Research Paper

Synthesis and Antibacterial and Antifungal Studies of Novel Nitrogen Containing Heterocycles from 5-Ethylpyridin-2-ethanol

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A novel series of chalcones, pyrimidines and imidazolinone is described; chalcones (4a-o) were prepared from the lead molecule 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde. Pyrimidine (5a-o) derivatives were prepared from the reaction of chalcones and guanidine nitrate in alkali media. Imidazolinones (6a-o) were synthesized from reaction of pyrimidine and oxazolone derivatives (prepared by Erlenmeyer azlactone synthesis). The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR, ^{1}H and ^{13}C NMR spectral data. All the products were screened against different strains of bacteria and fungi. Most of these compounds showed better inhibitory activity in comparison to the standard drugs.

Key words: Antibacterial, antifungal, chalcone, imidazolinone, pyrimidine

Chalcones, both natural or synthetic have been reported to exert a variety of biological activities such as antifungal[1], antibacterial[1,2], antimalarial[3,4], antiinflammatory[5], and anticancer[6]. Antimicrobial activity of these chalcones is attributed to the presence of a reactive α,β-unsaturated keto function that can be altered depending on the type and position of substituent on the aromatic rings. Pyrimidines, which are important constituents of nucleic acids, are of great importance due to their role in the current chemotherapy of AIDS. Derivatives of pyrimidines are of interest due to their antiHIV[7], antimalarial[8], analgesic[9], and antiinflammatory[10], activities.

The basic imidazole nucleus, present in azlactone containing oxazolone moiety, is of great importance for generating penicillin type of drug intermediates and synthetic hormonal compounds. Imidazolones or ketodihydroimidazoles are also known as oxoimidazolines contain a five- membered heterocyclic ring system with nitrogen atoms at positions 1 and 3 and carbonyl group at position 5. Oxoimidazolines have been reported to exhibit antibacterial[11,12], antifungal[13] and antimicrobial activites[14-17]. Imidazolinones have also been reported to possess fungicidal[18,19], herbicidal[19], and vasodilator activities[20].

Recently we have prepared chalcone, pyrimidine and amide derivatives and reported their antibacterial and antifungal activities[21-23]. All these observations and the essential role of heterocyclic chalcone, pyrimidine and imidazolinone derivatives in certain biological importance prompted us to synthesize these compounds for their antimicrobial activity.

MATERIALS AND METHODS

Laboratory chemicals were supplied by Rankem India Ltd. and Fisher Scientific Ltd. Melting points were determined using the open tube capillary method and were uncorrected. Purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene:ethyl acetate (75:25). The spots were observed by exposure to iodine vapours or by UV light. The IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). The ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as

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the internal standard in $CDCl_3$. Elemental analysis of the newly synthesized compounds were carried out on Carlo Erba 1108 analyzer**.**

Procedure for the synthesis of 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde (3):

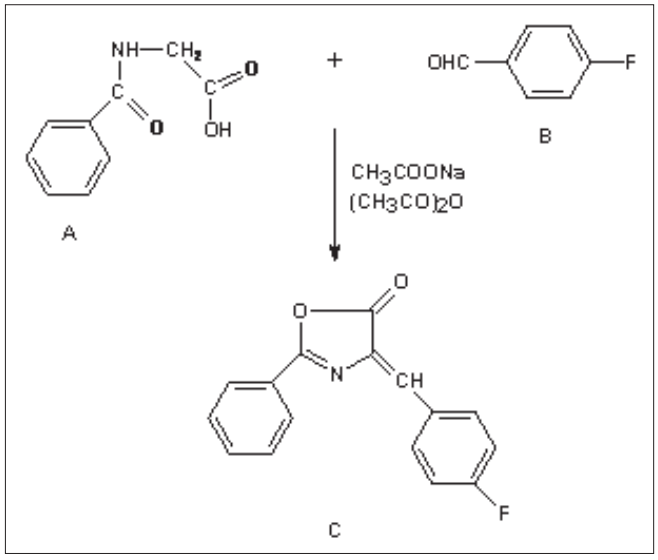
4-[2-(5-Ethylpyridin-2-yl)ethoxy]benzaldehyde (3) was synthesized by the method described in the literature[24,25]. Chalcones and pyrimidines were synthesized and characterized by the reported method[21-23].

General Process of oxazol-5*(4H)*-one (Erlenmeyer azlactone synthesis) (C):

A mixture of *p*-fluoro benzaldehyde (0.33 mol), hippuric acid (0.33 mol) and potassium acetate (0.33 mol) in acetic anhydride (0.83 mol) was refluxed with stirring for 15 min (reaction progress was monitored by TLC using (3:1 isohexane-ethyl acetate as eluent). The mixture was then cooled down and neutralised by addition of solid potassium carbonate. The solid product was separated by filtration, dried and purified by crystallization. The synthetic route has been shown in scheme 1.

