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European Journal of Experimental Biology, 2012, 2 (4):1302-1314

ISSN: 2248 –9215
CODEN (USA): EJEBAU

Design, synthesis and hypoglycemic activity of novel 2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N- substituted acetamide derivatives

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ABSTRACT

The work reports facile synthesis of novel 2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-substituted acetamide derivatives ***3(a-o),*** *accomplished in good yields in three steps, using conventional, mild reaction conditions. The synthesized compounds were evaluated for their hypoglycemic activity in Wister albino mice animal model and histopathological studies of kidney and liver were performed to check the toxicity effects of the synthesized derivatives. All derivatives have shown significant hypoglycemic activity.*

Key words: Thiazolidinedione, acetamide, hypoglycemic activity, Alloxan-induced diabetes.

INTRODUCTION

Diabetes is a major health problem today, as approximately 5% of the world's population suffers from diabetes. Type I is prevalent in 10% of diabetes patients and an autoimmune disease of the pancreas, which causes decreased insulin secretion. On the other hand, Type II is prevalent in 90% of the patients where insulin resistance and abnormal carbohydrate metabolism are considered to be the causative factors [1, 2].

The peroxisome proliferators activated receptors (PPARs) are a group of nuclear receptor isoforms that play a key role in the regulation of dietary fat storage and are a target for the development of treatments for type II diabetes, obesity and cardiovascular disease. TZDs at these receptors act as insulin sensitizers [3-6], therefore PPARs are legitimate molecular targets for the development of antidiabetic agents. 2, 4-Thiazolidinedione moiety is the generic feature of the glitazone, antidiabetic agents [7]. TZDs are a class of molecules that normalize elevated blood glucose level. TZDs (e.g., troglitazone, rosiglitazone, pioglitazone) improve insulin sensitivity in liver, muscle and fat tissues and thus counter acts insulin resistance, TZDs are effective in reducing glycosylated hemoglobin (HbA1c). These drugs, however, have been associated with liver, cardiovascular and hematological toxicity and body weight gain. This situation emphasizes the need to develop new , safer antidiabetic agents that could retain the insulin sensitizing properties of TZD and also have better efficacy. All these facts prompted us to investigate novel TZD as a candidate

for the development of hypoglycemic agent, in continuation of our earlier research work [8]. The structural feature of compounds synthesized in the present work was designed on rosiglitazone as the lead compound. The possible diagrammatic representation of synthesized derivative with PPAR γ receptor is shown in Fig.1. In the present work, we have modified the hydrophobic ring tail with the various substituents like aryl/heterocyclic / alicyclic groups and $-OCH_3$ group was incorporated in the structure with the hope to have better hypoglycemic activity due to its electron donating effect; the phenoxy ethyl group was replaced by phenoxy methyl group, in order to investigate the effect of substitution. The literature reveals that the presence of phenoxy alkyl linker (an ether linkage) increases the potency of the parent compound; here in the present work phenoxy methyl chain (an ether linkage) also has shown promising activity [9].

MATERIALS AND METHODS

2.1 Chemistry

The synthetic route of compounds is as outlined in Scheme 1. A series of 2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N- substituted acetamide **3(a-o)** were synthesized in three steps. 4-Hydroxy -3-methoxy benzaldehyde was taken as starting compound, to have methoxy group in the structure of final derivatives to investigate its electron donating effect on SAR. In the first step, Knoevenagel condensation of 4-hydroxy -3-methoxy benzaldehyde and 2, 4-thiazolidinedione was carried out to give 5-(4-hydroxy-3-methoxybenzylidene) thiazolidine-2,4-dione **1,** which on condensation with 2-chloro-N-substituted acetamide **2(a-o)** yielded the final derivatives.

The structures of compounds were confirmed by FTIR, ^{1}HNMR, Mass and elemental analysis.

2.2. Pharmacology [Hypoglycemic activity]

2.2.1 Animals and Treatment Wistar Albino rats of either sex weighing between 150-200gm were procured from Wokhardt Ltd. Aurangabad. Animals were housed in polypropylene cages and under standard condition of temperature (25 ± 2^{o}C), 12h/12h light/dark cycles and were fed with standard pelleted diet and water was given *ad libitum*. All the study protocols related to antidiabetic activity testing were approved from the Institutional Animal Ethics Committee and the ethical clearance was obtained from the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA/IAEC/Pharm. Chem. 07/2010-11/31).

Rats were kept on overnight fasting and had free access to water. Blood samples were collected by tail tapping method and the initial fasting blood glucose (BG) was estimated by digital Glucometer. Animals were made diabetic by single tail vein injection of alloxan (60 mg/kg). Dextrose 5% solution was administered via feeding bottle, to recover from early hypoglycemic phases. After 48 hrs, the blood was withdrawn by tail tapping method and blood glucose level was estimated. Each time tail of the animal was sterilized with spirit. The animals showing blood glucose levels above 250 mg/dl were selected for study and divided into experimental groups of 6 animals each. Thus, it was concluded that hyperglycemia was induced within 48 hrs and stabilized within 5 days [10].

2.2.2 Hypoglycemic Activity

One Day Study: Diabetic control Group (Group I) received distilled water only. Group II animals were orally fed with pioglitazone 30 mg/kg and synthesized compounds were screened for hypoglycemic activity at a fixed dose of 36 mg/kg body weight, given orally (homogenized suspension in 0.25% carboxy methyl cellulose (CMC)) in vivo alloxan induced diabetic rat model (Group III-Group XVIII). For One Day study animals were fasted over night and the fasting blood glucose, 0hr, levels were observed. Blood samples were removed from all animals at 0, 2, 4, 6 and 12 hrs. The data obtained was analyzed by one-way ANOVA followed by Dunnett test. The results were expressed as mean ± standard error of mean (SEM) for each group, $p<0.01$ was considered as statistically significant. The results are explained in Table 1.

Fifteen Days Study: Study animals were fasted overnight and the fasting blood glucose, levels were calculated. Now the compounds were administered at a fixed dose of 36 mg/kg orally (homogenized suspension in 0.25% CMC) for 15 days daily at a fixed time. After 15 days treatment was stopped and blood glucose level was measured, after 30 minutes of the administration of the last dose. During study, blood samples were removed from all animals at 7, 15 days and change in blood glucose was calculated. The data obtained was analyzed by one-way ANOVA followed by Dunnett test. The results were expressed as mean ± standard error of mean (SEM) for each group, $p<0.01$ was considered as statistically significant. The results are explained in Table 2.

