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# Design, synthesis and biological potential of some isoxazole and hydroxypyrimidine derivatives containing pyrido [2,3-*d*] pyrimidine nucleus *via* chalcone series

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Synthesis of 4-(2,4-dimethoxy-6-(5-substitutedphenylisoxazol-3-yl) pyrido[2,3-*d*] pyrimidin-7-yl)morpholine has been carried out by reaction of (E)-3-(2,4-dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-1-substituted phenylprop-2-en-1-one with hydroxylamine hydrochloride analogue to get the compounds **8a-f** and synthesis of 4-(2,4-dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-6-phenylpyrimidin-2-ol with urea to get various hydroxypyrimidine of the studied analogue to get the compounds **9a-f**. Structures of all the newly synthesized compounds have been characterized by instrumental method. Representative compounds of the synthesized product series have been tested and evaluated as antimicrobial agents.

**Keyword**: Isoxazole, hydroxypyrimidine, synthesis, biological activity

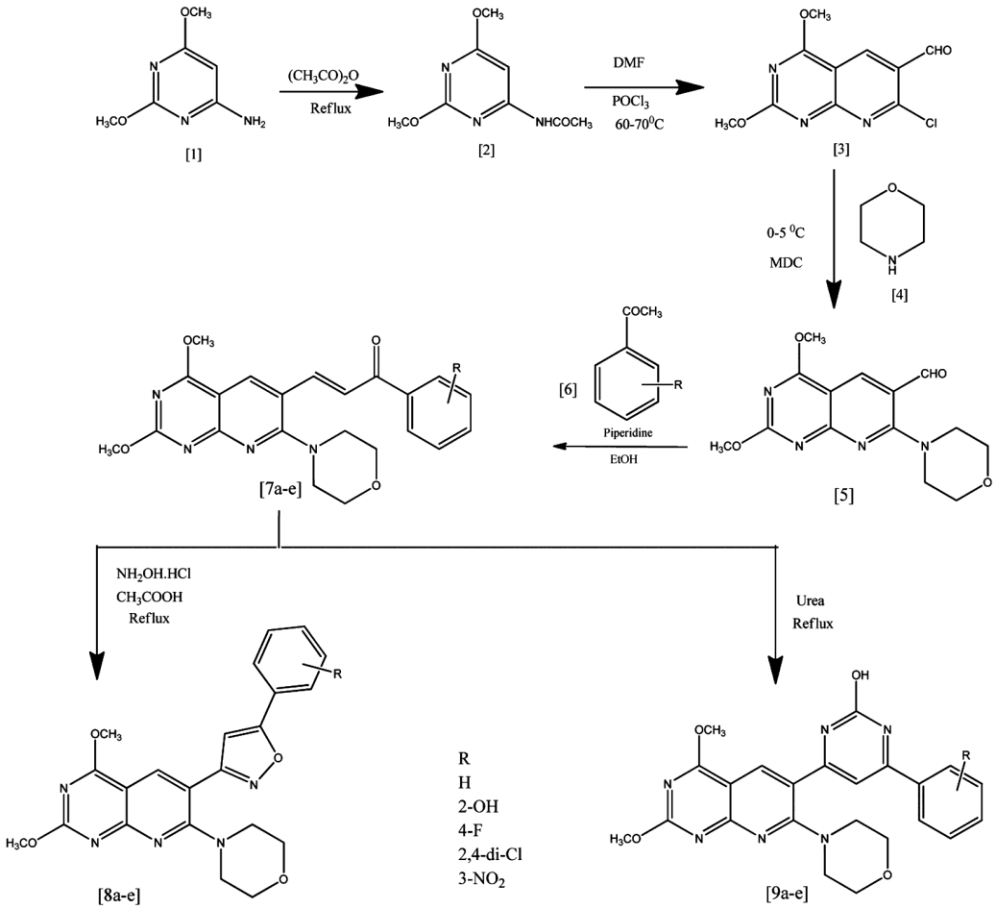
The great development in medicinal research in past has contributed much to the unequaled progress of medicine during that period. Improved and basically more meaningful biological test procedures and methods of diagnosis have provided better guidance in drug discovery by pointing out suggestive observation which could be used in the design of new prophylactic and therapeutic agents.

