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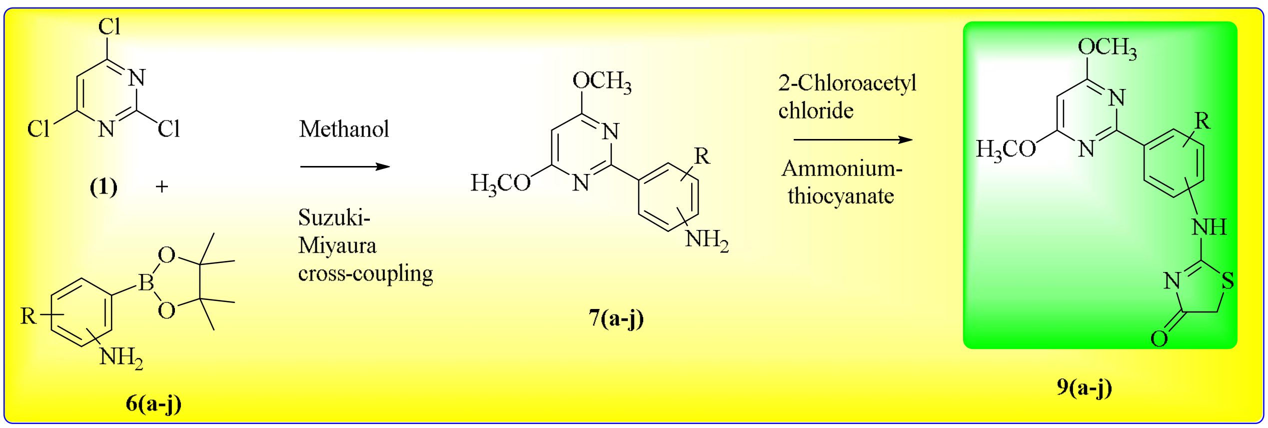
# Synthesis and Bioassaysof Somenovelpyrimidinyl-Thizolidin-4-One Derivatives VIA Suzuki Coupling

Himanshu R. Prajapati[1], Kishor H. Chikhalia[2], Janki J. Patel[3]
[1]*Department of Chemistry, School of Sciences, Gujarat University, Ahmedabad- 380009, Gujarat, India.*
[2, 3]*VNSGU, Surat, Gujarat, india 395007*

***Abstract: A novel series of 2-((4-(4,6-dimethoxypyrimidin-2-yl) phenyl) amino) thiazol-4(5H)-one derivatives(9a-j) have been synthesized VIA Suzuki-Miyaura cross-coupling. The structures of all the newly synthesized analogues were characterized by IR, $^1$H NMR, $^{13}$C NMR and mass spectroscopy. All synthesized derivatives were examined for their in vitro antibacterial activity against gram-positive & gram-negative bacteria as well as antifungal activity against different strains by using broth dilution technique. The consequences of antimicrobial study exposed that some of the newly synthesized compounds exhibit potent activity against the examined microbial strains.***
***Keywords:2, 4, 6-Trichloropyrimidine, Thiazolidin-4-one, Antibacterial activity, Antifungal activity, Suzuki-Miyaura cross-coupling.***

*Graphical abstract*




## I. INTRODUCTION

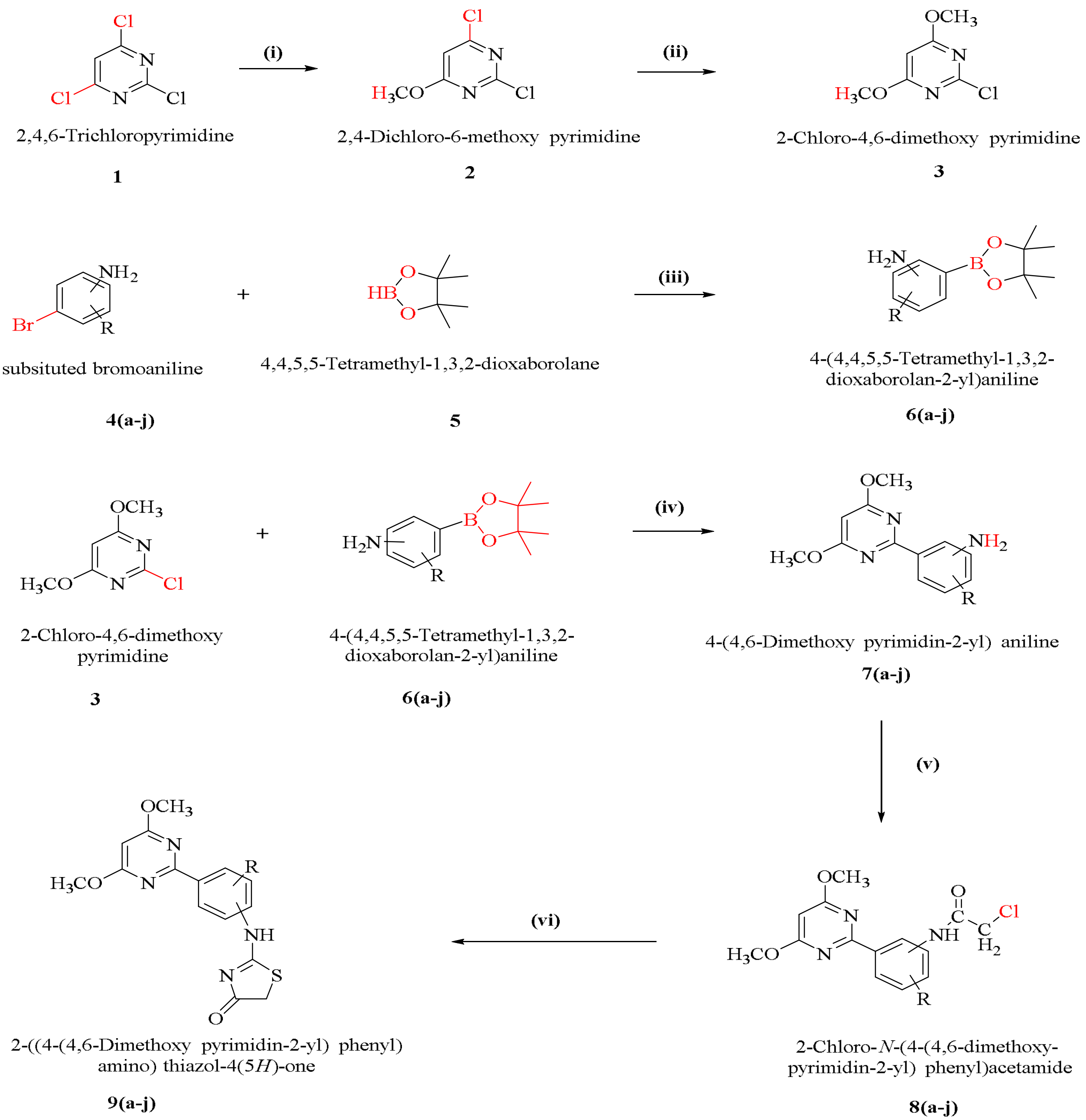
In recent years, fundamental challenges are the main improvement factor in drugs for microbial fungal and bacterial contaminations. The optimization of antimicrobial drug and the development of new drugs are problem areas in microbial chemotherapy[1]. Based on above circumstances, we decided to synthesize and combine some unreported thiazolidinone and pyrimidine derivatives. In medicinal chemistry one of the most frequently encountered heterocycle is 4-thiazolidinone, a saturated form of thiazole in which carbonyl group at fourth carbon, is being considered as a potent moiety [2]. Thiazolidinones are thought to be backbone unit in medicinal chemistry as they possess numerous pharmacological properties and biological activity [3] such as anti-HIVagent[4, 5], antibacterial activity [6-8],antifungal [9], anticancer [10], ant tuberculosis[11], anti-inflammatory [12-14], antiviral [15], antioxidant [16].

