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Data Article

Trimethylsilyl chloride catalyzed synthesis of fluoro substituted tetrahydropyrimidines: Molecular docking and antidiabetic studies

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ABSTRACT

A novel series of tetrahydropyrimidine derivatives containing azepino indole and aryl substitution was achieved by a multicomponent synthetic approach using Biginelli condensation. Various catalysts were employed in the reactions for yield increment but trimethylsilyl chloride gave the highest yield. Moreover, all synthesized molecules were checked for in vitro antidiabetic potential. In addition, molecular docking of these synthesized molecules was studied using barley alpha-amylase isozyme 1 (amy1) (1RPK). The result revealed that compounds **4a** and **4c** have a good inhibitory potential.

1. Rationale

Nitrogen-containing compounds have huge consideration in the field of medicinal chemistry and organic synthesis. The most investigated moiety containing nitrogen is pyrimidine analogous. Pyrimidine is the six-membered heterocyclic compound containing nitrogen atoms at 1st and 3rd positions. The word pyrimidine was first applied by Pinner from the combination of amidine and pyridine. Pyrimidines correspond to many kinds of compounds such as natural products (Variolin B, Meridianins), pharmacologically important molecules (Rosuvastatin), drugs (Imatinib, Dasatinib, Sulfadiazine), photophysical materials, and supramolecules [1–3] (Fig. 1). Pyrimidines have received a lot of interest for biological responses including antidiabetic [4,5], antibacterial [6,7], antiviral [8], anti-inflammatory [9], antiproliferative, and tumor [10,11]. Some pyrimidine analogues were identified as potent agents for the treatment of neurological disorders [12–14] and metabolic abnormalities [15].

Traditionally, pyrimidine structures are formed by the condensation of the 1,3-dicarbonyl compound with amidines, α, β-unsaturated ketones, or allylic and aryl compounds [16–18]. In the current scenario, many attempts have been done successfully toward the synthesis of pyrimidines from more readily available nitrogen sources, under mild reaction conditions, and more facile operational procedures including the multicomponent reaction approach [19–25]. Some of the marketed drugs contain pyrimidine core showed in Fig. 1. These encouraged us to discover newly factionalized tetrahydropyrimidine derivatives and evaluated them for their biological potency. We have been making continuous efforts to establish a new efficient protocol for the synthesis of bioactive entities [26–30].

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2. Procedure

2.1. Experimental

All chemicals, solvents, and media were purchased from Sigma Aldrich, Himedia, and another supplier. All purchased chemicals were used without further purification, reactions were continuously monitored by thin-layer chromatography (TLC) on silica gel-(G60 F254 (Merck)) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365 nm), or with iodine vapor or aq. $KMnO_4$. Melting points were determined using a Buchi B-540 capillary apparatus. NMR spectra were recorded on a Bruker Advance 400 MHz spectrometer (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) respectively in solvent DMSO-d_6 and chemical shifts are referenced to the solvent residual signals concerning tetramethylsilane. standard abbreviations are used to represent signal multiplicities for ^{1}H NMR spectrum s - singlet, d - doublet, t - triplet, q - quartet, m - multiplate. Elemental analysis was carried out on Euro EA 3000 elemental analyzer. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in EI (70eV) model using direct inlet probe technique and m/z is reported in atomic units per elementary charge.

2.1.1. General procedure for the synthesis of pyrimidines containing substituted azepino indole (4a-c)

To a stir solution of 4-(8-fluoro-1-oxo-2, 3, 4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-5-yl)benzaldehyde (100 mmol) and DMF (20 mL) at RT was added urea derivatives **(2a-c)** (300mmol), ethyl acetoacetate (250 mmol), trimethyl silyl chloride (400 mmol) was stir for 12 hours. Progress of the reaction was monitored by TLC. After completion of the reaction pour the reaction mass into the water. Solid precipitated out was filtered and washed with water. Dry the solid under vacuum at 60 °C to get compound **(4a-c)**.

