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Reduction in post-prandial hyperglycemic excursion through α-glucosidase inhibition by β-acetamido carbonyl compounds

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ABSTRACT

A series of β-acetamido carbonyl compounds ($\mathbf{S}_1$–$\mathbf{S}_7$) were prepared using Dakin-West reaction from different substituted aldehyde and acetophenone in the presence of lanthanum triflate as a solid catalyst. All the compounds were tested for their α-glucosidase inhibitory potential against rat intestinal α-glucosidase. The most potent rat intestinal α-glucosidase inhibitors $\mathbf{S}_5$ and $\mathbf{S}_7$ were tested for their antihyperglycemic activity following carbohydrate tolerance test. Both the compounds displayed antihyperglycemic activity equivalent to the standard drug acarbose.

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Postprandial hyperglycemia (PPHG) has emerged as a prominent and early defect in type II diabetes.[1] Type II diabetes subjects carry an excess risk for micro- and macrovascular diseases and possess higher risk for cardiovascular morbidity and mortality. Over the past two years several studies have identified PPHG as a better predictor of cardiovascular or even of all cause mortality as well as, an independent risk factor for atherosclerosis.[2] Targeting PPHG, therefore, may prove to represent the '*sine qua non*' for the 'return' of postprandial glucose values at a 'non-deleterious threshold' for early stages of the disease and latter in the progression of diabetes.[2]

Inhibition of α-glucosidase, an enzyme abundant in brush border of the small intestine, has been found to delay carbohydrate digestion, absorption, and thereby diminish PPHG level.[3–5] It has also proved to be a promising therapeutics strategy for reducing increased risk for diabetes, hypertension, dyslipidemia, obesity and cardiovascular diseases in patients with metabolic syndrome.[6] In the course of our search for potent α-glucosidase inhibitors from various sources,[7] we observed potent rat intestinal α-glucosidase inhibitory activity in β-acetamido carbonyl compounds. β-acetamido carbonyl compounds have gained considerable attention in organic synthesis owing to their importance as valuable building blocks for preparation of 1,3 amino alcohol,[8] β-amino acids[9] as well as for synthesis of various antibiotics.[10]

β-acetamido carbonyl compounds have been synthesized previously using several catalysts such as Iron (III) chloride, $CeCl_3{\cdot}7H_2O$, montmorillonite K-10 clay.[11] Recently, solid catalysts have gained importance due to environmental and economic considerations.[12] Among them, the application of lanthanum trifluoro methane sulphonate (lanthanum triflate) as a stable and solid acid catalyst in organic synthesis has been widely studied.[13] This catalyst is important from an environmental point of view, because it produces little waste, gives excellent activity and selectivity even on an industrial scale.

As a part of our interest in systematic investigation of chemical feature of β-acetamido-β-(4- nitrophenyl)-4-nitropropiophenone ($\mathbf{S}_5$) in relation to α-glucosidase inhibitory activity, we prepared various derivatives of Dakin-West reaction of acetamido ketones using Lanthanum triflate as a solid catalyst, from different substituted aldehyde and acetophenone (Scheme 1),[14]

To find the optimal conditions for synthesis, a mixture of benzaldehyde (2 mmol), acetophenone (2 mmol), acetyl chloride (3 mmol) and acetonitrile (5 ml) was stirred under various reaction conditions. It was observed that in absence of the catalyst (solid lanthanum triflate), product β-acetamido ketone was obtained only with 14% yield after 24 hrs. However, addition of 10 mol % of catalyst furnished β-acetamido carbonyl compound in excellent yields. Structures of the resulting Dakin-West reaction derivatives of acetamido ketone were confirmed by ^{1}H NMR and Mass analysis.[15] This report gives a simple and new synthetic methodology for the one-pot synthesis of β-acetamido ketone by coupling four components aromatic aldehydes, acetophenones, acetylchloride and acetonitrile in the presence of lanthanum triflate as a catalyst.

The biological significance of derivatives of β-acetamido carbonyl compounds ($\mathbf{S}_1$–$\mathbf{S}_7$) was established by screening them in vitro against rat intestinal α-glucosidase enzyme using *p*-nitrophenyl-α-D-glucopyranoside as substrate.[7] At initial screening

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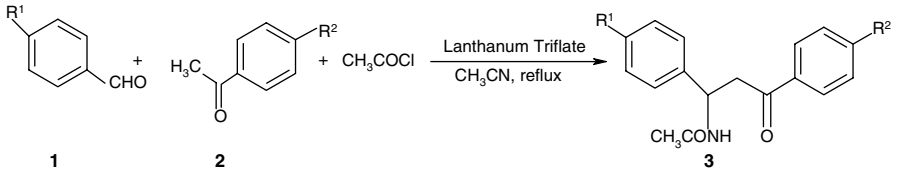

