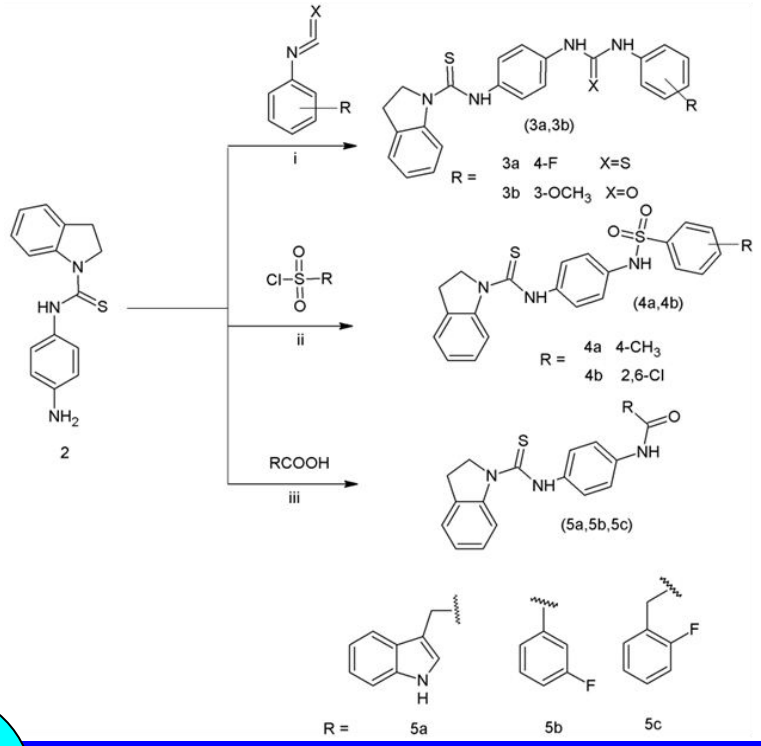

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Synthesis, characterization and evaluation of antidiabetic activity of novel indoline derivatives

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Abstract

Series of indoline derivatives were synthesized using N-(4-aminophenyl) indoline-1-carbothiamide as a precursor. The confirmation of synthesized compounds was done by ^{1}H-NMR, ^{13}C-NMR, LC-MS (ESI) and FT-IR. *In vitro* antidiabetic activity of synthesized indoline derivatives were examined by standard α-amylase inhibition assay. The compounds **4a** (IC_{50} = 52.1 µg/mL) and **4b** (IC_{50} = 57.7 µg/mL) showed potent α-amylase inhibition activity. The compounds **3a** (IC_{50} = 62.2 µg/mL) and **3b** (IC_{50} = 60.7 µg/mL) showed moderate antidiabetic activity.

Introduction

Diabetic is characterized by high blood glucose level. When a person has diabetes, the body either does not produce sufficient insulin or is unable to use its own insulin effectively. Inhibition of saccharide hydrolysing enzyme (α-amylase) have been useful as oral hypoglycemic drugs for the control of hyperglycemia mainly in patients with type-2 diabetes mellitus. Inhibition of this enzyme hold-up carbohydrate digestion and extend overall carbohydrate digestion time, causing a decrease in the rate of glucose absorption and, therefore, reducing the postprandial plasma glucose rise (Keri et al., 2015).

Heterocyclic compounds are the basis in antidiabetic treatment for many years. The hyperglycemia in diabetes mellitus is reduced by drugs like sulfonylurea and biguanides. However, there is a continuous search for alternative drugs for management of diabetes is still a challenge to the medicinal chemist.

In addition, the indoline nucleus is incorporated in various natural products such as alkaloids (Zhang et al., 2011). Encouraged by the above observations and considering the interesting pharmacological profile of indoline, N-(4-aminophenyl)indoline-1-carbothioamide scaffold based compounds were synthesized as antidiabetic agents. The biological activity and structure–activity relationship (SARs) of the newly synthesized indoline derivatives are also discussed.

