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Synthesis of β-Ketoamide Curcumin Analogues for Anti-Diabetic and AGEs Inhibitory Activities

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Abstract: Two different series of novel β-ketoamide curcumin analogues enriched in biological activities have been synthesized. The synthesized compounds were screened for their *in vitro* anti-diabetic and AGEs inhibitory activities and exhibited potent to good anti-diabetic and AGEs inhibitory activities. Further molecular docking study was also performed with the α-amylase enzyme.

Introduction

Diabetes mellitus (DM) is a major global health issue because most of the people are afflicted in each and every year nearly 300 million people as per the statistics [1-2]. Till now there are no curable drugs available in the market for diabetes mellitus. In addition to that for hyperglycemic patients, the excessive production of glucose leads to AGEs (advanced glycation end products) formation [3]. The formation of several AGE products leads to problems associated with diabetic related health disorders. Thus the inhibition of AGEs formation could hold back the intensity of complications in diabetic condition [4-7]. Several researchers have tried to develop a new drug candidate for diabetes mellitus. Among the various strategies available for developing anti-diabetic lead molecules, use of herbal biomolecules and derivatives of natural compounds draw a considerable interest because of their hypoglycemic effects.

Curcumin which is isolated from the root of Curcuma *Longa Linn* (turmeric plant) [8] has various biological applications including anti-diabetic property [9]. Apart from curcumin, several synthetic curcumin derivatives are also proved to be a better anti-diabetic agent as well as AGEs inhibitor [10-11]. Recently Sribalan *et al*. synthesized the water-soluble curcumin derivatives which served as an AGEs inhibitor [12].

Even though curcumin/curcuminoids has several biomedical applications, they have some drawbacks such as instability and poor metabolic property. The pharmacological studies proved that the presence of central β-diketone functionality of curcumin may leads to rapid metabolism of curcumin [13-15]. To improve the metabolic stability of curcumin, several structural modifications have been designed without the presence of β-diketone moieties of curcumin [16-19]. Mono carbonyl analogues of curcumin have shown better stability and activity than curcumin.

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Earlier studies also reported that the diarylidenyl-piperidone based mono carbonyl analogues of curcumin [20] and *o*-fluoro substituted piperidone bis-benzylidine curcumin analogues [21] were potent anticancer agents. Similarly, Katsori *et al*. [22] reported the piperidone ring incorporated in monocarbonyl curcumin exhibited *in vivo* anti-inflammatory activity. Based on the above literature reports, we have planned to synthesis the mono carbonyl analogues of curcumin derivatives (**Fig 1**).

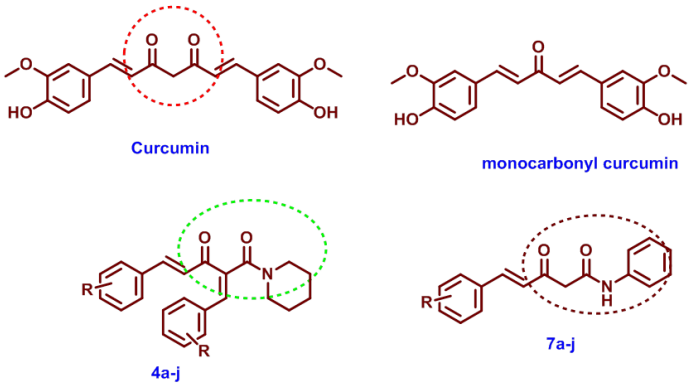


Fig 1: Curcumin and synthesized derivatives of curcumin.

The unstable *β*-diketone of curcumin is replaced with stable *β*-ketoamide with various bioactive units (piperidone/aryl amide core) in the *α*-carbon of the carbonyl group. The synthesized compounds were studied for an anti-diabetic activity like *α*-amylase inhibitory activity, *α*-glucosidase activity and AGEs inhibitory activity.

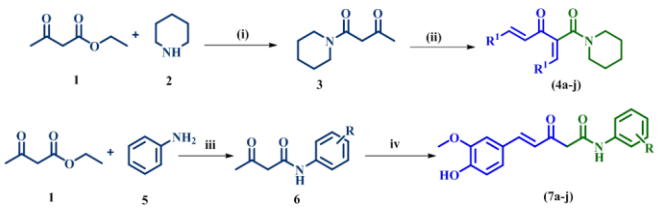
In addition, the 3D structures of the synthesized compounds were studied for *in silico* molecular docking studies against *α*-amylase enzyme to identify probable binding mode. Out of the several enzymes, *α*-amylase is an important enzyme because it is responsible for carbohydrate digestion (gives glucose) which leads to diabetes. So inhibitors of *α*-amylase can effectively retard the digestion as well as the assimilation at the early stages of starch digestion. This leads to the significant delay of postprandial hyperglycemia and found to be effective on insulin resistance [23]. *α*-amylase is considered to be one of the best targets for the development of type II diabetes therapeutic agents.

Results and Discussion

Chemistry

In the present work, two types of curcuminoids were synthesized. The precursor 1-(piperidine-1-yl)butane-1,3-dione (**3**) was prepared by adding equimolar amounts of piperidine and ethyl acetoacetate under reflux condition. The precursor (**3**) on reaction with different aromatic aldehydes afforded the expected curcuminoids (**4a-j**) in the presence of piperidine as a base. Similarly, another precursor 3-oxo-*N*-phenylbutanamide(**6**) was synthesized by refluxing equimolar amount of ethyl acetoacetate with various aromatic amines under toluene. The target (**7a-j**) compounds were prepared with vanillin and corresponding *N*-phenylbutanamide using boron oxide, tri-*n*-butyl borate and *n*-butyl amine as reported earlier [24].

