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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 acetylacetone (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 IC_{50} (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 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 antileishmanial and anti-inflammatory.[3] 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 pyrimdine scaffolds.[7] One example of our invention the use of indole scaffold in the treatment and prevention of diabetes has been described (Figure 1).[7–8]

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 overrun 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

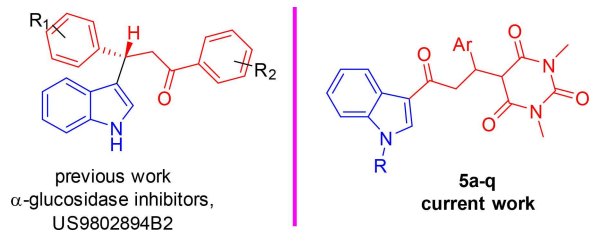

Figure 1. Previous and current study.

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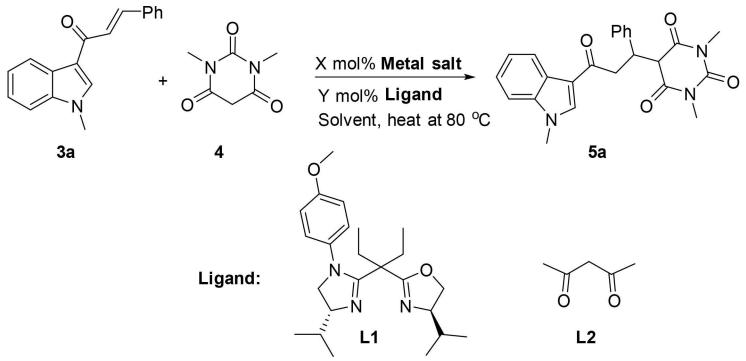
Table 1. Model example for investigation of the reaction parameters.



#	Solvent	Metal Salts	Ligands	Ligand : Metal mol %	Yield
1.	Toluene	$Cu(OTf)_2$	L1	10 : 11 mol%	No rxn[b]
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	$FeCl_3/PdCl_2$	L1	10 : 10 mol%	No rxn
7.	MeOH[a]	$FeCl_3/PdCl_2$	L2	10 : 10 mol%	55 %

[a] The reaction carried out at 60 °C. [b] No rxn: No reaction.

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

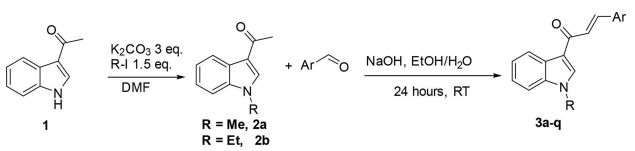
2.1. Synthesis

The requisite compounds chalcones were prepared by reaction of N-alkyl-3-acetylindole and aryl aldehyde derivatives stirring in $EtOH/H_2O$ (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.[14b]

Reaction of (*E*)-1-(1-methyl-1*H*-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-1*H*-indol-3-yl)-3-oxo-1-phenylpropyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-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.[10] 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 didnot 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_3OH at at 60 °C. All of the results are summarized in Table 2.

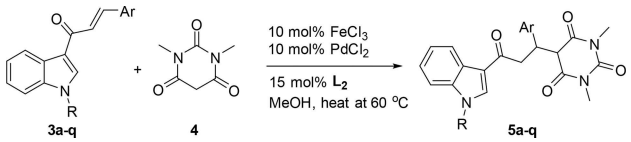


Scheme 1. Synthesis of the chalcones **3a–q**.

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 fluorophenyl ring (C12–C17) and pyrimidine moiety (C20–C21–N2–C22–N3–C23) are 22.41° and 41.07°, respectively. The angle between fluorophenyl 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.

Table 2. Substrate scope of desired compounds **5a–q**.



#	Chlacones 3a–q	Ar	R	Products 5a–q	[%] Yield 5a–q
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-Cl_2Ph	Et	**5d**	**55.1**
5.	**3e**	4-OMePh	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-CF_3Ph	Et	**5k**	**39.7**
12.	**3l**	Thiophinyl	Et	**5l**	**53.7**
13.	**3m**	Furanyl	Et	**5m**	**54.6**
14.	**3n**	3,4,5-OMe_3Ph	Et	**5n**	**35.5**
15.	**3o**	2-Napthyl	Et	**5o**	**37**
16.	**3p**	2,4,6-Me_3Ph	Et	**5p**	-
17.	**3q**	4-NO_2Ph	Et	**5q**	**34.6**

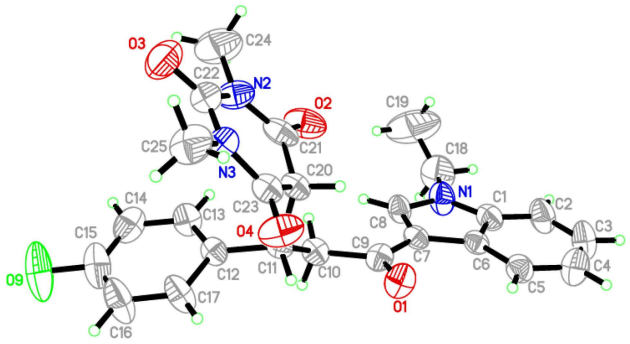


Figure 2. ORTEP diagram of the titled compounds **5g**. Displacement ellipsoids are plotted at the 40% probability level for non-H atoms.

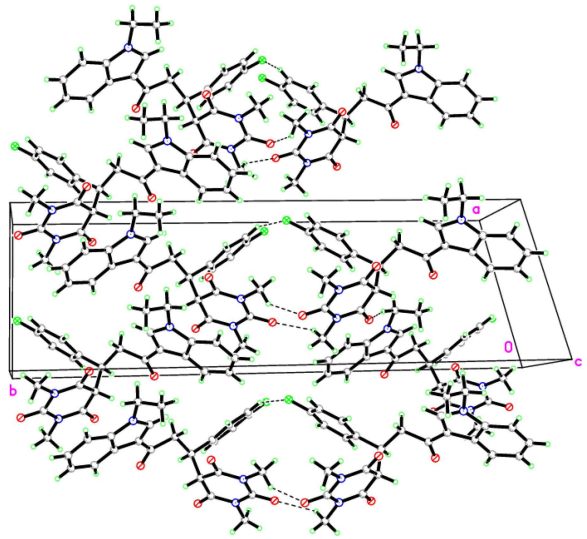


Figure 3. Molecular packing of titled compounds **5g** viewed hydrogen bonds which are drawn as dashed lines along b axis.

2.3. Biological Activity

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 α-glucosidase and on α-amylase, are compounds **5o**, **5k**, and **5l**. All other compounds were found to have only good to moderate activity ranging from 28.05 + 0.41 to 77.05 + 0.04 μM in the case of α-glucosidase, but in the range of 53.10 + 0.10 to 96.42 + 0.22 μM in the case of α-amylase. Structure activity relationship indicates the importance of the naphthyl moiety in **5o**, of the *p*-CF_3Ph propanone substituted indole in **5k**, and of a thiophene ring in **5l**. The most active compound is **5o**, which showed an IC_{50} = 13.02 + 0.01 μM and 21.71 + 0.82 μM, for α-glucosidase, and α - amylase respectively.