Where,

	R1	R2	
S_1 :	F	Br	($C_{17}H_{15}BrFNO_2$)
S_2 :	F	F	($C_{17}H_{15}F_2NO_2$)
S_3 :	NO_2	H	($C_{17}H_{16}N_2O_4$)
S_4 :	OH	F	($C_{12}H_{16}FNO_3$)
S_5 :	CH_3	NO_2	($C_{18}H_{18}N_2O_4$)
S_6 :	NO_2	NO_2	($C_{17}H_{15}N_3O_6$)
S_7 :	CH_3	Br	($C_{18}H_{18}BrNO_2$)

Scheme 1.

concentration (50 μg) from 5 mg/mL DMSO solution, enzyme inhibitory potential of compounds (in triplicate, means ± SD) was observed as follows. $\mathbf{S}_1$ (2.7 ± 0.3%); $\mathbf{S}_2$ (55.09 ± 13.18%); $\mathbf{S}_3$ (72.23 ± 1.52%); $\mathbf{S}_4$ (60.11 ± 0.27%); $\mathbf{S}_5$ (85.03 ± 7.97%); $\mathbf{S}_6$ (52.71 ± 0.00%) and $\mathbf{S}_7$ (95.12 ± 0.16%). Compounds displaying more than 60% enzyme inhibition were further analyzed for dose-response curve (Fig. 1). In this study, compound $\mathbf{S}_7$ emerged as most potent α-glucosidase inhibitor with IC_{50} value of 5.53 μM followed by $\mathbf{S}_5$ (9.07 μM), $\mathbf{S}_3$ (25.64 μM) and $\mathbf{S}_4$ (72.82 μM). In our test system we included standard α-glucosidase inhibitor drug acarbose as reference that displayed IC_{50} value of 6.38 μM.

For compounds $\mathbf{S}_5$ and $\mathbf{S}_7$ displayed enzyme inhibitory potential close to acarbose, they were selected for in vivo evaluation of their potential in mitigating postprandial blood glucose rise following carbohydrate tolerance test in rats.[16] Slama et al.[17] argued that postprandial glycemic excursion plays an important role in total hyperglycemia reflected by an increase in glycated haemoglobin and advocates delta-postprandial glycemia (the difference between postprandial and preprandial blood glucose level) as a more useful tool than conventional examination of absolute postprandial rise in blood glucose level. Analysis of postprandial delta-glycemia in our animal experiment (Fig. 2) revealed that compounds $\mathbf{S}_5$, $\mathbf{S}_7$ and drug acarbose were able to mitigate significantly the rise in postprandial glycemic excursion when compared with control, though compound $\mathbf{S}_7$ could not show degree of significance at 30th minute. The antihyperglycemic potential of compounds $\mathbf{S}_5$, $\mathbf{S}_7$ and acarbose was not significantly different.

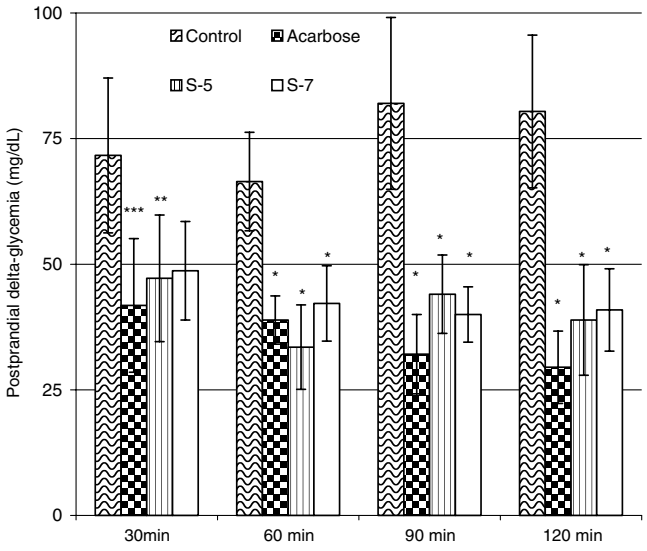

Figure 2. Postprandial delta-glycemia after carbohydrate feeding. Acarbose as well as test compounds S-5 and S-7 was able to check significantly the rise in plasma glucose values. ANOVA analysis was used to study the changes produced after carbohydrate feeding using Bonferroni's Multiple Comparison test to compare the differences between the groups. $^{*}p < 0.001$, $^{**}p < 0.05$, $^{***}p < 0.01$ when compared with control. Data represents mean ± SD, $N = 6$.