Piperidinylamide monocarbonyl analogues of curcumin (**4a-j**) were characterized by ^{1}H NMR, ^{13}C NMR and 1D-Dept 135 spectroscopy. The appearance of multiplets around 1.35 to 3.38 ppm in ^{1}H NMR indicates the presence of piperidine unit. In ^{13}C NMR, the appearance of amide carbonyl peak around 165.48 ppm and the appearance of carbonyl peak around 185.35 ppm confirmed the formation of an amide. In DEPT 135 the piperidine carbons appeared in the negative region which clearly indicates the piperidine unit present in the compound. Another, hybrid compounds of curcumin along with *N*-phenyl pentenamide (**7a-j**) were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. The appearance of singlet around 3.62 ppm and 2.42 ppm indicates the presence of O-CH_3 and CH_2 group. Similarly, in ^{13}C NMR also confirmed the carbonyl peak (194.83 ppm) and amide carbonyl peak (166.45 ppm) of the products. The synthetic route for *β*-ketoamide curcumin derivatives was represented in **Scheme 1**. The lists of synthesized compounds were represented in **Fig 2** and **Fig 3**.



Reagents and conditions: (i) Toluene, reflux, 80^{0}C, 24h (ii) Aldehyde, Piperidine, Toluene, Acetic acid, 80^{0}C, 3h (iii) Toluene, reflux, 80^{0}C, 2h (iv) Vanillin, B_2O_3, Tri -*n*-butyl borate, *n*-butyl amine, Ethyl acetate, Hot.HCl, 24h

Scheme 1: Synthetic route for *β*-ketoamide curcumin derivatives

Biological studies

In vitro α-amylase inhibition

All the synthesized compounds (**4a-j** and **7a-j**), parent curcumin and standard drug were evaluated for *in vitro α*-amylase inhibition at different concentrations (50-200 µg/mL). In the series of compounds (**4a-j**), most of the compounds showed equal to better inhibition than the standard acarbose. The compounds **4a**, **4e**, **4f**, **4g**, and **4i** showed better activity than acarbose as well as parent curcumin. Among the compounds, **4e** having the 4-hydroxy3-methoxy substituents showed least inhibitory concentration. The IC_{50} of the compounds is 1.5 fold better activities than curcumin and acarbose. The compounds **4b**, **4c** and **4d** containing hydroxyl and methoxy substituents showed moderate activity to standard. The thiophene substituted curcumin exhibited potent activity. The calculated inhibitory concentration is 25.07 µg/mL. But pyrrole substituents (**4j**) showed poor activity than standard as well as curcumin.

Similarly, in the second series, the compounds (**7a-j**) displayed a good to potent *α*-amylase inhibitory activity. The compounds **7d**, **7f**, **7h** and **7i** containing *p*-fluoro, *p*-sulfonamide, *p*-acetyl and *m*-dichlorophenyl substituents showed potent inhibitions. The calculated inhibitory concentration for **7i** is 20.67 µg/mL. It is the least IC_{50} value than others. The compounds **7c**, **7e**, **7g** and **7j** bearing naphthalene, *p*-chloro phenyl, *m*-acetyl phenyl and piperidine substituents showed potent activity than standard and equal activity towards curcumin. The compounds **7a** and **7b** containing phenyl and toluene substituents showed moderate activity than parent and standard. The IC_{50} values for all the compounds, curcumin and acarbose is represented in Table **1** & **2**.

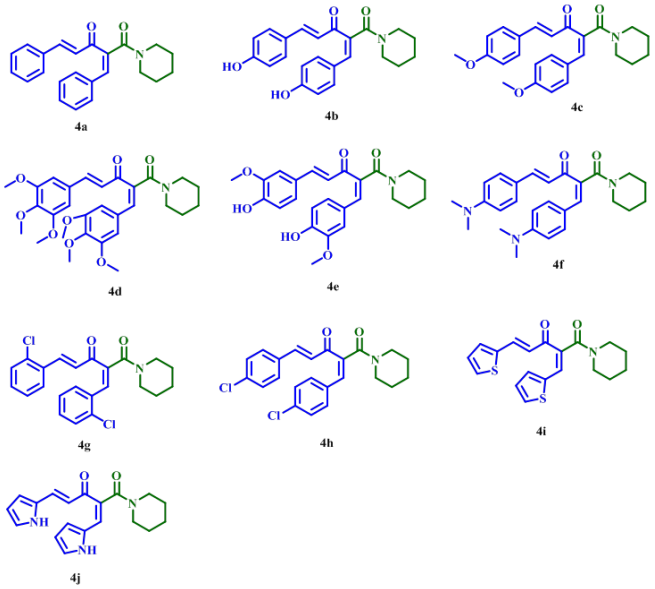


Fig 2: List of synthesized compounds (**4a-j**)

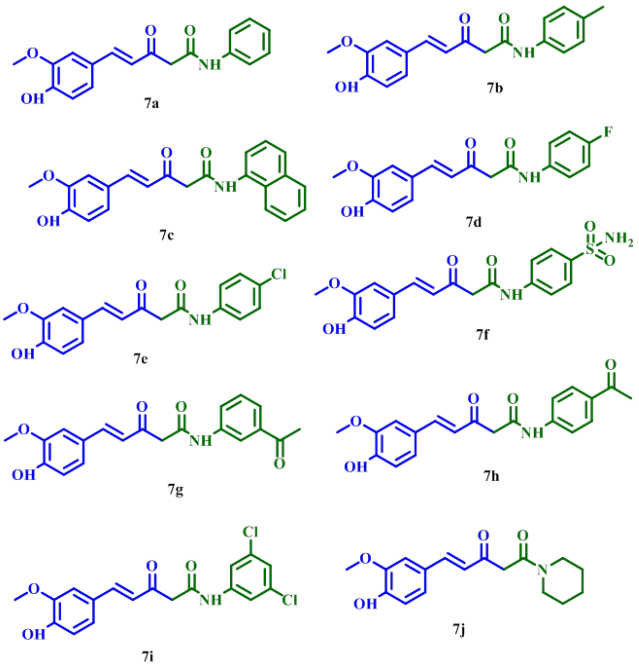


Fig 3: List of synthesized compounds (**7a-j**).

