Synthesis and biological evaluation of some novel furan derivatives

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Abstract: The present work involved cyclization of Schiff bases to azetidine-2-one and thiazolidine 4-one derivatives. The schiff bases (IIIa-j) were obtained upon reaction between electrophillic carbon atom of furfuraldehyde and nucleophillic nitrogen atom of amines. Azetidine-2-one derivatives (IVa-j) were obtained by reaction between imines and monochloro acetyl chloride in the presence of triethyl amine and 1, 4 dioxan. On the other hand, preparations of thiazolidine-4-ones (Va-j) were preceded by nucleophilic attack of sulphur of thioglycolic acid on imine carbon followed by intramolecular cyclization in the presence of $SnCl_2$. The structures of the compounds were confirmed by spectral and elemental analysis. The biological evaluation of the compounds like anti-microbial, antioxidant, analgesic, CNS depressant and anti-diabetic activity were determined. From the pharmacological investigation it was found that out of all the compounds IVa, IVb, IVe, IVf, IVh,Va, Vb, Ve, Vf, Vh had shown more potent activity.

Keywords: Azetidine-2-One, thiazolidine-4-one, anti-microbial, analgesic, anti diabetic.

INTRODUCTION

The five membered aromatic heterocyclic compounds were considered as important chemical entities due to various biochemical process (Dalvre *et al.,* 2002). Furan was considered as common structural motifs available in many natural products (Keay B.A. *et al.*, 1996). Its derivatives obtained from synthetic and natural resources have wide range of pharmaceutical interest because of biological activities. The furan derivatives showed interesting biological activity such as nematocidal (Bakker *et al.,* 1979), insecticidal (lyongar *et al.,* 1987), antibacterial (Matsura *et al.,* 1996), anti-fungal (Chan.*et al.,* 1975), antiviral (Hudson *et al.*, 1989), antioxidant (Malm Strom *et al.,* 2001), anti inflammatory (Beers *et al.,* 1997 and Zemi *et al.,* 2001) and anti-nociceptive (Lopez *et al.,* 2002 and Meotti *et al.,* 2003).

Among the metabolic abnormalities, the diabetes may be due to disturbance in production of glucose at hepatic level and clearance of plasma lipoprotein (Fajan *et al.,* 1997 and Goldberg *et al.,* 2001). Acute infections were also considered as a major factor for diabetes in controlling blood sugar level due to ketoacidosis, which cause more susceptible and resistance to infection for diabetic patient. Antioxidant system involved in bacterial activity was also impaired (Nirmal Joshi *et al*., 1999). Depression may also be responsible for diabetes complication. From the antidepressant therapy it was observed that improvements in glycemic control could be corrected with improvement in depressive symptoms (Mazze *et al.,* 1984 and Testa M.A., 1998). Even after controlling depressive symptom and general health status chronic pain was one of the major limiting factors. It affects the performance of self-care behavior, important for minimizing diabetes related complication (Bair *et al.,* 2003). Based on the above fact, the present work involves the synthesis of some new furan derivatives by cyclization of unsymmetrical imines, in the presence of chloro acetyl chloride and thioglycollic acid, with anti-diabetic, anti-microbial, analgesic, antidepressant and antioxidant activities to overcome associated disorders.

MATERIALS AND METHOD

All the chemicals used for the synthesis were reagent grade obtained from Sigma Aldrich and Merck Laboratory. The solvents were purified by standard laboratory procedure and free from atmospheric oxygen. The melting points were determined by open capillary method. The IR spectra were recorded by KBr pellet method on a Shimadzu 8201 PC FTIR spectrophotometer. Both ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6 using JEOL and Bruker 500 MHz-NMR spectrophotometers using TMS as internal reference standard. The masses of the compound were analyzed by ESI method using Thermo Fennigan mass spectrophotometer. Elemental analysis was recorded using Thermo Finnigan FLASH EA 1112 CHN analyzer. TLC was performed in precoated plastic sheet of silica gel g/UV-254 of 0.2mm thickness. The Schiff bases (IIIa-j) of furan were prepared as per literature procedure (Li Y *et al.,* 2003 and Akio Baba *et al.,* 1999)**.**

Synthesis of 4-(furan-2-yl)-1-phenylazetidin-2-ones (IVa-j)

The imines (IIIa-j, 10 mmol) were placed in 100mL round bottom flask followed by addition of 1,4- dioxan (20mL) and triethyl amine as base catalyst (0.5mL) and stirred for 1 hour under nitrogen atmosphere. The resulting solutions were cooled at 0-5^{o}C. During addition of chloro acetyl chloride, the internal temperature was strictly

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maintained below 8°C. After that the mixture was boiled for 8 hours, cooled to room temperature and kept overnight. The mixture was neutralized with 5% sodium bicarbonate solution after addition of ice. The compounds were washed with cold water and 50% ethyl acetate in petroleum ether and dried. The purification of compounds was performed using benzene and chloroform as mobile phase in column chromatographic technique.

Synthesis of 4-(furan-2-yl)-1-phenylthaizolidine-4-one (Va-j)

The substituted imines (IIIa-j, 0.02 mol) were dissolved in toluene (20mL) and $SnCl_2$ (0.05 mmol) was added as catalyst. After addition of thioglycolic acid (0.03 mol), reaction mixtures were stirred for an hour at room temperature. The mixtures were then refluxed in water bath for 12 hours and cooled again to room temperature. Compounds were dissolved in dichloro-methane. The organic layer was washed with 10% sodium bicarbonate finally with brine solutions, dried over sodium sulphate and evaporated to dryness. Purification of the compounds were done with petroleum ether and chloroform (2:8v/v) by chromatographic technique.

Biological Activity

Test microorganism and Medium

For the determination of anti-microbial activity bacteria *Staphylococcus aureus* ATCC12600, *Bacillus subtilis* ATCC 11775, *Enterobacter cloacae* ATCC13047 and the fungi *Candida albicans* ATCC 90028, *Aspergillus niger* ATCC1027 were used. Bacterial strains were cultured overnight at 37°C in LB-agar broth and fungal strains were cultured over night at 30°C in cornmeal agar media. Test strains were suspended in nutrient agar to give final density of $5X10^5$ cfu/mL.

Screening for anti-microbial activity (Zone of inhibition assay)

Anti-microbial activities of the compounds were determined by disc diffusion method (*Arslan et al.,* 2006). Sterilized 10% nutrient agar (20mL) was poured into each sterile petri dish after mixing the culture of micro-organism at the concentration of 150µL and allowed to solidify the plate. Test compounds were dissolved in dimethyl sulphoxide to make a stock solution of 1000µg/mL and the concentration of 100,150,200µg/mL of amoxycillin, streptomycin, nystatin and test compounds respectively. Wattmann filter paper was sterilized and dipped in test compounds, standards and solvent control respectively. Discs were placed on agar plates and incubated at 37°C for 24hrs for bacterial and 30°C for 24 hrs for fungi and the zone of inhibition was determined in millimeter.

