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# SYNTHESIS AND ANTIDIABETIC ACTIVITY OF THIAZOLIDINONE – THIOPHENE CONJUGATES

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## Abstract
2-Chloro-N-(aryl)-acetamides upon reaction with ammonium acetate in alcohol medium yields 2-(arylamino)-thiazol-4-one **(2a-i)**. The title compounds 5-aryl-2-(phenylamino)-5-(thiophen-3-ylmethylene)thiazol-4(5H)-ones **(3a-i)** were synthesized by reacting with 2-thiophene carbaldehyde **(1)** and 2-(arylamino)-thiazol-4-one in alcohol medium. All the new compounds were assigned on the basis of $^{1}$H-NMR, IR and Mass spectral data and evaluated for *In-Vitro* antidiabetic activity. Some of the tested compounds **3a, 3g, 3h, 3i** showed promising activity when compared to standard Acarbose.

## Introduction
Thiazolidinones are important group of heterocyclic compounds. 4- thiazolidinones are five membered ring compounds containing sulphur and nitrogen in it. Thiazolidinones is one of the privileged nucleus on which a lot of research was done in the past. Tetra hydro derivatives of thiazole is known as thiazolidine and oxo derivatives of thiazolidine is known as Thiazolidinones which has an atom of sulphur and nitrogen at position 1 and position 3 respectively, If it contains carbonyl compounds at 4th position known as thiazolin-4-one or 4-thiazolidinones which is taken for the current study, as it is considered as the important heterocyclic molecule in the field of medicinal chemistry because of its selectivity and affinity towards different bio-targets related to cancer which is the most important criteria in drug discovery.
Thiazolidinone derivatives are important pharmacophores with wide biological application that became basic for the discovery of innovative medicinal agents, such as hypoglycemic thiazolidinediones (Pioglitazone and its analogues), aldose reductase inhibitors (Epalrestat) , modern diuretics (etozoline), etc.The thiazolidinediones are reported to possess anti-infective[I], anticancer[II], antioxidant[III], antiyubercular[IV], antitumor[V], antibacterial[VI] activities etc.
Diabetes mellitus is considered as one of the major disorder characterized by chronic hyperglycemia, which is mainly due to diversified etiologies either genetics and environmental which are acting jointly. Diabetes is a very long term metabolic disorder with so many complications including renal, ocular, neurological, ocular, cardiovascular, and other inter-related problems. So many cases are reported with Type 2 diabetes mellitus, which is strongly

related to the obesity and sendenateray lifestyle factors. 2,4-Thiazolidinedione (TZD) were found to possess oral hypoglycemic activity. The later compounds act by increasing the tissue sensitivity especially adipose tissue, to insulin. The present work is aimed to develop a series of thiazolidinones and followed by evaluation for antidiabetic activity.

**Materials and methods**

Melting points were determined by the open capillary method and are uncorrected. Precoated silica gel plates (Merck, Silica gel 60 F254) were used for monitoring the TLC. IR spectra ($cm^{-1}$) were recorded by using Alpha Bruker IR spectrometer. $^1$H-NMR spectra were recorded on Bruker Avance-II 400 MHz NMR spectrometer. All spectra were obtained in $CDCl_3$ and DMSO. The mass spectrometry was recorded on LC-MS Shimadzu 2020 series in Electro spray ionization mode.

**Synthesis of 2-chloro-N-(aryl)-acetamides**

Aryl amines(0.01 mol) were dissolved in Dimethylformamide (20ml). Chloroacetyl chloride (0.01 mol) was added under the cold condition, and the reaction mixture was stirred for 3 hr at RT. The contents were poured into ice-cold water and the solid mass separated was filtered, washed with water. Recrystallization was carried out ethanol to get the pure compounds.

**Synthesis of 2-(aryl amino)-thiazol-4-ones (2a-i)**

Compounds obtained by the acetylation (0.013 mol) were taken in ethanol (20 ml). Ammonium thiocyanate (0.015 mol) was added to the above solution and refluxed for 1.5 hr and the contents were poured into ice-cold water and the solid formed was filtered, washed with water and finally recrystallization from ethanol to get the desired derivatives of thiazolidinones.

**General procedure for the synthesis of 5-aryl-2-(phenylamino)-5-(thiophen-3-ylmethylene)thiazol-4(5H)-one derivatives (3a-i)**

2-Thiophene carbaldehyde (**1)** (0.01 mol) were added to a well-stirred solution of compound **(2a-i)** (0.01 mo,) in glacial acetic acid (20 ml), which was buffered with sodium acetate (8 mol). The solution was refluxed for 4 hr.The yellow solid obtained was separated, washed with water, dried and the resulting crude product was recrystallized from alcohol to afford the pure title compounds[VII].(Table-1).

