Synthesis and Inhibitory Effect of Some Indole-Pyrimidine Based Hybrid Heterocycles on α-Glucosidase and α-Amylase as Potential Hypoglycemic Agents

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The Michael addition reaction of barbituric acid with chalcones incorporating the indole scaffold was achieved by using a highly efficient bimetallic Iron–palladium catalyst in the presence of acetyacetone (acac). This catalytic approach produced the desired products in a simple operation and low catalyst loading with acceptable yield of the new hybrids. All tested compounds were subjected for biological activity on α-glucosidase and α-amylase. The results revealed that all synthesized compounds exhibited very good activity against both enzymes when compared to positive control (acarbose). Moreover, compound 5o showed the best activity whereas its IC₅₀ (μM) are 13.02±0.01 and 21.71±0.82 for α-glucosidase and α-amylase respectively. Both compounds 5o and 5l exhibited high similarity in binding mode and pose with amylase protein (4UAC). The obtained data may be used for developing potential hypoglycemic agents.

1. Introduction

Heterocyclic compounds are of immense chemical and biological significance. In particular, azaheterocycles (nitrogen containing heterocycles) such as pyrimidines and indoles are structural constituents of many natural as well as synthetic bioactive drug-like molecules.[1] Substituted azaheterocycles have been referred as “privileged structures” since they are capable of binding to many receptors with high affinity and hydrogen bonding capacity. Naturally occurring nitrogen-based heterocycles such as reserpine, vinca alkaloids, bisindoles, indoloquinolines, opioid analgesics, carbolines and cinchona heterocycles such as reserpine, vinca alkaloids, bisindoles, indoloquinolines, opioid analgesics, carbolines and cinchona alkaloids are established source of lead molecules for diverse therapeutic areas.[2] Among the nitrogen containing heterocycles, indole is the parent core in a large number of bioactive naturally occurring compounds. Indole and its derivatives have received significant attention due to their wide range of biological activities including antimicrobial, anticancer, anti-HIV anti-inflammatory, and anti-oxidant.[2] In recent past, several nitrogen containing novel chemical entities emerged as drug molecules, for example, Atevirdine (anti-HIV); Camptothecin (CPT) (inhibitors of topoisomerase I);[4] Cryptolepine (inhibitors topoisomerase II).[5] Synthetic analogues of Cryptolepine such as IQDMA and benzo-pyrido-indole derivatives exhibited potent anticancer activity via interaction of DNA[6]. We are engaged in a research program for drug development as anti-diabetes based on indole and pyrimidine scaffolds.[7] One example of our invention the use of indole scaffold in the treatment and prevention of diabetes has been described (Figure 1).[7–9]

Diabetes Mellitus (DM) is a growing global health concern. In 2017, diabetes affected an estimated 426 million adults people (20–79 years) world-wide; by 2045 this numbers are expected to overun 629 million.[9] The release of free glucose from starch is mediated by two important enzymes: α-amylase and α-glucosidase. α-Amylase is a metalloenzyme that cleaves polysaccharide chains, semi-randomly creating shorter chains rapidly, whereas α-glucosidase breaks these shorter chains into free glucose. The inhibition of these two enzymes can delay digestion, and absorption of carbohydrates, and hence, impair

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the postprandial hyperglycemia. Therefore, the aim of our work was to synthesize, through a Michael addition to a series of indole containing chalcones, new heterocycles that may act as inhibitors of these two enzymes

2. Results and Discussion

2.1. Synthesis

The requisite compounds chalcones were prepared by reaction of N-alkyl-3-acetylindole and aryl aldehyde derivatives stirring in EtOH/H$_2$O (1:1) with NaOH at room temperature for 24 h. The product was produced in high yield (up to 90 %), as depicted in Scheme 1. The configuration of the chalcones obtained exclusively with E-geometry. The E configuration of these compounds was supposed in analogy with similar compounds, previously prepared by us, whose configuration was established through X-ray analysis.\(^{[16]}\)

Reaction of (E)-1-(1-methyl-1H-indol-3-yl)-3-phenylprop-2-en-1-one 3a with barbituric acid 4 was chosen as a model reaction to prepare 1,3-dimethyl-5-(3-(1-methyl-1H-indol-3-yl)-3-oxo-1-phenylpropyl)pyrimidine-2,4,6(1H,3H,5H)-trione 5a. Initially, the reaction of 3a with barbituric acid 4 carried out in toluene at 80 °C in the presence of Cu(OTf)$_2$/L1 (10:10 mol%) did not work all.\(^{[16]}\) However, upon using different solvents; THF, ACN, or Toluene/THF mixture, the reaction did not occur. Other metal salt as Zn(OTf)$_2$ did not facilitate the reaction under the same conditions. Additionally, one attempt with FeCl$_3$/PdCl$_2$ carried out in MeOH at 60 °C, the reaction did not occur at all. Only, Fe–Pd bimetallic system\(^{[11]}\) in MeOH at 60 °C provides the desired product in moderate yield (55 %) (Table 1). The molecular structures of target compounds 5a were determined by analysis of its spectroscopic data including $^1$H-, $^{13}$C-NMR, Fourier-transform infra-red (FT-IR) spectroscopy and X-ray crystal analysis.