Pyrimidine nucleus is present in RNA and DNA system as fundamental ring and play vital role in different biological activites such as antifungal [17], anti-HIV [18],antitumor [19],antioxidant and anticancer [20],antiviral [21],anti-inflammatory [22].In inorganic synthetic chemistry pyrimidine and their derivatives are well known as drugs as they are useful in the treatment of thyroid and leukemia as well as they are important agricultural chemicals.[23,24,25].

Suzuki–Miyaura (SM) cross-coupling is thought to be a potent technique to synthesize organic compounds as it provides new route for the formation of carbon–carbon bond in chemical industry as well as in pharmaceutical science.SM reaction employing palladium catalyst has received the attention of synthetic community as it provide convenient method to synthesize biaryl compounds through aryl boron and aryl halide (or pseudo-halide) [26].

The literature study reveals that both Pyrimidine and 4-thiazolidinone are significant pharmacophores and exhibits potent biological activities. From this observation, we have synthesized a new series of 4-thiazolidinone derivatives by incorporating the pyrimidine moiety for obtaining better antimicrobial activity agent. All the newly synthesized compounds have been screened for their antimicrobial activities.

## II. CHEMISTRY




**Where,** -R = H, $CH_3$, $OCH_3$, Cl, Br, CHO, $COCH_3$,
$-NH_2$ = 4-$NH_2$, 3-$NH_2$.

### *A. Reagents and conditions*

2,4,6-trichloro pyrimidine, $Et_3N$, NaOMe, 2h.(ii) NaOMe, Methanol, RT.(iii)Pinacolborane, $PdCl_2(PPh_3)_2$,KOAc,$N_2$ atmosphere, anhydrous DMSO, 80°C.(iv) $K_3PO_4$, $N_2$atmosphere, Catalyst $Pd(OAc)_2$ and D-t-BPF, refluxed temperature(90°C), 1,4-dioxane, 4h.(v)Chloro-acetyl-chloride, triethyl-amine, Dichloromethane, RT, 4h.(vi) Ammonium thiocyanate, absolute ethanol refluxed for 4h.

Scheme 1. Synthetic route for compounds 9a-j.

## III. RESULT AND DISCUSSION:

### *A. In vitro antibacterial activity*

The antimicrobial activities of pyrimidine and thizolidin-4-one are identified. The active pharmacophore thizolidin-4-one was annelated to the 2nd position of the parent pyrimidine motif through phenyl amino nucleus. It is proved that the methoxy group at 2nd and 4th site of pyrimidine ring was regarded as an important forecaster for the increase in activity. Based on this, we combine dpyrimidinyl- thizolidin-4-one and methoxy into single hybrid molecule and estimated their antibacterial and antifungal strengths against various bacteria such as E. coli MTCC 442 µg/ml, P. aeruginosa MTCC 741 µg/ml, S. aureus MTCC 96 µg/ml, S. pyogenus MTCC 443 µg/ml and fungus like C.albicans MTCC 227 µg/ml, A. niger MTCC 282 µg/ml and A. clavatus MTCC 1323 µg/ml. Strengths ofthe antibacterial and antifungal showed in Table 2 and Table 3 respectively.