Materials and Methods

The starting materials such as reagents and solvents used for the synthesis are of analytical grade and they are purchased from Sigma-Aldrich Chemical Co., Spectrochem Chemical Co, and Merck Chemical Co. Melting points were recorded by labtronics digital melting point apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO solvent on Bruker 300 MHz spectrophotometer using TMS as an internal standard. Infrared spectroscopy was recorded in the frequency range of 400-4000 cm^{-1} by Perkin

Elmer. The Mass spectra were recorded on a Waters Synapt G2 High detection Mass spectrometry. The thin layer chromatography (TLC) analysis was carried out using 5 × 20 cm plate coated with silica gel GF_{254}.

***Synthesis of N-(4-nitrophenyl)indoline-1-carbothioamide* (1)**

To a solution of indoline (10 g, 0.0835 mol) in 200 mL of THF, 4-nitrophenyl isothiocyanate (16.5 g, 0.0918 mol) was added at 0°C. The reaction mixture was stirred for 4 hours at room temperature. A yellow color solid (compound **1**) was obtained on concentration of reaction mixture under reduced pressure. Yield 80%; m.p 173-174°C; IR (KBr) ν_{max} in cm^{-1} : 3434, 3300 (N-H stretch), 3074 (C-H stretch, aromatic), 2919, 2850 (C-H stretch, aliphatic), 1532, 1319, (NO_2 stretch), 1477 (CH_2 bend), 1270 (C=S), 909 (C-N stretch); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.13 (t, 2H, *J* = 8.1 Hz), 4.32 (t, 2H, *J* = 8.2 Hz), 7.05 (td, 1H, *J* = 0.9, 7.9 Hz), 7.18 (td, 1H, *J* = 1.2, 8.1 Hz), 7.33 (d, 1H, *J* = 7.9 Hz), 7.71 (d, 2H, *J* = 9.9 Hz), 7.80 (d, 1H, *J* = 8.0 Hz), 8.19 (d, 2H, *J* = 9.9 Hz), 10.39 (s,1H); ^{13}C-NMR (DMSO-d_6) δ ppm: 26.6, 54.2, 116.0, 121.9, 123.9, 124.1, 125.6, 126.8, 134.3, 142.1, 142.2, 146.8, 177.5; LC-MS (ESI) calculated for ($C_{15}H_{13}N_3O_2S$) m/z $[M + H]^+$ 299.0, found m/z 300.0.

Synthesis of N-(4-aminophenyl)indoline-1-carbothioamide (2)

One hundred milliliter of 12N HCl, $SnCl_2$ (63.9 g, 0.338 mol) were added to a solution of compound **1** (10 g, 0.0338 mol) and the resulting reaction mass was stirred for 3 hours at room temperature. The completion of the reaction was monitored by TLC. The reaction mixture was diluted with 350 mL of cold water and basified with 40% sodium hydroxide up to pH 8. The basified solution was extracted with ethyl acetate (3 x 150 mL) and washed with double distilled water (1 x 60 mL) followed by brine solution (2 x 150 mL). The organic phase was dried over anhydrous sodium sulphate solution. The ethyl acetate layer was concentrated with rotary evaporator to afford compound **2**. Brown solid; Yield 72%; mp 209-210°C; IR (KBr) ν_{max} in cm^{-1} : 3398 (N-H stretch), 3055 (C-H stretch, aromatic), 2969 (C-H stretch, aliphatic), 1610 (N-H bend), 1447 (CH_2 bend), 1209 (C=S), 932 (C-N stretch) ; ^{1}H-NMR (DMSO-d_6) δ ppm: 3.08 (t, 2H, *J* = 8.1 Hz), 4.21 (t, 2H, *J* = 8.2 Hz), 5.05 (s, 2H), 6.52 (d, 2H, *J* = 8.7 Hz), 6.95 (t, 3H, *J* = 7.2 Hz), 7.12 (t, 1H, *J* = 7.8 Hz), 7.24 (d,1H, *J* = 7.9 Hz), 8.29 (d, 1H, *J* = 8.1 Hz), 9.41 (s, 1H) ; ^{13}C-NMR (DMSO-d_6) δ ppm: 26.7, 52.8, 113.3, 116.1, 122.5, 124.9, 126.1, 126.8, 128.5, 133.3, 143.4, 146.3, 178.5; LC-MS(ESI) calculated for ($C_{15}H_{15}N_3S$) m/z $[M + H]^+$ 269.1, found m/z 270.0.