To investigate the generality of this method, the reaction of barbituric acid and different enones was examined under the optimized reaction conditions (10 mol% of FeCl$_3$, 10 mol% of PdCl$_2$, and 15 mol% Acac, 1.0 equiv. chalcone and 1.1 equiv. barbituric acid in CH$_3$OH at at 60 °C. All of the results are summarized in Table 2.

2.2. X-Ray Crystallography

The structure of 5g was further confirmed by X-Ray structural study. The asymmetric unit contains one independent molecule that is shown in Figure 2. It was found to crystallize in Monoclinic Cc space group. The crystallographic data and refinement information are summarized in Table 3 and bond lengths are in normal ranges as shown in Table 4. The crystal structure reveals that the title compound is found in three planes, the angles between indole ring plane (C1–C8/N1) and fluoro phenyl ring (C12–C17) and pyrimidine moiety (C20–C21–N2–C22–N3–C23) are 22.41° and 41.07°, respectively. The angle between fluoro phenyl ring and pyrimidine ring is 57.88°. The crystal structure is stabilized by many non-classical hydrogen bonds along the b axis direction Figure 3, Table 5.

| # | Solvent   | Metal Salts | Ligands | Ligand: Metal mol % | Yield |
|---|-----------|-------------|---------|---------------------|-------|
| 1 | Toluene   | Cu(OTf)$_2$ | L1      | 10:11 mol %         | No rxn|
| 2 | Toluene   | Zn(OTf)$_2$ | L1      | 10:11 mol %         | No rxn|
| 3 | Toluene/THF | Zn(OTf)$_2$ | L1     | 10:11 mol %         | No rxn|
| 4 | THF       | Zn(OTf)$_2$ | L1      | 10:11 mol %         | No rxn|
| 5 | ACN       | Zn(OTf)$_2$ | L1      | 10:11 mol %         | No rxn|
| 6 | MeOH      | FeCl$_3$/PdCl$_2$ | L2 | 10:10 mol %         | 55 %  |
| 7 | MeOH$^{(i)}$ | FeCl$_3$/PdCl$_2$ | L2 | 10:10 mol %         | 55 %  |

[a] The reaction carried out at 60 °C. [b] No rxn: No reaction.
The present study seeks an alternative drug among series of synthesized compounds that can regulate the hyperglycemia by down-regulating alpha-glucosidase and alpha-amylase activity by using virtual and in vitro assays.

The data reported in Table 6 showed that the most active compounds, both on alpha-glucosidase and on alpha-amylase, are compounds 5o, 5k, and 5l. All other compounds were found to have only good to moderate activity ranging from 28.05 to 77.05 + 0.04 μM in the case of alpha-glucosidase, but in the range of 53.10 to 10.01 to 96.42 + 0.22 μM in the case of alpha-amylase. Structure activity relationship indicates the importance of the naphthyl moiety in 5o, of the p-CF3Ph propanone substituted indole in 5k, and of a thiophene ring in 5l. The most active compound is 5o, which showed an IC50 = 13.02 ± 0.01 μM and 21.71 ± 0.82 μM, for alpha-glucosidase, and alpha-amylase respectively.

2.4. Docking Studies

The compound 5o was selected for docking study with (4UAC) because of its strongest inhibitory activity among these derivatives. The X-ray crystal structure of (4UAC) was obtained from protein data bank (PDB ID: 4UAC).[12] Protein-ligand docking was operated by (OpenEye Scientific Software, Santa Fe, NM 87508).[13] The binding site of the protein was prepared by employing FRED RECEPTOR 2.2.5 (OpenEye Scientific Software, Santa Fe, NM 87508).

In the figure 4, we can find that compound 5o formed hydrogen bonds to ASN 191 AA through the oxygen of carbonyl linked to indole moiety. Moreover, this compound formed another HB with GLN 110 AA through the carbonyl of barbiturate ring. These two interactions are similar to acarbose formed another HB with GLN 110 AA through the carbonyl linked to indole moiety. Moreover, this compound exhibited high similarity to the potent compound 5i in the specific receptor, figure 5.