General preparation of the compounds 6a-o:

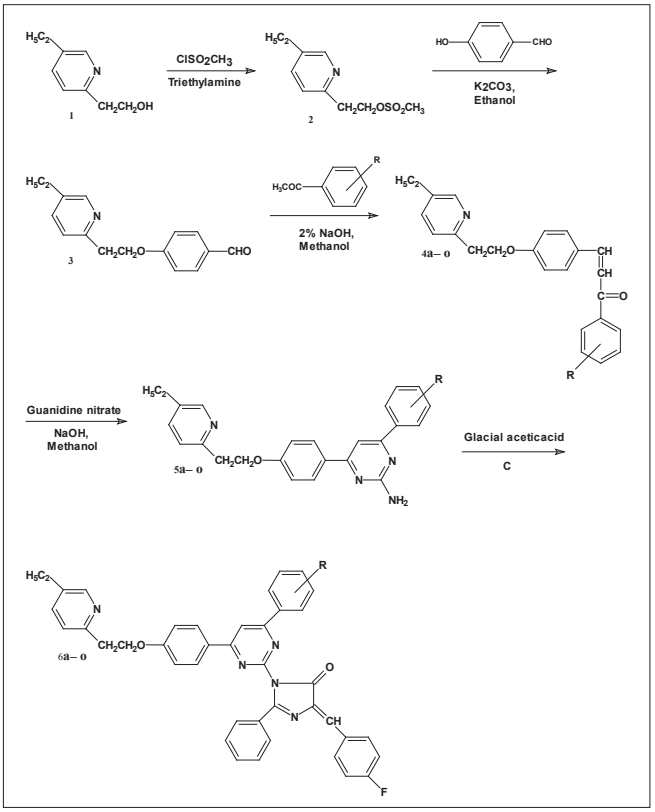
A mixture of 5a-o (0.01 mol) and an appropriate oxazolone (0.01 mol) in 50 ml acetic acid was refluxed for 6-8 h (reaction progress was monitored by TLC using 7.5:2.5 toluene-ethyl acetate as eluent). After completion of reaction; cooled and was poured into ice cold water. The precipitate was filtered and washed with water till pH neutral. The raw product was crystallized from ethanol. The synthetic route is shown in scheme 2 and general structure of 6a-o is represented in fig. 1.



Scheme 1: Synthetic protocol of oxazol-5(4H)-one (Erlenmeyer azlactone synthesis) (C)

1-(4-(2,4-dichloro-5-fluorophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6a):

Brown solid, m.p. 110-112°, yield 56%, R_f: 0.60;



Scheme 2: Synthetic protocol of 4a-o, 5a-o amd 6a-o

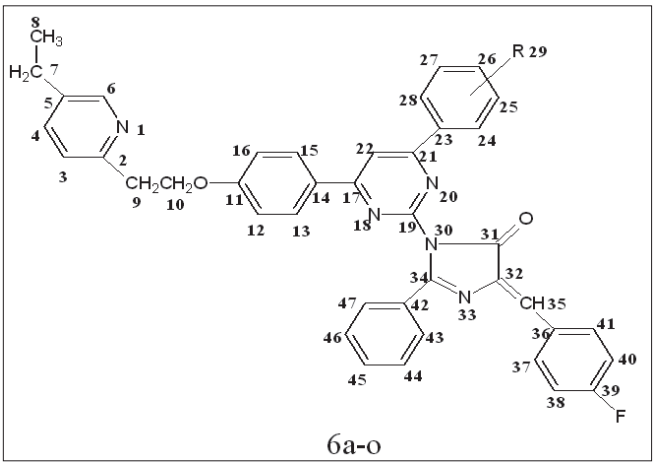


Fig. 1: General structures of imidazolinones 6a-o

IR (KBr, cm^{-1}) ν: 3062 (Ar-H), 2953, 2833 (-CH_2-), 1795 (-C=O of imidazolinone), 1654 (-C=N imidazolinone), 1612 (-C=N of pyrimidine), 1222, 1036 (C-O-C), 972 (C-F), 743 (C-Cl). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.17 (t, 3H, -CH_3), 2.35(s, 3H, -CH_3), 2.51 (q, 2H, -CH_2), 3.22 (t, 2H, -CH_2), 4.33 (t, 2H, -CH_2-O), 7.05-7.55 (m, 16H, Ar-H), 7.31 (s, 1H, -CH), 7.39-8.30 (m, 3H, pyridine-H), 7.81 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.4(C_{31}), 165.3(C_{19}), 164.5(C_{34}), 163.1(C_{17}), 161.0(C_{21}), 126.3-135.5 (C_{36}-C_{41}), 126.3-130.5 (C_{42}-C_{47}), 122.0-157.3 (C_2-C_6), 118.7-161.4 (C_{23}-C_{28}), 115.0-157.3 (C_{11}-C_{16}), 108.5 (C_{35}), 103.3 (C_{22}), 67.2 (C_{10}), 37.3 (C_9), 25.4 (C_7), 15.3 (C_8). Anal. calcd for $C_{41}H_{29}N_5O_2Cl_2F_2$: C 67.22, H 3.99, N 9.56; found C 67.20, H 3.95, N 9.54.

