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Synthesis and antimicrobial evaluation of 3-{[7-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)]pyrido[2,3-d] pyrimidin-4-yl}-1*N*-ethoxyphthalimido-2-substituted-imidazolidin-4-one derivatives

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Abstract: Synthesis of *N*-ethoxyphthalimide derivatized 3-{[7-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)]pyrido[2,3-d]pyrimidin-4-yl}-2-substituted-imidazolidin-4-one **(7a-e)** are described**.** 2-Amino-6-(2,4-dichlorophenyl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile **(2)** was prepared by the condensation of chalcone **(1)** with malononitrile, which on cyclization with formamide yielded 7-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)pyrido[2,3-d]pyrimidin-4-amine **(3)**. Schiff bases **(4a-e)** were obtained by the reaction of **(3)** with various aromatic aldehydes. These were converted to corresponding pyridopyrimidinylimidazolidinone derivatives **(5a-e)** by treating with glycine. Finally the targeted molecules **(7a-e)** were obtained by the base induced condensation of **(5a-e)** with bromoethoxyphthalimide **(6)**. Structure confirmation was accomplished by spectral studies (IR, ^{1}HNMR, ^{13}CNMR, Mass) and elemental analysis of all the synthesized compounds.

Keywords: Bromoethoxyphthalimide; Pyrimidine; Chalcone; Malononitrile; Formamide.

Introduction

Chalcones [1] constitute an important group of natural products and some of them possess wide range of biological activity such as antibacterial [2], antitumor [3], anticancer [4], antitubercular [5], antiviral [6] etc. Pyrimidines are essential structural units found in natural compounds (nucleic acids, vitamin B_1), synthetic drugs (barbiturates) and chemotherapeutic preparations (fluorouracil) [7]. Pyridopyrimidine nucleus is a ubiquitous feature of pharmacological interest and has been proven to be fertile source of medicinal agents such as antiviral [8], antitumor [9], antibacterial [10], anticancer [11], antiulcer [12], anticonvulsant [13], antihypertensive [14], antifungal [15], anti-AIDS [16], antiherps [17], antineoplastic [18], anti-P^{38}kinase [19], anti-inflammatory, antihistaminic [20], antiasthmatic, anti-Perkinsonion [21], cardiotonic [22], hepatoprotective, diuretic [23], antithyroid [24], substance for iodine fixation etc. Furthermore pyridopyrimidine derivatives show selective inhibition of tyrosine kinase fully suppressing the growth of many forms of malignant tumors [25-27], dehydrofolate reductase causing the death of many pathogenic microorganisms [28], α_1-adrenoreceptor antagonists and are used in medicine for various dysfunctions [29].

Imidazole scaffold is a powerful biophore fragment used as antibacterial [30-31], antifungal [32], antiherbicidal [33], antianalgesic [34], antioxidant [35-36], antiallergic [37], antitumoral [38], antiparasitic [39] and antihelmintic [38] etc. In view of these observations and in continuation of our work on different heterocycles assembled to alkoxyphthalimide functionality [40-42], it was thought worthwhile to synthesize new chemical entities incorporating these active pharmacophores in a single molecular framework using chalcones as basic building blocks, with the hope to achieve enhanced biological activity.

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Results and Discussion

A mixture of 2,4-dichloroacetophenone and anisaldehyde was stirred in ethanol in the presence of 30% aqueous NaOH solution gave the corresponding chalcone **(1)** in 70% yield. Cyclisation of **(1)** with malononitrile in methanol in the presence of ammonium acetate yielded 2-amino-6-(2,4-dichlorophenyl)-4-(4-methoxyphenyl) pyridine-3-carbonitrile **(2)**. IR, mass and ^{1}H NMR studies confirmed the formation of **(2)**.

The intense band at 2180 cm^{-1} showed C≡N stretching for the CN group attached to the pyridine ring while band for the NH_2 group appeared at 3435, 3380 cm^{-1} and ^{1}H NMR signal at δ 6.80 (singlet). Pyrido[2,3-d]pyrimidine derivative **(3)** was prepared by cyclocondesation of **(2)** with formamide in acetone under reflux for 6 hrs. Formation of this was confirmed by disappearance of IR band for the C≡N group. The protons of NH_2 group present in **(2)** were also present in **(3)**. Compound **(3)** when condensed with various arylaldehydes in presence of catalytic amount of glacial acetic acid produced corresponding Schiff's bases **(4a-e)** in high yield.

The ^{1}H NMR spectra of **(4a)** in $CDCl_3$ exhibited two signals: (δ in ppm) 7.57-7.26 (m, 12H, Ar-H) and 7.11 (s, 1H, N=CH). The chemical shifts of the aromatic protons depended on the nature of substituent present in the benzene ring. Arylidene derivatives **(4a-e)** on cyclisation with glycine furnished corresponding imidazolidinones **(5a-e)**. Formation of these was confirmed by disappearance of ^{1}H NMR signal for N=CH group and appearance of new IR band at 1710 cm^{-1} for C=O stretching and ^{1}H NMR signal at δ 10.18 (singlet) for NH and δ 3.42 for CH_2 group of imidazolidinone ring. Bromoethoxyphthalimide **(6)** was prepared by the reported method [43]. Condensation of **(5a-e)** with bromoethoxyphthalimide **(6)** in acetone/K_2CO_3 gave **(7a-e)**. IR, Mass, ^{1}H NMR, and ^{13}C NMR spectra confirmed this condensation. Free stretching vibration band for –NH group at 3398 cm^{-1}, which was present in its precursors **(5a-e)** was disappeared and a strong band at 1300-1100 cm^{-1} appeared for the C-N stretching confirmed the formation of a new C-N bond.