2.4. Docking Studies

The compound **5 o** 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 acrabose standard with receptor in its cocrystalized from.[12]

Compound **5o** exhibited high similarity to the potent derivative (compound **5l)** 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, 53.8%); All other spectral data are consistent with reported literature.[14c]

(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; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.47 (t, 3H, J = 7.2 Hz, CH_3), 2.29 (s, 3H, CH_3) 4.12 (q, 2H, J = 7.2 Hz, CH_2), 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), 7.81 (s, 1H, Ar–H), 8.44–8.46 (m, 1H, Ar–H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.4, 41.8, 109.6, 117.7, 122.5,

Table 3. Experimental details of **5g**.

Crystal data **5 g**	
Chemical formula	$C_{25}H_{24}FN_3O_4$
Mr	449.47
Crystal system, space group	Monoclinic, *Cc*
Temperature (K)	293
a, *b*, *c* (Å)	12.128 (5), 28.221 (12), 8.718 (3)
β (°)	129.532 (9)
V (Å^3)	2301.4 (16)
Z	4
Radiation type	Mo *K*α radiation
μ (mm^{-1})	0.09
Crystal size (mm)	0.33×0.20×0.09
Data collection	
Diffractometer	Bruker APEX-II D8 venture
Absorption correction	Multi-scan, SADABS Bruker 2014
θ_{max}	27.0°
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	21063, 4914, 2093
R_{int}	0.180
Refinement	
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.067, 0.184, 0.99
No. of reflections	4914
No. of parameters	302
No. of restraints	2
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.22, −0.15
CCDC	1877313

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

O9–C15	1.374 (16)	N1–C18	1.488 (10)
O1–C9	1.230 (10)	N2–C21	1.369 (12)
O2–C21	1.216 (9)	N2–C22	1.384 (11)
O3–C22	1.231 (11)	N2–C24	1.477 (14)
O4–C23	1.208 (9)	N3–C22	1.353 (11)
N1–C1	1.386 (11)	N3–C23	1.372 (11)
N1–C8	1.355 (10)	N3–C25	1.479 (10)
C1–N1–C8	108.3 (6)	O1–C9–C10	120.6 (7)
C1–N1–C18	126.0 (7)	O9–C15–C14	116.6 (10)
C8–N1–C18	125.7 (7)	O9–C15–C16	120.0 (13)
C21–N2–C22	123.7 (7)	N1–C18–C19	115.2 (9)
C21–N2–C24	119.2 (7)	O2–C21–N2	119.9 (7)
C22–N2–C24	117.0 (8)	O2–C21–C20	121.6 (8)
C22–N3–C23	124.4 (6)	N2–C21–C20	118.5 (7)
C22–N3–C25	117.5 (7)	O3–C22–N2	120.2 (9)
C23–N3–C25	118.1 (6)	O3–C22–N3	121.1 (8)
N1–C1–C2	129.6 (7)	N2–C22–N3	118.7 (8)
N1–C1–C6	107.6 (7)	O4–C23–N3	120.1 (7)
N1–C8–C7	110.8 (7)	O4–C23–C20	121.5 (8)
O1–C9–C7	121.3 (8)	N3–C23–C20	118.4 (7)

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

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
C10–H10B···O2	0.9700	2.3200	2.975 (12)	124.00
C14–H14A···O9^{i}	0.9300	2.3400	3.170 (13)	148.00
C18–H18A···O4^{ii}	0.9700	2.4500	3.364 (14)	156.00
C25–H25B···O3^{iii}	0.9600	2.5400	3.388 (15)	148.00

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 IC_{50} (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	**5q**	31.12±0.11	63.00±0.61
STD	**Acarbose (μM)**	2.35±0.13	0.75±0.07

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

122.9, 123.0, 123.4, 127.0, 128.0, 129.5, 132.6, 133.5, 136.6, 104.0, 140.9, 184.4; IR (KBr, cm^{-1}) ν_{max}=3043, 2979, 1643, 1585, 1523, 1486, 1447, 1388, 1308, 1299, 1205, 1205, 1185, 1087; [Anal. Calcd. for $C_{20}H_{19}NO$: 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, $C_{20}H_{19}NO$for 289.15.

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

Yield 1.56 g (5.04 mmol, 94.5%); All other spectral data are consistent with reported literature.[14d]

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

Yield 1.70 g (4.9 mmol, 92.8%); m.p. 168–169 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 148 (t, 3H, *J*=7.2 Hz, CH_3), 4.14 (q, 2H, *J*=7.2 Hz, CH_2), 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); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.3, 42.1, 109.8, 117.7, 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}) ν_{max} = 3046, 2971, 2926, 2872, 1653, 1595, 1582, 1527, 1464, 1392, 1238, 1200, 1124, 1098, 1057; [Anal. Calcd. for $C_{19}H_{15}Cl_2NO$: C, 66.29; H, 4.39; N, 4.07; Found: C, 66.42; H, 4.23; N, 4.36]; LC/MS (ESI, *m/z*): [M$^+$], found 344.10, $C_{19}H_{15}Cl_2NO$ for 343.05.

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

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

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

Yield 1.75 g (4.95 mmol, 92.8%); m.p. 139–140 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.49 (t, 3H, *J*=7.2 Hz, CH_3), 4.17 (q, 3H, *J*=7.2 Hz, CH_2), 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),

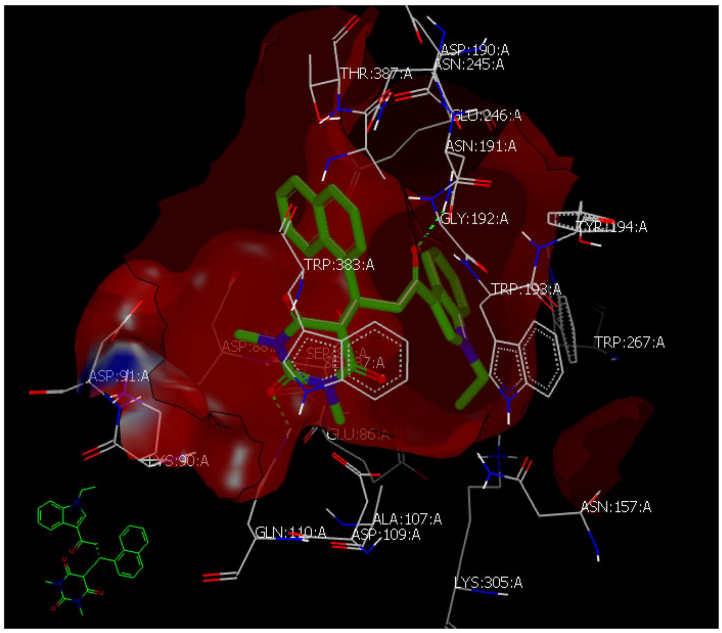


Figure 4. Snap shot visualization of **5o** docked with ID: **4AUC**, showing formation of two HBs interaction as illustrated by Vida