2.1.2. General procedure for the synthesis of pyrimidines containing substituted aryl halide (4d-j)

To a stir solution of aryl halide compounds **1a-d** (100 mmol) in DMF (15 mL) was added urea derivatives **(2a-c)** (300 mmol), ethyl acetoacetate or methyl acetoacetate (250 mmol), trimethyl silyl chloride (400 mmol) was refluxed for 10 hours. Progress of the reaction was monitored by TLC. After completion of the reaction cool the reaction mass for RT and precipitate solid was filtered out and washed with ethanol. Dry the solid under vacuum at 50 °C to get the compound **(4d-j)**.

2.1.2.1. Synthesized adducts

2.2. α-amylase inhibitory assay

In vitro antidiabetic activity of synthesized compounds (**4a-j**) has been screened against alpha-amylase (from Malt EC No. 232-588-1), using acarbose as a standard reference drug. The α-Amylase inhibition assay was performed using the 3,5-dinitrosalicylic acid (DNSA) method [31–33]. All the compounds were dissolved in 10% DMSO and were further dissolved in buffer at pH 6.9 to give concentrations ranging from 50-125 μg/mL. A volume of 200 μL of α-amylase solution (2 units/mL) was mixed with 200 μL of the dissolved compounds and was incubated for 10 minutes at 30°C. There 200 μL of starch solution (1% in water (w/v)) was added to each

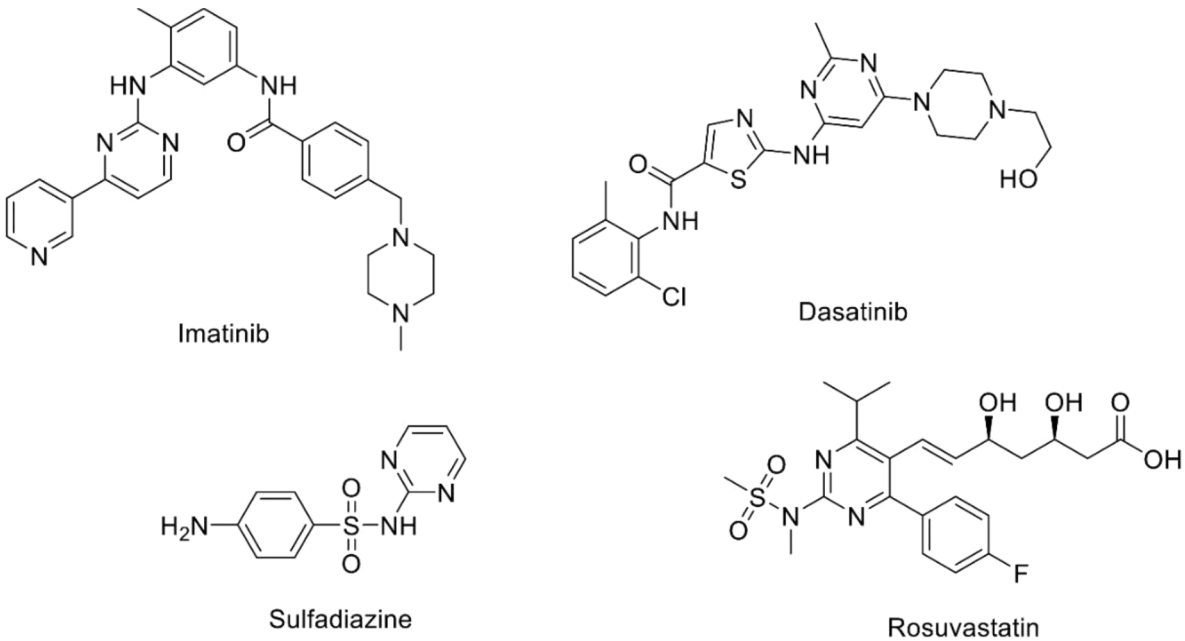


Fig. 1. Some marketed drug-containing pyrimidine moiety.

tube and incubated for 3 minutes. The reaction was terminated by the addition of 200 μL DNSA reagent (12g of sodium potassium tartrate tetrahydrate in 8.0 mL of 2 M NaOH and 20 mL of 96 mM of 3,5-dinitrosalicylic acid solution) and was boiled for 10 minutes in a water bath at 85-90°C. The mixture was cooled to ambient temperature and was diluted with 5 mL of distilled water, and the absorbance was measured at 540 nm using a UV-Visible spectrometer. The blank with 100% enzyme activity was prepared by replacing the dissolved compounds with 200 μL of a buffer. A blank reaction was similarly prepared using the dissolved compounds at each concentration in the absence of enzyme solution. A positive control was prepared using acarbose (100 μg/mL–50 μg/mL) and the reaction was performed similarly to the reaction with dissolved compounds as mentioned above. The α-amylase inhibitory activity was expressed as percent inhibition and was calculated using the equation given below. Triplicates have done for each sample.