The reaction conditions however were dependent upon the aromatic substituents in **(5a-e)**. Refluxing time for complete reaction varied between 18-24 hrs (Scheme). Analytical and spectral data for synthesized compounds are given in experimental section.

Experimental

General Procedures

Melting points of all synthesized compounds were taken in open capillary tubes and are therefore uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 4000 FT IR spectrometer and ^{1}H NMR spectra were determined on a Bruker DRX-300 (300 MHz FT NMR) spectrometer using TMS as internal standard. Mass spectra were recorded on a JEOL AccuTOF JMS-T100LC Mass spectrometer. All compounds gave satisfactory micro analytical results. Purity of the synthesized compounds was checked by TLC using silica gel-G plates, n-hexane-ethyl acetate as developing solvent and the spots were visualized in iodine chamber. Bromoethoxyphthalimide **(6)** and chalcone **(1)** were prepared by reported methods. In the text abbreviation hrs. stands for hours and s, d, t for singlet, doublet and triplet respectively.

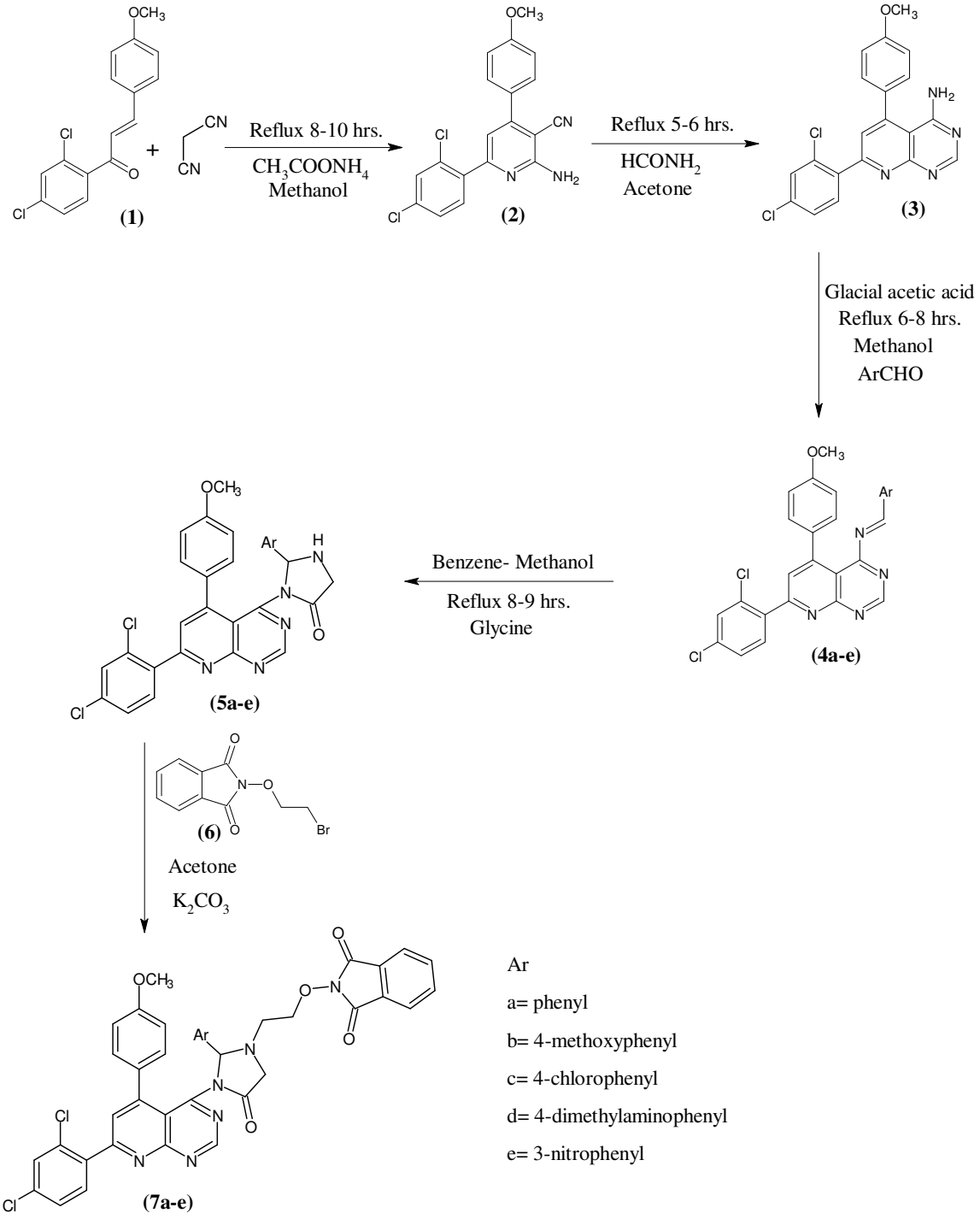
Synthesis of 2-amino-6-(2,4-dichlorophenyl)-4-(4-methoxyphenyl)pyridine-3-carbonitrile **(2)**:

Compound **(1)** (3.07 g, 0.01 mol) was dissolved in methanol (30 mL) and malononitrile (0.70 mL, 0.01 mol) was added drop wise with continuous stirring. The reaction mixture was refluxed on a water bath for 10 hrs. The contents were cooled and filtered. The filtrate was poured into crushed ice (50 g) with constant stirring. The resulting solid was filtered, washed with water, dried and recrystallized from absolute alcohol. Yield 53%, m.p. 160ºC; IR (KBr) cm^{-1}: 3435, 3380 (N-H str.), 3080 (C-H str., Ar-H), 2960 (C-H str., CH_3), 2180 (C≡N str.), 1060 (C-O str.), 805 (C-Cl str.); ^{1}H NMR ($CDCl_3$) δ: 7.76 (s, 1H, CH of pyridine ring), 7.55-7.10 (m, 7H, Ar-H), 6.80 (s, 2H, NH_2), 3.6 (s, 3H, OCH_3); Anal. Calcd. for $C_{19}H_{13}Cl_2N_3O$: C, 61.64; H, 3.54; N, 11.35. Found: C, 60.62; H, 3.25; N, 11.03%.

Synthesis of 7-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)pyrido[2,3-d]pyrimidin-4-amine **(3)**:

Compound **(2)** (3.70 g, 0.01 mole) was dissolved in acetone and formamide (9.8 mL) was added to it. The reaction mixture was refluxed for 5 hrs. Resultant mixture was cooled and filtered. The filtrate was poured on crushed ice and kept for 3 hrs at room temperature. Solid separated was filtered, dried and recrystallized from glacial acetic acid. Yield 57%, m.p.

110ºC; IR (KBr) cm^{-1}: 3455, 3366 (N-H str.), 3109 (C-H str., Ar-H), 2931 (C-H str., CH_3), 1029 (C-O str.), 821 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 7.95 (s, 1H, CH of pyrimidine ring), 7.77 (s, 1H, CH of pyridine ring), 7.53-7.12 (m, 7H, Ar-H), 6.84 (s, 2H, NH_2), 3.61 (s, 3H, OCH_3); Anal. Calcd. for $C_{20}H_{14}Cl_2N_4O$: C, 60.47; H, 3.55; N, 14.10. Found: C, 60.02; H, 3.38; N, 13.75%.



Scheme1.

Synthesis of 7-(2,4-dichlorophenyl)-5-(4-methoxphenyl)-N-(phenylmethylidene) pyrido[2,3-d]pyrimidin-4-amine **(4a)**:
A mixture of compound **(3)** (3.97 g, 0.01 mol) and benzaldehyde (1.06 mL, 0.01 mol) was refluxed in methanol (20 mL) containing a trace of acetic acid. The filtrate was concentrated by evaporating the solvent under reduced pressure. Crystals separated were filtered and recrystallized from ethanol. Yield 62%, m.p. 160ºC; IR (KBr) cm^{-1}: 3082 (C-H str., Ar-H), 2962 (C-H str., CH_3), 1587 (C=N str.), 1080 (C-O str.), 784 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 7.98 (s, 1H, CH of pyrimidine ring), 7.74 (s, 1H, CH of pyridine ring), 7.57-7.26 (m, 12H, Ar-H), 7.11 (s, 1H, N=CHAr), 3.69 (s, 3H, OCH_3); Anal. Calcd. for $C_{27}H_{18}Cl_2N_4O$: C, 66.81; H, 3.74; N, 11.54. Found: C, 66.22; H, 3.30; N, 11.09%.
Compounds **(4b-e)** were also prepared by similar method with minor change in reaction conditions.

7-(2,4-Dichloro)phenyl-5-(4-methoxy)phenyl-N-(4-methoxyphenylmethylidene) pyrido[2,3-d]pyrimidin-4-amine **(4b)**:
Yield 78%, m.p. 182ºC; IR (KBr) cm^{-1}: 3075 (C-H str., Ar-H), 2962 (C-H str., CH_3), 1583 (C=N str.), 1096 (C-O str.), 767 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 7.99 (s, 1H, CH of pyrimidine ring), 7.79 (s, 1H, CH of pyridine ring), 7.50-7.28 (m, 11H, Ar-H), 7.14 (s, 1H, N=CHAr), 3.64 (s, 3H, OCH_3); Anal. Calcd. for $C_{28}H_{20}Cl_2N_4O_2$: C, 65.25; H, 3.91; N, 10.87. Found: C, 64.62; H, 3.38; N, 10.42%.

N-(4-Chlorophenylmethylidene)-7-(2,4-dichloro)phenyl-5-(4-methoxyphenyl)pyrido [2,3-d]pyrimidin-4-amine **(4c)**:
Yield 69%, m.p. 154ºC; IR (KBr) cm^{-1}: 3090 (C-H str., Ar-H), 2964 (C-H str., CH_3), 1581 (C=N str.), 1088 (C-O str.), 786 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 7.96 (s, 1H, CH of pyrimidine ring), 7.75 (s, 1H, CH of pyridine ring), 7.55-7.32 (m, 11H, Ar-H), 7.19 (s, 1H, N=CHAr), 3.61 (s, 3H, OCH_3); Anal. Calcd. for $C_{27}H_{17}Cl_3N_4O$: C, 62.39; H, 3.30; N, 10.78. Found: C, 62.02; H, 3.18; N, 10.34%.