Chalcones vital bioactive secondary metabolites belonging to the flavonoids family[1,2]. These molecules have interesting biological activities including antimalarial[3], antioxidant[4], anticancer, antibacterial[5-7]. A Variety of Nitrogen containing heterocyclic compounds studied widely for the development of pharmaceutically important antimicrobial agents. Bicyclic nitrogen-containing heterocyclic compounds, for instance Pyrido[2,3-*d*]pyrimidines due to their outstanding therapeutic potential such as antitumor[8,9], antimicrobial[10], and antifungal activities[11]. Moreover these compounds are considered to be significant for synthetic drugs (*e.g.*, barbituric acid derivatives), chemotherapeutic agents (*e.g.*, sulfadiazine), and agricultural chemicals[12]. Furthermore, nitrogen containing heterocyclic compound Isoxazole derivatives have shown a remarkably broad spectrum of pharmacological and physiological activities and they are used as, Antibacterial[13-15], Anticholestermic[16], Anticancer[17], Anthelmintics[18]. Antiinflammatory[19-21], Fungicidal[22-24], Hypoglycemic[25], Nematocidal[26], Insecticidal[27], and Antiviral[28]. Finally hydroxyl-group is present in the biologically important pyrimidines (Cytosine, uracil, thymine), it is significant to have authentic hydroxypyrimidine available for the explanation of spectra and for biochemical comparisons.

## Results and Discussion

### Chemistry

The synthesis of *(E)*-3-(2,4-dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-1-substitute dphenylprop-2-en-1-one 7a-e (Scheme I), synthesis of 4-(2,4-dimethoxy-6-(5-substitutedphenylisoxazol-3-yl)pyrido[2,3-*d*]pyrimidin-7-yl)morpholine 8a-e (Scheme I), synthesis of 4-(2,4-dimethoxy-7-morpholinopyrido[2,3-d]pyrimidin-6-yl)-6-phenyl pyrimidin-2-ol **9a-e** have been adopted as shown in Scheme I. In the Infrared spectra of compound **7e** a stretching for C=N functionality of pyrimidine ring and C=C stretching in aromatic group at 1472 $cm^{-1}$. The aromatic C-H and C=C of aromatic ring at 3091, 1631 $cm^{-1}$. C-N stretching of morpholine ring at 1388 $cm^{-1}$ and –C-O-C linkage in morpholine ring at 1145 $cm^{-1}$. In the $^1$H NMR spectrum of compound **7a** there was an emphasized signal as triplet for the morpholine ring contain protons core at δ 2.4 and 2.55. The three singlet of methoxy group protons at δ 3.8 and 3.96 and




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

remaining protons resonated at δ 7.2-7.8 as multiplet signal due to CH protons. Moreover the compound **8c** showed a strong absorption band at 1622 $cm^{-1}$ due to the presence of the C=N stretching in isoxazole moiety. A broad stretching band for the C=N functionality and –C-O-C- group of pyrimidine ring at between 1495-1635 $cm^{-1}$ and 1100-1200 $cm^{-1}$. In the $^1$H NMR spectrum of compound **8a** there was an emphasized signal as triplet for the morpholine ring contain protons core at δ 2.5 and 2.6. The three singlet of methoxy group protons at δ 2.5 and 2.6 and remaining protons resonated in the region at δ 7.2-7.8 as multiplet signal due to CH proton. Aromatic proton resonated in the region at δ 6.0-6.2. Furthermore the compound **9e** showed a strong absorption band at 1606 $cm^{-1}$ due to the presence of the C=N stretching in Pyrimidine ring. The –C-O-C- group of pyrimidine ring is at 1117 $cm^{-1}$ and –OH stretching band at 3200 $cm^{-1}$. The $^1$H NMR spectrum of compound **9e** emphasized a signal as triplet for the morpholine ring contain protons core at δ 2.8 and 2.9. The three singlet of methoxy group protons at δ 3.37 and 3.39 and remaining protons appears in the region at δ 7.6-8.1 as multiplet signal due to CH proton. Hydroxy proton resonated in the region at δ 5.52. Moreover mass spectrometer produces charged particles (ions) from the title compound that showed molecular ion peak $M^+$ corresponding to their mass. The obtained elemental analysis values are in good with theoretical values.