In vitro α-glucosidase inhibition

The synthesized compounds (**4a-j** and **7a-j**), parent and standard drug were tested for *in vitro α*-glucosidase inhibition studies at various concentrations (50-200 µg/mL) and the IC_{50} values were calculated and presented in Table 2. The *α*-glucosidase studies gave the results similar to *α*-amylase inhibition. In the first series of compounds (**4a-j**), most of them showed a better inhibition than standard and curcumin. The compounds 3,4,5-trimethoxy phenyl **4d**, vanillin **4e**, *p*-chlorophenyl **4h** and pyrrole **4j** have shown better activity than acarbose as well as parent curcumin. Among the compounds, **4h** having the *p*-chlorophenyl substituents showed very good inhibition. The IC_{50} of the compounds is 1.5 fold better activities than curcumin and acarbose. The compound **4a**, **4c** containing phenyl and *p*-methoxyphenyl substituents showed nearer activity to curcumin and less activity to acarbose. The compound **4b**, **4f** and **4g** containing *p*-hydroxyl phenyl, *p-N,N*-dimethylaminophenyl and *o*-chloro phenyl substituents showed less activity to parent and standard. The thiophene substituted curcumin exhibited potent activity and the calculated IC_{50} values are approximately 1.5 fold higher than standard as well as a parent.

Similarly, the second series of compounds (**7a-j**) displayed a better *α*-glucosidase inhibitory activity. Compare to the first series, the compounds **7a-j** showed moderate activity. The compounds **7f**, **7i**, and **7j** containing *p*-sulfonamido phenyl, *m*-dichlorophenyl and piperidine substituents showed equal inhibition to standard and potent inhibition than the parent. Within this series, the piperidine substituted curcumin exhibited the highest inhibition. The calculated inhibitory concentration is 25.10 µg/mL. The compounds **7a**, **7d**, and **7e** bearing phenyl, *p*-fluorophenyl, *p*-chlorophenyl substituents showed moderate activity towards the standard and curcumin. The compounds **7b**, **7g** and **7h** containing *p*-toluene, *m*-acetyl phenyl, and *p*-acetyl phenyl substituents showed poor activity than parent and standard. The IC_{50} values of all the compounds, curcumin and acarbose against *α*-glucosidase are represented in Table **1** & **2**.

Table 1: *α*-amylase inhibition, *α*-glucosidase inhibition and AGEs inhibitory activity of compound **4a-j**.

S.no	Compound	*α*-amylase inhibition IC_{50}(µg/mL)	*α*-glucosidase inhibition IC_{50}(µg/mL)	AGE inhibition IC_{50}(µg/mL)
1	4a	30.92	39.63	130.24
2	4b	34.36	47.50	60.24
3	4c	44.64	34.97	65.45
4	4d	36.78	25.42	67.80
5	4e	21.29	24.89	90.43
6	4f	29.44	50.28	85.9
7	4g	24.26	44.15	154.3
8	4h	26.28	22.54	167.98
9	4i	25.07	26.43	116.54
10	4j	55.56	24.56	122.89
11	Curcumin	32.89	31.76	80.87
12	Acarbose	34.76	26.34	-
13	phloroglucinol	-	-	128.9

AGEs Inhibitory activity

In vitro AGEs inhibitory activities were also studied for the synthesized curcumin analogues and their inhibitory concentrations were calculated. Phloroglucinol and curcumin were used as a reference compounds to compare the activity. In the series (**4a-j**), several compounds showed a better inhibition than standard phloroglucinol. The compounds **4b**, **4c**, and **4d** showed a better activity than phloroglucinol as well as parent curcumin. Among the compounds, **4b** having the *p*-hydroxy phenyl substituents showed better inhibitory concentration. The compounds **4e** and **4f** containing vanillin and *p*-*N*,*N*-dimethyl phenyl substituents showed nearer activity to parent curcumin. The compounds **4a**, **4i** and **4j** having phenyl, thiophene and pyrrole substituents showed better activities than phloroglucinol. The other compounds showed moderate AGEs inhibitory activity.

In second series(**7a-j**), all the compounds showed potent AGEs inhibitory activity. The compounds **7f** and **7j** containing *p*-sulfonamide and piperidine substituents showed two-fold better inhibitions than curcumin and three-fold better inhibitions than phloroglucinol. Their IC_{50} values are 46.23 and 48.9 µg/mL correspondingly. The compounds **7b**, **7c**, **7g** and **7h** containing *p*-tolyl, naphthalene, *m*-acetylphenyl and *p*-acetylphenyl showed two-fold better inhibition than standard phloroglucinol. Remaining all the compounds showed equal activity towards curcumin. The IC_{50} values for all the compounds, curcumin and phloroglucinol is represented in Table **1** & **2**.

Table 2: *α*-amylase inhibition, *α*-glucosidase inhibition and AGE inhibitory activity of compound **7a-**j.

S.no	Compound	*α*-amylase inhibition IC_{50}(µg/mL)	*α*-glucosidase inhibition IC_{50}(µg/mL)	AGE inhibition IC_{50}(µg/mL)
1	7a	37.49	40.15	78.15
2	7b	45.07	58.65	65.73
3	7c	32.50	48.20	68.90
4	7d	22.08	39.31	76.89
5	7e	32.47	40.22	80.10
6	7f	25.24	29.10	46.23
7	7g	32.46	67.72	66.65
8	7h	25.10	55.10	66.40
9	7i	20.67	26.62	72.34
10	7j	32.15	25.10	48.90
11	Curcumin	32.89	31.76	80.87
12	Acarbose	34.76	26.34	-
13	phloroglucinol	-	-	128.9

Molecular docking studies

The molecular docking studies deals with the atomic-level interactions of ligand and target. The interactions of ligands with enzymes are influenced by the hydrophilic and hydrophobic bonding contributions of amino acid residues. Among different types of docking, protein-ligand docking is of special interest because of its application in pharmaceutical industry. All the synthesized compounds were studied for their molecular docking studies against *α*-amylase (1HNY) enzyme.