2.2.3 Histopathology: After 15 days of treatment, the synthesized derivative that has shown the maximum hypoglycemic activity as compared to other synthesized derivatives was selected for histopathological study, to find out the toxicity effect. The animals were sacrificed and histopathology was performed for renal, hepatic and pancreatic function. The liver and kidney were preserved in 20% formalin immediately after removal from the animal [11-15].

3. Experimental Protocol

Synthesis

All the recorded melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on JASCO FT-IR 5300 spectrophotometer using KBr powder. ^{1}HNMR spectra were recorded on Brucker advance II 400 ^{1}HNMR spectrophotometer at 300 MHz Frequency in $CDCl_3$ using TMS as internal standard and chemical shifts (δ) are given in ppm relative to TMS. Mass spectra of some compounds were scanned on TOF MS+ 484 spectrophotometer. The spectral data was in accordance with the assumed structures. All the reactions were monitored by TLC using precoated TLC plates and visualized by iodine vapors [Silica gel GF254 (E. Merck)].The absence of TLC spots for starting materials and appearance of new TLC spots at different R_f values ensured the completion of reaction. The IUPAC names of the synthesized compounds were assigned and verified by Cambridge software- Chem. Draw Ultra 8.0. Elemental analyses were recorded on FLASH EA112 series at Shimadzu Analytical Centre and found within ± 0.4% of theoretical values.

3.1. Synthesis of 5-(4-hydroxy-3-methoxybenzylidine)-2, 4-thiazolidinedione 1

A mixture of 4-hydroxy, 3-methoxy benzaldehyde (0.041 mol), 2, 4-thiazolidinedione (0.041 mol), benzoic acid (0.049 mol), piperidine and anhydrous toluene (50 ml) was stirred at 130^{0}C for 5 hrs. The reaction mixture was cooled and filtered [16]. The filter cake was washed with 50% methanol solution to afford 86% of the product as a yellow powder, R_f = 0.35 (n-hexane/ethyl acetate = 2:1). M.p. 210-212^{o}C, IR [KBr *ν* cm^{-1}] 3647, 3470, 3076, 1679, 618; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, -OCH_3), 5.3 (s, 1H, -OH), 6.8 -6.9 (m, 3H, Ar-H), 7.7 (s, 1H, -C=CH), 9.6(s, 1H, -NH).

3.2. Synthesis of (2-chloro-N-substituted) acetamide 2(a-o)

Aromatic / heterocyclic amine (1.0 mol) in chloroform (10 ml) was stirred in a conical flask and to this reaction mixture chloroacetyl chloride (1.5mol) was added drop wise under cold condition. Reaction mixture was stirred till completion of reaction, which was monitored by TLC. The characterization data of the synthesized compounds is given in supplementary data.

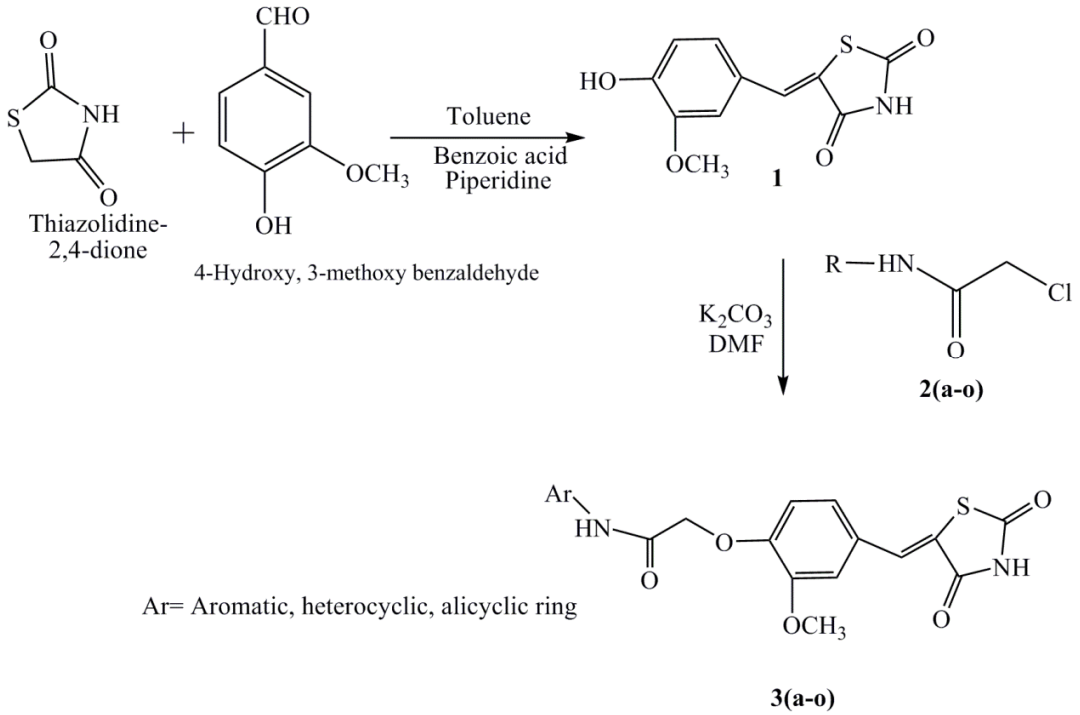
3.3 Synthesis of 2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N- substituted acetamide 3(a-o)

5-(4-Hydroxy-3-methoxybenzylidene)-2, 4-thiazolidenedione **1** (1.0 mol) and potassium carbonate (1.5 mol) in dimethyl formamide (DMF) was stirred in a flask and to this reaction mixture, chloro acetylated product **2,** (1.5 mol) in DMF was added. Reaction mixture was stirred at room temperature till the completion of reaction, which was monitored by TLC. After completion of reaction, water was added to get the solid, final product **3(a-o).** The characterization data of the synthesized compounds 3**(a-o)** is presented in Table 3.

3.3.1-(4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-Nphenyl acetamide 3a. IR [KBr *ν* cm^{-1}] 3504, 3462, 3050, 1664, 618, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, -OCH_3), 4.0 (s, 2H, CH_2), 6.9 -7.5 (m, 8H, Ar-H), 7.9 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 384, Analysis calculated for $C_{19}H_{16}N_2O_5S$ (384) C,59.30; H, 4.20; N, 7.29. Found: C, 59.65; H, 4.10 N, 7.35.

