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Antihyperglycemic activity of chalcone based novel 1-{3-[3-(substituted phenyl) prop-2-enoyl] phenyl} thioureas

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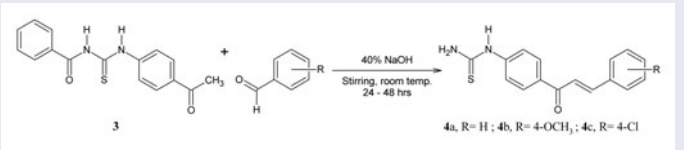
ABSTRACT

The present study describes the synthesis of novel chalcone based 1-{3-[3-(substituted phenyl) prop-2-enoyl] phenyl} thioureas (4a-c) using Claisen Schmidt condensation and investigates their protective role in diabetic conditions and associated oxidative stress. Spectral properties for the synthesized compounds were studied. Novel compounds were screened for antihyperglycemic effect in streptozotocin (STZ)-induced diabetic rats in a 6 week study and compound **4b** exhibited significant ($p \leq .05$) results similar to the standard drug glipizide. Treatment of diabetic animals with compound **4b** (10 and 20 mg/kg, body weight) for 12 weeks, reduced the increased blood glucose level significantly ($p \leq .01$) and restored attenuated serum biochemical parameters to normal levels. Altered antioxidant enzyme activity was also considerably ($p \leq .01$) restored to the standard normal range. β-apoptotic TUNEL assay indicated that compound **4b** (AI: 1.2 ± 0.05) could prevent further β-cell death in the pancreas of diabetic animals in a dose-dependent manner, which highlights its potentiality as an effective antihyperglycemic agent.

GRAPHICAL ABSTRACT



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Apoptosis; blood glucose lowering effect; catalase; chalcone; streptozotocin

Introduction

Diabetes is one of the major endocrine disorders of multiple etiologies and characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both.[1]

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Diabetes is becoming the third "silent killer" of mankind, after cancer and cardiovascular diseases, because of its high prevalence, morbidity, and mortality.[2] Type-2 diabetes is the most common form prevalent in 90–95% of diabetic patients and is characterized by insulin resistance in liver and peripheral tissues together with pancreatic β-cell defects.[3] According to the World Health Organization (WHO), diabetes deaths will get doubled by 2030 and 80% of this numerical increase will occur in developing countries including India.[4]

The treatment of diabetes is currently managed by exercise, calorie intake and oral hypoglycemics, prominent among them being sulfonylurea, biguanides, and thiazolidinones. Though treatment with a highly active thiazolidinone class of drugs has considerably improved the clinical situation, adverse effects of hepatotoxicity, weight gain, and edema still persist. Hence, there is a persistent need for exploration of new molecular targets and strategies to develop safer and effective anti-hyperglycemic, which can also cater to the management of long-term complications of type-2 diabetes mellitus (T2DM). During research into new anti-diabetic molecules, aminoalkyl guanidine analogs were reported as potential anti-hyperglycemic and food intake reducing agent.[5] 3 pyridine-2-yl-thioureido alkanoic acid esters were first reported as less toxic but potent anti-diabetic agents compared to 3-guanidino propionic acid.[6]

A recent literature survey has also highlighted the design and synthesis of a novel hybrid moiety comprising of sulfonyl urea and thiourea moiety responsible for hypoglycemic action with benzene sulfonamide group proved to possess thromboxane A_2 receptor (TPs) antagonistic action to cater to diabetes-induced cardiac complications.[7]

Diabetic complications are further aggravated due to oxidative stress, which plays an important role in causing insulin resistance, β-cell dysfunction, and impaired glucose tolerance.[8] Lower levels of antioxidant enzymes such as catalase and glutathione peroxidase in the β-cells of the pancreas in diabetic conditions make them susceptible to be attacked by reactive oxygen species (ROS) reported to be produced during oxidative stress.[8,9] Hence, hyperglycemic conditions increase the overall oxidative burden, which in turn promotes the release of several pro-inflammatory cytokines causing the apoptosis of β-cells.[8,10] Prolonged exposure of human islets to hyperglycemic conditions has been reported to increase β-cell apoptosis in a dose-dependent manner.[11] Thus, a decrease in the total number of β-cells either by uncontrolled apoptosis or disruptions in the normal homeostatic control could lead to a decrement in the β-cell mass.[12] This suggests that compounds which can enhance antioxidant enzyme activity level might prevent further β-cell damage and produce beneficial effects in diabetes.[13]