### *In vitro* antimicrobial activity

The antimicrobial activity of recently synthesized compounds (**7a-e**, **8a-e** and **9a-e**) was carried out by micro broth dilution method[29] according to National Committee for Clinical Laboratory Standards (NCCLS, 2002). The synthesized compounds were screened for antibacterial activity against a panel of selected pathogens Gram positive (*S. aureus* MTCC 96 and *S. pyogenus* MTCC 442), Gram negative (*E. Coli* MTCC 443 and *P. aeruginosa* MTCC 441) bacterial species and for antifungal activity, a group of preferred pathogens of fungal (*C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. calavatus* MTCC

1323) species were used. Ampicillin used as standard antibiotic drugs for antibacterial activity while Greseofulvin and Nystatin were used as standard drug for antifungal activity. 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. Each synthesised compounds were diluted to 1000 µg/mL, 500 µg/mL and 250 µg/mL concentration for primary screen. The drugs found active in primary screening were similarly diluted to 200 µg/mL, 100 µg/mL, 50 µg/mL, and 25 µg/mL concentrations for secondary screen. The minimum inhibitory concentration (MIC) was determined and recorded at the lowest concentration inhibiting growth of the organism. The results are summarized in Table I.

### *In vitro* antitubercular activity

*In vitro* antitubercular activity of all the newly synthesized compounds was determined by using Lowenstein-Jensen medium (conventional method) against Mycobacterial tuberculosis H37Rv strain as described by Rattan[30]. The observed results are presented in Table II in the form of inhibition (%), relative to that of standard antitubercular drugs Rifampicin and Isoniazid. Compounds demonstrating more than 80% inhibition in the primary screening were retested at lower concentration (MIC) in a Lowenstein-Jensen medium and evaluated for their MIC values. Five compounds exhibiting more than 80% inhibition were again screened to get their MIC values (Table II).

Compounds demonstrating more than 90% inhibition in the primary screening were retested at lower concentration (MIC) in a Lowenstein–Jensen medium and evaluated for their MIC values. The results are summarised in Table III. Among the compounds screened for antimycobacterial activity, compounds **7d** and **9d** (MIC = 50 µg/mL), **7a, 8c** and **8e** (MIC = 62.5 µg/mL) were found to possess the greatest potency against *Mycobacterium tuberculosis* (Table III). Other derivatives showed moderate to poor antimycobacterial activity. Moreover, other derivatives showed moderate to good antimycobacterial activity.

### Experimental Section

Melting points were measured by using open capillary tubes and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu FTIR 8401 spectrophotometer using KBr pellets. $^1$H NMR spectra were recorded in DMSO-$d_6$ on a Bruker Avance 400 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The apparent resonance multiplicity was described as: s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet). Mass spectra were

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 | *P. a* MTCC-441 | *C. a* MTCC-227 | *A. n* MTCC-282 | *A. c* MTCC-1323 |
| **7a** | 250 | 100 | 200 | 250 | 500 | 1000 | 250 |
| **7b** | 125 | 62.5 | 62.5 | 100 | 200 | 250 | 1000 |
| **7c** | 250 | 250 | 125 | 100 | 100 | 500 | 100 |
| **7d** | 250 | 125 | 125 | 62.5 | 500 | 100 | 100 |
| **7e** | 200 | 62.5 | 100 | 125 | 500 | 1000 | 1000 |
| **8a** | 250 | 200 | 100 | 200 | 500 | 100 | 100 |
| **8b** | 250 | 100 | 62.5 | 200 | 500 | 100 | 500 |
| **8c** | 250 | 62.5 | 250 | 200 | 500 | 500 | 100 |
| **8d** | 62.5 | 125 | 250 | 62.5 | 100 | 500 | 250 |
| **8e** | 100 | 125 | 250 | 250 | 500 | 200 | 500 |
| **9a** | 250 | 200 | 200 | 62.5 | 500 | >1000 | >1000 |
| **9b** | 200 | 200 | 100 | 100 | 500 | 1000 | 250 |
| **9c** | 125 | 100 | 125 | 100 | 1000 | 500 | 200 |
| **9d** | 62.5 | 250 | 62.5 | 125 | 500 | 1000 | 1000 |
| **9e** | 100 | 62.5 | 125 | 200 | 100 | 500 | 100 |
| A | 250 | 100 | 100 | 100 | – | – | – |
| B | – | – | – | – | 500 | 100 | 100 |
| C | – | – | – | – | 100 | 100 | 100 |

A: Ampicillin, B: Greseofulvin, C: Nystatin.