1-(4-(4-methoxyphenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6b):

Pale yellow solid, m.p. 109-113°, yield 60%, R_f: 0.62; IR (KBr, cm^{-1}) ν: 3064 (Ar-H), 2950, 2832 (-CH_2-), 1790 (-C=O of imidazolinone), 1653 (-C=N imidazolinone), 1614 (-C=N of pyrimidine), 1225, 1030 (C-O-C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.15 (t, 3H, -CH_3), 2.30 (s, 3H, -CH_3), 2.52 (q, 2H, -CH_2) , 3.26 (t, 2H, -CH_2), 3.83, (s, 3H, -OCH_3), 4.35 (t, 2H, -CH_2-O), 7.03-7.55 (m, 18H, Ar-H), 7.15 (s, 1H, -CH), 7.40-8.33 (m, 3H, pyridine-H), 7.89 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.6 (C_{31}), 165.2 (C_{19}), 164.2 (C_{34}), 163.3 (C_{17}), 160.4 (C_{21}), 126.7-135.3 (C_{36}-C_{41}), 126.3-130.5 (C_{42}-C_{47}), 122.2-157.3 (C_2-C_6), 115.2-157.1 (C_{11}-C_{16}),114.8-160.6 (C_{23}-C_{28}), 108.1 (C_{35}), 103.5 (C_{22}), 67.2 (C_{10}), 55.3 (C_{29}), 37.4 (C_9), 25.1 (C_7), 15.3 (C_8). Anal. calcd for $C_{42}H_{34}N_5O_3F$: C 74.65, H 5.07, N 10.36; found C 74.66, H 5.09, N 10.33.

1-(4-(2,4-dichlorophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6c):

Pale yellow solid, m.p. 105-108°, yield, 62%, R_f: 0.61; IR (KBr, cm^{-1}) ν: 3058 (Ar-H), 2950, 2832 (-CH_2-), 1791 (-C=O of imidazolinone), 1653 (-C=N imidazolinone), 1615 (-C=N of pyrimidine), 1225, 1037 (C-O-C), 743 (C-Cl). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.13 (t, 3H, -CH_3), 2.35 (s, 3H, -CH_3), 2.54 (q, 2H, -CH_2), 3.23 (t, 2H, -CH_2), 4.36 (t, 2H, -CH_2-O), 7.05-8.03 (m, 17H, Ar-H), 7.32 (s, 1H, -CH), 7.35-8.32 (m, 3H, pyridine-H), 7.83 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.6 (C_{31}), 165.3 (C_{19}), 163.9 (C_{34}), 163.1 (C_{17}), 160.5 (C_{21}), 127.4-135.7 (C_{23}-C_{28}), 126.0-135.5 (C_{36}-C_{41}), 126.2-130.5 (C_{42}-C_{47}), 122.8-157.4 (C_2-C_6), 114.5-157.6 (C_{11}-C_{16}), 108.7 (C_{35}), 103.5 (C_{22}), 67.7 (C_{10}), 37.7 (C_9), 25.1 (C_7), 15.1 (C_8). Anal. calcd for $C_{41}H_{30}N_5O_2Cl_2F$: C 68.91, H 4.23, N 9.80; found C 68.92, H 4.25, N 9.81.

1-(4-(4-hydroxyphenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6d):

Yellow solid, m.p. 205-207°, yield, 54%, R_f: 0.63; IR (KBr, cm^{-1}) ν: 3065(Ar-H), 3354 (-OH), 2953, 2833 (-CH_2-), 1794 (-C=O of imidazolinone), 1652(-C=N imidazolinone), 1612(-C=N pyrimidine), 1223, 1032(C-O-C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm):1.20 (t, 3H, -CH_3), 2.37 (s, 3H, -CH_3), 2.51 (q, 2H, -CH_2) , 3.24 (t, 2H, -CH_2), 4.34 (t, 2H, -CH_2-O), 6.79-7.55 (m, 18H, Ar-H), 7.26 (s, 1H, -CH), 7.37-8.35 (m, 3H, pyridine-H), 7.86 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 169.9 (C_{31}), 165.0 (C_{19}), 164.2 (C_{34}), 163.8(C_{17}), 160.2 (C_{21}), 126.5-135.6(C_{36}-C_{41}), 126.2-130.0 (C_{42}-C_{47}), 122.2-157.3 (C_2-C_6), 116.4-158.5 (C_{23}-C_{28}), 115.1-157.2 (C_{11}-C_{16}), 108.3 (C_{35}), 103.6 (C_{22}), 67.6 (C_{10}), 37.2 (C_9), 25.3 (C_7), 15.9(C_8). Anal. calcd for $C_{41}H_{32}N_5O_3F$: C 74.42, H 4.87, N 10.58; found C 74.40, H 4.85, N 10.55.