Several studies have demonstrated significant anti-hyperglycemic as well as the hypoglycemic effect of natural,[14] synthetic naphthyl chalcones[15] as well as chalcone coupled with aryloxypropanolamine and sulfonamide moiety in *in-vitro* and *in-vivo* models.[16–18] Chalcones have also shown promising anti-oxidant activity which can alleviate oxidative stress-related manifestations.[19]

Anti-hyperglycemic activity of hybrid moieties involving thiazolidinones with chalcone[20] and sulfonyl ureas has been reported.[21] Chalcones have demonstrated their modulatory effect on all major targets namely PTB1B, PPARγ, α-glucosidase, DPP-4, and aldose reductase and are prospective candidates amongst all other present ligands.[21,22] Recently series of hydroxy bis-chalcones,[23] 3′,5′-digeranylated chalcone[24] and

chalcone-triazole derivatives have been reported to exhibit good α-glucosidase inhibitory activities and stronger effect in reducing glucose level compared to the standard drug, acarbose.[25] Also, chalcones bearing electron donating or electron withdrawing substitutions were prepared and their glucose uptake activity was evaluated.[26] Chalcones with chloro, bromo, iodo, and hydroxy substitutions at position 2 on A-ring exhibited the highest activity with glucose median concentration better than that of pioglitazone and rosiglitazone.[26] Similarly, another reported series of chalcones suggested that presence of 3,4-methylenedioxy group on ring B and nitro/methoxy substituent on ring A in different positions exhibited a significant antihyperglycemic effect similar to that of lispro insulin and tolbutamide.[27] SARs and research findings published by Jung et al.[20] and Hsieh et al.[26] have also reiterated the significance of 4-alkoxy substitution on ring B of chalcones eliciting potent PPAR γ agonistic activity. Six trihydroxy chalcone derivatives were found to be promising candidates for PTB1B inhibition and the results concluded that the electron donating groups on B ring showed better inhibitory activity.[28]

To the best of our knowledge, there are no scientific reports on chalcone based novel thioureas as an anti-diabetic molecule. Based on the promissory effect of chalcones as well as thioureas individually in glucose lowering effect in hyperglycemic rats, the aim of this study was to synthesize chalcone based novel thiourea derivatives and to evaluate the anti-diabetic activity in streptozotocin (STZ) -induced diabetic rats

Results and discussion

Chemistry

The structures of the synthesized compounds were established by IR, ^{1}H- & 13C-NMR and mass spectral analysis. In the FT-IR spectra of compounds (**4a–c**), it was possible to observe the absorptions between 3263 and 3453 cm^{-1} relating to -NH stretch and absorptions at 1638-60 cm^{-1} from α, β unsaturated carbonyl moiety stretching. Thiocarbonyl is less polar than the carbonyl group, and consequently, the band is not intense and it is located at lower frequencies than carbonyl. The ^{1}H-NMR spectra for all synthesized compounds show the signals of aromatic protons of nitrogen in the range of 8.2–10.0 ppm. The signals for aromatic hydrogens are between 7.0 and 8.3 ppm. In these same regions are the vinylic protons of *trans* olefinic protons which have larger coupling constants than those of *cis* isomers. The 13C-NMR data of compounds (**4a–c**) showed a characteristic peak for −NHCSNH from δ180-181 and C=O peak at δ187–189. The vinylic carbons Cα and Cβ showed characteristic peaks at δ119–146. The OCH_3 carbons of **4b** showed distinct peaks at δ55 ppm. The ESI-Mass data shows the presence of M + 1 and pseudomolecular M + 23 ions (spectras provided in the supplementary file).