The MIC values of the synthesized compounds are observed in the varied range (25–500 µg/ml) of antibacterial activity against all the verified bacterial strains shown in Table 2. For gram-negative strains, compound 9e having electron-withdrawing group like 3-$COCH_3$ to phenyl nucleus appeared with MIC 25 and 50 against E. coli and P. aeruginosa respectively and for gram positive bacteria the same compound was seen to have value of MIC as 100 and 50 against S. aureus and S. pyogenus respectively. Against gram negative bacterial strains compounds 9c and 9h having $OCH_3$ group at 2nd and 3rd position of phenyl nucleus gave potent activity with MIC values 50, 50,100 and 25 respectively as well as for gram positive bacterial strains provided MIC values 100, 50, 100 & 50 respectively. Against gram negative bacterial strains compounds 9b and 9g having electron donating group like $CH_3$ group at 2nd and 3rd position of phenyl nucleus furnished potent activity with MIC values 500, 250,125 and 200 respectively as well as for gram positive bacterial strains gave MIC values 100, 62.5, 250 &100 respectively. Against gram negative bacterial strains for compound 9a without any substituent on phenyl nucleus donated better activity with MIC values 50 and 100. Remaining compounds appeared with moderate activity in terms of MIC values are shown in Table 2.Ciprofloxacin and Chloramphenicol were used as standard control drugs for antibacterial activity[1].

### *B. In vitro antifungal activity:*

The antifungal potency in terms of MIC values of newly synthesized compounds are precisely mentioned in Table 3. The MIC values of the compounds are observed in a varied range (100- >1000 µg/ml) against considered fungal strains. the antibacterial activity of newly synthesized compounds having electron-withdrawing group 9e with 3-$COCH_3$ seemed with value of MIC 100 and 100 against C. albicans MTCC 227and A.niger MTCC 282 respectively and for compound 9j with 3-CHO substituent to the phenyl nucleus looked with the values of MIC 250 and 100 against C.albicansMTCC 227and A.clavatusMTCC 1323 respectively gaveexcellent activity compared to the others. Nystatin and Greseofulvinwere used as standard control drugs for antifungal activity[1].

Table 2. In vitro antibacterial activity of newly synthesized compounds9a-j.

| Compound | -R | $-NH_2$ | MINIMAL INHIBITORY CONCENTRATION (µg/ml) | | | |
|---|---|---|---|---|---|---|
| | | | E.coli MTCC 442 | P.aeruginosa MTCC 441 | S.aureus MTCC 96 | S.pyogenus MTCC 443 |
| 9a | -H | $4-NH_2$ | 50 | 100 | 100 | 100 |
| 9b | $2-CH_3$ | $4-NH_2$ | 500 | 250 | 100 | 62.5 |
| 9c | $2-OCH_3$ | $4-NH_2$ | 50 | 50 | 100 | 50 |
| 9d | 3-Cl | $4-NH_2$ | 100 | 62.5 | 125 | 100 |
| 9e | $3-COCH_3$ | $4-NH_2$ | 25 | 50 | 100 | 50 |
| 9f | -H | $3-NH_2$ | 100 | 62.5 | 250 | 500 |
| 9g | $3-CH_3$ | $3-NH_2$ | 125 | 200 | 250 | 100 |
| 9h | $3-OCH_3$ | $3-NH_2$ | 100 | 25 | 100 | 50 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 9i | 3-Br | 3-$NH_2$ | 62.5 | 50 | 100 | 50 |
| 9j | 3-CHO | 3-$NH_2$ | 100 | 100 | 62.5 | 50 |
| Ciprofloxacin | - | | 25 | 25 | 50 | 50 |
| Chloramphenicol | - | | 50 | 50 | 50 | 50 |

S. aureus Staphylococcus aureus, E. coli Escherichia coli, P. aeruginosa Pseudomonas aeruginosa, S.pyogenus Streptococcus pyogenes.

Table 3.In vitro antifungal activity of newly synthesized compounds 9a-j.

| Compound | -R | -$NH_2$ | MINIMAL FUNGICIDAL CONCENTRATION (µg/ml) | | |
|---|---|---|---|---|---|
| | | | C.albicans MTCC 227 | A.niger MTCC 282 | A.clavatus MTCC 1323 |
| 9a | -H | 4-$NH_2$ | 100 | 500 | 250 |
| 9b | 2-$CH_3$ | 4-$NH_2$ | 250 | 250 | 500 |
| 9c | 2-$OCH_3$ | 4-$NH_2$ | 100 | 500 | 250 |
| 9d | 3-Cl | 4-$NH_2$ | 1000 | >1000 | 500 |
| 9e | 3-$COCH_3$ | 4-$NH_2$ | 100 | 100 | 250 |
| 9f | -H | 3-$NH_2$ | 250 | 500 | 1000 |
| 9g | 3-$CH_3$ | 3-$NH_2$ | 500 | 1000 | >1000 |
| 9h | 3-$OCH_3$ | 3-$NH_2$ | 250 | 100 | 250 |
| 9i | 3-Br | 3-$NH_2$ | 500 | >1000 | 250 |
| 9j | 3-CHO | 3-$NH_2$ | 250 | 500 | 100 |
| Nystatin | - | | 100 | 100 | 100 |
| Greseofulvin | - | | 500 | 100 | 100 |

A. niger Aspergillus niger, A. clavatus Aspergillus clavatus, C. albicans Candida albicans.

## IV. EXPERIMENTAL

### A. *Material and methods*

All the chemicals and solvents used for the synthesis work acquired from commercial sources, were of analytical grade, and used without further purification. 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 iodine. NMR spectra were recorded on 400 MHz BRUKER AVANCE instrument using TMS as internal standard (Chemical Shift in δ, ppm) and DMSO-$d_6$ as a solvent. Spectra were taken with a resonant frequency of 400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR. The splitting patterns are designated as follows; s, singlet; d, doublet; dd, doublet of doublets; t, triplet and m, multiplet. Elemental analysis was done on "Haraeus Rapid Analyser". The mass spectra were recorded on JOEL SX-102 (EI) model with 60 eV ionizing energy.