1-(4-(2,6-dichloro-5-fluorophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6e):

Brown solid, m.p. 110-112°, yield 55%, R_f: 0.61; IR (KBr, cm^{-1}) ν: 3057 (Ar-H), 2958, 2837 (-CH_2-), 1789 (-C=O of imidazolinone), 1653 (-C=N imidazolinone), 1616 (-C=N of pyrimidine), 1223, 1035 (C-O-C), 972 (C-F), 744 (C-Cl) . ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.16 (t, 3H, -CH_3), 2.32 (s, 3H, -CH_3), 2.56 (q, 2H, -CH_2) , 3.26 (t, 2H, -CH_2), 4.33 (t, 2H, -CH_2-O), 6.81-7.55 (m, 16H, Ar-H), 7.30 (s, 1H, -CH), 7.35-8.34 (m, 3H, pyridine-H), 7.80 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.1 (C_{31}), 165.2 (C_{19}), 164.3 (C_{34}), 163.8 (C_{17}), 160.5 (C_{21}), 126.2-135.5 (C_{36}-C_{41}), 126.1-130.5 (C_{42}-C_{47}), 122.7-157.3 (C_2-C_6), 118.3-161.4 (C_{23}-C_{28}), 114.6-157.5 (C_{11}-C_{16}), 108.9 (C_{35}), 103.5 (C_{22}), 67.1 (C_{10}), 37.4 (C_9), 25.8 (C_7),

15.7 (C_8). Anal. calcd for $C_{41}H_{29}N_5O_2Cl_2F_2$: C 67.22, H 3.99, N 9.56; found C 67.21, H 3.96, N 9.54.

1-(4-(4-methylphenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6f):
Pale yellow solid, m.p. 92-94°, yield 64%, R_f: 0.64; IR (KBr, cm^{-1}) ν: 3062 (Ar-H), 2953, 2836 (-CH_2-), 1798 (-C=O of imidazolinone), 1658 (-C=N imidazolinone), 1612 (-C=N of pyrimidine), 1222, 1035 (C-O-C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.19 (t, 3H, -CH_3), 2.33 (s, 3H, -CH_3), 2.54 (q, 2H, -CH_2) , 3.20 (t, 2H, -CH_2), 4.32 (t, 2H, -CH_2-O), 7.05-7.59 (m, 18H, Ar-H), 7.25 (s, 1H, -CH), 7.39-8.32 (m, 3H, pyridine-H), 7.85 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.3 (C_{31}), 165.5(C_{19}), 164.0(C_{34}), 163.5(C_{17}), 160.9 (C_{21}), 127.4-138.4 (C_{23}-C_{28}), 126.4-135.2 (C_{36}-C_{41}), 126.1-130.2 (C_{42}-C_{47}), 122.5-157.1 (C_2-C_6), 114.9-157.4 (C_{11}-C_{16}), 108.0 (C_{35}), 103.2 (C_{22}), 67.5 (C_{10}), 37.5 (C_9), 25.5 (C_7), 21.2 (C_{29}), 15.4 (C_8). Anal. calcd for $C_{42}H_{34}N_5O_2F$: C 76.46, H 5.19, N 10.62; found C 76.43, H 5.17, N 10.63.

1-(4-(1-phenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy) phenyl)pyrimidin-2-yl)-4-(4-fluoro- benzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6g):
Brown solid, m.p. 86-88° yield 53%, R_f: 0.58; IR (KBr, cm^{-1}) ν: 3063 (Ar-H), 2957, 2836 (-CH_2-), 1794 (-C=O of imidazolinone), 1655 (-C=N imidazolinone), 1615 (-C=N of pyrimidine), 1229, 1034 (C-O-C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.14 (t, 3H, -CH_3), 2.34 (s, 3H, -CH_3), 2.51 (q, 2H, -CH_2) , 3.22 (t, 2H, -CH_2), 4.35 (t, 2H, -CH_2-O), 7.05-7.85 (m, 19H, Ar-H), 7.23 (s, 1H, -CH), 7.32-8.40 (m, 3H, pyridine-H), 7.82 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.8(C_{31}), 165.9 (C_{19}), 164.3(C_{34}), 163.0(C_{17}), 160.5 (C_{21}), 127.5-133.0 (C_{23}-C_{28}), 126.1-135.1 (C_{36}-C_{41}), 126.4-130.5 (C_{42}-C_{47}), 122.2-157.3 (C_2-C_6), 114.2-157.6 (C_{11}-C_{16}), 108.1 (C_{35}), 103.6 (C_{22}), 67.3 (C_{10}), 37.6 (C_9), 25.7 (C_7), 15.3 (C_8). Anal. calcd for $C_{41}H_{32}N_5O_2F$: C 76.26, H 5.00, N 10.85; found C 76.21, H 5.01, N 10.82.

