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Design and Synthesis of Novel 2,5-substituted Pyrido[4,3-d] Pyrimidines: *In silico*, Anti-diabetic and Anti-inflammatory Studies

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ABSTRACT

Recently, there has been a growing interest in small drug molecules due to their ability to be easily customized with specific active sites of biomolecules. Sulfonyl-based compounds, in particular, have shown promise for various pharmacological applications and many of these drug molecules are now available in the commercial market. As a result, there is a significant increase in demand for small molecule compounds and their studies in pharmacological applications. In this context, we have presented a range of pyridopyrimidine derivatives functionalized with piperazine sulfonamides and various O-benzyl derivatives, characterized using various analytical tools. These compounds have demonstrated anti-diabetic and anti-inflammatory activities. The therapeutic activity of the compounds was also assessed through molecular docking studies, which supported the obtained results.

Keywords: Small molecules, Sulfonyl, Pyridopyridimines, Molecular docking, Anti-diabetic, Anti-inflammation.

INTRODUCTION

Small molecule drugs are artificially fashioned medicinal compounds that are designed to imitate, enhance, or reduce the effects of natural substances within the body.[1] Their structures are relatively simple and can be tailored to achieve specific therapeutic objectives.[2,3] Typically, they are stable and do not require special storage conditions. Their behaviour within the body is generally predictable, allowing for straightforward dosing methods, often in oral form, which patients find manageable.[4,5] These drugs can address a wide range of diseases due to their ability to navigate through the body, moving from the digestive system into the bloodstream and reaching their target sites by passing through cell membranes to access intracellular targets. They can be delivered in various forms, including pills, inhalers, suppositories, or injections, providing significant versatility.[6,7]

These small molecule drugs have proven to be more successful in the development of improved therapeutic medications, especially for conditions like diabetes and inflammation. These health ailments are critical as they contribute to various acute diseases, including cancer. Diabetes mellitus (DM) is a metabolic disorder characterized by different irregularities in insulin secretion, action, or both, leading to long-term damage and dysfunction in several organs.[8,9] There are three primary strategies for managing diabetes. The first focuses on inhibiting the excessive activity of the enzyme-amylase, while the second utilizes alternative sugar molecules with a low glycemic index.[10,11] The third strategy aims to enhance insulin secretion to ensure sufficient production of sugar molecules. Ongoing research is exploring the development of rare sugar molecules such as allulose and tagatose.[12-14] Nevertheless, the reduction of enzyme activity remains a crucial method for creating more effective drug molecules capable of managing diabetes effectively.

Heterocycles represent a highly significant and unique category of compounds, accounting for over fifty percent of all recognized organic compounds.[15-17] They exhibit a diverse array of physical, chemical, and biological characteristics, which include a wide range of reactivity and stability.[18,19] These compounds are abundantly found in nature and are essential to metabolic processes, as they are integral components of numerous natural products, including vitamins, hormones, antibiotics, alkaloids, pharmaceuticals, agrochemicals, dyes, and others.[20-24] Moreover, heterocyclic compounds are known for their enhanced solubility and ability to form salts, which improve oral absorption and bioavailability. In particular, heterocycles containing nitrogen and sulphur are foundational to many biologically active compounds and have a variety of applications across chemistry, biology, and other scientific disciplines.[25,26] Noteworthy examples include pyridopyrimidine and sulfonyl compounds, which are vital due to their extensive chemical, biological, agrochemical, and pharmacological properties.[27-30] Consequently, the application of these molecules has broadened across multiple research domains in chemistry, such as supramolecular chemistry, host-guest chemistry, light-emitting diodes, and coordination chemistry, among others.[31-33] In this study, we have developed a series of pyridopyridimine compounds containing piperazine sulfonamides and various O-benzyl derivatives as substituents. These compounds are expected to exhibit improved activity in diabetic and inflammation studies. Additionally, we conducted molecular docking studies for all synthesized compounds with enzyme 1-HNY, which is responsible for diabetes. The results showed that all compounds have a strong ability to bind with the enzyme at specific active sites, as indicated by the binding energy.

MATERIALS AND METHODS

All reactions were carried out with oven-dried glassware under inert conditions using LR grade reagents. The reactions were carried out with commercial solvents without degassing them prior to the reactions. All the synthesized compounds were characterized by IR, LCMS, ^{1}H-NMR, MR and ^{13}C-NMR analytical techniques. Melting points were measured with a Spectralab Check melt-1 apparatus and are uncorrected. Thin layer chromatography (TLC) was done using Silica Gel 60 F_{254} plates (0.25 mm thick), purchased from Merck. IR spectra were recorded using a Agilent Technologies Cary 630 FT-IR spectrometer. Mass spectra were obtained using Agilent Trap plus with an electrospray ionization (ESI) source and with Agilent Technologies 5975C mass spectrometer using HP-column (4.6 mm × 50 mm, 5µ) purchased from Agilent Technologies. UV spectrophotometer (Shimadzu Europa, UV–1601). ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d6, TFA using 300MHz and 400MHz Bruker NMR spectrometer with TMS as the internal standard. All the chemical shift values reported in the ^{1}H NMR spectra are in parts per million (ppm) on the δ scale from an internal standard of residual $CDCl_3$ (7.26 ppm) or the central peak of DMSO-d6 (2.50 ppm).

RESULTS AND DISCUSSION

Chemistry

Targeted molecules were created through the combination of two distinct synthetic pathways, successfully yielding two reactants (Compound **4** and **6**). The reactants utilized in the synthesis of pharmaceutical-active targeted molecules include pyridopyrimidines (4) and N-sulfonyl substituted piperazine compounds (**6**). The production of these reactants involved a series of multi-step reactions, as outlined below.

Synthesis of pyridopyrimidines (Compound 4a-4e)[34]

