Arabian Journal of Chemistry (2012) 5, 81–91

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Characterization and pharmacological evaluation of new pyridine analogs

Navin B. Patel *, Hemant R. Patel

Department of Chemistry, Veer Narmad South Gujarat University, Surat 395 007, India

Received 21 July 2010; accepted 23 July 2010
Available online 1 August 2010

KEYWORDS

Chalcone;
Pyrimidine;
Amide;
Microbial studies

Abstract Reaction of 5-ethyl pyridine-2-ethanol **1** and methane sulphonyl chloride gives corresponding sulphonate **2**; which on condensation with *p*-hydroxy benzaldehyde will give 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde **3**. A series of chalcones **4a–o** were prepared from **3** and substituted aromatic acetophenone. Chalcones **4a–o** further react with guanidine nitrate to give a series of pyrimidines **5a–o** which condense with 3,4-dichlorobenzylchloride to give amide derivatives **6a–o**. Newly synthesized compounds have been examined on the basis of spectral analysis. All the compounds were screened against different gram-positive and gram-negative bacteria. Most of these compounds showed better inhibitory activity in comparison with the standard drugs.

1. Introduction

The number of life-threatening infections caused by multidrug-resistant gram-positive pathogens has reached an alarming level in hospitals and community. Infections caused by these organisms pose a serious challenge to the scientific community and the need for an effective therapy has led to a search for novel antibacterial agents.

Amides, thioamides and carbamates are versatile intermediates in the synthesis of natural products. A large number of antibiotics contain amide linkage. Several derivatives of amides were prepared and found to possess different activities like antimicrobial (Aytemir et al., 2003; Yildiz Oren et al., 2004; Temiz-Arpacı et al., 2005) antibacterial (Desai and Chikhalia, 2005) antifungal, antimycobacterial activities and photosynthesis inhibition activity (Dolezal et al., 2002, 2006). Amide also possessed anti-inflammatory and analgesic activities (Zhong et al., 2009; Banoglu et al., 2007; Geronikaki et al., 2003). Several amides also displayed brain antihypoxic activity (Mitkov et al., 2007), antinociceptive (Onkol et al., 2004) and insecticidal activity (De Paula et al., 2000).

Literature survey reveals that various drugs for e.g. penicillin, pyrazinamide, indinavir, and ritonavir contain particular activities due to the amide linkage present in their structures.

The present study is concerned with the synthesis of the series of heterocyclic amides prepared from pyrimidine deriva-

* Corresponding author. Tel.: +91 0261 2264746; fax: +91 0261 2256012.
E-mail address: drnavin@satyam.net.in (N.B. Patel).

Peer review under responsibility of King Saud University.
doi:10.1016/j.arabjc.2010.07.028

Production and hosting by Elsevier

tives. Considering these findings, we thought of synthesizing the amide derivatives.

2. Experimental

2.1. General

Laboratory Chemicals were supplied by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the toluene:ethyl acetate (7.5:2.5) solvent system. 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 NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as the internal standard in $CDCl_3$. Elemental analysis of the newly synthesized compounds was carried out on a Carlo Erba 1108 analyzer.

2.2. General preparation of the compounds **4a–o**

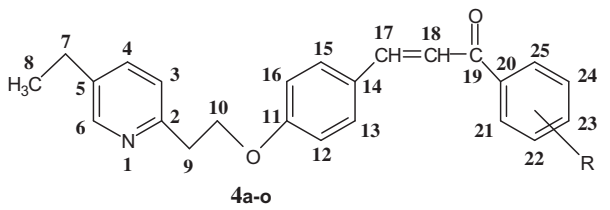
To a solution of **3** (4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde) (Gaonkar et al., 2006; Momose et al., 1991) (0.01 mol) in methanol (50 mL), different substituted aromatic acetophenones (0.01 mol) were added in the presence of 2% NaOH solution (5 mL) and the mixtures were stirred for 10–12 h at room temperature. The solvent was distilled off and crude product poured into ice water. The compound thus obtained was washed with water and recrystallized from ethanol to get the pure intermediate (Fig. 1).

2.2.1. 5-Ethyl-2-{[4-(1-(2,4-dichloro-5-fluorophenyl)-2-propan-1-one-3-yl)]phenoxy ethyl} pyridine (**4a**)

m.p. 121–123 °C. Yield 80%. R_f: 0.58. IR (KBr): t = 3062 (Ar-H), 2953, 2836 (–CH_2–), 1664 (–C═O), 1598(–CH═CH–), 1223, 1033 (C–O–C), 975 (C–F), 742 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.17 (t, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.16 (t, 2H, –CH_2), 4.32 (t, 2H, –CH_2–O), 7.00–7.84 (m, 6H, Ar–*H*), 7.10 (d, 1H, ═C*H*–CO), 7.18 (d, 1H, –C*H*), 7.36–8.28 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (*C*-8), 25.1 (*C*-7), 38.0 (*C*-9), 67.5 (*C*-10), 115.5–156.0 (*C*-11–*C*-16), 117.3–161.5 (*C*-20–*C*-25), 119.2 (*C*-18), 122.4–160.5 (*C*-2–*C*-6), 144.5 (*C*-17), 190.5 (*C*-19). Anal. calcd for $C_{24}H_{20}NO_2Cl_2F$: C64.88, H4.54, N3.15. Found C64.84, H4.50, N3.10.

2.2.2. 5-Ethyl-2-{[4-(1-(4-methoxyphenyl)-2-propan-1-one-3-yl)]phenoxyethyl} pyridine (**4b**)

m.p. 84–86 °C. Yield 72%. R_f: 0.56. IR (KBr): t = 3064 (Ar-H), 2947, 2835 (–CH_2–), 1663 (–C═O), 1596 (–CH═CH–), 1220, 1028 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (t, 3H, –CH_3), 2.57 (q, 2H, –CH_2), 3.19 (t, 2H, –CH_2), 3.84 (s, 3H, –OCH_3), 4.33 (t, 2H, –CH_2–O), 7.12 (d, 1H, ═C*H*–CO), 7.20 (d, 1H, –C*H*), 7.38–8.27 (m, 3H, Pyridine-*H*), 7.05–8.11 (m, 8H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (*C*-8), 25.5 (*C*-7), 37.0 (*C*-9), 55.5 (*C*-26), 66.4 (*C*-10), 115.0–116.4 (*C*-20–*C*-25), 115.2–155.5 (*C*-11–*C*-16), 118.5 (*C*-18), 124.0–160.0 (*C*-2–C-6), 143.5 (*C*-17), 189.5 (*C*-19). Anal. calcd for $C_{25}H_{25}NO_3$: C77.49, H6.50, N3.61. Found C77.42, H6.42, N3.54.



4a-o

Figure 1 Chalcones **4a–o**.

2.2.3. 5-Ethyl-2-{[4-(1-(2,4-dichlorophenyl)-2-propan-1-one-3-yl)]phenoxyethyl} pyridine (**4c**)

m.p. 95–97 °C. Yield 82%. R_f: 0.54. IR (KBr): t = 3066 (Ar-H), 2953, 2835 (–CH_2–), 1660 (–C═O), 1592 (–CH═CH–), 1218, 1030 (C–O–C), 740 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18 (t, 3H, –CH_3), 2.56 (q, 2H, –CH_2), 3.18 (t, 2H, –CH_2), 4.35 (t, 2H, –CH_2–O), 7.03–7.69 (m, 7H, Ar-*H*), 7.13 (d, 1H, ═C*H*–CO), 7.17 (d, 1H, –C*H*), 7.39–8.29 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (*C*-8), 25.8 (*C*-7), 38.5 (*C*-9), 67.3 (*C*-10), 114.5–156.5 (*C*-11–*C*-16), 119.5 (*C*-18), 122.0–159.5 (*C*-2–*C*-6), 127.3–141.5 (*C*-20–*C*-25), 144.0 (*C*-17), 190.8 (*C*-19). Anal. calcd for $C_{24}H_{21}NO_2Cl_2$: C67.61, H4.96, N3.29. Found C67.60, H4.90, N3.23.

2.2.4. 5-Ethyl-2-{[4-(1-(4-hydroxyphenyl)-2-propan-1-one-3-yl)]phenoxyethyl} pyridine (**4d**)

m.p. 178–179 °C. Yield 78%. R_f: 0.59. IR (KBr): t = 3057 (Ar-H), 2945, 2832 (–CH_2–), 1660 (–C═O), 1595 (–CH═CH–), 1216, 1033 (C–O–C), 3375 (–OH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, 3H, –CH_3), 2.58 (q, 2H, –CH_2), 3.15 (t, 2H, –CH_2), 4.36 (t, 2H, –CH_2–O), 5.15 (s, 1H, –O*H*), 7.01–8.05 (m, 8H, Ar-*H*), 7.12 (d, 1H, ═C*H*–CO), 7.19 (d, 1H, –C*H*), 7.37–8.31 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (*C*-8), 25.1 (*C*-7), 38.0 (*C*-9), 67.5 (*C*-10), 115.5-156.0 (*C*-11–*C*-16), 116.3–132.0 (*C*-20–*C*-25), 119.2 (*C*-18), 122.4–160.5 (*C*-2–*C*-6), 144.5 (*C*-17), 190.5 (*C*-19). Anal. calcd for $C_{24}H_{23}NO_3$: C77.19, H6.21, N3.75. Found C77.13, H6.16, N3.70.

2.2.5. 5-Ethyl-2-{[4-(1-(2,6-chloro-5-fluorophenyl)-2-propan-1-one-3-yl)]phenoxy ethyl}pyridine (**4e**)

m.p. 101–103 °C. Yield 85%. R_f: 0.53. IR (KBr): t = 3065 (Ar-H), 2955, 2837 (–CH_2–), 1657 (–C═O), 1589 (–CH═CH–), 1225, 1036 (C–O–C), 976 (C–F), 747 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (t, 3H, –CH_3), 2.55 (q, 2H, –CH_2), 3.17 (t, 2H, –CH_2), 4.33 (t, 2H, –CH_2–O), 7.03–7.32 (m, 6H, Ar-*H*), 7.11 (d, 1H, ═C*H*–CO), 7.19 (d, 1H, –C*H*), 7.37–8.29 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (*C*-8), 25.4 (*C*-7), 38.0 (*C*-9), 67.3 (*C*-10), 115.5–156.5 (*C*-11–*C*-16), 117.5–162.0 (*C*-20–*C*-25), 119.5 (*C*-18), 122.0–160.0 (*C*-2–*C*-6), 144.2 (*C*-17), 190.3 (*C*-19). Anal. calcd for $C_{24}H_{20}NO_2Cl_2F$: C64.88, H4.54, N3.15. Found C64.86, H4.50, N3.07.