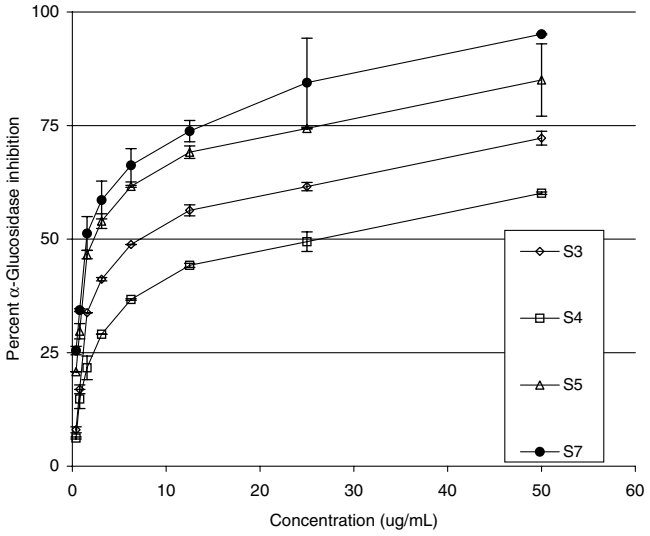

Figure 1. Concentration dependent rat intestinal α-glucosidase inhibitory activity of test compounds. Data represents mean ± SD, $N = 3$.

It can be envisaged from these results that in acetamido carbonyl compounds, the aldehyde ring plays important role in α-glucosidase inhibition and CH_3-substitution ($\mathbf{S}_5$ and $\mathbf{S}_7$) over this ring imparts better enzyme inhibitory activity than NO_2-substitution ($\mathbf{S}_3$ and $\mathbf{S}_6$). Furthermore, addition of different functional group over acetophenone ring may influence activity level of the compound. However, more number of compounds strategically synthesized using this approach is required to better explain the structure activity relationship.

Glucosidase inhibitors have proved their usefulness in reducing postprandial hyperglycemic excursion both in type I and type II diabetes and are drugs of choice for first-line treatment.[17] Amongst various types of glucosidase inhibitors, disaccharides, iminosugars, carbasugars, thiosugars and non-sugar derivatives like polyhydroxy compounds isolated from plants or microorganisms have provided significant therapeutic insights.[18] Compounds like β-acetamido

carbonyls in our report with no obvious structural similarity to both a carbohydrate skeleton and the polyhydroxy nature, therefore, present a novel class of α-glucosidase inhibitors and hence may add new insights in the search for better therapeutic agents than the existing drugs.