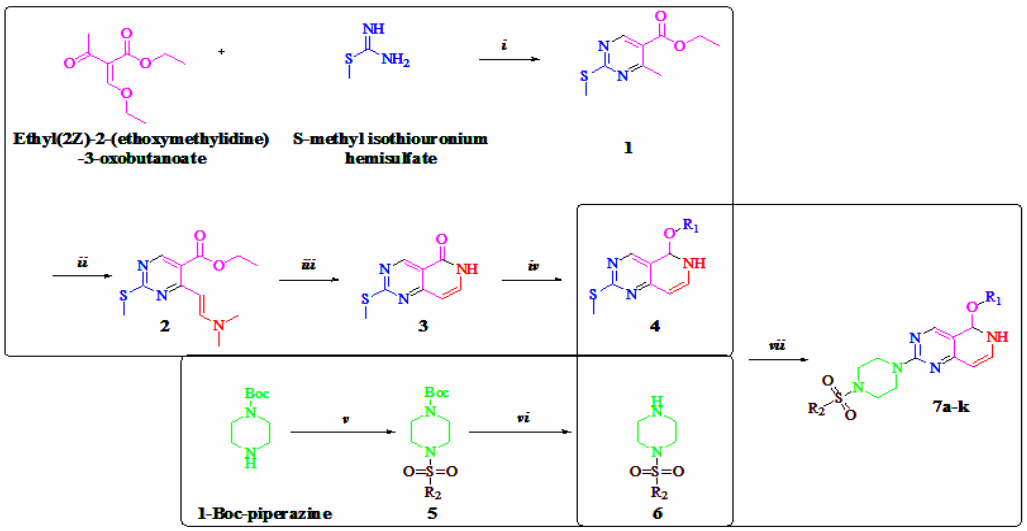
Ethyl(2Z)-2-(ethoxymethylidine)-3-oxo butanoate and S-methyl iso-thiouronium hemisulfate were combined in ethanol, followed by the addition of triethylamine. The resulting mixture was subjected to reflux for 15 h at 85°C, with the progress monitored via thin-layer chromatography. After the designated time, ice-water added, filtered and dried under reduced pressure, yielding compound **1**. This compound was then re-dissolved in DMF and refluxed at 100°C for another 15 h in the presence of DMF-DMA. The resulting product was diluted with water, filtered and dried at room temperature. This product 2 was then subjected to a subsequent reaction to synthesize pyridopyrimidine ring using ammonium acetate and ethanol as the solvent at 85°C. The cyclization occurred during this process, resulting in the formation of compound **3**. Additionally, alkyl-substituted pyridopyrimidines were synthesized from this compound. This straightforward substitution reaction was conducted with potassium carbonate as the base in DMF, along with the appropriate alkyl halides. The reaction was maintained at room temperature for 2 hours. After reaction completion, ice cold water was added, filtered and dried, yielding a pale brown to off white solid material intended for use as a reactant in the synthesis of the target molecule. This method successfully produced five different O-benzyl substituted pyridopyrimidines.

Synthesis of N-sulfonyl substituted piperazine derivatives (Compound 6a-6c)[35]

Boc-piperazine, along with aryl-substituted sulfonyl halide, was dissolved in DCM and stirred with triethylamine for 10 h at room temperature. The progress of the reaction was tracked using thin-layer chromatography. Following this period, the products were isolated through a solvent extraction method. The resulting solid product underwent a deprotection reaction, where compound **5** was re-dissolved in DCM, and trifluoroacetic acid was introduced as an acidic catalyst. This reaction was allowed to proceed for 2 h at room temperature, after which the final starting material (compound **6**) was extracted using DCM.

Synthesis of the targeted molecules (7a-7k)

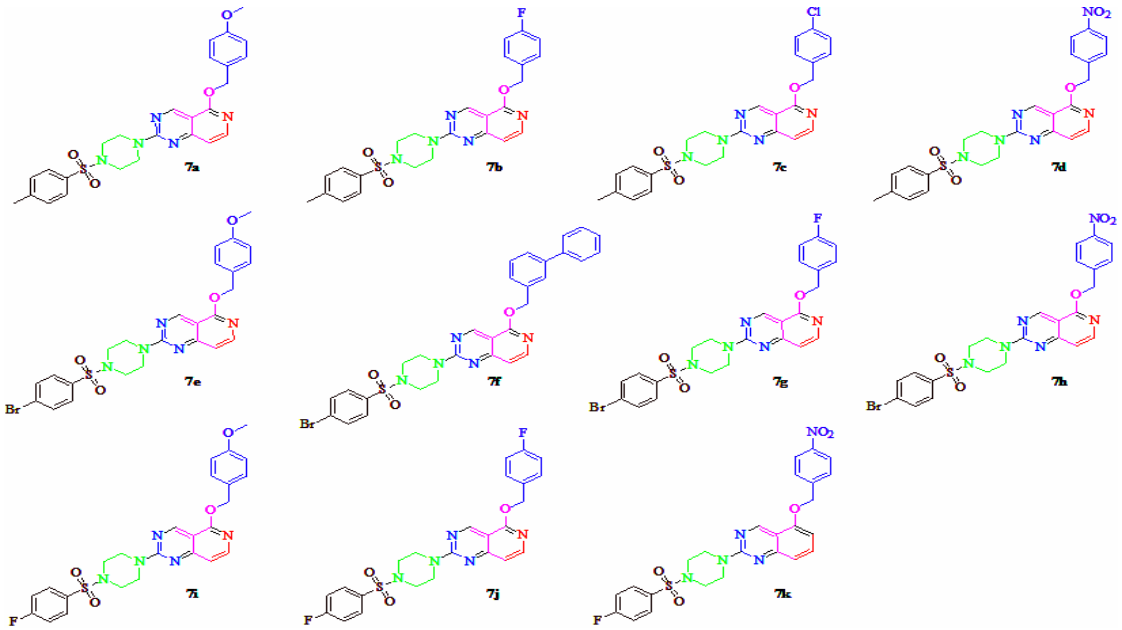
Compounds **4** and **6** were utilized for subsequent synthesis without undergoing any purification. Initially, compound **4** was treated with m-CPBA at 10-15°C in DMF solvent to get activated intermediate of compound **4** which was treated in situ with compound **6** and TEA at 10-15°C and the mixture was stirred for 2 to 5 hours at 25°C for the substitution process. Upon reaction completion which was monitored by TLC, ice cold water was added and solid was filtered, and the resulting series of compounds were synthesized and analysed using NMR (^{1}H and ^{13}C) and mass spectrometry techniques.



Reaction conditions:

i = TEA, Ethanol, 85 °C, 12-16 h; ***ii*** = DMF-DMA, DMF, 100 °C, 12-16 h; ***iii*** = Ammonium acetate, Ethanol, 85 °C, 12-16 h; ***iv***=Potassium carbonate, DMF, halide of R1, 25±5°C, 2h; ***v*** = TEA, DCM, R2 sulfonyl chloride, 25±5°C, 10h; ***vi*** = TFA, DCM, 25±5°C, 2h; ***vii*** = mCPBA, DMF, TEA, -20 to 25±5°C, 2-5 h

Scheme 1. Schematic representation of the chemical synthesis of biologically active targeted compounds (7a-k)



Scheme 2. Chemical structure of the series of all synthesized compounds

Analytical data for O-alkylated pyridopyrimidines (4a-4e)5-(4-Methoxy-benzyloxy)-2-methylsulfanyl-pyrido[4,3-d] pyrimidine (4a): Pale yellow solid; Yield: 86.4%; Melting point: 190.5-197.8°C; IR (KBr): 3026.6, 2946.5, 2846.5, 1664.3, 1615.8, 1571.1, 1354.9, 1254.2, 1176.0, 1030.6, 816.3; ^{1}H NMR: (400 MHz, DMSO-d6): δ ppm 9.23 (d, J = 0.4 Hz, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 6.92-6.89 (m, 2H), 6.55 (dd, J_1 = 7.6 Hz, J_2 = 0.4 Hz, 1H), 5.09 (s, 2H), 3.72 (bs, 3H), 2.55 (s, 3H); ESI (m/z): Calculated 313.08 and found 314.14 [M+1].