Antioxidant activity

The *in vitro* antioxidant activity was determined by 1, 1-diphenyl-2-picrylhydrazyl radical method which has been widely used to evaluate the free radical scavenging capacity of different antioxidants (Brand Williams W *et al*., 1995; Espin JC *et al.,* 2000; Yu L *et al.,* 2001 and Sadhu SK *et al*., 2003).

Animals

Albino mice of either sex, weighing about 25-30g were used for analgesic and CNS depressant activity where as healthy Wister rat of either sex weighing between 180-200 g were used for anti diabetic activity. Animals were maintained under standard environmental condition at temperature of 22±2°C and 45-50% relative humidity for 24 hrs each of dark and light cycle with proper diet. All the studies were done according to protocol approved by Institutional Animal Ethical Committee (IAEC) of Bansal College of Pharmacy (Reg.no-1252/ac/10/CPCSEA, Ref. no-BCP/IAEC/12/02).

Acute toxicity study

The acute oral toxicity study was performed according to OECD guideline no 423 (OECD, 2000) for both albino mice and Wister rats. The doses were fixed 2mg/kg (p.o) to 100mg/kg (p.o) for both mice and rats contain 5 in each group. The mortality and general were under observation for 14 days. The test compounds were nontoxic in the dose of 5-10 mg/kg body weight.

CNS depressant activity (Actophotometer)

The locomotor activity considered as index of wake fullness of mental activity. It could be determined by using actophotometer. The activity was performed on albino mice weighing between 25-30g. There were 12 groups of animals (6 in each group). Group 1 was treated with vehicle alone normal saline. Group-2 was treated with chlorpromazine 3mg/kg body weight. Group-3-12 was treated with test compounds. The basal activity score of all animals were recorded before and after administration of drug at 30 min and 60 min time interval.

Analgesic activity (Tail immersion Test)

Young albino mice of either sex 25-30g were used for study. This study used for morphine like compounds. The animals were consisted of 12 groups 6 in each group. Group-1 was considered as control, group-2 was used for standard morphine sulphate 5mg/kg and group-3 to 12 was used for test compounds. The animals were allowed to adopt the environment before study. The tails were marked 5 cm above and immersed in hot water of exactly 55ºC. The tail withdrawal time was noted down before and after administration of drug in seconds. The cut of time is 10sec and 1-5sec for treated and untreated animals respectively. If tail withdrawal time was more than 6 sec, indicates positive response.

Oral Glucose Tolerance Test on Rat (OGTT)

12 groups of animals were administered normal saline at the dose of 5mg/kg for test compounds followed by administration of glucose solution in the dose of 2g/kg after 30min of administration of drug. Blood sample was

withdrawn from dorsal vein at interval of 60, 120 and 180 mins. Blood glucose level was estimated using blood glucose test strip with elegance glucometer (Frankenbeng Germany) & GOD-POD kit (Acuurex,India) (Kadnur SV, 2005)

Evalution of anti-diabetic activity

Induction of diabetes

Streptazocine (STZ) was used in the dose of 60 mg/kg to induce insulin dependent diabetes (Patel *et al*., 2006). STZ was injected into rats intraperitoneally. After 48hrs of administration of STZ, the blood was collected by dorsal vein for determination of blood glucose level. The rat with fasting glucose level in range of 275-300 mg/100mL were considered as diabetic and considered for study.

Experimental protocol and dose schedule

The total periods for conductance of study were 21 days. The rats were divided into 13 groups consist of 6 animals in each group.

Group-1: Normal rats treated with vehicle alone saline 10 mL/kg p.o.

Group- 2: Diabetic control treated with STZ (60 mg/kg) dissolved in citrate buffer.

Group-3: Diabetic rat treated with Rosiglitazone 10 mg/kg (Ranbaxy,India).

Group-4 to 13: Diabetic rat treated with test compounds at 10mg/kg body weight

On 1,7,14 and 21 days of study after 2 hours of oral administration of drugs blood glucose levels and body wt. were measured, Blood samples were withdrawn through dorsal vein. On 21 days whole blood was collected by cardiac puncture. Blood sample were centrifuged at 3000 rpm for 10 mins to obtained serum. Blood glucose levels were estimated by GOD-POD kit (Accurex. India). All biochemical parameters were determined. Total cholesterol (Rafin, 1999), triglyceride by Hantzsch condensation method (Mac Donal RP, 1953), Serum urea and creatinine by method of Thomas (Thomas L, 1998), total protein (Tietz NW, 1986), HDL cholesterol (Burstein M., 1970) were measured.

STATISTICAL ANALYSIS

The results were shown as Mean ± SEM and comparison between standard and test compounds were made by one way ANOVA followed by Dunnetts test. Values of $p \leq 0.001$ were considered as significant.

RESULTS

Physical and Spectral data

4-Chloro-N-(Furan-2-ylmethylene)benzimine (IIIa)

Yield: 76%. Melting Point: 126-128^{o}C. IR (KBr, υ_{max}/cm^{-1}): 1709 (C=N), 742 (C-Cl). ^{1}H-NMR ($CDCl_3$, 500 MHz, δ/ppm): 7.50 (s, 1H,-N=CH- of imine); 7.40-7.38 (d, 1H, J=10Hz, Ar-H of furan); 7.30-7.29 (d, 2H, J=5 Hz, Ar-H of furan); 7.30-7.27(d, 2H, J=15Hz, Ar-H of phenyl ring); 7.20-7.18 (d, 2H, J=10Hz, Ar-H of phenyl ring). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ/ppm): 149.1; 147.1; 146.5; 143.9; 132.8; 123.7; 123.7; 109.9; 109.5; 103.2; 103.2. MS (*m/z*): 205.03 (100%); 207.03 (32%); 206.03 (12.3%).

4-bromo-N-(Furan-2-ylmethylene)benzimine (IIIb)

Yield: 75%. Melting Point: 138-140^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1671(C=N); 598 (C-Br). ^{1}H-NMR ($CDCl_3$, 500 MHz, δ/ppm): 7.47(s, 1H,-N=CH- of imine); 7.40-7.35 (d, 1H, J=20Hz, Ar-H of furan); 7.28-7.26 (d, 2H, J=10 Hz, Ar-H of furan); 7.26-7.24 (d, 2H, J=10Hz, Ar-H of phenyl ring); 7.17-7.13 (d, 2H, J=20Hz, Ar-H of phenyl ring). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ/ppm): 149.1; 147.9; 146.8; 143.5; 132.7; 123.6; 123.7; 109.1; 109; 103.8; 103.4. MS (*m/z*): 248.98 (100%); 250.98(32%); 249.98 (12.3%).