Experimental Section

General Procedure for the Synthesis of Chalcones 3a–q

The chalcones were prepared followed by reported procedure.[14]

(E)-1-(1-Methyl-1H-indol-3-yl)-3-phenylprop-2-en-1-one (3a)

Yield 0.75 g (2.8 mmol, 53.3%); All other spectral data are consistent with reported literature.[14]

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(p-tolyl)prop-2-en-1-one (3b)

Yield 1.34 g (4.63 mol, 86.8%); m.p. 85–86 °C; 1H-NMR (400 MHz, DMSO-d6) δ: 1.47 (t, 3H, J = 7.2 Hz, CH3), 2.29 (s, 3H, CH3) 4.12 (q, 2H, J = 7.2 Hz, CH3), 7.12 (d, 2H, J = 7.6 Hz, Ar–H), 7.22–7.28 (m, 4H, Ar–H & CH=CH), 7.45 (d, 2H, J = 8.0 Hz, Ar–H), 7.71 (d, 1H, J = 15.6 Hz, CH=CH), 8.44–8.46 (m, 1H, Ar–H); 13C-NMR (100 MHz, DMSO-d6) δ: 15.1, 21.4, 41.8, 109.6, 117.7, 122.5, 129.0/129.7

| Table 2. Substrate scope of desired compounds 5a–q. |
| --- |
| **3a–q** | **R** | **Ar** | **Chalcones** | **[%] Yield** |
| 1. | 3a | Ph | Me | 5a | 55 |
| 2. | 3b | 4-MePh | Et | 5b | 44.9 |
| 3. | 3c | 4-ClPh | Et | 5c | 60.2 |
| 4. | 3d | 2,4-CI2Ph | Et | 5d | 55.1 |
| 5. | 3e | 4-OEt | Et | 5e | 53 |
| 6. | 3f | 4-BrPh | Et | 5f | 39.3 |
| 7. | 3g | 4-FPh | Et | 5g | 47.6 |
| 8. | 3h | 3-FPh | Et | 5h | 46.8 |
| 9. | 3i | 3-MePh | Et | 5i | 46.6 |
| 10. | 3j | 3-BrPh | Et | 5j | 36.7 |
| 11. | 3k | 4-CF3Ph | Et | 5k | 39.7 |
| 12. | 3l | Thiophenyl | Et | 5l | 53.7 |
| 13. | 3m | Furanyl | Et | 5m | 54.6 |
| 14. | 3n | 3,4,5-OMePh | Et | 5n | 35.6 |
| 15. | 3o | 2-Naphthyl | Et | 5o | 37 |
| 16. | 3p | 2,4,6-Me2Ph | Et | 5p | - |
| 17. | 3q | 4-NO2Ph | Et | 5q | 34.6 |

Figure 2. ORTEP diagram of the titled compounds 5g. Displacement ellipsoids are plotted at the 40% probability level for non-H atoms.

Figure 3. Molecular packing of titled compounds 5g viewed hydrogen bonds which are drawn as dashed lines along b axis.
Table 3. Experimental details of 5g.

| Property                  | Value                        |
|---------------------------|------------------------------|
| Chemical formula          | C_25H_25F_12N_9O_14           |
| Mr                        | 669.57                       |
| Crystal system, space group| Monoclinic, Cc               |
| Temperature (K)           | 293                          |
| a, b, c (Å)               | 12.182 (5), 28.221 (12), 8.718 (3) |
| V (Å³)                    | 2301.4 (16)                  |
| Z                         | 4                            |
| Radiation type            | Mo Kα radiation              |
| μ (mm⁻¹)                  | 0.09                         |
| Crystal size (mm)         | 0.33 × 0.20 × 0.09           |

Diffraclorimeter: Bruker APEX-II DB venture
Absorption correction: Multi-scan, SADABS Bruker 2014

Table 4. Selected geometric parameters (Å, °) of 5g.

| Atom  | d     | e     | f     |
|-------|-------|-------|-------|
|      | C15   | C18   | C18   |
| O9    | 1.374 | 1.230 | 1.216 |
| C1    | 0.915 | 0.913 | 0.898 |
| C8    | 1.287 | 1.231 | 1.239 |
| C1    | 1.366 | 1.308 | 1.281 |
| N1    | 1.355 | 1.355 | 1.366 |
| N1    | 1.355 | 1.355 | 1.366 |
| C1-N1 | 0.581 | 0.581 | 0.581 |
| C1-N1 | 0.581 | 0.581 | 0.581 |
| C1-N1 | 0.581 | 0.581 | 0.581 |

Table 5. Hydrogen-bond geometry (Å, °) of 5g.

| D-H-A       | D-H     | D-H-A     | D-H-A     |
|-------------|---------|-----------|-----------|
| C10-H108   | 0.970   | 2.3200    | 2.975 (12) |
| C14-H14A   | 0.930   | 2.3400    | 3.170 (13) |
| C18-H18A   | 0.970   | 2.4500    | 3.364 (14) |
| C25-H25A   | 0.960   | 2.5200    | 3.388 (15) |

Symmetry codes: (i) x, -y+1, z+1/2; (ii) x+1/2, -y+1/2, z+3/2; (iii) x, y+1, z+1/2.