***Synthesis of 1-(4-fluorophenyl)-3-(4-(indoline-1-carbothioamido)phenyl)thiourea* (3a)**

To a solution of compound **2** (0.4 g, 0.0015 mol) in 12 mL of THF, 4-fluorophenyl isothiocyanate (0.3 g, 0.0019 mol) was added at 0°C. The reaction mixture was stirred for 4 hours at room temperature. The completion of reaction was confirmed by TLC. The concentrated reaction mixture was extracted with ethyl acetate (1 x 50 mL) and 2N HCl (1 x 25 mL). The resulting ethyl acetate layer was washed with brine solution (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate solution. The ethyl acetate layer was concentrated with rotary evaporator to afford compound **3a.** Pal yellow solid; Yield 32%; mp 259-261°C; IR (KBr) ν_{max} in cm^{-1} : 3424 (N-H stretch), 2926 (C-H stretch, aromatic), 2581 (C-H stretch, aliphatic), 1590 (N-H bend), 1449 (CH_2 bend), 1291 (C-N stretch), 1211 (C=S), 761 (CH bend); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.10 (t, 2H, *J* = 8.3 Hz), 4.26 (t, 2H, *J* = 8.1 Hz), 6.99 (t, 1H, *J* = 7.8 Hz), 7.13-7.15 (m, 3H), 7.29 (d, 1H, *J* = 8.3 Hz), 7.27-7.50 (m, 6H), 8.09 (d, 1H, *J* = 8.4 Hz), 9.76 (s, 3H) ; ^{13}C-NMR (DMSO-d_6) δ ppm: 26.7, 53.3, 114.8, 115.1, 123.0, 123.6, 125.2, 126.0, 126.4, 133.7, 135.7, 143.0, 157.8, 160.2,178.2, 179.9; LC-MS (ESI) calculated for ($C_{22}H_{19}FN_4S_2$) m/z $[M + H]^+$ 422.1, found m/z 423.0.

***Synthesis of 1-(4-(indoline-1-carbothioamido)phenyl)-3-(3-methoxy phenyl)urea* (3b)**

3b was prepared from compound **2** (0.5 g, 0.0018 mol) in 15 mL of THF, 3-methoxy phenyl isocynate (0.322 g, 0.0024 mol) was added at 0°C as procedure mentioned above for **3a**. White solid; Yield 76% ; mp 246-248°C; IR (KBr) ν_{max} in cm^{-1} : 3287 (NH stretch), 2950 (CH stretch, aromatic), 2838 (CH stretch, aliphatic), 1649 (C=O), 1558 (NH bend), 1491 (CH_2 bend), 1291 (C-N amide), 1230 (C=S), 1160 (C-O), 763 (CH bend); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.10 (t, 2H, *J* = 8.1 Hz), 3.70 (s, 3H), 4.27 (t, 2H, *J* = 8.1 Hz), 6.52 (dd, 1H, *J* = 2.1, 8.1 Hz), 6.92 -7.00 (m, 2H), 7.11-7.27 (m, 6H), 7.43 (d, 2H, *J* = 8.7 Hz), 8.23 (d, 1H, *J* = 8.2 Hz), 9.41 (d, 2H, *J* = 9.1 Hz), 9.67 (s, 1H) ; ^{13}C-NMR (DMSO-d_6) δ ppm: 26.7, 53.1, 54.8, 103.5, 106.8, 110.1, 116.1, 117.6, 122.8, 125.0, 125.8, 126.2, 129.4, 133.6, 136.9, 141.2, 141.2, 143.2, 152.7, 159.6, 178.4 ; LC-MS (ESI) calculated for ($C_{23}H_{22}N_4O_2S$) m/z $[M + H]^+$418.1, found m/z 419.1.