In the first series of compounds (**4a-j**), the ligand **4e** showed the highest number of hydrogen bond interactions than other derivatives. The hydrogen bonded amino acid residues were found to be GLY225, PHE229, SER3, TYR2 and ARG291. And also it showed a very good binding energy (-310.4 KJ/mol). The compound **4h** showed four hydrogen bond interactions with the amino acid residues (TYR2, SER3, Lys227, and PRO228). Similarly, the compound **4i** showed four hydrogen bond interactions with amino acid residues (THR6, GLN7, ASP402, and ARG252). Their binding energies were found to be -303.49 KJ/mol and -279.59 KJ/mol correspondingly. The molecular docking results suggested that the compounds **4e**, **4h** and **4i** could be better bioactive compounds against the docking of *α*-amylase inhibition. The remaining compounds were moderate bio-active compounds against enzyme inhibition. The same results were obtained in the experimental *α*-amylase inhibitory studies.

Table3: Molecular docking interaction of synthesized compounds **(4a-j)** against *α*-amylase enzymes**.**

Entry	Compound	1HNY		
		Binding energy (KJ/mol)	**No.of hydrogen bonding**	**Amino acid residues**
1	**4a**	-273.64	1	ASP402
2	**4b**	-285.6	4	ARG219, PRO228, SER3, TYR2
3	**4c**	-302.75	1	ASP147
4	**4d**	-332.36	2	HIS299, ASP300,
5	**4e**	-310.4	5	GLY225, PHE229, SER3, TYR2, ARG291
6	**4f**	-297.34	-	-
7	**4g**	-310.40	1	ASP402
8	**4h**	-303.49	4	TYR2, SER3, Lys227, PRO228
9	**4i**	-279.59	4	THR6, GLN7, ASP402, ARG252
10	**4j**	-273.20	-	-

In the second series of compounds (**7a-j**), the ligand **7d** showed the four number of hydrogen bond interactions with amino acid residues (GLN390, LYS322, ARG343 and CYS378). The binding energy of the compound is -277.79 KJ/mol correspondingly. The compound **7f** showed three hydrogen bond interactions with ASP402, ARG398 and PRO223. And also the binding energy of **7f** compound is found be -276.93 KJ/mol. Similarly, the compound **7i** showed three hydrogen bond interactions with amino acid such as GLU390, ARG343 and CYS378. The binding energy of the compound is found to be -295.73 KJ/mol. The remaining compounds showed a moderate number of hydrogen bonding interactions and binding energies. In the second series, the molecular docking results suggested that the compounds **7d**, **7f** and **7i** could be better bioactive compounds against the docking of *α*-amylase inhibition. The remaining compounds were moderate bioactive compounds against enzyme inhibition. Similar to the previous series of compounds, the same results were obtained in the experimental *α*-amylase inhibitory studies.

From this study, it is clearly evidenced that the *β*-ketoamide curcuminoids could be used as inhibitors for *α*-amylase. The molecular docking studies also proved the compounds have very good *α*-amylase inhibitory activity. The molecular docking results for compounds **4a-j** and **7a-j** are represented in Table 3 & 4. The protein-ligand interaction for the compounds **4e** and **7d** is represented in Fig **4** and **5**.

Table 4: Molecular docking interaction of synthesized compounds **(7a-j)** against *α*-amylase**.**

Entry	Compound	1HNY		
		Binding energy (KJ/mol)	**No. of hydrogen bonding**	**Amino acid residues**
1	**7a**	-289.28	-	-
2	**7b**	-272.67	-	-
3	**7c**	-305.7	2	ASN5, LYS227,
4	**7d**	-277.79	4	GLN390,LYS322, ARG343, CYS378
5	**7e**	-275.72	2	ASP300, GLN63
6	**7f**	-276.93	3	ASP402, ARG398, PRO223
7	**7g**	-307.96	1	THR163
8	**7h**	-299.68	1	ALA310
9	**7i**	-295.73	3	GLU390, ARG343, CYS378
10	**7j**	-254.86	2	ARG291, THR6

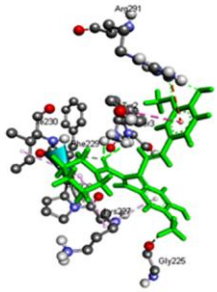


Fig 4: Binding of **4e** into the α-amylase (1HNY)

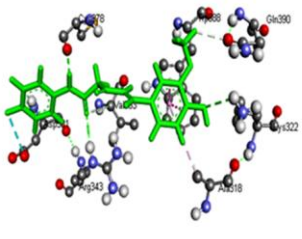


Fig 5: Binding of **7d** into the α-amylase (1HNY)

Conclusion

The *β*-ketoamide curcumin derivatives were synthesized and *in vitro* biological applications were studied. As expected, these compounds have enhanced anti-diabetic, AGEs inhibition activities than the parent and standard. The molecular docking studies also proved that the curcuminoids could be a good *α*-amylase inhibitor.

Experimental section

Chemistry

All the solvents used were analytical grade and purchased from Spectrochem and Sigma-Aldrich. Reactions were monitored by TLC analysis on precoated silica gel 60 F_{254} in TLC sheets (0.2mm thickness, Merck plate) and 60-120 mesh Merck silica gel used for column chromatography. Petroleum ether and ethyl acetate were used as the eluents. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300 MHz and 75 MHz instruments, $CDCl_3$ and DMSO-d_6 were used as an internal solvent. Chemical shift values were represented in δ (ppm) and coupling constants are mentioned in terms of Hz with the internal references TMS. Melting point was determined by open capillary tube using sigma melting point apparatus.