Table 6. Results of the α-glucosidase and α-Amylase inhibitory activity of the synthesized compounds 5a–q.

| #  | Compounds | α-Glucosidase IC₅₀ (μM) | α-Amylase |
|----|-----------|-------------------------|-----------|
| 1  | 5a        | 65.14 ± 0.17            | 93.25 ± 0.10 |
| 2  | 5b        | 53.15 ± 0.12            | 80.17 ± 0.05 |
| 3  | 5c        | 49.75 ± 0.01            | 71.24 ± 0.20 |
| 4  | 5d        | 58.21 ± 0.09            | 96.42 ± 0.22 |
| 5  | 5e        | 61.42 ± 0.78            | 88.45 ± 0.32 |
| 6  | 5f        | 53.15 ± 0.12            | 78.25 ± 0.10 |
| 7  | 5g        | 69.75 ± 0.01            | 86.42 ± 0.22 |
| 8  | 5h        | 61.10 ± 0.42            | 89.45 ± 0.44 |
| 9  | 5i        | 73.15 ± 0.12            | 95.25 ± 0.10 |
| 10 | 5j        | 77.05 ± 0.04            | 86.42 ± 0.22 |
| 11 | 5k        | 20.49 ± 0.44            | 47.11 ± 0.09 |
| 12 | 5l        | 22.28 ± 0.48            | 35.42 ± 0.60 |
| 13 | 5m        | 64.35 ± 0.08            | 82.15 ± 0.50 |
| 14 | 5n        | 53.15 ± 0.12            | 93.25 ± 0.10 |
| 15 | 5o        | 13.02 ± 0.01            | 21.71 ± 0.82 |
| 16 | 5p        | 31.12 ± 0.11            | 63.00 ± 0.61 |

STD Acarbose (μM) 2.35 ± 0.13 0.75 ± 0.07

α-Glucosidase and α-Amylase are expressed with mean ± SD of triplicates.

(E)-3-(4-Chlorophenyl)-1-(1-ethyl-1H-indol-3-yl)prop-2-en-1-one (3c)

Yield 1.56 g (50.4 mmol, 94.5%); All other spectral data are consistent with reported literature.[14d]

(E)-3-(2,4-Dichlorophenyl)-1-(1-ethyl-1H-indol-3-yl)prop-2-en-1-one (3d)

Yield 1.70 g (4.9 mol, 92.8%); m.p. 168–169°C; 1H-NMR (400 MHz, DMSO-d₆): δ: 14.8 (t, 3H, J = 7.2 Hz, CH₃); 4.14 (q, 2H, J = 7.2 Hz, CH₂); 7.15–7.19 (m, 1H, Ar–H); 7.23–7.28 (m, 4H, Ar–H & CH–CH); 7.35 (d, 1H, J = 2.4 Hz, Ar–H); 7.56 (d, 1H, J = 8.0 Hz, Ar–H); 7.80 (s, 1H, Ar–H); 7.98 (d, 1H, J = 15.2 Hz, CH–CH); 8.42–8.43 (m, 1H, Ar–H); 13C NMR (100 MHz, DMSO-d₆): δ: 15.3, 42.1, 109.8, 122.9, 123.2, 123.9, 127.1, 127.5, 128.4, 130.1, 132.4, 134.1, 135.8, 135.8, 136.7, 184.1; IR (KBr, cm⁻¹) νmax = 3046, 2971, 2926, 2872, 1653, 1595, 1582, 1527, 1464, 1392, 1238, 1200, 1124, 1098, 1057; [Anal. Calcd. for C₂₃H₁₇NO: C, 83.01; H, 6.62; N, 4.84; Found: C, 83.41; H, 6.12; N, 4.32]; LC/MS (ESI, m/z): [M⁺], found 290.32, C₂₃H₁₇NO for 289.15.

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (3e)

Yield 1.60 g (5.2 mmol, 98.1%); All other spectral data are consistent with reported literature.[14d]

(E)-3-(4-Bromophenyl)-1-(1-ethyl-1H-indol-3-yl)prop-2-en-1-one (3f)

Yield 1.75 g (4.95 mmol, 92.8%); m.p. 139–140°C; 1H-NMR (400 MHz, DMSO-d₆): δ: 1.49 (t, 3H, J = 7.2 Hz, CH₃); 4.17 (q, 2H, J = 7.2 Hz, CH₂); 7.23–7.29 (m, 4H, Ar–H & CH–CH); 7.41 (q, 4H, J = 6.8 Hz, Ar–H); 7.64 (d, 1H, J = 15.2 Hz, CH–CH); 7.82 (s, 1H, Ar–H),
8.42–8.45 (m, 1H, ArH); $^1$C-NMR (100 MHz, DMSO-\(d_6\)) $\delta$: 15.1, 41.8, 109.8, 117.6, 122.7, 123.0, 123.6, 123.8, 124.4, 126.9, 129.5, 131.9, 133.7, 134.3, 136.7, 139.5, 183.8; IR (KBr, cm\(^{-1}\)) $\nu_{\text{max}} = 3449, 3041, 2977, 1645, 1610, 1588, 1525, 1481, 1469, 1454, 1399, 1310, 1241, 1267, 1268, 1016$; [Anal. Calcd. for C\(_{19}\)H\(_{16}\)BrNO: C, 64.42; H, 4.55; N, 3.95; Found: C, 64.31; H, 4.67; N, 4.15]; LC/MS (ESI, \(m/z\)): [M$^+\]$, found 354.18, C\(_{19}\)H\(_{16}\)BrNO for 353.04.

