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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SOME NEW AMINO PYRIMIDINEBASED SCHIFF BASES AND ITS 4-THIAZOLIDINONESDERIVATIVES

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Abstract
Schiff basesand its 4-thiazolidinones derivatives have occupied a unique place in medicinal chemistry. They are the most important class of compounds possessing different biological properties. Knowing this fact, schiff bases **[3a-3g]**and its 4-oxo-thiazolidines**[4a-4g]**based compounds have been synthesized. The structures of all newly synthesized compounds were characterized by using FTIR, ^{1}H NMR, ^{13}C NMR and LCMS.All the newly designed compounds were also screened for the non-automated in vitro antimicrobial activity against selected pathogens. The Minimum Inhibitory Concentration (MIC) was determined and recorded at the lowest concentration inhibiting growth of the organism.

Key words
Schiff base, Thiazolidinones, Amino pyrimidine, Antimicrobial activity

Introduction

There are various biologically active molecules which contain nitrogen, sulphur and oxygen as hetero atoms always drawn the concern of chemist over the years mainly due to their biological importance.Azomethine group (–CH=N–) containing compounds typically known as schiff bases have been synthesised by the condensation of primary amines with active carbonyls. They can be considered as a subclass of imines. Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications such as antitubercular[i] antimicrobial[ii], antiviral[iii], anticonvulsant[iv], antioxidant[v], antimalarial[vi], antitumor[vii,viii]etc.. Small ring heterocyclic containing nitrogen, sulphur and oxygen as hetero atoms gained great importance due to their important medicinal properties.
Thiazolidinones are thiazolidine derivatives which have sulphur and nitrogen atoms at position 1, 3 respectively while carbonyl group at position 2,4 or 5 respectively.Particularly, 4-thiazolidinones have been shown to have various important biological activities such as anti-inflammatory[ix,x], antimicrobial[xi,xii], and anti-HIV[xiv,xv].4-Thiazolidinone is a saturated form of thiazole with carbonyl group(>C=O) on fourth carbon, has been considered as a

magic moiety. Based on the wide spectrum of biological profile of schiff bases and 4-thiazolidinones and their increasing importance in pharmaceutical and biological field, it was thought of interest to synthesize some new heterocyclic ring containing schiff bases and thiazolidin-4-one moieties with potential biological activities. 4-Thiazolidinonederivativessynthesized by condensation reaction of schiff bases withthioglycolic acid in suitable solvent media.

Experimental

All the chemicals and solvents used for the reaction were of analytical reagent (AR) grade. Purity of the compounds were checked by TLC using aluminium sheets Silica Gel 60 F-254 (Merck) plates of 0.25 mm thickness and detection of the components were made by exposure to UV light or keeping the plates in iodine chamber. Melting points of all synthesizedcompounds were resolute in open capillary method and are uncorrected. Infrared spectra were recorded on Shimadzu FTIR 8401 spectrophotometer using KBr pellets in the range 4,000-400 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance (Bruker Scientific Corporation Ltd., Switzerland) DPX400 MHz spectrometer with $CDCl_3$ (^{1}H NMR) as a solvent and TMS as an internal standard at 400 and 100 MHz operating frequencies. IR, ^{1}H NMR, ^{13}C NMR and LCMS data are consistent with the assigned structures. The chemical shifts are expressed in parts per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet) and m (multiplet). The coupling constants (J) are given in Hertz (Hz). All the newly synthesized compounds were analysed for carbon, hydrogen and nitrogen by the Perkin-Elmer 2400 CHN series-II elemental analyser (Perkin-Elmer, USA). Reference drugs forantimicrobial activity are Ampicillin, Chloramphenicol, Ciprofloxacin, Griseofulvin, Nystatin used of commercial grade.

Preparation of 1-(2',4'-dichloro-5'-fluorophenyl)-3-(4"-methoxyphenyl)-2-en-1-one [1]

Claisen-Schmidt condensation reaction was carried out in 250 ml conical flask. 2,4-dichloro-5-fluoro acetophenone (0.01mole) and para methoxy benzaldehyde (0.01mole) were dissolved in alcohol, 10% NaOH solution was added as catalyst. The reaction mixture was stirred for 24 hours on a magnetic stirrer at room temperature. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice, neutralized with dilute hydrochloric acid and the mixture was agitated for 5 to 10 minutes. The product was separated by filtration and recrystallized from ethanol (Yellow solid, Yield 85%, m.p.145 $^{\circ}C$). Synthetic pathway for preparation of titled compounds is shown in the reaction scheme 1.