General procedure for the synthesis of 1-(piperidine-1-yl) butane-1,3-dione (3):

The compound **3** was prepared by following the reported literature [25, 26].

General procedure for the synthesis of *β*-ketoamide curcumin analogues (4a-j):

A mixture of 1-(piperidine-1-yl) butane-1,3-dione **3** (0.3 g, 0.00118 mol) and corresponding aldehyde (0.46 g, 0.00236 mol) was dissolved in toluene. To that mixture, piperidine (0.00236 mol) and glacial acetic acid were added and the reaction mixture was stirred at 80 ˚C. After the completion of the reaction, the mixture was extracted with ethyl acetate (50 mL), washed with water (50 mL) and brine solution (50 mL). The organic layer was separated and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography using petroleum ether: ethyl acetate to give the desired product.

*(E)-2-((E)-benzylidene)-5-phenyl-1-(piperidine-1-yl) pent-4-ene-1,3-dione (**4a**):*

Yield 75%. Pale yellow solid, Mp: 118-120 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.80 (d, 1H, *J*=15.6 Hz), 7.66 (s, 1H), 7.58-7.63 (m, 5H), 7.38-7.46 (m, 5H), 7.19 (d, 1H, *J*=15.6 Hz), 3.23-3.83 (m, 4H), 1.55-1.68 (m, 2H), 1.25-1.42 (m, 4H). ^{13}C NMR (75 MHz $CDCl_3$): δ 186.89, 166.81, 145.10, 138.64, 136.65, 134.86, 133.75, 130.76, 130.46, 129.98, 129.03, 128.94, 128.69, 121.92, 47.64, 42.42, 26.08, 25.35, 24.51. ESI-MS calculated.m/z 345.47 found 346.10 $[M+1]^+$.

*E)-2-((E)-4-hydroxybenzylidene)-5-(4-hydroxyphenyl)-1-(piperidin-1-yl)pent-4-ene-1,3-dione (**4b**):*

Yield 67%. Yellow solid, Mp: 190-192 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 9.87 (bs, 2H), 7.58-7.63 (m, 2H), 7.52 (d, 2H, *J*= 7.5 Hz), 7.43 (d, 2H, *J*=8.7 Hz), 7.17 (d, 1H, *J*=15.6 Hz), 6.79-6.84 (m, 4H), 3.36-3.78(m, 4H), 1.36-2.00 (m, 6H). ^{13}C NMR (75 MHz $CDCl_3$): δ 184.75, 165.48, 158.78, 158.60, 142.40, 136.82, 132.06, 130.66, 129.02, 124.24, 122.97, 116.48, 114.52, 114.45, 45.64, 40.24, 24.36, 23.65, 22.75. ESI-MS calculated.m/z 377.16 found 378.15 $[M+1]^+$.

*(E)-2-((E)-4-methoxybenzylidene)-5-(4-methoxyphenyl)-1-(piperidin-1-yl)pent-4-ene-1,3-dione (**4c**):*

Yield 78%. Yellow solid, Mp: 142-144 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.76 (d, 1H, *J*= 15.6 Hz), 7.62 (s, 1H), 7.53-7.58 (m, 4H), 7.05 (d, 1H, *J*=15.3 Hz), 6.89-6.93 (m, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 3.78-3.81 (m, 2H), 3.23-3.32 (m, 2H), 1.39-1.71 (m, 6H). ^{13}C NMR (75 MHz $CDCl_3$): δ 186.48, 167.49, 161.77, 161.49, 144.49, 138.37, 134.24, 132.06, 130.44, 127.56, 126.30, 119.51, 114.46, 114.41, 55.50, 55.45, 47.63, 42.37, 26.17, 25.45, 24.51. ESI-MS calculated.m/z 405.19 found 428.18 $[M+Na]^+$.

*(E)-1-(piperidin-1-yl)-2-((Z)-3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)pent-4-ene-1,3-dione (**4d**):*

Yield 70%. Yellow solid. Mp: 140-142 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.72 (d, 1H, *J*=15.6 Hz), 7.57 (s, 1H), 7.06 (d, 1H, *J*=15.3 Hz), 6.86 (s, 2H), 6.83 (s, 2H), 3.91 (bs, 6H), 3.90 (bs, 6H), 3.87 (bs, 6H), 3.16-3.60 (m, 4H), 1.42-1.70 (m, 6H). ^{13}C NMR (75 MHz $CDCl_3$): δ 186.55, 167.09, 153.52, 153.30, 145.25, 140.69, 140.10, 138.70, 135.72, 130.24, 129.04, 121.21, 107.12, 105.90, 61.08, 56.30, 56.22, 47.71, 42.36, 26.21, 25.56, 24.47. ESI-MS calculated.m/z 525.25 found 526.20 $[M+1]^+$.

*(E)-2-((Z)-4-hydroxy-3-methoxybenzylidene)-5-(4-hydroxy-3-methoxyphenyl)-1-(piperidin-1-yl)pent-4-ene-1,3-dione (**4e**):*

Yield 70%. Red solid. Mp: 106-108 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.72 (d, 1H, *J*= 15.3 Hz), 7.59 (s, 1H), 7.13-7.19 (m, 3H), 7.06 (s, 1H), 6.90-6.95 (m, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.17-3.41 (m, 4H), 1.28-1.42 (m, 6H). ^{13}C NMR (75 MHz $CDCl_3$): δ 186.58, 167.78, 148.79, 148.47, 147.12, 146.98, 145.09, 139.07, 138.83, 127.23, 125.86, 125.13, 123.51, 119.37, 114.95, 114.86, 111.62, 110.24, 55.02, 55.95, 47.66, 42.33, 26.14, 25.50, 24.44. ESI-MS calculated.m/z 437.18 found 438.17 $[M+1]^+$.