2.3. Molecular Docking

All the synthesized compounds were screened against the crystal structure of barley alpha-amylase isozyme 1 (amy1) in complex with acarbose by AutoDock vina. The protein (PDB ID: 1RPK) was retrieved from RCS Protein Data Bank (http://www.rcsb.org). All the molecules sketched using ChemDraw ultra-14.0, molecules in CDX format have been converted to MOL format using ChemBio3D ultra-14.0. All MOL files are converted into pdb format using open babel. Molecules in pdb format projected to AutoDock vina and selected as ligand molecules and save as pdbqt format. Protein preparation was done by the AutoDock Vina, deleted water molecules, add polar hydrogen and at the end addition of Kollman charge and saved as pdbqt format. The docking between receptor and ligand was performed using a spacing of 0.4 Å between the grid points was used. The binding site box size was set to (11 × 12 × 17 Å) to encompass the entire active site. The selected residues of the receptor were defined to be a part of the binding site and ligand-protein interaction visualized by Biovia Discovery studio.

2.4. Spectral data

2.4.1. Ethyl 4-(4-(8-fluoro-1-oxo-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indol-5-yl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)

Yield 80%, mp 256 °C-258 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.65 (s, 1H, NH), 9.25 (s, 1H, NH), 8.24 (t, J=5.6 Hz, 1H, NH), 7.81 (s, 1H, NH), 7.60 (d, J=8 Hz, 2H, Ar), 7.44-7.31 (m, 4H, Ar), 5.22 (d, J=3.2 Hz, 1H, Chiral), 4.02 (q, J=14 Hz, 2H, OCH_2), 3.38 (m, 2H, CH_2), 3.03 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 1.14 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 168.83, 165.81, 160.04, 157.71, 152.61, 149.07, 144.75, 137.26, 135.62, 131.14, 128.46, 127.11, 126.37, 123.63, 112.34, 110.17, 109.91, 101.18, 100.93, 99.54, 59.76, 54.18, 42.33, 29.20, 18.32, 14.60. m/z: 485.23 (M+23). Elemental Analysis: $C_{25}H_{23}FN_4O_4$, calculated: C, 64.93; H, 5.01; N, 12.11; Found: C, 65.01; H, 5.02; N, 12.08.

2.4.2. Ethyl 4-(4-(8-fluoro-1-oxo-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indol-5-yl)phenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)

Yield 76.0%, mp 254 °C-256 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.62 (s, 1H, NH), 8.22 (s, 1H, NH), 8.02 (d, J=3.9 Hz, 1H, Ar), 7.60 (d, J=8.4 Hz, 2H, Ar), 7.47 (s, 1H, NH), 7.44-7.31 (m, 3H, Ar), 5.26 (d, J=3.6 Hz, 1H, Chiral), 4.06 (q, J=14.1 Hz, 2H, OCH_2), 3.39 (m, 2H, CH_2), 3.13 (s, 3H, CH_3), 3.05 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 1.15 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 168.49, 165.59, 160.02, 156.91, 153.11, 150.72, 143.52, 136.86, 135.08, 130.77, 128.03, 126.49, 125.90, 123.20, 111.91, 109.46, 102.34, 100.45, 59.61, 52.27, 41.90, 29.76, 28.74, 16.08, 14.07. m/z: 477.28, Elemental Analysis: $C_{26}H_{25}FN_4O_4$, calculated: C, 65.54; H, 5.29; N, 11.76; Found: C, 65.50; H, 5.24; N, 11.78.

