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Efficient procedure with new fused pyrido[2,3-*d*]pyrimidine derivatives as potent antimicrobial agents

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A four-step preparation of compounds containing a pyrimidine moiety is presented. This synthesis involves especially a Vilsmeier–Haack reaction and the synthesized compounds screened for their antibacterial activity against Gram-positive and Gram-negative organisms, as well as for antifungal activities. Structures of all the newly synthesized compounds were confirmed by their FTIR, ^{1}H NMR, mass spectral and elemental analysis data. Some of the newly synthesized compounds show excellent antimicrobial activity and appear to be the most proficient members of the series.

Keywords: 4-Amino-2,6-dimethoxypyrimidine, pyrido[2,3-*d*]pyrimidines, Schiff base, antimicrobial activity

The treat for convenient microbial infections has become essential and demanding due to the urgent multiplication of multiple drug-resistant organisms[1,2]. Antimicrobial resistant (AMR) is a phenomenon of infectious microbial flora to resist antimicrobial agents to which it was previously sensitive[3]. Thus, there is a vital need to improve drug resistance by finding more useful pharmacological agents. In addition Nitrogen sulphur and oxygen containing heterocycles are of significant interest for designing various chemical substances that may serve as lead for discovering novel bioactive agents.

The diversity in the biological response of 4-thiazolidinones has attracted the attention of many researchers to explore this framework for its potential. It is, therefore, of prime importance that the study of this topic and the development of new synthetic strategies should be based on the most recent knowledge, emerging from the latest research[4]. Moreover, thiazolidin-4-one derivatives are also reported to have important biological activities such as anti-inflammatory[5], anti-tuberculosis[6], anti-cancer[7], anti-tumor[8], anti-HIV[9], anti-bacterial[10], anti-fungal[11], anti-oxidant[12], anti-viral[13], anti-convulsant[14], diuretics[15], nematicidal[16], anti-histaminic[17] activity, etc. The presence of heterocycles in all kinds of organic compounds applied in biology, pharmacology, optics, electronics, material sciences, and so on is very well known. Between them, oxygen, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers due to their biological activities and unique structures that led to several applications in different areas of agrochemical and pharmaceutical research as well[18].

To alleviate the multi drug resistance dilemma, nitrogen, sulfur and oxygen based compounds appeared with promising therapeutic agents. These include various pyrimidine, Schiff base, and 4-thiazolidinone moieties which appears with good biological potential.