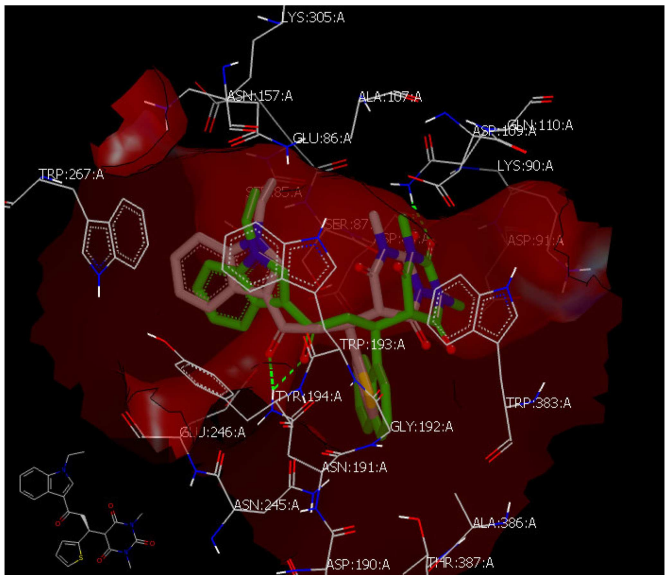


Figure 5. Snap shot visualization of compound **5l** overlays with **5o** and shown same binding mode and pose with receptor.

8.42–8.45 (m, 1H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 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, 133.3, 136.7, 139.5, 183.8; IR (KBr, cm^{-1}) ν_{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) δ: 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); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 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}) ν_{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) δ: 1.47 (t, 3H, J = 6.0 Hz, CH_3), 4.15 (q, 2H, J = 6.0 Hz, CH_2),

6.94–7.00 (m, 1H, Ar–H), 7.24–7.29 (m, 7H, J = 6.8 Hz, Ar–H & CH=CH), 7.67 (d, 1H, J = 15.2 Hz, CH=CH), 7.83 (s, 1H, Ar–H), 8.43–8.45 (m, 1H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.3, 42.0,109.9, 114.0 & 114.2, 116.6 & 116.8, 117.7, 122.9, 123.2, 123.7, 124.4, 125.0, 127.0, 130.4 & 130.5, 133.9, 136.8, 137.7 & 137.8, 139.6, 162.4, 164.1, 184.8; IR (KBr, cm^{-1}) ν_{max} = 3459, 3049, 2977, 1646, 1611, 1588, 1524, 1486, 1463, 1449, 1391, 1311, 1245, 1268, 1260, 1011; [Anal. Calcd. for $C_{19}H_{16}FNO$: C, 77.80; H, 5.50; N, 4.77; Found: C, 77.95; H, 5.37; N, 4.48]; LC/MS (ESI, *m/z*): [M$^+$], found 294.21, $C_{19}H_{16}FNO$ for 293.12.

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(m–tolyl)prop-2-en-1-one (3i)

Yield 1.28 g (4.42 mmol, 82.9%); m.p. 116–117 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.54 (t, 3H, J = 7.2 Hz, CH_3), 2.38 (s, 3H, CH_3), 4.22 (q, 2H, J = 7.2 Hz, CH_2), 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); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.3, 41.8, 109.7, 117.7, 122.6, 123.1, 123.4, 123.6, 125.3, 127.0, 128.6, 130.6, 133.7, 135.3, 136.7, 138.4, 138.4, 141.2, 184.3; IR (KBr, cm^{-1}) ν_{max} = 3046, 2977, 1644, 1589, 1525, 1482, 1449, 1389, 1304, 1297, 1206, 1204, 1188, 1088; [Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84; Found: C, 83.35; H, 6.51; N, 4.73]; LC/MS (ESI, *m/z*): [M$^+$], found 290.24, $C_{20}H_{19}NO$ for 289.15.

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

Yield 1.60 g (4.53 mmol, 84.8%); m.p. 126–127 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.54 (t, 3H, J = 5.6 Hz, CH_3)„ 4.22 (q, 2H, J = 5.6 Hz, CH_2), 7.25–7.36 (m, 5H, Ar–H & CH=CH), 7.49 (t, 2H, J = 8.8 Hz, Ar–H), 7.68–7.78 (m, 2H, J = 15.2 Hz, Ar–H & CH=CH), 7.92 (s, 1H, Ar–H), 8.50–8.53 (m, 1H, Ar–H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.3, 42.0, 109.9, 117.7, 122.9, 123.01, 123.2, 123.8, 125.1, 127.05, 127.3, 130.3, 130.4, 132.6, 134.03, 136.8, 137.6, 139.3, 183.7; IR (KBr, cm^{-1}) ν_{max} = 3445, 3042, 2971, 1643, 1617, 1585, 1521, 1482, 1467, 1455, 1399, 1312, 1242, 1261, 1264, 1012; [Anal. Calcd. for $C_{19}H_{16}BrNO$: C, 64.42; H, 4.55 N, 3.95; Found: C, 64.65; H, 4.38; N, 4.17]; LC/MS (ESI, *m/z*): [M$^+$ found 354.19, $C_{19}H_{16}BrNO$ for 353.04.

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(4-(trifluoromethyl)phenyl) prop-2-en-1-one (3k)

Yield 1.7 g (4.9 mmol, 92.7%); m.p. 150–151 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.54 (t, 3H, J = 7.2 Hz, CH_3), 4.23 (q, 2H, J = 7.2 Hz, CH_2), 7.31–7.39 (m, 3H, Ar–H), 7.44 (d, 1H, J = 15.2 Hz, CH=CH), 7.61 (d, 2H, J = 8.0 Hz, Ar–H), 7.69 (d, 2H, J = 8.0 Hz, Ar–H), 7.80 (d, 1H, J = 15.2 Hz, CH=CH), 7.92 (s, 1H, Ar–H), 8.49–8.51 (m, 1H, Ar–H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.1, 41.7, 109.7, 112.3, 114.6, 117.7, 121.4, 122.6, 123.1, 123.4, 126.9, 127.4, 133.8, 136.7, 144.03, 152.0, 183.8; IR (KBr, cm^{-1}) ν_{max} = 3441, 3037, 2981, 1652, 1624, 1596, 1532, 1475, 1471, 1456, 1388, 1327, 1246, 1275, 1252, 1011; [Anal. Calcd. for $C_{20}H_{16}F_3NO$: C, 69.96; H, 4.70; N, 4.08; Found: C, 70.12; H, 4.92; N, 4.40]; LC/MS (ESI, *m/z*): [M$^+$], found 344.24, $C_{20}H_{16}F_3NO$ for 343.12

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(thiophen-2-yl)prop-2-en-1-one (3l)

Yield 1.46 g (5.19 mmol, 97.2%); m.p. 119–120 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.47 (t, 3H, J = 7.6 Hz, CH_3), 4.14 (q, 2H, J = 7.6 Hz, CH_2), 6.98 (t, 1H, J = 7.6 Hz, Ar–H), 7.10 (d, 1H, J = 15.6 Hz, CH=CH), 7.24–7.30 (m, 5H, Ar–H), 7.81 (s, 1H, Ar–H), 7.86 (d, 1H, J = 15.6 Hz, CH=CH), 8.45–8.44 (m, 1H, Ar–H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.1, 41.8, 109.7, 117.6, 122.6, 122.8, 123.1, 123.5, 126.9, 127.5, 128.1, 130.9, 133.6, 133.7, 136.7, 140.8, 183.6; IR (KBr, cm^{-1}) ν_{max} = 3474, 3106, 3073, 2970, 2928, 1632, 1560, 1522, 1486, 1447, 1388, 1360, 1207, 1103, 1085,; [Anal. Calcd. for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98; Found: C, 72.82; H, 5.15; N, 5.10]; LC/MS (ESI, *m/z*): [M$^+$], found 282.23, $C_{17}H_{15}NOS$ for 281.09.