IR (KBr, cm^{-1}): 3035 (=CH), 1650 (-C=O), 1537 (C=C), 1105 (OCH_3), 1229 (C-O-C), 1010 (C-F), 836 (C-Hbending of 1, 4 disubstituted benzene ring), 759 (C-Cl).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):** 3.9 (s, 3H, OCH_3), 5.9 (d, J=9.4 Hz, lH, -CO-CH=), 7.9 (d, J=9.3 Hz, 1H, Ar-CH=), 6.8-7.8 (m, 9H, Ar-H).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):** 54.4(OCH_3), 113.2(CH), 138.4(CH), 114.5(CH), 116.2(CH), 118.0(CH), 121.5(=CH),145.1(=CH), 134.5(C-Cl), 128.0(C-Cl), 164.7(C-F), 135.3(C), 140.6(C), 143.5(C), 147.2(C),188.4 (CO);Found C, 62.12; H, 3.55 $C_{16}H_{11}Cl_2FO$ requires C, 62.16; H, 3.58%.

Preparation of 4-(2',4'-dichloro-5'-fluorophenyl)-6-(4"-methoxyphenyl)-pyrimidin-2-amine [2]

Entitled compound was prepared at reflux temperature by condensation reaction of prepared chalcone (0.01mole), in 250ml round bottom flask with guanidine hydrochloride by using alcohol as solvent and 40% NaOH solution was added to make pH basic**.**The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was

poured into crushed ice, neutralized with dilute hydrochloric acid and the mixture was agitated for 5 to 10 minutes. The product was separated by filtration and recrystallized from ethanol.Synthetic pathway for preparation of title compounds is shown in reaction Scheme 1 (White solid, Yield 80%, m.p.115 °C).

IR (KBr, cm^{-1}): 3452.01(NH_2), 3036(=CH), 1538(C=C), 2829(-OCH_3), 1230(=C-O-C), 1020(C-F), 830(C-Hbending of 1, 4 disubstituted benzene ring), 765(C-Cl).**^{1}H NMR(400 MHz, $CDCl_3$, δ ppm):** 3.85(s, 3H, OCH_3), 5.15(s, 2H, NH_2), 5.9 (d, J = 9.4 Hz, lH, CO-CH=), 7.9(1H, Ar-CH=), 6.8-8.0(m, 7H, Ar-H).Found C, 56.0; H, 3.28, N, 11.50 $C_{17}H_{12}Cl_2N_3FO$ requires C, 56.06; H,3.32; N, 11.54%.

General preparation of N-(substituted benzylidene)-4-(2', 4'-dichloro-5'-fluorophenyl)-6-(4''-methoxyphenyl)-pyrimidin-2-amine [3a-3g]

A mixture of synthesized amino pyrimidine [2](0.01mole) and appropriate benzaldehyde (0.01mole) in alcohol was refluxed on water bath in presence of glacial acetic acid for 4-5 hours. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice, neutralized with saturated solution of sodium bicarbonate and the mixture was agitated for some time.The product was separated by filtration and recrystallized from ethanol to give [3a-3g].

N-(4'''-methoxybenzylidene)-4-(2',4'-dichloro-5''-fluorophenyl)-6-(4''-methoxyphenyl)-pyrimidin-2-amine [3a]: Yield 80%, m.p. 109°C.**IR (KBr, cm^{-1}):**1575(-CH=N-), 3040(=CH), 1540(C=C), 1103(C-OCH_3), 1250(C-O-C), 1015(C-F), 836(C-H bending 1,4 disubstitutedbenzene ring), 760(C-Cl), 153.5(C=N), 2840(OCH_3 stretching).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):**3.82 (s, 3H,-OCH_3), 3.9(s, 3H, OCH_3), 6.2-7.8 (m, 11H, Ar-H), 8.5 (s, 1H, N=CH-).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):** 161.4(C-F),122.2(C-Cl),132.5(CH),129.3(C-Cl), 129.7(C), 118.7(CH), 162.6(C), 167.8(C=N), 104.1(CH), 162.8(C=N), 160.1(N=CH,azomethine),126.1(CH), 130.2(CH), 144.4(CH), 163.0(C-O ether), 55.9(OCH_3), 125.4(C), 128.5(CH), 114.8(CH), 160.7(C-O ether);MS (m/z): 481.6 (M^+). Found C, 62.20; H, 3.72; N, 8.70$C_{25}H_{18}N_3FCl_2O_2$requires C, 62.26; H, 3.76; N, 8.73%.