Results and Discussion

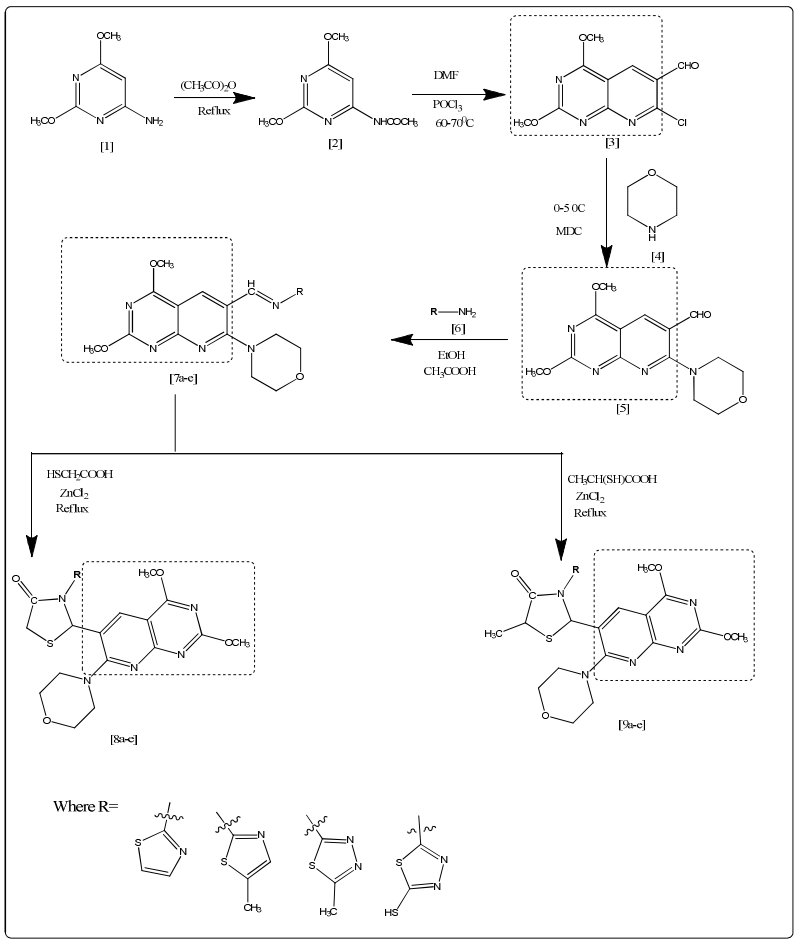
Chemistry

The strategy acquired for the synthesis of **7a-d**, **8a-d** and **9a-d** is depicted in Scheme I. The attack of sulphur nucleophile on imine carbon followed by intramolecular cyclization with elimination of water gives 2, 3-disubstituted-4-thiazolidinones **(8a-d)** and 2,3-disubstituted-5-methyl-4-thiazolidinones **(9a-d)** derivatives which were confirmed by spectral analysis.

The formation of the compounds was confirmed by their FT-IR, ^{1}H NMR, mass spectra as well as elemental analysis. As an example, in the IR spectrum of compound **7c**, characteristic is the N=CH stretching vibration, which appear as an intense band at 1622 cm^{-1}. There was no absorption in between 3300-3400 cm^{-1} which confirmed that free amino group of thiazole ring is converted into a proposed imine. The structural element characteristic for the thiazole nucleus, namely; the stretching vibration band for the C=N, C-S-C linkage and CH_3 stretching were observed at 1545, 679 and 1382 cm^{-1} respectively. In morpholine ring the

stretching vibration band for the C-N and C-O-C linkage was observed at 1369 and 1130 cm^{-1}. Several bands appeared at 1476 and 3073 cm^{-1} are due to the stretching of C=C and C-H vibrations of aromatic ring and the stretching vibration band for OCH_3 group is observed at 1183 cm^{-1} respectively. The ^1H NMR spectrum of compound **7a-d** did not only show the absence of NH_2 protons of amine unit as singlet signal at between δ 5-6 ppm but exerted a singlet at higher field at δ 8.6 ppm for -CH=N proton of the imine group. Moreover the compound **7c** showed emphasized signal as singlet for the methyl group protons of thiazole core at δ 2.56 ppm. The two singlet of methoxy group protons are observed at δ 3.68 and 3.77 ppm.

The strong absorption band observed at 1650 -1750 $cm^{-1}$for the presence of C=O group and 600 -700 cm^{-1} for the presence of C-S-C linkage of thiazolidine unit in both **8a-d** and **9a-d**. There was no absorption in the region of 1605-1621 cm^{-1} which signifying the disappearance of imine group in this structure. Moreover the compound **9a** showed a strong absorption band at 1350 cm^{-1} due to the presence of the CH_3 group attached on the C-5 position of thiazolidine ring which also confirmed the cyclo-condensation of imine. A broad stretching band for the C=N functionality and OCH_3 group of pyrimidine ring is observed at between 1495-1635 cm^{-1} and 1100-1200 cm^{-1} respectively. The ^1H NMR spectrum of compound **8d** showed two doublet of doublet at δ 3.6 (J = 4.8 Hz) and 3.9 ppm (J = 4.6 Hz) due to CH_X and CHy protons of active methylene group of the thiazolidine ring. The ^1H NMR spectrum of compound **9a** showed diagnostic peaks at δ 5.8 and 4.0 ppm (J = 7.3 Hz) as singlet and quartet due to Ar-CH and CH-CH_3 proton of the thiazolidine ring system. The disappearance of the N=CH proton at between δ 8-9 ppm as singlet also supported presence of thiazolidine ring in compound **8e** and **9a**. The other remaining aromatic protons appeared as a multiplet signal at between δ 6.8-7.8 ppm along



Scheme I — Methodical synthetic route for the target compounds **7a-e**, **8a-e** and **9a-e**