4-Chloro-3-nitro-N-(Furan-2-ylmethylene)benzimine (IIId)

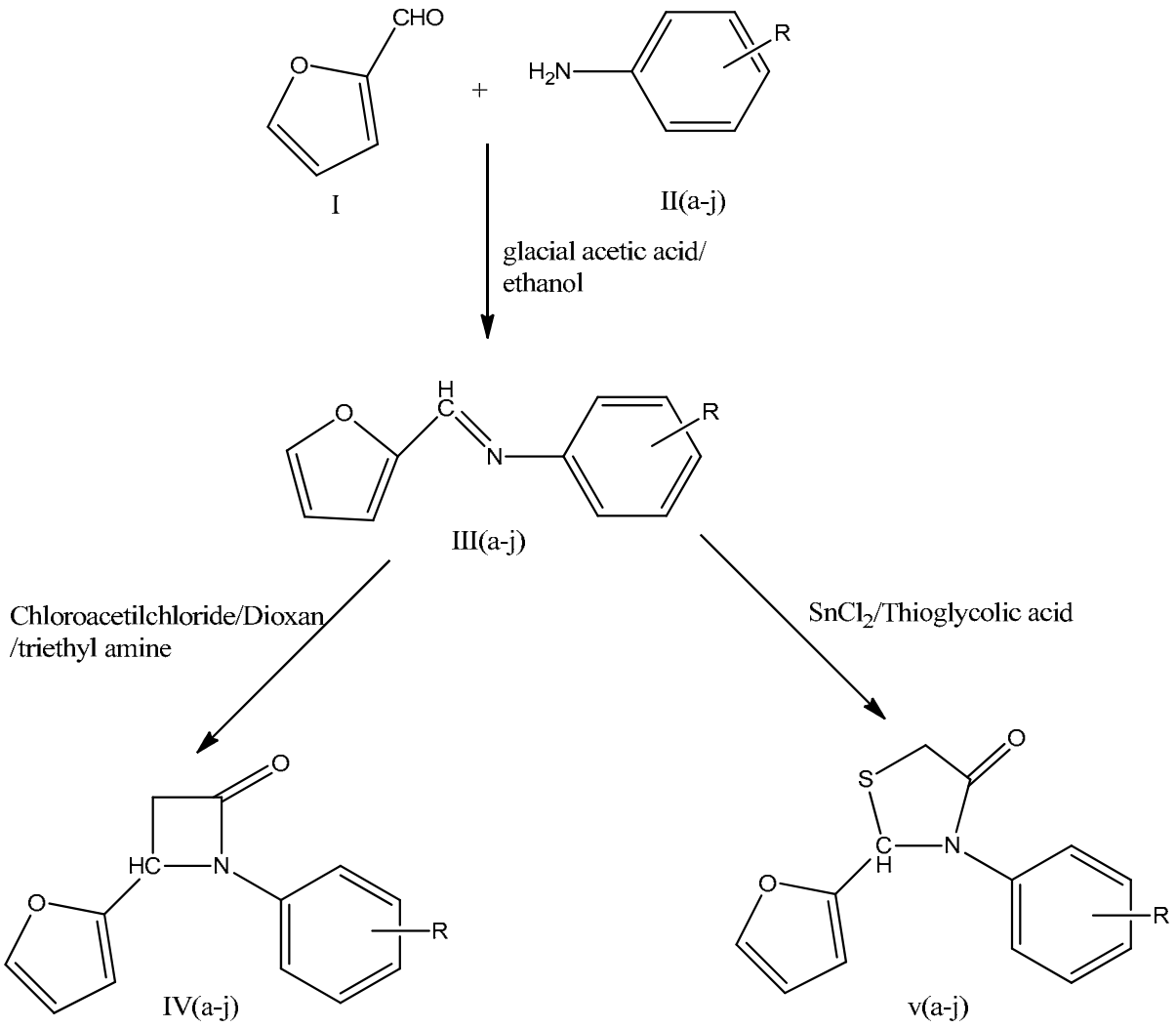
Yield: 73%. Melting Point: 141-143^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1650(C=N); 1508 (C-NO_2); 791(C-Cl). ^{1}H-NMR ($CDCl_3$, 500 MHz, δ/ppm): 8.1(s, 1H, of phenyl ring); 7.6-7.58(d, 1H, J=10Hz, Ar-H, of phenyl ring); 7.48 (s,1H,-N=CH- of imine); 7.31-7.28 (d, 1H, J=15Hz, Ar-H of furan); 6.30-6.28 (d, 2H, J=10Hz, Ar-H of furan). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ/ppm): 150.1; 149.1; 148; 146.5; 143.9; 131.8; 129.7; 127.7; 118.5; 109.9; 108.2. MS (*m/z*): 250.01 (100%); 252.01 (32.1%); 251.02 (12.1%).

3,4-Dichloro-N-(Furan-2-ylmethylene)benzamine (IIIe)

Yield: 72%. Melting Point: 145-146^{o}C. IR (KBr, υ_{max}/cm^{-1}): 1650(C=N); 791(C-Cl). ^{1}H-NMR ($CDCl_3$, 500 MHz, δ/ppm): 7.52 (s, 1H,-N=CH- of imine); 7.40-7.37 (d, 1H, J=15Hz, Ar-H of phenyl ring); 7.20-7.18 (d, 1H, J=10 Hz, Ar-H of phenyl ring); 7.10-7.08 (d, 1H, J=10 Hz, Ar-H of furan); 6.30-6.28 (d, 2H, J=10Hz, Ar-H of furan). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ/ppm): 149.13; 148.6; 146.3; 143.8; 134.7; 131.8; 131.6; 124; 121.7; 109.9; 109.2. MS (*m/z*): 238.01(100%); 240.01(62.1%); 239.02(12.1%).

3,4-Diifluoro-N-(Furan-2-ylmethylene)benzamine (IIIf)

Yield: 70%; Melting Point: 123-125^{0}C; IR (KBr, υ_{max}/cm^{-1}): 1650(C=N); 1221(C-F). ^{1}H-NMR ($CDCl_3$, 500 MHz, δ/ppm): 7.53(s, 1H, -N=CH- of imine); 7.40-7.38(d, 1H, J=10Hz, Ar-H of phenyl ring); 7.00-6.98(d, 1H, J= 10 Hz, Ar-H of phenyl ring); 6.94-6.92(d, 1H, J=10 Hz, Ar-H of furan); 6.32-6.28(d, 2H, J=20Hz, Ar-H of furan). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ/ppm): 150.8; 148.5; 148; 146.5; 143.9; 134.7; 119.5; 118.4; 111.2; 109.9; 109.2; 46. MS (*m/z*): 207.05 (100%); 208.05(12.1%).