All the novel compounds (**4a–c**) were screened for *in vivo* antihyperglycemic activity for 6 weeks. Diabetes was induced in Wistar rats by injecting STZ intraperitoneally (50 mg/kg, body weight). Rats showing high blood glucose level of 260–300 mg/dl were selected for the study. Results suggested that the synthesized compounds had significant ($p \leq .05$) normalizing effect of blood glucose level (BGL) post 6 weeks. Amongst the three compounds, compound **4b** was significantly comparable ($p \leq .01$) to the standard drug, glipizide as shown in (Table S6, Fig. S8, supplementary file). Oral Glucose tolerance tests were carried out to test whether these compounds can cope up with the

sudden increase in glucose load. Oral treatment by compounds **4(a-c)** caused a significant ($p \leq .05$) decrease in the hyperglycemia peak after glucose loading in rats. Percentage reduction of elevated BGL by compounds **4a** and **4c** was quite fast in the range of 47–55% compared to 19% exhibited by glipizide over a period of 1 hr (post glucose load) followed by 66% and 40% respectively. Compound **4b** exhibited a slow but sustained reduction of elevated BGL (27% in 60 min, 74% in 2 h), a better profile compared to glipizide (60% in 2 hours) as shown in Figure S9, Table S7 (Supplementary file). Based on the superior performance of compound **4b**, it was selected for long-term antidiabetic study in STZ-induced diabetic rat model for 12 weeks.

Acute toxicity studies on male Wistar albino rats (90–120 g) revealed that the LD_{50} for the oral administration of the drug was found to be in between >5 and 50 mg/kg of body weight, according to class 2 of ATC methodology.[29,30] The animals were treated with doses of 10 mg/kg and 20 mg/kg, body weight with no lethality and toxic reactions.

In vivo antidiabetic study results for 12 weeks showed, that continuous treatment by compound **4b** at two different dose levels (10 and 20 mg/kg, body weight) reduced the elevated blood glucose levels(BGL) significantly ($p \leq .01$) (Fig. 1A). In the oral glucose tolerance test (OGTT), performed on the sixth week of treatment, compound **4b** caused a rapid and significant ($p \leq .001$) decrease (21% at 10 mg/kg and 52% in 20 mg/kg) in BGL levels, in a dose-dependent manner. Interestingly, compound **4b** resembled the pattern exhibited by standard drug glipizide, which showed 48% decline in BGL, 60 min post-glucose pulse (Fig. 1B). The above finding suggests, that compound **4b** may have therapeutic potential in post-prandial hyperglycemia.

The effect of compound **4b** on antioxidant enzyme activity was monitored. Administration of 20 mg/kg dose of compound **4b** to diabetic rats resulted in a significant decrease ($p \leq .01$) of thiobarbituric acid reactive substances (TBARS), superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) to near-control levels which indicated improved oxidative status in the pancreatic tissues (Fig. 1C). Oral administration of test compound to diabetic groups CI and C2 restored the altered levels of blood urea nitrogen (BUN) ($p \leq .05$), creatinine ($p \leq .01$), serum triglycerides ($p \leq .05$) to equilibrium (Fig. 1D,1E and 1H) post 9–12 weeks suggesting its renoprotective potential in long-term diabetic complications.

In order to further study and establish the regenerative potential of compound **4**b in pancreatic islet cells, we investigated its effect in the prevention of rate of β-cell apoptosis in the pancreas of diabetic rats by TUNEL assay as shown in Table 1. Compound **4b** (20 mg/kg) showed significantly reduced ($p < .01$) apoptotic index (1.2 ± 0.05) compared to that of STZ control (15.5 ± 0.02) in a dose-dependent manner as shown in Figure 2. Higher apoptotic index in the diabetic state compared to low apoptotic index in treated rats suggests that compound **4b** by its anti-apoptotic effect could prevent further β-cell death in the pancreas of diabetic animals and thus be partly accountable for the increase in β-cell number.