2.4.3. Ethyl 4-(4-(8-fluoro-1-oxo-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indol-5-yl)phenyl)-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)

Yield 70.5%, mp 262 °C-264 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.62 (s, 1H, NH), 8.22 (t, J=5.7 Hz, 1H, NH), 7.61 (d, J=8.1 Hz, 2H, Ar), 7.47-7.31 (m, 4H, Ar), 5.28 (s, 1H, Chiral), 4.06 (q, J=12.1 Hz, 2H, OCH_2), 3.38 (m, 2H, CH_2), 3.20 (s, 3H, CH_3), 3.05 (m, 2H, CH_2), 2.82 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 1.17 (t, J=6.9 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 168.44, 165.22, 160.03, 156.92, 152.86, 149.94, 140.49, 136.87, 134.96, 131.19, 128.11, 126.96, 125.82, 123.17, 112.02, 109.81, 102.21, 100.78, 59.82, 41.88, 33.89, 30.55, 28.72, 16.08, 14.03. Mass m/z: 491.37 Elemental Analysis: $C_{27}H_{27}FN_4O_4$, calculated: C, 66.11; H, 5.55; N, 11.42; Found: C, 66.20; H, 5.51; N, 11.46.

2.4.4. Ethyl-4-(4-fluoro-3-isocyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)

Yield 87.0%, mp 198 °C-200 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.31 (s, 1H, NH), 7.80 (s, 1H, NH), 7.69 (m, 2H, Ar), 7.45 (t, J=9.0 Hz, 1H, Ar), 5.22 (d, J=3.0, 1H, Chiral), 3.95 (q, J=6.0 Hz, 2H, OCH_2), 2.26 (s, 3H, CH_3), 1.02 (t, J=6.3 Hz, 3H, CH_3), ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.28, 163.53, 160.15, 151.95, 149.68, 142.69, 134.33, 131.84, 117.13, 114.15, 100.21, 98.36, 59.61, 53.36, 18.06, 14.15. Mass m/z: 304.14, Elemental Analysis: $C_{15}H_{14}FN_3O_3$, calculated: C, 59.40; H, 4.65; N, 13.85; Found: C, 59.38; H, 4.63; N, 13.82.

2.4.5. Ethyl 4-(4-fluoro-3-isocyanophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e)

Yield 87.0%, mp 205 °C-208 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.99 (d, J=3.0 Hz, 1H, NH), 7.71-7.60 (m, 2H, Ar), 7.47 (t, J=9.0 Hz, 1H, Ar), 5.22 (d, J=3.0, 1H, Chiral), 4.05-3.98 (m, 2H, OCH_2), 3.11 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 1.09 (t, J=6.0 Hz, 3H, CH_3), ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.21, 163.32, 159.93, 152.45, 151.74, 141.78, 134.13, 131.44, 116.87, 113.90, 100.99, 99.87, 59.58,

51.66, 29.73, 16.07, 13.92. Mass m/z: 318.50, Elemental Analysis: $C_{16}H_{16}FN_3O_3$, calculated: C, 60.56; H, 5.08; N, 13.24; Found: C, 60.58; H, 5.10; N, 13.22.

2.4.6. 5-(5-(ethoxycarbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-2-fluorobenzoic acid (4f)

Yield 78.20%, mp: 208 °C-210 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.26 (s, 1H, COOH), 9.25 (d, J=1.2 Hz, 1H, NH), 7.77 (q, J=7.2 Hz, 2H, Ar) 7.49-7.46 (m, 1H, NH), 7.26 (q, J=10.5 Hz, 1H), 5.22 (d, J=3.0, 1H, Chiral), 3.97 (q, J=7.2 Hz, 2H, OCH_2), 2.26 (s, 3H, CH_3), 1.07 (t, J=7.2 Hz, 3H, CH_3), ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.30, 162.16, 158.76, 152.10, 148.86, 141.30, 132.70, 129.98, 119.25, 117.29, 99.12, 59.45, 53.50, 17.93, 14.07. Mass m/z: 323.12, Elemental Analysis: $C_{15}H_{15}FN_2O_5$, calculated: C, 55.90; H, 4.69; N, 8.69; Found: C, 55.95; H, 4.63; N, 8.68.