Compound no	R	Compound no	R
IIa, IIIa, IVa, Va	4-chloro	IIf, IIIf, IVf, Vf	3,4-difluoro
IIb, IIIb, IVb, Vb	4-bromo	IIg, IIIg, IVg, Vg	2-fluoro-5-nitro
IIc, IIIc, IVc, Vc	4-nitro	IIh, IIIh, IVh, Vh	3-chloro-4-fluoro
IId, IIId, IVd, Vd	3-nitro-4-chloro	IIi, IIIi, IVi, Vi	2-fluoro
IIe, IIIe, IVe, Ve	3,4-dichloro	IIj, IIIj, IVj, Vj	3-methyl-4-nitro

Scheme 1

Table 1: Elemental analysis of synthesized compounds (IVa-j)

Compound No	Molecular Formula	Elemental analysis (Calculated)	Elemental analysis (Found)
IVa	$C_{13}H_{10}ClNO_2$	C-63.04, H-4.07, N-5.66	C-63.02, H-3.17, N-4.66
IVb	$C_{13}H_{10}BrNO_2$	C-53.45, H-3.45, N-4.79	C-53.15, H-3.05, N-4.29
IVc	$C_{13}H_{10}N_2O_4$	C-60.47, H-3.9, N-10.85	C-60.37, H-3.7, N-10.35
IVd	$C_{13}H_9ClN_2O_4$	C-53.35, H-3.1, N-9.57	C-53.23, H-2.8, N-9.27
IVe	$C_{13}H_9Cl_2NO_2$	C-55.34, H-3.22, N-4.96	C-55.14, H-3.12, N-4.26
IVf	$C_{13}H_9F_2NO_2$	C-62.65, H-3.64, N-5.62	C-62.15, H-3.24, N-5.32
IVg	$C_{13}H_9FN_2O_4$	C-56.53, H-3.28, N-10.14	C-56.23, H-3.18, N-10.04
IVh	$C_{13}H_9ClFNO_2$	C-58.77, H-3.41, N-5.27	C-58.27, H-2.41, N-5.17
IVi	$C_{13}H_{10}FNO_2$	C-67.53, H-4.36, N-6.06	C-67.23, H-4.16, N-5.09
IVj	$C_{14}H_{12}N_2O_4$	C-61.76, H-4.44, N-10.29	C-60.96, H-4.24, N-10.19

Table 2: Elemental analysis of synthesized compounds (Va-j)

Compound No	Molecular Formula	Elemental analysis (Calculated)	Elemental analysis (Found)
Va	$C_{13}H_{10}ClNO_2S$	C-55.82, H-3.6, N-5.01	C-55.72, H-3.3, N-4.39
Vb	$C_{13}H_{10}BrNO_2S$	C-48.16, H-3.11, N-4.32	C-48.06, H-2.91, N-4.22
Vc	$C_{13}H_{10}N_2O_4S$	C-53.79, H-3.47, N-9.65	C-53.59, H-3.27, N-9.75
Vd	$C_{13}H_9ClN_2O_4S$	C-48.08, H-2.79, N-8.63	C-47.78, H-2.48, N-8.43
Ve	$C_{13}H_9Cl_2NO_2S$	C-49.7, H-2.89, N-4.46	C-49.5, H-2.19, N-4.26
Vf	$C_{13}H_9F_2NO_2S$	C-55.51, H-3.23, N-4.98	C-55.49, H-3.13, N-4.78
Vg	$C_{13}H_9FN_2O_4S$	C-50.65, H-2.94, N-9.09	C-50.25, H-2.74, N-8.09
Vh	$C_{13}H_9ClFNO_2S$	C-52.44, H-3.05, N-4.7	C-51.04, H-2.95, N-4.67
Vi	$C_{13}H_{10}FNO_2S$	C-59.5, H-3.83, N-5.32	C-59.2, H-3.33,N-5.12
Vj	$C_{14}H_{12}N_2O_4S$	C-55.25, H-3.97, N-9.21	C-54.75, H-3.27, N-9.01

2-Fluoro-4-nitro-N-(Furan-2-ylmethylene)benzamine (IIIg)

Yield: 50%. Melting Point: 129-130^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1640(C=N); 1548 (C-NO_2); 1201 (C-F). ^{1}H-NMR ($CDCl_3$, 500 MHz, δ/ppm): 7.90-7.88 (d, 1H, J=10 Hz, Ar-H of phenyl ring); 7.80-7.78(d, 1H, J= 10 Hz, Ar-H of phenyl ring); 7.57 (s, 1H,-N=CH- of imine); 7.42-7.38 (d, 1H, J=20 Hz, Ar-H of furan); 6.36-6.34 (d, 2H, J=10 Hz, Ar-H of furan). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ/ppm): 154.8; 149.1; 148.3; 145.5; 143.8; 142.1; 124.8; 119.5; 118.4; 111.2; 108.9; 107.2. MS (*m/z*): 234.04(100%); 235.05(12.1%); 236.05 (1.3%).

3-Choloro-4-fluoro-N-(Furan-2-ylmethylene)benzamine (IIIh):

Yield: 76%. Melting Point: 133-136^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1644(C=N); 1100 (C-F); 781(C-Cl). ^{1}H-NMR ($CDCl_3$, 500 MHz, δ/ppm): 7.52(s, 1H,-N=CH- of imine); 7.42-7.40(d, 1H, J=10 Hz, Ar-H of phenyl ring), 7.20-7.18 (s, 1H, J=10 Hz, Ar-H of phenyl ring); 7.10-6.99 (d, 1H, J=5Hz, Ar-H of phenyl ring); 6.80-6.78(d, 1H, J=10 Hz, Ar-H of furan); 6.31-6.28 (d, 2H, J=15Hz, Ar-H of furan). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ/ppm): 161.3; 149.1; 146.5; 146; 143.9; 124.7; 122.1; 121.6; 118.4; 109.9; 107.2. MS (*m/z*): 223.02(100%); 225.05(32.1%); 224.02(12.3%).

2-Fluoro-N-(Furan-2-ylmethylene)benzamine (IIIi)

Yield: 75. Melting Point: 138-140^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1655(C=N); 1200 (C-F). ^{1}H-NMR ($CDCl_3$, 500 MHz, δ/ppm): 7.56(s, 1H,-N=CH- of imine); 7.41-7.38 (d, 2H, J=15 Hz, Ar-H of phenyl ring); 7.20-7.18(d, 2H, J=10 Hz, Ar-H of phenyl ring); 7.10-6.99(d, 1H, J=5Hz, Ar-H of furan); 6.30-6.28 (d, 2H, J=10 Hz, Ar-H of furan). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ/ppm): 154.1; 149. 1; 146.5; 143.9; 136; 128.9; 125.7; 123.9; 116.8; 116.8; 109.9; 107.5. MS (*m/z*): 189.06 (100%); 190.06 (12.3%).