5-[(4-fluorophenyl)methoxy]-2-(methylsulfanyl)pyrido[4,3-d]pyrimidine (4b): Off-white solid; Yield: 73.7%; Melting point: 210.2-216.8°C; IR (KBr): 3071.3, 3024.7, 1936.4, 1660.5, 1615.8, 1567.3, 1354.9, 1224.4, 1161.1, 808.8; ^{1}H NMR: (400 MHz, DMSO-d6): δ ppm 9.23 (d, J = 0.4 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.43-7.39 (m, 2H), 7.21-7.16 (m, 2H), 6.57 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 5.15 (s, 2H), 2.58 (s, 3H); ESI (m/z): Calculated 301.07 and found 302.12 [M+1].

5-[(4-chlorophenyl)methoxy]-2-(methylsulfanyl)pyrido[4,3-d]pyrimidine (4c): Beige solid; Yield: 79.2%; Melting point: 179.5-187.7°C; IR (KBr): 3026.6, 2950.2, 1664.3, 1615.8, 1571.1, 1533.8, 1358.6, 1205.8, 911.3, 816.3, 762.2; ^{1}H NMR: (400 MHz, DMSO- d6): δ ppm 9.19 (d, J = 0.8 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.39-7.32 (m, 4H), 7.21-7.16 (m, 2H), 6.54 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 5.12 (s, 2H), 2.55 (s, 3H); ESI (m/z): Calculated 317.79 and found 320.04 [M+2].

2-(methylsulfanyl)-5-[(4-nitrophenyl) methoxy]pyrido[4,3-d]pyrimidine (4d): Off-white solid; Yield: 86.4%; Melting point: 220.1-226.4°C; IR (KBr): 3069.5, 3021.0, 1671.7, 1615.8, 1567.3, 1518.9, 1351.2, 1205.8, 1084.7, 816.3; ^{1}H NMR: (400 MHz, DMSO-d6): δ ppm 9.19 (s, 1H), 8.17 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 7.6 Hz, 1H), 5.28 (s, 2H), 2.55 (s, 3H); ESI (m/z): Calculated 328.06 and found 329.08 [M+1].

5-[([1,1'-biphenyl]-3-yl)methoxy]-2-(methylsulfanyl)pyrido[4,3-d]pyrimidine (4e): Pale brown solid; Yield: 76.5%; Melting point: 200.3-209.4°C; IR (KBr): 3084.4, 3024.7, 1664.3, 1615.8, 1567.3, 1533.8, 1358.6, 1205.8, 1084.7, 807.0; ^{1}H NMR: (400 MHz, DMSO-d6): δ ppm 9.24 (d, J = 0.4 Hz, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.68 (s, 1H), 7.64-7.58 (m, 3H), 7.49-7.42 (m, 3H), 7.39-7.32 (m, 2H), 6.58 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 5.24 (s, 2H), 2.67 (s, 3H); ESI (m/z): Calculated 359.11 and found 360.12 [M+1].

Analytical data for N-sulfonyl substituted piperazine derivatives (6a-6c)

1-(4-methylbenzene-1-sulfonyl) piperazine (6a): White solid; Yield: 65%;

Melting point: 203.5-208.4°C; IR (KBr): 3311.7, 2953.9, 2912.9, 2851.4, 1599.0, 1444.3, 1338.1, 1161.1,1095.8,732.4; ^{1}H NMR: (400MHz, DMSO-d6): δ ppm 7.56 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8 Hz, 2H), 2.71-2.67 (m, 8H), 2.37 (s, 3H); ESI (m/z): Calculated 240.09 and found 241.07 [M+1].

1-(4-bromobenzene-1-sulfonyl) piperazine (6b): Pale yellow solid; Yield: 67%; Melting point: 211.3-214.4°C; IR(KBr): 3367.6, 3091.8, 2864.5, 1668.0, 1574.8, 1354.9, 1170.4, 1067.9, 935.6, 751.1; ^{1}H NMR: (400 MHz, DMSO-d6): δ ppm 7.89 (d, J = 8.4 Hz, 2H), 7.67 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 2.89 (s, 8H); ESI (m/z): Calculated 305.19 and found 306.95 [M+2].

1-(4-fluorobenzene-1-sulfonyl) piperazine (6c): White solid; Yield: 64%; Melting point: 207.7-211.2°C; IR (KBr): 3321.1, 3108.6, 2952.1, 2920.4, 2851.4, 1593.4, 1496.5, 1340.0, 1170.4, 1094.0, 732.4; ^{1}H NMR: (400 MHz, DMSO-d6): δ ppm 7.99-796 (m, 2H), 7.92-7.83 (m, 2H), 3.13 (t, J = 4.8 Hz, 4H), 2.86 (t, J = 4.8 Hz, 4H); ESI (m/z): Calculated 244.06 and found 245.03 [M+1].

Analytical data for target molecules (7a-7k)

5-(4-Methoxy-benzyloxy)-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-pyrido[4,3-d] pyrimidine (7a): Off-white solid; Yield: 63%; Melting point: 162.3-167.4°C; IR (KBr): 3583.8, 2924.1, 2857.0, 1656.8, 1621.4, 1578.5, 1448.1, 1354.9, 1287.8, 1250.5,978.4, 818.8, 728.7. ^{1}H NMR: (400MHz, DMSO); δ ppm: 8.98 (bs, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 7.6 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 6.84 (d, J = 8 Hz, 2H), 6.21 (d, J = 7.6 Hz, 1H), 4.95 (bs, 2H), 3.92 (bs, 4H), 3.66 (bs, 3H), 2.90 (bs, 4H), 2.33 (bs, 3H). ^{13}C NMR:.161.02, 160.37, 160.04, 159.77, 158.75, 143.79, 142.70, 131.83, 129.88, 129.28, 127.57, 113.96, 110.00, 108.36-107.53 (m), 104.49, 55.07, 49.79, 45.66, 42.71, 40.37, 20.98. ESI (m/z): Calculated 505.18 and found 506.19 [M+1]; Anal. calcd for $C_{26}H_{27}N_5O_4S$: C, 61.77; H, 5.38; N, 13.85; O, 12.66, S, 6.34%; found: C, 61.92; H, 5.47; N, 13.98, S, 6.41%.