2.4.7. 5-(5-(ethoxycarbonyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-2-fluorobenzoic acid (4g)

Yield 75.2%, mp 220 °C-223 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.04 (s, 1H, COOH), 8.05 (d, J=3.0 Hz, 1H, NH), 7.78 (q, J=6.0 Hz, 1H, Ar), 7.47 (t, J=3.0 Hz, 1H, Ar), 7.26 (q, J=9.0 Hz, 1H, Ar), 5.24 (d, J=3.3 Hz, 1H, Chiral), 4.03 (q, J=6.0 Hz, 2H, OCH_2) 3.11 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 1.11 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.60, 162.25, 158.85, 153.05, 151.27, 140.55, 132.47, 129.98, 119.25, 117.49, 102.17, 59.85, 51.94, 29.92, 16.20, 14.10. Mass m/z: 337.18 Elemental Analysis: $C_{16}H_{17}FN_2O_5$, calculated: C, 57.14; H, 5.10; N, 8.33; Found: C, 57.15; H, 5.09; N, 8.36.

2.4.8. 5-(5-(ethoxycarbonyl)-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl)-2-fluorobenzoic acid (4h)

Yield 72.0%, mp 223 °C-225 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.03 (s, 1H, COOH), 7.76 (q, J=6.0 Hz, 1H, Ar), 7.46 (m, 1H, Ar), 7.26 (q, J=9.0 Hz, 1H, Ar), 5.29 (s, 1H, Chiral), 4.01 (t, J=9.0 Hz, 2H, OCH_2), 3.17 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 1.13 (t, J=6.0 Hz, 3H, CH_3), ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.06, 164.88, 162.29, 158.88, 152.69, 150.22, 137.16, 132.63, 130.29, 119.25, 117.57, 102.02, 59.70, 33.76, 30.56, 16.05, 13.91. Mass m/z: 351.14. Elemental Analysis: $C_{17}H_{19}FN_2O_5$, calculated: C, 58.28; H, 5.47; N, 8.00; Found: C, 58.31; H, 5.49; N, 8.04.

2.4.9. Ethyl-4-(3-(ethoxycarbonyl)-4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i)

Yield 78.3%, mp 188 °C-190 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.27 (d, J=1.2 Hz, 1H, NH), 7.78 (t, J=3.0 Hz, 2H, Ar), 7.51 (m, 1H, NH), 7.28 (q, J=12.0 Hz, 1H, Ar), 5.23 (d, J=3.0 Hz, 1H, Chiral), 4.31 (d, J=7.2 Hz, 2H, OCH_2), 3.98 (q, J=6.0 Hz, 2H, OCH_2), 2.26 (s, 3H, CH_3), 1.29 (t, J=6.0 Hz, 3H, CH_3), 1.09 (t, J=6.0 Hz, 3H, CH_3), ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.14, 163.55, 161.83, 158.43, 152.92, 148.88, 141.39, 132.88, 129.64, 118.20, 117.37, 98.88, 61.13, 59.32, 53.34, 17.77, 14.01, 13.95. Mass m/z: 351.20, Elemental Analysis: $C_{17}H_{19}FN_2O_5$, calculated: C, 58.28; H, 5.47; N, 8.00; Found: C, 58.26; H, 5.47; N, 7.98.

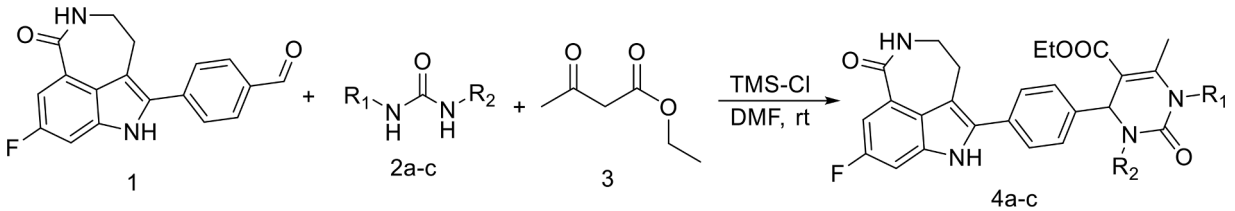
2.4.10. Ethyl-4-(4-fluoro-3-(methoxycarbonyl)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j)