Table I — Antimicrobial activity of the synthesised compounds

Compd	Minimal bactericidal concentration µg/mL				Minimal fungicidal concentration µg/mL		
	Gram positive				Gram negative		
	S. a MTCC-96	*S. p* MTCC-442	*E. c* MTCC-443	*K. p* MTCC-441	*C. a* MTCC-227	*A. n* MTCC-282	*A. c* MTCC-1323
7a	50	50	200	3.125	100	100	100
7b	12.5	50	6.25	12.5	100	100	100
7c	100	100	200	12.5	50	50	100
7d	12.6	12.5	3.125	100	50	100	50
8a	100	50	12.5	100	100	50	50
8b	6.25	100	3.125	50	50	100	50
8c	100	100	100	100	100	50	100
8d	12.5	50	3.125	50	50	100	50
9a	100	6.25	12.5	25	50	25	50
9b	6.25	12.5	25	50	25	50	50
9c	12.5	6.25	12.5	25	50	50	25
9d	100	100	6.25	12.5	100	100	50
A	3.125	3.125	3.125	3.125	–	–	–
B	–	–	–	–	3.125	3.125	3.125

A=Ciprofloxacin, (Standard Drugs for antibacterial activity) B = Ketoconazole (Standard Drugs for antifungal activity).

with singlet in between δ 3.5-3.9 ppm corresponding to the methoxy group protons. Finally, mass spectra of all the title compounds showed molecular ion peak M+ corresponding to their mass which is also in agreement with its proposed structure. The obtained elemental analysis values are in good agreement with theoretical data.

In vitro antimicrobial activity

In vitro antibacterial and antifungal activity of newly synthesized compounds **(7a-d), (8a-d) and (9a-d)** was carried out by micro broth dilution method according to National Committee for Clinical Laboratory Standards (NCCLS, 2002)[19]. A panel of selected pathogens Gram positive (*Staphylococcus aureus* MTCC 96 and *Bacillus cereus* MTCC 430) and Gram negative (*Escherichia coli* MTCC 443 and *Klebsiella pneumonia* MTCC 109) bacterial species used for antibacterial activity whereas for antifungal activity, a panel of selected fungal pathogens (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus calavatus* MTCC 1323) species were used. 2% DMSO solution was used as diluent to get desired concentration of drugs to test upon standard bacterial and fungal strains. The zone of inhibition produced by each compound was measured in µg/ml. The minimum inhibitory concentration (MIC) was determined and recorded at the lowest concentration inhibiting growth of the organism. Ciprofloxacin were used as standard antibiotic drugs for antibacterial activity while Ketoconazole were used as standard drug for antifungal activity (Table I).

Experimental Section

All the chemicals and solvents used for the synthesis work acquired from commercial sources were of analytical reagent (AR) grade. Melting points were determined by using open capillary tubes and are uncorrected. TLC was checked on E-Merck pre-coated 60 F254 plates and the spots were rendered visible by exposing to UV light or keeping the plates in iodine chamber. IR spectra were recorded on a Shimadzu FTIR 8401 spectrophotometer using potassium bromide pellets. ^{1}H NMR were recorded on a Bruker Avance 400 MHz spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using DMSO as a solvent and TMS as an internal standard at 400 MHz. Chemical shifts are reported in parts per million (ppm). The following abbreviations have been used to explain the observed multiplicities: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Elemental analyses were carried out by Perkin-Elmer 2400 series-II elemental analyser (Perkin-Elmer, USA).

Preparation of N-(2, 6-dimethoxypyrimidin-4-yl) acetamide, 2

(0.01 mole) of compound (1) (10 mL) of Acetic anhydride and 1-2 drops of acetic acid was added and the mixture was heated under reflux for 6 h. The reaction mixture was poured into crushed ice (200 g) with stirring. The progress of reaction was monitored

by TLC using ethyl acetate: hexane (6:4) as eluent. The solid product obtained was filtered, washed with water and dried. The crude product was purified by crystallization from acetone to get the title compound (2).

Preparation of 7-Chloro-2, 4 –dimethoxy pyrido[2,3-*d*]pyrimidin-6-carbaldehyde, 3

A mixture of compound (2) (0.810 mg, 5 m mol) in DMF (4.0 mL, 50 m mol), $POCl_3$ (0.5 ml, 5 m mol) was added at room temperature, producing a semi-solid mass. A clear solution appeared after stirring for 4 h at room temperature. It was further stirred for 6 h. The reaction mixture was poured into crushed ice (200 g) with stirring. The separated solid was filtered off and washed thoroughly with water. The progress of reaction was monitored by TLC using ethyl acetate: hexane (6:4) as eluent. The solid product obtained was filtered, washed with water and dried. The crude product was purified by crystallization from acetone to get the title compound (3).

