Synthesis a Number of Unimpeachable Pyrimidine Derivatives

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Abstract

An uncomplicated and efficient method for synthesis of 1,2,3,4-tetrahydropyrimidine derivatives was accomplished from N-(2,4-bis(trifluoromethyl)phenyl)-3-oxobutanamide, dissimilar aldehyde and urea using few drops of conc. HCl added and refluxed with ethanol with good yield and no auxiliary purification requirement for compound. The structures of the products were supported by FTIR, $^1$HMR and mass spectral data and microbiological activity completed of all compounds.

Keywords: N-(2,4-bis(trifluoromethyl)phenyl)-3-oxobutanamide; HCl, urea only refluxed.

INTRODUCTION

Recently, synthesis of tetrahydropyrimidine and their derivatives is of high interest in organic chemistry. The pyrimidine fragment is present in various biologically active compounds, many of which have been found use in medical practice1,2. Thus, recently, much attention has been paid to derivatives of pyrimidine, including their hydrogenation products.

Molecular docking of tetrahydropyrimidine derivatives have been studied by Sun et al.1. Ghorai and co-workers have reported a convenient synthetic route to 2-aryl-
Ntosylazetidines and their ZnX$_2$ mediated regioselective nucleophilic ring opening reactions for the synthesis of tetrahydropyrimidine$^2$. Baltork and co-workers$^3$ have synthesized chemo selective tetrahydropyrimidines using nano as reusable solid acid catalyst under microwave irradiation. Zhao et al. were synthesized fluoroalkylated multifunctional 1,2,3,4-tetrahydropyrimidines for the first time by the reaction of 3-fluoroalkyl-3-anilinoacrylic acid esters with primary amines and formaldehyde under mild conditions$^4$. Muravyova et al. have carried out multicomponent reactions with ultrasonic activation used as key methods for the synthesis of tetrahydropyrimidine derivatives$^5$. And few Fluoro Containing Pyrimidine Derivatives$^6$ synthesis 4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-iso-propyl-N-phenyl)-2-thithioxopyrimidine-5-carboxamide and this pyrimidine derivatives$^7-11$.

Literature survey shows that lots of work has been done for tetrahydropyrimidines. Many researchers have been synthesized tetrahydropyrimidines using different methods$^{12-14}$. Recently, one-pot multicomponent reactions have emerged as a powerful tool in synthetic organic chemistry because of their significant advantages$^{15-18}$. Polyethylene glycol-mediated facile one-pot synthesis of polysubstituted tetrahydropyrimidines under mild and green reaction conditions have been developed by Kidwai et al.$^{19}$. Iodine catalyst one pot synthesis of tetrahydro pyrimidine derivatives have been reported by Veerababurao et al.$^{20}$.

We have developed a new modesty for the synthesis N-(2,4-bis(trifluoromethyl)phenyl)-4-(4-substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4a-h) with the advantage of fine yield and environmentally easiness (Scheme-a).

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{HN} \quad \text{O} \\
\text{H}_2\text{N} & \quad \text{O} \\
\text{CHO} & \\
\text{R} & \\
\text{O} & \\
\end{align*}
\]

**Scheme a**

**METHOD**

To the mixture of N-(2,4-bis(trifluoromethyl)phenyl)-3-oxobutanamide, Different Aromatic aldehyde and urea in ethanol was added few drops of Conc. HCl with stirring for 17 hrs.. After 24 hrs reaction mass pour in water, Insoluble solid was generated, it is pyrimidine derivatives. Then filter and crystallization by ethanol.
RESULTS & DISCUSSION

N-(2,4-bis(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxamide (4a)

Yield: 65%; mp 175°C; Anal. Calcd. for C20H15F6N3O2: C, 54.18; H, 3.41; F, 25.71; N, 9.48; O, 7.22; Found: C, 54.20; H, 3.40; F, 25.70; N, 9.50; O, 7.20%; IR (cm⁻¹): 3238 (N-H stretching of amide), 3105 (C-H stretching of aromatic ring), 2974 (C-H asymmetrical stretching of CH3 group), 2877 (C-H symmetrical stretching of CH3 group), 1637 (C=O stretching of amide), 1573, 1556 (C=O stretching of cyclic) 1508 (N-H deformation of pyrimidine ring), 1454 (C-H asymmetrical deformation of CH3 group), 1394 (C-H symmetrical deformation of CH3 group), 1294 (C-N-C stretching vibration of pyrimidine ring), 1084 (C-F stretching), 827 (para-substituted), 734 (C-H in out plane deformation of aromatic ring); ¹H NMR (DMSO-d6) δ ppm: 2.02 (s, 3H, H), 5.53 (s, 1H, H), 6.96-6.99 (d, 1H, H), 7.10-7.17 (dd', 2H, H), 7.26-7.28 (dd', 2H, H), 7.49-7.54 (m, 1H, H), 7.67 (s, 1H, H), 8.20-8.23 (d, 1H, H), 8.83 (s, 1H, H), 9.70 (s, 1H, H); MS: m/z 443.