*(E)-2-((Z)-4-(dimethylamino)benzylidene)-5-(4-(dimethylamino)phenyl)-1-(piperidin-1-yl)pent-4-ene-1,3-dione (**4f**):*

Yield 67%. Red solid. Mp: 100-102 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.74 (d, 1H, *J*=15.3 Hz), 7.62 (s, 1H), 7.41-7.51 (m, 4H), 6.96 (d, 1H, *J*=15.3 Hz), 6.61-6.68 (m, 4H), 3.73-3.89 (m, 6H), 3.02 (s, 12H), 1.60-1.92 (m, 6H). ^{13}C NMR (75 MHz $CDCl_3$): δ 183.70, 163.30, 151.82, 151.58, 144.69, 140.38, 138.97, 132.34, 132.26, 130.43, 124.27, 122.28, 111.75, 111.65, 47.48, 42.26, 40.13, 40.02, 26.14, 25.28, 24.56. ESI-MS calculated.m/z 431.26 found 432.10 $[M+1]^+$.

*(E)-2-((Z)-2-chlorobenzylidene)-5-(2-chlorophenyl)-1-(piperidin-1-yl)pent-4-ene-1,3-dione (**4g**):*

Yield 70%.Yellow solid. Mp: 148-150 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.82 (s, 1H), 7.66 (d, 2H, J=7.8 Hz), 7.19-7.44 (m, 8H), 3.17-3.77 (m, 4H), 1.25-1.54 (m, 6H).^{13}C NMR (75 MHz $CDCl_3$): δ 195.66, 165.61, 141.14, 138.26, 138.23, 135.68, 135.11, 134.56, 134.55, 132.04, 131.45, 131.24, 130.34, 130.09, 129.70, 129.66, 127.17, 124.15, 47.48, 42.20, 25.88, 25.16, 24.34. ESI-MS calculated.m/z 413.09 found 414.20 $[M+1]^+$.

*(E)-2-((E)-4-chlorobenzylidene)-5-(4-chlorophenyl)-1-(piperidin-1-yl)pent-4-ene-1,3-dione (**4h**):*

Yield 68%. Yellow solid. Mp: 70-72 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.74 (d, 1H, *J*=15.6 Hz), 7.59 (s, 1H), 7.51-7.56 (m, 4H), 7.32-7.39 (m, 4H), 7.13 (d, 1H, *J*=15.6 Hz). ^{13}C NMR (75 MHz $CDCl_3$): δ 186.2, 166.35, 143.79, 137.26, 136.71, 136.69, 136.53, 133.07, 131.96, 131.14, 129.79, 129.25, 129.18, 121.84, 47.58, 42.38, 26.13, 25.33, 24.34. ESI-MS calculated.m/z 413.09 found 414.20 $[M+1]^+$.

*(2Z,4E)-1-(piperidin-1-yl)-5-(thiophen-2-yl)-2-(thiophen-2-ylmethylene)pent-4-ene-1,3-dione (**4i**):*

Yield 79%. Yellow solid. Mp: 142-144 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ. 7.91 (d, 1H, *J*=15.3 Hz), 7.81 (s, 1H), 7.51 (d, 2H, 5.1 Hz), 7.41 (d, 2H, *J*=4.8 Hz), 7.07-7.10 (m, 2H), 6.91 (d, 1H, *J*=15.0 Hz), 3.25-3.41 (m, 4H), 1.25-1.46 (m, 6H). ^{13}C NMR (75 MHz $CDCl_3$): δ 185.31, 166.53, 140.31, 137.25, 137.18, 134.12, 133.34, 132.43, 131.67, 131.38, 129.23, 128.49, 128.06, 120.68, 47.58, 42.54, 26.26, 25.35, 24.59. ESI-MS calculated.m/z 357.09 found 356.23 $[M-1]^-$.

*(2E,4E)-2-((1H-pyrrol-2-yl)methylene)-1-(piperidin-1-yl)-5-(1H-pyrrol-2-yl)pent-4-ene-1,3-dione(**4j**):*

Yield 55%. Yellow solid, Mp: 102-104 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 10.20 (bs, 2H), 7.77 (d, 1H, *J*=15.3 Hz), 7.72 (s, 1H), 7.10 (d, 1H, *J*=8.4 Hz), 6.94 (d, 1H, *J*=15.6 Hz), 6.73-6.89(m, 3H), 6.39-6.36 (m, 2H), 3.44-3.94 (m, 4H), 1.40-1.94 (m, 6H). ^{13}C NMR (75MHz $CDCl_3$): 186.25, 169.22, 134.23, 131.63, 129.91, 129.55, 129.09, 128.59, 127.39, 126.87, 125.39, 124.49, 119.20, 111.02, 48.29, 42.83, 26.28, 25.69, 24.44. ESI-MS calculated.m/z 323.16 found 322.15 $[M-1]^-$.

General procedure for the synthesis of 3-oxo-N-phenylbutanamide (6):

A mixture of ethyl acetoacetate (**1)** (1.36 mL, 0.01097 mol) and corresponding aromatic amine (**5)** (0.978 mL, 0.01097 mol) in toluene was taken into a round bottom flask and refluxed under stirring for 2 h. After completion of the reaction, the product was extracted with ethyl acetate (50 mL), washed with water (50 mL) and brine solution (50 mL). The organic layer was separated and dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the desired product.