Table 1. Physical constant of newly synthesized compounds 9a-j.

| Compound | -R | -$NH_2$ | Molecular Formula | M.P $^0$C | Yield % | Elemental Analysis | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | % C | % H | % N |
| 9a | -H | 4-$NH_2$ | $C_{15}H_{14}N_4O_3S$ | 198–199 | 77 | R | 54.53 | 4.27 | 16.96 |
| | | | | | | F | 54.58 | 4.31 | 17.00 |
| 9b | 2-$CH_3$ | 4-$NH_2$ | $C_{16}H_{16}N_4O_3S$ | 292-299 | 72 | R | 55.80 | 4.68 | 16.27 |
| | | | | | | F | 55.85 | 4.72 | 16.32 |
| 9c | 2-$OCH_3$ | 4-$NH_2$ | $C_{27}H_{16}Cl_2N_2O_3S$ | 282-290 | 70 | R | 53.32 | 4.47 | 15.55 |
| | | | | | | F | 53.37 | 4.52 | 15.60 |
| 9d | 3-Cl | 4-$NH_2$ | $C_{15}H_{13}ClN_2O_3S$ | 293-298 | 72 | R | 49.39 | 3.59 | 15.36 |
| | | | | | | F | 49.44 | 3.64 | 15.40 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 9e | 3-$COCH_3$ | 4-$NH_2$ | $C_{17}H_{16}N_4O_4S$ | 291-297 | 73 | R | 54.83 | 4.33 | 15.04 |
| | | | | | | F | 54.88 | 4.38 | 15.09 |
| 9f | -H | 3-$NH_2$ | $C_{15}H_{14}N_4O_3S$ | 291-294 | 78 | R | 54.53 | 4.27 | 16.96 |
| | | | | | | F | 54.49 | 4.22 | 16.91 |
| 9g | 3-$CH_3$ | 3-$NH_2$ | $C_{16}H_{16}N_4O_3S$ | 275-278 | 70 | R | 55.80 | 4.68 | 16.27 |
| | | | | | | F | 55.76 | 4.64 | 16.23 |
| 9h | 3-$OCH_3$ | 3-$NH_2$ | $C_{16}H_{16}N_4O_4S$ | 274-279 | 73 | R | 53.32 | 4.47 | 15.55 |
| | | | | | | F | 53.29 | 4.43 | 15.51 |
| 9i | 3-Br | 3-$NH_2$ | $C_{15}H_{13}BrN_4O_3S$ | 288-292 | 75 | R | 44.02 | 3.20 | 13.69 |
| | | | | | | F | 44.07 | 3.25 | 13.74 |
| 9j | 3-CHO | 3-$NH_2$ | $C_{16}H_{14}N_4O_4S$ | 198–199 | 77 | R | 53.62 | 3.94 | 15.63 |
| | | | | | | F | 53.67 | 4.00 | 15.68 |

### *B. Synthesis of 2, 4-dichloro-6-methoxy pyrimidine (2)*

To a stirred solution of 2,4,6-trichloro pyrimidine (0.1 mol) and $Et_3N$(0.1mmol)in methanol(5mL)at room temperature, solution of NaOMe (20 ml, 0.5M in MeOH) was addeddrop-wise by keeping temperature at 0-5 °C followed by stirring for 2 hour.Progress of the reaction was continuously monitored by TLC using ethyl acetate:*n*-hexane (6:4) as eluent. After completion of reaction, reaction mixture was poured in the beaker containing crushed ice followed by further stirring for 30 minutes. Obtained precipitates was then filtered, washed with water and purified by recrystallization from absolute alcohol to get the title compound. Yield: 85% [27].

### *C. Synthesis of 2-chloro-4, 6-dimethoxy pyrimidine (3)*

To the solution of 2,4-dichloro-6-methoxy pyrimidine (0.040 mol) in methanol(5ml), solution of NaOMe (20 ml, 0.5M in MeOH) was addeddrop-wise for 30 minutes followed by stirring for 12 hours. Progress of the reaction was monitored frequently by TLC using ethyl acetate:*n*-hexane (6:4) as eluent. After completion, reaction mixture was dumped in to water. Produced solid precipitates were collected by filtration followed by washing with water and purification by means of recrystallization from aqueous ethanol to get title compound. Yield: 89% [28].

### *D. General procedure for the synthesis of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline(6a-j)*

To a flask charged with compound3(0.0017mol), mixture of4,4,5,5-Tetramethyl-1,3,2-dioxaborolane(Pinacolborane)( 0.0019mol), $PdCl_2(PPh_3)_2$ (0.00056 mol) and KOAc (0.0051 mol) in DMSO (5 ml) under nitrogen atmosphere was added. Reaction mixture was stirred at 80°C 12 hours. Reaction progress was monitored by TLC using MeOH: DCM (1:9) as eluent. On completion, reaction mixture was allowed to cool down and poured in water(4×30 ml) followed by separation of organic portion with help of DCM. Organic layer was then separated, dried by anhydrous MgSO4 and subjected to evaporation under reduced pressure results in appearance of titled yellow colored compound. Yield: 82%. [29].

### *E. General procedure for synthesis of 4-(4, 6-dimethoxy pyrimidin-2-yl) aniline (7a-j)*

In a 100 ml RBF kept in nitrogen atmosphere, boronic acid (1.5 equiv),$Pd(OAc)_2$ (5.0mol%), $PPh_3$(10.0mol%) and $K_3PO_4$ (2.0 equiv) was added along with2-Chloro-4,6-dimethoxy pyrimidine (1 g,) in dry 1,4-dioxane (30 ml).The mixture was stirred for 4 hours at 90°C under nitrogen atmosphere. Progress of the reaction was monitored by TLC using ethyl acetate: hexane (1:9) as eluent. After completion of reaction, the residue was cooled to ambient temperature then the slurry was filtered toremove salt. The filtrate was washed with i-PrOAc.To remove residualboronic acid the solution was treated withi-PrOAc and 1 NNaOH aq. Furthermore, organic crude was separated by means of solvent extraction by using DCM. The organiclayer was separated, dried and removed under reduced pressure in order to get desired compound. Yield: 79%[30].