Preparation of 2, 4 – dimethoxy-7-morpholino pyrido[2, 3-*d*]pyrimidine-6-carbaldehyde, 5

A solution of morpholine (4) (1.75 g, 20 m mol) in 10 ml of dichloromethane was gradually added under stirring to an ice-cooled mixture of compound (3). After stirring for 30 min. at 0-5°C the mixture was washed with 3 x 10 ml of water in order to remove unreacted morpholine and its salt. The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The dry, flake-like residue were recrystallized from 1, 4-dioxane. The progress of reaction was monitored by TLC using chloroform: methanol (9:1) as eluent. The crude product was purified by crystallization from acetone to get the title compound (5).

General Preparation of substituted Schiff bases, 7a-e

A solution of (4) (2.0 g, 20 m mol) in 20 ml ethanol was added to equimolecular quantities of an amine (6) add 1-2 drop of acetic acid. The reaction mixture was refluxed for 3 h at 60-70ºC, separated solid was filtered off and washed thoroughly with water. The progress of reaction was monitored by TLC using ethyl acetate: hexane (6:4) as eluent. The solid product obtained was filtered, washed with water and dried. The crude product was purified by crystallization from acetone to get the title compound (7).

General preparation of 2, 3-disubstituted-4-thiazolidinone, 8a-e

A mixture of substituted substituted Schiff base (7) (3.56 g, 1 mol), DMF (50 ml), pinch of $Zncl_2$ and thioglycolic acid (1.84 g, 2 mol) was refluxed for 12 - 15 hours. Excess solvent was distilled off under reduced pressure. Progress of reaction was monitored by TLC using ethyl acetate: hexane (4:6). After the completion of reaction it was cooled and the product was filtered, washed with dilute sodium bicarbonate solution to remove unreacted acid and dried over anhydrous Na_2SO_4 to get substituted 4-thiazolidinone derivatives.

General preparation of 2, 3-disubstituted-5-methyl-4-thiazolidinone, 9a-e

A mixture of substituted Schiff- base (7) (3.56 g, 1 mol), DMF (50 mL), $Zncl_2$ and thiolacticacid (1.84 g, 2 mol) was refluxed for 12-15 hours. Excess solvent was distilled off under reduced pressure. Progress of the reaction was monitored by TLC using ethyl acetate: hexane (4:6). After the completion of the reaction it was cooled and the product was filtered, washed with dilute sodium bicarbonate solution to remove unreacted acid and dried over anhydrous Na_2SO_4 to get substituted 4-thiazolidinones derivatives.

All the synthesised compounds (7a-d), (8a-d) and (9a-d) were characterised by IR, ^{1}H NMR, and MS as well as elemental analysis. The characteristic data of the entire synthesised compounds are given in the spectral analysis data.

Specrtal and analytical analysis data

***N*-(2, 6-dimethoxypyrimidin-4-yl) acetamide, 2**: White solid, m.p: 107-110ºC; Yield: 82%; IR (KBr, Vmax/cm^{-1}): 3076 (C-H str., aromatic), 1593 (C=C str., aromatic), 1591 (C=N str., pyrimidine ring), 1370 (CH_3 str.), 1681 (C=O str.), 3179 (-NH str. 2ºamine), 1177 (-OCH_3 str.); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 9.52 (s, 1H, 2ºamide), 2.54 (s, 3H, CH_3), 3.64 (s, 3H,OCH_3), 3.73 (s, 3H, OCH_3), 8.31 (s, 1H, Ar-H); MS *m/z* 198.08 (M^+ +1) Anal. Calcd. For $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31%. Found C, 48.76; H, 5.65; N, 21.35%.

7-Chloro-2,4-dimethoxypyrido[2,3-*d*]pyrimidine-6-carbaldehyde, 3: Light-yellow, m.p: 115-120ºC; Yield: 77%; IR (KBr, Vmax/cm^{-1}): 3076 (C-H str., aromatic), 1593 (C=C str., aromatic), 1591 (C=N str.), 1681 (C=O str. aldehyde), 2785-2845 (C-H str. Aldehyde), 709 (C-Cl str.), 1177 (-OCH_3 str.); ^{1}H

NMR (400 MHz, DMSO-d_6, δ ppm): 9.52 (s, 1H, -CHO), 3.61 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 8.33 (s, 1H, Ar-H); MS *m/z* 254.2 (M^+ +1) Anal. Calcd. For $C_{10}H_8ClN_3O$: C, 47.35; H, 3.18; N, 16.57 %. Found C, 47.32; H, 3.15; N, 16.54%.