Table II — *In vitro* mycobacterial screening data of the synthesised compounds at concentration 250 µg/mL

| Compd | % Inhibition |
|---|---|
| **7a** | 94 |
| **7b** | 62 |
| **7c** | 64 |
| **7d** | 89 |
| **7e** | 69 |
| **8a** | 59 |
| **8b** | 68 |
| **8c** | 92 |
| **8d** | 60 |
| **8e** | 80 |
| **9a** | 91 |
| **9b** | 50 |
| **9c** | 89 |
| **9d** | 79 |
| **9e** | 68 |
| Isoniazid | 99 |
| Rifampicin | 98 |

Table III — *In vitro* mycobacterial activity data of the synthesised compounds exhibiting greater inhibition against *M. tuberculosis* H37Rv (MICs, µg/mL)

| Compd | % Inhibition | MIC (µg/mL) |
|---|---|---|
| **7a** | 94 | 62.5 |
| **7d** | 89 | 50 |
| **8c** | 92 | 62.5 |
| **8e** | 80 | 62.5 |
| **9d** | 89 | 50 |
| Rifampicin | 98 | 40 |
| Isoniazid | 99 | 0.20 |

obtained with an APEX II FT-ICR mass spectrometer (Bruker Daltonics Inc.). Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel GF254 with detection by ultraviolet. Silica gel (200~300mesh; Qingdao Chemical Co., China) was used for column chromatography. Elemental analyses were approved out by Perkin-Elmer 2400 series-II elemental analyser (Perkin-Elmer, USA).

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

To (0.01 mole) of 2,6-dimethoxypyrimidin-4-amine **1**, (10 mL) of acetic anhydride and using glacial acetic acid 1-2 drop was added and the mixture was under reflux for 6 h. The reaction mixture was poured into crushed ice with stirring. The reaction was monitored by TLC with ethyl acetate: hexane (6:4) as eluent. The solid product obtained was filtered, washed with water and dried. The product was purified by crystallization from acetone to get the title compound **2**.

White solid, m.p.107°C. Yield 82%. 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%. IR (KBr): 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. 2° amine), 1177 $cm^{-1}$ (-$OCH_3$ str.); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 9.52 (s, 1H, 2° amide), 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).

**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 Dimethylformamide (DMF) (4.0 mL, 50 m mol), $POCl_3$ (0.5 mL, 5 m mol) was added at RT, producing a semi-solid mass. A clear solution appeared after stirring for 4 h at RT. It was further stirred for 6 h. The reaction mixture was poured into crushed ice with stirring. The resulting solid were filtered off, washed with water and dried at RT in a vacuum oven. Reaction progress was monitored by TLC using ethyl acetate: hexane (6:4) as eluent. The crude product was purified by crystallization from acetone to get the title compound **(3)**.

Light-yellow, m.p.115°C. Yield 77%. 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%; IR (KBr): 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 $cm^{-1}$ (-$OCH_3$ str.); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 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).

**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 (MDC) was slowly 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 × 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. Reaction was monitored by TLC using chloroform: methanol (9:1) as eluent. The compound(5) was purified by crystallization from acetone to get the title compound **(5)**.

Light-yellow, m.p.102°C. Yield 70%. 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%; IR (KBr): 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 $cm^{-1}$ (C-N str., morpholine ring); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 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).

***(E)*-3-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*] pyrimidin-6-yl)-1-substitutedphenylprop-2-en-1-one, 7a**

A mixture of (5) (2.0 g, 20 mmol) in ethanol was added into an acetophenone (6) (1.04 g) in 5 mL ethanol containing 4-5 drops piperidine. The reaction mixture was refluxed for 2 h at 60-70°C, the yellow compound which separated out was filtered and washed with water. The development of reaction was monitored by TLC using chloroform: methanol (9:1) as eluent. The crude product (7a) was purified by crystallization from absolute alcohol to get the title compound **(7a)** in good yield with high purity. Similarly, the remaining compounds **(7a-e)** were synthesised by his given method.

**Synthesis of 4-(2,4-dimethoxy-6-(5-substituted phenylisoxazol-3-yl)pyrido[2,3-*d*]pyrimidin-7-yl)mor pholine, 8a**

A mixture of compound (7) (0.01mol in 30 mL alcohol) and hydroxylamine hydrochloride (0.01mol in 10 mL alcohol) was reflux for 8 hours. After the competition of reaction it was dumped in ice cold water. Progress of the reaction was monitored by using TLC. Crude product was filtered, washed with water, dried and recrystallised from ethanol to get the tital compound **(8a)** in good yield with high purity. In the same way, the remaining compounds **(8a-e)** were synthesised by this same method.

**Synthesis of 4-(2,4-dimethoxy-7-morpholinopyrido [2,3-*d*]pyrimidin-6-yl)-6-phenylpyrimidin-2-ol, 9a**

A mixture of compound (7) (0.1 mole in alcohol) and urea (0.639g in 25 mL alcohol) and HCl (5mL) was refluxed for 3 hours on water-bath at 75°C. After the completion of the reaction, reaction mixture was hot filtered to avoid traced of impurities and then allow it cool at RT followed by crystallization as a consequence. Progress of the reaction was monitored by using TLC using chloroform: methanol (9:1) as eluent. Likewise, the remaining compounds **(9a-e)** were synthesised by this given method.