### *F. General procedure for the synthesis of 2-chloro-N-(4-(4,6-dimethoxy pyrimidin-2-yl) phenyl)acetamide (8a-j)*

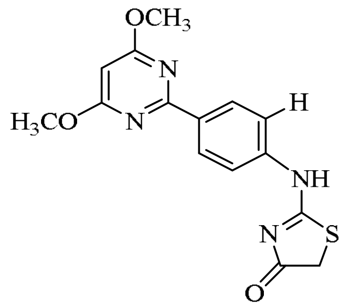
To a mixture of 4-(4,6-dimethoxy pyrimidin-2-yl) aniline(0.0045 mol) in dichloromethane (10 ml) chloro-acetyl-chloride (0.0045 mol) and triethyl-amine (0.0045 mol) was added by keeping 0-5°C and stirred for 4 hours at room temperature. Progress of the reaction was monitored by TLC using ethyl acetate: hexane (2:8) as eluent. After the completion of reaction, the excess solvent was removed under vacuum and remained crude was treated with crushed ice to afford a solid product. The solid obtained was filtered, washed with water, neutralized and recrystallized from absolute alcohol to get the title compound. Yield: 98%[31].

*G. General procedure for the synthesis of 2-((4-(4,6-dimethoxy pyrimidin-2-yl) phenyl) amino) thiazol-4(5H)-one (9a-j)*

A solution of 2-chloro-*N*-(4-(4,6-dimethoxy pyrimidin-2-yl) phenyl) acetamide (10 mmol) and ammonium thiocyanate (15 mmol) in absolute ethanol (30 ml) was refluxed for 4 h and allowed to stand overnight. Progress of the reaction was monitored by TLC using ethyl acetate: hexane (2:8) as eluent. On completion of reaction, solid precipitates were collected by filtration, washed and recrystallized from aqueous ethanol to get the title compound. Yield: 77%. [32].

## V. CHARACTERISATION OF PRODUCTS

*A. 2-((4-(4,6-Dimethoxypyrimidin-2-yl) phenyl) amino) thiazol-4(5H)-one:*

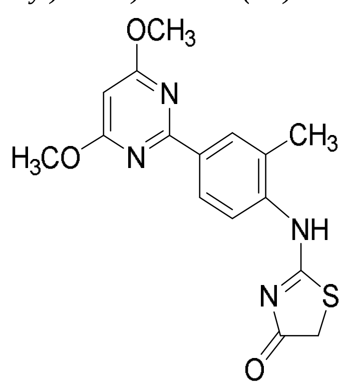


Compound 9a

1) *IR (vmax cm$^{-1}$):*1080 (C-$OCH_3$ ether stretching in pyrimidine ring), 1455 (C=C alkene stretching in aromatic ring), 1682 (C=O aryl ketone stretching in thiazolidinone ring), 3020 (C-H alkane stretching in aromatic ring), 3340 (-NH amine stretching in aromatic amine)
2) *$^{1}$H NMR (400 MHz, DMSO-$d_6$) δppm:* 3.820 (s, 2H, -$CH_2$ (active methylene)), 3.954 (s, 6H, -$OCH_3$), 6.174 (s, 1H, -CH), 7.206 (s, 1H, -NH, $D_2O$ exchangeable), 7.214-7.572 (m, 4H, aromatic –H).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 35.15, 53.74, 96.06, 121.15, 130.88, 134.26, 141.15, 168.44, 172.95, 174.78, 182.42.

ESIMS (m/z): 330.48 (M+). mp198-199°C. Anal. Calcd for $C_{15}H_{14}N_4O_3S$ (330.08): C, 54.53
; H, 4.27; N, 16.96; found: C, 54.58; H, 4.31; N, 17.00.

*B. 2-((4-(4,6-Dimethoxypyrimidin-2-yl)-2-methylphenyl) amino) thiazol-4(5H)-one:*



Compound 9b

1) *IR (vmax cm$^{-1}$):* 1085 (C-$OCH_3$ ether stretching in pyrimidine ring), 1360 (-$CH_3$alkane banding in aromatic substituent), 1470 (C=C alkene stretching in aromatic ring), 1690 (C=O aryl ketone stretching in thiazolidinone ring), 2865 (-$CH_3$ alkane stretching in aromatic substituent), 3028 (C-H alkane stretching in aromatic ring), 3355 (-NH amine stretching in aromatic amine)
2) *$^{1}$H NMR (400 MHz, DMSO-$d_6$) δppm:* 2.284 (s, 3H, -$CH_3$), 3.827 (s, 2H, -$CH_2$ (active methylene)), 3.956 (s, 6H, -$OCH_3$), 5.156 (s, 1H, -NH, $D_2O$ exchangeable), 6.174 (s, 1H, -CH), 7.014-7.512 (m, 3H, aromatic –H).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 18.17, 35.15, 53.74, 96.97, 117.73, 127.50, 128.96, 132.70, 136.14, 139.27, 168.14, 173.21, 176.17, 182.42.

ESIMS (m/z): 344.32 (M+). mp292-299°C. Anal. Calcd for $C_{16}H_{16}N_4O_3S$ (344.09): C, 55.80
;H, 4.68; N, 16.27; found: C, 55.85; H, 4.72; N, 16.32.