4-Nitro-3-methyl-N-(Furan-2-ylmethylene)benzamine (IIIj)

Yield: 72 %. Melting Point: 145-146^{0}C. IR (KBr, υ_{max}/cm^{-1}): 2950(CH_3); 1649(C=N); 1540 (C-NO_2). ^{1}H-NMR ($CDCl_3$, 500 MHz, δ/ppm): 8.10-7.99 (d, 2H, J=5Hz, Ar-H of phenyl ring); 7.50(s, 1H,-N=CH- of imine); 7.40-7.37(d, 1H, J=15 Hz, Ar-H of phenyl ring); 7.30-7.28(d, 1H, J=10 Hz, Ar-H of furan); 6.30-6.28(d, 2H, J=10 Hz, Ar-H of furan).2.35(s,3H, -CH_3). ^{13}C-NMR ($CDCl_3$, 500 MHz, δ/ppm): 155; 149.1; 147.6; 146.5; 143.9; 137.6; 124.8; 122.3; 120.2; 109.9; 109.1; 15.7. MS (*m/z*): 230.07(100%); 231.07(32.1%).

1-(4-Chlorophenyl)-4-(furan-2-yl)azetidin-2-one (IVa)

Yield: 69%. Melting Point: 205-206^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1690(C=O); 1280(C-N); 1201 (C-C); 783(C-Cl). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.32-7.30 (d, 2H, J=10 Hz, Ar-H of phenyl ring); 7.28-7.26(d, 2H,J=10Hz,Ar-H of phenyl ring); 7.04-7.7.02(d, 2H, J=10 Hz, Ar-H of furan); 6.24-6.22(d, 1H,J=10Hz,Ar-H of furan); 5.08(s,1H,-CH-N- of azetidin-2-one); 3.49 (s,1H,-CH_2-CO of azetidin-2-one); 3.24(s,1H,-CH_2-CO of azetidin-2-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 170.9; 151.1; 141.5; 139.8; 129.9; 129.1; 129.1; 123; 123; 110; 53.8; 45.2. MS (*m/z*): 247.04(100%), 249.07(32.1%), 248.04 (12.1%).

1-(4-Bromophenyl)-4-(furan-2-yl)azetidin-2-one (IVb)

Yield: 68%. Melting Point: 218-219^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1698(C=O); 1280(C-N); 1210 (C-C); 598(C-Br). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.32-7.29(d, 2H, J=15Hz, Ar-H of phenyl ring); 7.27-7.26(d, 2H,J= 5 Hz, Ar-H of phenyl ring); 7.14-7.12(d, 2H, J=10 Hz, Ar-H of furan); 6.22-6.20(d, 1H, J=10Hz,Ar-H of furan); 5.18(s, 1H,-CH-N- of azetidin-2-one); 3.4 (s,1H,-CH2-CO of azetidin-2-one), 3.24 (s,1H,-CH_2-CO of azetidin-2-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.9; 153.1; 141.3; 139.7; 129.3; 129.1; 129.1; 123.5; 123; 110; 53.56; 43.2. ; MS (*m/z*): 290.99(100%); 292.99(97.1%); 291.99 (14.1%).

1-(4-Nitrophenyl)-4-(furan-2-yl)azetidin-2-one (IVc):

Yield: 67%. Melting Point: 202-203^{o}C. IR (KBr, υ_{max}/cm^{-1}): 1694(C=O); 1510 (C-NO_2); 1278(C-N); 1201 (C-C). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.35-7.33(d, 2H, J=10Hz, Ar-H of phenyl ring); 7.28-7.25(d, 2H,J=15Hz,Ar-H of phenyl ring); 7.04-7.02(d, 2H, J=10 Hz, Ar-H of furan); 6.25-6.22(d, 1H, J=15Hz,Ar-H of

furan); 5.28(s, 1H,-CH-N- of azetidin-2-one); 3.49 (s,1H,-CH_2-CO- of azetidin-2-one); 3.24(s,1H,-CH_2-CO- of azetidin-2-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 170.8; 161.1; 143.5; 137.8; 132.9; 129.8; 129.1; 125; 123; 110; 56.8; 42.2. MS (*m/z*): 258.06 (100%).

1-(4-Chloro-3-nitrophenyl)-4-(furan-2-yl)azetidin-2-one (IVd)

Yield: 69%. Melting Point: 209-210^{0}C. IR (KBr, υ_{max}/cm^{-1}):1693(C=O); 1510 (C-NO_2); 1280(C-N); 1271(C-C); 783 (C-Cl). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.97(s, 1H,Ar-H of phenyl ring); 7.58-7.56(d, 1H,J= 10Hz,Ar-H of phenyl ring); 7.43-7.7.41 (d, 2H, J=10 Hz, Ar-H of phenyl ring); 7.22-7.20(d, 1H,J=10Hz,Ar-H of furan); 6.18-6.16 (d, 2H, J=10Hz, Ar-H of furan); 5.58 (s,1H,-CH-N azetidin-2-one); 3.59 (s,1H,-CH_2-CO azetidin-2-one); 3.34 (s,1H,-CH_2-CO azetidin-2-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.9; 155.1; 149.8; 141.5; 140.7; 130.8; 129.1; 116.9; 110; 105.12; 57.8; 40.2. MS (*m/z*): 292.03(100%); 294.02(32%); 293.03(14.3%).

1-(3, 4-Dichloro phenyl)-4-(furan-2-yl)azetidin-2-one (IVe)

Yield: 69%. Melting Point: 212-214^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1700(C=O); 1301(C-N); 1261(C-C); 783 (C-Cl). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.38-7.36 (d, 1H,J= 10 Hz,Ar-H of phenyl ring); 7.19-7.16(d, 1H, J=15Hz,Ar-H of phenyl ring); 7.15(s,1H,Ar-H of phenyl ring); 6.94-6.92(d, 1H, J=10Hz, Ar-H of furan); 6.54-6.50 (d, 2H, J=20Hz, Ar-H of furan); 5.15 (s,1H,-CH-N- azetidin-2-one); 3.59 (s,1H,-CH_2-CO azetidin-2-one),3.24(s,1H,-CH_2-CO azetidin-2-one. ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 173.9; 154.1; 143.5; 143.1; 133.8; 130.6; 129.1; 123.4; 121.1; 121.1; 110; 105.9; 53.8; 43.2. MS (*m/z*): 281.00 (100%); 283.02(32%); 282.03(14.3%).