Conclusions

Thus, the present study demonstrates the anti-hyperglycemic potential of compound **4b**, a representative of chalcone based novel thioureas, in STZ-induced diabetic rats and

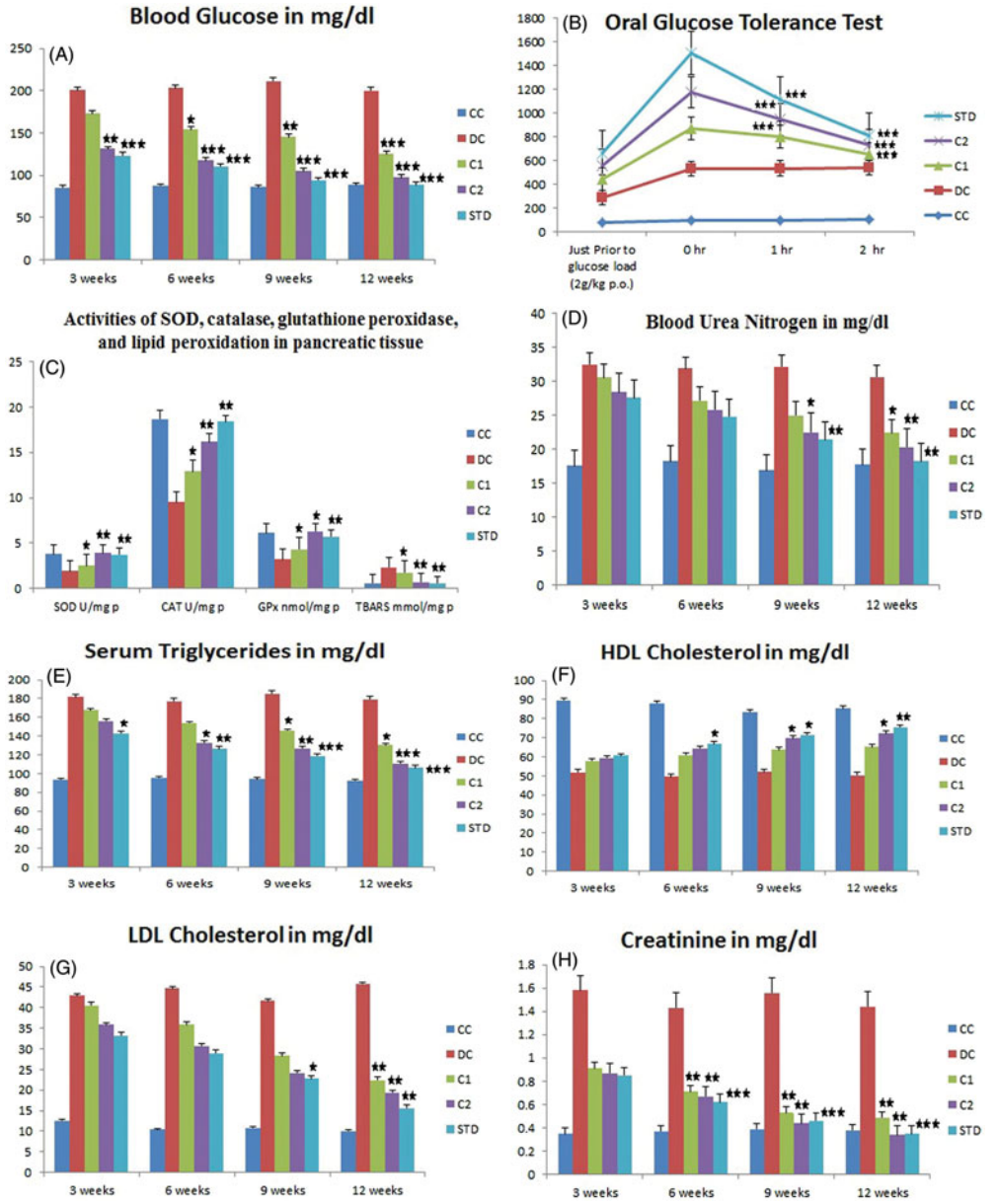

Figure 1. Effect of compound **4b** on blood glucose (1A), OGTT (1B), antioxidant enzyme activity (1C), and BUN (1D) level in STZ-induced diabetic rats over a period of 12 weeks. Effect of compound **4b** on serum triglycerides (1E), HDL cholesterol (1F), LDL cholesterol (1G) and creatinine (1H) level in STZ-induced diabetic rats over a period of 12 weeks.

provides evidence that the protective effects are possibly due to the restoration of biochemical and antioxidant status and suppression of apoptotic events in the pancreas tissue. The improvement in the lipid and renal profile in diabetic animals after treatment with the novel compound **4b** suggests they could be beneficial in preventing long-term diabetic complications as well. Further detailed *in vivo* studies need to be done to provide insights into the explicit molecular mechanism underlying their actions.