2.2.6. 5-Ethyl-2-{[4-(1-(4-methylphenyl)-2-propan-1-one-3-yl)]phenoxyethyl} pyridine (**4f**)

m.p. 115–120 °C. Yield 80%. R_f: 0.55. IR (KBr): t = 3060 (Ar-H), 2950, 2835 (–CH_2–), 1662 (–C═O), 1599 (–CH═CH–), 1223, 1033 (C–O–C). ^{1}H NMR ($CDCl_3$,

400 MHz): δ = 1.16 (t, 3H, –CH_3), 2.34 (s, 3H, –CH_3), 2.55 (q, 2H, –CH_2), 3.18 (t, 2H, –CH_2), 4.32 (t, 2H, –CH_2–O), 6.84–7.84 (m, 8H, Ar-*H*), 7.11 (d, 1H, =C*H*–CO), 7.19 (d, 1H, –C*H*), 7.39–8.30 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (*C*-8), 21.7 (*C*-26), 25.8 (*C*-7), 37.4 (*C*-9), 67.4 (*C*-10), 115.0–155.3 (*C*-11–*C*-16), 119.7 (*C*-18), 123.4–160.9 (*C*-2–*C*-6), 127.5–142.4 (*C*-20–*C*-25), 144.2 (*C*-17), 190.0 (*C*-19). Anal. calcd for $C_{25}H_{25}NO_2$: C80.83, H6.78, N3.77. Found C80.81, H6.74, N3.71.

*2.2.7. 5-Ethyl-2-{[4-(1-(1-phenyl)-2-propan-1-one-3-yl)]phenoxyethyl}pyridine (**4g**)*

m.p. 90–92 °C. Yield 83%. R_f: 0.53. IR (KBr): t = 3055 (Ar-H), 2947, 2832 (–CH_2–), 1657 (–C=O), 1596 (–CH=CH–), 1217, 1029 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18 (t, 3H, –CH_3), 2.56 (q, 2H, –CH_2), 3.17 (t, 2H, –CH_2), 4.30 (t, 2H, –CH_2–O), 7.01–7.81 (m, 9H, Ar-*H*), 7.13 (d, 1H, =C*H*–CO), 7.18 (d, 1H, –C*H*), 7.38–8.32 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (*C*-8), 25.5 (*C*-7), 38.2 (*C*-9), 67.3 (*C*-10), 115.5–156.2 (*C*-11–*C*-16), 119.5 (*C*-18), 122.4–160.5 (*C*-2–*C*-6), 127.8–138.0 (*C*-20–*C*-25), 144.5 (*C*-17), 190.2 (*C*-19). Anal. calcd for $C_{24}H_{23}NO_2$: C80.64, H6.49, N3.93. Found C80.63, H6.45, N3.86.

*2.2.8. 5-Ethyl-2-{[4-(1-(4-fluorophenyl)-2-propan-1-one-3-yl)]phenoxyethyl }pyridine (**4h**)*

m.p. 100–103 °C. Yield 79%. R_f: 0.54. IR (KBr): t = 3062 (Ar-H), 2953, 2838 (–CH_2–), 1661 (–C=O), 1594 (–CH=CH–), 1222, 1037 (C–O–C), 970 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18 (t, 3H, –CH_3), 2.56 (q, 2H, –CH_2), 3.16 (t, 2H, –CH_2), 4.33 (t, 2H, –CH_2–O), 7.05–7.79 (m, 8H, Ar-*H*), 7.14 (d, 1H, =C*H*–CO), 7.19 (d, 1H, –C*H*), 7.39-8.29 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (*C*-8), 25.3 (*C*-7), 38.0 (*C*-9), 67.0 (*C*-10), 115.5–156.5 (*C*-11–*C*-16), 116.5–168.0 (*C*-20–*C*-25), 119.5 (*C*-18), 122.5–160.3 (*C*-2–*C*-6), 144.2 (*C*-17), 190.3 (*C*-19). Anal. calcd for $C_{24}H_{22}NO_2F$: C76.78, H5.91, N3.73. Found C76.74, H5.86, N3.66.

*2.2.9. 5-Ethyl-2-{[4-(1-(2,4-fluorophenyl)-2-propan-1-one-3-yl)]phenoxyethyl }pyridine (**4i**)*

m.p. 75–78 °C. Yield 81%. R_f: 0.57. IR (KBr): t = 3064 (Ar-H), 2949, 2834 (–CH_2–), 1658 (–C=O), 1598 (–CH=CH–), 1217, 1030 (C–O–C), 973 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (t, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.15 (t, 2H, –CH_2), 4.30 (t, 2H, –CH_2–O), 6.87–7.77 (m, 7H, Ar-*H*), 7.12 (d, 1H, =C*H*–CO), 7.17 (d, 1H, –C*H*), 7.38–8.32 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (*C*-8), 25.6 (*C*-7), 38.4 (*C*-9), 67.5 (*C*-10), 105.5–169.5 (*C*-20–*C*-25), 115.1–156.2 (*C*-11–*C*-16), 119.2 (*C*-18), 122.4–160.5 (*C*-2–*C*-6), 144.0 (*C*-17), 190.1 (*C*-19). Anal. calcd for $C_{24}H_{21}NO_2F_2$: C73.27, H5.38, N3.56. Found C73.25, H5.34, N3.49.

*2.2.10. 5-Ethyl-2-{[4-(1-(4-bromophenyl)-2-propan-1-one-3-yl)]phenoxyethyl}-pyridine (**4j**)*

m.p. 102–104 °C. Yield 85%. R_f: 0.56. IR (KBr): t = 3064 (Ar-H), 2953, 2830 (–CH_2–), 1660 (–C=O), 1595 (–CH=CH–), 1225, 1032 (C–O–C), 858 (C-Br). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, 3H, –CH_3), 2.55 (q, 2H, –CH_2), 3.18 (t, 2H, –CH_2), 4.34 (t, 2H, –CH_2–O), 7.00–8.01 (m, 8H, Ar-*H*), 7.13 (d, 1H, =C*H*–CO), 7.16 (d, 1H, –C*H*), 7.37–8.30 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (*C*-8), 24.5 (*C*-7), 38.2 (*C*-9), 67.1 (*C*-10), 115.5–156.0 (*C*-11–*C*-16), 118.5 (*C*-18), 121.4–159.5 (*C*-2–*C*-6), 132.1–136.9 (*C*-20–*C*-25), 144.2 (*C*-17), 189.5 (*C*-19). Anal. calcd for $C_{24}H_{22}NO_2Br$: C66.06, H5.08, N3.21. Found C66.03, H5.02, N3.15.

*2.2.11. 5-Ethyl-2-{[4-(1-(3,4-dichlorophenyl)-2-propan-1-one-3-yl)]phenoxyethyl} pyridine (**4k**)*

m.p. 105–110 °C. Yield 84%. R_f: 0.55. IR (KBr): t = 3067 (Ar-H), 2947, 2829 (–CH_2–), 1664 (–C=O), 1593 (–CH=CH–), 1220, 1031 (C–O–C), 744 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (t, 3H, –CH_3), 2.55 (q, 2H, –CH_2), 3.19 (t, 2H, –CH_2), 4.32 (t, 2H, –CH_2–O), 7.01–7.76 (m, 7H, Ar-*H*), 7.11 (d, 1H, =C*H*–CO), 7.18 (d, 1H, –C*H*), 7.38–8.32 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (*C*-8), 25.1 (*C*-7), 37.2 (*C*-9), 66.5 (*C*-10), 114.5–155.2 (*C*-11–*C*-16), 119.8 (*C*-18), 122.4–160.5 (*C*-2–*C*-6), 130.4–139.5 (*C*-20–*C*-25), 143.5 (*C*-17), 188.9 (*C*-19). Anal. calcd for $C_{24}H_{21}NO_2Cl_2$: C67.61, H4.96, N3.29. Found C67.58, H4.90, N3.23.

*2.2.12. 5-Ethyl-2-{[4-(1-(4-chlorophenyl)-2-propan-1-one-3-yl)]phenoxyethyl} pyridine (**4l**)*

m.p. 138–140 °C. Yield 88%. R_f: 0.53. IR (KBr): t = 3028 (Ar-H), 2944, 2827 (–CH_2–), 1659 (–C=O), 1596 (–CH=CH–), 1224, 1037 (C–O–C), 746 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, 3H, –CH_3), 2.57 (q, 2H, –CH_2), 3.18 (t, 2H, –CH_2), 4.30 (t, 2H, –CH_2–O), 7.03–7.86 (m, 8H, Ar-*H*), 7.10 (d, 1H, =C*H*–CO), 7.19 (d, 1H, –C*H*), 7.37–8.32 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (*C*-8), 24.8 (*C*-7), 38.3 (*C*-9), 67.3 (*C*-10), 114.5–156.0 (*C*-11–*C*-6), 118.2 (*C*-18), 121.5–160.8 (*C*-2–*C*-6), 129.5–140.5 (*C*-20–*C*-25), 144.5 (*C*-17), 190.5 (*C*-19). Anal. calcd for $C_{24}H_{22}NO_2Cl$: C73.56, H5.66, N3.57. Found C73.52, H5.61, N3.55.

*2.2.13. 5-Ethyl-2-{[4-(1-(3-methoxyphenyl)-2-propan-1-one-3-yl)]phenoxyethyl} pyridine (**4m**)*

m.p. 75–80 °C. Yield 70%. R_f: 0.52. IR (KBr): t = 3066 (Ar-H), 2952, 2833 (–CH_2–), 1664 (–C=O), 1594 (–CH=CH–), 1220, 1032 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, 3H, –CH_3), 2.58 (q, 2H, –CH_2), 3.16 (t, 2H, –CH_2), 3.85 (s, 3H, –OCH_3) 4.34 (t, 2H, –CH_2–O), 6.96–8.11 (m, 8H, Ar-*H*), 7.11 (d, 1H, =C*H*–CO), 7.16 (d, 1H, –C*H*), 7.39-8.30 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (*C*-8), 25.5 (*C*-7), 38.5 (*C*-9), 55.5 (*C*-26), 68.5 (*C*-10), 115.3–156.5 (*C*-11–*C*-16), 117.3–161.5 (*C*-20–*C*-25), 119.2 (*C*-18), 122.6–161.5 (*C*-2–*C*-6), 144.1 (*C*-17), 190.1 (*C*-19). Anal. calcd for $C_{25}H_{25}NO_3$: C77.49, H6.50, N3.61. Found C77.45, H6.48, N3.52.