2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyr imidin-6-carbaldehyde, 5: Light-yellow, m.p: 102-105°C; Yield: 70; IR (KBr, Vmax/cm^{-1}): 3078 (C-H str., aromatic), 1598 (C=C str., aromatic), 1590 (C=N str.), 1681 (C=O str. aldehyde), 2785 – 2845 (C-H str. Aldehyde) 1136 (C-O-C str., morpholine ring), 1374 (C-N str., morpholine ring); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 9.52 (s, 1H, -CHO), 3.62 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 8.34 (s, 1H, Ar-H), 2.36 (t, 4H,CH_2 morpholine ring), 2.42 (t, 4H, morpholine ring); MS *m/z* 305.11 (M^+ +1) %; Anal. Calcd. For $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41%. Found C, 55.23; H, 5.33; N, 18.44%.

***(E)*-N-((2, 4-dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl) methylene) thiazol-2-amine, 7a**: Orange solid; m.p: 190-194°C; Yield: 72; IR (KBr, Vmax/cm^{-1}): 3070 (C-H str., aromatic), 1483 (C=C str., aromatic), 1451 (-C=C-C- str., aromatic), 1558 (C=N str.), 1547 (C=N str., imine), 1187 (OCH_3 str.), 1138 (C-O-C str., morpholine ring), 1375 (C-N str., morpholine ring); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.35 (t, 4H, CH_2 , morpholine), 2.42 (t, 4H, CH_2, morpholine), 3.66 (s, 3H, -OCH_3), 3.75 (s, 3H, -OCH_3), 8.55 (s, 1H, CH=N), 7.24 (s, 1H, Ar-H), 7.35 (s, 1H, Ar-H), 7.47 (s, 1H, Ar-H); MS *m/z* 387.5 (M^+ +1) %; Anal. Calcd. For $C_{17}H_{18}N_6O_3S$: C, 52.85; H, 4.70; N, 21.75%. Found C, 52.82; H, 4.74; N, 21.72%.

***(E)*-N-((2, 4-dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl) methylene) -5-methylthiazol-2-amine, 7b**: Orange solid; m.p: 188-191°C; Yield: 70; IR (KBr, Vmax/cm^{-1}): 3073 (C-H str., aromatic), 1476 (C=C str., aromatic), 1467 (-C=C-C- str.,aromatic), 1558 (C=N str.), 1622 (C=N str., imine), 1183 (OCH_3 str.), 1130 (C-O-C str., morpholine ring), 1369 (C-N str., morpholine ring), 1545 (C=N str. thiazole) 679 (C-S-C linkage, thiazole), 1382 (-CH_3 str. thiazole); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.38 (t, 4H, CH_2 , morpholine), 2.40 (t, 4H, CH_2,morpholine), 3.68 (s, 3H,-OCH_3), 3.77 (s, 3H,-OCH_3), 8.61 (s, 1H, CH=N), 7.23 (s, 1H, Ar-H), 2.56 (s, 3H, -CH_3), 7.46 (s, 1H, Ar-H); MS *m/z* 401.2 (M^+ +1) %; Anal. Calcd. For $C_{18}H_{20}N_6O_3S$: C, 53.99; H, 5.03; N, 20.99%. Found C, 53.96; H, 5.07; N, 20.96%.

***(E)*-N-((2,4-dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl) methylene) -5-methyl-1, 3, 4-thiadiazol-2-amine, 7c**: Orange solid; m.p: 167-170°C; Yield: 65%; Anal. Calcd. For $C_{17}H_{19}N_7O_3S$: C, 50.86; H, 4.77; N, 24.42%. Found C, 50.83; H, 4.75; N, 24.45%; IR (KBr, Vmax/cm^{-1}): 3088 (C-H str., aromatic), 1486 (C=C str., aromatic), 1459 (-C=C-C- str.,aromatic), 1565 (C=N str.), 1628 (C=N str., imine), 1179 (OCH_3 str.), 1143 (C-O-C str., morpholine ring), 1377 (C-N str., morpholine ring), 1366 (-CH_3 str.); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.38 (t, 4H, CH_2 , morpholine), 2.41 (t, 4H, CH_2,morpholine), 3.68 (s, 3H,-OCH_3), 3.78 (s, 3H,-OCH_3), 8.60 (s, 1H, CH=N), 7.24 (s, 1H, Ar-H), 2.54 (s, 3H, -CH_3) ; MS *m/z* 402.2 (M^+ +1).