The structures of the title compounds were characterized by $^1$H NMR, IR, MS and elemental analysis, and their data are listed below.

***(E)*-3-(2,4-Dimethoxy-7-morpholinopyrido[2,3-d]pyrimidin-6-yl)-1-phenylprop-2-en-1-one, 7a**: Yield: 77%; m.p. 118°C. Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.78. Found: C, 65.04; H, 5.49; N, 13.75%; IR (KBr): 3015 (C-H str. In aromatic ring), 1596 (C=N str., pyrimidine ring), 1508 (C=C str., aromatic), 1650 (CH=CH-C=Ostr. In chalcone), 1145 (-C-O-C str. In morpholine ring), 1363 (-C-N str. In morpholine ring), 1168 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.45 (t, 4H, $CH_2$ morpholine), 2.55 (t, 4H, $CH_2$ morpholine), 3.84 (s, 3H, -$OCH_3$), 3.96 (s, 3H, -$OCH_3$), 7.79 (s, 1H, Ar-H), 6.96 (d, 1H, CH), 7.10 (d, 1H, CH), 7.2-7.8 (m, 5H, CH) ; MS: *m/z* 407.5 ($M^+$ +1).

***(E)*-3-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one, 7b**: Yield: 76%; m.p. 132°C. Anal. Calcd for $C_{22}H_{22}N_4O_5$: C, 62.55; H, 5.25; N, 13.26. Found: C, 62.58; H, 5.23; N, 13.28%; IR (KBr): 3010 (C-H str. In aromatic ring), 1592 (C=N str., pyrimidine ring), 1507 (C=C str., aromatic), 1652 (CH=CH-C=Ostr. In chalcone), 1140 (-C-O-C str. In morpholine ring), 1362 (-C-N str. In morpholine ring), 3200 (-C-OH str.), 1167 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.47 (t, 4H, $CH_2$ morpholine), 2.54 (t, 4H, $CH_2$ morpholine), 3.87 (s, 3H, -$OCH_3$), 3.94 (s, 3H, -$OCH_3$), 7.75 (s, 1H, Ar-H), 6.94 (d, 1H, CH), 7.11 (d, 1H, CH), 5.51 (s, 1H, -OH), 7.1-7.6 (m, 4H, CH); MS: *m/z* 423.4 ($M^+$ +1).

***(E)*-3-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-1-(4-fluorophenyl)prop-2-en-1-one, 7c**: Yield: 68%; m.p. 109°C. Anal. Calcd for $C_{22}H_{21}N_4FO_4$: C, 62.26; H, 4.99; N, 13.20. Found: C, 62.23; H, 4.96; N, 13.22%; IR (KBr): 3018 (C-H str. In aromatic ring), 1594 (C=N str., pyrimidine ring), 1508 (C=C str., aromatic), 1650 (CH=CH-C=Ostr. In chalcone), 1144 (-C-O-C str. In morpholine ring), 1362 (-C-N str. In morpholine ring), 968 (C-F str.), 1168 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.40 (t, 4H, $CH_2$ morpholine), 2.48 (t, 4H, $CH_2$ morpholine), 3.84 (s, 3H, -$OCH_3$), 3.97 (s, 3H, -$OCH_3$), 7.77 (s, 1H, Ar-H), 6.90 (d, 1H, CH), 7.10 (d, 1H, CH), 7.1-7.7 (m, 4H, CH); MS: *m/z* 425.4 ($M^+$ +1).

***(E)*-1-(2,4-Dichlorophenyl)-3-(2,4-dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)prop-2-en-1-one, 7d**: Yield: 70%; m.p. 128°C. Anal. Calcd for $C_{22}H_{20}Cl_4N_4O_4$: C, 55.59; H, 4.24; N, 11.79. Found: C, 55.57; H, 4.28; N, 11.75%; IR (KBr): 3015 (C-H str. In aromatic ring), 1596 (C=N str., pyrimidine ring), 1509

(C=C str., aromatic), 1652 (CH=CH-C=O str. In chalcone), 1145 (-C-O-C str. In morpholine ring), 1365 (-C-N str. In morpholine ring), 693 (C-Cl str.), 1168 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.26 (t, 4H, $CH_2$ morpholine), 2.27 (t, 4H, $CH_2$ morpholine), 2.77 (s, 3H, -$OCH_3$), 2.84 (s, 3H, -$OCH_3$), 6.82 (s, 1H, Ar-H), 7.53 (d, 1H, CH), 7.77 (d, 1H, CH), 7.1-7.4 (m, 3H, CH); MS: *m/z* 476.4 ($M^+$ +1).