N-(4'''-nitrobenzylidene)-4-(2',4'-dichloro-5-fluorophenyl)-6-(4''-methoxyphenyl) pyrimidin-2-amine [3b]: Yield 78%, m.p.125°C. **IR (KBr,cm^{-1}):**1585(-CH=N-), 3045(=CH), 1542(C=C), 1106(C-OCH_3), 1252(C-O-C), 1012(C-F), 830(C-H bending 1, 4disubstitutedbenzene ring), 762(C-Cl), 1532(C=N), 2842(OCH_3),1505(C-NO_2).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):**3.82(s, 3H,-OCH_3), 3.9(s, 3H, OCH_3), 6.8-7.8(m, 11H, Ar-H), 8.6 (s, 1H, N=CH-).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**164.4(C-F), 121.1(C-Cl), 133.5(C), 128.3(C), 128.5(C), 118.0(CH), 160.6(C), 166.0(C), 160.6(C), 103.1(CH), 124.5(C), 127.3(CH),114.5(CH),159.9(C=N),55.9(OCH_3), 128.5(C),161.1(N=CH), 123.3(C), 129.3(CH), 156.5(C-NO_2), 120.0(C); MS (m/z):495.0(M^+). Found C, 57.85; H, 3.0; N, 11.30$C_{24}H_{15}N_4FCl_2O_3$ requires C, 57.97; H, 3.04; N, 11.27%.

N-(2'''-fluorobenzylidene)-4-(2',4'-dichloro-5'**-fluorophenyl)-6-(4''-methoxyphenyl)-pyrimidin-2-amine [3c]:**Yield 81%, m.p. 140°C.**IR(KBr,cm^{-1}):**1538(C=C**),**3028**(**=CH), 1575(C=N),1220(C-O-C), 1076(C-F),1578(C=NH), 1170(C-F), 805(C-Cl), 745, 815(C-H bending 1,2 and 1,4disubstitutedbenzene ring).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):**9.1(s, 1H, N=CH-), 3.83(s, 3H, OCH_3), 7.2-8.8(m, 11H Ar-H).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**163.2(C-F), 121.2(C-Cl), 131.5(C), 127.3(C), 128.7(C), 118.2(CH), 161.6(C), 166.5(C), 161.6(C), 105.1(CH), 126.0(C), 129.0(CH), 113.5(CH), 161.2(C), 56.2(OCH_3), 128.0(C), 162.0(N=CH),160.0(C-F), 116.1(C), 133.2(CH), 125.2(CH), 129.5(CH), 119.0(CH);MS (m/z):470.28(M^+). Found C, 61.25; H, 3.20; N, 8.90$C_{24}H_{15}N_3F_2Cl_2OC$ requires 61.28; H, 3.21; N, 8.94%.

N-(4'''-fluorobenzylidene)-4-(2',4'-dichloro-5'**-fluorophenyl)-6-(4''-methoxyphenyl)-pyrimidin-2-amine [3d]: Y**ield 75%, m.p.138°C. **IR (KBr, cm^{-1}):**1570(C=NH),1542(C=C),

3025(=CH), 1245(C-O-C), 1076(C-F),1570(C=NH), 805(C-Cl), 815(C-H bending 1, 4disubstitutedbenzene ring), 1030(C-F).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):**8.7(s, 1H, N=CH-), 3.83(s, 3H, OCH_3), 7.2-8.8(m, 11H Ar-H).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**165.0(C-F), 123.5(C-Cl), 134.0(C), 130.1(C), 130.5(C), 120.1(CH), 162.1(C), 170.5(C), 163.8(C=N), 106.3(CH), 126.1(C), 130.1(CH), 113.1(CH), 161.2(C), 55.9(OCH_3), 127.5(C), 162.3(N=CH), 167.1(C=N), 132.4(CH); MS (m/z):470.20 (M^+). Found C, 61.24; H, 3.20; N 8.92 $C_{24}H_{15}N_3F_2Cl_2O$ requires C 61.28; H 3.21; N 8.94%.

N-(2'"-hydroxybenzylidene)-4-(2',4'-dichloro-5-fluorophenyl)-6-(4"-methoxyphenyl)-pyrimidin-2-amine [3e]. Yield 78%, m.p.151°C. **IR (KBr, cm^{-1}):** 1565(-N=CH-), 3045(=CH), 1542 (C=C), 1106(C-OCH_3),1252(C-O-C ether linkage), 1020(C-F), 815(C-H bending 1,2 disubstituted benzene ring), 765(C-Cl), 1534(C=N), 2842(OCH_3), 1225(Ar-OH).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):**3.80(s, 3H,-OCH_3),5.2(s,1H, Ar-OH), 6.2-7.8 (m, 11H, Ar-H), 8.4 (s, 1H, N=CH-).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):** 168.4(C-F), 125.1(C-Cl), 135.1(C), 130.7(C), 126.7(C), 121.0(CH), 165.1(C), 171.5(C), 162.6(C), 107.0(CH), 126.1(C), 130.1(CH), 116.1(CH), 160.7(C), 61.2(OCH_3), 126.1(C), 166.5(N=CH), 127.5(C), 135.6(CH), 117.0(CH), MS (m/z): 468.20 (M^+). Found C, 61.50; H, 3.40; N, 8.95 $C_{24}H_{16}N_3FCl_2O_2$ requires C, 61.55; H, 3.44; N, 8.97%.