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(furan-2-yl)prop-2-en-1-one (3m)

Yield 1.35 g (5.09 mmol, 95.4%); m.p. 74–75 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.54 (t, 3H, J = 7.2 Hz, CH_3), 4.23 (q, 2H, J = 7.2 Hz, CH_2), 7.32–7.37 (m, 3H, Ar–H), 7.42 (d, 1H, J = 15.6 Hz, CH=CH), 7.61 (d, 2H, J = 8.0 Hz, Ar–H), 7.69 (d, 2H, J = 8.0 Hz, Ar–H), 7.75 (d, 1H, J = 15.2 Hz, CH=CH), 7.92 (s, 1H, Ar–H), 8.49–8.51 (m, 1H, Ar–H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.1, 41.7, 109.7, 112.3, 114.6, 117.7, 121.3, 123.0, 123.4, 126.9, 127.4, 133.8, 136.7, 144.0, 152.0, 183.7; IR (KBr, cm^{-1}) ν_{max} = 3478, 3102, 3075, 2972, 2929, 1631, 1562, 1524, 1488, 1442, 1389, 1365, 1204, 1102, 1086; [Anal. Calcd. for $C_{17}H_{15}NO_2$: 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 266.27, $C_{17}H_{15}NO_2$ for 265.11.

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

Yield 1.1 g (3.01 mmol, 56.4%); m.p. 197–198 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.53 (t, 3H, J = 7.6 Hz, CH_3), 3.87 (s, 3H, OCH_3) 3.90 (s, 6H, OCH_3), 4.23 (q, 2H, J = 7.6 Hz, CH_2), 6.83 (s, 2H, 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); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.2, 41.8, 56.2, 60.9, 105.4, 109.7, 117.6, 122.6, 123.1, 123.2, 123.5, 127.0, 130.9, 133.8, 136.8, 141.3, 153.4, 184.1; IR (KBr, cm^{-1}) ν_{max} = 3452, 3103, 2977, 2942, 2831, 1639, 1581, 1566, 1522, 1463, 1447, 1419, 1392, 1337, 1250, 1147, 1121, 1002; [Anal. Calcd. for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83; Found: C, 72.46; H, 6.12; N, 3.51]; LC/MS (ESI, *m/z*): [M$^+$], found 366.20, $C_{22}H_{23}NO_4$ for 365.16.

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(naphthalen-2-yl)prop-2-en-1-one (3o)

Yield 0.9 g (2.7 mmol, 51.8%); m.p. 113–114 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.46 (t, 3H, J = 7.2 Hz, CH_3), 4.14 (q, 2H, J = 7.2 Hz, CH_2), 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, 3H, J = 15.2 Hz, CH=CH & Ar–H), 8.46–8.48 (m, 1H, Ar–H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.1, 41.8, 109.7, 117.7, 122.6, 123.1, 123.5, 123.8, 123.9, 126.5, 126.9, 127.0, 127.7, 128.4, 129.8, 132.8, 133.4, 133.9, 134.0, 136.7, 141.1, 184.1; IR (KBr, cm^{-1}) ν_{max} = 3478, 3105, 3049, 2968, 2926, 2879, 1642, 1578, 1505, 1468, 1388, 1294, 1208, 1141, 1085; [Anal. Calcd. for $C_{23}H_{19}NO$: 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, $C_{23}H_{19}NO$ for 325.15.

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-mesitylprop-2-en-1-one (3p)

Yield 1.10 g (3.4 mmol, 64.9%); m.p. 83–84 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.52 (t, 3H, J = 7.6 Hz, CH_3), 2.29 (s, 3H, CH_3) 2.36 (s, 6H, CH_3), 4.22 (q, 2H, J = 7.6 Hz, CH_2), 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), 8.50–8.53 (m, 1H, Ar–H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.3, 21.1, 21.3,41.9, 109.8, 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}) ν_{max} = 3041, 2974, 1641, 1584, 1525, 1483, 1447, 1385, 1302, 1294, 1206, 1188, 1089, 1062; [Anal. Calcd. for $C_{22}H_{23}NO$: 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; $C_{22}H_{23}NO$ for 317.18.

(E)-1-(1-Ethyl-1H-indol-3-yl)-3-(4-nitrophenyl)prop-2-en-1-one (3q)

Yield 0.95 g (2.9 mmol, 55.5%); m.p. 179–180 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.45 (t, 3H, J = 7.2 Hz, CH_3), 4.1 (t, 2H, J = 7.2 Hz, CH_2), 7.24–7.30 (m, 5H, Ar–H & CH=CH), 7.55 (d, 2H, J = 8.8 Hz, Ar–H), 8.13 (d, 2H, J = 8.8 Hz, Ar–H), 8.17 (d, 1H, J = 15.2 Hz, CH=CH), 8.25 - 8.27 (m, 1H, Ar–H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.1, 41.9, 109.9, 116.2, 122.5, 123, 123.6, 126.5, 128.5, 134.3, 136.6, 137.9, 141.7, 147.2, 150.8, 194.1; IR (KBr, cm^{-1}) ν_{max} = 3472, 3116, 3069, 3049, 2973, 1744, 1679, 1638, 1529, 1462, 1423, 1378, 1285, 1205, 1129, 1110, 1052; [Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74; Found: C, 71.51; H, 5.19; N, 8.95]; LC/MS (ESI, *m/z*): [M$^+$], found 321.19, $C_{19}H_{16}N_2O_3$ for 320.12.

General Procedure for the Preparation of 5a-q

$FeCl_3$ (0.025 mmol), $PdCl_2$ (0.025 mmol), and acetylacetone (0.075 mmol) were added into a solution of enone (0.5 mmol) and barbituric acid (0.55 mmol) in freshly distilled CH_3OH (2 ml). After stirring at room temperature for 24 h, the mixture was diluted with H_2O (10 ml) and extracted with EtOAc (3×15 ml). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo* and purified by column chromatography on silica gel (200–300 mesh, gradient eluted with EtOAc–petroleum ether = 1 : 10–1: 5) to gain the pure product.