*2.2.14. 5-Ethyl-2-{[4-(1-(3-fluorophenyl)-2-propan-1-one-3-yl)]phenoxyethyl} pyridine (**4n**)*

m.p. 87–90 °C. Yield 80%. R_f: 0.54. IR (KBr): t = 3062 (Ar-H), 2956, 2835 (–CH_2–), 1660 (–C=O), 1597 (–CH=CH–), 1219, 1032 (C–O–C), 976 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.11 (t, 3H, –CH_3), 2.53(q, 2H, –CH_2), 3.14 (t, 2H, –CH_2), 4.31 (t, 2H, –CH_2–O), 7.00–7.58 (m, 8H, Ar-*H*), 7.13 (d, 1H, =C*H*–CO), 7.18 (d, 1H, –C*H*), 7.39-8.30 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 (*C*-8), 25.3 (*C*-7), 38.0 (*C*-9), 55.8 (*C*-26), 67.5 (*C*-10), 114.5–164.0 (*C*-20–*C*-25), 115.5–156.1 (*C*-11–*C*-16), 119.2 (*C*-18), 122.5–160.5 (*C*-2–*C*-6), 144.8 (*C*-17), 189.5 (*C*-19), Anal. calcd for $C_{24}H_{22}NO_2F$: C76.78, H5.91, N3.73. Found C76.72, H5.86, N3.70.

*2.2.15. 5-Ethyl-2-{[4-(1-(3,4-difluorophenyl)-2-propan-1-one-3-yl)]phenoxyethyl} pyridine (**4o**)*

m.p. limpid. Yield 82%. R_f: 0.55. IR (KBr): t = 3060 (Ar-H), 2950, 2835 (–CH_2–), 1662 (–C═O), 1599 (–CH═CH), 1223, 1033 (C–O–C), 978 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.12 (t, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.16 (t, 2H, –CH_2), 4.32 (t, 2H, –CH_2–O), 7.02–7.56 (m, 7H, Ar-*H*), 7.14 (d, 1H, ═C*H*–CO), 7.19 (d, 1H, –C*H*), 7.37–8.28 (m, 3H, Pyridine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (*C*-8), 25.1 (*C*-7), 38.2 (*C*-9), 67.1 (*C*-10), 115.5–156.0 (*C*-11–*C*-16), 116.3–155.5 (*C*-20–*C*-25), 119.6 (*C*-18), 122.4–160.2 (*C*-2–*C*-6), 144.5 (*C*-17), 190.5 (*C*-19). Anal. calcd for $C_{24}H_{21}NO_2F_2$: C73.27, H5.38, N3.56. Found C73.21, H5.33, N3.48.

*2.3. General preparation of the compounds **5a–o***

A mixture of freshly prepared solution of sodium ethoxide (0.02 mol Na in 50 mL ethanol), **4a–o** (0.01 mol) and guanidine nitrate (0.01 mol) was refluxed for 8–12 h; reaction progress was monitored by TLC (tolune:ethyl acetate, 7.5:2.5). After completion of reaction, the mixture was concentrated under vacuum and the remaining reaction mass was poured into crushed ice; the solid was separated out and stirred for 1 h to maintain neutral pH with dilute glacial acetic acid. The mass was filtered and washed with water, dried and recrystallized from ethanol (Fig. 2).

*2.3.1. 5-Ethyl-2-{[4-(6-(2,4-dichloro-5-fluorophenyl)-2-aminopyrimidin-4-yl)] phenoxyethyl} pyridine (**5a**)*

m.p. 95–98 °C. Yield 74%. R_f: 0.42. IR (KBr): t = 3355, 3222 (–NH_2), 3062 (Ar-H), 2954, 2837 (–CH_2–), 1602 (–C═N), 1225, 1036 (C–O–C), 973 (C-F), 745 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.17 (t, 2H, –CH_2), 4.33 (t, 2H, –CH_2–O), 5.18 (s, 2H, –NH_2), 6.90–7.82 (m, 8H, Ar-*H*), 7.39–8.32 (m, 3H, Pyridine-*H*), 7.84 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (*C*-8), 25.2 (*C*-7), 38.0 (*C*-9), 67.0 (*C*-10), 103.5 (*C*-22), 114.0–154.4 (*C*-11–*C*-16), 118.7–161.4 (*C*-24–*C*-29), 123.5–160.5 (*C*-2–*C*-6), 160.7 (*C*-21), 163.2 (*C*-17), 165.0 (*C*-19) Anal. calcd for $C_{25}H_{21}N_4OCl_2F$: C62.12, H4.38, N11.59. Found C62.06, H4.32, N11.52.

*2.3.2. 5-Ethyl-2-{[4-(6-(4-methoxyphenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5b**)*

m.p. 100–102 °C. Yield 52%. R_f: 0.40. IR (KBr): t = 3352, 3224 (–NH_2), 3065 (Ar-H), 2957, 2834 (–CH_2–), 1609 (–C═N), 1223, 1033 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, 3H, –CH_3), 2.53 (q, 2H, –CH_2), 3.18 (t, 2H, –CH_2), 3.83 (s, 3H, –OCH_3) 4.34 (t, 2H, –CH_2–O), 5.12 (s, 2H, –NH_2), 6.89–7.84 (m, 8H, Ar-*H*), 7.40–8.32 (m, 3H, Pyridine-*H*), 7.86 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (*C*-8), 25.0 (*C*-7), 37.5 (*C*-9), 55.8 (*C*-30), 67.3 (*C*-10), 103.4 (*C*-22), 114.5–160.5 (*C*-24–*C*-29), 115.3–155.5 (*C*-11–*C*-16), 123.8–161.0 (*C*-2–*C*-6), 160.5 (*C*-21), 164.5 (*C*-17), 165.1 (*C*-19), Anal. calcd for $C_{26}H_{26}N_4O_2$: C73.22, H6.14, N13.14. Found C73.14, H6.08, N13.07.

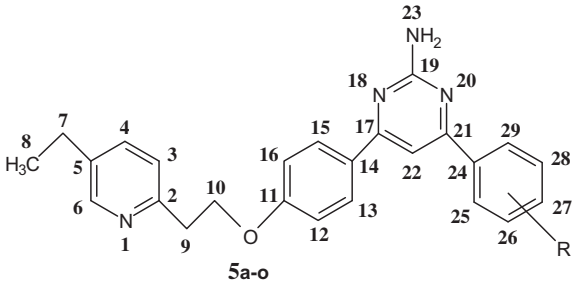


Figure 2 Pyrimidines **5a–o**.

*2.3.3. 5-Ethyl-2-{[4-(6-(2,4-dichlorophenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5c**)*

m.p. 115–118 °C. Yield 78%. R_f: 0.43. IR (KBr): t = 3358, 3227 (–NH_2), 3057 (Ar-H), 2953, 2836 (–CH_2–), 1607 (–C═N), 1227, 1037 (C–O–C), 746 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, 3H, –CH_3), 2.52 (q, 2H, –CH_2), 3.16 (t, 2H, –CH_2), 4.32 (t, 2H, –CH_2–O), 5.22 (s, 2H, –NH_2), 6.88–7.81 (m, 8H, Ar-*H*), 7.39–8.32 (m, 3H, Pyridine-*H*), 7.86 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (*C*-8), 26.1 (*C*-7), 37.3 (*C*-9), 67.5 (*C*-10), 104.2 (*C*-22), 115.1–155.2 (*C*-11–*C*-16), 123.6–161.9 (*C*-2–*C*-6), 127.4–135.5 (*C*-24–*C*-29), 160.5 (*C*-21), 163.6 (*C*-17), 165.1 (*C*-19). Anal. calcd for $C_{25}H_{22}N_4OCl_2$: C64.52, H4.76, N12.04. Found C64.46, H4.69, N12.00.

*2.3.4. 5-Ethyl-2-{[4-(6-(4-hydroxyphenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5d**)*

m.p. > 300 °C. Yield 50%. R_f: 0.44. IR (KBr): t = 3355, 3224 (–NH_2), 3064 (Ar-H), 2955, 2832 (–CH_2–), 1600 (–C═N), 1220, 1032 (C–O–C), 3357 (–OH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.15 (t, 2H, –CH_2), 4.33 (t, 2H, –CH_2–O), 9.85 (s, 1H, –O*H*), 5.12 (s, 2H, –NH_2), 6.84–7.78 (m, 8H, Ar-*H*), 7.39–8.30 (m, 3H, Pyridine-*H*), 7.85 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7 (*C*-8), 25.5 (*C*-7), 37.6 (*C*-9), 67.3 (*C*-10), 103.5 (*C*-22), 115.7–155.7 (*C*-11–*C*-16), 116.3–158.5 (*C*-24–*C*-29), 122.9–159.9 (*C*-2–*C*-6), 160.3 (*C*-21), 163.8 (*C*-17), 165.2 (*C*-19), Anal. calcd for $C_{25}H_{24}N_4O_2$: C72.80, H5.86, N13.58. Found C72.74, H5.78, N13.52.

*2.3.5. 5-Ethyl-2-{[4-(6-(2,6-chloro-5-fluorophenyl)-2-aminopyrimidin-4-yl)] phenoxyethyl}pyridine (**5e**)*

m.p. 105–108 °C. Yield 76%. R_f: 0.40. IR (KBr): t = 3348, 3219 (–NH_2), 3062 (Ar-H), 2953, 2830 (–CH_2–), 1606 (–C═N), 1220, 1034 (C–O–C), 975 (C–F), 747 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.12 (t, 3H, –CH_3), 2.55 (q, 2H, –CH_2), 3.16 (t, 2H, –CH_2), 4.31 (t, 2H, –CH_2–O), 5.24 (s, 2H, –NH_2), 6.91–7.83 (m, 8H, Ar-*H*), 7.38–8.30 (m, 3H, Pyridine-*H*), 7.85 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (*C*-8), 25.1 (*C*-7), 38.2 (*C*-9), 67.2 (*C*-10), 103.2 (*C*-22), 113.9–154.1 (*C*-11–*C*-16), 118.3–161.4 (*C*-24–*C*-29), 123.0–160.4 (*C*-2–*C*-6), 160.5 (*C*-21), 163.0 (*C*-17), 165.4 (*C*-19), Anal. calcd for $C_{25}H_{21}N_4OCl_2F$: C62.12, H4.38, N11.59. Found C62.04, H4.31, N11.55.