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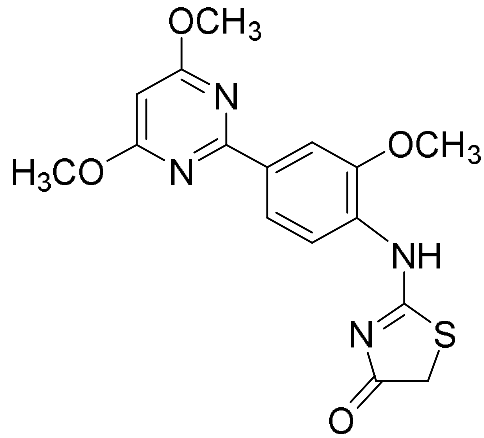
*C. 2-((4-(4,6-Dimethoxypyrimidin-2-yl)-2-methoxyphenyl) amino) thiazol-4(5H)-one:*

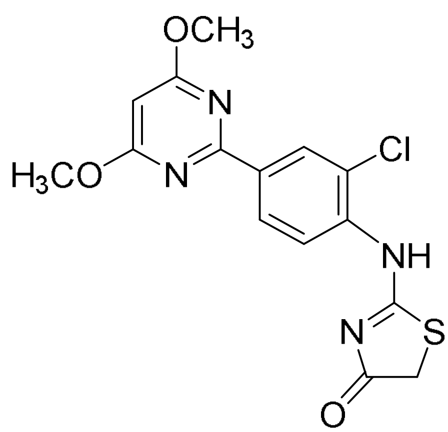



Compound 9c

1) *IR (vmax cm$^{-1}$)*:1120 (C-$OCH_3$ ether stretching in pyrimidine ring), 1485 (C=C alkene stretching in aromatic ring), 1686 (C=O aryl ketone stretching in thiazolidinone ring), 3033 (C-H alkane stretching in aromatic ring), 3390 (-NH amine stretching in aromatic amine).
2) *$^1$H NMR (400 MHz, DMSO-$d_6$) δppm:* 3.814 (s, 3H, -$OCH_3$), 3.823 (s, 2H, -$CH_2$ (active methylene)), 3.956 (s, 6H, -$OCH_3$), 5.448 (s, 1H, -NH, $D_2O$ exchangeable), 6.176 (s, 1H, -CH), 7.023-7.240 (m, 3H, aromatic –H).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 35.15, 53.74, 56.78, 96.97, 116.99, 118.47, 124.38, 133.03, 135.43, 155.02, 168.14, 173.21, 176.17, 182.42.

ESIMS (m/z): 360.72 (M+). mp282-290°C. Anal. Calcd for $C_{27}H_{16}Cl_2N_2O_3S$ (360.09): C, 53.32
;H, 4.47; N, 15.55; found: C, 53.37; H, 4.52; N, 15.60.

*D. 2-((2-Chloro-4-(4,6-dimethoxypyrimidin-2-yl) phenyl) amino) thiazol-4(5H)-one:*




Compound 9d

1) *IR (vmax cm$^{-1}$):* 815 (-Cl stretching in aromatic substituent), 1150 (C-$OCH_3$ ether stretching in pyrimidine ring), 1495 (C=C alkene stretching in aromatic ring), 1690 (C=O aryl ketone stretching in thiazolidinone ring), 3090 (C-H alkane stretching in aromatic ring), 3395 (-NH amine stretching in aromatic amine)
2) *$^1$H NMR (400 MHz, DMSO-$d_6$) δppm:* 3.833 (s, 2H, -$CH_2$ (active methylene)), 3.955 (s, 6H, -$OCH_3$), 6.049 (s, 1H, -NH, $D_2O$ exchangeable), 6.174 (s, 1H, -CH), 7.024-7.665 (m, 3H, aromatic –H).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 35.15, 53.74, 96.97, 120.02, 124.78, 129.55, 133.60, 135.28, 138.63, 168.14, 173.21, 176.17, 182.42.

ESIMS (m/z): 364.84 (M+). mp293-298°C. Anal. Calcd for $C_{15}H_{13}ClN_2O_3S$ (364.04): C, 49.39
;H, 3.59; N, 15.36; found: C, 49.44; H, 3.64; N, 15.40.

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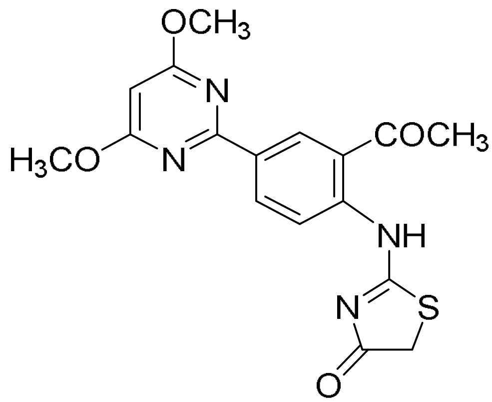
*E. 2-((2-Acetyl-4-(4,6-dimethoxypyrimidin-2-yl) phenyl) amino) thiazol-4(5H)-one:*

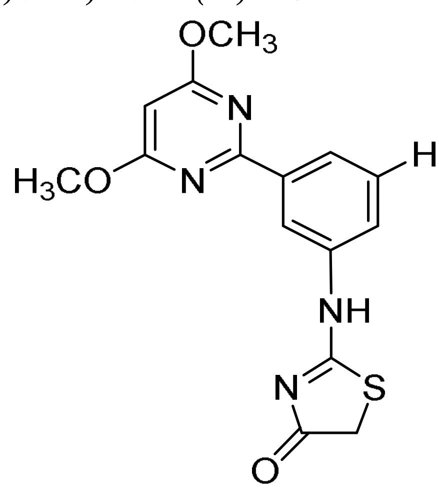


Compound 9e

1) *IR (vmax cm$^{-1}$):* 1113 (C-$OCH_3$ ether stretching in pyrimidine ring), 1380 (-$CH_3$ alkane banding in aromatic substituent), 1482 (C=C alkene stretching in aromatic ring), 1694 (C=O aryl ketone stretching in thiazolidinone ring), 2885 (-$CH_3$ alkane stretching in aromatic substituent), 3130 (C-H alkane stretching in aromatic ring), 3359 (-NH amine stretching in aromatic amine).
2) *$^1$H NMR (400 MHz, DMSO-$d_6$) δppm:* 2.540 (s, 3H, -$COCH_3$), 3.828 (s, 2H, -$CH_2$ (active methylene)), 3.959 (s, 6H, -$OCH_3$), 6.180 (s, 1H, -CH), 7.182-8.164 (m, 3H, aromatic –H), 9.881 (s, 1H, -NH, $D_2O$ exchangeable).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 28.27, 35.15, 53.74, 96.97, 119.30, 119.72, 129.40, 131.12, 132.72, 142.23, 168.14, 173.21, 176.17, 182.42, 202.32.