1,3-Dimethyl-5-(3-(1-methyl-1H-indol-3-yl)-3-oxo-1-phenyl-propyl)pyrimidine-2,4,6(1H,3H,5H)-trione (5a)

Yield 230 mg (0.55 mmol, 55%); m.p. 185–186 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 3.06 (s, 3H, NCH_3), 3.11 (s, 3H, NCH_3), 3.34–3.36 (dd, 1H, J = 11.2 Hz, 3.6 Hz, $CH_{2(a)}$), 3.87 (s, 3H, NCH_3), 3.96–4.00 (m, 2H, $CH_{2(e)}$& CH), 4.49–4.46 (m, 1H, CH), 2.48–2.58 (m, 1H, CH_2), 3.82–3.92 (m, 1H, CHN), 7.11–7.13 (m, 2H, Ar–H), 7.26–7.35 (m, 6H, Ar–H), 7.93 (s, 1H,Ar–H), 8.34–8.39 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 28.0, 28.1, 33.6, 41.0, 44.9, 53.2, 109.6, 116.5, 122.6, 122.7, 123.4, 126.2, 127.3, 128.2, 128.6, 135.7, 137.4, 138.4, 151.0, 167.9, 168.3, 192.2; IR (KBr, cm^{-1}) ν_{max} = 3439, 3111, 3108, 3056, 2951, 1679, 1637, 1536, 1530, 1442, 1425, 1375, 1335, 1223, 1145, 1081; [Anal. Calcd. for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07; Found: C, 69.23; H, 5.41; N, 9.95]; LC/MS (ESI, *m/z*): [M$^+$], found 418.20, $C_{24}H_{23}N_3O_4$ for 417.17.

1,3-Dimethyl-5-(3-(1-methyl-1H-indol-3-yl)-3-oxo-1-(p–tolyl) propyl)pyrimidine-2,4,6(1H,3H,5H)-trione (5b)

Yield 200 mg (0.45 mmol, 44.9%); m.p. 155–156 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.55 (t, 3H, J = 4.2 Hz, NCH_2CH_3), 2.29 (s, 3H, CH_3), 3.07 (s, 3H, NCH_3), 3.11 (s, 3H, NCH_3), 3.32–3.34 (dd, 1H, J = 11.2 Hz, 3.6 Hz, $CH_{2(a)}$), 3.95–3.99 (m, 2H, $CH_{2(e)}$& CH), 4.23 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 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), 7.36–7.38 (m, 1H, Ar–H), 7.97 (s, 1H,Ar–H), 8.39–8.40 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 21.1, 28.0, 28.1, 41.2, 41.8, 44.6, 53.3, 109.7, 116.5, 122.6, 122.8, 123.3, 126.5, 127.2, 129.3, 134.1, 135.4, 136.4, 137.9, 151.1, 168.0, 148.4, 192.4; IR (KBr, cm^{-1}) ν_{max} = 3437, 3114, 3101, 3059, 2955, 1678, 1636, 1539, 1448, 1426, 1371, 1335, 1227, 1142, 1084; [Anal. Calcd. for $C_{26}H_{27}N_3O_4$: 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, $C_{26}H_{27}N_3O_4$ for 445.20.

5-(1-(4-Chlorophenyl)-3-(1-ethyl-1H-indol-3-yl)-3-oxopropyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5c)

Yield 280 mg (0.60 mmol, 60.2%); m.p. 166–167 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.55 (t, 3H, J = 4.2 Hz, NCH_2CH_3), 3.11 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 3.35–3.37(dd, 1H, J = 11.2 Hz, 5.0 Hz, $CH_{2(a)}$), 3.96 (t, 1H, J = 6.4 Hz, $CH_{2(e)}$), 3.98 (d, 1H, J = 2.8 Hz, CH), 4.23 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.44–4.49 (m, 1H, CH), 7.12 (d, 2H, J = 5.6 Hz, Ar–H), 7.24 (d, 2H, J = 5.6 Hz, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.37–7.39 (m, 1H, Ar–H), 7.95 (s, 1H,Ar–H), 8.33–8.37 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 27.3, 28.4, 41.1, 41.9, 43.6, 53.1, 109.8, 116.5, 121.8, 122.7, 123.4, 126.5, 129.1, 129.2, 134.1, 135.2, 136.7, 137.8, 151.0, 167.3, 168.0, 192.3; IR (KBr, cm^{-1}) ν_{max} = 3443, 2983, 1745, 1692, 1685, 1651, 1531, 1466, 1428, 1375, 1289, 1205, 1109, 1057; [Anal. Calcd. for $C_{25}H_{24}ClN_3O_4$: C, 64.44; H, 5.19; Cl, 7.61; N, 9.02; Found: C, 64.53; H, 5.32; N, 9.21]; LC/MS (ESI, *m/z*): [M$^+$], found 466.20, $C_{25}H_{24}ClN_3O_4$ for 465.15.

5-(1-(2,4-Dichlorophenyl)-3-(1-ethyl-1H-indol-3-yl)-3-oxoprop-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5d)

Yield 275 mg (0.55 mmol, 55.1%); m.p. 149–150 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.54 (t, 3H, J = 4.8 Hz, NCH_2CH_3), 3.20 (s, 3H, NCH_3), 3.22 (s, 3H, NCH_3), 3.37–3.39 (dd, 1H, J = 10.8 Hz, 4.0 Hz, $CH_{2(a)}$), 3.38–3.71 (dd, 1H, J = 10.8 Hz, 6.4 Hz, $CH_{2(a)}$), 3.86 (d, 1H, J = 2.4 Hz, CH), 4.23 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 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), 7.28 (d, 1H, J = 4.8 Hz, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) 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}) ν_{max} = 3449, 29.80, 17.47, 1694, 1681, 1653, 1530, 1461, 1427, 1379, 1288, 1201, 1104, 1052; [Anal. Calcd. for $C_{25}H_{23}Cl_2N_3O_4$: 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, $C_{25}H_{23}Cl_2N_3O_4$ for 499.11.

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

Yield 245 mg (0.53 mmol, 53.1%); m.p. 128–129 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.55 (t, 3H, J = 5.2 Hz, NCH_2CH_3), 3.09 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3), 3.31–3.34 (dd, 1H, J = 11.2 Hz, 3.6 Hz, $CH_{2(a)}$), 3.76 (s, 3H, OCH_3), 3.93–3.98 (m, 2H, $CH_{2(e)}$& CH), 4.23 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.39–4.44 (m, 1H, CH), 6.85 (d, 2H, J = 6.0 Hz, Ar–H), 7.50 (d, 2H, J = 6.0 Hz, Ar–H), 7.28–7.31 (m, 2H, Ar–H), 7.36–7.38 (m, 1H, Ar–H), 7.97 (s, 1H,Ar–H), 8.38–8.41 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 28.0, 28.2, 41.4, 41.8, 44.2, 53.4, 55.2, 109.7, 113.9, 116.6, 122.6, 122.7, 123.3, 126.5, 128.5, 130.4, 134.1, 136.5, 151.0, 159.2, 168.0, 168.5, 192.0; IR (KBr, cm^{-1}) ν_{max} = 3434, 3103, 2985, 2947, 2835, 1749, 1673, 1647, 1582, 1523, 1516, 1421, 1374, 1331, 1241, 1208, 1126, 1101, 1006; [Anal. Calcd. for $C_{26}H_{27}N_3O_5$: C, C, 67.66; H, 5.90; N, 9.10; Found: C, 66.71; H, 5.97; N, 9.21]; LC/MS (ESI, *m/z*): [M$^+$], found 462.30, $C_{26}H_{27}N_3O_5$ for 461.20.