5-(4-Fluoro-benzyloxy)-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-pyrido[4,3-d]pyrimidine (7b): Off white solid; Yield: 65%; Melting point: 159.3-165.8°C; IR (KBr): 3047.1, 2922.2, 2857.0, 1656.8, 1623.3, 1578.5, 1511.4, 1349.3, 1157.3, 941.2, 818.2, 730.6; ^{1}H NMR: (400MHz, DMSO); δ ppm: 8.98 (s, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 8 Hz, 2H), 7.38 (d, J = 8 Hz, 2H), 7.33-7.29 (m, 2H), 7.11 (t, J = 8.8 Hz, 2H), 6.22 (d, J = 7.6 Hz, 1H), 5.01 (s, 2H), 3.92 (s, 4H), 2.91-2.89 (m, 4H), 2.32 (s, 3H); ^{13}C NMR: (300 MHz, DMSO-d6) δ ppm 161.03, 160.40, 160.04, 159.83, 143.80, 142.12, 133.48, 131.81, 129.88, 129.78, 127.57, 115.48, 115.20, 109.97, 108.04, 107.76, 107.48, 104.69, 49.75, 46.60, 45.66, 44.57, 42.73, 20.98; ESI (m/z): Calculated 493.15 and found 494.14 [M+1]; Anal: calcd for $C_{25}H_{24}FN_5O_3S$: C, 60.84; H, 4.90; F, 3.85; N, 14.19; O, 9.73; S, 6.50. found: C, 60.89; H, 4.95; N, 14.24; S, 6.56%.

5-(4-Chloro-benzyloxy)-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-pyrido[4,3-d]pyrimidine (7c): Off white solid; Yield: 68%; Melting point: 167.8-171.5°C; IR (KBr): 3047.1, 2924.1, 2845.8, 1660.5, 1625.1, 1582.3, 1541.3, 1507.7, 1448.1, 1358.6, 1256.1, 1162.9, 1092.1, 1017.6, 971.0, 931.8, 821.9, 721.2; ^{1}H NMR: (400MHz, DMSO); δ ppm: 8.98 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8 Hz, 2H), 7.40-7.34 (m, 4H), 7.27 (d, J = 8.4 Hz, 2H), 6.24 (d, J = 7.6Hz, 1H), 5.02 (s, 2H), 3.93 (bs, 4H), 2.91 (bs, 4H), 2.33 (s, 3H). ^{13}C NMR: (400MHz, DMSO-d6, Catalytic amount of TFA was used for better dissolution) δ ppm: 161.49, 160.87, 160.53, 160.30, 144.25, 142.64, 136.75, 132.67, 132.35, 130.51, 130.33, 128.98, 128.03, 110.44, 105.17, 50.32, 46.12, 43.22, 42.61, 29.67, 21.40. ESI (m/z): Calculated 509.13 and found 510.06 [M+1]; Anal: calcd for $C_{25}H_{24}ClN_5O_3S$: C, 58.88; H, 4.74; Cl, 6.95; N, 13.73; O, 9.41; S, 6.29; found: C, 59.05; H, 7.03; N, 13.86, S, 6.40%.

5-(4-Nitro-benzyloxy)-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-pyrido[4,3-d] pyrimidine (7d): Off white solid; Yield: 62.5%; Melting point: 138.2-144.5°C; IR (KBr): 3060.1, 2857.0, 1653.1, 1619.5, 1584.1, 1522.6, 1449.9, 1349.3, 1246.8, 1164.8, 941.2, 820.0; ^{1}H NMR: (400MHz, DMSO-d6): δ ppm 9.01 (s, 1H), 8.19 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8 Hz, 2H), 6.31 (d, J = 8 Hz, 1H), 5.21 (s, 2H), 3.97 (bs, 4H), 2.95 (bs, 4H), 2.37 (s, 3H); ^{13}C NMR: (300MHz, DMSO-d6) δ ppm 161.08, 160.45, 160.08, 158.38, 146.83, 145.02, 144.53, 143.83, 143.37, 142.29, 131.80, 129.91, 128.53, 127.61, 123.70, 109.95,

104.98, 50.79, 50.26, 45.69, 45.00, 42.76, 21.01; ESI (m/z): Calculated 520.15 and found 521.14 [M+1]; Anal: calcd for $C_{25}H_{24}N_6O_5S$: C, 57.68; H, 4.65; N, 16.14; O, 15.37; S, 6.16. found: C, 57.75; H, 4.71; N, 16.22; S, 6.22%.

2-[4-(4-Bromo-benzenesulfonyl)-piperazin-1-yl]-5-(4-methoxy-benzyloxy)-pyrido[4,3-d]pyrimidine (7e): Off white solid; Yield: 73%; Melting point: 155.5-162.0°C; IR (KBr): 3084.4, 2937.1, 2862.6, 1662.4, 1619.5, 1578.5, 1511.4, 1353.0, 1246.8, 1155.5, 818.2, 756.6; ^{1}H NMR: (300MHz, DMSO-d6): δ ppm 9.02 (s, 1H), 7.85-7.82 (m, 3H), 7.66 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.24 (d, J = 7.5 Hz, 1H), 4.99 (s, 2H), 3.96 (bs, 4H), 3.71 (s, 3H), 3.0 (bs, 4H); ESI (m/z): Calculated 569.07 and found 570.9 [M+2]. Anal: calcd for $C_{25}H_{24}BrN_5O_4S$: C, 52.64; H, 4.24; Br, 14.01; N, 12.28; O, 11.22; S, 5.62; found: C, 52.71; H, 4.28; N, 12.34, S, 5.69%.

5-(Biphenyl-3-ylmethoxy)-2-[4-(4-bromo-benzenesulfonyl)-piperazin-1-yl]-pyrido[4,3-d] pyrimidine (7f): Off white solid; Yield: 69%; Melting point: 162.5-169.9°C; IR(KBr): 3464.6, 2857.0, 1658.7, 1621.4, 1578.5, 1509.6, 1448.1, 1354.9, 1250.5, 1161.1, 948.6, 820.0752.9; ^{1}H NMR: (400MHz, DMSO): δ ppm 9.04 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.61-7.55 (m, 4H), 7.47-7.36 (m, 4H), 7.27 (d, J = 7.6 Hz, 1H), 6.28 (d, J = 7.6 Hz, 1H), 5.15 (s, 2H), 3.97 (bs, 4H), 3.0 (s, 4H); ^{13}C NMR: (400 MHz, DMSO-d6); δ ppm 160.99, 160.42, 159.99, 159.78, 142.17, 140.46, 139.80, 137.94, 134.25, 132.48, 129.41, 129.19, 128.87, 127.51, 127.30, 126.62, 126.14, 125.89, 109.96, 104.60, 50.40, 45.49, 42.66; ESI (m/z): Calculated 616.52 and found 618.0 [M+2]; Anal: calcd for $C_{30}H_{26}BrN_5O_3S$: C, 58.44; H, 4.25; Br, 12.96; N, 11.36; O, 7.79; S, 5.20. found: C, 58.49; H, 4.29; N, 11.40; S, 5.25%.