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(4-fluorophenyl)prop-2-en-1-one (3g)
Yield 1.40 g (4.77 mmol, 89.4%); m.p. 94–95 °C; $^1$H-NMR (400 MHz, DMSO-\(d_6\)) $\delta$: 1.44 (t, 3H, \(J = 7.2\) Hz, CH\(_3\)), 4.12 (q, 2H, \(J = 7.2\) Hz, CH\(_2\)), 7.96–7.02 (m, 2H, Ar–H), 7.15–7.30 (m, 4H, Ar–H & CH=CH), 7.49 – 7.54 (m, 2H, Ar–H), 7.65–7.70 (m, 1H,CH–CH), 7.82 (s, 1H, Ar–H), 8.41–8.45 (m, 1H, Ar–H); $^1$C-NMR (100 MHz, DMSO-\(d_6\)) $\delta$: 15.1, 41.8, 109.8, 115.7, 115.9, 117.6, 122.6, 123.0, 123.5, 123.7, 126.8, 129.5, 131.6, 133.7, 136.7, 139.6, 164.8, 183.8; IR (KBr, cm\(^{-1}\)) $\nu_{\text{max}} = 3451, 3047, 2979, 1642, 1613, 1589, 1524, 1482, 1468, 1450, 1397, 1313, 1242, 1269, 1262, 1015$; [Anal. Calcd. for C\(_{19}\)H\(_{16}\)FNO: C, 77.80; H, 5.50; N, 4.77; Found: C, 78.05; H, 5.59; N, 4.61]; LC/MS (ESI, \(m/z\)): [M$^+\]$, found 294.280, C\(_{19}\)H\(_{16}\)FNO for 293.12.

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(3-fluorophenyl)prop-2-en-1-one (3h)
Yield 1.40 g (4.77 mmol, 89.4%); m.p. 84–85 °C; $^1$H-NMR (400 MHz, DMSO-\(d_6\)) $\delta$: 1.47 (t, 3H, \(J = 6.0\) Hz, CH\(_3\)), 4.15 (q, 2H, \(J = 6.0\) Hz, CH\(_2\)),

Figure 4. Snap shot visualization of 5o docked with ID: 4AUC, showing formation of two HBs interaction as illustrated by Vida

Figure 5. Snap shot visualization of compound 5l overlays with 5o and shown same binding mode and pose with receptor.
 Yield 1.28 g (4.42 mmol, 82.9%); m.p. 161–163 ºC; 1H-NMR (400 MHz, DMSO-d6) δ: 1.54 (t, 3H, J = 6.4 Hz, CH3), 2.38 (s, 3H, CH3), 4.22 (q, 2H, J = 6.7 Hz, CH2), 7.17 (d, 1H, J = 3.6 Hz, Ar–H), 7.24–7.47 (m, 7H, Ar–H & CH–CH), 7.78 (d, 1H, J = 15.2 Hz, CH–CH), 7.9 (s, 1H, Ar–H), 8.50–8.53 (m, 1H, Ar–H). 13C-NMR (100 MHz, DMSO-d6) δ: 15.1, 21.3, 41.8, 109.7, 117.7, 122.6, 123.1, 123.4, 123.5, 127.0, 128.6, 130.6, 133.7, 135.3, 136.7, 138.4, 141.2, 184.3; IR (KBr, cm−1) νmax = 3046, 2977, 1644, 1589, 1525, 1482, 1449, 1389, 1304, 1297, 1206, 1204, 1188, 1088; [Anal. Calcd. for C41H36FNO: C, 76.96; H, 5.70; N, 5.28; Found: C, 76.55; H, 5.95; N, 5.10]; LC/MS (ESI, m/z): [M+] found 282.23, C21H16FNO for 281.09.

(E)-1-(Ethyl-1H-indol-3-yl)-3-(4-methylphenyl)prop-2-en-1-one (3i)

Yield 1.1 g (3.01 mmol, 56.4%); m.p. 197–198 ºC; 1H-NMR (400 MHz, DMSO-d6) δ: 1.53 (t, 3H, J = 6.7 Hz, CH3), 2.38 (s, 3H, OCH3) (3H, 6H, OCH3), 4.23 (q, 2H, J = 7.0 Hz, CH2), 6.93 (s, 1H, Ar–H), 7.26 (d, 1H, J = 15.2 Hz, CH–CH), 7.30–7.37 (m, 3H, Ar–H), 7.71 (d, 1H, J = 15.2 Hz, CH–CH), 7.93 (s, 1H, Ar–H), 8.49–8.51 (m, 1H, Ar–H). 13C-NMR (100 MHz, DMSO-d6) δ: 15.2, 41.8, 56.2, 60.9, 105.4, 109.7, 117.6, 112.6, 121.3, 123.2, 123.5, 127.0, 130.9, 133.8, 136.8, 141.3, 153.4, 184.1; IR (KBr, cm−1) νmax = 3452, 3103, 2977, 2942, 2831, 1639, 1581, 1566, 1522, 1463, 1447, 1419, 1392, 137, 1250, 1147, 1121, 1002; [Anal. Calcd. for C35H33NO2: C, 72.31; H, 6.34; N, 3.83]; LC/MS (ESI, m/z): [M+] found 366.28, C25H28NO3 for 361.15.