3.3.2 N-(4-Chlorophenyl)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-2-methoxy phenoxy) acetamide 3b. IR [KBr *ν* cm^{-1}] 3499, 3458, 3042, 1661, 613,742, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, -OCH_3), 4.6 (s, 2H, CH_2), 6.9 -7.5 (m, 7H, Ar-H), 7.9 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 419.1 (M+1), 202.2, 292.12, Analysis calculated for $C_{19}H_{15}ClN_2O_5S$ (418) C,54.4; H, 3.61; N, 6.69 Found: C, 54.21; H, 3.75; N, 6.57.

3.3.3 2-(4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-(4-nitro phenyl) acetamide 3c. IR [KBr *ν* cm^{-1}] 3509, 3468, 3044, 1667, 611, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, -OCH_3), 4.0 (s, 2H, CH_2), 6.9 -7.5 (m, 7H, Ar-H), 8.1 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 430.2 (M+1), 202.2, Analysis calculated for $C_{19}H_{15}N_3O_7S$ (429) C,53.1; H, 3.52; N, 9.79, Found: C, 54.21; H, 3.75; N, 6.57.



Scheme 1: Synthetic protocol

3.3.4 2-(4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-(3-nitro phenyl) acetamide 3d. IR [KBr *v* cm^{-1}] 3509, 3469, 3040, 1662, 618, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, -OCH_3), 4.0 (s, 2H, CH_2), 6.9 -7.5 (m, 7H, Ar-H), 7.9 (s, 1H, -C= CH) , 9.8 (S, 1H, -NH), MS m/z 430.2 (M+1), 202.2, Analysis calculated for $C_{19}H_{15}N_3O_7S$ (429) C,53.1; H, 3.52; N, 9.79, Found: C, 54.21; H, 3.75; N, 6.57.

3.3.5 2-(4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-p-tolyl acetamide 3e. IR [KBr *v* cm^{-1}] 3509, 3454, 3059, 1672, 618, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm), 2.3 (s, 3H, -CH_3), 3.8 (s, 3H, -OCH_3), 4.0 (s, 2H, CH_2), 6.9 -7.5 (m, 7H, Ar-H), 7.9 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 430.2 (M+1), 202.2, Analysis calculated for $C_{20}H_{18}N_2O_5S$ (398) C, 60.2; H, 4.55; N, 7.03, Found: C, 60.7; H, 4.32; N, 7.09.

3.3.6 2-(4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-o-tolyl acetamide 3f. IR [KBr *v* cm^{-1}] 3507, 3452, 3045, 1674, 620, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm), 2.3 (s, 3H, -CH_3), 3.8 (s, 3H, -OCH_3), 4.0 (s, 2H, CH_2), 6.9 -7.5 (m, 7H, Ar-H), 7.9 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 401 (M+1), 202.2, Analysis calculated for $C_{20}H_{18}N_2O_5S$ (398) C,60.2; H, 4.55; N, 7.03, Found: C, 60.7; H, 4.32; N, 7.09.

3.3.7 5-(4-(2-(1H-Imidazol-1-yl)-2-oxoethoxy)-3-methoxybenzylidene) thiazolidine-2,4-dione 3g. IR [KBr *v* cm^{-1}] 3503, 3466, 3039, 1669, 623, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, -OCH_3), 5.05 (s, 2H, CH_2), 6.9 -8.1 (m, 6H, Ar-H), 7.9 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 360.2 (M+1), 202.2, Analysis calculated for $C_{16}H_{13}N_3O_5S$ (359) C,53.48; H, 3.62; N, 11.69, Found: C, 53.32; H, 3.21; N, 11.73.

3.3.8 5-(3-Methoxy-4-(2-oxo-2-(piperidin-1-yl) ethoxy) benzylidene) thiazolidine-2,4-dione 3h. IR [KBr *v* cm^{-1}] 3510, 3469, 3041, 1657, 612, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, -OCH_3), 4.2 (s, 2H, CH_2), 6.9 -7.5 (m, 3H, Ar-H), 7.9 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 377.2 (M+1), 202.2, Analysis calculated for $C_{18}H_{20}N_2O_5S$ (376) C,57.43; H, 5.36; N, 7.44, Found: C, 57.29; H, 5.21; N, 7.33.

3.3.9 2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-(4-methoxy phenyl) acetamide 3i. IR [KBr *v* cm^{-1}] 3497, 3452, 3049, 1661, 611, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, -OCH_3), 4.5 (s, 2H, CH_2), 6.9 -7.5 (m, 7H, Ar-H), 7.9 (s, 1H, -C= CH), 9.8 (S, 1H, -NH), MS m/z 415.1 (M+1), 202.2, Analysis calculated for $C_{20}H_{18}N_2O_6S$ (414) C,57.87; H, 4.38; N, 6.76, Found: C, 57.81; H, 4.24; N, 6.59.

3.3.10 2-(4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N, N-diphenyl acetamide 3j. IR [KBr *v* cm^{-1}] 3502, 3466, 3053, 1669, 611, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, $-OCH_3$), 4.6 (s, 2H, CH_2), 6.9 -7.5 (m, 13H, Ar-H), 7.9 (s, 1H, -C=CH), 9.9 (S, 1H, -NH), MS m/z 461.1 (M+1), 202.2, Analysis calculated for $C_{25}H_{20}N_2O_5S$ (460) C,65.20; H, 4.38; N, 6.08, Found: C, 65.12; H, 4.27; N, 6.03.

3.3.11 4-(2-(4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-2 methoxy phenoxy) acetamido) benzoic acid 3k. IR [KBr *v* cm^{-1}] 3509, 3454, 3059, 1672, 618,^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, $-OCH_3$), 4.6 (s, 2H, CH_2), 6.9 -7.5 (m, 7H, Ar-H), 7.9 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 429.2 (M+1), 202.2, Analysis calculated for $C_{20}H_{16}N_2O_7S$ (428) C,56.07; H,3.76; N, 6.54, Found: C, 56.02; H, 3.68; N, 6.41.