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

Yield 200 mg (0.39 mmol, 39.3%); m.p. 159–160 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.55 (t, 3H, J = 5.2 Hz, NCH_2CH_3), 3.12 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 3.34–3.37 (dd, 1H, J = 11.2 Hz, 4.0 Hz, $CH_{2(a)}$), 3.96 & 3.98 (dd, 1H, J = 11.2 Hz, 6.4 Hz, $CH_{2(e)}$), 3.98 (d, 1H, J = 2.4 Hz, CH), 4.23 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.44–4.46 (m, 1H, CH), 7.06 (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

(m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 28.2, 28.3, 41.2, 41.8, 43.6, 52.8, 109.8, 116.5, 122.0, 122.6, 122.7, 123.4, 126.4, 129.3, 131.8, 134.0, 134.5, 138.1, 150.9, 167.8, 168.0, 192.1; IR (KBr, cm^{-1}) ν_{max} = 3452, 3116, 3043, 2974, 1744, 1679, 1638, 1526, 1462, 1423, 1378, 1285, 1205, 1110, 1052, 1009; [Anal. Calcd. for $C_{25}H_{24}BrN_3O_4$: C, 58.83; H, 4.74; N, 8.23; Found: C, 59.11; H, 4.59; N, 8.33]; LC/MS (ESI, *m/z*): [M^+], found 510.17, $C_{25}H_{24}BrN_3O_4$ for 509.10.

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; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.55 (t, 3H, J = 5.2 Hz, NCH_2CH_3), 3.10 (s, 3H, NCH_3), 3.14 (s, 3H, NCH_3), 3.35–3.38 (dd, 1H, J = 11.2 Hz, 3.6 Hz, $CH_{2(a)}$), 3.94–3.99 (m, 2H,$CH_{2(e)}$& CH), 4.23 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.45–4.59 (m, 1H, CH), 6.96 (t, 2H, J = 4.0 Hz, Ar–H), 7.15 (t, 2H, J = 4.0 Hz, Ar–H), 7.27–7.31 (m, 2H, Ar–H), 7.37–7.39 (m, 1H, Ar–H), 7.96 (s, 1H,Ar–H), 8.37–8.38 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 28.11, 28.3, 41.4, 41.7, 43.7, 53.2, 109.8, 115.5, 115.7, 121.9, 122.7, 123.4, 127.3, 129.1, 129.2, 134.1, 136.5, 139.1, 149.0, 167.0, 168.2, 191.2; IR (KBr, cm^{-1}) ν_{max} = 3471, 3118, 2951, 1745, 1682, 1639, 1614, 1588, 1528, 1463, 1445, 1420, 1375, 1273, 1206, 1114, 1053; [Anal. Calcd. for $C_{25}H_{24}FN_3O_4$: C, 66.80; H, 5.38; N, 9.35; Found: C, 67.02; H, 5.54; N, 9.47]; LC/MS (ESI, *m/z*): [M^+], found 450.20, $C_{25}H_{24}FN_3O_4$ for 449.18.

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

Yield 210 mg (0.47 mmol, 46.8%); m.p. 188–189 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.55 (t, 3H, J = 5.2 Hz, NCH_2CH_3), 3.11 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3), 3.37–3.40 (dd, 1H, J = 11.2 Hz, 3.6 Hz, $CH_{2(a)}$), 3.95–3.98 (m, 2H,$CH_{2(e)}$& CH), 4.22–4.26 (m, 2H CH), 4.24 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.45–4.59 (m, 1H, CH), 6.89–6.92 (m, 1H,Ar–H), 6.94–6.98 (m, 2H, Ar–H), 7.23–7.25 (m, 1H, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.37–7.39 (m, 1H, Ar–H), 7.96 (s, 1H,Ar–H), 8.36–8.38 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.3, 28.2, 28.4, 41.1, 41.9, 44.1, 35.1, 109.8, 115.1, 115.2, 121.0, 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}) ν_{max} = 3471, 3118, 2951, 1745, 1682, 1639, 1614, 1588, 1528, 1463, 1445, 1420, 1375, 1273, 1206, 1114, 1053; [Anal. Calcd. for $C_{25}H_{24}FN_3O_4$: C, 66.80; H, 5.38; N, 9.35; Found: C, 67.13; H, 5.61; N, 9.41]; LC/MS (ESI, *m/z*): [M^+], found 450.24, $C_{25}H_{24}FN_3O_4$ for 449.18.

5-(3-(1-Ethyl-1H-indol-3-yl)-3-oxo-1-(m–tolyl)propyl)-1, 3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5i)

Yield 194 mg (0.44 mmol, 46.6%); m.p. 125–126 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.56 (t, 3H, J = 5.2 Hz, NCH_2CH_3), 2.29 (s, 3H, CH_3), 3.06 (s, 3H, NCH_3), 3.10 (s, 3H, NCH_3), 3.34–3.37 (dd, 1H, J = 11.2 Hz, 3.6 Hz, $CH_{2(a)}$), 3.94–3.99 (m, 2H, $CH_{2(e)}$& CH), 4.24 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.37–4.49 (m, 1H, CH), 6.90 (d, 1H, J = 5.2 Hz, Ar–H), 6.93 (s, 1H, Ar–H), 7.06 (d, 1H, J = 5.2 Hz, Ar–H), 7.15 (t, 1H, J = 5.2 Hz, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.36–7.38 (m, 1H, Ar–H), 7.98 (s, 1H,Ar–H), 8.39–8.41 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 21.3, 27.9, 28.1, 41.0, 41.8, 45.0, 53.4, 109.7, 116.6, 122.6, 122.7, 123.3, 124.3, 126.5, 128.1, 128.4, 128.9, 134.1, 136.5, 138.4, 151.0, 168.0, 168.5, 192.3; IR (KBr, cm^{-1}) ν_{max} = 3438, 3113, 3104, 3058, 2954, 1677, 1632, 1534, 1447, 1427, 1372, 1336, 1225, 1143, 1081; [Anal. Calcd. for $C_{26}H_{27}N_3O_4$: C, 70.09; H, 6.11; N, 9.43; Found: C, 70.29; H, 6.33; N, 9.57]; LC/MS (ESI, *m/z*): [M^+], found 446.31, $C_{26}H_{27}N_3O_4$ for 445.20.

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

Yield 187 mg (0.37 mmol, 36.7%); m.p. 130–131 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.56 (t, 3H, J = 5.2 Hz, NCH_2CH_3), 3.11 (s, 3H, NCH_3), 3.16 (s, 3H, NCH_3), 3.34–3.37 (dd, 1H, J = 11.2 Hz, 4.0 Hz, $CH_{2(a)}$), 3.92–3.97 (m, 2H $CH_{2(e)}$& CH), 4.24 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.41–4.43 (m, 1H, CH), 7.10 (d, 1H, J = 5.2 Hz, Ar–H), 7.15 (t, 1H, J = 5.2 Hz, Ar–H), 7.29–7.32 (m, 2H, Ar–H), 7.33 (d, 1H, J = 1.2 Hz, Ar–H), 7.37–7.39 (m, 2H, Ar–H), 7.97 (s, 1H,Ar–H), 8.37–8.38 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 28.1, 28.2, 40.9, 41.9, 44.2, 53.1, 109.8, 116.4, 122.7, 122.8, 123.4, 126.4, 130.2, 130.4, 131.2, 131.7, 134.1, 136.5, 138.2, 141.2, 150.9, 167.7, 168.0, 191.9; IR (KBr, cm^{-1}) ν_{max} = 3453, 3119, 3047, 2975, 1748, 1674, 1633, 1528, 1464, 1426, 1371, 1282, 1204, 1118, 1059, 1001;[Anal. Calcd. for $C_{25}H_{24}BrN_3O_4$: C, 58.83; H, 4.74; N, 8.23; Found: C, 58.69; H, 4.47; N, 8.45]; LC/MS (ESI, *m/z*): [M^+], found 510.18, $C_{25}H_{24}BrN_3O_4$ for 509.10.