*2.3.6. 5-Ethyl-2-{[4-(6-(4-methylphenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5f**)*

m.p. 133–136 °C. Yield 78%. R_f: 0.42. IR (KBr): t = 3355, 3220 (–NH_2), 3057 (Ar-H), 2952, 2834 (–CH_2–), 1610 (–C═N), 1220, 1034 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, 3H, –CH_3), 2.33 (s, 3H, –CH_3), 2.53 (q, 2H, –CH_2), 3.17 (t, 2H, –CH_2), 4.32 (t, 2H, –CH_2–O), 5.15 (s, 2H, –NH_2), 6.89–7.80 (m, 8H, Ar-*H*), 7.39–8.30 (m, 3H, Pyri-

dine-*H*), 7.85 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (*C*8), 21.7 (*C*30), 25.5 (*C*7), 37.5 (*C*9), 67.5 (*C*10), 103.2 (*C*22), 115.0–155.4 (*C*11–*C*16), 123.4–160.9 (*C*2–*C*6), 129.2–144.4 (*C*24–*C*29), 160.9 (*C*21), 163.5 (*C*17), 165.5 (*C*19), Anal. calcd for $C_{26}H_{26}N_4O$: C76.07, H6.38, N13.65. Found C76.00, H6.32, N13.57.

*2.3.7. 5-Ethyl-2-{[4-(6-(1-phenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl}pyridine (**5g**)*

m.p. 110–115 °C. Yield 65%. R_f: 0.44. IR (KBr): *t* = 3356, 3225 (–NH_2), 3058 (Ar-H), 2952, 2832 (–C*H*$_2$–), 1605 (–C═N), 1227, 1038 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, 3H, –C*H*$_3$), 2.52 (q, 2H, –C*H*$_2$), 3.18 (t, 2H, –C*H*$_2$), 4.30 (t, 2H, –C*H*$_2$–O), 5.20 (s, 2H, –N*H*$_2$), 6.89–7.82 (m, 8H, Ar-*H*), 7.38–8.31 (m, 3H, Pyridine-*H*), 7.87 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (*C*8), 25.1 (*C*7), 38.2 (*C*9), 67.2 (*C*10), 103.7 (*C*22), 114.9–154.1 (*C*11–*C*16), 118.7–161.4 (*C*24–*C*29), 123.6–160.4 (*C*2–*C*6), 160.5 (*C*21), 163.2 (*C*17), 164.9 (*C*19), Anal. calcd for $C_{26}H_{24}N_4O$: C75.73, H6.10, N14.13. Found C75.68, H6.04, N14.10.

*2.3.8. 5-Ethyl-2-{[4-(6-(4-fluorophenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5h**)*

m.p. 244–246 °C. Yield 70%. R_f: 0.45. IR (KBr): *t* = 3356, 3222 (–NH_2), 3064 (Ar-H), 2950, 2835 (–C*H*$_2$–), 1602 (–C═N), 1226, 1036 (C–O–C), 975 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, 3H, –C*H*$_3$), 2.53 (q, 2H, –C*H*$_2$), 3.17 (t, 2H, –C*H*$_2$), 4.31 (t, 2H, –C*H*$_2$–O), 5.16 (s, 2H, –N*H*$_2$), 6.88–7.80 (m, 8H, Ar-*H*), 7.39-8.32 (m, 3H, Pyridine-*H*), 7.84 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (*C*8), 25.4 (*C*7), 38.3 (*C*9), 67.4 (*C*10), 103.9 (*C*22), 114.1–154.3 (*C*11–*C*16), 116.0–163.0 (*C*24–*C*29), 123.9–160.9 (*C*2–*C*6), 160.7 (*C*21), 163.0 (*C*17), 164.5 (*C*19), Anal. calcd for $C_{25}H_{23}N_4OF$: C72.45, H5.59, N13.52. Found C72.35, H5.54, N13.48.

*2.3.9. 5-Ethyl-2-{[4-(6-(2,4-fluorophenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5i**)*

m.p. 135–139 °C. Yield 72%. R_f: 0.41. IR (KBr): *t* = 3347, 3225 (–NH_2), 3066 (Ar-H), 2945, 2832 (–C*H*$_2$–), 1604 (–C═N), 1220, 1034 (C–O–C), 978 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, 3H, –C*H*$_3$), 2.54 (q, 2H, –C*H*$_2$), 3.16 (t, 2H, –C*H*$_2$), 4.32 (t, 2H, –C*H*$_2$–O), 5.18 (s, 2H, –N*H*$_2$), 6.90–7.83 (m, 8H, Ar-*H*), 7.37–8.30 (m, 3H, Pyridine-*H*), 7.86 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (*C*8), 25.4 (*C*7), 38.1 (*C*9), 67.8 (*C*10), 103.5 (*C*22), 114.2–153.9 (*C*11–*C*16), 116.6–164.5 (*C*24–*C*29), 123.5–160.8 (*C*2–*C*6), 160.5 (*C*21), 163.2 (*C*17), 164.4 (*C*19), Anal. calcd for $C_{25}H_{22}N_4OF_2$: C69.43, H5.13, N12.96. Found C69.37, H5.08, N12.92.

*2.3.10. 5-Ethyl-2-{[4-(6-(4-bromophenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5j**)*

m.p. 115–117 °C yield. 77%. R_f: 0.40. IR (KBr): *t* = 3354, 3225 (–NH_2), 3057 (Ar-H), 2952, 2837 (–C*H*$_2$–), 1608 (–C═N), 1224, 1032 (C–O–C), 860 (C-Br). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15(t, 3H, –C*H*$_3$), 2.53 (q, 2H, –C*H*$_2$), 3.18 (t, 2H, –C*H*$_2$), 4.33 (t, 2H, –C*H*$_2$–O), 5.14 (s, 2H, –N*H*$_2$), 6.86–7.81 (m, 8H, Ar-*H*), 7.38–8.33 (m, 3H, Pyridine-H), 7.85(s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (*C*8), 25.1 (*C*7), 38.8 (*C*9), 67.7 (*C*10), 103.9 (*C*22), 114.1–154.2 (*C*11–*C*16), 123.1–132.1 (*C*24–*C*29), 123.8–160.6 (*C*2–*C*6), 160.7 (*C*21), 163.1 (*C*17), 164.5 (*C*19), Anal. calcd for $C_{25}H_{23}N_4OBr$: C63.16, H4.88, N11.79. Found C63.11, H4.82, N11.73.

*2.3.11. 5-Ethyl-2-{[4-(6-(3,4-dichlorophenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5k**)*

m.p. 125–130 °C. Yield 73%. R_f: 0.43. IR (KBr): *t* = 3356, 3227 (–NH_2), 3066 (Ar-H), 2955, 2838 (–C*H*$_2$–), 1605 (–C═N), 1225, 1037 (C–O–C), 748 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, 3H, –C*H*$_3$), 2.55 (q, 2H, –C*H*$_2$), 3.15 (t, 2H, –C*H*$_2$), 4.35 (t, 2H, –C*H*$_2$–O), 5.17 (s, 2H, –N*H*$_2$), 6.92-7.83 (m, 8H, Ar-*H*), 7.41–8.30 (m, 3H, Pyridine-*H*), 7.84 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 (*C*8), 25.4 (*C*7), 38.3 (*C*9), 67.5 (*C*10), 103.8 (*C*22), 114.1–154.3 (*C*11–*C*16), 123.6–160.8 (*C*2–*C*6), 127.0–133.5 (*C*24–*C*29), 160.5 (*C*21), 160.5 (*C*21), 163.1 (*C*17), 164.5 (*C*19), Anal. calcd for $C_{25}H_{22}N_4OCl_2$: C64.52, H4.76, N12.04. Found C64.48, H4.71, N12.00.

*2.3.12. 5-Ethyl-2-{[4-(6-(4-chlorophenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5l**)*

m.p. 92–95 °C. Yield 74%. R_f: 0.42. IR (KBr): *t* = 3356, 3227 (–NH_2), 3066 (Ar-H), 2955, 2838 (–C*H*$_2$–), 1611 (–C═N), 1225, 1037 (C–O–C), 748 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz):δ = 1.17 (t, 3H, –C*H*$_3$), 2.53 (q, 2H, –C*H*$_2$), 3.14 (t, 2H, –C*H*$_2$), 4.33 (t, 2H, –C*H*$_2$–O), 5.10 (s, 2H, –N*H*$_2$), 6.91–7.82 (m, 8H, Ar-*H*), 7.40–8.31 (m, 3H, Pyridine-*H*), 7.83 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7 (*C*8), 25.7 (*C*7), 38.5 (*C*9), 67.4 (*C*10), 103.7 (*C*22), 114.2–154.1 (*C*11–*C*16), 123.9–161.0 (*C*2–*C*6), 128.9–134.5 (*C*24–*C*29), 160.5 (*C*21), 163.4 (*C*17), 164.1 (*C*19), Anal. calcd for $C_{25}H_{23}N_4OCl$: C69.68, H5.38, N13.00. Found C69.63, H5.34, N12.98.

*2.3.13. 5-Ethyl-2-{[4-(6-(3-methoxyphenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5m**)*

m.p. 98–111 °C. Yield 54% R_f: 0.44. IR (KBr): *t* = 3356, 3225 (–NH_2), 3066 (Ar-H), 2956, 2838 (–C*H*$_2$–), 1609 (–C═N), 1220, 1033 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, 3H, –C*H*$_3$), 2.53 (q, 2H, –C*H*$_2$) 3.17 (t, 2H, –C*H*$_2$), 3.82 (s, 3H, –OC*H*$_3$), 5.22 (s, 2H, –N*H*$_2$), 4.34 (t, 2H, –C*H*$_2$–O), 6.90–7.85 (m, 8H, Ar-*H*), 7.40–8.33 (m, 3H, Pyridine-*H*), 7.85 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (*C*8), 25.6 (*C*7), 38.5 (*C*9), 55.7 (*C*30), 67.8 (*C*10), 103.2 (*C*22), 113.9–154.5 (*C*11–*C*16), 114.9–160.0 (*C*24–*C*29), 123.1–160.5 (*C*2–C6), 160.1 (*C*21), 163.2 (*C*17), 164.3 (*C*19). Anal. calcd for $C_{26}H_{26}N_4O_2$: C73.22, H6.14, N13.14. Found C73.18, H6.10, N13.10.