1-(4-(4-fluorophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6h):
Dark brown solid, m.p. 160-162°, yield 57%, R_f: 0.63; IR (KBr, cm^{-1}) ν: 3068 (Ar-H), 2955, 2832 (-CH_2-), 1793 (-C=O of imidazolinone), 1653 (-C=N imidazolinone), 1618 (-C=N of pyrimidine), 1226, 1039 (C-O-C), 974 (C-F). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.20 (t, 3H, -CH_3), 2.36 (s, 3H, -CH_3), 2.56 (q, 2H, -CH_2) , 3.23 (t, 2H, -CH_2), 4.36 (t, 2H, -CH_2-O), 7.05-8.15 (m, 18H, Ar-H), 7.28 (s, 1H, -CH), 7.37-8.38 (m, 3H, pyridine-H), 7.86 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.4 (C_{31}), 165.6 (C_{19}), 164.6 (C_{34}), 163.6 (C_{17}), 160.3 (C_{21}), 126.0-135.0 (C_{36}-C_{41}), 126.1-130.7 (C_{42}-C_{47}), 122.3-157.7 (C_2-C_6), 116.0-162.9 (C_{23}-C_{28}), 114.3-157.6 (C_{11}-C_{16}), 108.6 (C_{35}), 103.5 (C_{22}), 67.5 (C_{10}), 37.4 (C_9), 25.6 (C_7), 15.1 (C_8). Anal. calcd for $C_{41}H_{31}N_5O_2F_2$: C 74.19, H 4.71, N 10.55; found C 74.15, H 4.69, N 10.50.

1-(4-(2,4-fluorophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluoro benzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6i):
Brown solid, m.p. 105-107° yield 59%, R_f: 0.64; IR (KBr, cm^{-1}) ν: 3066 (Ar-H), 2953, 2833 (-CH_2-), 1795 (-C=O of imidazolinone), 1654 (-C=N imidazolinone), 1613 (-C=N of pyrimidine), 1225, 1035 (C-O-C), 975 (C-F). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.22 (t, 3H, -CH_3), 2.39 (s, 3H, -CH_3), 2.58 (q, 2H, -CH_2) , 3.19 (t, 2H, -CH_2), 4.37 (t, 2H, -CH_2-O), 6.74-7.55 (m, 17H, Ar-H), 7.30 (s, 1H, -CH), 7.35-8.35 (m, 3H, pyridine-H), 7.84 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.7 (C_{31}), 165.7 (C_{19}), 164.3 (C_{34}), 163.3 (C_{17}), 160.4 (C_{21}), 105.2-164.5 (C_{23}-C_{28}), 126.3-135.6 (C_{36}-C_{41}), 126.3-130.6 (C_{42}-C_{47}), 122.2-157.5 (C_2-C_6), 114.5-157.7 (C_{11}-C_{16}), 108.3 (C_{35}), 103.7 (C_{22}), 67.2 (C_{10}), 37.4 (C_9), 25.8 (C_7), 15.9 (C_8). Anal. calcd for $C_{41}H_{30}N_5O_2F_3$: C 72.24, H 4.44, N 10.27; found C 72.21, H 4.42, N 10.22.

1-(4-(4-bromophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6j):
Brown solid, m.p. 102-104° yield 63%, R_f: 0.61; IR (KBr, cm^{-1}) ν: 3063 (Ar-H), 2954, 2836 (-CH_2-), 1794 (-C=O of imidazolinone), 1656 (-C=N imidazolinone), 1610 (-C=N of pyrimidine), 1225, 1033 (C-O-C), 864 (C-Br) . ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.18 (t, 3H, -CH_3), 2.31 (s, 3H, -CH_3), 2.53 (q, 2H, -CH_2) , 3.24 (t, 2H, -CH_2), 4.33 (t, 2H, -CH_2-O), 7.05-7.78 (m, 18H, Ar-H), 7.31 (s, 1H, -CH), 7.41-8.39 (m, 3H, pyridine-H), 7.87 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.4 (C_{31}), 165.3 (C_{19}), 164.7 (C_{34}), 163.2 (C_{17}), 160.5 (C_{21}), 123.1-132.1 (C_{23}-C_{28}), 126.6-135.4 (C_{36}-C_{41}), 126.6-130.3 (C_{42}-C_{47}), 122.2-157.6 (C_2-C_6), 115.2-157.2 (C_{11}-C_{16}), 108.4

(C_{35}), 103.5 (C_{22}), 67.2 (C_{10}), 37.2 (C_9), 25.4 (C_7), 15.6 (C_8). Anal. calcd for $C_{41}H_{31}N_5O_2FBr$: C 67.96, H 4.31, N 9.66; found C 67.90, H 4.30, N 9.68.