***Synthesis of N-(4-(tosylamino) phenyl)indoline-1-carbothio amide* (4a)**

To a solution of compound **2** (0.4 g, 0.00150 mol) in 10 mL of THF, pyridine (0.474 mL, 0.006 mol) was added at 0°C followed by 4-toluene sulfonyl chloride (0.285 g, 0.00150 mol) in 2 mL 1,2-dichloroethane was added. The reaction mixture was stirred for 3 hours at room temperature. The completion of reaction was confirmed by TLC. The concentrated reaction mixture was extracted with ethyl acetate (1 x 50 mL), double distilled water (1 x 50 mL), and 2N HCl (1 x 30 mL). The resulting ethyl acetate layer was washed with brine solution (1 x 100 mL) and sodium bicarbonate solution (1 x 50 mL). The ethyl acetate layer was concentrated with rotary evaporator to afford compound **4a**. White solid; Yield 48% mp 220-222°C; IR (KBr) ν_{max} in cm^{-1} : 3423 (N-H stretch), 3282, 3059 (C-H stretch, aromatic),

2921 (C-H stretch, aliphatic), 1595 (N-H bend), 1516 (CH_2 bend), 1371, 1154 (S=O), 749 (C-H bend); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.34 (s, 3H), 3.08 (t, 2H, *J* = 8.4 Hz), 4.22 (t, 2H, *J* = 8.4 Hz), 6.95-7.09 (m, 3H), 7.11 (t, 1H, *J* = 7.8 Hz), 7.20-7.27 (m, 3H), 7.35 (d, 2H, *J* = 8.1 Hz), 7.64 (d, 2H, *J* = 8.1 Hz), 8.9 (d, 1H, *J* = 8.1 Hz), 9.63 (s, 1H), 10.18 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ ppm: 20.9, 26.6, 53.1, 116.0, 120.1, 123.0, 125.1, 125.66, 126.3, 126.6, 129.6, 133.6, 134.2, 136.2, 136.7, 142.8, 143.1, 178.1;LC-MS (ESI) calculated for ($C_{22}H_{21}N_3O_2S_2$) m/z [M + H]$^+$ 423.1, found m/z 424.0.

***Synthesis of N-(4-{[(2,6-dichlorophenyl)sulfonyl] amino}phenyl) indoline-1-carbothio amide* (4b)**

4b was prepared from compound **2** and 2,6-dichlorobenzene-1-sulfonyl chloride added as procedure mentioned above for **4a**. The reaction mixture was stirred for 3 hours at room temperature. Red solid; Yield 37% ; mp 215-217°C; IR (KBr) ν_{max} in cm^{-1} : 3432 (N-H stretch), 3360, 3099 (C-H stretch, aromatic), 2922, 2850 (C-H stretch, aliphatic), 1600 (N-H bend), 1519 (CH_2 bend), 1387, 1165 (S=O), 747 (C-H bend); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.09 (t, 2H, *J* = 8.1 Hz), 4.21 (t, 2H, *J* = 8.2 Hz), 7.04-7.07 (m, 2H), 7.14 (d, 1H, *J* = 8.5 Hz), 7.23 -7.26 (m, 3H), 7.52-7.71 (m, 3H), 8.10 (d, 1H, *J* = 8.4 Hz), 9.63 (s,1H), 10.78 (s,1H) ; ^{13}C-NMR (DMSO-d_6) δ ppm: 27.1, 53.7, 116.5, 119.6, 123.5, 125.6, 126.3, 126.8, 127.6, 130.7, 132.4, 133.7, 134.2, 134.92, 136.8, 143.4,178.7 ; LC-MS (ESI) calculated for ($C_{21}H_{17}Cl_2N_3O_2S_2$) m/z [M + H]$^+$ 477.0, found m/z 477.9.