*2.3.14. 5-Ethyl-2-{[4-(6-(3-fluorophenyl)-2-aminopyrimidin-4-yl)]phenoxyethyl} pyridine (**5n**)*

m.p. 95–100 °C. Yield 72%. R_f: 0.43. IR (KBr): *t* = 3352, 3225 (–NH_2), 3065 (Ar-H), 2957, 2838 (–C*H*$_2$–), 1601 (–C═N), 1218, 1029 (C–O–C), 976 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, 3H, –C*H*$_3$), 2.52 (q, 2H, –C*H*$_2$), 3.18 (t, 2H, –C*H*$_2$), 4.33 (t, 2H, –C*H*$_2$–O), 5.14 (s, 2H, –N*H*$_2$), 6.88–7.84 (m, 8H, Ar-*H*), 7.40–8.32 (m, 3H, Pyridine-*H*), 7.84 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 (*C*7), 38.3 (*C*9), 67.4 (*C*10), 103.5 (*C*22), 114.1–154.3 (*C*11–*C*16), 115.5–163.5 (*C*24–*C*29), 123.8–161.8 (*C*2–*C*6), 160.7 (*C*21), 163.0 (*C*17), 164.3 (*C*19), Anal. calcd for $C_{25}H_{23}N_4OF$: C72.45, H5.59, N13.52. Found C72.40, H5.54, N13.49.

*2.3.15. 5-Ethyl-2-{[4-(6-(3,4-difluorophenyl)-2-aminopyrimidine-4-yl)]phenoxyethyl} pyridine (**5o**)*

m.p. 115–118 °C. Yield 74%. R_f: 0.44. IR (KBr): t = 3357, 3218 (–NH_2), 3062 (Ar-H), 2957, 2832 (–CH_2–), 1602 (–C═N), 1225, 1034 (C–O–C), 975 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, 3H, –CH_3), 2.53 (q, 2H, –CH_2), 3.17(t, 2H, –CH_2), 4.34 (t, 2H, –CH_2–O), 5.20 (s, 2H, –NH_2), 6.89–7.85 (m, 8H, Ar-*H*), 7.39–8.33 (m, 3H, Pyridine-*H*), 7.86 (s, 1H, Pyrimidine-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (*C*8), 25.9 (*C*7), 37.9 (*C*9), 68.0 (*C*10), 102.9 (*C*22), 114.0–154.1 (*C*11–*C*16), 115.0–149.5 (*C*24–*C*29), 123.6–160.9 (*C*2–*C*6), 160.6 (*C*21), 162.9 (*C*17), 163.5 (*C*19). Anal. calcd for $C_{25}H_{22}N_4OF_2$: C69.43, H5.13, N12.96. Found C69.38, H5.06, N12.92.

*2.4. General preparation of the compounds **6a–o***

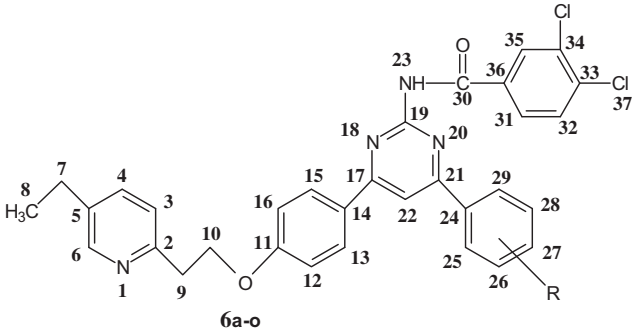
A solution of the **5a–o** (0.01 mol) and the appropriate benzoyl chloride (0.02 mol) in pyridine (10 mL) was heated under reflux for 6–8 h and continued till the reaction completed. The progress of reaction was monitored by TLC (tolune:ethyl acetate, 7.5:2.5). After completion of the reaction, the mass was dumped into ice cold water; the solid obtained was filtered, washed with cold water until neutral pH and dried and recrystallized from ethanol Fig. 3.

*2.4.1. 5-Ethyl-2-{[4-(6-(2,4-dichloro-5-fluorophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]pheno-xyethyl} pyridine (**6a**)*

m.p. 135–137 °C. Yield 67%. R_f: 0.61. IR (KBr): t = 3064 (Ar-H), 2957, 2832 (–CH_2–), 1610 (–C═N), 1225, 1033 (C–O–C), 1674 (Amide-1), 1533 (Amide-2), 1246 (Amide-3), 975 (C–F), 747 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, 3H, –CH_3), 2.32 (s, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.15 (t, 2H, –CH_2), 4.35 (t, 2H, –CH_2–O), 7.05–8.14 (m, 11H, Ar-*H*), 7.32–8.32 (m, 3H, Pyridine-*H*), 7.86 (s, 1H, Pyrimidine-*H*), 9.32 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7 (*C*8), 21.5 (*C*37), 25.8 (*C*7), 37.6 (*C*9), 67.3 (*C*10), 103.7 (*C*22), 115.3–155.6 (*C*11–*C*16), 123.3–160.6 (*C*2–*C*6), 127.2–144.6 (*C*24–*C*35), 161.4 (*C*21), 161.0 (*C*19), 163.2 (*C*17), 165.1 (*C*36), Anal. calcd for $C_{32}H_{23}N_4O_2Cl_4F$: C58.56, H3.53, N8.54. Found C58.56, H3.53, N8.54.

*2.4.2. 5-Ethyl-2-{[4-(6-(4-methoxyphenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)] phenoxyethyl}pyridine (**6b**)*

m.p. 70–72 °C. Yield 63%. R_f: 0.63. IR (KBr): t = 3063 (Ar-H), 2956, 2838 (–CH_2–), 1612 (–C═N), 1675 (Amide-1), 1534 (Amide-2), 1245 (Amide-3) 1226, 1038 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, 3H, –CH_3), 2.29 (s, 3H, –CH_3), 2.50 (q, 2H, –CH_2), 3.18 (t, 2H, –CH_2), 4.33 (t, 2H, –CH_2–O), 7.03–8.14 (m, 11H, Ar-*H*), 7.33–8.31 (m, 3H, Pyridine-*H*), 7.82 (s, 1H, Pyrimidine-*H*), 9.31 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (*C*8), 21.8 (*C*37), 25.5 (*C*7), 37.4 (*C*9), 67.4 (*C*10), 103.7 (*C*22), 115.3–155.2 (*C*11–*C*16), 123.8–161.0 (*C*2–*C*6), 127.0–144.6 (*C*24–*C*35), 161.3 (*C*21), 161.7 (*C*19), 163.4 (*C*17), 165.5 (*C*36), Anal. calcd for $C_{33}H_{28}N_4O_3Cl_2$: C66.11, H4.71, N9.35. Found C66.09, H4.73, N9.35.



6a-o

Figure 3 Benzamido pyrimidines **6a–o**.

*2.4.3. 5-Ethyl-2-{[4-(6-(2,4-dichlorophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)] phenoxyethyl} pyridine (**6c**)*

m.p. 112–115 °C. Yield 65%. R_f: 0.64. IR (KBr): t = 3061 (Ar-H), 2954, 2833 (–CH_2–), 1677 (Amide-1), 1604 (–C═N), 1535 (Amide-2), 1246 (Amide-3), 1224, 1036 (C–O–C), 746 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.17 (t, 3H, –CH_3), 2.34 (s, 3H, –CH_3), 2.55 (q, 2H, –CH_2), 3.16 (t, 2H, –CH_2), 4.32 (t, 2H, –CH_2–O), 7.00–8.10 (m, 11H, Ar-*H*), 7.33–8.33 (m, 3H, Pyridine-*H*), 7.82 (s, 1H, Pyrimidine-*H*), 9.30 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (*C*8), 21.5 (*C*37), 25.4 (*C*7), 37.6 (*C*9), 67.8 (*C*10), 103.3 (*C*22), 115.2–155.0 (*C*11–*C*16), 123.0–160.4 (*C*2–*C*6), 127.4–144.0 (*C*24–*C*35), 161.2 (*C*21), 161.4 (*C*19), 163.3 (*C*17), 165.6 (*C*36). Anal. calcd for $C_{32}H_{24}N_4O_2Cl_4$: C60.21, H3.79, N8.78. Found C60.22, H3.73, N8.78.

*2.4.4. 5-Ethyl-2-{[4-(6-(4-hydroxyphenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6d**)*

m.p. 116–118 °C. Yield, 61%. R_f: 0.59. IR (KBr): t = 3367 (–OH), 3057 (Ar-H), 2953, 2835 (–CH_2–), 1671 (amide-1), 1604 (–C═N), 1534 (amide-2), 1245 (amide-3), 1223, 1034 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, 3H, –CH_3), 2.33 (s, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.17(t, 2H, –CH_2), 4.34 (t, 2H, –CH_2–O), 7.08–8.20 (m, 11H, Ar-*H*), 7.33–8.32(m, 3H, Pyridine-*H*), 7.83 (s, 1H, Pyrimidine-*H*), 9.33 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (*C*8), 21.7 (*C*37), 25.6 (*C*7), 37.5 (*C*9), 67.5 (*C*10), 103.4 (*C*22), 115.2–155.6 (*C*11–*C*16), 123.5–160.9 (*C*2–*C*6), 127.5–144.1 (*C*24–*C*35), 161.4 (*C*21), 161.6 (*C*19), 163.1 (*C*17), 165.7 (*C*36). Anal. calcd for $C_{32}H_{26}N_4O_3Cl_2$: C65.65, H4.48, N9.57. Found C65.62, H4.43, N9.55.

*2.4.5. 5-Ethyl-2-{[4-(6-(2,6-chloro-5-fluorophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]pheno-xyethyl} pyridine (**6e**)*

m.p. 122–124. Yield, 69%. R_f: 0.64. IR (KBr): t = 3063 (Ar-H), 2955, 2836 (–CH_2–), 1676 (Amide-1), 1610 (–C═N), 1533 (Amide-2), 1245 (Amide-3), 1217, 1036 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, 3H, –CH_3), 2.28 (s, 3H, –CH_3), 2.57 (q, 2H, –CH_2), 3.20 (t, 2H, –CH_2), 4.35 (t, 2H, –CH_2–O), 7.09–8.09 (m, 11H, Ar-*H*), 7.34–8.32 (m, 3H, Pyridine-*H*), 7.80 (s, 1H, Pyrimidine-*H*), 9.33 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6 (*C*8), 21.6 (*C*37), 25.8 (*C*7), 37.7 (*C*9), 67.9 (*C*10), 103.7 (*C*22), 115.2–155.1 (*C*11–*C*16), 123.7–160.8 (*C*2–*C*6), 127.6–144.6 (*C*24–*C*35), 161.0 (*C*21), 161.5 (*C*19), 163.4 (*C*17), 165.4 (*C*36). Anal. calcd for $C_{32}H_{23}N_4O_2Cl_4F$: C58.56, H3.53, N8.54. Found C58.53, H3.50, N8.55.