7-(2,4-Dichloro)phenyl-5-(4-methoxy)phenyl-N-(4-dimethylaminophenylmethyli- dene)pyrido[2,3-d]pyrimidin-4-amine **(4d)**:
Yield 73%, m.p. 149ºC; IR (KBr) cm^{-1}: 3092 (C-H str., Ar-H), 2969 (C-H str., CH_3), 1584 (C=N str.), 1083 (C-O str.), 766 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 7.94 (s, 1H, CH of pyrimidine ring), 7.78 (s, 1H, CH of pyridine ring), 7.53-7.21 (m, 11H, Ar-H), 7.15 (s, 1H, N=CHAr), 3.65 (s, 3H, OCH_3), 2.84 (s, 6H, $N(CH_3)_2$); Anal. Calcd. for $C_{29}H_{23}Cl_2N_5O$: C, 65.91; H, 4.39; N, 13.25. Found: C, 65.52; H, 4.08; N, 12.83%.

7-(2,4-Dichloro)phenyl-5-(4-methoxy)phenyl-N-(3-nitrophenylmethylidene)pyrido [2,3-d]pyrimidin-4-amine **(4e)**:
Yield 65%, m.p. 132ºC; IR (KBr) cm^{-1}: 3042 (C-H str., Ar-H), 2942 (C-H str., CH_3), 1567 (C=N str.), 1058 (C-O str.), 789 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 7.92 (s, 1H, CH of pyrimidine ring), 7.77 (s, 1H, CH of pyridine ring), 7.58-7.24 (m, 11H, Ar-H), 7.11 (s, 1H, N=CHAr), 3.66 (s, 3H, OCH_3); Anal. Calcd. for $C_{27}H_{17}Cl_2N_5O_3$: C, 61.14; H, 3.23; N, 13.20. Found: C, 60.82; H, 3.08; N, 12.93%.

Synthesis of 3-[7-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)]pyrido[2,3-d] pyrimidin-4-yl)-2-phenyl-imidazolidin-4-one **(5a)**:
To the Schiff base **(4a)** (4.85 g, 0.01 mol) in dry benzene and methanol (1:1, 30 mL), glycine (0.75 g, 0.01 mol) was added with constant stirring. The reaction mixture was kept under reflux for 7 hrs. Water formed during the reaction was removed in a Dean Stark apparatus using azeotropic distillation. Solid separated was filtered from remaining concentrated solution and pressed dry. Some of this was recrystallized from ethanol and rest was used for the next step. Yield 52%, m.p. 110ºC; IR (KBr) cm^{-1}: 3398 (N-H str.), 3083 (C-H str., Ar-H), 2949 (C-H str., CH_3), 1710 (C=O str.), 1079 (C-O str.), 765 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 10.18 (s, 1H, NH), 7.94 (s, 1H, CH of pyrimidine ring), 7.79 (s, 1H, CH of pyridine ring), 7.58-7.18 (m, 12H, Ar-H), 3.64 (s, 3H, OCH_3), 3.42 (s, 2H, NCH_2C of imidazolidinone ring); Anal. Calcd. for $C_{29}H_{21}Cl_2N_5O_2$: C, 64.21; H, 3.90; N, 12.91. Found: C, 64.02; H, 3.55; N, 12.36%.
Compounds **(5b-e)** were also prepared in similar method with required change in reflux time.

3-{7-(2,4-Dichlorophenyl)-5-(4-methoxyphenyl)pyrido[2,3-d]pyrimidin-4-yl)}-2-(4-methoxyphenyl)-imidazolidin-4-one **(5b)**:
Yield 55%, m.p. 105ºC; IR (KBr) cm^{-1}: 3452 (N-H str.), 3113 (C-H str., Ar-H), 2990 (C-H str., CH_3), 1734 (C=O str.), 1090 (C-O str.), 759 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 10.13 (s, 1H, NH), 7.98 (s, 1H, CH of pyrimidine ring), 7.73 (s, 1H, CH of pyridine ring), 7.60-7.23 (m, 11H, Ar-H), 3.61 (s, 3H, OCH_3), 3.12 (s, 2H, NCH_2C of imidazolidinone ring); Anal. Calcd. for $C_{30}H_{23}Cl_2N_5O_3$: C, 62.94; H, 4.05; N, 12.23. Found: C, 62.29; H, 3.70; N, 12.10%.

2-(4-Chlorophenyl)-3-{7-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)pyrido[2,3-d] pyrimidin-4-yl)}imidazolidin-4-one **(5c)**:
Yield 53%, m.p. 116ºC; IR (KBr) cm^{-1}: 3460 (N-H str.), 3097 (C-H str., Ar-H), 2967 (C-H str., CH_3), 1737 (C=O str.), 1087 (C-O str.), 774 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 10.38 (s, 1H, NH), 7.96 (s, 1H, CH of pyrimidine ring), 7.75 (s, 1H, CH of pyridine ring), 7.56-7.17 (m, 11H, Ar-H), 3.63 (s, 3H, OCH_3), 3.33 (s, 2H, NCH_2C of imidazolidinone ring); Anal. Calcd. for $C_{29}H_{20}Cl_3N_5O_2$: C, 60.36; H, 3.49; N, 12.14. Found: C, 60.09; H, 3.20; N, 11.80%.