Yield 68.2%, mp 180 °C-182 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.31 (s, 1H, NH), 7.79 (m, 2H, Ar), 7.52 (m, 1H, NH), 7.30 (q, J=12.0 Hz, 1H, Ar), 5.22 (d, J=3.0 Hz, 1H, Chiral), 3.96 (t, J=3.0 Hz, 2H, OCH_2), 3.83 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.07 (t, J=9.0 Hz, 3H, CH_3), ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.24, 164.14, 161.95, 158.53, 152.02, 149.03, 141.50, 133.20, 129.78, 117.95, 117.50, 98.89, 59.45, 53.40, 52.49, 17.91, 14.04. Mass m/z: 337.18, Elemental Analysis: $C_{16}H_{17}FN_2O_5$, calculated: C, 57.14; H, 5.10; N, 8.33; Found: C, 57.11; H, 5.15; N, 8.32.

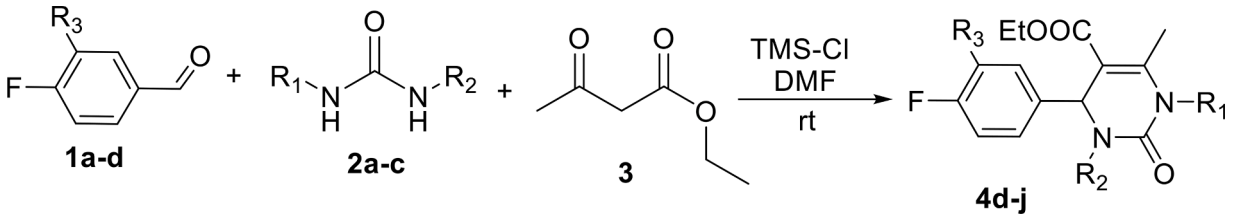
3. Data, value and validation

3.1. Chemistry

For the synthesis of targeted tetrahydropyrimidine derivatives (**4a-j**) was achieved by the Biginelli condensation reaction of aldehydes, 1,3-dicarbonyl compound, and substituted urea. This reaction was carried out in two schemes with the variation of aldehydes and substation of urea. Three derivatives outlined in scheme 1 which are synthesized using azepino indole-based aldehyde, ethyl acetoacetate, and substituted urea whereas compounds 4d-j were synthesized using a cyclo condensation reaction of substituted benzaldehyde (1a-d), ethyl acetoacetate (3), and substituted ammonia (2a-c) outlined in scheme 2. For the synthesis of compound 4a-j, optimized reaction conditions for 4a under various solvents such as polar protic and polar aprotic solvents. Using EtOH as solvent at reflux condition, the isolated yield was only 24% whereas using *p*-TSA as catalyst yield increment was observed up to 60%. By using TMS-Cl (10 mol%) catalyst, we found a good yield. Therefore, we increased the amount of catalyst (20 mol%) and observed yield up to



Scheme 1. Azepino indole-based tetrahydropyrimidine derivatives.



Scheme 2. Aryl halide substituted tetrahydropyrimidine derivatives.

80%. After this point, no yield increment was observed with an increased amount of catalyst. The final optimal condition was in DMF solvent at room temperature and using TMS-Cl (20 mol%) as a catalyst (Table 1).

3.2. α-amylase inhibition study

All synthesized molecules 4a-j were evaluated for in vitro antidiabetic assay by α-amylase inhibition strategy. The assay was performed on various concentrations such as 50 μg/mL, 75 μg/mL, and 100 μg/mL. We found that compound 4a had a good binding score in the molecular docking study and on performing an antidiabetic assay we got good results for the same molecule. From all synthesized compounds, 4a and 4c were found to be more active with inhibition of 39.18 ± 0.11, and 38.40 ± 0.22 respectively at a concentration of 50 μg/mL. All results of the assay were compared with the reference drug acarbose. Amongst all compounds, **4a** containing azepino and indole ring with urea-based pyrimidine ring showed good inhibition near the drug. The results of all compounds are outlined in Table 2.