**(Z)-2-(4-nitrophenylamino)-5-(thiophen-3-ylmethylene)thiazol-4(5H)-one (3d):** FT-IR (KBr, v, $cm^{-1}$): 3271 (NH), 2920 (C- H), 1669 (C=O), 1633(C=N), 1543 (C=C), $^1$H-NMR (DMSO-d6, TMS, 400 MHz) δ : 6.82-8.15(m, Ar-H, 9H), 8.39(s,NH,1H). MS (m/z): 331.37(M+).

**(Z)-2-(4-fluorophenylamino)-5-(thiophen-3-ylmethylene)thiazol-4(5H)-one (3f):** FT-IR (KBr, v, $cm^{-1}$): 3251 (NH), 3040 (C- H), 1674 (C=O), 1620(C=N), 1462(C=C), $^1$H-NMR (DMSO-d6, TMS, 400 MHz) δ : 6.79-8.12(m, Ar-H, 8H), 8.14(s,NH,1H). MS (m/z):304.36(M+).

**(Z)-2-(4-chlorophenylamino)-5-(thiophen-3-ylmethylene)thiazol-4(5H)-one (3g):** FT-IR (KBr, v, $cm^{-1}$): 3268(NH), 2992(C- H), 1693 (C=O), 1633(C=N), 1535C=C), $^1$H-NMR (DMSO-d6, TMS, 400 MHz) δ : 6.69-7.94(m, Ar-H, 8H), 8.54(s,NH,1H). MS (m/z):320.82(M+).

**(Z)-2-(4-bromophenylamino)-5-(thiophen-3-ylmethylene)thiazol-4(5H)-one (3h):** FT-IR (KBr, v, $cm^{-1}$): 3272 (NH), 3045(C- H), 1672 (C=O), 1637(C=N), 1563C=C), $^1$H-NMR (DMSO-d6, TMS, 400 MHz) δ : 6.78-7.92(m, Ar-H, 8H), 8.68(s,NH,1H). MS (m/z):365.27(M+).

**(Z)-2-(phenylamino)-5-(thiophen-3-ylmethylene)thiazol-4(5H)-one (3i):** FT-IR (KBr, v, $cm^{-1}$): 3286 (NH), 3077(C- H), 1721(C=O), 1609(C=N), 1564C=C), $^1$H-NMR (DMSO-d6, TMS, 400 MHz) δ : 6.82-7.92(m, Ar-H, 8H), 8.16(s,NH,1H). MS (m/z):286.37(M+).

**In-vitro anti-diabetic assay**

**Alpha-Amylase Inhibitory Assay**

A total of 500 µl of test samples (10-50 µg/ml) and standard drug were added to α-amylase (0.5mg/ml), 500 µl of 0.2 mM phosphate buffer (pH 6.9) and then incubated at 25°C for 10 min.1% starch solution (500 µl)in 0.02 M sodium phosphate buffer (pH 6.9) was added to all the test tubes and further incubated at 25°C for 10 min. 3, 5 dinitro salicylic acid (1ml) was added to stop the reaction and kept in boiling water bath for 5 min and cooled to room temperature. The absorbance was measured at 540 nm using Elisa plate reader. Acarbose served as the standard. All the reactions were carried out in triplicates. The reaction mixture, devoid of the test sample, served as control[VIII]. (Table-2).The percentage inhibition of was calculated by using the following formula:

% inhibition = 100 × [V t / V C - 1]

Where, V t = absorbance of the test sample, V c = absorbance of control

**Alpha-Glucosidase Inhibitory Assay**

To a 1ml with 0.2 M Tris buffer pH 8.0, add 2% maltose solution (1ml), followed by addition of test samples 20 (µl) and incubated at 37°C for ten min..By adding 1ml of α-glucosidase enzyme (1U/ml), the reaction was started and followed by incubation for 10 min at 37°C. 20 µl of p-nitrophenyl—D-glucopyranoside solution was added as a substrate and incubated for additional 20 min at 37°C . Measurement of p-nitrophenol which was liberated was done at 405nm with Elisa micro plate reader. Acarbose served as the standard and a control was set up in parallel without the test substance. All the experiments were performed in triplicates[VIII]. The percentage inhibition was calculated by using the above following formula.(Table-2).

**Results and Discussion**

In the present work, a new series of 5-aryl-2-(phenylamino)-5-(thiophen-3-ylmethylene)thiazol-4(5H)-ones **(3a-i)** derivatives were synthesized by reacting 2-(arylamino)-thiazol-4-ones and 2-thiophene carbaldehyde in alcohol medium. All the new compounds were assigned on the spectral data**.** The reaction sequence is outlined in **Scheme-01**. The purity of the compounds was ascertained by TLC. Recrystallization was done by selecting appropriate solvents. The physical data of the compounds is given in table-1.