1-(4-(3,4-dichlorophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6k):

Brown solid, m.p. 75-78° yield 61%, R_f: 0.62; IR (KBr, cm^{-1}) ν: 3060 (Ar-H), 2952, 2834 (-CH_2-), 1798 (-C=O of imidazolinone), 1658 (-C=N imidazolinone), 1609 (-C=N of pyrimidine), 1220, 1034 (C-O-C), 748 (C-Cl) . ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.20 (t, 3H, -CH_3), 2.36 (s, 3H, -CH_3), 2.50 (q, 2H, -CH_2) , 3.23 (t, 2H, -CH_2), 4.35 (t, 2H, -CH_2-O), 7.05-7.86 (m, 17H, Ar-H), 7.21 (s, 1H, -CH), 7.33-8.35 (m, 3H, pyridine-H), 7.82 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.6 (C_{31}), 165.0 (C_{19}), 164.1 (C_{34}), 163.1 (C_{17}), 161.0 (C_{21}), 127.0-133.8 (C_{23}-C_{28}), 126.7-135.4 (C_{36}-C_{41}), 126.5-130.6 (C_{42}-C_{47}), 122.1-157.4 (C_2-C_6), 114.3-157.3 (C_{11}-C_{16}), 108.5 (C_{35}), 103.0 (C_{22}), 67.1 (C_{10}), 37.2 (C_9), 25.7 (C_7), 15.1 (C_8). Anal. calcd for $C_{41}H_{30}N_5O_2Cl_2F$: C 68.91, H 4.23, N 9.80; found C 68.88, H 4.20, N 9.79.

1-(4-(4-chlorophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6l):

Pale yellow solid, m.p. 135-138°, yield 67%, R_f: 0.58; IR (KBr, cm^{-1}) ν: 3061(Ar-H), 2951, 2837(-CH_2-), 1792(-C=O imidazolinone), 1652 (-C=N imidazolinone), 1615(-C=N pyrimidine), 1227, 1037(C-O-C), 742(C-Cl) . ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.15(t, 3H, -CH_3), 2.34(s, 3H, -CH_3), 2.52(q, 2H, -CH_2) , 3.22(t, 2H, -CH_2), 4.34 (t, 2H, -CH_2-O), 7.05-7.98(m, 18H, Ar-H), 7.32(s, 1H, -CH), 7.36-8.29(m, 3H, pyridine-H), 7.82 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 171.2(C_{31}), 164.9(C_{19}), 164.3 (C_{34}), 163.2 (C_{17}), 160.4 (C_{21}), 128.9-134.3 (C_{23}-C_{28}), 126.4-135.4 (C_{36}-C_{41}), 126.6-130.0 (C_{42}-C_{47}), 122.2-157.4 (C_2-C_6), 114.5-157.6 (C_{11}-C_{16}), 108.2 (C_{35}), 103.6 (C_{22}), 67.8 (C_{10}), 37.8 (C_9), 25.1 (C_7), 15.5 (C_8). Anal. calcd for $C_{41}H_{31}N_5O_2ClF$: C 72.40, H 4.59, N 10.30; found C 72.39, H 4.57, N 10.32.

1-(4-(3-methoxyphenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6m):

Yellow solid, m.p. 84-87° yield 59%, R_f: 0.63; IR(KBr, cm^{-1}) ν: 3063(Ar-H), 2952, 2831(-CH_2-), 1797 (-C=O imidazolinone), 1657 (-C=N imidazolinone), 1616 (-C=N pyrimidine), 1220, 1036 (C-O-C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.18(t, 3H, -CH_3), 2.36(s, 3H, -CH_3), 2.57(q, 2H, -CH_2) , 3.24(t, 2H, -CH_2), 3.73(s, 3H, -OCH_3), 4.36(t, 2H, -CH_2-O), 6.73-7.55(m, 18H, Ar-H), 7.24(s, 1H, -CH), 7.40-8.35(m, 3H, pyridine-H), 7.84 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.0 (C_{31}), 165.2 (C_{19}), 164.4(C_{34}), 163.8(C_{17}), 160.3(C_{21}), 126.3-135.5(C_{36}-C_{41}), 126.4-130.6(C_{42}-C_{47}), 122.3-157.3 (C_2-C_6), 111.2-161.1(C_{23}-C_{28}), 114.5-157.6(C_{11}-C_{16}), 108.1(C_{35}), 103.4(C_{22}), 67.2 (C_{10}), 55.8(C_{29}), 37.3(C_9), 25.2(C_7), 15.7(C_8). Anal. calcd for $C_{42}H_{34}N_5O_3F$: C 74.65, H 5.07, N 10.36; found C 74.63, H 5.04, N 10.34.