*2.4.6. 5-Ethyl-2-{[4-(6-(4-methylphenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6f**)*

m.p. 132–134 °C. Yield 71%. R_f: 0.67. IR (KBr): t = 3063 (Ar-H), 2954, 2832 (–CH_2–), 1672 (Amide-1), 1614 (–C═N), 1537 (Amide-2), 1250 (Amide-3), 1222, 1031 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (t, 3H, –CH_3), 2.30 (s, 3H, –

CH_3), 2.53 (q, 2H, –CH_2), 3.17 (t, 2H, –CH_2), 4.30 (t, 2H, –CH_2–O), 7.05–8.16 (m, 11H, Ar-*H*), 7.34–8.30 (m, 3H, Pyridine-*H*), 7.84 (s, 1H, Pyrimidine-*H*), 9.30 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5 (*C*8), 21.7 (*C*37), 25.6 (*C*7), 37.5 (*C*9), 67.6 (*C*10), 103.5 (*C*22), 115.0–155.4 (*C*11–*C*16), 123.3–160.8 (*C*2–*C*6), 127.5–144.4 (*C*24–*C*35), 161.0 (*C*21), 161.5 (*C*19), 163.5 (*C*17), 165.3 (*C*36), Anal. calcd for $C_{33}H_{28}N_4O_2Cl_2$: C67.93, H4.84, N9.60. Found C67.90, H4.83, N9.58.

*2.4.7. 5-Ethyl-2-{[4-(6-(1-phenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxyethyl} pyridine (**6g**)*

m.p. 128–130 °C. Yield 65%. R_f: 0.64. IR (KBr): t = 3063 (Ar-H), 2954, 2835 (–CH_2–), 1677 (Amide-1), 1606 (–C═N), 1534 (Amide-2), 1245 (Amide-3), 1223, 1033 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.17 (t, 3H, –CH_3), 2.35 (s, 3H, –CH_3), 2.51 (q, 2H, –CH_2), 3.18 (t, 2H, –CH_2), 4.35 (t, 2H, –CH_2–O), 7.00–8.18 (m, 11H, Ar-*H*), 7.35–8.31 (m, 3H, Pyridine-*H*), 7.83 (s, 1H, Pyrimidine-*H*), 9.33 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 (*C*8), 21.4 (*C*37), 25.9 (*C*7), 37.3 (*C*9), 67.9 (*C*10), 103.4 (*C*22), 115.3–155.7 (*C*11–*C*16), 123.0–160.5 (*C*2–*C*6), 127.1–144.0 (*C*24–*C*35), 161.2 (*C*21), 161.2 (*C*19), 163.6 (*C*17), 165.4 (*C*36), Anal. calcd for $C_{32}H_{26}N_4O_2Cl_2$: C67.49, H4.60, N9.84. Found C67.45, H4.63, N9.82.

*2.4.8. 5-Ethyl-2-{[4-(6-(4-fluorophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6h**)*

m.p. 190–192 °C. Yield 63%. R_f: 0.68. IR (KBr): t = 3066 (Ar-H), 2956, 2838 (–CH_2–), 1677 (Amide-1), 1608 (–C═N), 1533 (Amide-2), 1250 (Amide-3), 1220, 1034 (C–O–C), 974 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13(t, 3H, –CH_3), 2.32 (s, 3H, –CH_3), 2.52 (q, 2H, –CH_2), 3.16 (t, 2H, –CH_2), 4.34 (t, 2H, –CH_2–O), 7.10–8.12 (m, 11H, Ar-*H*), 7.34–8.34 (m, 3H, Pyridine-*H*), 7.86 (s, 1H, Pyrimidine-*H*), 9.36 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (*C*8), 21.5 (*C*37), 25.4 (*C*7), 37.2 (*C*9), 67.5 (*C*10), 103.8 (*C*22), 115.2–155.8 (*C*11–*C*16), 123.9–161.3 (*C*2–*C*6), 127.9–145.4 (*C*24–*C*35), 161.4 (*C*21), 162.0 (*C*19), 163.9 (*C*17), 166.0 (*C*36), Anal. calcd for $C_{32}H_{25}N_4O_2Cl_2F$: C65.42, H4.29, N9.54. Found C65.43, H4.25, N9.53.

*2.4.9. 5-Ethyl-2-{[4-(6-(2,4-fluorophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6i**)*

m.p. 98–100 °C. Yield, 71%. R_f: 0.62. IR (KBr): t = 3062 (Ar-H), 2952, 2836 (–CH_2–), 1676 (Amide-1), 1612 (–C═N), 1536 (Amide-2), 1247 (Amide-3), 1224, 1034 (C–O–C), 976 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, 3H, –CH_3), 2.34 (s, 3H, –CH_3), 2.55 (q, 2H, –CH_2), 3.15 (t, 2H, –CH_2), 4.31 (t, 2H, –CH_2–O), 7.07–8.12 (m, 11H, Ar-*H*), 7.36–8.36 (m, 3H, Pyridine-*H*), 7.87 (s, 1H, Pyrimidine-*H*), 9.40 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (*C*8), 21.5 (*C*37), 25.3 (*C*7), 37.2 (*C*9), 67.0 (*C*10), 103.8 (*C*22), 115.0–156.1 (*C*11–*C*16), 123.8–160.2 (*C*2–*C*6), 127.5–144.8 (*C*24–*C*35), 161.3 (*C*21), 161.2 (*C*19), 163.6 (*C*17), 165.1 (*C*36), Anal. calcd for $C_{32}H_{24}N_4O_2Cl_2F_2$: C63.48, H4.00, N9.25. Found C63.45, H4.01, N9.23.

*2.4.10. 5-Ethyl-2-{[4-(6-(4-bromophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6j**)*

m.p. 183–184 °C. Yield, 66%. R_f: 0.68. IR (KBr): t = 3065 (Ar-H), 2956, 2837(–CH_2–), 1673 (Amide-1), 1604 (–C═N), 1536 (Amide-2), 1246 (Amide-3), 1222, 1037 (C–O–C), 858 (C–Br). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.20 (t, 3H, –CH_3), 2.38 (s, 3H, –CH_3), 2.50 (q, 2H, –CH_2), 3.19 (t, 2H, –CH_2), 4.38 (t, 2H, –CH_2–O), 7.15–8.20 (m, 11H, Ar-*H*), 7.37–8.36 (m, 3H, Pyridine-*H*), 7.82 (s, 1H, Pyrimidine-*H*), 9.32 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7 (*C*8), 21.6 (*C*37), 25.4 (*C*7), 37.4 (*C*9), 67.2 (*C*10), 104.0 (*C*22), 115.8–155.7 (*C*11–*C*16), 123.3–161.8 (*C*2–*C*6), 127.8–144.2 (*C*24–*C*35), 161.4 (*C*21), 161.2 (*C*19), 163.0 (*C*17), 165.6 (*C*36). Anal. calcd for $C_{32}H_{25}N_4O_2Cl_2Br$: C59.28, H3.89, N8.64. Found C59.21, H3.84, N8.60.

*2.4.11. 5-Ethyl-2-{[4-(6-(3,4-dichlorophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6k**)*

m.p. 150–151 °C. Yield 59%. R_f: 0.62. IR (KBr): t = 3068 (Ar-H), 2954, 2839 (–CH_2–), 1675 (Amide-1), 1606 (–C═N), 1535 (Amide-2), 1246 (Amide-3), 1227, 1034 (C–O–C), 750 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (t, 3H, –CH_3), 2.33 (s, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.14 (t, 2H, –CH_2), 4.34 (t, 2H, –CH_2–O), 7.10–8.10 (m, 11H, Ar-*H*), 7.32–8.28 (m, 3H, Pyridine-*H*), 7.80 (s, 1H, Pyrimidine-*H*), 9.34 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (*C*8), 21.5 (*C*37), 25.8 (*C*7), 37.8 (*C*9), 67.6 (*C*10), 103.7 (*C*22), 115.3–155.6 (*C*11–*C*16), 123.8–160.6 (*C*2–*C*6), 127.5–145.0 (*C*24–*C*35), 161.3 (*C*21), 161.4 (*C*19), 163.8 (*C*17), 165.3 (*C*36). Anal. calcd for $C_{32}H_{24}N_4O_2Cl_4$: C60.21, H3.79, N8.78. Found C60.26, H3.74, N8.71.

*2.4.12. 5-Ethyl-2-{[4-(6-(4-chlorophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6l**)*

m.p. 163–165 °C. Yield 62%. R_f: 0.64. IR (KBr): t = 3063 (Ar-H), 2955, 2834 (–CH_2–), 1672 (Amide-1), 1611 (–C═N), 1533 (Amide-2), 1243 (Amide-3), 1224, 1036 (C–O–C), 745 (C–Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (t, 3H, –CH_3), 2.33 (s, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.14 (t, 2H, –CH_2), 4.34 (t, 2H, –CH_2–O), 7.10–8.10 (m, 11H, Ar-*H*), 7.32–8.28 (m, 3H, Pyridine-*H*), 7.80 (s, 1H, Pyrimidine-*H*), 9.34 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (*C*8), 21.5 (*C*37), 25.8 (*C*7), 37.8 (*C*9), 67.6 (*C*10), 103.7 (*C*22), 115.3–155.6 (*C*11–*C*16), 123.8–160.6 (*C*2–*C*6), 127.5–145.0 (*C*24–*C*35), 161.3 (*C*21), 161.4 (*C*19), 163.8 (*C*17), 165.3 (*C*36), Anal. calcd for $C_{32}H_{25}N_4O_2Cl_3$: C63.64, H4.17, N9.28. Found C63.60, H4.15, N9.25.