General procedure for the synthesis of (7a-j):

A mixture of boric anhydride (0.0825 g, 0.001185 mol) and corresponding phenyl butanamide (0.30 mL, 0.001693 mol) was dissolved in ethyl acetate (5 mL) and stirred for 30 min at room temperature under nitrogen atmosphere. Then the 4-hydroxy 3-methoxybenzaldehyde (0.257 g, 0.001693 mol) and tri *n*-butyl borate (0.4 mL, 0.001693 mol) were added to the reaction mixture and stirred for an hour. Then *n*-butylamine was added dropwise over 15 min and again stirred for 3 hours at ambient temperature. After completion of the reaction, warmed hydrochloric acid (60 ˚C) (5 mL, 0.4 N) was added to the reaction mixture and stirring was continued for an hour. Then the reaction mixture was diluted with water and extracted with ethyl acetate (20 mL). The ethyl acetate layer was washed with water (20 mL) and brine solution (20 mL). The organic layer was separated and dried over anhydrous sodium sulphate and evaporated under reduced pressures to give desired product. The obtained product was purified by column chromatography.

*(E)-5-(4-hydroxy-3-methoxyphenyl)-3-oxo-N-phenylpent-4-enamide (**7a**):*

Yield 58%. White solid, Mp: 166-168 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.76 (s, 1H), 7.54-7.59 (m, 3H), 7.31-7.37 (m, 2H), 7.08-7.14 (m, 3H), 6.88 (d, 1H, *J*=8.4 Hz), 3.62 (s, 3H), 2.46 (s, 2H). ^{13}C NMR (75 MHz $CDCl_3$): 194.83, 166.45, 149.18, 147.24, 139.65, 138.23, 133.94, 128.28, 125.70, 124.13, 123.64, 119.30, 115.04, 111.46, 55.06, 26.21. ESI-MS calculated. m/z 311.12 found 312.01 $[M+1]^+$.

*(E)-5-(4-hydroxy-3-methoxyphenyl)-3-oxo-N-(p-tolyl)pent-4-enamide (**7b**):*

Yield 45%. White solid, Mp: 194-196 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 9.19 (s, 1H), 7.50 (d, 2H, *J*=8.1 Hz), 7.44 (s, 1H), 7.31 (d, 1H, *J*=7.5 Hz), 7.15 (d, 1H, *J*=15.6 Hz), 7.05 (d, 2H, *J*=8.1 Hz), 6.99 (d, 1H, *J*=15.6 Hz), 6.79 (d, 1H, *J*=8.4 Hz), 3.57 (s, 3H), 2.38 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (75 MHz $CDCl_3$): 186.39, 166.54, 149.25, 147.38, 140.30, 135.76, 134.33, 133.87, 129.31, 126.20, 124.78, 119.85, 115.19, 111.70, 55.64, 26.83, 20.75. ESI-MS calculated m/z 325.13 found 326.21 $[M+1]^+$.

*(E)-5-(4-hydroxy-3-methoxyphenyl)-N-(naphthalen-1-yl)-3-oxopent-4-enamide (**7c**):*

Yield 58%. Brown solid, Mp: 112-114 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 9.41 (s, 1H), 7.65-7.70 (m, 3H), 7.50 (s, 1H), 7.33 (d, 1H, *J*=8.1 Hz), 7.18 (d, 1H, *J*=8.4 Hz), 6.98- 7.08 (m, 5H), 6.86 (d, 1H, *J* =8.1 Hz), 3.62 (s, 3H), 2.44 (s, 2H). ^{13}C NMR (75 MHz $CDCl_3$): 195.69, 167.19, 149.28, 147.34, 140.98, 134.59, 133.85, 132.22, 128.00, 127.63, 125.82, 125.60, 125.20, 124.61, 121.87, 121.22, 115.21, 112.16, 55.38, 26.37. ESI-MS calculated/z 361.13 found 362.30 $[M+1]^+$.

*(E)-N-(4-fluorophenyl)-5-(4-hydroxy-3-methoxyphenyl)-3-oxopent-4-enamide (**7d**):*

Yield 65%. White solid, Mp: 160-162 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.71 (s, 1H), 7.52-7.56 (m, 3H), 7.06-7.11 (m, 2H), 7.01 (d, 2H, *J*=9.0 Hz), 6.89 (d, 1H, *J*=8.4 Hz), 3.66 (s, 3H), 2.47 (s, 2H). ^{13}C NMR (75 MHz $CDCl_3$): 195.18, 166.66, 149.37, 147.40, 140.26, 134.57, 134.06, 126.08, 124.52, 121.36, 121.26, 115.34, 115.23, 115.06, 111.63, 55.43, 26.62. ESI-MS calculated.m/z 329.11 found 330.01 $[M+1]^+$.

*(E)-N-(4-chlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)-3-oxopent-4-enamide (**7e**):*

Yield 72%. Yellow solid, Mp: 150-152 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 10.28 (s, 1H), 9.31(s, 1H), 8.11 (s, 1H), 7.74 (d, 2H, *J*=8.7 Hz), 7.44 (d, 2H, *J*=8.7 Hz), 7.28-7.24(m, 2H), 7.19-7.16(m, 2H), 3.71 (s, 3H), 3.61 (s, 2H). ESI-MS calculated. m/z 345.08 found 346.17 $[M+1]^+$.

*(E)-5-(4-hydroxy-3-methoxyphenyl)-3-oxo-N-(4-sulfamoylphenyl)pent-4-enamide (**7f**):*

Yield 56%. White solid, Mp: 158-160 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 8.85 (s, 1H), 7.43-7.48 (m, 3H), 6.90 (s, 2H), 6.56 -6.71 (m, 6H), 3.73 (s, 3H), 2.50 (s, 2H). ^{13}C NMR (75 MHz $CDCl_3$): 196.67, 165.67, 151.84, 151.34, 147.58, 145.45, 130.11, 129.99, 127.37, 127.22, 119.65, 115.30, 112.48, 111.79, 111.12, 55.67, 45.93. ESI-MS calculated.m/z 390.09 found 391.38 $[M+1]^+$.