3.3.12 5-(3-Methoxy-4-(2-morpholino-2-oxoethoxy) benzylidene) thiazolidine-2, 4-dione 3l . IR [KBr *v* cm^{-1}] 3493, 3452, 3045, 1669, 611, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, $-OCH_3$), 4.8 (s, 2H, CH_2), 6.9 -7.5 (m, 3H, Ar-H), 7.9 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 379.1(M+1), 202.2, Analysis calculated for $C_{17}H_{18}N_2O_6S$ (378) C,53.96; H,4.79; N, 7.40, Found: C, 53.87; H, 4.61; N, 7.31.

3.3.13 2-(4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-(pyrimidin - 2 -yl) acetamide 3m. IR [KBr *v* cm^{-1}] 3501, 3467, 3056, 1669, 612, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, $-OCH_3$), 4.7 (s, 2H, CH_2), 6.9 -7.5 (m, 6H, Ar-H), 7.9 (s, 1H, -C=CH), 9.9 (S, 1H, -NH), MS m/z 387.1 (M+1), 202.2, Analysis calculated for $C_{17}H_{14}N_4O_5S$ (386) C,52.84; H,3.65; N, 14.50, Found: C, 52.89; H, 3.58; N, 14.44.

3.3.14 5-(3-Methoxy-4-(2-oxo-2-(pyrrolidin-1-yl) ethoxy) benzylidene) thiazolidine-2, 4- dione 3n. IR [KBr *v* cm^{-1}] 3501, 3452, 3040, 1669, 619, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, $-OCH_3$), 4.0 (s, 2H, CH_2), 6.9 -7.5 (m, 3H, Ar-H), 7.9 (s, 1H, -C=CH), 9.8 (S, 1H, -NH), MS m/z 363.1 (M+1), 202.2, Analysis calculated for $C_{17}H_{18}N_2O_5S$ (362) C,56.34; H,5.01; N, 7.73, Found: C, 56.27; H, 5.07; N, 7.58.

3.3.15 2-(4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-(2-hydroxy phenyl) acetamide 3o. IR [KBr *v* cm^{-1}] 3501, 3459, 3055, 1669, 613, ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 3.8 (s, 3H, $-OCH_3$), 4.6 (s, 2H, CH_2), 6.9 -7.5 (m, 7H, Ar-H), 7.9 (s, 1H, -C=CH), 9.9 (S, 1H, -NH), MS m/z 401.2 (M+1), 202.2, Analysis calculated for $C_{19}H_{16}N_2O_6S$ (400) C,56.99; H,4.03; N, 7.0, Found: C, 56.83; H, 4.09; N, 7.08.

RESULTS AND DISCUSSION

In the present work fifteen novel 2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N- substituted acetamide derivatives were synthesized. In ^{1}HNMR spectra presence of characteristic singlet at δ 7.7-7.9 ppm for benzylidiene proton confirms formation of **1**. Formation of chloro acetylated intermediate was characterized by singlet at δ 4.1-4.3 ppm.

In the in vivo hypoglycemic study the activity of derivatives was evaluated by alloxan induced hyperglycemia in Wistar albino rat model[17-. Biological activity was expressed in terms of change in blood glucose level. Most of the synthesized compounds showed moderate hypoglycemic activity and compound no. **3e, 3f, 3j, 3c** and **3d** have shown significant decrease in blood glucose level.

In diabetic control rat, liver shows congested liver tissue with congested sinusoid and centrilobular necrosis with sparse infiltrate of lymphocytes and neutrophils. In the diabetic rat treated with standard drug, Pioglitazone (30 mg/kg), liver shows normal hepatic architecture with absence of fatty change and necrosis. The central vein, portal tract and sinusoids appear normal. Where as, the diabetic rat treated with derivative **3e** (36 mg/kg), liver shows normal hepatic architecture with absence of fatty change and necrosis. The results of histopathological investigations of liver are shown in Fig. 2. .

In diabetic control rat, kidney shows glomerular hemorrhage, internal tubular hemorrhage and kidney swelling. In the diabetic rat treated with standard drug, Pioglitazone (30 mg/kg), kidney slide shows mild glomerular hemorrhage and normal architecture. Where as, in the diabetic rat treated with derivative **3e** (36 mg/kg), kidney slide shows mild internal tubular hemorrhage and mild vascular congestion, as shown in Fig.3.

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In diabetic control rat, pancreas shows areas of necrosis of acinar cells with surrounding inflammatory exudates. In the diabetic rat treated with standard drug, Pioglitazone (30 mg/kg), pancreas shows acinar architecture with

intervening stroma and sparse infiltrate of lymphocytes along with the congested blood vessels. In the diabetic rat treated with derivative **3e** (36 mg/kg), pancreas shows normal histology with intact acinar architecture of pancreas with intervening stroma and sparse infiltrate of lymphocytes along with congested blood vessels. The results of histopathological investigations of pancreas are shown in Fig. 4. .

Thus, pretreatment of animals with the compound **3e** for 21 days showed the normal hepatic, renal and pancreatic histopathology, when compared with diabetic control group among diabetic animals. This shows that, derivative **3e** is non toxic.

Table 1: Hypoglycemic activity of compounds 3(a-o) (One Day Study).

Groups	0 hr	2 hr	4 hr	6 hr	12 hr
Diabetic Control	319.00±3.78	319.67±2.02	316.63±2.96	318.33±1.85	322.00±7.02
Std.	310.64±8.09	165.00±3.60**	145.67±4.09**	137.00±2.64**	119.33±2.96**
3a	302.00±7.50	271.00±9.01**	231.00±1.15*	193.67±2.60**	176.00±0.57**
3b	276.62±17.63	247.34±14.05**	217.66±5.81**	192.33±1.76**	169.31±1.76**
3c	286.33±25.27	249.33±15.23*	216.33±5.36**	193.00±2.64**	169.65±2.08**
3d	271.33±9.20	242.36±5.20**	213.00±3.05**	192.00±1.15**	170.00±0.57**
3e	259.33±25.65	234.61±17.45**	209.33±5.84**	183.00±3.21**	161.65±2.72**
3f	256.69±16.19	224.00±7.63**	198.33±1.76**	177.64±2.02**	159.00±2.08**
3g	321.00±23.09	313.00±23.11	313.38±23.54	309.00±20.25	307.68±19.88
3h	281.67±14.17	252.00±6.65**	230.00±1.52**	210.00±0.57**	189.00±0.57**
3i	262.00±13.42	240.00±7.57**	216.00±3.21**	197.65±0.88**	179.36±0.88**
3j	253.00±8.71	230.64±4.33**	207.65±2.33**	175.61±3.93**	162.34±2.90**
3k	311.64±21.09	258.69±5.78*	229.63±1.76**	207.00±1.73**	185.00±0.57**
3l	282.00±3.21	253.00±3.05**	233.00±1.73**	210.66±0.88**	184.31±1.45**
3m	289.69±6.76	268.67±0.88**	256.00±1.15**	242.69±1.20**	230.00±0.57**
3n	295.00±7.55	266.69±2.18**	254.00±1.15**	239.35±0.88**	219.00±0.57**
3o	279.00±11.01	258.00±5.50**	231.69±1.76**	209.37±1.20**	184.96±1.20**