3-{7-(2,4-Dichlorophenyl)-5-(4-methoxyphenyl)pyrido[2,3-d]pyrimidin-4-yl)}-2-(4-dimethylaminophenyl)-imidazolidin-4-one **(5d)**:
Yield 67%, m.p. 98ºC; IR (KBr) cm^{-1}: 3465 (N-H str.), 3107 (C-H str., Ar-H), 2977 (C-H str., CH_3), 1730 (C=O str.), 1087 (C-O str.), 774 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 10.38 (s, 1H, NH), 7.98 (s, 1H, CH of pyrimidine ring), 7.71 (s, 1H, CH of pyridine ring), 7.55-7.22 (m, 11H, Ar-H), 3.67 (s, 3H, OCH_3), 3.33 (s, 2H, NCH_2C of imidazolidinone ring), 2.82 (s, 6H, $N(CH_3)_2$); Anal. Calcd. for $C_{31}H_{26}Cl_2N_6O_2$: C, 63.59; H, 4.48; N, 14.35. Found: C, 63.22; H, 4.10; N, 14.03%.

3-{7-(2,4-Dichlorophenyl)-5-(4-methoxyphenyl)pyrido[2,3-d]pyrimidin-4-yl)}-2-(3-nitrophenyl)-imidazolidin-4-one **(5e)**:
Yield 59%, m.p. 80ºC; IR (KBr) cm^{-1}: 3473 (N-H str.), 3077 (C-H str., Ar-H), 2950 (C-H str., CH_3), 1690 (C=O str.), 1081 (C-O str.), 764 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 10.21 (s, 1H, NH), 7.92 (s, 1H, CH of pyrimidine ring), 7.75 (s, 1H, CH of pyridine ring), 7.62-7.21 (m, 11H, Ar-H), 3.68 (s, 3H, OCH_3), 3.30 (s, 2H, NCH_2C of imidazolidinone ring); Anal. Calcd. for $C_{29}H_{20}Cl_2N_6O_4$: C, 59.30; H, 3.43; N, 14.31. Found: C, 59.02; H, 3.20; N, 14.04%.

Synthesis of 3-{[7-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)]pyrido[2,3-d] pyrimidin-4-yl}-1N-ethoxyphthalimido-2-phenyl-imidazolidin-4-one **(7a)**:
A mixture of compound **(5a)** (5.42 g, 0.01 mol) and bromoethoxyphthalimide **(6)** (2.70 g, 0.01 mol) in acetone and K_2CO_3 (2.76 g, 0.02 mol) was refluxed for 24 hrs in a round bottomed flask. It was cooled at room temperature and the solid separated was filtered on a Wattman filter paper. The filtrate was slowly poured on crushed ice while constant stirring. Solid obtained was filtered and washed twice with ice cooled water. It was recrystallized from rectified spirit. Yield 67%, m.p. 140ºC; IR (KBr) cm^{-1}: 3081 (C-H str., Ar-H), 2936 (C-H str., CH_3), 2840 (C-H str., CH_2), 1732 (C=O str.), 1462 (N-O str.), 1026 (C-O str.), 823 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 7.95 (s, 1H, CH of pyrimidine ring), 7.76 (s, 1H, CH of pyridine ring), 7.59-7.16 (m, 16H, Ar-H), 4.82 (t, 2H, OCH_2), 3.68 (s, 3H, OCH_3), 3.21 (t, 2H, NCH_2); ^{13}C NMR δ: 168.58 (CO, cyclic), 150.6 (C near N of pyridine ring), 149.13 ($C\text{-}OCH_3$), 118.76 (C of phenyl ring), 45.9 ($O\text{-}CH_3$), 45.15 (CH_2 of imidazolidinone ring), 40.38 (CH of imidazolidinone ring), 36.73 (CH_2-O), 34.52 (CH_2-N); MS: m/z: 732 $[M]^+$; Anal. Calcd. for $C_{39}H_{28}Cl_2N_6O_5$: C, 64.03; H, 3.86; N, 11.49. Found: C, 63.59; H, 3.41; N, 11.02%.

Compounds (**7b-e)** were also synthesized by similar method with minor change in reaction conditions.

3-{[7-(2,4-Dichlorophenyl)-5-(4-methoxyphenyl)]pyrido[2,3-d]pyrimidin-4-yl)}-1N-ethoxyphthalimido2-(4-methoxyphenyl)-imidazolidin-4-one **(7b)**:
Yield 70%, m.p. 75ºC; IR (KBr) cm^{-1}: 3032 (C-H str., Ar-H), 2935 (C-H str., CH_3), 2853 (C-H str., CH_2), 1700 (C=O str.), 1375 (N-O str.), 1059 (C-O str.), 773 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 7.99 (s, 1H, CH of pyrimidine ring), 7.72 (s, 1H, CH of pyridine ring), 7.54-7.14 (m, 15H, Ar-H), 4.62 (t, 2H, OCH_2), 3.63 (s, 3H, OCH_3), 3.35 (t, 2H, NCH_2); ^{13}C NMR δ: 168.24 (CO, cyclic), 150.63 (C near N of pyridine ring), 149.09 ($C\text{-}OCH_3$), 120.46 (C of phenyl ring), 45.94 ($O\text{-}CH_3$), 45.87 (CH_2 of imidazolidinone ring), 40.79 (CH of imidazolidinone ring), 36.68 (CH_2-O), 34.5 (CH_2-N); MS: m/z: 762 $[M]^+$; Anal. Calcd. for $C_{40}H_{30}Cl_2N_6O_6$: C, 63.08; H, 3.97; N, 11.03. Found: C, 62.80; H, 3.64; N, 10.78%.