1-(3,4-Difluoro phenyl)-4-(furan-2-yl)azetidin-2-one (IVf)

Yield: 72%; Melting Point: 225-227^{0}C; IR (KBr, υ_{max}/cm^{-1}): 1691(C=O); 1310(C-N); 1261(C-C); 1010(C-F). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.80-7.78 (d, 1H, J=10Hz, Ar-H of phenyl ring); 7.00-6.98 (d, 2H, J=10Hz, Ar-H of phenyl ring); 6.54-6.50 (d, 2H, J=20Hz, Ar-H of furan); 6.24-6.22(d, 2H, J=10Hz, Ar-H of furan); 5.48 (s, 1H, -CH-N- of azetidin-2-one); 3.49 (s, 1H,-CH_2-CO of azetidin-2-one),3.24(s,1H,-CH_2-CO of azetidin-2-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 172.9; 152.1; 149.7; 145.5; 141.7; 138.8; 118.8; 117.9; 111.7; 110; 105.9; 56.8; 45.2. MS (*m/z*): 249.06(100%).

1-(2-Fluoro-4-nitrophenyl)-4-(furan-2-yl)azetidin-2-one (IVg)

Yield: 69%. Melting Point: 229-230^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1671(C=O); 1553(C-NO_2); 1300(C-N); 1201(C-C); 1013(C-F). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.95(s, 1H, Ar-H of phenyl ring); 7.68-7.66(d, 1H, J=10Hz, Ar-H of phenyl ring); 7.43-7.7.41(d, 1H, J=10 Hz, Ar-H of phenyl ring); 7.28-7.26(d, 1H, J=10Hz,Ar-H of furan); 7.14-7.12(d, 2H, J=10Hz, Ar-H of furan); 5.48(s,1H,-CH-N of azetidin-2-one); 3.59 (s,1H,-CH_2-CO of azetidin-2-one), 3.14 (s,1H,-CH_2-CO of azetidin-2-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 176.8; 163.9; 152.1; 145.6; 140.5; 133.9; 124.1; 116.9; 110.9; 110; 105.9; 63.8; 43.2. MS (*m/z*): 276.05 (100%); 277.06 (14.3%).

1-(3-Chloro-4-fluorophenyl)-4-(furan-2-yl)azetidin-2-one (IVh)

Yield: 69%. Melting Point: 255-256^{o}C. IR (KBr, υ_{max}/cm^{-1}): 1751(C=O); 1344(C-N); 1290(C-C); 1013(C-F); 789 (C-Cl). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.38-7.34(d, 1H, J=20Hz, Ar-H of phenyl ring); 7.14-7.10(d, 1H, J=20Hz, Ar-H of phenyl ring); 7.09 (s, 1H, Ar-H of phenyl ring); 6.98-6.96(d, 1H, J=10Hz, Ar-H of furan); 6.54-6.52(d, 2H, J=10Hz, Ar-H of furan); 5.16 (s, CH-N- of azetidin-2-one); 3.39 (s, 1H,-CH_2-CO- of azetidin-2-one); 3.14 (s, 1H,-CH2-CO of azetidin-2-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 175.9; 158.1; 154.1; 142.5; 138.9; 123.6; 125.3; 119; 117.1; 112.2; 105.9; 58.8; 48.2. MS (*m/z*): 265.03 (100%), 267.03 (32.3%).

1-(2-Fluorophenyl)-4-(furan-2-yl)azetidin-2-one (IVi)

Yield: 71%. Melting Point: 214-215^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1731(C=O); 1324(C-N); 1199(C-C); 1017(C-F). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.48-7.46(d, 1H,J= 10Hz,Ar-H of phenyl ring); 7.22 -7.20(d, 1H,J= 10Hz,Ar-H of phenyl ring); 7.19-7.15(d, 1H,J=20Hz,Ar-H of phenyl ring); 7.09-7.07(d, 1H,J= 10Hz,Ar-H of phenyl ring); 6.95-6.93(d, 1H,J=10Hz,Ar-H of furan); 6.34-6.32 (d, 2H, J=10Hz, Ar-H of furan); 5.28(s,1H,-CH-N- of azetidin-2-one); 3.59 (s,1H,-CH_2-CO of azetidin-2-one),3.14(s,1H,-CH_2-CO of azetidin-2-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm):173.8; 163.8; 151.7; 141.5; 127.8; 126; 124.6; 123.3; 115.7; 110.9; 104.9; 73.8; 43.2. MS (*m/z*): 231.07 (100%); 232.07(14.5%).

1-(3-Methyl-4-nitrophenyl)-4-(furan-2-yl)azetidin-2-one (IVj):

Yield: 71%. Melting Point: 219-220^{0}C. IR (KBr, υ_{max}/cm^{-1}): 2950(CH_3); 1731(C=O); 1540 (C-NO_2); 1324(C-N); 1199(C-C). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 8.12(s, 1H, Ar-H of phenyl ring); 7.48-7.46(d, 1H, J=10Hz,Ar-H of phenyl ring); 7.42-7.40 (d, 1H,J= 10Hz,Ar-H of phenyl ring); 7.12-7.10(d, 1H, J=10Hz, Ar-H of furan); 6.44-6.42 (d, 2H, J=10Hz, Ar-H of furan); 5.28 (s, 1H, -CH-N- of azetidin-2-one); 3.79 (s, 1H, -CH_2-CO azetidin-2-one); 3.24(s, 1H,-CH_2-CO of azetidin-2-one); 2.35(s,3H,-CH_3) ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 170.9; 151.1; 147.7; 144.7; 141.5; 136.5; 122.2; 121.2; 119.5; 110; 105.9; 53.8; 43.2; 15.7. MS (*m/z*): 272.08 (100%); 273.08(16%).