(E)-1-(Ethyl-1H-indol-3-yl)-3-(4-fluorophenyl)prop-2-en-1-one (3j)

Yield 0.99 g (2.75 mmol, 51.8%); m.p. 113–114 ºC; 1H-NMR (400 MHz, DMSO-d6) δ: 1.46 (t, 3H, J = 7.2 Hz, CH3), 4.14 (q, 2H, J = 7.2 Hz, CH2), 7.23–7.28 (m, 3H, Ar–H), 7.38–7.42 (m, 3H, Ar–H & CH–CH), 7.69 – 7.78 (m, 4H, Ar–H), 7.89 (d, 1H, J = 15.2 Hz, CH–CH & Ar–H), 8.46–8.48 (m, 1H, Ar–H). 13C-NMR (100 MHz, DMSO-d6) δ: 15.1, 41.8, 109.7, 112.7, 122.6, 123.1, 123.5, 123.8, 123.9, 126.5, 126.7, 127.9, 128.4, 129.8, 132.8, 133.4, 133.9, 134.0, 136.7, 141.1, 184.1; IR (KBr, cm−1) νmax = 3478, 3105, 2948, 2968, 2926, 2879, 1642, 1578, 1505, 1468, 1388, 1294, 1208, 1141, 1085; [Anal. Calcd. for C21H19FN2O: C, 84.89; H, 5.89; N, 4.30; Found: C, 84.96; H, 6.11; N, 4.62]; LC/MS (ESI, m/z): [M+] found 326.10, C13H16FNO for 325.15.

(E)-1-(Ethyl-1H-indol-3-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (3k)

Yield 1.10 g (3.4 mmol, 64.9%); m.p. 83–84 ºC; 1H-NMR (400 MHz, DMSO-d6) δ: 1.52 (t, 3H, J = 7.6 Hz, CH3), 2.29 (s, 3H, CH3), 2.36 (s, 6H, CH3), 4.22 (q, 2H, J = 7.6 Hz, CH2), 6.91 (s, 2H, Ar–H), 6.99 (d, 1H, J = 16.4 Hz, CH–CH), 7.30–7.38 (m, 3H, Ar–H), 7.80 (s, 1H, Ar–H), 7.93 (d, 1H, J = 16.4 Hz, CH–CH), 8.05–8.83 (m, 1H, Ar–H). 13C-NMR (100 MHz, DMSO-d6) δ: 15.3, 21.1, 21.3, 140.9, 108.8, 117.8, 122.7, 123.2, 123.6, 127.1, 129.1, 129.3, 132.3, 133.8, 136.8, 136.9, 137.9, 139.6, 184.5; IR (KBr, cm−1) νmax = 3041, 2974, 1614, 1584, 1525, 1483, 1447, 1385, 1302, 1294, 1206, 1188, 1086; [Anal. Calcd. for C33H29NO2: C, 83.24; H, 7.30; N, 4.41; Found: C, 83.52; H, 7.19; N, 4.61]; LC/MS (ESI, m/z): [M+] found 318.20, C21H16FNO for 317.18.
5-(1-(4-Chlorophenyl)-3-(1-ethyl-1H-indol-3-yl)-3-oxopropyl)-1,3-dimethylpyrimidin-2,4,6(1H,3H,5H)-trione (5c)

Yield 275 mg (0.55 mmol, 55.1%); m.p. 149–150 °C; 1H-NMR (600 MHz, CDCl₃) δ: 1.54 (t, 3H, J = 4.8 Hz, NCH₂CH₃), 3.20 (3H, NCH₃), 3.22 (s, 3H, NCH₃), 3.37–3.39 (dd, 1H, J = 10.8 Hz, 4.0 Hz, CH₂N), 3.38–3.71 (dd, 1H, J = 10.8 Hz, 6.4 Hz, Ar, CH₂), 3.86 (dd, 1H, J = 2.4 Hz, CH), 4.23 (q, 2H, J = 4.8 Hz, NCH₂CH₃), 4.90–4.93 (m, 1H, CH), 7.20 & 7.23 (dd, 1H, J = 5.6 Hz, 1.6 Hz, Ar-H), 7.28–7.32 (m, 2H, Ar-H), 7.35–7.38 (m, 2H, Ar-H), 7.40 (d, 1H, J = 1.6 Hz, Ar-H), 7.85 (s, 1H, Ar-H); 13C-NMR (150 MHz, CDCl₃) δ: 15.2, 28.2, 29.5, 38.9, 41.0, 42.1, 52.9, 109.8, 114.9, 122.6, 122.9, 123.2, 123.5, 127.2, 128.4, 129.8, 130.0, 133.9, 134.9, 135.9, 137.0, 150.1, 167.9, 168.4, 192.1; IR (KBr, cm⁻¹) νmax = 3449, 2940, 1747, 1694, 1681, 1653, 1530, 1461, 1427, 1379, 1288, 1201, 1104, 1052; [Anal. Calc. for C₂₃H₂₁ClN₂O₃; C, 60.01; H, 4.63; N, 8.40; Found: C, 69.89; H, 4.71; N, 8.32] LC/MS (ESI, m/z): [M⁺] found 500.21, C₂₃H₂₁ClN₂O₃ for 499.11.