3.3. Molecular Docking

All synthesized compounds were screened against 1RPK protein. The protein (PDB ID: 1RPK) was retrieved from RCS Protein Data Bank. The result of the docking study for active molecules into the active site of the enzyme displayed various interactions, especially conventional hydrogen bond, π-π stacked, carbon-hydrogen bond, and π-alkyl. Found active compounds (**4a, 4c**) were docked and all exhibited noticeable interaction with nucleotides. The virtual screening revealed that all the inhibitors (8a–j) except a few showed strong affinities with almost similar docking scores (Table 3). For synthesized molecule (**4a**), indole ring interacts with amino acids TYR-105 with π-π stacked and CYS-95, VAL-47 with π-alkyl, and TYR-131, ALA-96 with conventional hydrogen bond Molecule **4c**, indole ring containing fluorine atom interact with SER-48 and TYR-52 with conventional hydrogen bond halogen interaction respectively. The pyrimidine ring's nitrogen atom interacts with GLC amino acid with a carbon-hydrogen bond. Aryl ring showed interaction with DAF amino acid with π-alkyl interaction. Docked pose image for compounds 4a and 4c is illustrated in Figs. 2a and 2b. Therefore, the molecular docking study exhibited that many compounds have significant interactions within the active site residues of α-amylase receptor which might be the cause of remarkable α-amylase inhibition activity.

4. Conclusion

Azepino indole-based tetrahydropyrimidine derivatives have achieved good yields by employing trimethylsilyl chloride catalyst in the reaction. Results of biological activity revealed that the compound 4a exhibited good inhibition with 39.18 ± 0.11, 51.51 ± 0.90,

Table 1
Optimization of reaction condition for compound **4a**.

Entry	Catalyst (mol%)	Reaction Condition[a]	Time (h)	Yield (%)[b]
1	-	Ethanol, Reflux	24	24
2	-	Methanol, Reflux	24	trace
3	-	MeCN, Reflux	24	18
4	-	DMF, rt	24	trace
5	TMS-Cl (10%)	DMF, rt	12	75
6	**TMS-Cl (20%)**	**DMF, rt**	**12**	**80**
7	TMS-Cl (25%)	DMF, rt	12	79
8	Con. HCl (20%)	Ethanol, Reflux	15	58
9	Con. HCl (20%)	Methanol, Reflux	20	40
10	Con. HCl (20%)	MeCN, Reflux	18	52
11	*p*-TSA (10%)	MeCN, Reflux	12	40
12	*p*-TSA (10%)	Ethanol, Reflux	15	60

[a] 4-(8-fluoro-1-oxo-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-5-yl)benzaldehyde (1 mmol), Urea 1.5 mmol), Ethyl acetoactate (1.5 mmol) and solvents at different temperature
[b] Isolated yield
Bold value indicates final optimal condition

Table 2
α-amylase inhibition assay of compounds 4a-j.

Entry	Compound	Concentration 50 µg/mL	75 µg/mL	100 µg/mL
1	4a	39.18 ± 0.11	51.51 ± 0.90	67.34 ± 0.81
2	4b	34.59 ± 0.44	47.17 ± 0.35	61.81 ± 0.57
3	4c	38.40 ± 0.22	50.15 ± 0.47	65.57 ± 0.83
4	4d	23.29 ± 0.19	31.85 ± 0.43	45.89 ± 1.31
5	4e	24.21 ± 0.37	44.04 ± 0.28	47.57 ± 0.09
6	4f	30.15 ± 1.05	40.64 ± 0.39	55.04 ± 0.59
7	4g	31.19 ± 0.04	39.43 ± 0.26	55.10 ± 0.33
8	4h	25.68 ± 0.29	33.92 ± 0.89	48.02 ± 0.07
9	4i	32.11 ± 0.08	43.34 ± 0.41	57.08 ± 0.13
10	4j	29.89 ± 0.28	38.72 ± 0.80	53.66 ± 0.24
11	Acarbose	40.51 ± 0.29	53.16 ± 0.50	70.29 ± 0.18

Table 3
Docking score of screened compounds and Acarbose against 1RPK receptor.