Table 1. Apoptotic value of pancreatic tissue sections.

Groups	Apoptotic Index (AI)
CC (Control rats)	0.6 ± 0.01**
DC (Diabetic control rats)	15.5 ± 0.02
C1(Compound **4b**) 10 mg/kg b.w	5.6 ± 0.01*
C2 (Compound **4b**) 20 mg/kg b.w	1.2 ± 0.05**
Standard Glipizide (1mg/kg b.w./day)	0.8 ± 0.03**

Approximately 200 cells were counted per field, five fields were examined per slide and five slides were examined per group. The percentage of TUNEL-positive apoptotic cells was denoted as an apoptotic index (AI). Results are analyzed by t-test and one-way analysis of variance (ANOVA) confirmed by post hoc Dennett's test. Values are given as mean ± SEM for each group's animals. $^{**}p < .01$ and $^{*}p < .05$, significant differences when compared with diabetic control animals.

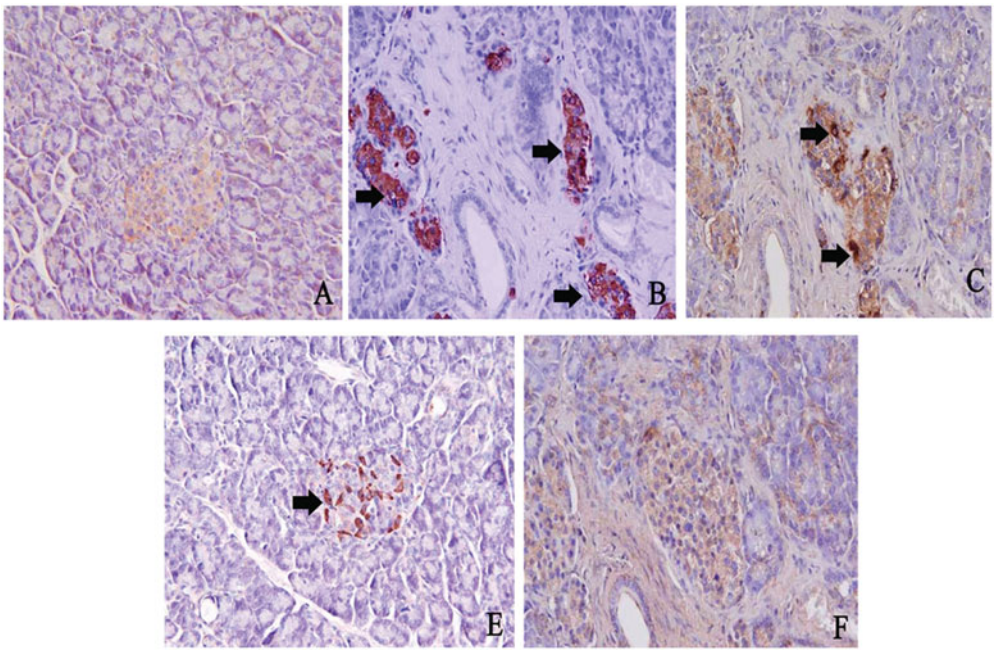

Figure 2. Immunohistochemistry photomicrographs of apoptotic cells in pancreatic sections (40X) of rats. Brown stained cells indicate apoptosis. Arrow represents the expression of TUNEL-positive apoptotic cells. Section A shows a normal histological section with well-arranged cells. Section B shows the marked increment of apoptotic events in the pancreatic section of STZ-induced diabetic rats. Section C shows the TUNEL-positive apoptotic cells moderately expressed in a pancreatic section of diabetic rat treated by compound **4b** (10 mg/kg). Section D depicts minimal expression of apoptotic cells in a pancreatic section of diabetic rat treated by compound **4b** (20 mg/kg). In the case of standard Glipizide (1 mg/kg) (E), showed normal apoptotic events of pancreatic sections of diabetic rats.