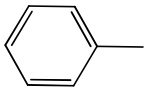
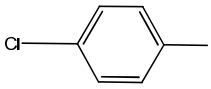
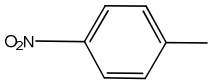
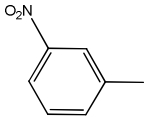
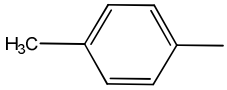
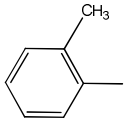
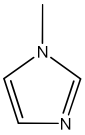
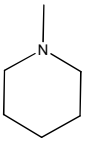
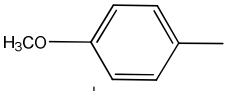
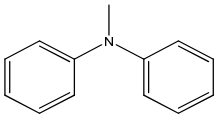
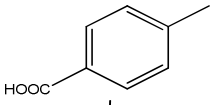
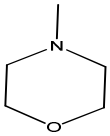
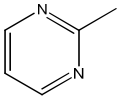
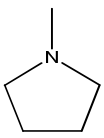
test compound = 36 mg/kg; orally, reference standard, piogiltazone = 30 mg/kg; orally
*the results are expressed as mean ±sem. the data is analyzed using one-way analysis of variance (anova) followed by dunnett test; (n=6), ** p < 0.01, *p < 0.05, ns- non significant*

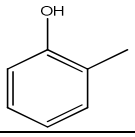
Table 2: Hypoglycemic activity of compounds 3(a-o) (Fifteen Days Study).

Groups	0 hr	7 th day	15 th day
Diabetic Control	319.00±3.78	321.33±3.18	318.34±4.80
Std.	310.64±8.09	120.63±3.48**	104.33±2.33**
3a	302.00±7.50	230.65±8.41**	175.00±1.73**
3b	276.62±17.63	229.68±4.66**	169.00±0.57**
3c	286.33±25.27	224.00±6.11**	169.36±0.88**
3d	271.33±9.20	220.33±0.80**	168.67±1.76**
3e	259.33±25.65	229.34±15.60**	158.64±2.90**
3f	256.69±16.19	217.38±7.53**	159.00±1.15**
3g	321.00±23.09	311.00±19.08	313.00±19.39
3h	281.67±14.17	232.69±3.28**	189.00±0.57**
3i	262.00±13.42	218.00±3.78**	179.36±0.88**
3j	253.00±8.71	219.00±5.29**	159.00±0.57**
3k	311.64±21.09	250.00±4.72**	185.00±1.15**
3l	282.00±3.21	228.00±1.73**	185.33±0.66**
3m	289.69±6.76	271.61±4.95**	260.00±5.19**
3n	295.00±7.55	276.00±3.60**	265.00±3.78**
3o	279.00±11.01	231.36±2.33**	185.00±2.30*

*test compound = 36 mg/kg; orally; reference standard, piogiltazone = 30 mg/kg; orally the results are expressed as mean ±sem. the data is analyzed using one-way analysis of variance (anova) followed by dunnett test (n=6), ** p < 0.01, *p < 0.05, ns- non significant*

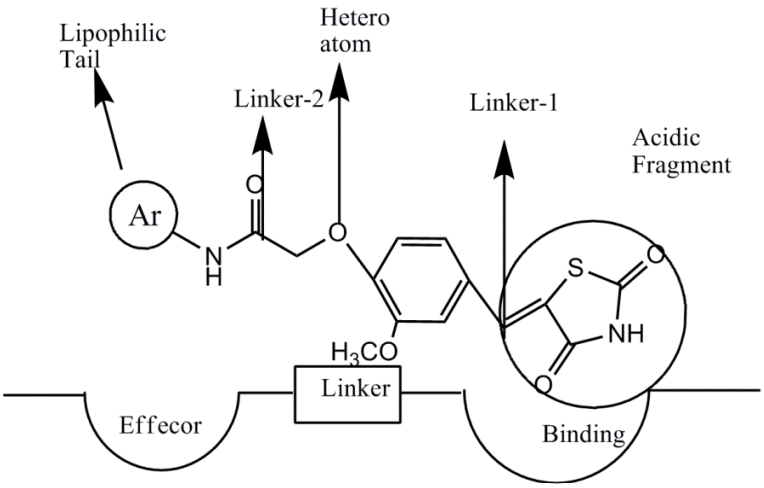
Table 3: Physical Characterization of 3(a-o).

Sr. No.	R	Molecular Formula	Molecular Wt.	% Yield	m.p.^{0}C*	R_f value**
3a		$C_{19}H_{16}N_2O_5S$	384.4	75%	280-282	0.42
3b		$C_{19}H_{15}ClN_2O_5S$	418.8	78%	296-298	0.46
3c		$C_{19}H_{15}N_3O_7S$	429.4	78%	320-322	0.62
3d		$C_{19}H_{15}N_3O_7S$	429.4	80%	320-322	0.68
3e		$C_{20}H_{18}N_2O_5S$	398.4	78%	310-312	0.70
3f		$C_{20}H_{18}N_2O_5S$	398.4	68%	310-312	0.51
3g		$C_{16}H_{13}N_3O_5S$	359.3	73%	280-284	0.44
3h		$C_{18}H_{20}N_2O_5S$	376.4	72%	260-262	0.59
3i		$C_{20}H_{18}N_2O_6S$	414.4	75%	294-296	0.73
3j		$C_{25}H_{20}N_2O_5S$	460.5	79%	266-268	0.65
3k		$C_{20}H_{16}N_2O_7S$	428.4	85%	330-332	0.68
3l		$C_{17}H_{18}N_2O_6S$	378.4	83%	264-266	0.74
3m		$C_{17}H_{14}N_4O_5S$	386.3	80%	340-342	0.68
3n		$C_{17}H_{18}N_2O_5S$	362.4	78%	278-280	0.70