5-(3-(1-Ethyl-1H-indol-3-yl)-3-oxo-1-(4-(trifluoromethyl)phenyl) propyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5k)

Yield 198 mg (0.40 mmol, 39.7%); m.p. 168–169 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.55 (t, 3H, J = 5.2 Hz, NCH_2CH_3), 3.11 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.40 & 3.43 (dd, 1H, J = 11.2 Hz, 4.0 Hz, $CH_{2(a)}$), 3.98 & 4.01 (dd, 1H, J = 11.2 Hz, 4.0 Hz, $CH_{2(e)}$), 4.03 (d, 1H, J = 0.8 Hz, CH), 4.24 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.55–4.57 (m, 1H, CH), 7.26–7.33 (m, 2H, Ar–H), 7.35–7.38 (m, 3H, Ar–H), 7.54 (d, 2H, J = 5.6 Hz, Ar–H), 7.97 (s, 1H,Ar–H), 8.33–8.35 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 28.6, 28.3, 41.1, 41.8, 43.4, 52.8, 109.8, 116.3, 122.6, 122.8, 123.4, 125.6, 1257, 126.7, 128.2, 134.0, 136.5, 143.7, 150.9, 167.7, 167.8, 192.0; IR (KBr, cm^{-1}) ν_{max} = 3423, 3119, 2982, 1749, 1688, 1636, 1525, 1461, 1421, 1380, 1326, 1207, 1159, 1116, 1070; [Anal. Calcd. for $C_{26}H_{24}F_3N_3O_4$: C, 62.52; H, 4.84; N, 8.41; Found: C, 62.33; H, 5.11; N, 8.63]; LC/MS (ESI, *m/z*): [M^+], found 500.20, $C_{26}H_{24}F_3N_3O_4$ for 499.17.

5-(3-(1-Ethyl-1H-indol-3-yl)-3-oxo-1-(thiophen-2-yl) propyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5l)

Yield 224 mg (0.54 mmol, 53.7%); m.p. 154–155 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.56 (t, 3H, J = 4.8 Hz, NCH_2CH_3), 3.15 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.39–3.43 (m, 2H, $CH_{2(a)}$), 3.98–4.01 (dd, 1H, J = 11.2 Hz, 6.4 Hz, $CH_{2(e)}$), 4.05 (d, 1H, J = 2.4 Hz, CH), 4.24 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.82–4.83 (m, 1H, CH), 6.86 (d, 1H, J = 2.0 Hz, Ar–H), 6.90 (t, 1H, J = 2.8 Hz, Ar–H), 7.16 (d, 1H, J = 3.6 Hz, Ar–H), 7.29–7.37 (m, 2H, Ar–H), 7.37–7.38 (m, 1H, Ar–H), 7.96 (s, 1H,Ar–H), 8.38–8.40 (m, 1H, Ar–H);^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 28.2, 28.4, 39.6, 41.8, 42.7, 53.0, 109.7, 116.4, 122.7, 123.3, 124.9, 125.7, 126.4, 126.9, 128.3, 134.2, 136.5, 141.5, 151.2, 167.6, 167.9, 191.9; IR (KBr, cm^{-1}) ν_{max} = 3458, 3104, 3051, 2974, 2928, 1748, 1662, 1563, 1530, 1460, 1425, 1381, 1317, 1273, 1200, 1148, 1128, 1051; [Anal. Calcd. for $C_{23}H_{23}N_3O_4S$: C, 63.14; H, 5.30; N, 9.60; Found: C, 63.35; H, 5.41; N, 9.48]; LC/MS (ESI, *m/z*): [M^+], found 438.10, $C_{23}H_{23}N_3O_4S$ for 437.14.

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

Yield 230 mg (0.55 mmol, 54.6%); m.p. 188–189 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.55 (t, 3H, J = 4.8 Hz, NCH_2CH_3), 3.18 (s, 3H, NCH_3), 3.21 (s, 3H, NCH_3), 3.39–3.41 (dd, 1H, J = 11.2 Hz, 6.4 Hz, $CH_{2(a)}$), 3.81 & 3.84 (dd, 1H, J = 11.2 Hz, 6.0 Hz, $CH_{2(e)}$), 3.96 (d, 1H, J = 2.4 Hz, CH), 4.24 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.57–4.59 (m, 1H, CH), 6.11 (d, 1H, J = 2.4 Hz, Ar–H), 6.26 (q, 1H, J = 1.6 Hz, Ar–H), 7.26–7.37 (m, 1H, Ar–H), 7.29–7.32 (m, 2H, Arq-H), 7.37–7.38 (m, 1H, Ar–H),

7.95 (s, 1H,Ar–H), 8.38–8.40 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 28.3, 28.4, 38.1, 39.7, 41.8, 51.5, 107.0, 109.7, 110.5, 116.4, 122.7, 123.4, 126.5, 129.9, 134.2, 136.5, 142.2, 151.4, 152.8, 167.6, 167.9, 191.8; IR (KBr, cm^{-1}) ν_{max} = 3427, 3116, 2978, 2932, 1744, 1642, 1655, 1530, 1460, 1422, 1394, 1272, 1202, 1145, 1114; [Anal. Calcd. for $C_{23}H_{23}N_3O_5$: C, 65.55; H, 5.50; N, 9.97; Found: C, 65.73; H, 5.63; N, 10.09]; LC/MS (ESI, *m/z*): [M^+], found 422.20, $C_{23}H_{23}N_3O_5$ for 421.16.

5-(3-(1-Ethyl-1H-indol-3-yl)-3-oxo-1-(3,4,5-trimethoxyphenyl) propyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (5n)

Yield 185 mg (0.35 mmol, 35.5%); m.p. 170–171 °C; ^{1}H-NMR (600 MHz, CDl_3) δ: 1.56 (t, 3H, J = 4.8 Hz, NCH_2CH_3), 3.12 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.34–3.36 (dd, 1H, J = 10.8 Hz, 4.0 Hz, $CH_{2(a)}$), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.95–3.99 (m, 2H, $CH_{2(e)}$ & CH), 4.24 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.39–4.41 (m, 1H, CH), 6.39 (s, 2H,Ar–H), 7.30–7.33 (m, 2H, Ar–H), 7.37–7.39 (m, 1H, Ar–H), 7.97 (s, 1H,Ar–H), 8.38–8.40 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 28.2, 28.3, 41.4, 41.9, 44.7, 51.1, 53.0, 60.8, 60.9, 109.7, 115.1, 116.5, 122.7, 122.8, 123.3, 126.5, 132.6, 134.0, 134.7, 136.5, 151.0, 153.2, 168.1, 168.3, 192.4; IR (KBr, cm^{-1}) ν_{max} = 3435, 3105, 2983, 2946, 2839, 1748, 1677, 1646, 1589, 1526, 1512, 1423, 1376, 1331, 1243, 1209, 1127, 1104, 1003; [Anal. Calcd. for $C_{28}H_{31}N_3O_7$: C, 64.48; H, 5.99; N, 8.06; Found: C, 64.31; H, 6.09; N, 8.24]; LC/MS (ESI, *m/z*): [M^+], found 522.20, $C_{28}H_{31}N_3O_7$ for 521.22.