***Synthesis of 2-(1H-indol-3-yl)-N-(4-(indoline-1-carbo thioamido)phenyl)acetamide* (5a)**

To a solution of compound **2** (0.4 g, 0.0015 mol) in 12 mL, 3-indole acetic acid (0.316 g, 0.00181 mol), EDCI.HCl (0.37 g, 0.00195 mol) and HOBt (0.202 g, 0.0015 mol) was added. The mixture was cooled to 0°C and triethylamine (0.818 mL, 0.006 mol) was added. The reaction mixture was stirred for 8 hours at room temperature. The completion of reaction was confirmed by TLC. The concentrated reaction mixture was extracted with ethyl acetate (1 x 50 mL), double distilled water (1 x 50 mL), and 2N HCl (1 x 30 mL). The resulting ethyl acetate layer was washed with brine solution (1 x 100 mL) and sodium bicarbonate solution (1 x 40 mL). The ethyl acetate layer was concentrated with rotary evaporator to afford compound **5a**. Pale yellow solid; Yield 40%; mp 243-245°C; IR (KBr) ν_{max} in cm^{-1} : 3406 (N-H stretch), 3310, 3184 (C-H stretch, aromatic), 2904 (C-H stretch, aliphatic), 1657 (C=O), 1527 (N-H bend), 1482 (CH_2 bend), 1291 (C-N), 1254 (C=S), 788 (C-H bend); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.09 (t, 2H, *J* = 8.1 Hz), 3.72 (s, 2H), 4.24 (t, 2H, *J* = 8.1 Hz), 6.97 (td, 2H, *J* = 1.2, 6.9 Hz), 7.0-7.15 (m, 2H), 7.28 (m, 4H), 7.35 (d, 1H, *J* = 8.1 Hz), 7.54 -7.62 (m, 3H), 8.16 (d, 1H, *J* = 8.3 Hz), 9.67 (s, 1H), 10.12 (s, 1H), 10.92 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ ppm: 26.7, 33.7, 53.1, 108.6, 111.35, 116.0, 118.3, 118.6, 118.9, 120.9, 122.9, 123.8, 125.1, 126.3, 127.2, 133.6, 135.0, 136.1, 136.2, 143.1, 169.5, 178.4; LC-MS (ESI) calculated for ($C_{25}H_{22}N_4OS$) m/z [M + H]$^+$ 426.1, found m/z 427.1.

***Synthesis of 3-fluoro-N-(4-(indoline-1-carbothio amido)phenyl)benzamide* (5b)**

5b was prepared from compound 2 and 3-fluorobenzoic acid added as procedure mentioned above **5a**. The reaction mixture was stirred for 7 hours at room temperature. White solid; Yield 24% ; mp 220-222°C; IR (KBr) ν_{max} in cm^{-1} : 3422 (N-H), 3336, 3271 (C-H stretch aromatic), 2930 (C-H stretch aliphatic), 1657 (C=O), 1593 (N-H bend), 1516 (CH_2 bend), 1388 (C-F), 1317 (C-N), 746 (C-H bend); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.17 (t, 2H, *J* = 8.1 Hz), 4.27 (t, 2H, *J* = 8.4 Hz), 6.99 (t, 1H, *J* = 7.2 Hz), 7.15 (t, 1H, *J* = 8.1 Hz), 7.32 (d, 1H, *J* = 7.2 Hz), 7.36 (d, 2H, *J* = 8.7 Hz), 7.47 (t, 1H, *J* = 7.8 Hz), 7.56-7.63 (m, 1H), 7.71 (d, 2H, *J* = 8.5 Hz), 7.76-7.83 (m, 2H), 8.15 (d, 1H, *J* = 8.4 Hz), 9.75 (s, 1H), 10.33 (s,1H) ; ^{13}C-NMR (DMSO-d_6) δ ppm: 26.7, 53.2, 114.5, 116.0, 118.3, 120.3, 123.8, 125.1, 126.3, 130.5, 130.6, 133.7, 135.5, 135.8, 137.2, 143.0, 160.7, 163.1, 163.9, 178.4 ; LC-MS (ESI) calculated for ($C_{22}H_{18}FN_3OS$) m/z [M + H]$^+$ 391.1, found m/z 392.0.