5-(3-(1-Ethyl-1H-indol-3-yl)-3-oxo-1-(p-toly)propyl)pyrimidin-2,4,6(1H,3H,5H)-trione (5b)

Yield 200 mg (0.45 mmol, 44.9%); m.p. 155–156 °C; 1H-NMR (600 MHz, CDCl₃) δ: 1.55 (t, 3H, J = 4.2 Hz, NCH₂CH₃), 2.29 (s, 3H, CH₃), 3.07 (s, 3H, NCH₃), 3.11 (s, 3H, NCH₃), 3.32–3.34 (dd, 1H, J = 11.2 Hz, 3.6 Hz, CH₃), 3.95–3.99 (m, 2H, CH₂NCH₃&CH), 4.23 (q, 2H, J = 4.8 Hz, NCH₂CH₃), 4.38–4.44 (m, 1H, CH), 7.01 (d, 2H, J = 5.6 Hz, Ar-H), 7.06 (d, 2H, J = 5.2 Hz, Ar-H), 7.28–7.31 (m, 2H, Ar-H), 7.36–7.58 (m, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 8.39–8.40 (m, 1H, Ar-H); 13C-NMR (150 MHz, CDCl₃) δ: 12.2, 21.1, 28.0, 28.1, 41.2, 41.8, 44.6, 53.3, 109.7, 116.5, 122.6, 122.8, 123.7, 129.3, 134.1, 135.4, 136.4, 137.9, 151.1, 168.0, 148.4, 192.4; IR (KBr, cm⁻¹) νmax = 3437, 3114, 3101, 3059, 2955, 1678, 1636, 1539, 1448, 1426, 1371, 1335, 1227, 1142, 1084; [Anal. Calc. for C₁₂H₁₂N₂O₂; C, 70.09; H, 6.11; N, 9.43; Found: C, 69.87; H, 5.95; N, 9.63] LC/MS (ESI, m/z): [M⁺] found 446.28, C₁₂H₁₁N₂O₂ for 445.20.

5-(1-(4-Methoxyphenyl)-3-(1-ethyl-1H-indol-3-yl)-3-oxopropyl)-1,3-dimethylpyrimidin-2,4,6(1H,3H,5H)-trione (5f)

Yield 200 mg (0.39 mmol, 39.3%); m.p. 159–160 °C; 1H-NMR (600 MHz, CDCl₃) δ: 1.55 (t, 3H, J = 5.2 Hz, NCH₂CH₃), 3.12 (s, 3H, NCH₃), 3.16 (s, 3H, NCH₃), 3.34–3.37 (dd, 1H, J = 11.2 Hz, 4.0 Hz, CH₂O), 3.96 & 3.98 (dd, 1H, J = 11.2 Hz, 6.4 Hz, CH₂O), 3.98 (d, 1H, J = 2.4 Hz, CH), 4.23 (q, 2H, J = 4.8 Hz, NCH₂CH₃), 7.04 (d, 2H, J = 5.6 Hz, Ar-H), 7.29–7.31 (m, 2H, Ar-H), 7.37–7.39 (m, 1H, Ar-H), 7.40 (d, 2H, J = 5.6 Hz, Ar-H), 7.94 (s, 1H, Ar-H); 8.35–8.36
5-(3-(1-Ethyl-1H-indol-3-yl)-1-(4-fluorophenyl)-3-oxopropyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5g)

Yield 214 mg (0.48 mmol, 47.6%); m.p. 185–186°C; 1H-NMR (600 MHz, CDCl₃) δ: 1.55 (t, 3H, J = 5.2 Hz, NCH₂CH₃), 3.11 (3H, NCH), 3.15 (3H, NCH), 3.37–3.40 (dd, 1H, J = 11.2 Hz, 3.6 Hz, CH₃O), 3.95–3.98 (m, 2H, CH₂N), 4.22–4.26 (2H, CH₂), 4.24 (q, 2H, J = 4.8 Hz, CH₂N), 4.45–4.59 (m, 1H, CH), 6.89–6.92 (m, 1H, ArH), 6.94–6.98 (m, 2H, ArH), 7.23–7.25 (m, 1H, ArH), 7.29–7.31 (m, 2H, ArH), 7.32–7.39 (m, 1H, ArH), 7.56 (s, 1H, ArH), 8.06–8.38 (m, 1H, ArH); 13C-NMR (150 MHz, CDCl₃) δ: 15.3, 28.2, 28.4, 41.1, 41.9, 44.1, 35.1, 90.8, 115.1, 115.2, 120.1, 122.7, 122.9, 123.5, 127.0, 129.5, 130.3, 134.2, 136.6, 137.9, 138.7, 150.2, 167.9, 168.3, 191.1; IR (KBr cm⁻¹) νmax = 3471, 3118, 2951, 1745, 1682, 1639, 1614, 1588, 1528, 1463, 1445, 1420, 1375, 1273, 1206, 1114, 1053; [Anal. Calcd. for C₂₉H₂₃F₂N₃O₃: C 62.34, H 5.11, N 9.48; LC/MS (ESI, m/z): [M⁺] found 540.2, C₂₉H₂₃F₂N₃O₃ for 549.18].