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

Yield 178 mg (0.37 mmol, 37.0%); m.p. 85–86 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.56 (t, 3H, J = 4.8 Hz, NCH_2CH_3), 3.02 (s, 3H, NCH_3), 3.09 (s, 3H, NCH_3), 3.45–3.47 (dd, 1H, J = 10.8 Hz, 3.6 Hz, $CH_{2(a)}$), 4.08–4.15 (m, 2H, $CH_{2(e)}$ & CH), 4.24 (q, 2H, J = 4.8 Hz, NCH_2CH_3), 4.60–4.64 (m, 1H, CH), 7.29–7.32 (m, 3H, Ar–H), 7.36–7.39 (m, 1H, Ar–H), 7.45–7.47 (m, 2H, Ar–H), 7.63 (s, 1H,Ar–H), 7.75–7.79 (m, 3H, Ar–H), 8.00 (s, 1H,Ar–H), 8.39–8.40 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.4, 28.4, 28.8, 41.2, 41.8, 44.2, 52.4, 108.9, 113.5, 116.5, 121.5, 121.9, 123.5, 125.3, 126.0, 126.2, 126.5, 127.1, 127.6, 128.2, 128.9, 130.7, 134.3, 137.2, 140.6, 158.2, 168.6, 169.4, 192.4; IR (KBr, cm^{-1}) ν_{max} = 3438, 3106, 2983, 2944, 2832, 1745, 1678, 1643, 1585, 1528, 1516, 1424, 1370, 1332, 1243, 1205, 1128, 1103, 1005; [Anal. Calcd. for $C_{29}H_{27}N_3O_4$: C, 72.33; H, 5.65; N, 8.73; Found: C, 72.49; H, 5.41; N, 8.85]; LC/MS (ESI, *m/z*): [M^+], found 482.30, $C_{29}H_{27}N_3O_4$ for 481.20.

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

Yield 165 mg (0.35 mmol, 34.6%); m.p. 198–199 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.55 (t, 3H, J = 4.8 Hz, NCH_2CH_3), 2.21 (s, 3H, CH_3), 3.23 (s, 3H, NCH_3), 3.34–3.37 (dd, 1H, J = 12.0 Hz, 4.4 Hz, $CH_{2(a)}$), 3.93 & 3.96 (dd, 1H, J = 12.0 Hz, 4.4 Hz, $CH_{2(e)}$), 4.21–4.26 (m, 4H, CH & NCH_2CH_3), 7.28–7.31 (m, 2H, Ar–H), 7.38 (t, 3H, J = 6.0 Hz, Ar–H), 7.88 (s, 1H,Ar–H), 8.17 (d, 2H, J = 6.0 Hz, Ar–H), 8.25–8.27 (m, 1H, Ar–H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 15.2, 29.0, 29.3, 38.7, 41.9, 42.5, 50.2, 109.9, 116.2, 122.4, 122.9, 123.8, 125.9, 126.5, 127.1, 129.3, 133.6, 142.7, 144.8, 151.5, 167.8, 168.6, 192.1; IR (KBr, cm^{-1}) ν_{max} = 3379, 3125, 2980, 1761, 1690, 1634, 1532, 1517, 1460, 1381, 1215, 1078; [Anal. Calcd. for $C_{25}H_{24}N_4O_6$: C, 63.02; H, 5.08; N, 11.76; Found: C, 62.84; H, 5.25; N, 12.01]; LC/MS (ESI, *m/z*): [M^+], found 477.20, $C_{25}H_{24}N_4O_6$ for 476.17

Single Crystal X-ray Crystallography

The compound of **5g** was obtained as single crystals by slow evaporation from ethanol solution of the pure compound at room temperature. Data were collected on a Bruker APEX-II D8 Venture area diffractometer, equipped with graphite monochromatic Mo $K\alpha$ radiation, λ = 0.71073 Å at 293 (2) K. Cell refinement and data reduction were carried out by Bruker SAINT. SHELXT[15] was used to solve structure. The final refinement was carried out by full-matrix least-squares techniques with anisotropic thermal data for non-hydrogen atoms on. CCDC 1877313 contains the supplementary crystallographic data for this compound can be obtained free of charge from the Cambridge Crystallographic Data Centre *via*www.ccdc.cam.ac.uk/data_request/cif.

Biological Activitiy Assays

Reagents

α-glucosidase type 1 from baker's yeast (G5003; Sigma-Aldrich, St. Louis, MO, USA), *p*-nitrophenyl α-D-glucopyranoside (N1377, Sigma-Aldrich), sodiumphosphatemonobasic (S3139, Sigma-Aldrich), sodiumphosphatedibasic (S5136, Sigma-Aldrich), andacarbose (A8980, Sigma-Aldrich), DMSO (Dimethylsulfoxide), α-amylase from *Aspergillus oryzae* (Sigma Aldrich), starch, DNS (3, 5-dinitrosalicylic acid), sodiumpotassiumtartratetetrahydrate.

α-Glucosidase Inhibition Assay

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). *p*-Nitrophenyl α-D-glucopyranoside (10 mM) and α-glucosidase solutions (1 U/ml) were solubilized in 0.1 M sodium phosphate buffer (pH 7.0). All the reagents were manufactured shortly before use and warmed to 37 °C in a water bath. Sodium phosphate buffer (0.1 M, 158 μl per well) was added to a 96-well plate. α-Glucosidase (20 μl) and 2 μl of sample were added to 20 μl of *p*-nitrophenyl α-D-glucopyranoside. In the 200-μl final reaction volume (0.02 U/well, 0.1 U/ml) the substrate concentration was adjusted to 10 mM. The background signal due to the sample color was measured at 405 nm with the PerkinElmer Wallac Victor3 spectrophotometer (PerkinElmer, Waltham, MA, USA) prior to adding the enzyme. Immediately following α-glucosidase addition, absorbance was measured at 405 nm 8 times at 1-min intervals.[16]

α Amylase Assay

Briefly, 250 μL (0.4 mg/mL) was preincubated with 250 μL of α-amylase solution for 10 min at 25 °C in one set of tubes. In another set of tubes α-amylase was preincubated with 250 μL of phosphate buffer (pH 6.9). 250 µL of starch solution at increasing concentrations (0.2–1% (w/v)) was added to both sets of reaction mixtures to start the reaction. The mixture was then incubated 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 maltose standard curve and converted to reaction velocities.

Calculation of Inhibition Efficiency

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

tration and calculated by logarithmic regression analysis from the mean inhibitory values.

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[13b] 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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