***Synthesis of 2-(2-fluorophenyl)-N-(4-(indoline-1-carbo-thioamido)phenyl)acetamide* (5c)**

5c was prepared from compound **2** and 2-fluorophenylacetic acid added as procedure mentioned above **5a**. This reaction was carried out at room temperature for 7 hours. Yellow solid; Yield 24% ; mp 220-222°C; IR (KBr) ν_{max} in cm^{-1} : 3328 (N-H stretch), 3289, 3066 (C-H stretch, aromatic), 2632 (C-H stretch, aliphatic), 1672 (C=O), 1600 (N-H bend), 1510 (CH_2 bend), 1388 (C-F), 1317 (C-N), 744 (C-H bend); ^{1}H-NMR (DMSO-d_6) δ ppm: 3.10 (t, 2H, *J* = 8.4 Hz), 3.73 (s, 2H), 4.25 (t, 2H, *J* = 8.4 Hz), 6.97 (t, 1H, *J* = 6.6 Hz), 7.11-7.21 (m, 3H), 7.27 (d, 4H, *J* = 6.8 Hz), 7.31-7.42 (m, 1H), 7.54 (d, 2H, *J* = 8.6 Hz), 8.16 (d, 1H, *J* = 8.3 Hz), 9.69 (s, 1H), 10.23 (s, 1H) ; ^{13}C-NMR (DMSO-d_6) δ ppm: 26.7, 36.2, 53.1, 115.1, 116.0, 118.9, 122.9, 123.0, 124.1, 125.1, 126.3, 128.7, 128.7, 131.9, 133.6, 135.2, 143.0, 159.4, 161.8, 167.8, 178.4 ; LC-MS(ESI) calculated for ($C_{23}H_{20}FN_3OS$) m/z [M + H]$^+$ 405.1, found m/z 406.0.

In vitro antidiabetic activity of indoline derivatives

The α-amylase inhibitory activities were performed by (Nickavar and Amin, 2011), which was originally proposed by (Patil et al., 2013). The solution of compounds was prepared in DMSO to give the various concentrations (50, 100, 150, 200 and 250 µg/mL). 500 µg/mL α-amylase solutions prepared in 0.02M sodium phosphate buffer (pH 6.9) was added to different concentrations of the compounds and incubated for 15 min at 25°C. After 10 min, 500 µg/mL of 1% starch solution in 0.02M of sodium phosphate buffer was added to each tube. The mixture was further incubated at 25°C for 10 min. Then the reaction mixture was terminated by adding 0.5 mL

of DNS reagent (12.0 g of sodium potassium tartrate tetrahydrate in 8 mL of 2 M NaOH and 96 mM 3,5-dinitrosalicylic acid solution) and the contents were heated in a boiling water bath for 5 min. The absorption of resulting reaction mixture was measured at 540 nm. Acarbose was used as positive control/standard. The antidiabetic activity of the compounds was determined by the inhibition of α-amylase. The percentage of inhibition was calculated by the equation:

$$\% \text{ inhibition} = [(A_C - A_S) / A_C] \times 100$$

Where, A_C and A_S are the absorbance of the control and sample respectively

To calculate the IC_{50} (the concentration of a sample required to inhibit the activity of a given enzyme by 50%) values for each sample, the %inhibition was plotted against the sample concentration and a logarithmic regression curve was established.