(E)-5-(((2,4-dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)methylene) amino) -1, 3, 4-thiadiazol-2-thiol, 7d: Orange solid; m.p: 164-168°C; Yield: 68; IR (KBr, Vmax/cm^{-1}): 3072 (C-H str., aromatic), 1476 (C=C str., aromatic), 1458 (-C=C-C- str.,aromatic), 1554 (C=N str.), 1631 (C=N str., imine), 1183 (OCH_3 str.), 1137 (C-O-C str., morpholine ring), 1367 (C-N str., morpholine ring), 2575 (-SH str.); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.47 (t, 4H, CH_2, morpholine), 2.47 (t, 4H, CH_2, morpholine), 3.96 (s, 3H, -OCH_3), 3.97 (s, 3H, -OCH_3), 7.67 (s, 1H, CH=N), 6.94 (s, 1H, Ar-H), 8.79 (s, 1H, -SH) ;MS *m/z* 420.4 (M^+ +1) %; Anal. Calcd. For $C_{16}H_{17}N_7O_3S_2$: C, 45.81; H, 4.08; N, 23.37%. Found C, 45.85; H, 4.05; N, 23.33%.

2-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyr imidin-6-yl)-3-(thiazol-2-yl) thiazolidin-4-one, 8a: Reddish solid; m.p: 175-180°C; Yield: 70; IR (KBr, Vmax/cm^{-1}): 3347 (C-H str., aromatic), 2988 (C-H str., alkane), 1561 (C=C str., aromatic), 1471 (-C=C-C- str., aromatic), 1679 (C=O str., thiazolidine), 689 (C-S-C linkage, thiazolidine ring); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.39 (t, 4H, CH_2 , morpholine), 2.42 (t, 4H, CH_2, morpholine), 3.66 (s, 3H, -OCH_3), 3.74 (s, 3H, -OCH_3), 6.99 (s, 1H, Ar-H), 3.95 (concealed doublet, 1H, CHx), 4.62 (concealed doublet, 1H, CHy), 5.72 (s, 1H, CH), 7.39-7.67 (m, 2H, Ar -H); MS *m/z* 461.2 (M^+ +1) %; Anal. Calcd. For $C_{19}H_{20}N_6O_4S_2$: C, 49.55; H, 4.38; N, 18.25%. Found C, 49.52; H, 4.35; N, 18.28%.

2-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyr imidin-6-yl)-3-(5-methylthiazol-2-yl) thiazolidin-4-one, 8b: Orange solid; m.p: 170-174°C; Yield: 70; IR (KBr, Vmax/cm^{-1}): 3059 (C-H str., aromatic), 1475 (C=C str., aromatic), 1473 (-C=C-C- str.,aromatic), 1562 (C=N str.), 1178 (OCH_3 str.), 1129 (C-O-C str., morpholine ring), 1360 (C-N str., morpholine ring),

1666 (C=O str., thiazolidine), 678 (C-S-C linkage, thiazolidine ring); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.30 (t, 4H, CH_2, morpholine), 2.39 (t, 4H, CH_2, morpholine), 3.60 (s, 3H, -OCH_3), 3.71(s, 3H, -OCH_3), 2.57 (s, 3H,CH_3), 6.98 (s, 1H, Ar-H), 3.84 (d, 1H, *J* = 5.2, CHx), 3.98 (d, 1H, *J* = 5.2, CHy), 5.91 (s, 1H, CH), 7.44 (s, 1H, Ar -H); MS *m/z* 475.3 (M^+ +1) %; Anal. Calcd. For $C_{20}H_{22}N_6O_4S_2$: C, 50.62; H, 4.67; N, 17.71%. Found C, 50.65; H, 4.64; N, 17.74%.