ESIMS (m/z): 372.74 (M+). mp291-297°C. Anal. Calcd for $C_{17}H_{16}N_4O_4S$ (372.09): C54.83
;H, 4.33; N, 15.36; found: C, 54.88; H, 4.38; N, 15.09.

*F. 2-((3-(4,6-Dimethoxypyrimidin-2-yl) phenyl) amino) thiazol-4(5H)-one:*

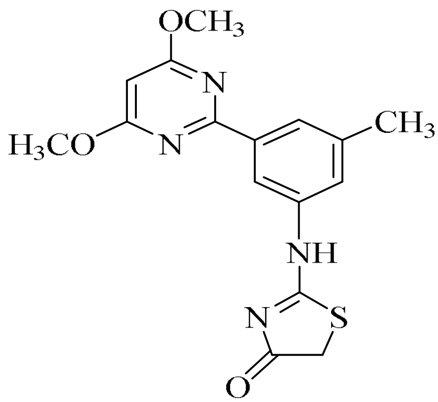


Compound 9f

1) *IR (vmax cm$^{-1}$):*1099 (C-$OCH_3$ ether stretching in pyrimidine ring), 1475 (C=C alkene stretching in aromatic ring), 1694 (C=O aryl ketone stretching in thiazolidinone ring), 3062 (C-H alkane stretching in aromatic ring), 3345 (-NH amine stretching in aromatic amine).
2) *$^1$H NMR (400 MHz, DMSO-$d_6$ )δppm:* 3.836 (s, 2H, -$CH_2$(active methylene)), 3.968 (s, 6H, -$OCH_3$), 6.187 (s, 1H, -CH), 6.742-7.349 (m, 3H, aromatic –H),7.545 (s, 1H, -NH, $D_2O$ exchangeable).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 35.15, 53.74, 96.97, 121.68, 122.38, 126.26, 128.85, 139.22, 140.29, 168.14, 173.21, 174.78, 182.42.

ESIMS (m/z): 330.68 (M+). mp291-294°C. Anal. Calcd for $C_{15}H_{14}N_4O_3S$ (330.08): C, 54.53
;H, 4.27; N, 16.96; found: C, 54.49; H, 4.22; N, 16.91.

*G. 2-((3-(4,6-Dimethoxypyrimidin-2-yl)-5-methylphenyl) amino) thiazol-4(5H)-one:*

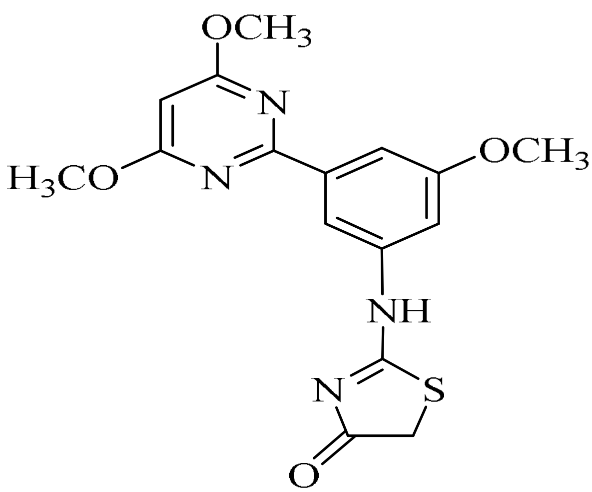


Compound 9g

1) *IR (vmax $cm^{-1}$):* 1120 (C-$OCH_3$ ether stretching in pyrimidine ring), 1399 (-$CH_3$ alkane banding in aromatic substituent), 1469 (C=C alkene stretching in aromatic ring), 1696 (C=O aryl ketone stretching in thiazolidinone ring), 2866 (-$CH_3$ alkane stretching in aromatic substituent), 3033 (C-H alkane stretching in aromatic ring), 3320 (-NH amine stretching in aromatic amine)
2) *$^1$H NMR (400 MHz, DMSO-$d_6$) δppm*: 2.353 (s, 3H, -$CH_3$), 3.836 (s, 2H, -$CH_2$ (active methylene)), 3.968 (s, 6H, -$OCH_3$), 5.331 (s, 1H, -NH, $D_2O$ exchangeable), 6.187 (s, 1H, -CH), 6.666-7.233 (m, 3H, aromatic –H).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 21.81, 35.15, 53.74, 96.92, 121.60, 125.80, 126.54, 135.43, 135.95, 140.21, 167.46, 173.33, 174.78, 182.42.

ESIMS (m/z): 344.32 (M+). mp275-278°C. Anal. Calcd for $C_{16}H_{16}N_4O_3S$ (344.09): C, 55.80 ;H, 4.68; N, 16.27; found: C, 55.76; H, 4.64; N, 16.23.