The title compounds were evaluated for *In-vitro* antidiabetic activity by alpha amylase and alpha glucosidase methods. Acarbose was used as standard for comparison purpose.In the anti-diabetic activity, the tested compounds **3a, 3g, 3h, 3i** showed potent activity when compared to the standard Acarbose. The presence of electron withdrawing groups on the thiazolidinone ring may responsible for the high anti-diabetic activity.

**Conclusion**

The main objective of this particular work, was to synthesize substituted thiazolidinone derivatives and followed by their antidiabetic activity. The new compounds were assigned on the basis of spectral data. Some of the tested compounds showed promising *In-Vitro* antidiabetic activity, when compared to the standard Acarbose.

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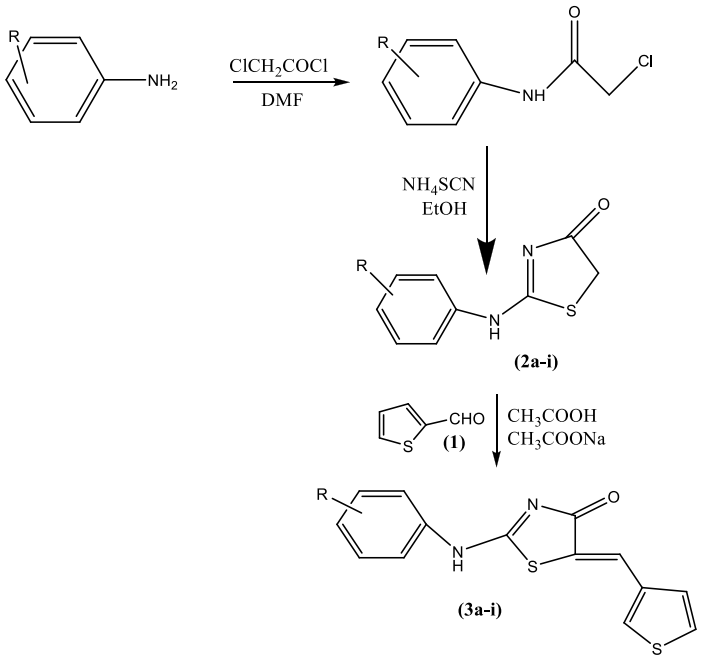
**Table-1: Physical data of Thiazolidinone derivatives (3a-i)**

| **Comp** | **R-$NH_2$** | **Molecular Formula** | **Molecular Weight** | **MP ($^oC$)** | **Yield (%)** |
|---|---|---|---|---|---|
| 3a | 2,4-$(Cl)_2$ | $C_{14}H_8Cl_2N_2OS_2$ | 355.26 | 112-14 | 68 |
| 3b | 3-Cl-4-F | $C_{14}H_8ClFN_2OS_2$ | 338.81 | 102-04 | 69 |
| 3c | 2-Cl-4-$NO_2$ | $C_{14}H_8ClFN_3O_3S_2$ | 365.81 | 154-56 | 66 |
| 3d | 4-$NO_2$ | $C_{14}H_9N_3O_3S_2$ | 331.37 | 94-96 | 58 |
| 3e | 4-OH | $C_{14}H_9FN_3O_3S_2$ | 302.37 | 133-35 | 59 |
| 3f | 4-F | $C_{14}H_9ClFN_2OS_2$ | 304.36 | 146-48 | 64 |
| 3g | 4-Cl | $C_{14}H_9ClN_2OS_2$ | 320.82 | 166-68 | 63 |
| 3h | 4-Br | $C_{14}H_9ClBrN_2OS_2$ | 365.27 | 174-76 | 62 |
| 3i | $C_6H_5$ | $C_{14}H_{10}N_2OS_2$ | 286.37 | 183-85 | 61 |

**Table-2: Antidiabetic activity of Thiazolidinone derivatives ($IC_{50}$ values) (3a-i)**

| **Comp** | **Alpha amylase** | **Alpha glucosidase** |
|---|---|---|
| 3a | **22.32** | 28.58 |
| 3b | **24.18** | **25.99** |
| 3c | 32.36 | 30.15 |
| 3d | 33.58 | 34.59 |
| 3e | 36.45 | 34.22 |
| 3f | 37.44 | 34.20 |
| 3g | **23.65** | **25.10** |
| 3h | **24.25** | **24.19** |
| 3i | **22.15** | **25.45** |
| Std | **22.44** | **24.54** |

**Scheme-01**

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