2-(2, 4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl) -3- (5-methyl-1, 3, 4-thiadiazol-2-yl) thiazolidin-4-one, 8c: Light-yellow solid; m.p: 152-155°C; Yield: 60; IR (KBr, Vmax/cm^{-1}): 3058 (C-H str., aromatic), 1473 (C=C str., aromatic), 1570 (C=N str.), 1454 (-C=C-C- str.,aromatic), 1176 (OCH_3 str.), 1137 (C-O-C str., morpholine ring), 1380 (C-N str., morpholine ring), 1561 (C=C str., aromatic), 1684 (C=O str., thiazolidine), 678 (C-S-C linkage, thiazolidine ring); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.38 (t, 4H, CH_2, morpholine), 2.46 (t, 4H, CH_2, morpholine), 3.68 (s, 3H, -OCH_3), 3.75 (s, 3H, -OCH_3), 2.59 (s, 3H, CH_3), 6.98 (s, 1H, Ar-H), 3.50 (d, 1H, *J* = 4.7 Hz, CHx), 4.67 (d, 1H, *J* = 4.8Hz, CHy), 5.77 (s, 1H, CH); MS *m/z* 476.3 (M^+ +1) %; Anal. Calcd. For $C_{19}H_{21}N_7O_4S_2$: C, 47.99; H, 4.45; N, 20.62%. Found C, 47.95; H, 4.41; N, 20.58%.

2-(2, 4-Dimethoxy-7-morpholinopyrido[2, 3-*d*]pyrimidin-6-yl) -3- (5-mercapto-1, 3, 4-thiadiazol-2-yl) thiazolidin-4-one, 8d: Light-yellow solid; m.p: 147-151ºC; Yield: 65; IR (KBr, Vmax/cm^{-1}): 3064 (C-H str., aromatic), 1480 (C=C str., aromatic), 1571 (C=N str.), 1190 (OCH_3str.), 1472 (-C=C-C- str.,aromatic), 1133 (C-O-C str., morpholine ring), 1376 (C-N str., morpholine ring), 1679 (C=O str., thiazolidine), 669 (C-S-C linkage, thiazolidine and ring) 2578 (-SH str.); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.35 (t, 4H, CH_2 , morpholine), 2.43 (t, 4H, CH_2, morpholine), 3.66 (s, 3H, -OCH_3), 3.72 (s, 3H, -OCH_3), 8.34 (s, 1H, SH), 6.98 (s, 1H, Ar-H), 3.64 (d, 1H, *J* = 4.8Hz, CHx), 3.95 (d, 1H, *J* = 4.6, CHy), 5.78 (s, 1H, CH); MS *m/z* 494.4 (M^+ +1) %; Anal. Calcd. For $C_{18}H_{19}N_7O_4S_3$: C, 43.80; H, 3.88; N, 19.86%. Found C, 43.84; H, 3.85; N, 19.83%.

2-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-5-methyl-3- (thiazol-2-yl) thiazolidin-4-one, 9a: Light-orange solid; m.p: 183-186ºC; Yield: 69; IR (KBr, Vmax/cm^{-1}): 3058 (C-H str., aromatic), 1460 (C=C str., aromatic), 1565 (C=N str.), 1471 (-C=C-C- str.,aromatic),, 1176 (OCH_3 str.), 1133 (C-O-C str., morpholine ring), 1368 (C-N str., morpholine ring), 1676 (C=O str., thiazolidine), 1363 (CH_3 str.), 678 (C-S-C linkage, thiazolidin ring); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.37 (t, 4H, CH_2 , morpholine), 2.45 (t, 4H, CH_2, morpholine), 3.66 (s, 3H, -OCH_3), 3.76 (s, 3H, -OCH_3), 6.97 (s, 1H, Ar-H), 3.6 (s, 3H, CH_3), 4.4 (q, 1H, *J* = 7.4,-CH-CH3), 5.72 (s, 1H, CH), 7.38-7.63 (m, 2H, Ar -H); MS *m/z* 475.2 (M^+ +1) %; Anal. Calcd. For $C_{20}H_{22}N_6O_4S_2$: C, 50.62; H, 4.67; N, 17.71%. Found C, 50.65; H, 4.65; N, 17.75%.