*H. 2-((3-(4,6-Dimethoxypyrimidin-2-yl)-5-methoxyphenyl) amino) thiazol-4(5H)-one:*

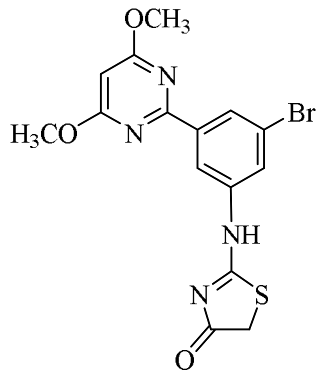


Compound 9h

1) *IR (vmax $cm^{-1}$):*1166 (C-$OCH_3$ ether stretching in pyrimidine ring), 1590 (C=C alkene stretching in aromatic ring), 1691 (C=O aryl ketone stretching in thiazolidinone ring), 3099 (C-H alkane stretching in aromatic ring), 3430 (-NH amine stretching in aromatic amine).
2) *$^1$H NMR (400 MHz, DMSO-$d_6$) δppm:* 3.800 (s, 2H, -$CH_2$ (active methylene)),3.807 (s, 3H, -$CH_3$), 3.957 (s, 6H, -$OCH_3$), 4.024 (s, 1H, -NH, $D_2O$ exchangeable), 6.183 (s, 1H, -CH), 6.409-7.035 (m, 3H, aromatic –H).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 35.15, 53.74, 56.03, 96.92, 109.28, 112.81, 115.08, 137.83, 138.24, 163.27, 167.46, 173.33, 174.78, 182.42.

ESIMS (m/z): 360.28 (M+). mp274-279°C. Anal. Calcd for $C_{16}H_{16}N_4O_4S$ (360.09): C, 53.32 ;H, 4.47; N, 15.55; found: C, 53.29; H, 4.43; N, 15.51.

*I. 2-((3-Bromo-5-(4,6-dimethoxypyrimidin-2-yl) phenyl) amino) thiazol-4(5H)-one:*

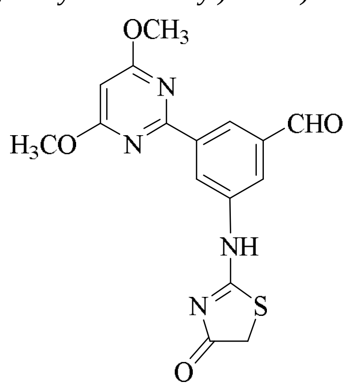



Compound 9i

1) *IR (vmax cm$^{-1}$):*795 (-Br stretching in aromatic ring substituent), 1160 (C-$OCH_3$ ether stretching in pyrimidine ring), 1566 (C=C alkene stretching in aromatic ring), 1689 (C=O aryl ketone stretching in thiazolidinone ring), 3096 (C-H alkane stretching in aromatic ring), 3440 (-NH amine stretching in aromatic amine).
2) *$^1$H NMR (400 MHz, DMSO-$d_6$) δppm:* 3.834 (s, 2H, -$CH_2$ (active methylene)), 3.967 (s, 6H, -$OCH_3$), 5.339 (s, 1H, -NH, $D_2O$ exchangeable), 6.207 (s, 1H, -CH), 6.976-7.482 (m, 3H, aromatic –H).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 35.15, 53.74, 96.92, 122.10, 122.46, 122.57, 130.44, 136.95, 137.56, 140.16, 167.46, 173.33, 174.78, 182.42.

ESIMS (m/z): 408.32 (M+). mp288-292°C. Anal. Calcd for $C_{15}H_{13}BrN_4O_3S$ (407.99): C, 44.02 ;H, 3.20; N, 13.69; found: C, 44.07; H, 3.25; N, 13.74.

*J. 3-(4,6-Dimmethoxypyrimidin-2-yl)-5-((4-oxo-4,5-dihyrothiazol-2-yl) amino) benzaldehyde:*




Compound 9j

1) *IR (vmax cm$^{-1}$):* 1240 (C-$OCH_3$ ether stretching in pyrimidine ring), 1495 (C=C alkene stretching in aromatic ring), 1699 (C=O aryl ketone stretching in thiazolidinone ring), 1735 (-CHO aldehyde stretching in aromatic substituent), 3080 (C-H alkane stretching in aromatic ring), 3489 (-NH amine stretching in aromatic amine)
2) *$^1$H NMR (400 MHz, DMSO-$d_6$) δppm:* 3.836 (s, 2H, -$CH_2$ (active methylene)), 3.959 (s, 6H, -$OCH_3$), 5.158 (s, 1H, -NH, $D_2O$ exchangeable), 6.193 (s, 1H, -CH), 7.357-7.825 (m, 3H, aromatic –H), 9.983 (s, 1H, -CHO).
3) *$^{13}$C NMR (100 MHz, DMSO-$d_6$):* 35.15, 53.74, 96.92, 128.06, 128.61, 129.82, 132.48, 137.56, 140.16, 167.46, 173.33, 174.78, 182.42, 191.66.

ESIMS (m/z): 358.44 (M+). mp198–199°C. Anal. Calcd for $C_{16}H_{14}N_4O_4S$ (358.07): C, 53.62 ;H, 3.94; N, 15.63; found: C, 53.67; H, 4.00; N, 15.68.

## VI. CONCLUSION

We have established an efficient method to synthesize series of novel 2-((4-(4,6-dimethoxypyrimidin-2-yl)phenyl)amino)thiazol-4(5H)-one derivatives. The structures of newly synthesized compounds were characterized by$^1$H NMR, $^{13}$C NMR and mass spectral analysis and were also tested for their antibacterial activity against various bacterial strains such as E. coli, P. aeruginosa, S. aureus and S. pyogenesalong withthe antifungal activity against various fungal strains such as C. albicans, A. niger and A. clavatus. The antimicrobial activities of the newly synthesized compounds 9a-j was evaluated and it revealed that compounds 9eand9jwere potent antimicrobial agents against the tested microorganisms whereas other analogues showed reasonable activity against different strains.

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