2-[4-(4-Bromo-benzenesulfonyl)-piperazin-1-yl]-5-(4-fluoro-benzyloxy)-pyrido[4,3-d]pyrimidine (7g): White solid; Yield: 66%; Melting point: 133.5-139.8°C; IR(KBr): 3088.1, 2898.0, 2860.7, 1671.7, 1619.5, 1578.5, 1507.7, 1448.1, 1354.9, 1250.5, 1159.2, 1008.2, 946.7, 818.2, 756.6; ^{1}H NMR: (400MHz, DMSO-d6): δ ppm 9.03 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.67 (dd, J_1 = 2 Hz, J_2 = 6.8 Hz, 2H), 7.37-7.33 (m, 2H), 7.16 (t, J = 8.8 Hz, 2H), 6.27 (d, J = 7.6 Hz, 1H), 5.05 (s, 2H), 3.97 (bs, 4H), 3.01-2.99 (m, 4H); ^{13}C NMR: (400MHz, DMSO-d6 Catalytic amount of TFA was used for better dissolution): δ ppm 166.06, 163.61, 162.36,161.14, 160.54, 160.14, 160.03, 146.93, 145.04, 142.32, 131.72, 131.39, 130.74-130.49, 128.59, 123.74, 116.84, 116.61, 110.04, 105.00, 50.32, 45.67, 44.89, 42.83; ESI (m/z): Calculated 558.42 and found 560 [M+2]. Anal: calcd for $C_{24}H_{21}BrFN_5O_3S$: C,51.62; H, 3.79; Br, 14.31; F, 3.40; N, 12.54; O, 8.60; S, 5.74; found: C, 51.73; H, 3.84; N, 12.61, S, 5.79%.

2-[4-(4-Bromo-benzenesulfonyl)-piperazin-1-yl]-5-(4-nitro-benzyloxy)-pyrido[4,3-d]pyrimidine (7h): Pale yellow solid; Yield: 61%; Melting point: 175-181.9°C; IR(KBr): 3062.0, 2924.1, 2857.0, 1660.5, 1621.4, 1578.5, 1353.0, 1248.7, 1170.4, 948.6, 820.0, 732.4, 547.9; ^{1}H NMR: (400MHz, DMSO-d6): δ ppm 9.02 (s, 1H), 8.19 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 6.32 (d, J = 7.6 Hz, 1H), 5.21 (s, 2H), 3.98 (bs, 4H), 3.01 (bs, 4H); ESI (m/z): Calculated 584.04 and found 586.8 [M+2]. Anal; calcd for $C_{24}H_{21}BrN_6O_5S$: C, 49.24; H, 3.62; Br, 13.65; N, 14.36; O, 13.66; S, 5.48. found: C, 49.31; H, 3.69; N, 14.42; S, 5.55%.

2-[4-(4-Fluoro-benzenesulfonyl)-piperazin-1-yl]-5-(4-methoxy-benzyloxy)-pyrido[4,3-d]pyrimidine (7i): Off white solid; Yield: 62%; Melting point: 139.5-145.9°C; IR(KBr): 2931.6, 2858.9, 1656.8, 1619.9, 1584.1, 1515.2, 1356.6, 1252.4, 1170.4, 944.9, 820.0, 739.9; ^{1}H NMR: (400MHz, DMSO) δ ppm: 9.02 (s, 1H), 7.85-7.74 (m, 3H), 7.48-7.43 (m, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.24 (d, J = 7.6 Hz, 1H), 4.99 (s, 2H), 3.97 (s, 4H), 3.70 (s, 3H), 2.99 (s, 4H); ^{13}C NMR: (300 MHz, TFA) δ ppm 167.85, 167.73, 157.98, 152.29, 151.28, 146.26, 129.69-129.28, 126.71, 116.49-116.05, 114.57, 108.42, 98.88, 54.74, 52.44, 44.76, 44.59, 44.21; ESI (m/z): Calculated 509.15 and found 510.4 [M+1]; Anal: calcd for $C_{25}H_{24}FN_5O_4S$: C, 58.93; H, 4.75; F, 3.73; N, 13.74; O, 12.56; S, 6.29. found: C, 59.05; H, 4.79; N,13.80; S, 6.34%.

2-[4-(4-Fluoro-benzenesulfonyl)-piperazin-1-yl]-5-(4-fluoro-benzyloxy)-pyrido[4,3-d]pyrimidine (7j): Off white solid; Yield: 65%; Melting point: 131.4-139.5°C; IR (KBr):

3065.7, 2898.0, 2845.8, 1543.1, 1511.4, 1496.5, 1349.3, 1250.5, 1170.4, 836.8, 821.9, 739.9; ^{1}H NMR: (400MHz, DMSO): δ ppm 8.98 (s, 1H), 7.85-7.70 (m, 3H), 7.45-7.39 (m, 2H), 7.33-7.30 (m, 2H), 7.10 (t, J = 8.8 Hz, 2H), 6.23 (d, J = 7.6 Hz, 1H), 5.02 (s, 2H), 3.94 (s, 4H), 2.96 (s, 4H); ESI (m/z): Calculated 497.13 and found 498.4 [M+1]; Anal: calcd for $C_{24}H_{21}F_2N_5O_3S$: C, 57.94; H, 4.25; F, 7.64; N, 14.08; O, 9.65; S, 6.45. found: C, 57.99; H, 4.28; N, 14.12; S, 6.48%.

2-[4-(4-Fluoro-benzenesulfonyl)-piperazin-1-yl]-5-(4-nitro-benzyloxy)-pyrido[4,3-d]pyrimidine (7k): Off white solid; Yield: 65%; Melting point: 157.2-162.6°C; IR (KBr): 3073.2, 2862.6, 1660.5, 1623.3, 1578.5, 1515.2, 1343.7, 1244.9, 1149.9, 1099.6, 944.9, 820.0, 732.4; ^{1}H NMR: (400MHz, DMSO-d6) δ ppm 9.02 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.84-7.74 (m, 2H), 7.52-7.43 (m, 4H), 6.31 (d, J = 7.6 Hz, 1H), 5.22 (s, 2H), 3.98 (s, 4H), 2.99 (s, 4H); ^{13}C NMR: (300MHz, DMSO-d6) δ ppm 166.39, 163.05, 161.09, 160.45, 160.06, 159.98, 146.82, 144.99, 142.27, 131.60, 131.22, 130.70, 130.57, 130.43, 128.51, 123.71, 116.85 and 116.55 (d), 109.94, 104.97, 50.24, 45.62, 44.81, 42.73; ESI (m/z): Calculated 524.17 and found 525.11 [M+1]; Anal: calcd for $C_{24}H_{21}FN_6O_5S$: C, 54.96; H, 4.04; F, 3.62; N, 16.02; O, 15.25; S, 6.11. found: C, 55.05; H, 4.09; N, 16.09; S, 6.16%.