2-(4-Chlorophenyl)-3-{[7-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)]pyrido[2,3-d] pyrimidin-4-yl)}-1N-ethoxyphthalimido-imidazolidin-4-one **(7c)**:
Yield 66%, m.p. 89ºC; IR (KBr) cm^{-1}: 3057 (C-H str., Ar-H), 2952 (C-H str., CH_3), 2860 (C-H str., CH_2), 1716 (C=O str.), 1368 (N-O str.), 1025 (C-O str.), 740 (C-Cl str.); ^1H NMR ($CDCl_3$) δ: 7.94 (s, 1H, CH of pyrimidine ring), 7.77 (s, 1H, CH of pyridine ring), 7.63-7.22 (m, 15H, Ar-H), 4.53 (t, 2H, OCH_2), 3.64 (s, 3H, OCH_3), 3.27 (t, 2H, NCH_2); ^{13}C NMR δ: 168.80 (CO, cyclic), 150.95 (C near N of pyridine ring), 149.00 ($C\text{-}OCH_3$), 116.64 (C of phenyl ring), 45.95 ($O\text{-}CH_3$), 45.21 (CH_2 of imidazolidinone ring), 40.34 (CH of imidazolidinone ring), 36.89 (CH_2-O), 34.47 (CH_2-N); MS: m/z: 766 $[M]^+$; Anal. Calcd. for

$C_{39}H_{27}Cl_3N_6O_5$: C, 61.15; H, 3.55; N, 10.97. Found: C, 61.02; H, 3.10; N, 10.45%.

3-{[7-(2,4-Dichlorophenyl)-5-(4-methoxyphenyl)]pyrido[2,3-d]pyrimidin-4-yl)}-2-(4-dimethylaminophenyl)-1N-ethoxyphthalimido-imidazolidin-4-one **(7d)**:
Yield 69%, m.p. 104ºC; IR (KBr) cm^{-1}: 3077 (C-H str., Ar-H), 2932 (C-H str., CH_3), 2862 (C-H str., CH_2), 1726 (C=O str.), 1369 (N-O str.), 1028 (C-O str.), 747 (C-Cl str.); ^{1}H NMR ($CDCl_3$) δ: 7.92 (s, 1H, CH of pyrimidine ring), 7.76 (s, 1H, CH of pyridine ring), 7.53-7.16 (m, 15H, Ar-H), 4.57 (t, 2H, OCH_2), 3.64 (s, 3H, OCH_3), 3.37 (t, 2H, NCH_2), 2.87 (s, 6H, $N(CH_3)_2$); ^{13}C NMR δ: 168.09 (CO, cyclic), 150.72 (C near N of pyridine ring), 149.51 (C-OCH_3), 110.85 (C of phenyl ring), 45.90 (O-CH_3), 45.14 (CH_2 of imidazolidinone ring), 40.36 (CH of imidazolidinone ring), 36.75 (CH_2-O), 34.53 (CH_2-N); MS: m/z: 775 $[M]^+$; Anal. Calcd. for $C_{41}H_{33}Cl_2N_7O_5$: C, 63.57; H, 4.29; N, 12.66. Found: C, 63.29; H, 4.20; N, 12.22%.

3-{[7-(2,4-Dichlorophenyl)-5-(4-methoxyphenyl)]pyrido[2,3-d]pyrimidin-4-yl)}-1N-ethoxyphthalimido-2-(3-nitrophenyl)-imidazolidin-4-one **(7e)**:
Yield 73%, m.p. 126ºC; IR (KBr) cm^{-1}: 3127 (C-H str., Ar-H), 2943 (C-H str., CH_3), 2842 (C-H str., CH_2), 1686 (C=O str.), 1559 (N-O str.), 1088 (C-O str.), 763 (C-Cl str.); ^{1}H NMR ($CDCl_3$) δ: 7.98 (s, 1H, CH of pyrimidine ring), 7.75 (s, 1H, CH of pyridine ring), 7.63-7.21 (m, 15H, Ar-H), 4.52 (t, 2H, OCH_2), 3.63 (s, 3H, OCH_3), 3.41 (t, 2H, NCH_2); ^{13}C NMR δ: 168.12 (CO, cyclic), 150.77 (C near N of pyridine ring), 149.62 (C-OCH_3), 110.69 (C of phenyl ring), 45.95 (O-CH_3), 45.18 (CH_2 of imidazolidinone ring), 40.30 (CH of imidazolidinone ring), 36.65 (CH_2-O), 34.59 (CH_2-N); MS: m/z: 777 $[M]^+$; Anal. Calcd. for $C_{39}H_{27}Cl_2N_7O_7$: C, 60.32; H, 3.50; N, 12.63. Found: C, 60.09; H, 3.30; N, 12.42%.

Table 1. Results of antimicrobial activity of synthesized compounds
Zone of inhibition of growth in mm (activity index)

Compds.	Antibacterial activity				Antifungal activity	
	Bacillus subtilis	Eschirichia coli	Klebsiella pneumoniae	Pseudomonas aeruginosa	Candida albicans	Aspergillus fumigatus
5a	8(0.53)	9(0.56)	10(0.56)	7(0.41)	12(0.60)	17(0.77)
5b	8(0.53)	8(0.50)	8(0.44)	8(0.47)	14(0.70)	16(0.73)
5c	9(0.60)	11(0.69)	11(0.61)	10(0.59)	19(0.95)	18(0.82)
5d	7(0.47)	7(0.44)	10(0.56)	6(0.35)	12(0.60)	15(0.68)
5e	6(0.40)	10(0.63)	9(0.50)	9(0.53)	18(0.90)	19(0.86)
7a	11(0.73)	11(0.69)	12(0.67)	11(0.65)	21(1.05)	23(1.05)
7b	9(0.60)	13(0.81)	14(0.78)	10(0.59)	20(1.00)	23(1.05)
7c	12(0.80)	15(0.94)	16(0.89)	12(0.70)	24(1.20)	28(1.27)
7d	10(0.67)	14(0.88)	13(0.72)	10(0.59)	19(0.95)	20(0.91)
7e	10(0.67)	12(0.75)	12(0.67)	9(0.53)	25(1.25)	27(1.23)
Standard	15	16	18	17	20	22