Results

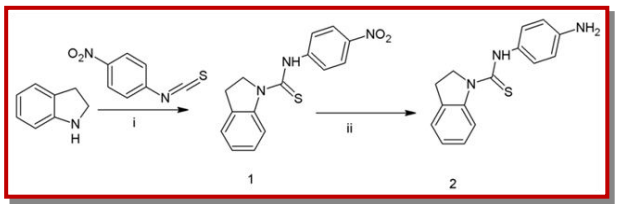
The intermediate 1 was prepared (Sidoova et al., 1998) by using indoline with the reagent 4-nitrophenyl isothiocyanate. The FT-IR spectrum of intermediate 1 had strong absorption about 3300 cm^{-1}, 1270 cm^{-1} corresponds to NH (thiocarboxamide) and C=S, respectively. The ^{1}H-NMR spectrum of intermediate 1 exhibited characteristic thiocarbamide NH at δ 10.4 ppm and in the case of ^{13}C-NMR, characteristic thiocarbamide carbon (C=S) observed at δ 177.5 ppm. The nitro group in intermediate 1 was reduced to equivalents of $SnCl_2$. $2H_2O$ in 12N HCl.

FT-IR spectrum of intermediate 2 showed the characteristics absorption at 3398 cm^{-1} for amine group. In ^{1}H-NMR the nitro group reduction was confirmed by characteristics broad at δ 5.05 ppm. For the synthesis of new series of indoline derivatives the intermediate -2 was used as a common scaffold. The synthetic path way for intermediate 2 is outlined below:

Scheme 1

The amide derivatives **5a**, **5b** and **5c** were prepared by coupling reagent EDCI (Jing et al., 2009). For all amide derivatives NH proton were observed between δ 9.7 and 10.1 ppm as a broad singlet in ^{1}H-NMR. In the ^{13}C-NMR of all new carboxamide carbons observed between δ 163.9 and 178.4 ppm.

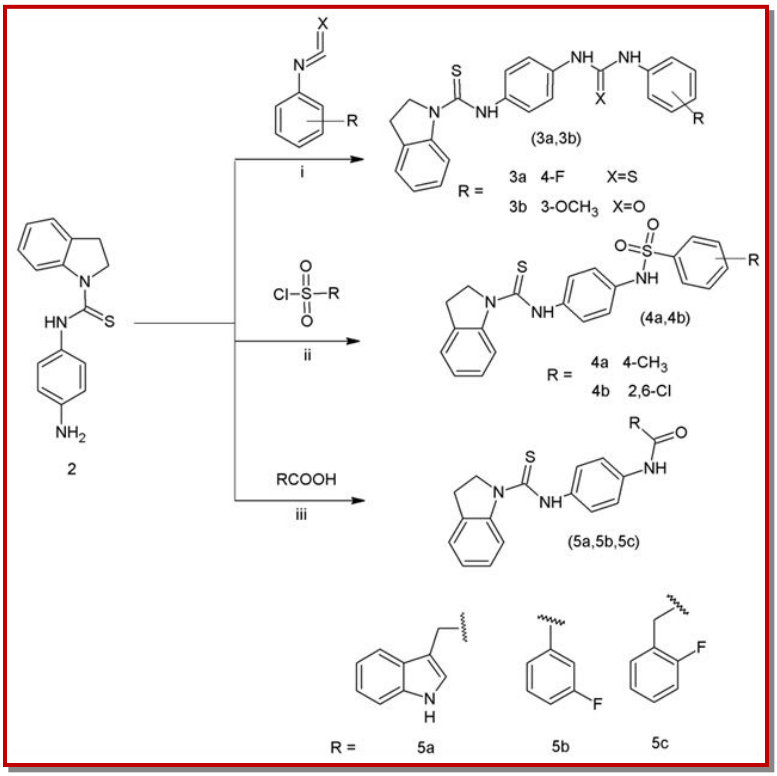
The compound **3a** and **3b** were obtained by reacting intermediate 2 with 4-fluoro phenyl isothiocynate and 3-methoxy-phenyl isocyanate. In ^{13}C-NMR, characteristics the new thiourea carbon (C=S) and urea carbon (C=O) seen at δ 179.9 and 159.6 respectively.