Table-3: Antimicrobial data of Compounds (IVa-j)

Compound No.	Gram Positive bacterias						Gram negative bacterias						Fungus					
	Staphylococcus aureus			*Bacillus substilis*			*Escherichia coli*			*Enterobacter cloacae*			*Aspergillus niger*			*Candida albicans*		
	Zone of inhibitions (mm)																	
	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml
IVa	10	13	15	11	13	15	18	20	20.5	10.6	13	15	9	10.5	13	10	12	15
IVb	11	16	18	11	13.5	16	17	19	21	11.5	16	18	11	13	15	11	14	15
IVc	16	19	21	17	16.1	18	19.8	22	23.2	16.1	19	21	16	17	18	16	18	19
IVd	15	18	20	18	15	19	21	22	24	15	18	20	15	17	18.3	15	17	19
IVe	17	21	22	17	17	19.5	22	23.6	25	17.4	21	22	17	17.5	19	17	21	22
IVf	14	18	20	14	13	15	17	19	21	17	18	20	14	16	18	14	16	17
IVg	12	17	19	12	12	17	19	21	22	15	17	19	12	14	16.5	12	13	15
IVh	19	23	25	19	18	19	21	22	23	20	23	25	19	21	23	19	21	22
IVi	13	15	19	13	13	14	18	20	23	13	15	19	13	19	21	21	22	23
IVj	11	18	19	11	11.2	17	19	21	22.7	15	18	19	11	14	17	11	14	18
Amoxycillin	10	12	14.1	12	14	17.1	13	18	22.1	12	14	17.1	-	-	-	-	-	-
Streptomycin	11	13	16	11	13	16	19	21	22	11	13	16	-	-	-	-	-	-
Nystatin	-	-	-	-	-	-	-	-	-	-	-	-	10	13.5	16	10	13.5	16

Table-4: Antimicrobial data of Compounds (Va-j):

Compound No.	Gram Positive bacterias						Gram negative bacterias						Fungus					
	Staphylococcus aureus			*Bacillus substilis*			*Escherichia coli*			*Enterobacter cloacae*			*Aspergillus niger*			*Candida albicans*		
	Zone of inhibitions (mm)																	
	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	250 µg/ml
Va	10	13	15	11	13	15	18	20	20.5	10.6	13	15	9	10.5	13	10	12	15
Vb	11	16	18	11	13.5	16	17	19	21	11.5	16	18	11	13	15	11	14	15
Vc	16	19	21	17	16.1	18	19.8	22	23.2	16.1	19	21	16	17	18	16	18	19
Vd	15	18	20	18	15	19	21	22	24	15	18	20	15	17	18.3	15	17	19
Ve	17	21	22	17	17	19.5	22	23.6	25	17.4	21	22	17	17.5	19	17	21	22
Vf	14	18	20	14	13	15	17	19	21	17	18	20	14	16	18	14	16	17
Vg	12	17	19	12	12	17	19	21	22	15	17	19	12	14	16.5	12	13	15
Vh	19	23	25	19	18	19	21	22	23	20	23	25	19	21	23	19	21	22
Vi	13	15	19	13	13	14	18	20	23	13	15	19	13	19	21	21	22	23
Vj	11	18	19	11	11.2	17	19	21	22.7	15	18	19	11	14	17	11	14	18
Amoxycillin	10	12	14.1	12	14	17.1	13	18	22.1	12	14	17.1	-	-	-	-	-	-
Streptomycin	11	13	16	11	13	16	19	21	22	11	13	16	-	-	-	-	-	-
Nystatin	-	-	-	-	-	-	-	-	-	-	-	-	10	13.5	16	10	13.5	16

Table 5: Observation for antioxidant activity in terms of DPPH method

Compound no	% Scavenging [mean ± SEM]				
	25 µg/ml	50 µg/ml	75 µg/ml	100 µg/ml	125 µg/ml
IVa	15.61 ±06	21.31±0.026	23.41±0.098	36.97±0.15	47.32±0.026
IVb	18.06±0.01	28.56±0.06	31.91±0.05	52.75±0.12	60.20±0.14
IVc	21.21±0.12	31.37±0.09	38.22±0.24	43.44±0.15	56.53±0.16
IVd	12.39±0.05	25.60±0.025	37.24±0.16	56.52±0.052	63.70±0.01
IVe	8.83±0.098	14.95±0.026	45.00±0.023	56.24±0.05	65.01±0.11
IVf	17.26±0.25	29.56±0.13	40.40±0.16	51.50±0.09	57.47±0.12
IVg	14.10±0.13	32.12±0.25	41.51±0.12	52.97±0.01	62.29±0.11
IVh	35.00±0.12	58.23±0.01	65.31±0.18	75.00±.0.08	82.13±0.14
IVi	25.00±0.17	50.11±0.05	62.03±0.2	75.80±0.03	85.00±0.08
IVj	28.44±0.03	37.09±0.12	48.89±0.14	55.60±0.21	72.48±0.12
Va	15.61 ±06	21.31±0.026	23.41±0.098	36.97±0.15	47.32±0.026
Vb	18.06±0.01	28.56±0.06	31.91±0.05	52.75±0.12	60.20±0.14
Vc	21.21±0.12	31.37±0.09	38.22±0.24	43.44±0.15	56.53±0.16
Vd	12.39±0.05	25.60±0.025	37.24±0.16	56.52±0.052	63.70±0.01
Ve	8.83±0.098	14.95±0.026	45.00±0.023	56.24±0.05	65.01±0.11
Vf	17.26±0.25	29.56±0.13	40.40±0.16	51.50±0.09	57.47±0.12
Vg	14.10±0.13	32.12±0.25	41.51±0.12	52.97±0.01	62.29±0.11
Vh	35.00±0.12	58.23±0.01	65.31±0.18	75.00±.0.08	82.13±0.14
Vi	25.00±0.17	50.11±0.05	62.03±0.2	75.80±0.03	85.00±0.08
Vj	28.44±0.03	37.09±0.12	48.89±0.14	55.60±0.21	72.48±0.12
STD (Ascorbic acid)	22.28±0.12	41.03±0.19	52.06±0.2	75.02±0.09	96.10±0.18

Table 6: CNS Depressant Activity of synthesized compounds (Actophotometer)

Treatment (i.p.)	Drug (mg/kg)	Mean reaction without drug (sec)	Reaction Response	
			30 min	1 hr
Control	0.2ml/kg	778.2±1.18	778.6±1.38	777.8±1.74
Standard	3	656±1.50	491.3±1.81***	178.7±1.71***
Compound IVa	10	677.7±1.85	349.3±1.24***	137.2±1.05***
Compound IVb	10	549.7±1.50	284±1.25***	133±1.83***
Compound IVe	10	451.2±1.50	218.3±1.16***	131.5±1.25***
Compound IVf	10	422.8±1.61	230.3±1.8***	125.8±1.6***
Compound IVh	10	443.3±1.61	232.3±1.81***	113.2±1.97***
Compound Va	10	428.5±1.09	238.2±1.79***	117±1.89***
Compound Vb	10	464.3±1.49	229.7±1.88***	121.2±1.22***
Compound Ve	10	566±6.9	342.2±1.56***	156±1.51***
Compound Vf	10	443.7±1.07	274.2±2.17***	142±1.40***
Compound Vh	10	484±1.06	269.8±1.76***	118.5±2.89***

3-(4-Chlorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Va)

Yield: 78%; Melting Point: 193-194^{0}C; IR (KBr, υ_{max}/cm^{-1}): 1691(C=O); 1284 (C-N); 785 (C-Cl). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.42-7.40 (d, 2H, J=10 Hz, Ar-H of phenyl ring); 7.28-7.24(d, 2H, J=20Hz, Ar-H of phenyl ring); 7.04-7.02 (d, 2H, J= 10Hz, Ar-H of furan); 6.26-6.24 (d, 2H, J=10Hz, Ar-H of furan); 6.15 (s, 1H, -CH-N of thiazolidine-4-one); 3.49 (s, 1H,S-CH_2-CO of thiazolidine-4-one), 3.24(s, 1H,S-CH_2-CO of thiazolidine-4-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.2; 151.6; 142.1; 139.9; 129.9; 129.1; 129.1; 123; 123; 110.6; 106.7, 57.7; 31.2. MS (*m/z*): 279.01(100%); 281.07 (36.1%).