Antimicrobial activity

All the synthesized compounds were evaluated for their antibacterial and antifungal activities. Pure cultures of pathogenic strains used were *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (bacteria), *Candida albicans* and *Aspergillus fumigatus* (fungi). These were sub cultured and characterized by standard methods of identification [44]. Both the activities were carried out by Cup or well method. For antibacterial activity nutrient agar medium was autoclaved (15 Psi, 121° C, 15 min). These were inoculated with suspension of organisms by spread plate method [45]. With the help of sterile borer required number of wells was made in the medium and subsequently these wells were filled

with 500 ppm DMF solution of synthesized compounds. These Petri-dishes were sealed with paraffin and incubated at 37° C in an incubator. Petri-dishes were examined for zone of inhibition after 24 hrs. Ciprofloxacin was used as standard (control). Ten compounds have been screened. Antifungal activity was observed on sabouraud dextrose agar media using similar method (*vide supra*). Fluconazole was used as standard. Results for antibacterial and antifungal activity are represented in table **1**. On the basis of zone size inhibition studies activity index is also prepared and conclusions are drawn.

Antibacterial activity

Minimum Inhibitory Concentration was found above 500 ppm. All the compounds have shown good activity against *E. coli* and *K. peumoniae* (activity index 0.43-0.93). Weaker or insignificant activity is shown by most of the compounds against *P. aeruginosa*. This series of compounds are moderately active against *B. subtilis*. Compounds **(5a-e)** which do not possess ethoxyphthalimide moiety in its molecular framework show lower activity than compounds **(7a-e)**. This indicates the enhancement of activity due to presence of this moiety in the molecule. In **(7a-e)** series **(7c)** has shown highest activity which may be attributed to presence of extra chloro substituent in the molecule.

Antifungal activity

Remarkable activity was noticed only above 500 ppm concentration of synthesized compounds. It is clear from the table that maximum number of compounds show stronger antifungal activity. Compounds **(7a)**, **(7b)**, **(7c)** and **(7e)** show higher activity index than control. Activity of **(5c)**, **(5e)** and **(7d)** are comparable to the standard. Other compounds show moderate activity. It is also observed that activities of all the compounds are similar on both the fungal strains. It is obvious from the zone size interpretative chart that compounds are strong antifungal than of their antibacterial activity. Moreover alkoxyphthalimide pharmacophore when present in the molecule enhanced activity appreciably.

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References

[1] Ishidia, S.; Matsuda, A.; Kawamura, Y.; Yamanaka, *Chemotherapy*, **1960**, *8*, 146; *Chem. Abstr.* **1960**, *54*, 22844c.

[2] Hogale, M. B.; Dhore, N. P.; Shelar, A. R.; Pawar, P. K. *Orient. J. Chem.* **1986**, *2*, 55; *Chem. Abstr.* **1960**, *54*, 325030.

[3] Vibhute, Y. B.; Wadje, S. S. *Indian J. Exptl. Biol.* **1976**, *14*, 739.

[4] Yamakawa, T.; Kagechika, H.; Kawachi, E.; Hashimoto, Y.; Shudo, K. *J. Med. Chem.* **1990**, *33*, 1430.

[5] Bhatt, A. K.; Bhamaria, R. P.; Mrs Patel, M. R.; Bellare, R. A.; Deliwala, C. V. *Indian J. Chem.* **1972**, *10*, 694; *Chem. Abstr.* **1973**, *78*, 119650n.

[6] Ninomiya, Y.; Shimma, N.; Ishitsuka, H. *Antiviral Res.* **1990**, *13*, 61.

[7] Barton, D. H. R.; Ollis, W. D. *Comprehensive Organic Chemistry*; Peramon Press: New York, **1979**.

[8] Nasr, M. N.; Gineinah, M. M. *Arch. Pharm.* **2002**, *335*, 289.

[9] Gangjee, A.; Adair, O.; Queener, S. F. *J. Med. Chem.* **1999**, *42*, 2447.

[10] Ghorab, E. M.; Lee, S.; Siyal, C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem.* **1998**, *141*, 257.

[11] Bar, T.; Zimmermann, P.; Boer, R.; Gekeler, V.; Isc, W.; Boss, H.; Olrich, W. R. PCT Int. Appl. WO 97, 19, 946 (Ci 107D 471/04) June 5, **1997**, CHAPPT 95/3, 322, November 24, **1995**; *Chem. Abstr.* **1997**, *127*, 81463.

[12] Brown, T. H.; Ife, R. J.; Leach, C. A. Eur. Pat. Appl. EP 404, 355(CL CO7D 471/04), December 27, **1990**, GB Appl 89/12, 336, May 30, **1989**, 14; *Chem. Abstr.* **1991**, *114*, 164273.