*2.4.13. 5-Ethyl-2-{[4-(6-(3-methoxyphenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6m**)*

m.p. 95–96 °C. Yield 67%, R_f: 0.66. IR (KBr): t = 3064 (Ar-H), 2956, 2836 (–CH_2–), 1673 (Amide-1), 1605 (–C═N), 1536 (Amide-2), 1244 (Amide-3) 1221, 1034 (C–O–C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, 3H, –CH_3), 2.30 (s, 3H, –CH_3), 2.54 (q, 2H, –CH_2), 3.16 (t, 2H, –CH_2), 4.31 (t, 2H, –CH_2–O), 7.05–8.17 (m, 11H, Ar-*H*), 7.34–8.33 (m, 3H, Pyridine-*H*), 7.85 (s, 1H, Pyrimidine-*H*), 9.31 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (*C*8), 25.6 (*C*7), 38.5 (*C*9), 55.7 (*C*30), 67.8 (*C*10), 103.2 (*C*22), 113.9–154.5 (*C*11–*C*16), 114.9–160.0 (*C*24–*C*29), 123.1–160.5 (*C*2–C6), 160.1 (*C*21), 163.2 (*C*17), 164.3 (*C*19), Anal. calcd for $C_{33}H_{28}N_4O_3Cl_2$: C66.11, H4.71, N9.35; found C66.08, H4.70, N9.34.

*2.4.14. 5-Ethyl-2-{[4-(6-(3-fluorophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6n**)*

m.p. 98–100 °C. Yield 65%, R_f: 0.61. IR (KBr): t = 3066 (Ar-H), 2954, 2836 (–CH_2–), 1675 (Amide-1), 1606 (–C=N), 1536 (Amide-2), 1245 (Amide-3), 1224, 1036 (C–O–C), 977 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.21(t, 3H, –CH_3), 2.32 (s, 3H, –CH_3), 2.56(q, 2H, –CH_2), 3.18(t, 2H, –CH_2), 4.35(t, 2H, –CH_2–O), 7.12–8.20 (m, 11H, Ar-*H*), 7.35–8.32 (m, 3H, Pyridine-*H*), 7.86 (s, 1H, Pyrimidine-*H*), 9.32 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6 (*C*8), 21.4 (*C*37), 25.9 (*C*7), 37.4 (*C*9), 67.3 (*C*10), 103.7 (*C*22), 115.3–155.4 (*C*11–*C*16), 123.6–160.5 (*C*2–*C*6), 127.8–144.2 (*C*24–*C*35), 161.4 (*C*21), 161.4 (*C*19), 163.2 (*C*17), 165.2 (*C*36), Anal. calcd for $C_{32}H_{25}N_4O_2Cl_2F$: C65.42, H4.29, N9.54. Found C65.44, H4.26, N9.53.

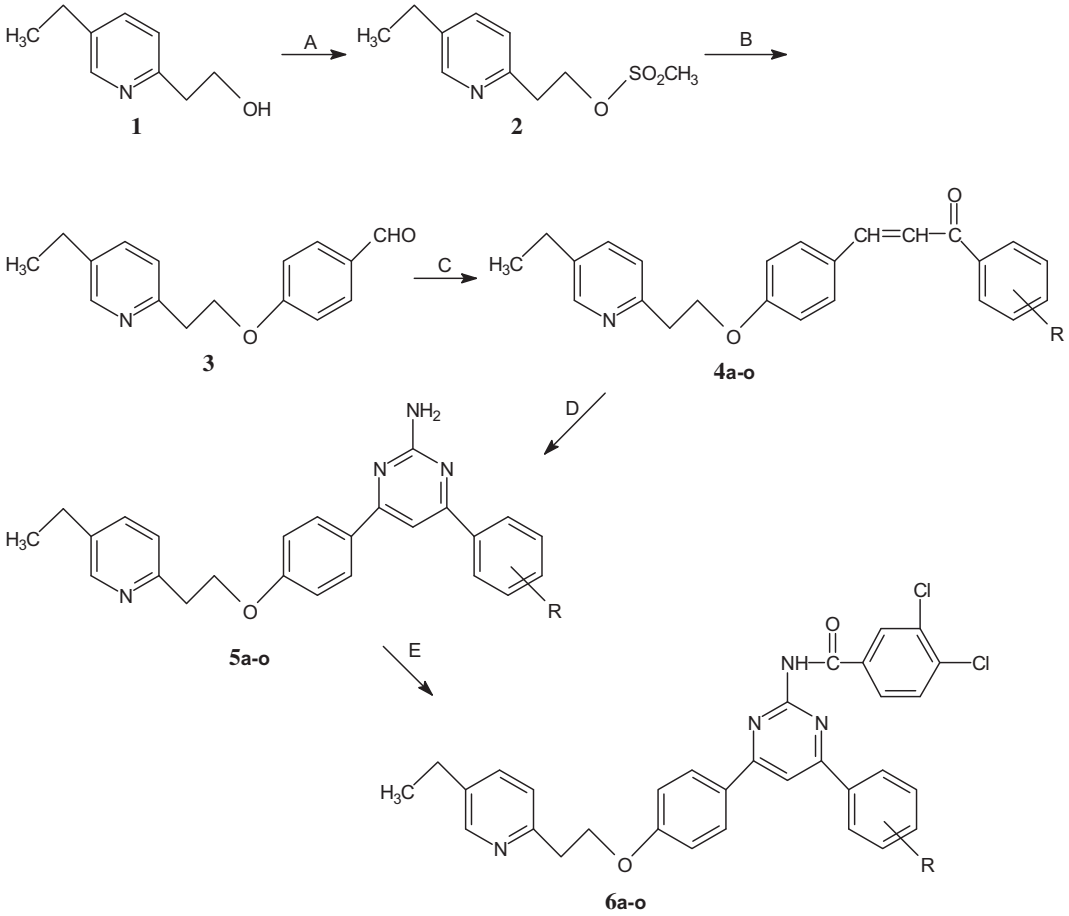
*2.4.15. 5-Ethyl-2-{[4-(6-(3,4-fluorophenyl)-2-(3,4-dichlorobenzamidopyrimidin-4-yl)]phenoxy ethyl} pyridine (**6o**)*

m.p. 178–180 °C. Yield 67%, R_f: 0.65. IR (KBr): t = 3065 (Ar-H), 2953, 2835 (–CH_2–), 1676 (Amide-1), 1610 (–C=N), 1533 (Amide-2), 1246 (Amide-3), 1221, 1032 (C–O–C), 974 (C–F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (t, 3H, –CH_3), 2.35 (s, 3H, –CH_3), 2.55 (q, 2H, –CH_2), 3.17 (t, 2H, –CH_2), 4.33 (t, 2H, –CH_2–O), 7.11–8.16 (m, 11H, Ar-*H*), 7.34–8.31 (m, 3H, Pyridine-*H*), 7.87 (s, 1H, Pyrimidine-*H*), 9.34 (s, 1H –N*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (*C*8), 21.5 (*C*37), 25.5 (*C*7), 37.3 (*C*9), 67.3 (*C*10), 103.3 (*C*22), 115.2–155.0 (*C*11–*C*16), 123.7–160.6 (*C*2–*C*6), 127.2–144.7 (*C*24–*C*35), 161.5 (*C*21), 161.4(*C*19), 163.5(*C*17), 165.5(*C*36), Anal. calcd for $C_{32}H_{24}N_4O_2Cl_2F_2$: C63.48, H4.00, N9.25. Found C63.42, H4.02, N9.24.

3. Results and discussion

3.1. Chemistry

The synthesis of chalcones, pyrimidines and amide derivatives is outlined in Scheme 1. First the chalcones (**4a**–**o**) were prepared from 5-ethyl-2-[4-(carboxalehyde)phenoxyethyl]pyridine with different substituted aromatic acetophenones in diluted methanolic sodium hydroxide solution at room temperature. The compounds (**5a**–**o**) were synthesized from different chalcones with guanidine nitrate and sodium hydroxide in methanol. The compounds (**6a**–**o**) were prepared from different pyrimidines and 3,4-dichloro benzoyl chloride. The purity of the compounds was determined by TLC and elemental analysis and all the synthesized heterocycles were confirmed by ^{1}H NMR, ^{13}C NMR and IR spectra.



Scheme 1 Synthesis of the compounds **4a**–**o**, **5a**–**o** and **6a**–**o**. Reagents and conditions: (A) methane sulphonyl chloride, toluene, triethylamine; (B) 4-hydroxy benzaldehyde, ethanol, NaOH; (C) substituted acetophenone, methanol, 2% NaOH; (D) guanidine nitrate, sodium ethoxide, Ethanol; (E) 3,4-dichloro benzoyl choride, pyridine.

From the IR sharp band was observed at 1662 cm^{-1} for –C═O and at 1599 cm^{-1} for –CH═CH– of chalcones **4a–o**. The ^{1}H NMR spectra exhibited one doublet at δ 7.11 attributed to the ═CH–CO– protons. In the ^{13}C NMR spectra of chalcones, –CH═CH– carbon appeared at the δ 144.2 and 119.7 ppm, respectively. The higher field resonances at δ 190.0 ppm were attributed to the carbonyl group present in chalcone. The structures of compounds **5a–o** and **6a–o** were also established by using IR and NMR spectroscopy. The IR of pyrimidine, disappearance of –C═O band at 1662 cm^{-1} and appearance of asymmetric and symmetric new broad bands at 3355 cm^{-1} and 3220 cm^{-1} for $–NH_2$, respectively. A new signal was observed at δ 5.15 and δ 7.85 for the $–NH_2$ and –CH in pyrimidine ring, respectively. From the ^{13}C

Table 1 Antimicrobial activity of compounds **4a–o**, **5a–o** and **6a–o**.