Experimental

Chemistry

The synthetic route used to synthesize title compounds as outlined in Figure 3. Three test compounds 1-{3-[3-(substituted phenyl) prop-2-enoyl] phenyl} thioureas [4a-c] were prepared by Claisen Schmidt condensation between substituted acetophenone [1] and substituted aromatic aldehydes in methanol under basic conditions.[31]

Synthetic procedure of 1-{3-[3-phenyl) prop-2-enoyl] phenyl} thioureas (4a–c)

N-[(3-acetylphenyl) carbamothioyl] benzamide [3] (2.98 g, 10 mmol) was dissolved in 15–20 ml of 95% ethanol. NaOH solution (1 g, 50 mmol) was added dropwise to solubilizes compound 3. Substituted benzaldehydes (10 mmol) separately dissolved in 10 ml of ethanol was then added and the reaction mixture was stirred for 24–48 h[31] as represented in Figure 3. The reaction mixture was poured into ice-cold water, acidified with 6 N HCl using pH indicator paper till it becomes neutral. The mixture was extracted with 200 ml of ether and the ether extract was washed with saturated $NaHCO_3$. The extract was dried until the solvent evaporates off and the solid product was recrystallized with acetone/methanol to get yellow to orange-colored crystals.

Spectral data of 1-{3-[3-phenyl) prop-2-enoyl] phenyl} thioureas (4a)

Yellowish solid, Yield 50%; mp 138–140 °C (from methanol); IR ν_{max} 3338 (aromatic-NH), 1674 (−CO) cm^{-1}; ^{1}H-NMR (DMSO-d6, 300 MHz): $\delta = 8.29$ (d, 2 H, aromatic H2′-6′, $J = 8.86$ Hz), 8.20 (br s, 1 H, NH), 8.06 (d, 1 H, Hß, $J = 9$ Hz), 7.8 (d, 2 H, aromatic H3′-5′, $J = 8.86$ Hz), 7.74 (d, 4 H, aromatic H2″-6″ , $J = 8.55$ Hz), 7.68 (d, 1 H, H_α, $J = 9$ Hz), 7.40 (d, 2 H, aromatic H3″-5″ , $J = 8.55$ Hz) ppm. 13C-NMR (DMSO-d6, 400 MHz): $\delta = 188.1$ (−CO), 181.6 (−NHCSNH), 144.4 (C_β), 135.2 (C4″), 129.9 (C3″5″), 130.9 (C2″ 6″), 129.3 (C1′), 122.4 (C4′), 129.2 (C 3′5 ′), 121.5 (C_α), 122.4 (C1″), 121.5 (C2′6′) ppm. ESI-MS (*m/z*) [M^++23]: 305.23. Analytically calculated (%) for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.0; N, 9.92, S, 11.36. Found: C, 67.84; H, 4.9; N, 9.90, S, 11.28.

Spectral data of 1-{3-[3-(4′-methoxy phenyl) prop-2-enoyl] phenyl} thioureas (4b)

Light brownish solid, yield 70%; mp: 170–172 °C (from methanol); IR ν_{max} 3453 (aromatic-NH), 1638 (−CO) cm^{-1}; ^{1}H-NMR (DMSO-d6, 300 MHz): $\delta = 8.19$ (1 H, br, s, NH), 8.07 (1 H, d, Hß, $J = 8.7$ Hz), 7.83 (2 H, d, H2″ -6″ , $J = 8.7$ Hz), 7.91 (2 H, d,