Sr. No.	Compound	Docking score (ΔG kcal/mol)
1	4a	-7.5
2	4b	-7.1
3	4c	-7.5
4	4d	-5.9
5	4e	-6.1
6	4f	-6.4
7	4g	-6.4
8	4h	-6.1
9	4i	-6.3
10	4j	-6.2
11	Acarbose	-7.5

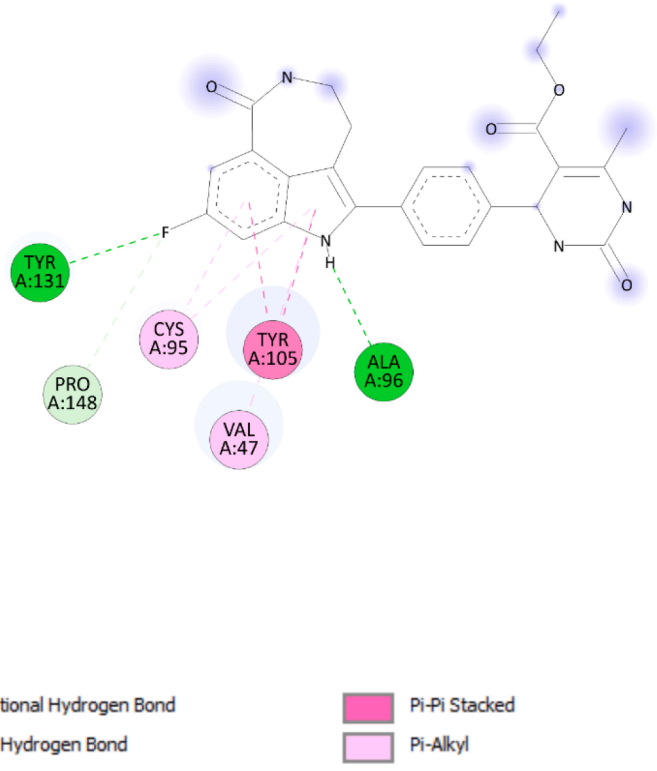


Fig. 2a. 2D representation of ligand (4a) and protein interaction visualized by Discovery studio.

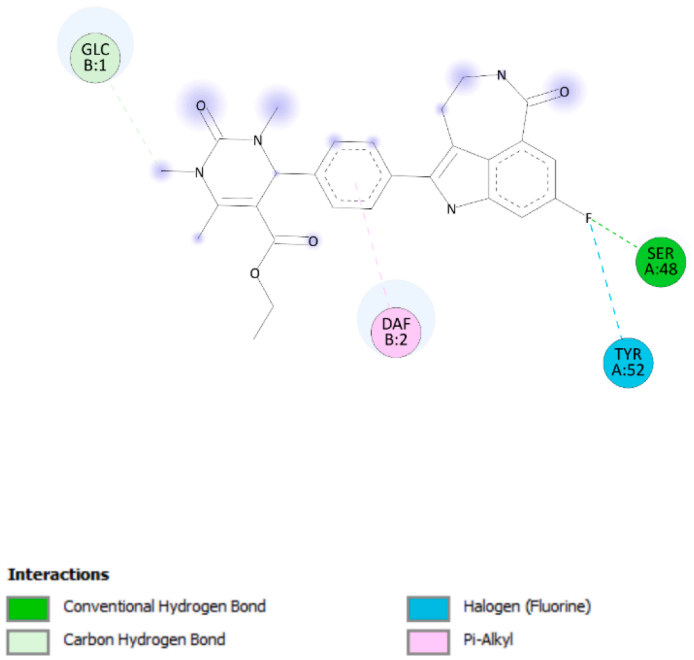


Fig. 2b. 2D representation of ligand (4c) and protein interaction visualized by Discovery studio.

67.34 ± 0.81 in 50, 75, 100 µg/mL concentration respectively. Molecular docking for those compounds was performed and possessed good binding affinity compared to others.

Specifications Table

Subject area	Organic Chemistry, Biochemistry, Spectroscopy, Computational Chemistry
Compounds	Fluoro substituted tetrahydropyrimidines
Data category	Spectral, synthesized
Data acquisition format	NMR, IR, Mass spectra, Elemental analysis
Data type	Analyzed
Procedure	Trimethylsilyl chloride catalyzed synthesis of tetrahydropyrimidine derivatives by condensation of aldehydes, substituted urea and active methylene
Data accessibility	Manuscript and supplementary data enclosed with this article

Declaration of competing interest

The authors report no conflict of interest.

Data availability

Supplementary data is openly available at figshare using this link, "https://doi.org/10.6084/m9.figshare.19707511".

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cdc.2022.100904.

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