*(E)-N-(3-acetylphenyl)-5-(4-hydroxy-3-methoxyphenyl)-3-oxopent-4-enamide (**7g**):*

Yield 50%. White solid, Mp: 166-168 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 10.12 (s, 1H,), 8.28 (s, 1H), 8.05 (d, 1H, *J*=8.1 Hz), 7.68 (d, 1H, *J*=7.5 Hz), 7.50 (s, 1H), 7.41-7.46 (m, 2H), 7.20 (d, 1H, *J*=8.4 Hz), 7.06 (d, 1H, *J*=8.4 Hz), 6.85 (d, 1H, *J*=15.6 Hz), 3.61 (s, 3H), 2.60 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz $CDCl_3$): 197.46, 195.10, 166.94, 149.33, 147.32, 140.30, 138.86, 137.25, 133.80, 128.81, 125.77, 124.15, 123.90, 123.52, 119.02, 115.19, 111.50, 55.19, 26.33. ESI-MS calculated.m/z 353.13 found 354.97 $[M+1]^+$.

*(E)-N-(4-acetylphenyl)-5-(4-hydroxy-3-methoxyphenyl)-3-oxopent-4-enamide (**7h**):*

Yield 67%. White solid, Mp: 192-194 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 10.43 (s, 1H), 7.85-7.94 (m, 6H), 7.49 (s, 1H), 7.04 (d, 1H, *J*=8.1 Hz), 6.84 (d, 1H, *J*=8.1 Hz), 3.59 (s, 3H), 2.58 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz $CDCl_3$): 195.61, 194.32, 166.50, 149.07, 146.96, 142.44, 139.64, 133.45, 131.69, 128.54, 125.19, 123.45, 118.08, 114.84, 111.19, 54.64, 25.63, 25.50. ESI-MS calculated.m/z 353.13 found 354.97 $[M+1]^+$.

*(E)-N-(3,5-dichlorophenyl)-5-(4-hydroxy-3-methoxyphenyl)-3-oxopent-4-enamide (**7i**):*

Yield 58%. Yellow solid, Mp: 198-200 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 10.18 (s, 1H,), 8.60 (d, 1H, *J*=6.6 Hz), 7.74 (s, 2H), 7.48 (s, 1H), 7.03-7.12 (m, 3H), 6.85 (d, 1H, *J*=8.1 Hz), 3.67 (s, 3H), 2.42 (s, 2H). ^{13}C NMR (75 MHz $CDCl_3$): 195.02, 167.26, 149.55, 147.46, 140.71, 140.50, 134.76, 133.67, 125.97, 124.24, 123.65, 117.73, 115.36, 111.57, 55.44, 26.58. ESI-MS calculated.m/z 379.04 found 380.09 $[M+1]^+$.

*(E)-5-(4-hydroxy-3-methoxyphenyl)-1-(piperidin-1-yl)pent-4-ene-1,3-dione (**7j**)*:

Yield 45%. Orange solid, Mp: 146-148 ^{0}C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.43 (s, 1H), 7.04-7.11(m, 3H), 6.88 (d, 1H, *J*=15.6 Hz), 4.08-4.15 (m, 2H), 3.86 (s, 3H), 3.64-3.79 (m, 2H), 2.40 (s, 2H), 1.23-1.31 (m, 6H). ^{13}C NMR (75 MHz $CDCl_3$): 195.66, 167.26, 148.54, 146.98, 139.68, 133.79, 125.51, 125.29, 115.05, 111.70, 56.00, 47.56, 42.26, 26.53, 26.14, 25.34, 24.48. ESI-MS calculated. m/z 303.15 found 304.91$[M+1]^+$.

α-Amylase inhibition activity:

The alpha amylase inhibition assay was carried out by following the reported literature[27].

α-Gluosidase inhibition activity:

Alpha-glucosidase activities were performed according to the literature reported[27].

AGEs inhibition activity:

The AGEs inhibitory study was performed by following the literature[12].

Molecular docking study

The rigid molecular docking studies were performed by using HEX 8.0 software[28].The three-dimensional structure of synthesized compounds (**4a-j** and **7a-j**) were constructed using ChemBio 3D ultra 13.0 software, and then they were energetically minimized using MMFF94 with a maximum number of iteration of 5000 and minimum RMS gradient of 0.10[29]. The crystal structures of Protein (PDB ID: 1HNY) were taken from Protein Data bank (www.rcsb.org). The docked complexes were visualized using discovery studio 4.1 client.

Supporting information

Supporting information contains spectra for the synthesized compounds.

Acknowledgements

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Keywords: AGEs inhibitor, *α*-amylase inhibition, *α*-glucosidase inhibition, *β*-ketoamide curcumin.

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

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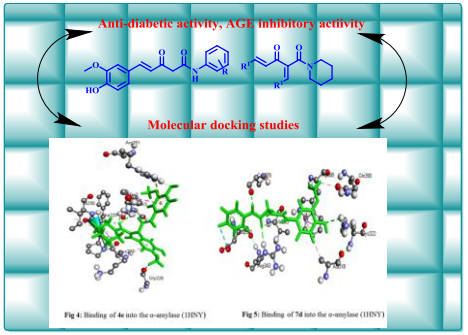
Text for Table of Contents

Two different series of novel *β*-ketoamide curcumin analogues enriched in biological activities have been synthesized. The synthesized compounds were screened for their *in vitro* anti-diabetic and AGEs inhibitory activities and exhibited potent to good anti-diabetic and AGEs inhibitory activities. Further molecular docking study was also performed with the *α*-amylase enzyme.



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Synthesis of *β*-Ketoamide Curcumin Analogues for Anti-Diabetic and AGEs Inhibitory Activities

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