Molecular docking studies

Molecular docking studies are essential for improving our understanding of the interactions between drugs and biomolecules, which is important for drug design research. Molecular docking provides a three-dimensional view of these interactions, making it possible to identify a medicine molecule's active site. This knowledge is crucial for comprehending how minute structural modifications may affect how biomolecules interact with one another. As a result, it is impossible to overestimate the significance of these investigations in the creation of therapeutic drugs.[36,37] This work enables precise measurements of a molecule's strength and binding capacity to a protein or enzyme, especially when it comes to 3D visualization of hydrogen bonding interactions. In this particular instance, α-amylase, a protein molecule linked to diabetes, was chosen from the protein data bank.[38]

Binding energy is crucial in the process of molecular docking. It serves as an indicator of the interaction strength between ligands and receptors at a binding site, providing insights into the characteristics of the ligand-receptor complex formed through these interactions, particularly its affinity and stability. This measure can also be used to evaluate the success of the binding process. Binding energy encompasses various interactions, including hydrogen bonds, van der Waals forces, and π-π interactions. A negative binding energy indicates the energy released during the binding interaction. When the binding energy is negative, it suggests that the interaction is energetically favourable, resulting in a potential energy for the complex that is lower than that of the individual ligands and receptors. Consequently, a more negative binding energy correlates with greater stability. In this docking analysis, all ligands exhibited significantly negative binding energy values.

The results of the docking studies for all synthesized compounds are thoroughly detailed in Table 1, highlighting their interactions with specific amino acid residues and their three-dimensional interactions are shown in Fig. 1-3. All synthesized compounds exhibited negative values, with most showing nearly equivalent values. However, the compounds featuring methyl sulfonyl substituents **(7a-7d)** demonstrated the most negative values overall. Conversely, the fluoro -substituted sulfonyl series presented average binding constant values between -8.2 and -8.9 Kcal/mol. Notably, compound **7f** had the lowest value, while **7e** had the highest, indicating differing stability levels. It is worth mentioning that these compounds did not form any hydrogen bonds; nonetheless, they engaged in various other interactions with multiple amino acid residues, leading to the observed negative binding energy values. Compound **7e** interacts with several amino acids, including ASP 197, ILE 235, TRP 59, HIS 201, ELU 165, ELU 162, ALA 198, and LYS 200, through four distinct types of electrostatic interactions: Pi-Anion, Pi-Sigma,

Pi-Pi T-shaped, and Pi-Alkyl. Additionally, it engages in Pi-stacked, Pi-Sigma, Pi-Pi T-shaped, and Pi-Alkyl interactions with TRP 59, TYR 62, LEU 165, LEU 162, ALA 198, and ILE 235. Both compounds **7i** and **7j** exhibit one hydrogen bonding interaction each, alongside a variety of other electrostatic interactions, including Carbon H bond, Pi-Anion, Pi-Sigma, Pi-Alkyl, unfavourable Acceptor, and halogen interactions. Compound **7i** interacts with ASP 197, ASP 300, GLU 233, TRP 59, LEU 162, and ALA 198, while compound **7j** interacts with GLN 63, TRP 59, THR 163, ILE 235, ASP 197, GLU 233, HIS 201, and ALA 198. Compounds **7b**, **7c**, and **7h** also formed a couple of hydrogen bonds, along with an additional bonding interaction. Compound **7h** exhibits an additional Pi-Pi stacked interaction, alongside one conventional and one carbon-hydrogen bonding interaction. These interactions involve the amino acid residues ALA 106, TRP 59, and TYR 62, respectively. In contrast, compound **7b** features a total of seven interactions, which include two distinct types of hydrogen bonding. These interactions are associated with seven different amino acid residues: HIS 305, ASP 197, TRP 59, GLU 233, HIS 201, TYR 62, ALA 198, and LEU 162. On the other hand, compound **7c** is characterized by five interactions, including two hydrogen bonding interactions, which are linked to the amino acid residues ARG 398, SER 289, ASP 402, PHE 335, PRO 332, PRO 4, and PHE 406. Additionally, compounds **7a**, **7g**, and **7k** each demonstrate three hydrogen bonding interactions, along with several other π-interactions. For compound **7a**, interactions were identified involving conventional and carbon-hydrogen bonding with three amino acid residues: ARG 398, SER 289, and THR 11. Additionally, five different amino acid residues ASP 402, PHE 335, PRO 4, PHE 406, and PRO 332 contribute to three distinct π-π interactions. Similarly, compound **7g** exhibits hydrogen bonding interactions with three different amino acids, while two residues, THR 163 and TYR 62, participate in three types of π-interactions, including Pi-Sigma, Pi-Pi T-shaped, and stacked modes. Compound **7k** shares the same hydrogen bonding interactions as **7g** but features three π-interactions and one halogen interaction involving three amino acid residues. Lastly, compound **7d** demonstrates the highest number of hydrogens bonding interactions, totalling four, although it only includes two distinct types of hydrogen bonds, which are also commonly observed in other compounds. Furthermore, four different amino acids in **7d** engage in four π-interactions, resulting in a total of eight interactions with the protein. This study concludes that all synthesized compounds can form stable complexes with protein 1HNY through various interactions, including hydrogen bonding, π-π interactions, and electrostatic interactions with specific amino acid residues.

Table 1: Results obtained from the molecular docking studies of all synthesised compounds with enzyme 1-HNY

Compound No	Affinity Kcal/mol	Number of hydrogen bonds	Interaction with amino acid residue	Type of Interaction	Hydrogen bond distance
7a	-9.3	3	ARG 398	Conventional H bond	3.06
			SER 289		
			THR 11	Carbon H Bond	3.64, 3.43
			ASP 402	Pi-Pi-anion and cation	3.91,3.35,4.81
			PHE 335	Pi-Pi T-shaped	5.14
			PRO 4		
			PHE 406		
			PRO 332	Pi-Alkyl	4.83,5.01,4.32
7b	-9.1	2	HIS 305	Conventional H bond	3.07
			ASP 197	Carbon H bond	3.62
			TRP 59	Halogen	3.30
			GLU 233	Pi-Anion	4.29
			HIS 201		
			TYR 62	Pi-Pi T-shaped	5.16,4.99
				Pi-Stacked	