Scheme 1: Reagents and conditions: (i) 4-nitrophenyl isothiocyanate, THF, 0°C; (ii) $SnCl_2$, 12N HCl, RT, 0°C

The sulfonamide derivates **4a** and **4b** were prepared (Macıas et al., 2002) by reaction between corresponding sulfonyl chloride and key intermediate-2 and corresponding sulfonyl chloride. The ^{1}H-NMR of synthesised sulfonamide derivatives showed new singlet peak at δ 9.6 ppm and 9.6 ppm. The synthetic scheme for the preparation of thiourea, urea, sulfonaminde and carboxamide derivatives are shown in Scheme 2.

The antidiabetic activities of all the above indoline derivatives were examined by standard α-amylase inhibition assay. The inhibition efficiency of all synthesized compounds was tested at a concentration ranging from 50 to 250 µg/mL. The %inhibition and IC_{50} values of all indoline derivatives are listed in Table I.



Scheme 2: Reagents and conditions (i) Pyridine, Dichloroethane, 90°C; (ii) THF, 0°C; (iii) EDCI, HOBt, TEA, THF, 0°C

Table I

Antidiabetic activity of indoline derivatives (α-amylase inhibition activity)

Compound	%Inhibition					IC_{50} (μg/mL)
	50 μg/mL	100 μg/mL	150 μg/mL	200 μg/mL	250 μg/mL	
3a	45.3	60.1	68.3	80.7	86.9	62.2
3b	44.5	61.1	69.3	81.2	86.3	60.7
4a	48.3	60.8	68.7	80.5	87.1	52.1
4b	47.6	59.3	67.5	77.4	86.3	57.7
5a	31.5	51.5	61.1	63.4	69.2	119.8
5b	31.7	50.3	60.1	64.9	69.1	121.1
5c	30.3	43.4	54.3	59.8	65.9	145.9
Acarbose	48.5	62.7	76.1	87.7	94.8	48.1

Discussion

The present work demonstrates the antidiabetic activity of indoline derivatives tested on α-amylase inhibition activity. The compound **4a** has tosylamino phenyl group substitution was most effective against inhibition assay (IC_{50} = 52.1 μg/mL) and **4b** has a sulfonyl with dichloro group substitution also effective against inhibition assay (IC_{50} = 57.7 μg/mL) comparable with standard drug acarbose (IC_{50} = 48.1 μg/mL). The compounds **3a** and **3b** having thiourea and urea substituent showed moderate α-amylase inhibition activity (IC_{50} = 62.2 μg/mL) and (IC_{50} = 60.7 μg/mL). The compounds **5a**, **5b** and **5c** did not show noticeable activity.

Indoline based nucleus has been reported to consist of various biological properties such as antimicrobial (Adel et al., 2000; Olgena and Ozkan, 2009; Abdel-Rahman et al., 2004; Sing and Luntha, 2009), anti-cancer (Sovic et al., 2014; Pengzhan et al., 2014; Xu et al., 2015; Jin et al., 2013), antidiabetic (Sato et al., 2014), anti-inflammatory (Fur-man et al., 2014; Rajanarendar et al., 2013), antitubulin (Chang et al., 2006). But indoline based target com-pounds have been poorly investigated their antidiabetic activity (Sato et al., 2014). The synthesized indoline-1 carbothioamide with different urea, thiourea, sulfona-mide are tested on α-amylase inhibition activity. The compounds **4a** and **4b** showed standard acarbose near IC_{50} value of absorbance measured at 540 nm.

Alpha-amylase inhibitory activities of ascidians (Prabhu and Ananthan, 2014), *Gossypium arboreum* (Kazeem et al., 2013), *Newbouldia laevis* (Kolawole and Akanji, 2013) and *Lantana camara* (Swamy and Sinniah, 2015) were reported.

The above result showed that 4a and 4b inhibit α-amylase due to presence of sulfonamide substitution. Furthermore, all moderate active of indoline based compounds have amide group substitution.

Conclusion

Compounds **4a** and **4b** reported have potent *in vitro* α-amylase inhibition activity, similarly the compounds **3a** and **3b** were found to be moderate α-amylase inhibition activity.

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Conflict of Interest

All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work.

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