***(E)*-3-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-1-(2-nitrophenyl)prop-2-en-1-one, 7e**: Yield: 78%; m.p. 145°C. Anal. Calcd for $C_{22}H_{21}N_5O_6$: C, 58.53; H, 4.69; N, 15.51. Found: C, 58.56; H, 4.66; N, 15.55%; IR (KBr): 3091 (C-H str. In aromatic ring), 1592 (C=N str., pyrimidine ring), 1507 (C=C str., aromatic), 1652 (CH=CH-C=O str. In chalcone), 1145 (-C-O-C str. In morpholine ring), 1388 (-C-N str. In morpholine ring), 1352 (-N=O str. In nitro group), 1167 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.40 (t, 4H, $CH_2$ morpholine), 2.45 (t, 4H, $CH_2$ morpholine), 3.82 (s, 3H, -$OCH_3$), 3.96 (s, 3H, -$OCH_3$), 7.75 (s, 1H, Ar-H), 6.91 (d, 1H, CH), 7.12 (d, 1H, CH), 7.1-7.5 (m, 4H, CH); MS: *m/z* 452.4 ($M^+$ +1).

**4-(2,4-Dimethoxy-6-(5-phenylisoxazol-3-yl)pyrido[2,3-*d*]pyrimidin-7-yl)morpholine, 8a**: Yield:75%; m.p. 145°C. Anal. Calcd for $C_{22}H_{21}N_5O_4$: C, 63.00; H, 5.05; N, 16.70. Found: C, 63.04; H, 5.02; N, 16.37%; IR (KBr): 3098 (C-H str.In aromatic ring), 1538 (C=N str., pyrimidine ring), 1488 (C=C str., aromatic), 1624 (-C=N str. In isoxazolemoiety), 1178 (-C-O-C str. In morpholine ring), 1377 (-C-N str. In morpholine ring), 1154 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.55 (t, 4H, $CH_2$ morpholine), 2.69 (t, 4H, $CH_2$ morpholine), 3.78 (s, 3H, -$OCH_3$), 3.89 (s, 3H, -$OCH_3$), 6.69 (s, 1H, Ar-H), 6.00 (s, 1H, Ar-H), 7.05-7.56 (m, 5H, Ar-H); MS: *m/z* 420.3 ($M^+$ +1).

**2-(3-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)isoxazol-5-yl)phenol, 8b**: Yield:68 %; m.p. 140°C. Anal. Calcd for $C_{22}H_{21}N_5O_5$: C, 60.68; H, 4.86; N, 16.08. Found: C, 60.65; H, 4.83; N, 16.05%; IR (KBr): 3095 (C-H str. In aromatic ring), 1537 (C=N str., pyrimidine ring), 1489 (C=C str., aromatic), 1623 (-C=N str. In isoxazolemoiety), 1174 (-C-O-C str. In morpholine ring), 1375 (-C-N str. In morpholine ring), 3205 (-C-OH str.), 1154 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.58 (t, 4H, $CH_2$ morpholine), 2.67 (t, 4H, $CH_2$ morpholine), 3.77 (s, 3H, -$OCH_3$), 3.87 (s, 3H, -$OCH_3$), 6.69 (s, 1H, Ar-H), 6.03 (s, 1H, Ar-H), 5.48 (s, 1H, -OH), 7.02-7.53 (m, 4H, Ar-H); MS: *m/z* 436.5 ($M^+$ +1).

**4-(6-(5-(4-Fluorophenyl)isoxazol-3-yl)-2,4-dimethoxypyrido[2,3-*d*]pyrimidin-7-yl)morpholine, 8c**: Yield: 68%; m.p. 159°C. Anal. Calcd for $C_{22}H_{20}N_5FO_4$: C, 60.41; H, 4.61; N, 16.01. Found: C, 60.44; H, 4.64; N, 16.04%; IR (KBr): 3097 (C-H str. In aromatic ring), 1536 (C=N str., pyrimidine ring), 1486 (C=C str., aromatic), 1622 (-C=N str. In isoxazolemoiety), 1176 (-C-O-C str. In morpholine ring), 1376 (-C-N str. In morpholine ring), 968 (-C-F str.), 1152 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.52 (t, 4H, $CH_2$ morpholine), 2.66 (t, 4H, $CH_2$ morpholine), 3.74 (s, 3H, -$OCH_3$), 3.87 (s, 3H, -$OCH_3$), 6.65 (s, 1H, Ar-H), 6.03 (s, 1H, Ar-H), 7.01-7.50 (m, 4H, Ar-H); MS: *m/z* 438.3 ($M^+$ +1).