			ALA 198	Pi-Alkyl	5.22,4.90,4.55
			LEU 162	Pi-Sigma	3.88,3.82
7c	-9.5	2	ARG 398	Conventional H bond	3.09
			SER 289	Carbon H Bond	3.52
			ASP 402	Pi-Pi-anion and cation	3.34 3.87
			PHE 335	Pi-Pi T-shaped	5.28
			PRO 332		
			PRO 4		
			PHE 406	Pi-Alkyl	5.01,4.40,4.40,4.55
7d	-8.6	4	GLY 403 SER 289		
			ARG 421	Conventional H bond	2.18,2.14,1.74
			PRO 332	Carbon H Bond	3.56
			ASP 402	Pi-Anion	4.56
			PHE 85		
			PHE 65	Pi-Pi T-shaped	5.00
			PRO 4	Alkyl and Pi-Alkyl	5.20,4.27,4.96,4.58
7e	-7.9	-	ASP 197	Pi-Anion	4.89
			ILE 235	Pi-Sigma	3.79,3.9
			TRP 59		
			HIS 201	Pi-Pi T-shaped	4.78,5.69
			ELU 165		
			ELU 162		
			ALA 198		
			LYS 200	Pi-Alkyl	5.38,5.06,5.44,4.72
7f	-10.1	-	TRP 59		
			TYR 62	Pi-Pi T-shaped	5.51,5.30,4.52,5.58,5.32
			LEU 165	Pi-Stacked	
			LEU 162		
			ALA 198	Pi-Alkyl	5.43,5.24,5.40,4.85,5.03,4.59
			ILE 235	Pi-Sigma	3.65
7g	-8.8	3	TYR 151	Conventional H bond	2.02
			ASP 300		
			GLU 233	Carbon H Bond	3.30,3.42
			THR 163	Pi-Sigma	3.90
			TYR 62	Pi-Pi T-shaped and Stacked	3.67,5.32
7h	-8.8	2	ALA 106	Conventional H bond	2.67
			TRP 59	Carbon H bond	3.57
			TYR 62	Pi-Pi Stacked	4.69,3.83,3.67,3.96,5.01
7i	-8.2	1	ASP 197	Carbon H bond	3.32
			ASP 300		
			GLU 233	Pi-Anion	4.01,4.71,4.40
			TRP 59	Pi- Sigma	3.50
			LEU 162		
			ALA 198	Pi-Alkyl	4.56,5.57,5.08,4.57
7j	-8.8	1	GLN 63	Conventional H bond	2.5
			TRP 59	Halogen	3.51
			THR 163	Unfavourable Acceptor	2.72
			ILE 235	Pi-Sigma	3.54
			ASP 197		
			GLU 233	Pi-Anion	4.70,4.10
			HIS 201	Pi-Pi T-shaped	5.17,4.84
			ALA 198	Pi-Alkyl	4.94,5.27
7k	-8.9	3	ARG 80		
			HIS 185	Conventional H bond	2.52,2.48
			GLU 181	Carbon H Bond	3.54
			ASP 188	Pi-Anion	4.08,3.79
			TYR 67	Pi-Pi T-shaped	
				Pi-Stacked	4.72,5.02,5.34
			LYS 178	Halogen	3.61,3.12

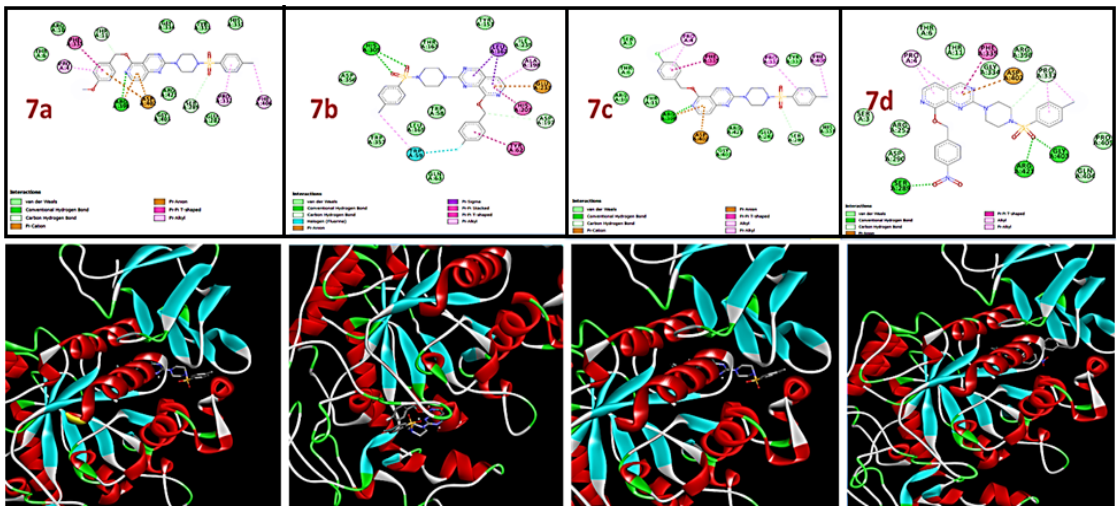


Fig. 1. Three dimensional interactions of the compounds 7a-7d with 1-HNY enzyme's active sites

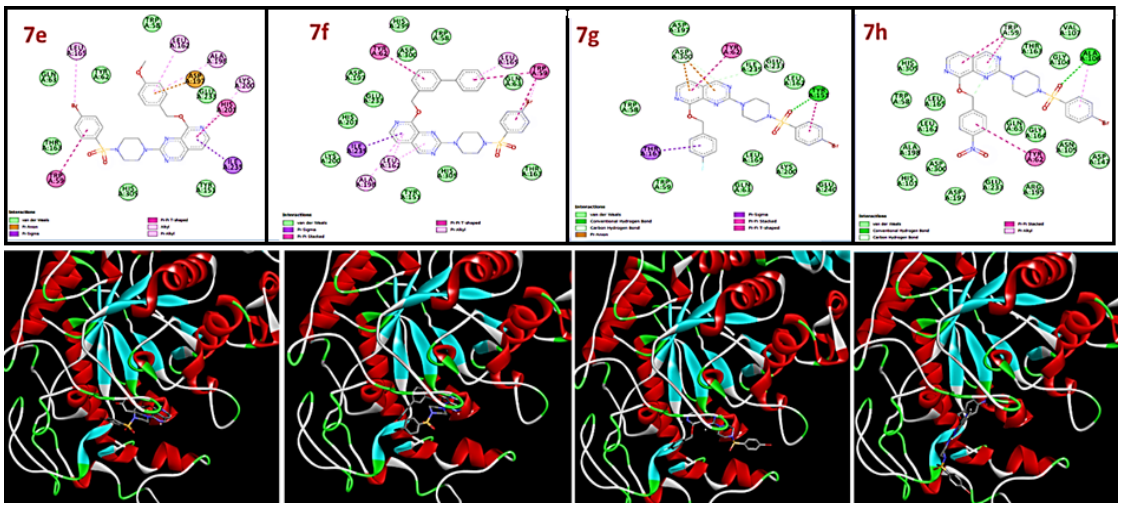


Fig. 2. Three dimensional interactions of the compounds 7e-7h with 1-HNY enzyme's active sites