N-(2,4-bis(trifluoromethyl)phenyl)-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4b)

Yield: 60%; mp 179°C; Anal. Calcd. for C20H14ClF6N3O2: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.33; H, 2.90; Cl, 7.48; F, 23.80; N, 8.74; O, 6.75%; IR (cm⁻¹): 3266 (N-H stretching of amide), 3173 (C-H stretching of aromatic ring), 2966 (C-H asymmetrical stretching of CH3 group), 2883 (C-H symmetrical stretching of CH3 group), 1633(C=O stretching of amide), 1573 (C=O stretching of cyclic) 1550 (N-H deformation of pyrimidine ring), 1500 (C-H asymmetrical deformation of CH3 group), 1450 (C-H symmetrical deformation of CH3 group), 1297 (C-N-C stretching vibration of pyrimidine ring), 1087 (C-F stretching), 827 (para-substituted); MS: m/z 478.

N-(2,4-bis(trifluoromethyl)phenyl)-4-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4c)

Yield: 68%; mp 187°C; Anal. Calcd. for C20H14ClF6N3O2: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.34; H, 2.97; Cl, 7.40; F, 23.87; N, 8.70; O, 6.72%; IR (cm⁻¹): 3386 (N-H stretching of amide), 3163 (C-H stretching of aromatic ring), 2983 (C-H asymmetrical stretching of amide), 3163 (C-H stretching of aromatic ring), 2983 (C-H symmetrical stretching of CH3 group), 2877 (C-H symmetrical stretching of CH3 group), 1637 (C=O stretching of amide), 1541(C=O stretching of cyclic) 1501 (N-H deformation of pyrimidine ring), 1497 (C-H asymmetrical deformation of CH3 group), 1451 (C-H symmetrical deformation of CH3 group), 1297
(C-N-C stretching vibration of pyrimidine ring), 1080 (C-F stretching), 824 (para-substituted); MS: m/z 478.

**N-(2,4-bis(trifluoromethyl)phenyl)-4-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4d)**

Yield: 64%; mp 184°C; Anal. Calcd. for C_{20}H_{14}ClF_6N_3O_2: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.36; H, 2.95; Cl, 7.42; F, 23.80; N, 8.75; O, 6.70%; IR (cm⁻¹): 3376 (N-H stretching of amide), 3167 (C-H stretching of aromatic ring), 2983 (C-H asymmetrical stretching of CH₃ group), 2873 (C-H symmetrical stretching of CH₃ group), 1677 (C=O stretching of amide), 1547 (C=O stretching of cyclic) 1503 (N-H deformation of pyrimidine ring), 1497 (C-H asymmetrical deformation of CH₃ group), 1457 (C-H symmetrical deformation of CH₃ group), 1293 (C-N-C stretching vibration of pyrimidine ring), 1100 (C-F stretching), 869 (C-Cl stretching), 837 (para-substituted); MS: m/z 478.

**N-(2,4-bis(trifluoromethyl)phenyl)-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4e)**

Yield: 59%; mp 181°C; Anal. Calcd. for C_{20}H_{14}F_7N_3O_2: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.36; H, 2.97; Cl, 7.40; F, 23.82; N, 8.70; O, 6.77%; IR (cm⁻¹): 3356 (N-H stretching of amide), 3165 (C-H stretching of aromatic ring), 2985 (C-H asymmetrical stretching of CH₃ group), 2872 (C-H symmetrical stretching of CH₃ group), 1677 (C=O stretching of amide), 1542 (C=O stretching of cyclic) 1505 (N-H deformation of pyrimidine ring), 1490 (C-H asymmetrical deformation of CH₃ group), 1457 (C-H symmetrical deformation of CH₃ group), 1290 (C-N-C stretching vibration of pyrimidine ring), 1083 (C-F stretching), 837 (para-substituted); MS: m/z 478.