**4-(6-(5-(2,4-Dichlorophenyl)isoxazol-3-yl)-2,4-dimethoxypyrido[2,3-*d*]pyrimidin-7-yl)morpholine, 8d**: Yield: 74%; m.p. 109°C. Anal. Calcd for $C_{22}H_{19}Cl_2N_5O_4$: C, 54.11; H, 3.92; N, 14.34. Found: C, 54.15; H, 3.86; N, 14.37%; IR (KBr): 3094 (C-H str. In aromatic ring), 1539 (C=N str., pyrimidine ring), 1486 (C=C str., aromatic), 1622 (-C=N str. In isoxazolemoiety), 1178 (-C-O-C str. In morpholine ring), 1372 (-C-N str. In morpholine ring), 689 (-C-Cl str.), 1150 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.19 (t, 4H, $CH_2$ morpholine), 2.24 (t, 4H, $CH_2$ morpholine), 2.57 (s, 3H, -$OCH_3$), 2.62 (s, 3H, -$OCH_3$), 6.26 (s, 1H, Ar-H), 6.09 (s, 1H, Ar-H), 7.10-7.42 (m, 3H, Ar-H); MS: *m/z* 489.4 ($M^+$ +1).

**4-(2,4-Dimethoxy-6-(5-(3-nitrophenyl)isoxazol-3-yl)pyrido[2,3-*d*]pyrimidin-7-yl)morpholine, 8e**: Yield: 71%; m.p.169°C. Anal. Calcd for $C_{22}H_{20}N_6O_6Br$: C, 56.89; H, 4.34; N, 18.10. Found: C, 56.86; H, 4.37; N, 18.13%; IR (KBr): 3098 (C-H str. In aromatic ring), 1535 (C=N str., pyrimidine ring), 1488 (C=C str., aromatic), 1625 (-C=N str. In isoxazolemoiety), 1172 (-C-O-C str. In morpholine ring), 1373 (-C-N str. In morpholine ring), 1342 (N=O str. In nitro group), 1150 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.51 (t, 4H, $CH_2$ morpholine), 2.67 (t, 4H, $CH_2$ morpholine), 3.76 (s, 3H, -$OCH_3$), 3.88 (s, 3H, -$OCH_3$), 6.60 (s, 1H, Ar-H), 6.05 (s, 1H, Ar-H), 7.03-7.52 (m, 4H, Ar-H); MS: *m/z* 465.3 ($M^+$ +1).

**4-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-6-phenylpyrimidin-2-ol, 9a**: Yield:77%; m.p.148°C. Anal. Calcd for $C_{23}H_{22}N_6O_4$: C, 61.87; H, 4.97; N, 18.82. Found: C, 61.84; H, 4.93; N, 18.85%; IR (KBr): 3011 (C-H str. In aromatic ring), 1608 (C=N str., pyrimidine ring), 1468 (C=C str., aromatic), 3206 (-C-OH str.), 1175 (-C-O-C str. In morpholine ring), 1358 (-C-N str. In morpholine ring), 1119 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.63 (t, 4H, $CH_2$ morpholine), 2.88 (t, 4H, $CH_2$ morpholine), 3.23 (s, 3H, -$OCH_3$), 3.37 (s, 3H, -$OCH_3$), 6.13 (s, 1H, CH), 5.80 (s, 1H, OH), 6.47 (s, 1H, CH), 7.12-7.62 (m, 5H, Ar-H); MS: *m/z* 447.3 ($M^+$ +1).

**4-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-6-(2-hydroxyphenyl)pyrimidin-2-ol, 9b**: Yield: 70%; m.p.141°C. Anal. Calcd for $C_{23}H_{22}N_6O_5$: C, 59.73; H, 4.79; N, 18.17. Found: C, 59.76; H, 4.76; N, 18.14%; IR (KBr): 3002 (C-H str. In aromatic ring), 1606 (C=N str., pyrimidine ring), 1464 (C=C str., aromatic), 3200 (-C-OH str.), 1170 (-C-O-C str. In morpholine ring), 1353 (-C-N str. In morpholine ring), 1389 (N=O str. In nitro group), 1117 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.60 (t, 4H, $CH_2$ morpholine), 2.86 (t, 4H, $CH_2$ morpholine), 3.24 (s, 3H, -$OCH_3$), 3.39 (s, 3H, -$OCH_3$), 6.10 (s, 1H, CH), 5.44 (s,1H, OH), 5.87 (s, 1H, OH), 6.46 (s, 1H, CH), 7.15-7.67 (m, 4H, Ar-H); MS: *m/z* 463.4 ($M^+$ +1).