N-(2'"-chlorobenzylidene)-4-(2',4'-dichloro-5-fluorophenyl)-6-(4"-methoxyphenyl)-pyrimidin-2-amine [3f]. Yield 78%, m.p.162°C. **IR (KBr, cm^{-1}):**1570(N=CH), 1585(C=C), 1635(C=C), 1607(C=N), 1256(C-O-C ether linkage), 762(C-Cl), 2840(OCH_3) 3126(=CH), 750(C-H bending of 1, 2 disubstituted benzene ring), 760(C-Cl), 1132(C-F). **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):** 3.81(s, 3H, OCH_3), 6.6-8.0(m, 11H, Ar-H), 8.3(s, 1H, N=CH-).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**164.7(C-F), 122.2(C-Cl), 136.5(C), 129.3(C), 129.7(C), 119.1(CH), 162.2(C), 171.2(C), 169.1(C), 108.1(CH), 125.4(C), 134.5(CH), 134.1 (CH), 114.5 (CH), 160.7(C), 56.8(OCH_3), 128.5(C), 162.2(N=CH), 138.0(C), 133.2(CH), 135.0(CH), 136.0(CH), 138.6(CH), 143.4(C); MS (m/z):486.74 (M^+).Found C, 59.22; H, 3.10; N, 8.60 $C_{24}H_{15}N_3FCl_3O$ requires C, 59.22; H, 3.10; N, 8.63%.

N-(4'"-chlorobenzylidene)-4-(2',4'-dichloro-5-fluorophenyl)-6-(4"-methoxyphenyl)-pyrimidin-2-amine [3g]. Yield 78%, m.p.155 °C.**IR (KBr, cm^{-1}):**1570(C=NH),1635(C=C), 3030(=CH), 1607(C=N), 1260(C-O-C ether linkage),740(C-H bending of 1, 2 disubstituted benzene ring), 765(C-Cl), 1130(C-F), 760(C-Cl), 2835(OCH_3). **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):**9.2(s, 1H, N=CH-), 3.83(s, 3H, OCH_3), 7.2-8.0(m, 11H Ar-H).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**166.1(C-F), 123.2(C-Cl), 131.6(C), 132.1(C), 134.2(C), 119.3(CH), 162.6(C=N), 172.1(C), 162.6(C), 104.1(CH), 125.4(C), 128.5(CH), 115.1(CH), 160.7(C), 55.9(OCH_3), 128.5(C), 163.1(N=CH), 138.2(C-Cl), 133.3(CH), 131.6(CH), 134.1(C).MS (m/z):451.28(M^+). Found C, 63.85; H, 3.30; N, 9.30 $C_{24}H_{15}N_3FCl_2O$ requires C, 63.87; H, 3.35; N, 9.31%.

General preparation of 3-{4-(2, 4-dichloro-5-fluorophenyl)-6-(4-methoxyphenyl)pyrimidine-2-yl}-2-(4-methoxyphenyl)thiazolidin-4-one [4a-4g]

Thioglycolic acid (0.01mole) was reacted with 0.01mole of [3a-3e] in dry toluene (60ml) was refluxed on water bath using Dean-Stark water separator for 6-8 hours. Excess of toluene was then distilled off and the resulting viscous liquid was treated with saturated $NaHCO_3$ solution to remove unreacted thioglycolic acid. The resulting products were separated and washed with water, dried and recrystallized from alcohol [4a-4g].

3-{4'-(2",4"-dichloro-5"-fluorophenyl)-6-(4'"-methoxyphenyl)pyrimidine-2-yl}-2-(4'""-methoxyphenyl)thiazolidin-4-one [4a]. Yield 83%, m.p.131°C. **IR (KBr, cm^{-1}):**1687(>C=O, Thiazolidine ring),3010(=CH), 1594(C=C), 1570(C=N), 840(C-H bending of 1,4-disubstituted benzene), 695(C-S-C), 1238(C-O-C), 2834(OCH_3), 761(C-Cl), 1150(C-F), 2840(*p*-OCH_3).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):** 3.70(q, 2H, -CH_2), 3.8(s, 3H, P-

OCH_3), 3.82(s, 3H, P-OCH_3), 6.00 (s, 1H, -CH-Ar), 6.50-7.60(m, 11H, Ar-H).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**161.4(C-F), 120.1(C-Cl), 134.5(CH),126.1(C-Cl), 128.1(CH), 129.1(C), 65.1(C), 99.5(CH), 156.1(C), 162.1(N-C-N), 170.1(C=O), 33.5(CH_2), 65.6(N-C-S), 55.8(OCH_3), 159.2(C), 113.1(CH), 136.2(CH), 131.3(CH), 133.1(CH);MS (m/z):556.42 (M^+).Found C, 58.25; H, 3.60; N, 7.50 $C_{27}H_{20}N_3FSCl_2O_3$ requires C, 58.28; H, 3.62; N, 7.55%.