1-(4-(3-fluorophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6n):

Brown solid, m.p. 115-118°, yield 56%, R_f: 0.64; IR (KBr, cm^{-1}) ν: 3067(Ar-H), 2955, 2835(-CH_2-), 1795 (-C=O imidazolinone), 1653 (-C=N imidazolinone), 1613(-C=N pyrimidine), 1225, 1030(C-O-C), 973(C-F) . ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.16(t, 3H, -CH_3), 2.38(s, 3H, -CH_3), 2.56(q, 2H, -CH_2), 3.24 (t, 2H, -CH_2), 4.35 (t, 2H, -CH_2-O), 6.93-7.55 (m, 18H, Ar-H), 7.21 (s, 1H, -CH), 7.39-8.38 (m, 3H, pyridine-H), 7.87 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.4 (C_{31}), 165.8 (C_{19}), 164.9 (C_{34}), 163.0 (C_{17}), 160.0 (C_{21}), 126.0-135.2 (C_{36}-C_{41}), 126.7-130.7 (C_{42}-C_{47}), 122.3-157.4 (C_2-C_6), 115.5-163.4 (C_{23}-C_{28}), 114.3-157.6 (C_{11}-C_{16}), 108.7 (C_{35}), 103.5 (C_{22}), 67.4 (C_{10}), 37.2 (C_9), 25.8 (C_7), 15.3 (C_8). Anal. calcd for $C_{41}H_{31}N_5O_2F_2$: C 74.19, H 4.71, N 10.55; found C 74.20, H 4.72, N 10.53.

1-(4-(3,4-difluorophenyl)-6-(4-(2-(5-ethylpyridin-2-yl)ethoxy)phenyl)pyrimidin-2-yl)-4-(4-fluorobenzylidene)-2-phenyl-1H-imidazol-5(*4H*)-one (6o):

Brown solid, m.p. 137-140° yield 58%, R_f: 0.62; IR (KBr, cm^{-1}) ν: 3064 (Ar-H), 2956, 2835 (-CH_2-), 1794 (-C=O of imidazolinone), 1653 (-C=N imidazolinone), 1613 (-C=N of pyrimidine), 1223, 1037 (C-O-C), 970 (C-F) . ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 1.23 (t, 3H, -CH_3), 2.34 (s, 3H, -CH_3), 2.51 (q, 2H, -CH_2) , 3.25 (t, 2H, -CH_2), 4.39 (t, 2H, -CH_2-O), 7.01-7.92 (m, 17H, Ar-H), 7.27 (s, 1H, -CH), 7.38-8.33 (m, 3H, pyridine-H), 7.82 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 170.6 (C_{31}), 165.2 (C_{19}),

164.3 (C_{34}), 163.2 (C_{17}), 160.4 (C_{21}), 126.2-135.5 (C_{36}-C_{41}), 126.3-130.5 (C_{42}-C_{47}), 122.3-157.4 (C_2-C_6), 117.6-150.0 (C_{23}-C_{28}), 114.2-157.5 (C_{11}-C_{16}), 108.8 (C_{35}), 103.7 (C_{22}), 67.8 (C_{10}), 37.5 (C_9), 25.0 (C_7), 15.1 (C_8). Anal. calcd for $C_{41}H_{30}N_5O_2F_3$: C 72.24, H 4.44, N 10.27; found C 72.26, H 4.42, N 10.25.

RESULTS AND DISCUSSION

The MICs of synthesized compounds were carried out by broth microdilution method as described by Rattan[26]. Antibacterial activity was screened against two gram positive (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenus* MTCC 443) and two gram negative (*Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 2488) bacteria, ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323, greseofulvin was used as a standard antifungal agent. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh, India.

The minimum bactericidal concentrations (MBCs) of 4a-o, 5a-o and 6a-o are shown in Table 1. From the screening data, most of the compounds possessed better antibacterial activity (MBC, 50-250 µg/ml) against *S. aureus*; chalcones 4b, 4f and 4h with 4-OCH_3, 4-CH_3 and 4-F group showed MBC value in the range between 62.5-100 µg/ml against *E. coli;* 4h at 100 µg/ml against *P. aeruginosa*; 4f and 4h bearing 4-CH_3 and 4-F at 100-150 µg/ml while remaining 4b, 4d and 4n having 4-OCH_3, 4-OH and 3-F showed comparable activity against *S. aureus* with ampicillin. The remaining chalcones showed less activity against all four bacterial species. The pyrimidine 5b and 5i containing 4-OCH_3 and 2,4-F possessed more activity of 62.5 µg/ml against *E. coli*; 5h having 4-F at 100 µg/ml against *S. aureus* and *S. pyogeneus*; 5i containing 2,4-F at 150 µg/ml against *S. aureus;* 5l having 4-Cl at 100 µg/ml against *P. aeruginosa* and at 150 µg/ml against *S. aureus*. The remaining pyrimidines displayed less activity against all four bacterial species comparable to ampicillin. Imidazolinones 6j having 4-Br at 100 µg/ml against *E. coli* and 250 µg/ml against *S. aureus;* 6a, 6d, 6f, 6h, 6i, 6j, 6k, 6n and 6o containing 2,4-Cl, 5-F, 4-OH, 4-CH_3, 4-F, 2,4-F, 4-Br, 3,4-Cl, 3-F and 3,4-F grpups at 200-250 µg/ml against *S. aureus* were comparable with ampicillin.