5-(3-(1-Ethyl-1H-indol-3-yl)-1-(3-fluorophenyl)-3-oxopropyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5j)

Yield 214 mg (0.48 mmol, 47.6%); m.p. 185–186°C; 1H-NMR (600 MHz, CDCl₃) δ: 1.55 (t, 3H, J = 5.2 Hz, NCH₂CH₃), 3.11 (3H, NCH), 3.15 (3H, NCH), 3.37–3.40 (dd, 1H, J = 11.2 Hz, 3.6 Hz, CH₃O), 3.95–3.98 (m, 2H, CH₂N), 4.22–4.26 (2H, CH₂), 4.24 (q, 2H, J = 4.8 Hz, CH₂N), 4.45–4.59 (m, 1H, CH), 6.89–6.92 (m, 1H, ArH), 6.94–6.98 (m, 2H, ArH), 7.23–7.25 (m, 1H, ArH), 7.29–7.31 (m, 2H, ArH), 7.32–7.39 (m, 1H, ArH), 7.56 (s, 1H, ArH), 8.06–8.38 (m, 1H, ArH); 13C-NMR (150 MHz, CDCl₃) δ: 15.3, 28.2, 28.4, 41.1, 41.9, 44.1, 35.1, 90.8, 115.1, 115.2, 120.1, 122.7, 122.9, 123.5, 127.0, 129.5, 130.3, 134.2, 136.6, 137.9, 138.7, 150.2, 167.9, 168.3, 191.1; IR (KBr cm⁻¹) νmax = 3471, 3118, 2951, 1745, 1682, 1639, 1614, 1588, 1528, 1463, 1445, 1420, 1375, 1273, 1206, 1114, 1053; [Anal. Calcd. for C₂₉H₂₃F₂N₃O₃: C 62.34, H 5.11, N 9.48; LC/MS (ESI, m/z): [M⁺] found 540.2, C₂₉H₂₃F₂N₃O₃ for 549.18].
Yield 185 mg (0.35 mmol, 35.5%); m.p. 170–171 

5-(3-(1-Ethyl-1H-indol-3-yl)-1-(naphthalen-2-yl)-3-oxopropyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5b)

Yield 178 mg (0.37 mmol, 37.0%); m.p. 7.88 (s, 1H, Ar-H), 8.17 (d, 2H, J = 4.8 Hz, CH_2O), 4.21–4.26 (m, 4H, CH_2O & CH_3). 

Concentration of α-glucosidase and substrate. Sodium phosphate buffer (0.1 M) was adjusted by 0.1 N HCl to pH 7.0 with a pH meter (Thermo Fisher Scientific Inc., Waltham, MA, USA) prior to adding the enzyme. Immediately following α-glucosidase addition, absorbance was measured at 405 nm 8

Briefly, 250 L of amylase solution for 10 min at 25°C and then boiled for 15 min after the addition of 250 μL of DNS to stop the reaction. The amount of reducing sugars released was determined spectrophotometrically using a malondialdehyde curve and reaction to velocity reactions.

Calculation of Inhibition Efficiency

The inhibitory concentration 50% (IC_{50}) values were determined from the plots of percent inhibition versus log inhibitor concen-
Docking Studies

A virtual library of designed compounds was energy minimized using the MMFF94 force field, which was followed by the generation of multi-conformers using the Omega application. The entire energy-minimized library was docked with the prepared catalytic domain of (PDB code: 4UAC)\(^{12}\) using the FRED application in OpenEye software\(^{13a}\) to generate a physical property (ΔG) reflecting the predicted energy profile of the ligand-receptor complex. The Vida application can be employed as a visualization tool to show the potential binding interactions of the ligands with the receptor of interest.

3. Conclusion

The present study mainly focuses on the synthesis of novel indole-pyrimidine based chemical entities for the improved anti-diabetic activity. The new series of indole-pyrimidine based compounds obtained via bimetallic catalytic system which has a dramatic effect in promoting the Michael addition reaction. The synthesized compounds screened against wide range of α-glucosidase inhibition and α-amylase assay inhibitory activity. Docking study describes that both barbiturate and acyl indole parts participate in HB while the aryl linker occupy the receptor through lipophilic-lipophilic interactions.

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Conflict of Interest

The authors report no declarations of interest.

Keywords: bimetallic catalysis · Lewis acid · Michael addition · indoles · barbituric acid · α-amylase · α-glucosidase · docking studies

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