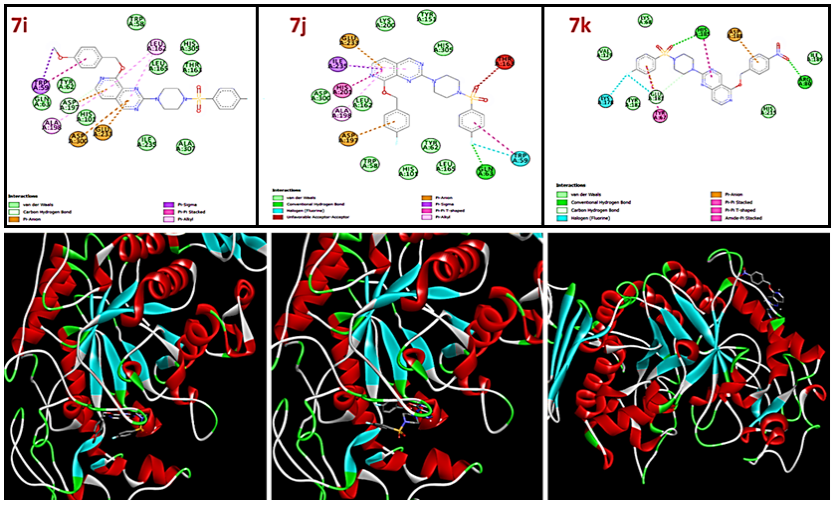


Fig. 3. Three dimensional interactions of the compounds 7i-7k with 1-HNY enzyme's active sites

Biological studies

Antidiabetic activity (α-amylase inhibition technique)[39]

Carbohydrates differ from simple molecules because they consist of sugar units linked together to form a polymeric structure, which acts as a source of energy during digestion. This process relies on various enzymes that are vital for breaking down carbohydrates, which leads to the release of glucose molecules and can result in spikes in blood sugar levels. Due to concerns about sucrose consumption, researchers have begun exploring alternative sugars like allulose and sorbose as healthier options.[40,41] However, the high production costs associated with these alternatives pose challenges to their commercial viability. Improving existing methods to lower glucose levels may offer promising opportunities for developing new treatments for diabetes. Among the enzymes involved in carbohydrate digestion, α-amylase plays a significant role in transforming carbohydrates into sugar units. Therefore, moderating the activity of α-amylase could be a viable strategy for managing diabetes.[42]

From this point forward, the synthesized compounds were tested for their ability to prevent diabetes, and the outcomes were displayed in a bar diagram (Fig. 4) alongside reference medication molecules. The activity of every compound has been tested at five different concentrations ranging from 0-400 µg/mL. Compound **7k** has demonstrated greater activity than drug molecules, even though few derivatives have attempted to match the activity of typical drug molecules and only exhibit modest activity. Compounds **7f** and **7h** have reduced activity at increasing concentration levels; hence, they display 75% and 77% inhibition percentages, respectively, whereas the typical drug molecule displays 87%. In general, studies have demonstrated that fluoro and methyl substituent sulfonyl derivatives have superior activity compared to their bromo substituent derivatives.

Anti-inflammatory activity (BSA denaturation technique)[43]

Inflammation is an initial stage ailment for various significant diseases, including cancer, that can have a profound impact on lifespan.[44-46] This can lead to abnormal protein activity, resulting in either heightened or diminished functionality. Excessive protein activity often leads to the cell's demise. Additionally, compounds used for diabetic activity also exhibit anti-inflammatory properties. Fig. 5 compares the activity of compounds with conventional therapeutic molecules using the BSA inhibition technique. The standard drug molecule has demonstrated better action at every concentration; however, only compound **7c** has attained the standard drug molecule's inhibitory%. Compounds **7b, 7f,** and **7i** have the least activity and have only achieved 75–77% at higher concentrations, whereas all other compounds have demonstrated moderate activity. Nevertheless, based on comprehensive lab studies, the majority of the compounds exhibit medium activity, making them potentially claimable as moderate therapeutic agents.

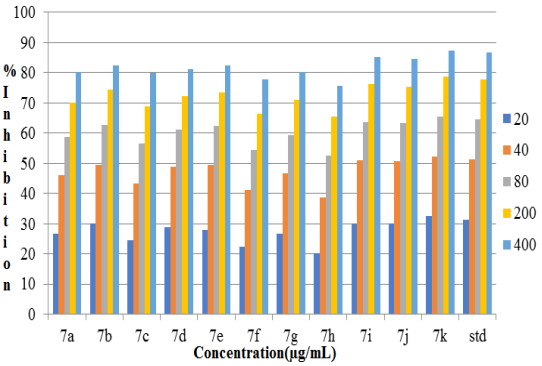


Fig. 4. Anti-diabetic activity of synthesised compounds with standard drug molecule (acarbose)

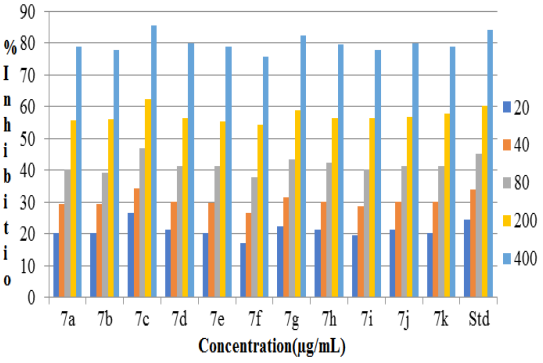


Fig. 5. Anti-inflammatory activity of the all-synthesised compounds with standard drug molecule (diclofenac sodium)

CONCLUSION

The synthesized compounds have been thoroughly characterized using various spectroscopic techniques, which confirms their chemical structures. The compounds were evaluated for molecular docking studies, and the results indicate that all compounds exhibited negative binding energies. Furthermore, these compounds demonstrated the capacity to

engage in multiple types of interactions, including hydrogen bonding, π-π interactions, and electrostatic interactions. Such interactions may contribute to the enhanced efficacy of the compounds in *in-vitro* studies related to diabetes and inflammation. Notably, compounds having fluoro and methyl substituted benzenesulfonyl groups exhibited superior activity in diabetes and inflammation studies. Consequently, these findings suggest that the synthesized library of compounds may possess significant therapeutic potential against diabetes and inflammation.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article

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