Minimum fungicidal concentrations (MFCs) are shown in Table 2. Most of the compounds possessed very good antifungal activity against *C. albicans*; their MFC range between 100-500 µg/ml. In chalcones, 4c, 4d, 4g, 4h, 4m and 4n containing 2,4-Cl, 4-OH, phenyl, 4-F, 3-OCH_3 and 3-F at 200-500 µg/ml; 5o having 3,4-F at 200 µg/ml against *C. albicans*, while remaining pyrimidines are less active against *A. niger* and *A. clavatus* compared with greseofulvin. Imidazolinones, 6c containing 2,4-Cl displayed more at 100 µg/ml against *C. albicans, A. niger* and *A. clavatus* with greseofulvin and nystatin*;* 6e and 6h having 2,6-Cl, 5-F and 4-F at 250 µg/ml against *C. albicans*, while other imidazolinones show moderate activity against *C. albicans* with greseofulvin. Remainning imidazolinones are less active against two fungal *A. niger* and *A. clavatus*.

In overall microbial analysis; all compounds are comparable with *S. aureus* and *C. albicans*. Chalcones having methoxy, methyl, hydroxy and fluoro groups, pyrimidines with methoxy, difluoro and chloro

TABLE 1: ANTIBACTERIAL ACTIVITY OF COMPOUND 4A-O, 5A-O AND 6A-O

Compounds	R	Minimal bactericidal concentration µg/ml			
		Gram negative		Gram positive	
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*
4b	4-OCH_3	100	150	250	250
4d	4-OH	150	200	250	250
4f	4-CH_3	100	150	100	250
4h	4-F	62.5	100	150	150
4n	3-F	250	500	250	500
5b	4-OCH_3	62.5	150	250	250
5c	2,4-Cl	500	500	250	500
5f	4-CH_3	200	200	250	250
5h	4-F	250	250	100	100
5i	2,4-F	62.5	150	150	200
5j	4-Br	250	250	200	200
5k	3,4-Cl	250	250	250	250
5l	4-Cl	250	100	150	250
5n	3-F	500	500	250	250
6a	2,4-Cl,5-F	500	500	250	250
6d	4-OH	500	500	250	500
6f	4-CH_3	125	200	250	250
6h	4-F	150	250	250	250
6i	2,4-F	500	500	250	250
6j	4-Br	100	150	250	250
6k	3,4-Cl	500	500	200	200
6n	3-F	500	250	250	200
6o	3,4-F	500	500	250	500
Ampicillin		100	100	250	100

TABLE 2: ANTIFUNGAL ACTIVITY OF COMPOUND 4A-O, 5A-O AND 6A-O

Compounds	R	Minimal fungicidal concentration μg/ml		
		C. albicans	*A. niger*	*A. clavatus*
4c	2,4-Cl	500	500	1000
4d	4-OH	500	500	1000
4g	Phenyl	200	500	500
4h	4-F	250	>1000	>1000
4m	3-OCH_3	500	500	500
4n	3-F	500	1000	1000
5a	2,4-Cl,5-F	500	500	1000
5b	4-OCH_3	500	>1000	>1000
5c	2,4-Cl	500	>1000	>1000
5d	4-OH	500	500	1000
5e	2,6-Cl,5-F	500	500	500
5f	4-CH_3	500	500	500
5g	Phenyl	500	500	500
5h	4-F	500	250	250
5i	2,4-F	500	1000	1000
5l	4-Cl	500	500	500
5n	3-F	500	1000	1000
5o	3,4-F	200	200	200
6c	2,4-Cl	100	100	100
6e	2,6-Cl,5-F	250	>1000	>1000
6f	4-CH_3	500	1000	1000
6h	4-F	250	1000	1000
6j	4-Br	500	1000	1000
6k	3,4-Cl	500	1000	1000
6m	3-OCH_3	500	500	500
6n	3-F	500	250	500
Nystatin		100	100	100
Greseofulvin		500	100	100

substitutents and imidazolinones having, chloro, dichloro, fluoro and difluoro are more active group against *S. aureus* and *C. albicans*. Imidazolinone 6c 2,4-Cl is comparable with both nystatin and greseofulvin.

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