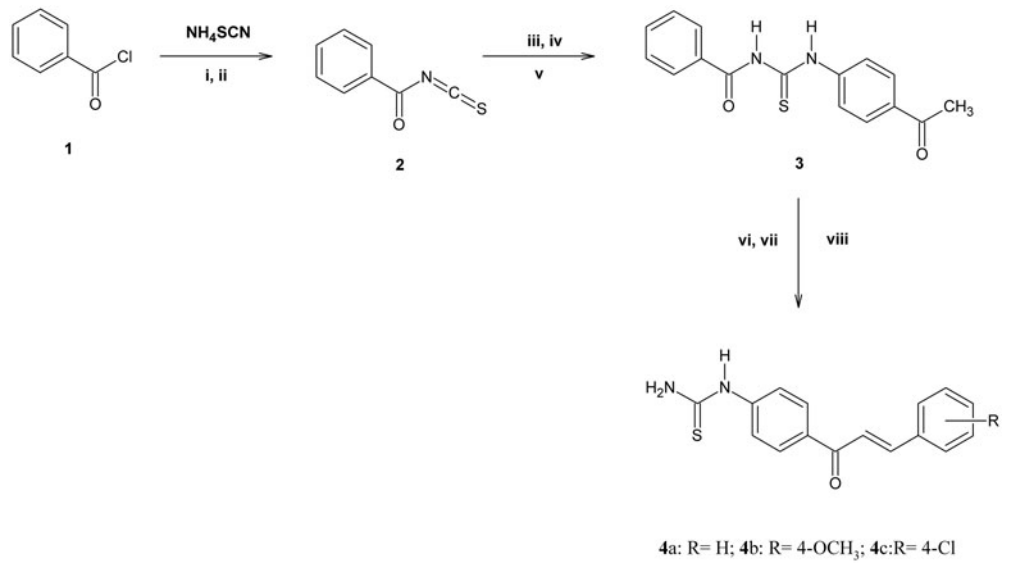

Figure 3. Reagents and conditions: (i) acetone (ii) reflux 10–15 min (iii) reflux (iv) 30 min-1 hr (v) 4-amino acetophenone (vi) 40% NaOH; stirring (vii) RT (viii) substituted benzaldehyde.

aromatic H2′-6′, $J = 7.2$ Hz), 7.61 (2 H, d, aromatic H3″ -5″, $J = 8.7$Hz), 7.49 (2 H, d, aromatic H3′-5′, $J = 7.2$Hz), 6.95 (1 H, d, H_α, J = 8.7Hz), 3.85 (3 H, s, $-COCH_3$) ppm. ^{13}C-NMR (DMSO-d6, 400 MHz): $\delta = 188.0$ (−CO), 181.6 (-NHCSNH), 161.7 (C4′), 144.3 (C_β), 135.0 (C4″), 130.0 (C2″ C6″), 128.2 (C3″ 5″), 128.9 (C1′), 127.8 (3′5′), 120.0 (C_α), 114.8 (C1″), 119.9 (C2′6′), 55.8 (-OCH_3) ppm. ESI-MS (*m/z*) (M^++69): 380. Analytically calculated (%) for $C_{17}H_{16}N_2O_2S$: C, 65. 36, H, 5.16, N, 8.97, S, 10.26. Found: C, 65.30, H, 5.00; N, 8.23, S, 10.0.

Spectral data of 1-{3-[3-(4′-chloro phenyl) prop-2-enoyl] phenyl} thioureas (4c)

Deep yellowish solid, Yield: 65%; m.p: 160–174 °C (from methanol); IR (KBr) ν_{max} 3341(NH) 1671 (CO) cm^{-1}, ^{1}H-NMR (300 MHz, DMSO-d6): $\delta = 10.07$ (br s, 1 H, NH), 8.12 (d, 1 H, H_α, $J = 8$ Hz), 7.90–7.99 (m, 4 H, Ar-H), 7.67–7.74 (m, 4 H, Ar-H), 7.51 (d, 1 H, H_β, $J = 8$ Hz) ppm. ^{13}C-NMR (DMSO-d6, 400 MHz): $\delta = 187.7$ (−CO), 144.6 (C_β), 131.0 (C4″), 131.0 (C4′), 130.5 (C3′5 ′), 129.4 (C2″6″), 130.9 (C2′6′), 124.0 (C3″5″), 119.1 (C_α) ppm. ESI-MS (*m/z*): (M^++23): 339.16. Analytically calculated (%) for $C_{16}H_{13}ClN_2OS$: C, 60.66; H, 4.14; N, 8.84, S, 10.12. Found: C, 61.05; H, 4.10; N, 8.78, S, 10.20%.

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