1, 50.7, 102.0 and 141.7 ppm respectively, are proof of further evidence of its structure.

ANTIBACTERIAL ACTIVITY

All the newly synthesized compounds 4(a-g) were screened for their antibacterial activity against Gram-positive bacteria *viz*. *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11) and *Staphylococcus aureus* (MTCC 96), and Gram-negative bacteria *viz*. *Pseudomonas aeruginosa* (MTCC 741), *Klobsinella aerogenes* (MTCC 39) and *Chromobacterium violaceum* (MTCC 2656) by disc diffusion method (NCCLs, 1982). For the antibacterial assay standard inoculums (1-2 × 10^7 c.f.u/mL 0.5 Mc Farland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The discs measuring 6.26 mm in diameter were prepared from Whatman no.1 filter paper and sterilized by dry heat at 140 ^{o}C for 1 h.

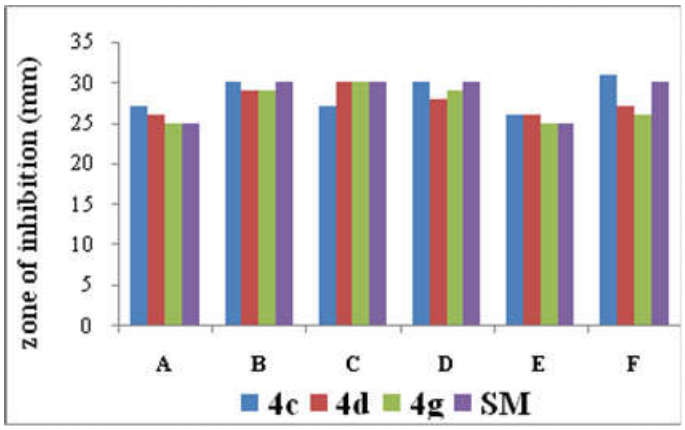


Fig. 2. Comparison of zone of inhibition (mm) of selected compounds and standard drugs: A) *B. subtilis*; B) *B. sphaericus*; C) *S. aureus*; D) *P. aeruginosa*; E) *K. aerogenes*; F) *C. Violaceum*

The sterile discs previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37 ^{o}C. The inhibition zones were measured and compared with the standard drug streptomycin. The zones of inhibition are presented in Table 1. The antibacterial screening data reveal that all the tested compounds 4(a-g) showed moderate to good inhibition towards all the tested strains.

Table 1. Antibacterial activity of compounds 4(a-g)

Compound	zone inhibition at 50 μg/mL (mm)					
	B. subtilis	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
4a	15	18	10	19	13	20
4b	11	14	12	13	21	19
4c	27	30	27	30	26	31
4d	26	29	30	28	26	27
4e	15	11	23	21	17	19
4f	12	12	16	19	11	10
4g	25	29	30	29	25	26
Streptomycin	25	30	30	30	25	30

Compounds 4c, 4d and 4g exhibited potent inhibitory activity compared to standard drug at the tested concentrations. The results also reveal that the presence of 3-fluorophenyl (4c) or 4-chlorophenyl (4d) or benzyl (4g) substituent on pyrazole ring might be the reason for the significant inhibitory activity. The comparison of zone of inhibition value (in mm) of the selected compounds 4 and standard drug against different bacteria is presented in Fig. 2.

Conclusion

A new series of pyrazolyl-dihydropyrimidinones 4(a-g) have been synthesized and evaluated for their antibacterial activity against various bacterial strains. The screened compounds 4c, 4d and 4g exhibited potent antibacterial activity compared to standard drug at the tested concentrations. The other

compounds also showed appreciable activity against the test bacteria and emerged as potential molecules for further development.

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