Comp.	*R*	Minimal bactericidal concentration μg/ml				Minimal fungicidal concentration μg/ml		
		Gram negative		Gram positive				
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
4a	2,4-Cl,5-F	200	250	1000	1000	1000	500	500
4b	4-OCH_3	100	150	250	250	1000	1000	1000
4c	2,4-Cl	150	500	500	500	500	500	1000
4d	4-OH	150	200	250	250	500	500	1000
4e	2,6-Cl,5-F	500	250	500	1000	1000	500	500
4f	4-CH_3	100	150	100	250	1000	1000	1000
4g	H	500	1000	1000	1000	200	500	500
4h	4-F	62.5	100	150	150	250	> 1000	> 1000
4i	2,4-F	250	250	500	500	1000	1000	1000
4j	4-Br	500	500	500	250	1000	> 1000	> 1000
4k	3,4-Cl	500	500	1000	1000	1000	> 1000	> 1000
4l	4-Cl	500	250	500	250	1000	500	500
4m	3-OCH_3	500	500	1000	1000	500	500	500
4n	3-F	250	500	250	500	500	1000	1000
4o	3,4-F	125	250	500	500	1000	1000	1000
5a	2,4-Cl,5-F	150	250	500	500	500	500	1000
5b	4-OCH_3	62.5	150	250	250	500	> 1000	> 1000
5c	2,4-Cl	500	500	250	500	500	> 1000	> 1000
5d	4-OH	250	200	500	500	500	500	1000
5e	2,6-Cl,5-F	250	150	1000	1000	500	500	500
5f	4-CH_3	200	200	250	250	500	500	500
5g	H	250	250	500	500	500	500	500
5h	4-F	250	250	100	100	500	250	250
5i	2,4-F	62.5	150	150	200	500	1000	1000
5j	4-Br	250	250	200	200	1000	1000	1000
5k	3,4-Cl	250	250	250	250	1000	500	500
5l	4-Cl	250	100	150	250	500	500	500
5m	3-OCH_3	250	250	500	500	1000	500	500
5n	3-F	500	500	250	250	500	1000	1000
5o	3,4-F	250	500	500	250	200	200	200
6a	2,4-Cl,5-F	250	500	150	250	500	500	500
6b	4-OCH_3	250	100	150	150	1000	500	500
6c	2,4-Cl	500	250	250	250	1000	> 1000	> 1000
6d	4-OH	250	200	500	500	500	500	500
6e	2,6-Cl,5-F	250	250	500	250	500	> 1000	> 1000
6f	4-CH_3	200	250	250	500	100	200	200
6g	H	500	1000	500	500	1000	500	500
6h	4-F	150	200	500	500	500	1000	1000
6i	2,4-F	100	250	100	100	500	500	500
6j	4-Br	100	500	500	500	1000	> 1000	> 1000
6k	3,4-Cl	500	250	500	500	100	100	100
6l	4-Cl	250	250	250	500	1000	500	500
6m	3-OCH_3	500	500	1000	1000	1000	1000	1000
6n	3-F	500	500	1000	500	500	1000	1000
6o	3,4-F	250	500	250	250	> 1000	> 1000	> 1000
Gentamycin		0.05	1	0.25	0.5	–	–	–
Ampicillin		100	100	250	100	–	–	–
Chloroamphenicol		50	50	50	50	–	–	–
Ciprofloxacin		25	25	50	50	–	–	–
Norfloxacin		10	10	10	10	–	–	–
Nystatin		–	–	–	–	100	100	100
Greseofulvin		–	–	–	–	500	100	100

NMR, pyrimidine –CH carbon appeared at δ 103.2. The three bands were observed at 1672 cm^{-1}, 1537 cm^{-1} and 1250 cm^{-1} of amide –C═O, –NH– and C–N, respectively. Similarly the disappearance of NH_2 and the appearance of a signal at δ 9.25 due to –NHCO provided further evidence for the conversion of compound **5**–**6** and also ^{13}C NMR spectra showing the amide signal at δ 165.3 ppm confirmed this.

On the basis of the above-mentioned spectral data, compounds **4a**–**o**, **5a**–**o** and **6a**–**o** were confirmed.

3.2. Antimicrobial activity

The MICs of synthesized compounds were carried out by broth micro dilution method as described by Rattan (2000).

3.3. Antibacterial activity

The minimal bactericidal concentrations (MBCs) of the tested compounds are shown in Table 1. The different compounds **4a**–**o**, **5a**–**o** and **6a**–**o** were tested *in vitro* against two gram-positive (*S. aureus* MTCC 96, *S. pyogenus* MTCC 443) and two-gram negative (*E. coli* MTCC 442, *P. aeruginosa* MTCC 441) bacteria. From the screening data, most of the compounds possessed very good antibacterial activity (MBC, 50–250 μg/ml) against *S. aureus*; some of them showed excellent activity with ampicillin. Chalcones **4b** (**4-OCH_3**), **4f** (**4-CH_3**) and **4h** (**4-F**) showed MBC in the range between 62.5 and 100 μg/ml while ampicillin has MBC 100 μg/ml against *E. coli* which indicates that these compounds have excellent activity, while other chalcones **4c** (**2,4-Cl**), **4d** (**4-OH**) and **4o** (**3,4-F**) possessed MBC 125–150 μg/ml against *E. coli* and **4h** (**4-F**) exhibited very good activity against *P. aeruginosa*. Compounds **4f** (**4-CH_3**) and **4h** (**4-F**) displayed excellent activity in the range of 100–150 μg/ml while remaining **4b** (**4-OCH_3**), **4d** (**4-OH**) and **4n** (**3-F**) were comparable against *S. aureus* with ampicillin. Compound **4h** (**4-F**) has MBC 150 μg/ml which was comparatively good against *S. pyogenus*. The remaining chalcones possessed moderate to poor activity against all four bacterial species. For pyrimidines, **5b** (**4-OCH_3**) possessed MBC 62.5 μg/ml against *E. coli* and MBC 150 μg/ml against *P. aeruginosa* comparable with ampicillin. Compound **5e** (**2,6-Cl,5-F**) exhibited MBC 150 μg/ml against *P. aeruginosa*. Compound **5h** (**4-F**) possessed MBC 100 μg/ml against *S. aureus* and *S. pyogeneus*. Compound **5i** (**2,4-F**) possessed MBC 62.5 μg/ml against *E. coli* and MBC 150 μg/ml against *S. aureus* and showed good activity as that of ampicillin. Compound **5l** (**4-Cl**) showed MBC 100 μg/ml against *P. aeruginosa* and MBC 150 μg/ml against *S. aureus*. Other pyrimidines displayed moderate to poor activities against all four bacterial species. Amides **6i** (**2,4-F**) and **6j** (**4-Br**) showed MBC 100 μg/ml against *E. coli* which is same as ampicillin. Compound **6b** (**4-OCH_3**) showed MBC 100 μg/ml against *P. aeruginosa;* comparable with ampicillin. Compounds **6a** (**2,4-Cl, 5-F**), **6b** (**4-OCH_3**) and **6i** (**2,4-F**) showed MBC 100–150 μg/ml against *S. aureus* while ampicillin itself showed MBC 250 μg/ml which indicates that these compounds are highly active. Compound **6i** (**2,4-F**) showed MBC 100–150 μg/ml against *S. pyogeneus*. Remaining amides possessed moderate to poor activities against all four bacterial species.

3.4. Antifungal activity

Minimal fungicidal concentrations (MFCs) of the synthesized compounds are shown in Table 1. For *in vitro* antifungal activity, three fungal species *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323 were used and compared with the standard drug greseofulvin. Chalcones **4g** (–**H**) and **4h** (**4-F**) showed excellent activity of 200–250 μg/ml; **4c** (**2,4-Cl**), **4d** (**4-OH**), **4m** (**3-OCH_3**) and **4n** (**3-F**) possessed very good activity of 500 μg/ml with greseofulvin (500 μg/ml) against *C. albicans* whereas chalcones possessed moderate to poor activity against *A. niger* and *A. clavatus*. Pyrimidines **5o** (**3,4-F**) possessed good activity of 200 μg/ml against *C. albicans,* which is comparable with greseofulvin (500 μg/ml). Amides **6f** (**4-CH_3**) and **6k** (**3,4-Cl**) displayed excellent activity of 100 μg/ml against *C. albicans* and comparable with greseofulvin and nystatin. Compound **6k** (**3,4-Cl**) possessed very good activity of 100 μg/ml against *A. niger* and *A. clavatus*. From the antifungal results it can be concluded that compound **6k** (**3,4-Cl**) is very active like the standard drugs.

4. Conclusions

Chalcones **4b**, **4f** and **4h** are found to be excellent against all bacteria; where as pyrimidines **5b** and **5i** are very effective and comparable with the standard drug. Amides **6i**, **6j**, **6b** and **6a** are more active and are comparable with the standard drugs.

Antifungal activities of chalcones **4g** and **4h** are more effective against all three fungal species. For pyrimidines, **5o** was found comparable against *C. albicans*, while amides **6f** and **6k** are more effective against three fungal species. These results make new chalcone, pyrimidine and amide derivatives interesting for further synthetic and biological evaluation.

Acknowledgements

The authors thank the Professor and Head, Department of Chemistry for laboratory facilities, Dhanji Rajani, Microcare Laboratory, Surat, for antimicrobial activity; Atul Ltd. for IR spectra; C.D.R.I., Lucknow for elemental analysis and S.A.I.F., Chandigarh for ^{1}H NMR and ^{13}C NMR spectral analyses.

References

Aytemir, M., Hider, R.C., Erol, D., Ozalp, M., Ekizoglu, M., 2003. Turk. J. Chem. 27, 445–452.

Banoglu, E., Sukuroglu, M., Caliskanergun, B., Nacakbaytas, S., Aypar, E., Aark, M., 2007. Turk. J. Chem. 31, 677–687.

De Paula, V.F., De A Barbosa, L.C., Demuner, A.J., Pilo-Veloso, D., Picanco, M.C., 2000. Pest Manag. Sci. 56, 168–174.

Desai, A.D., Chikhalia, K.H., 2005. Eur. J. Chem. 2, 15–20.

Dolezal, M., Miletin, M., Kunes, J., Kralova, K., 2002. Molecules 7, 363–373.

Dolezal, M., Palek, L., Vinsova, J., Buchta, V., Jampilek, J., Kralova, K., 2006. Molecules 11, 242–256.

Gaonkar, S.L., Rai, K.M.L., Prabhuswamy, B., 2006. Eur. J. Med. Chem. 41, 841–846.

Geronikaki, A., Hadjipavlou-Litina, D., Chatziopoulos, C., Soloupis, G., 2003. Molecules 8, 472–479.

Mitkov, J., Danchev, N., Nikolova, I., Zlatkov, A., 2007. Acta Pharm. 57, 361–370.
Momose, Y. et al., 1991. Chem. Pharm. Bull. 396, 1440.
Onkol, T., fethi sahin, M., Yildirim, E., Erol, K., Ito, S., 2004. Arch. Pharm. Res. 27, 1086–1092.
Rattan, A., 2000. Antimicrobials in Laboratory Medicine, Churchill B I, Livingstone, New Delhi, p. 85.
Temiz-Arpacı, O., Ozdemir, A., Yalcın, I., Yıldız, I., Akı-Sener, E., Altanlar, N., 2005. Arch. Pharm. Chem. Life Sci. 338, 105–111.
Yildiz Oren, I., Aki-sener, E., Ertas, C., Temiz arpaci, O., Yalcin, I., Altanlar, N., 2004. Turk. J. Chem. 28, 441–449.
Zhong, G., Hu, J., Zhao, K., Chen, L., Hu, W., Qiu, M., 2009. Bioorg. Med. Chem. Lett. 19, 516–519.