3-{4'-(2",4"-dichloro-5"-fluorophenyl)-6-(4'"-methoxyphenyl)pyrimidine-2-yl}-2-(4""-nitrophenyl)thiazolidin-4-one [4b]. Yield 78%, m.p.161°C. **IR (KBr, cm^{-1}):**1680(>C=O, Thiazolidine ring),3077(=CH), 1590(C=C), 1535(C=N), 745(C-H bending of 1,4-disubstituted benzene), 690(C-S-C), 1240(C-O-C), 2840(OCH_3), 755(C-Cl), 1145(C-F).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):** 3.69(q, 2H, -CH_2), 3.9(s, 3H, -OCH_3) 5.9(s, 1H, -CH-Ar), 6.80-7.80(m, 11H, Ar-H).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**146.8(C-NO_2), 121.0(CH), 121.2(CH), 126.7(CH), 129.6(CH), 146.3(C), 165.4(C-F), 125.1(C-Cl), 134.1(CH), 132.1(C-Cl), 128.7(CH), 127.1(C), 63.0(C), 103.1(CH), 160.1(C), 165.1(N-C-N), 121.2(C=O), 35.6(CH_2), 66.1(N-C-S); MS (m/z):557.38 (M^+). Found C, 54.60; H, 3.0; N, 9.78 $C_{26}H_{17}N_4FSCl_2O_4$ requires C, 54.65; H, 3.0; N, 9.81%.

3-{4'-(2",4"-dichloro-5"-fluorophenyl)-6-(4'"-methoxyphenyl)pyrimidine-2-yl}-2-(2""-flourophenyl)thiazolidin-4-one [4c]. Yield 85%, m.p.127°C. **IR (KBr, cm^{-1}):**1564 (C=N), 1142(C-F), 3026(=CH), 1526 C=C), 653 (C- Cl),1675(>C=O, Thiazolidine ring), 1235(C-O-C), 1011(C-F), 777(C-Cl stretching).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):** 3.89(s, 3H, p-OCH_3), 3.76(q, 2H, –CH_2), 6.99-8.20(m, 11H, Ar-H).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**159.1(C-F), 120.1(C-Cl), 134.8(CH), 130.3(C-Cl), 135.7(CH), 134.7(C), 65.2(C), 104.1(CH), 158.1(C-F), 159.5(N-C-N), 172.5(C=O), 36.1(CH_2), 56.2(N-C-S), 161.3(C-F), 116.4(CH), 128.5(CH), 125.3(CH), 135.0(CH), 98.9(C); MS (m/z):557.38 (M^+).Found C, 56.03; H, 3.07; N, 7.50 $C_{26}H_{17}N_3F_2SCl_2O_2$ requires C, 56.03; H, 3.07; N, 7.54%.

3-{4'-(2",4"-dichloro-5"-flourophenyl)-6-(4'"-methoxyphenyl)pyrimidine-2-yl}-2-(4""-flourophenyl)thiazolidin-4-one [4d]. Yield 82%, m.p.138°C. **IR (KBr, cm^{-1}):**3030(=CH),1528(C=C)**,** 2845(*p*-OCH_3)**,** 1560 (C=N),1675(>C=O, Thiazolidine ring),1235(C-O-C symmetric stretching), 1022(C-F), 780(C-Cl).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):** 3.90(s, 3H, *p*-OCH_3), 3.77(q, 2H, –CH_2), 6.1(s, 1H, CH-Ar), 6.90-7.90(m, 11H, Ar-H).**^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**163.4(C-F), 121.2(C-Cl), 133.5(CH), 130.1(C-Cl), 136.7(CH), 134.7(C), 64.5(C), 103.1(CH), 160.5(C), 165.2(N-C-N), 175.1(C=O), 32.8(CH_2), 55.2(N-C-S), 165.2(C-F), 115.6(CH), 131.4(CH); MS (m/z):544.38 (M^+).Found C, 57.35; H, 3.10; N, 7.70 $C_{26}H_{17}N_3F_2SCl_2O_2$ requires C, 57.36; H, 3.14; N, 7.72%.

3-{4'-(2",4"-dichloro-5"-fluorophenyl)-6-(4'"-methoxyphenyl)pyrimidine-2-yl}-2-(4""-hydroxyphenyl)thiazolidin-4-one [4e]. Yield 76%, m.p.145 °C. **IR (KBr, cm^{-1}):**1682(>C=O, Thiazolidine ring),3076(=CH), 1591(C=C), 1534(C=N), 746(C-H bending), 695(C-S-C), 1238(C-O-C), 2835(OCH_3), 766(C-Cl), 1180(C-F), 1220(Ar-OH).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):** 3.72(q, 2H, -CH_2), 3.89(s, 3H, -OCH_3), 6.20(s, 1H, -CH-Ar), 5.1(s,1H, Ar-OH), 6.80-7.90(m, 11H, Ar-H). **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**165.4(C-F), 123.1(C-Cl), 133.5(CH), 129.3(C-Cl), 128.7(CH), 129.7(C), 64.0 (C), 101.5(CH), 159.0(C), 161.1(N-C-N), 171.2(C=O), 33.6(CH_2), 54.8(N-C-S), 165.2(C-F), 115.6(CH), 115.6(CH), 129.4(CH); MS (m/z):526.39 (M^+).Found C, 59.30; H, 3.40; N, 7.95 $C_{26}H_{18}N_3FSCl_2O_2$ requires C, 59.32; H, 3.44; N, 7.98%.