2-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-5-methyl-3-(5-methylthiazol-2-yl) thiazolidin-4-one, 9b: Light-orange solid; m.p: 179-182ºC; Yield: 65; IR (KBr, Vmax/cm^{-1}): 3056 (C-H str., aromatic), 1462 (C=C str., aromatic), 1575 (C=N str.), 1481 (-C=C-C- str.,aromatic), 1173 (OCH_3 str.), 1144 (C-O-C str., morpholine ring), 1374 (C-N str., morpholine ring), 1692 (C=O str., thiazolidine), 1354 (CH_3 str.), 680 (C-S-C linkage, thiazolidine ring); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.35 (t, 4H, CH_2 , morpholine), 2.44 (t, 4H, CH_2, morpholine), 3.68 (s, 3H, -OCH_3), 3.74 (s, 3H, -OCH_3), 2.31 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.6 (q, 1H, *J* = 7.9 Hz, -CH-CH_3), 6.94 (s, 1H, CH-Ar), 5.93 (s, 1H, CH), 7.46 (s, 1H, Ar -H); MS *m/z* 489.4 (M^+ +1) %; Anal. Calcd. For $C_{21}H_{24}N_6O_4S_2$: C, 51.62; H, 4.95; N, 17.20%. Found C, 51.65; H, 4.92; N, 17.17%.

2-(2, 4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl) -5-methyl-3- (5-methyl-1, 3, 4-thiadiazol-2-yl) thiazolidin-4-one, 9c: Light-orange solid; m.p: 173-177ºC; IR (KBr, Vmax/cm^{-1}): 3088 (C-H str., aromatic), 1482 (C=C str., aromatic), 1559 (C=N str.), 1476 (-C=C-C- str.,aromatic), 1184 (OCH_3 str.), 1135 (C-O-C str., morpholine ring), 1375 (C-N str., morpholine ring), 1687 (C=O str., thiazolidine), 1349 (CH_3 str.), 689 (C-S-C linkage, thiazolidine ring) ; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.38 (t, 4H, CH_2 , morpholine), 2.46 (t, 4H, CH_2, morpholine), 3.66 (s, 3H, -OCH_3), 3.74 (s, 3H,-OCH_3), 2.57 (s, 3H, CH_3), 1.40 (s, 1H, CH_3), 6.97 (s, 1H, Ar-H), 4.0 (q, 1H, *J* = 7.3 Hz, -CH-CH_3), 5.75 (s, 1H, CH); MS *m/z* 490.5 (M^+ +1) ; Yield: 67%; Anal. Calcd. For $C_{20}H_{23}N_7O_4S_2$: C, 49.07; H, 4.74; N, 20.03%. Found C, 49.04; H, 4.71; N, 20.05%.

2-(2, 4-Dimethoxy-7-morpholinopyrido [2, 3-*d*] pyrimidin-6-yl) -3-(5-mercapto-1, 3, 4-thiadiazol-2-yl) -5-methylthiazolidin -4-one, 9d: Light-orange solid; m.p: 148-152ºC; Yield: 72; IR (KBr, Vmax/cm^{-1}):

3078 (C-H str., aromatic), 1479 (C=C str., aromatic), 1563 (C=N str.), 1471 (-C=C-C- str.,aromatic), 1186 (OCH_3 str.), 1142 (C-O-C str., morpholine ring), 1377 (C-N str., morpholine ring), 1676 (C=O str., thiazolidine), 1361 (CH_3 str.), 686 (C-S-C linkage, thiazolidine ring), 2550 (-SH. Str.) ; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.38 (t, 4H, CH_2, morpholine), 2.42 (t, 4H, CH_2, morpholine), 3.67 (s, 3H,-OCH_3), 3.75 (s, 3H, -OCH_3), 1.43 (s, 3H, CH_3), 4.7 (q, 1H, J = 7.6 Hz, -CH-CH_3), 5.93 (s, 1H, CH), 7.26 (s, 1H, Ar-H), 8.37 (s, 1H, SH); MS *m/z* 508.6 (M^+ +1) %; Anal. Calcd. For $C_{19}H_{21}N_7O_4S_3$: C, 44.96; H, 4.17; N, 19.32%. Found C, 44.92; H, 4.15; N, 19.36%.

Conclusion

In conclusion, we have verified a feasible, extensive and very effective method for the synthesis of novel Schiff bases (7a-d), 2,3-disubstituted-4-thiazolidinone (8a-d) and 2,3-disubstituted-5-methyl-4-thiazolidinone (9a-d) derivatives was performed. The screening results revealed that all the compounds exhibited moderate to excellent activities against all the pathogenic strains. Among the newly synthesized compounds possessing electron donating or withdrawing group such as methyl, methoxy, sulfhydryl etc have been identified as the most potent antibacterial and antifungal agents.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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