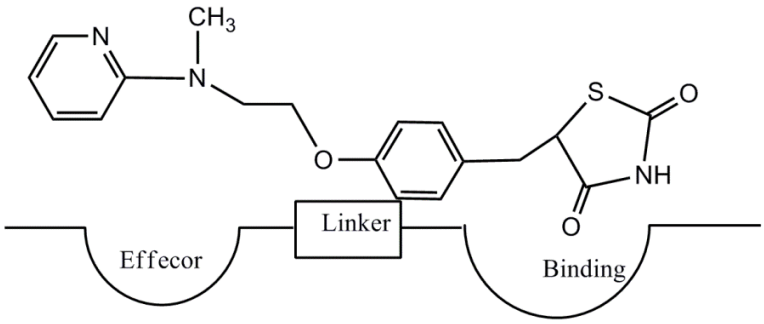
3o		$C_{19}H_{16}N_2O_6S$	400.4	68%	348-350	0.51

** melting points were uncorrected*

*** solvent system chosen for Rf value determination was benzene: methanol (9.5: 0.5)*



3(a-o)



Rosiglitazone

Fig. 1: Possible diagrammatic receptor representation

Structure Activity Relationship (SAR):

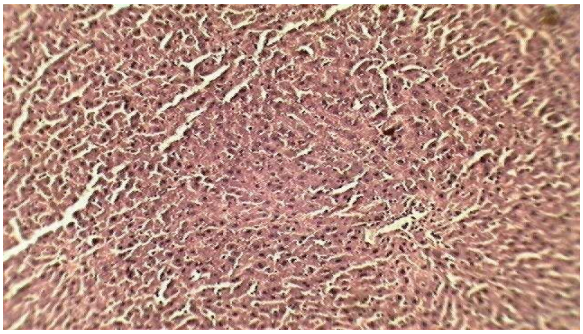
Thiazolidinedione ring is important for activity. Unsubstituted N-H at 3rd position of thiazolidinedione ring is important for activity. Presence of phenoxy methyl chain (an ether linkage) has shown promising activity. Attachment of phenyl ring (either with or without substitution) at 5th position has resulted in moderate hypoglycemic activity.

Electron donating methoxy group in the final derivatives has significantly contributed towards hypoglycemic activity. Other electron donating groups like methyl **(3e, 3f)** attached to the phenyl ring increases hypoglycemic activity; especially when attached at para position of phenyl ring than rather than when attached at ortho position.

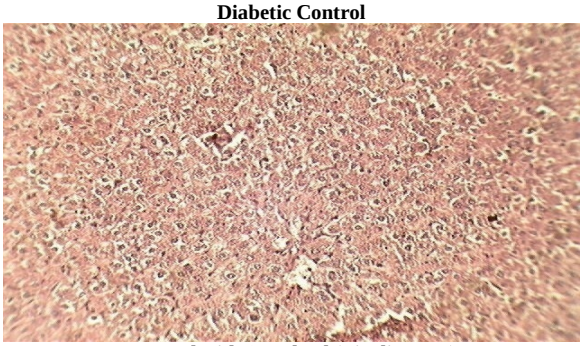
When substituents are heterocyclic; like 2-amino pyrimidine **(3m**), shows activity less significant than aromatic substituent. Compound having imidazole as substituent **(3g)** has shown non significant activity. The presence of alicyclic substituent i.e. morpholin and pyrrolidine in the final derivatives have contributed towards nearly non

significant activity. This might be due to the non-aromatic nature of these rings and unavailability of free primary nitrogen at the receptor binding sites; required for hydrogen bonding.

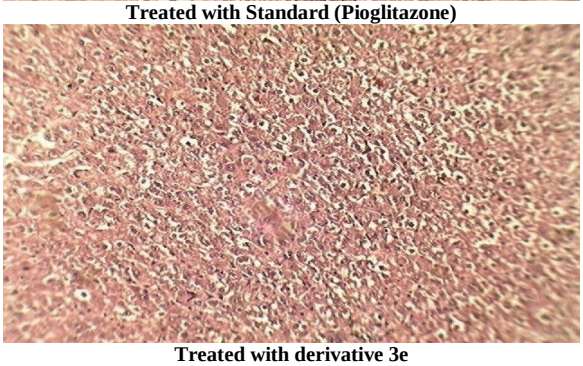
To summarize, the designed **2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N- substituted acetamide 3(a-o)** have shown remarkable hypoglycemic activity in alloxan induced diabetic rat model.



Diabetic Control

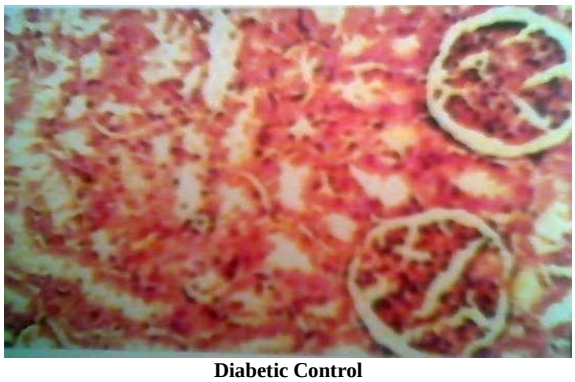


Treated with Standard (Pioglitazone)



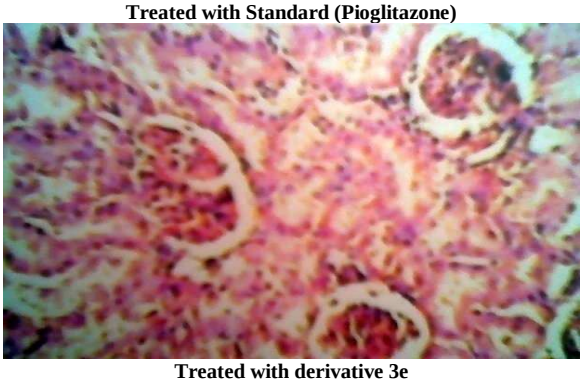
Treated with derivative 3e

Fig. 2: Histopathological investigations of liver.