[13] Shafik, R. M.; Eshba, N. H.; Nabil, H.; El-Semary, M. M.; Abdelkreem, F. M. *Alexandra J. Pharm. Sci.* **1995**, *9*, 55; *Chem. Abstr.* **1995**, *123*, 1332611.

[14] Furuya, S.; Ohtaki, T. Eur. Pat. Appl. EP, **1994**, 608565; *Chem. Abstr.* **1994**, *14*, 205395.

[15] Singh, G.; Singh, G.; Yadav, A. K.; Mishra, A. K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *107*, 165.

[16] Bowlin, T. H. Eur. Pat. Appl. EP, 472, 181 (ClA61K31/70), August 26, **1992**, US Appl 517,

042, August 22, 28, **1990**; *Chem. Abstr.* **1992**, *117*, 70267.
[17] Verheggen, I.; Aerschol, A. V.; Snoeck, R. *J. Med. Chem.* **1993**, *36*, 2033.
[18] Whi-Gun, C.; Thomos, C. K. C.; Ching-Jer, C. *Tetrahedron* **1998**, *54*, 8661.
[19] Chen, J. J.; Dunn, J. P.; Goldstein, D. M. Stahl (F Hoff-mann-La Roche Ag Switz) PCT Int. Appl. WO, **2002**, 064594 A2 207, 2002, CM, **2002**.
[20] Binet, J.; Defosse, G.; Synthelabo, S. A.; Fr-Demande, F. R. **2**, 666, 582 (ClCO7D40 114) 13 Mar **1992**, Appl, 90/11, 100, 07Sep **1990**, C A; *Chem. Abstr.* **1993**, *118*, 6986c.
[21] Naithani, P. K.; Srivastava, V. K.; Gupta, T. K.; Shanker, K. *J. Indian Chem. Soc.* **1991**, *68*, 422.
[22] Heber, D.; Heers, C.; Ravens, U. *Pharmazie* **1993**, *48*, 537.
[23] Moustafa, H.; Shibl, M. F.; Hilal, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180(2)*, 459.
[24] Nakasima, T. *Nippon. Kakin. Gakkaishi.* **1994**, *31*, 412; *Chem. Abstr.* **1995**, *122*, 1047324.
[25] Bridges, A. *J. Chem. Rev.* **2001**, *101*, 2541.
[26] Daub, H.; Specht, K.; Ullrich, A. *Nat. Rev. Drug Discov.* **2004**, *3*, 1001.
[27] Rewcastle, G. W.; Denny, W. A.; Showwalter, H. D. H. *Curr. Org. Chem.* **2000**, *4*, 679.
[28] Wollein, G.; Troschute, R.; *J. Heterocycl. Chem.* **2002**, *39*, 1195.
[29] Connolly, T. J.; Matchett, M.; Sarma, K. *Org. Process Res. and Dev.* **2005**, *9*, 80.
[30] Goker, H.; Kus, C.; Boykin, D. W.; Yildiz, S.; Altanlar, N. *Bioorg. Med. Chem.* **2007**, *17*, 2233.
[31] Dasai, N. C.; Shah, M. D.; Bhavsar, A. M.; Saxena, A. K. *Indian J. Chem.* **2008**, *47B*, 1135.
[32] Ayhan-Kilcigil, G.; Altanlar, N. *Turk J. Chem.* **2006**, *30*, 223.
[33] Liebl, R.; Randte, R.; Mildenberger, H.; Bauer, K.; Bieringer, H. *Chem. Abstr.* **1998**, *108(1)*, 6018.
[34] Mohamed, B. G.; Abdel-Alim, A. A.; Hussein, M. A. *Acta. Pharm.* **2006**, *29*, 31.
[35] Ates-Alagoz, Z.; Kus, C.; Coban, T. *J. Enzyme Inhib. Med. Chem.* **2005**, *20*, 325.
[36] Ayhan-Kilcigil, G.; Kus, C.; Coban, T. Can-Eke, B.; Iscan, M.; *J. Enzyme Inhib. Med. Chem.* **2004**, *20*, 129.
[37] Nakano, H.; Inoue, T.; Kawasaki, N.; Miyataka, H.; Taguchi, T.; Inagaki, N.; Nagai, H.; Satoh, T. *Chem. Pharm. Bull.* **1999**, *47*, 1573.
[38] Denny, W. A.; Rewcastle, G. W.; Bagley, B. C. *J. Pharm. Sci.* **2004**, *33*, 814.
[39] Valdez, J.; Cedillo, R.; Hernandez-Campos, A.; Yepez, L.; Hernandez-Luis, F.; Navarrete-Vazquez, G.; Tapia, A.; Cortes, R.; Hernandez, M.; Castillo, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2221.
[40] Sharma, C.; Thadhaney, B.; Pemawat, G.; Talesara, G. L. *Indian J. Chem.* **2008**, *47B*, 1892,.
[41] Ojha, S.; Bapna, A.; Talesara, G. L. *ARKIVOC* **2008**, *xi*, 112.
[42] Bapna, A.; Ojha, S.; Talesara, G. L. *Indian J. Chem.* **2008**, *47B*, 1096.
[43] Bauer, L.; Suresh, K. S. *J. Org. Chem.* **1963**, *28*, 1604.
[44] Black, J. G. *Microbiology Principles and Explorations*, 4th Edition; Prentice Hall: New Jersey, **1999**, 363.
[45] Bisen, P. S.; Verma, K. *Hand Book of Microbiology*, 1st Edition; CBS publishers: New Delhi, **1996**.