3-{4'-(2",4"-dichloro-5"-fluorophenyl)-6-(4'"-methoxyphenyl)pyrimidine-2-yl}-2-(2""-chlorophenyl)thiazolidin-4-one [4f]. Yield 81%, m.p.141°C. **IR (KBr, cm^{-1}):**1682(>C=O, Thiazolidine ring),3076(=CH), 1591(C=C), 1534(C=N), 746(C-H bending), 695(C-S-C), 1238(C-O-C), 2835(OCH_3), 766(C-Cl), 1180(C-F), 56.5(S-C-N).**^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):** 3.71(q, 2H, -CH_2), 3.88(s, 3H, -OCH_3), 6.20 (s, 1H, -CH-Ar), 6.80-7.90(m,

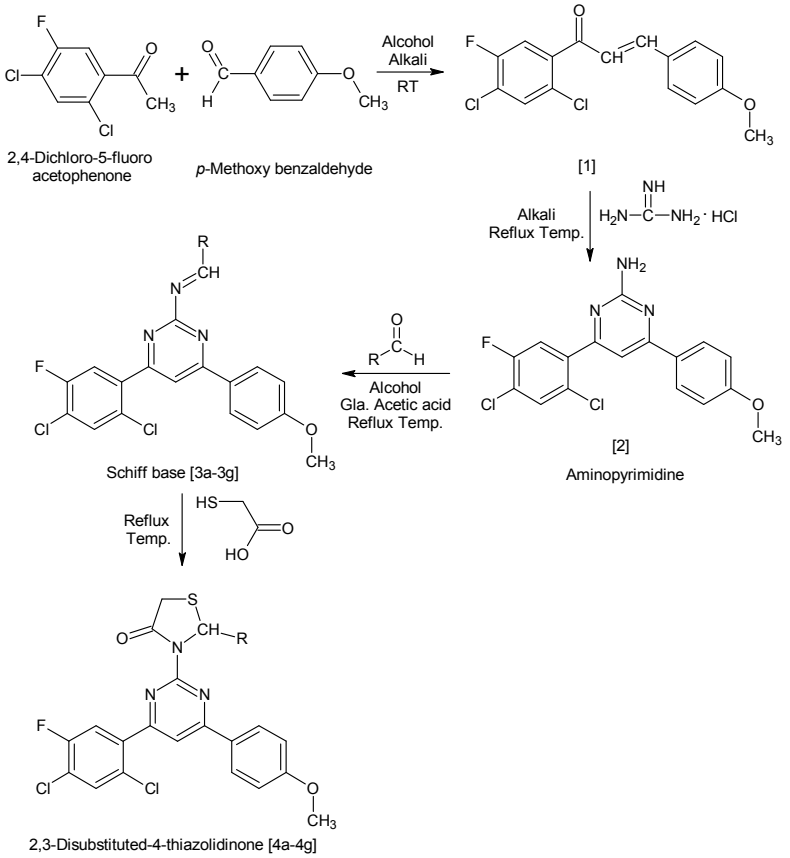
11H, Ar-H). **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**134.1(C-Cl), 128.8(CH), 128.6(CH), 128.8(CH), 130.2(CH), 102.8(CH);MS (m/z):578.5 (M^+).Found C, 53.82; H, 2.90; N, 7.20%$C_{26}H_{17}N_3F_2SCl_3O_2$ requires C,53.86; H, 2.95; N, 7.25%.

3-{4'-(2",4"-dichloro-5"-fluorophenyl)-6-(4'"-methoxyphenyl)pyrimidine-2-yl}-2-(4""-chlorophenyl)thiazolidin-4-one [4g]. Yield 87%, m.p. 150 °C. **IR (KBr, cm^{-1}):**1680(>C=O, Thiazolidine ring),3075(=CH), 1590(C=C), 1535(C=N), 746(C-H bending), 695(C-S-C), 1238(C-O-C), 2834(OCH_3), 765(C-Cl), 1180(C-F), 65.6(S-C-N). **^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):** 3.71(q, 2H, -CH_2), 3.88(s, 3H, -OCH_3) 6.20(s, 1H, -CH-Ar), 6.80-7.90(m, 11H, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):**134.1(C-Cl), 128.8(CH), 128.6(CH), 128.8(CH), 130.2(CH), 102.8(CH); MS (m/z): 579.80 (M^+).Found C, 53.83; H, 2.91; N, 7.20 $C_{26}H_{17}N_3F_2SCl_3O_2$ requires C,53.86;H, 2.95; N, 7.25%.