**4-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-6-(4-fluorophenyl)pyrimidin-2-ol, 9c**: Yield: 68%;m.p.160°C. Anal. Calcd for $C_{23}H_{21}N_6FO_4$: C, 59.48; H, 4.56; N, 18.09. Found: C, 59.44; H, 4.53; N, 18.06%; IR (KBr): 3002 (C-H str. In aromatic ring), 1606 (C=N str., pyrimidine ring), 1464 (C=C str., aromatic), 3200 (-C-OH str.), 1170 (-C-O-C str. In morpholine ring), 1353 (-C-N str. In morpholine ring), 1389 (N=O str. In nitro group), 1117 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.63 (t, 4H, $CH_2$ morpholine), 2.88 (t, 4H, $CH_2$ morpholine), 3.25 (s, 3H, -$OCH_3$), 3.35 (s, 3H, -$OCH_3$), 6.16 (s, 1H, CH), 5.84 (s, 1H, OH), 6.43 (s, 1H, CH), 7.10-7.51 (m, 4H, Ar-H); MS: *m/z* 565.3 ($M^+$ +1).

**4-(2,4-Dichlorophenyl)-6-(2,4-dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)pyrimidin-2-ol, 9d**: Yield: 69%; m.p. 169°C. Anal. Calcd for $C_{23}H_{20}Cl_2N_6O_4$: C, 53.60; H, 3.91; N, 16.31. Found: C, 53.63; H, 3.94; N, 16.34%; IR (KBr): 3002 (C-H str. In aromatic ring), 1606 (C=N str., pyrimidine ring), 1464 (C=C str., aromatic), 3200 (-C-OH str.), 1170 (-C-O-C str. In morpholine ring), 1353 (-C-N str. In morpholine ring), 1389 (N=O str. In nitro group), 1117 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.62 (t, 4H, $CH_2$ morpholine), 2.86 (t, 4H, $CH_2$ morpholine), 3.21 (s, 3H, -$OCH_3$), 3.38 (s, 3H, -$OCH_3$), 6.11 (s, 1H, CH), 5.83 (s, 1H, OH), 6.40 (s, 1H, CH), 7.02-7.42 (m, 3H, Ar-H); MS: *m/z* 516.4 ($M^+$ +1).

**4-(2,4-Dimethoxy-7-morpholinopyrido[2,3-*d*]pyrimidin-6-yl)-6-(3-nitrophenyl)pyrimidin-2-ol, 9e**: Yield: 79%; m.p. 181°C. Anal. Calcd for $C_{23}H_{21}N_7O_6$: C, 56.21; H, 4.31; N, 19.95. Found: C, 56.24; H, 4.34; N, 19.92%; IR (KBr): 3002 (C-H str. In aromatic ring), 1606 (C=N str., pyrimidine ring), 1464 (C=C str., aromatic), 3200 (-C-OH str.), 1170 (-C-O-C str. In morpholine ring), 1353 (-C-N str. In morpholine ring), 1389 (N=O str. In nitro group), 1117 $cm^{-1}$ (C-O-C str. In alkanyl ether); $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.80 (t, 4H, $CH_2$ morpholine), 2.90 (t, 4H, $CH_2$ morpholine), 3.37 (s, 3H, -$OCH_3$), 3.39 (s, 3H, -$OCH_3$), 6.58 (s, 1H, CH), 5.52 (s, 1H, OH), 7.26 (s, 1H, CH), 7.61-8.12 (m, 4H, Ar-H); MS: *m/z* 492.4 ($M^+$ +1).

## Conclusion

In conclusion, new isoxazole and hydroxypyrimidine **8a-e** and **9a-e** prepared in efficient reactions starting from 4-amino-2,6-dimethoxypyrimidine by following the existing synthetic routes. Both **8a-e** and **9a-e** form solvates when recrystallized from absolute alcohol. The developed synthetic routes greatly facilitate the exploration of compounds from **8a-e** and **9a-e** and expected to find useful applications in pharmaceuticals and functional materials.

## Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/58776.

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