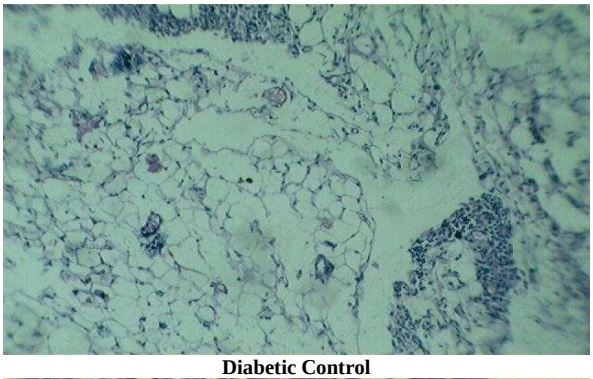
Diabetic Control

Treated with Standard (Pioglitazone)

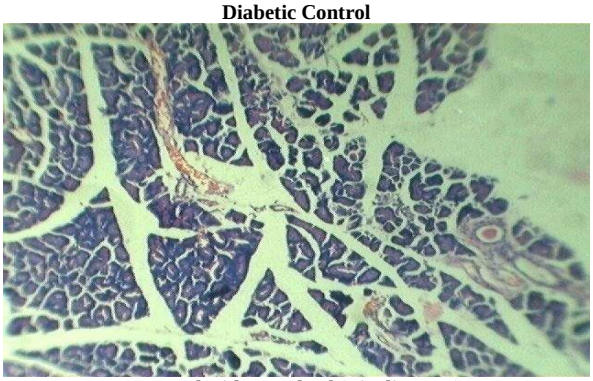


Treated with derivative 3e

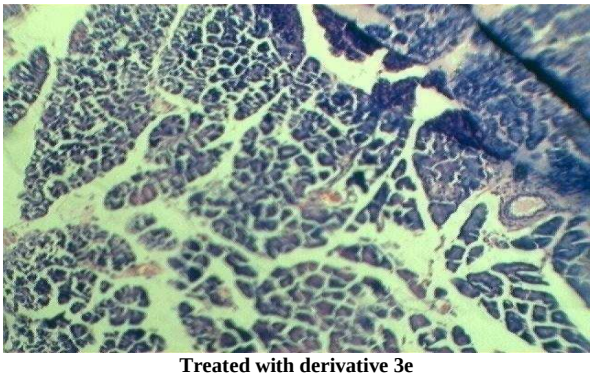
Fig. 3: Histopathological investigations of kidney.



Diabetic Control



Treated with Standard (Pioglitazone)



Treated with derivative 3e

Fig. 4: Histopathological investigations of pancreas.

CONCLUSION

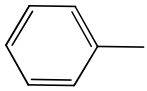
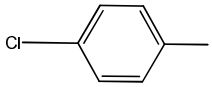
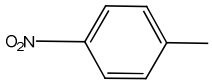
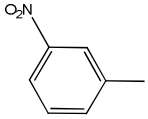
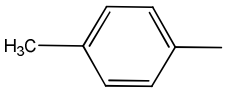
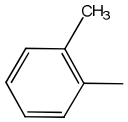
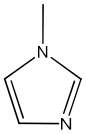
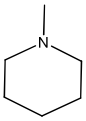
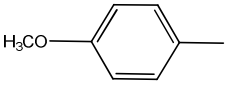
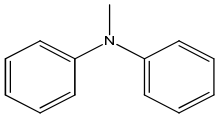
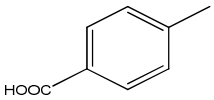
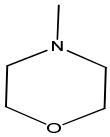
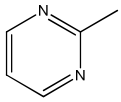
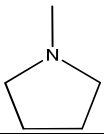
This communication illustrates a facile synthesis of 2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N- substituted acetamide **3(a-o)** which have exhibited significant hypoglycemic activity in alloxan induced diabetic rat model.

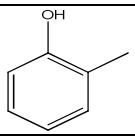
Acknowledgements
Authors are grateful to Mrs. Fatma Rafiq Zakaria, the Chairman, Maulana Azad Education Trust and Dr. M. H. Dehghan, Principal, Y.B Chavan College of Pharmacy, Aurangabad for encouragement and support.

REFERENCES

[1] R. Chakrabarti and R. Rajagopalan, *Current Science* **, 2002,** 83, 1533-1538.
[2] H. King, R.E. Aubert, W.H. Herman, *Diab. Care*, **1998** , 21, 1414–1431.
[3] V.J. Ram, *Drugs Today*, **2003,** 39609–632.
[4] J.M. Lehmann, L.B. Moore, T.A. Smith Oliver, W.O. Wilkinson, T.M. Willson, S.A. Kliewer, *J. Biol. Chem*., **1995,** 270, 12953–12956.
[5] K .G. Lambe, J.D. Tugwood, *Eur. J. Biochem.*, **1996,** 2391–7.
[6] J. Berger, P. Bailey, C. Biswas, C.A. Cullinan, W. Doebber, N.S. Hayes, R. Sapestein, R.G. Smith, M.D. Leibowitz, *Endocrinology* , **1996,** 137, 4189–4195.
[7] J. M. Way, W. W. Harington, K. K. Brown, W. K. Gottschalk, S. S. Sundseth, T.A. Mansfield, R. K. Ramchandran, T. M. Wilson, S. A. Kliewer , *Endocrinology,* **2001,** 142 269.
[8] A. Nikalje, D. Deshpande, H. Une, *European Journal of Experimental Biology*, **2012**, 2(2), 343-353.
[9] B. R. Prashantha, M.J. Najan, *Bioorg. Med. Chem. Letter*, **2010**, 1-4.
[10 R. Murugan, S. Anbazhagan, S. Narayanan, *Eur. J. Med. Chem.*, **2009,** 44, 3272-3279.
[11] W. L. Dunn**,** Hand Book of Histopathological and Histochemical Techniques, 3rd ed. Redwood Burn, Ltd., Trowbridge & Esher, **1974.**
[12] Evaluation of hepatoprotective activity of stem bark of Pterocarpus marsupium Roxb, https://tspace.library.utoronto.ca/bitstream/1807/8672/1/ph05041.pdf
[13] Hepato protective activity of Sapindus mukorossi and Rheumemodi extracts: In vitro and in vivo studies, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2708371.
[14] B. Ragavan, S. Krishnakumari. *African J. Biomedical Res.* **2006,** 9, 189-197.
[15] S. Reitmen, S. A. Frankel, *Am. J. Clin. Pathol*. **1957,** 28 56-63.
[16] S.M. Lee, R. Jeon, *Arch. Pharm. Res*. **2005,** 28, 377-381.
[17] H.D. Une, T. Deshpande , *Euro. J. Exp. Biol.*, **2011**, 1 (2), 139-149.
[18] R. Choure, N. Vaidya , K.S. Pitre**,** *Der Chemica Sinica*, **2011,** 2 (1), 129-135.
[19] P. B. Aswar , B.S. Kuchekar , *Asian Journal of Plant Science and Research*, **2011**, 1 (3), 91-102.
[20] A. Sangal, *Advances in Applied Science Research*, **2011**, 2 (4), 440-450.
[21] M.V. Kumudhavalli , B. Jaykar, *Der Pharmacia Sinica*, **2012**, 3 (1):1-4