Results and discussion

Chemistry

The synthesis of the target compounds were carried out as outlined in reactionscheme 1. Chalcone was prepared by the Claisen-Schmidtcondensation reaction of 2,4-dichloro-5-flouro acetophenone and 4-methoxy benzaldehyde in alcohol and10% NaOH solution was used as basic medium. The prepared chalcone condensed with guanidine hydrochloride at reflux temperature gave amino pyrimidine. Synthesized amino pyrimidine was chosen as starting material to design several schiff bases [3a-3g]and 4-thizolidinones [4a-4g]. The schiff bases N-substitutedphenyl-benzylidene)-4-(2', 4'-dichloro-5-flourophenyl)-6-(4"-methoxyphenyl)-pyrimidin-2-amine [3a-3g] were obtained in quantitative yield according to method described previously. Further cyclocondensation of synthesized schiff bases [3a-3g] with thioglycolic acid gave desired 4-thiazolidinone [4a-4g] derivatives respectively.



R= C_6H_4-4-OCH_3, C_6H_4-4-NO_2 C_6H_4-2-F, C_6H_4-4-F, C_6H_4-4-OH, C_6H_4-2-Cl, C_6H_4-4-Cl

Scheme 1

As an example, in the IR spectrum of compound 3a, characteristic is the CH=N stretching vibration, which appear as an intense band at 1575 cm^{-1}. The absence of characteristic band of NH_2 group of pyrimidine moiety in between 3300-3400 cm^{-1}confirmed the formation of the proposed schiff base. The FTIR spectra of the schiff base was also exhibited bands corresponding to the structural characteristic for the (3a); the stretching vibration band for the -C=N functionality, -C-O-C linkage and -OCH_3 stretching observed at 1535, 1250 and 2840 cm^{-1} respectively. Several medium intensity bands appeared at 1540 and 3040 cm^{-1} region of the spectra were due to the stretching of C=C and =C-H vibrations of aromatic ring. The ^{1}H NMR spectrum of compound 3adid not only show the absence of NH_2 protons of pyrimidineunit (s, at δ 3-4 ppm) but also indicateda singlet at higher field (δ 8.5 ppm) for -CH=N- proton which is characteristic value of -CH- proton of the imine group. Intense signals were observed as a singlet for the two methoxy group protons at δ 3.82 ppm and 3.9 ppm which confirms two methoxyphenyl nuclei. The aromatic protons forthe substituted benzene ring were found again in the range at δ 6.2-7.8 ppm as multiplet signal.The titled compounds 2, 3-disubstituted-4-thiazolidinones [4a-4g] were obtained by the attack of sulphur nucleophile on imine carbon followed by intramolecular cyclization with elimination of water. The FTIR spectra of the synthesised compound 4a showed the strong absorption band at 1680 and 675 cm-1 confirmed the presence of cyclic amido C=O group and C-S-C linkage of 4-thiazolidinone unit. There was no absorption in the region of 1605-1621 cm^{-1}which signified the disappearance of azomethine group in this structure. A broad stretching band for the C=N functionality and OCH_3 observed at 1540 and 2847 cm^{-1} respectively. Besides these bands, characteristic bands also appeared for the aromatic nucleus of the synthesized product 4a at 1590and 2970 cm^{-1} respectively because of C=C functionality and =C-H stretching vibrations. ^{1}H NMRspectra 4a showed the peak at δ 3.70 ppm (q, 2H, -CH_2), and multiple peaksobserved between δ 6.50-7.60 ppm for aromatic hydrogen.
Furthermore, the mass spectrum of compounds **3a** and **4a** showed M^+ peak at m/z 576.3 and 555.5 (100%) respectively along with other fragment peaks, which further supported the structure of compounds **3a** and**4a**.The obtained elemental analysis values are also in good agreement with theoretical data.Thus; the structures of all the synthesized compounds were confirmed on the base of all these spectra.

Antimicrobial activity

All the synthesised compounds were evaluated for their antibacterial activity against two Gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442) and two Gram-negative bacteria (*Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 441) by using ampicillin, chloramphenicol and ciprofloxacin as the standard antibacterial drugs. Antifungal activity was screened against three fungal species (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323) by using griseofulvin and nystatin as the standard antifungal drugs. The minimal inhibitory concentration (MIC) values of all the synthesised compounds were determined in terms of μg/ml by the Broth micro dilution method according to National Committee for Clinical Laboratory Standards[xvi]. The results are summarised in **Table 1**.