**N-(2,4-bis(trifluoromethyl)phenyl)-4-(3-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (f)**

Yield: 68%; mp 188°C; Anal. Calcd. for C_{20}H_{14}F_7N_3O_2: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.43; H, 2.90; Cl, 7.42; F, 23.80; N, 8.73; O, 6.74%; IR (cm⁻¹): 3374 (N-H stretching of amide), 3145 (C-H stretching of aromatic ring), 2984 (C-H asymmetrical stretching of CH₃ group), 2874 (C-H symmetrical stretching of CH₃ group), 1647 (C=O stretching of amide), 1544 (C=O stretching of cyclic) 1500 (N-H deformation of pyrimidine ring), 1474 (C-H asymmetrical deformation of CH₃ group), 1454 (C-H symmetrical deformation of CH₃ group), 1284 (C-N-C stretching vibration of pyrimidine ring), 1074 (C-F stretching), 834 (para-substituted); MS: m/z 461.
**Synthesis a Number of Unimpeachable Pyrimidine Derivatives**

*N-(2,4-bis(trifluoromethyl)phenyl)-4-(2-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4g)*

Yield: 57%; mp 170°C; Anal. Calcd. for C_{20}H_{14}F_{7}N_{3}O_{2}: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.44; H, 2.91; Cl, 7.43; F, 23.85; N, 8.75; O, 6.66%; IR (cm^{-1}): 3366 (N-H stretching of amide), 3166 (C-H stretching of aromatic ring), 2988 (C-H asymmetrical stretching of CH_{3} group), 2874 (C-H symmetrical stretching of CH_{3} group), 1647 (C=O stretching of amide), 1544 (C=O stretching of cyclic) 1508 (N-H deformation of pyrimidine ring), 1474 (C-H asymmetrical deformation of CH_{3} group), 1458 (C-H symmetrical deformation of CH_{3} group), 1286 (C-N-C stretching vibration of pyrimidine ring), 1088 (C-F stretching), 837 (para-substituted); MS: m/z 461.

*N-(2,4-bis(trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine -5-carboxamide (4h)*

Yield: 59%; mp 178°C; Anal. Calcd. for C_{21}H_{17}F_{6}N_{3}O_{3}: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.45; H, 2.90; Cl, 7.49; F, 23.91; N, 8.70; O, 6.60%; IR (cm^{-1}): 3363 (N-H stretching of amide), 3154 (C-H stretching of aromatic ring), 2966 (C-H asymmetrical stretching of CH_{3} group), 2874 (C-H symmetrical stretching of CH_{3} group), 1666 (C=O stretching of amide), 1534 (C=O stretching of cyclic) 1557 (N-H deformation of pyrimidine ring), 1513 (C=C stretching of aromatic ring), 1475 (C-H asymmetrical deformation of CH_{3} group), 1406 (C-H symmetrical deformation of CH_{3} group), 1344 (C-NO2 symmetrical deformation of NO2 group), 1311 (C-N-C stretching vibration of pyrimidine ring), 1241 (C-N stretching), 1153 (C-F stretching), 831 (para-substituted), 760 (C-H in out plane deformation of aromatic ring); MS: m/z 473.

**Antimicrobial evaluation**

Total of the Prepared compounds (4a-h) were experienced for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method \(^{17-19}\) with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 443, two Gram-negative bacteria *Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282, *Aspergillus clavatus* MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and gresofulvin as regular drugs.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, definted as the lowly concentration of the compound preventing the
observable growth, were determined by using micro dilution broth method according to NCCLS standards.

**Minimal Inhibition Concentration [MIC]:**

The main advantage of the ‘Broth Dilution Method’ for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

- Serial dilutions were prepared in primary and minor screening.
- The control tube containing no antibiotic is immediately subcultured by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37°C overnight.
- The MIC of the control organism is read to check the accuracy of the drug concentrations.
- The lowest concentration inhibiting growth of the organism is recorded as the MIC.
- The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.

**In vitro Antimicrobial Screening Results for (4a-h)**

<table>
<thead>
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<th>Code</th>
<th>Minimal inhibition concentration (µg mL⁻¹)</th>
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<tr>
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<td>Gram-positive</td>
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<tr>
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</table>
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Anti bacterial activity with Grampositive bacteria

- **Staphylococcus aureus**
- **Streptococcus pyogenes**

Anti bacterial activity with Grampositive bacteria

- **Escherichia coli**
- **Pseudomonas aeruginosa**

Anti bacterial activity with Grampositive bacteria

- **Candida albicans**
- **Aspergillus Niger**
- **Aspergillus clavatus**
CONCLUSION

In height, we include synthesized of novel 1,2,3,4-tetrahydropyrimidine derivatives using easy and proper method. This method produces these products in unparalleled yields and difficulty-free workup. Product is isolated by unproblematic filtration. The isolated products are very pure and do not need any column purification. This study opens up a new area of useful synthesis of potentially biologically active novel pyrimidine derivatives compounds.

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