Characterization data of compounds 2(a-o)

Sr. No	R	Molecular Formula	Molecular Wt.	% Yield	m. p.^{0}C *	R_f value**
2a		C_8H_8ClNO	169	65%	128-130	0.38
2b		$C_8H_7Cl_2NO$	204	70%	170-172	0.49
2c		$C_8H_7ClN_2O_3$	214	68%	185-188	0.41
2d		$C_8H_7ClN_2O_3$	214	70%	112-115	0.43
2e		$C_9H_{10}ClNO$	183	68%	164-166	0.41
2f		$C_9H_{10}ClNO$	183	66%	162-164	0.37
2g		$C_5H_5ClN_2O$	144	73%	76-78	0.38
2h		$C_7H_{12}ClNO$	161	75%	86-88 (b.p.)	0.48
2i		$C_9H_{10}ClNO_2$	199	67%	122-124	0.44
2j		$C_{14}H_{12}ClNO$	245	68%	119-121	0.38
2k		$C_9H_8ClNO_3$	213	74%	264-266	0.44
2l		$C_6H_{10}ClNO_2$	163	73%	96-98 (b.p.)	0.45
2m		$C_6H_6ClN_3O$	171	79%	150-152	0.43
2n		$C_6H_{10}ClNO$	147	71%	46-48	0.41

2o		$C_8H_8ClNO_2$	185	70%	234-236	0.37

** Melting points were uncorrected*

*** Solvent system chosen for Rf value determination was Benzene: methanol (9.5: 0.5)*

Spectral data of intermediates 2(a-o)

6.2.1. 2-Chloro-N-phenylacetamide 2a:IR [KBr *v* cm^{-1}] 3058, 3489, 1640; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.2 (s, 2H, -CH_2), 7.0 -7.6 (m, 5H, Ar-H), 7.3 (s, 1H, -NH)

6.2.2. 2-Chloro-N-(4-chlorophenyl) acetamide 2b:
IR [KBr *v* cm^{-1}] 3052, 3484, 1639, 742; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -7.6 (m, 4H, Ar-H), 7.3 (s, 1H, -NH)

6.2.3. 2-Chloro-N-(4-nitrophenyl) acetamide 2c: IR [KBr *v* cm^{-1}] 3049, 3482, 1635; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -8.1 (m, 4H, Ar-H), 7.2 (s, 1H, -NH)

6.2.4. 2-Chloro-N-(3-nitrophenyl) acetamide 2d: IR [KBr *v* cm^{-1}] 3056, 3481, 1648; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -8.1 (m, 4H, Ar-H), 7.2 (s, 1H, -NH)

6.2.5. 2-Chloro-N-p-tolylacetamide 2e: IR [KBr *v* cm^{-1}] 3041, 3475, 1631; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -7.6 (m, 4H, Ar-H), 7.2 (s, 1H, -NH)

6.2.6. 2-Chloro-N-o-tolylacetamide 2f: IR [KBr *v* cm^{-1}] 3047, 3479, 1645; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -7.6 (m, 4H, Ar-H), 7.2 (s, 1H, -NH)

6.2.7. 2-Chloro-1-(1H-imidazol-1-yl) ethanone 2g: IR [KBr *v* cm^{-1}] 3052, 3493, 1649; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -8.1 (m, 3H, Ar-H).

6.2.8. 2-Chloro-1-(piperidin-1-yl) ethanone 2h: IR [KBr *v* cm^{-1}] 3039, 3469, 1633; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 1.5 -3.5 (m, 5H, Ar-H).

6.2.9. 2-Chloro-N-(4-methoxyphenyl)acetamide 2i: IR [KBr *v* cm^{-1}] 3046, 3499, 1642; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 6.9 -7.5(m, 4H, Ar-H), 7.2 (s, 1H, -NH).

6.2.10. 2-Chloro-N,N-diphenylacetamide 2j :IR [KBr *v* cm^{-1}] 3051, 3479, 1630; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -7.6 (m, 10H, Ar-H).

6.2.11. 4-(2-Chloroacetamido) benzoic acid 2k: IR [KBr *v* cm^{-1}] 3056, 3481, 1635; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -7.6 (m, 4H, Ar-H), 7.2 (s, 1H, -NH)

6.2.12. 2-Chloro-1-morpholinoethanone 2l : IR [KBr *v* cm^{-1}] 3049, 3482, 1635; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -7.6 (m, 4H, Ar-H).

6.2.13. 2-Chloro-N-(pyrimidin-2-yl) acetamide 2m: IR [KBr *v* cm^{-1}] 3052, 3479, 1637; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.5 -8.0 (m, 3H, Ar-H), 9.1 (s, 1H, -NH)

6.2.14. 2-Chloro-1-(pyrrolidin-1-yl) ethanone 2n: IR [KBr *v* cm^{-1}] 3052, 3493, 1649; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 1.8-3.0 (m, 4H, Ar-H).

6.2.15. 2-Chloro-N-(2-hydroxyphenyl) acetamide 2o: IR [KBr *v* cm^{-1}] 3058, 3489, 1640; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm) 4.1 (s, 2H, -CH_2), 7.0 -7.6 (m, 4H, Ar-H), 7.2 (s, 1H, -NH).