The antibacterial screening of schiff base **[3a-3g]**and 4-thiazolidinone derivatives **[4a-4g]** pointed out that in Gram-positive bacteria, compounds **3b and 3g** (MIC=100 μg/ml) showed an outstanding inhibitory effect against *Staphylococcus aureus* as compared to ampicillin (MIC=250 μg/ml) and admirable to chloramphenicol and ciprofloxacin (MIC=50 μg/ml). Compounds**3c**and **4d** (MIC=100 μg/ml), **4g** (MIC=125 μg/ml) and **4e** (MIC=250 μg/ml)

showed equipotential activity to ampicillin (MIC=250 µg/ml) while compounds**3a**, **3d** found to possess comparable activity to ampicillin (MIC=250 µg/ml) and modest to chloramphenicol and ciprofloxacin (MIC=50 µg/ml) against *Staphylococcus aureus* organism. In case of inhibiting *Streptococcus pyogenes*, compounds **3c** (MIC=100 µg/ml) exhibited inhibitory effect as same as ampicillin (MIC=100 µg/ml) and less effective than chloramphenicol and ciprofloxacin (MIC=50 µg/ml) whereas compounds **3b**, **4b**,**3e, 4c** and **4f**(MIC=125 µg/ml)exerted significant potential to ampicillin (MIC=100 µg/ml) and less potential to chloramphenicol and ciprofloxacin (MIC=50 µg/ml) against *Streptococcus pyogenes*.

In case of inhibiting Gram-negative bacteria, compounds **3d, 4f, 4g** (MIC=62.5 µg/ml) demonstrated excellent activity compared to ampicillin (MIC=100 µg/ml) while compounds**3b, 4d** (MIC=100 µg/ml) showed equipotential to ampicillin (MIC=100 µg/ml) and less potential to chloramphenicol (MIC=50 µg/ml) and ciprofloxacin (MIC=25 µg/ml) against *Escherichia coli*. Compounds **3f**, **4b**, **4d**(MIC = 100 µg/ml) exerted equipotent to ampicillin (MIC=100 µg/ml) and mild to chloramphenicol (MIC=50 µg/ml) and modest ciprofloxacin (MIC=25 µg/ml) against *Pseudomonas aeruginosa*. The remaining compounds showed moderate to good activity to inhibit the growth of bacterial pathogens and were found less effective than the employed standard drugs. The antibacterial results revealed that most of the prepared compounds showed improved activity against the Gram-negative bacteria rather than Gram-positive bacteria.

From *in vitro* antifungal activity data, it is found that compounds **3b**, **4b** and **4d** (MIC=100 µg/ml) similarly **3f**(MIC=250 µg/ml) displayed highest antifungal activity against *Candida albicans* as compared to griseofulvin (MIC=500 µg/ml) and modest to nystatin (MIC=100 µg/ml) while compounds**3a**, **3d**, **3e**, **4c**,**4g** (MIC=500 µg/ml) showed the same potency as griseofulvin (MIC=500 µg/ml) against *Candida albicans*. Compounds **3d** (MIC=100 µg/ml) depicted equipotent to griseofulvin (MIC=100 µg/ml) and nystatin (MIC=100 µg/ml) against *Aspergillusniger*. Compounds **3g** and **4f**(MIC=100 µg/ml) found equipotent to griseofulvin (MIC=100 µg/ml) and nystatin (MIC=100 µg/ml) against *Aspergillus clavatus*.

Table 1: *In vitro*antimicrobialactivity of the synthesized compounds **[3a-3g]** and **[4a-4g]**

Antimicrobial activity (MIC) µg/ml							
Entry	**Antibacterial activity**				**Antifungal activity**		
	Gram Positive Bacteria		**Gram Negative Bacteria**		**Fungus**		
	S.aureus	***S.pyogenes***	***E.coli***	***P.aerug***	***C.albican***	***A. niger***	***A.clavatus***
3a	500	200	250	250	500	1000	>1000
3b	100	100	100	200	100	>1000	>1000
3c	100	100	125	125	1000	>10000	>1000
3d	250	250	62.5	250	500	100	>1000
3e	500	125	250	125	500	250	500
3f	250	200	200	200	250	>1000	>1000
3g	100	100	125	125	500	>1000	>100
4a	250	250	250	250	>1000	>1000	>1000
4b	250	100	250	100	100	250	250
4c	200	125	200	250	500	1000	500
4d	100	100	100	100	100	>1000	>1000

4e	250	250	250	100	1000	>1000	>1000
4f	250	125	62.5	100	250	>1000	100
4g	125	100	62.5	100	500	>1000	>1000
A	250	100	100	100	–	–	–
B	50	50	50	50	–	–	–
C	50	50	25	25	–	–	–
D	–	–	–	–	500	100	100
E	–	–	–	–	100	100	100

A: Ampicillin, B: Chloramphenicol, C: Ciprofloxacin, D: Greseofulvin, E: Nystatin

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