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14. *General procedure for the preparation of* β-*acetamido ketones or keto esters.* To a stirred solution of benzaldehyde (2 mmol) and acetophenone (2 mmol) in acetonitrile (5 ml) were added acetyl chloride (3 mmol) and lanthanum triflate (10%). The mixture was refluxed for 3–5 h following the progress of the reaction by TLC. After completion of the reaction, the mixture was poured into crushed ice (50 ml) and extracted with dichloromethane. The organic layer was dried over anhy. Na_2SO_4 and concentrated under vacuum. The crude product was purified by normal column chromatography to obtain of β-acetamido ketones.
15. NMR data: *Compound* (**S_1**). *β-acetamido-β-(4-fluorophenyl)-4-bromopropiophenone.* Mp 221 °C, yield 87%. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.90 (s, 3H), 3.25 (dd, J = 7.03 and 14.06 Hz, 1H), 3.70 (dd, J = 7.81 and 14.85 Hz, 1H), 5.05 (dd, J = 7.80 and 15.62 Hz, 1H), 6.90 (d, J = 8.59 Hz, 2H), 7.25–7.32 (m, 2H), 7.45 (d, J = 6.25 and J = 8.59, 2H), 7.90–8.00 (m, 2H); FABMS: 364 (M^++1); IR (KBr, cm^{-1}): 3286, 1690, 1641, 1542, 1395, 1370, 1088, 892, 816, 759.*Compound* (*S_2*). *β-acetamido-β-(4-fluorophenyl)-4-fluoropropiophenone*. Mp 94 °C, yield 84%. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.94 (s, 3H), 3.30 (dd, J = 6.25 and 16.40 Hz, 1H), 3.60 (dd, J = 7.81 and 17.19 Hz, 1H), 5.40 (dd, J = 7.03 and 14.06 Hz, 1H), 6.90 (d, J = 8.59 Hz, 2H), 7.10 (d, J = 8.59, 2H), 7.30–7.40 (m, 2H), 7.95–8.03 (m, 2H); FABMS: 304.1 (M^++1); IR (KBr, cm^{-1}): 3270, 3075, 1687, 1640, 1508, 1409, 1354, 1214, 1158, 1098, 993, 831, 751, 599. *Compound* (*S_3*). *β-acetamido-β-(4-nitrophenyl)-propiophenone*. Mp 150 °C, yield 80%, ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.91 (s, 3H), 3.40 (dd, J = 5.82 and 17.55 Hz, 1H), 3.65 (dd, J = 8.04 and 17.55 Hz, 1H), 5.50 (dd, J = 6.58 and 13.16 Hz, 1H), 7.40–7.60 (m, 5H), 7.85 (d, J = 6.58, 2H), 8.15 (d, J = 8.7, 2H); FABMS: 313.1 (M^++1); IR (KBr, cm^{-1}): 3310, 3046, 1686, 1649, 1582, 1513,1352, 1285, 1077,751, 658. *Compound* (*S_4*). *β-acetamido-β-(4-hydroxyphenyl)-4-fluoropropiophenone*. Mp 132 °C, yield 85%, ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.90 (s, 3H), 3.35 (dd, J = 6.25 and 16.40 Hz, 1H), 3.65 (dd, J = 7.03 and 16.40 Hz, 1H), 5.40 (dd, J = 7.03 and 14.06 Hz, 1H), 6.95 (d, J = 8.59, 2H), 7.35 (d, J = 5.46 2H) 8.00–8.30 (m, 2H); FABMS: 302 (M^++1); IR (KBr, cm^{-1}): 3260, 3030, 2850, 1658, 1629, 1515, 1459, 1350, 1278, 860, 745. *Compound* (*S_5*). *acetamido-β-(4-methylphenyl)-4-nitropropiophenone*. Mp 85 °C, yield 78%, ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.90 (s, 3H), 2.15 (s, 3H), 3.25 (dd,J = 6.23 and 16.99 Hz, 1H), 3.60 (dd, J = 6.90 and 16.99 Hz, 1H), 5.35 (dd, J = 6.79 and 13.97 Hz, 1H), 6.90–7.07 (m, 4H), 7.90 (d, J = 8.68, 2H), 8.15 (d, J = 8.68 2H); FABMS: 327 (M^++1); IR (KBr, cm^{-1}): 3256, 3034, 2276, 1660, 1601, 1515, 1372, 1241, 970, 828, 670. *Compound* (*S_6*). *β-acetamido-*β*-(4-nitrophenyl)-4-nitropropiophenone*. Mp 152 °C, yield 82%, ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.90 (s, 3H), 3.44 (dd, J = 6.58 and 17.8 Hz, 1H), 3.80 (dd, J = 8.04 and 17.55 Hz, 1H), 5.55 (dd, J = 7.3 and 13.8 Hz, 1H), 7.62 (d, J = 8.10 Hz, 1H), 8.10-8.20 (m, 4H), 8.24–8.40 (m, 4H); FABMS: 358(M^++1); IR (KBr, cm^{-1}): 3280, 3072, 1690, 1646, 1590, 1530, 1358, 1073, 995, 816, 759. *Compound* (*S_7*). *acetamido-β-(4-methylphenyl)-4-bromopropiophenone*. Mp 116 °C, yield 80%, ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.88 (s, 3H), 2.30 (s, 3H), 3.25 (dd, J = 6.57 and 15.77 Hz, 1H), 3.55 (dd, J = 6.57 and 15.77 Hz, 1H), 5.40 (dd, J = 7.88 and 14.46 Hz, 1H), 7.00–7.25 (m, 5H), 7.60 (d, J = 7.88, 2H), 7.85 (d, J = 7.88, 2H); FABMS: 360 (M^++1); IR (KBr, cm^{-1}): 3301, 2928, 1680, 1642, 1545, 1374,1220, 1032, 755.
16. *Animal experiment*. Male Wistar rats weighing between 195 and 215 g were obtained from National Institute of Nutrition (CPCSEA Reg. No. 154, registered by Government of India dated 22 October 1999) Hyderabad. The animals were housed in standard polyvinyl cages. The room temperature was maintained at 22 ± 1 °C with an alternating 12 h light-dark cycle. Food and water were provided ad libitum. Experiments were performed as per the Institutional Animal Ethical Committee norms. The rats were divided into four groups viz control, standard, S-5 and S-7, containing six rats in each group. All the animals were kept for overnight fasting. Next day forenoon blood was collected from retro orbital plexus in EDTA containing tubes, and plasma glucose levels for basal ('0'-h) value were measured by glucose-oxidase test method using auto blood analyzer instrument (Bayer EXPRESS PLUS). Standard drug acarbose and the test samples **S_5** and **S_7** were suspended in normal saline and were administered orally in the dose of 100-mg/kg-body weight. The control group of animals were given only normal saline. Fifteen minutes after acarbose and test sample treatment, animals were fed with soluble-starch dissolved in normal saline at a dose of 2-g/kg-body weight. Thereafter, blood was collected at the intervals of 30, 60, 90 and 120th minutes post starch feeding. Plasma was separated out for glucose measurement as described above.
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