3-(4-Bromophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vb)

Yield: 80; Melting Point: 185-186^{0}C; IR (KBr, υ_{max}/cm^{-1}): 1693(C=O); 1270 (C-N); 596 (C-Br). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.32-7.29(d, 2H, J=15Hz, Ar-H of phenyl ring); 7.28-7.27(d, 2H, J=10Hz, Ar-H of phenyl ring); 7.14-7.12(d, 1H, J=10Hz, Ar-H of furan); 6.24-6.22(d, 2H,J=10Hz, Ar-H of furan); 6.15(s, 1H, -CH-N of thiazolidine-4-one); 3.47 (s,1H,S-CH_2-CO of thiazolidine-4-one),3.24(s,1H,S-CH_2-CO of thiazolidine-4-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.5; 151.3; 142.4; 139.7; 129.6; 127.1; 127.1; 123.8; 122.9; 110.6; 106.7; 57.7; 31.2. MS (*m/z*): 324.96(100%).

Table 7: Analgesic Activity of synthesized compounds (Tail Flick by Hot Immersion Method)

Treatment (i.p.)	Drug (mg/kg)	Mean response without drug (sec)	Mean Reaction Response	
			After 30 min	After 1 hr
Control	0.2ml/kg	2.66±0.012	2.76±0.04	2.81±0.07
Standard	3	2.36±0.09	3.87±0.21***	5.69±0.18***
Compound IVa	10	1.69±0.018	2.77±0.05***	3.66±0.11***
Compound IVb	10	2.04±0.19	2.86±0.07***	3.84±0.15***
Compound IVe	10	2.31±0.13	3.3±0.2***	4.26±0.18***
Compound IVf	10	2.03±0.09	3.22±0.18***	4.14±0.22***
Compound IVh	10	2.27±0.11	3.15±0.13***	4.13±0.16***
Compound Va	10	2.14±0.07	3.02±0.05**	3.95±0.12***
Compound Vb	10	2.16±0.07	3.03±0.13**	3.96±0.21***
Compound Ve	10	1.69±0.18	3.22±0.18**	5.69±0.18***
Compound Vf	10	2.04±0.19	3.87±0.21***	4.14±0.22**

After immersion in water at 55ºC

Table 8: OGTT blood glucose level (mg/dl) by synthesized compounds

Treatment (mg/kg body wt)	0min	60min	120min	180min
Control	91.5±2.23	106.2±3.02	103±7	93.67±1.00
Standard	91.5±2.23	110.0±3.94	108±1.89	97.83±0.47***
Compound IVa (10)	95±2.23	125.3±1.22	110.±1.28	99±0.96***
Compound IVb (10)	95±2.23	128 ±0.93	114±2.6	97.8±0.27***
Compound IVe (10)	89.25±2.23	138±0.94	121±2.81	98.17±0.70***
Compound IVf (10)	91.17±1.30	141.3±0.91	130.5±2.43	96±0.85***
Compound IVh (10)	92.83±0.87	136.6±0.87	125.5±1.83	93.5±1.4***
Compound Va (10)	93.83±0.6	152.2±7.34	132±0.85	90.83±0.47***
Compound Vb (10)	91.2±2.21	126.3±1.23	115±2.6	93.5±2.46***
Compound Ve (10)	93.83±0.6	182.7±1.5	143.3±3.12	93.5±2.46***
Compound Vf (10)	96.33±0.98	191.8±4.7	149.2±2.38	95±1.82***
Compound Vh (10)	92.62±0.87	153.2±1.23	130±2.4	91.33±2.12***

3-(4-Nitrophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vc):

Yield: 78%. Melting Point: 183-184^{0}C. IR (KBr, υ_{max}/cm^{-1}): 1701(C=O); 1515 (C-NO_2); 1276 (C-N). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.42-7.40 (d, 2H, J=10 Hz, Ar-H of phenyl ring); 7.32-7.30 (d, 1H, J= 10Hz, Ar-H of phenyl ring); 7.24-7.22 (d, 2H, J=10Hz, Ar-H of furan); 6.22-6.20 (d, 2H, J=10Hz, Ar-H of furan); 6.10(s,1H, -CH-N of thiazolidine-4-one); 3.59 (s, 1H, S-CH_2-CO of thiazolidine-4-one); 3.24 (s, 1H, S-CH_2-CO of thiazolidine-4-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.2; 151.6; 142.1; 139.9; 129.9; 129.1; 129.1; 123.4; 123.3; 110.2; 106.7; 52.7; 29.2. MS (*m/z*): 290.04(100%).

3-(4-Chloro-3-nitrophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vd):

Yield-79%; Melting Point: 190-191^{0}C; IR (KBr, υ_{max}/cm^{-1}): 1695 (C=O); 1510 (C-NO_2); 1280(C-N); 788 (C-Cl). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.97(s, 1H, Ar-H of phenyl ring); 7.58-7.56 (d, 1H, J= 10Hz, Ar-H of phenyl ring); 7.43-7.41 (d, 1H, J= 10Hz, Ar-H of phenyl ring); 7.28-7.26 (d, 1H, J=10Hz, Ar-H of furan); 6.44-6.42(d, 2H, J=10Hz, Ar-H of furan); 6.15 (s, 1H, -CH-N of thiazolidine-4-one); 3.69 (s, 1H, S-CH_2-CO of thiazolidine-4-one); 3.14(s, 1H,S-CH_2-CO of thiazolidine-4-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.9; 151.3; 149.2; 142.1; 140.7; 130; 129.9; 124.5; 116.9; 110.6; 106.7; 57.7; 31.2. MS (*m/z*): 324(100%); 325.99 (36.5%).

3-(3,4-Dichlorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Ve)

Yield: 77%; Melting Point: 178-179^{o}C; IR (KBr, υ_{max}/cm^{-1}): 1710(C=O); 1311(C-N); 783 (C-Cl). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.38-7.36 (d, 1H, J=10Hz, Ar-H of phenyl ring); 7.15(s, 1H, Ar-H of phenyl ring); 7.05-7.03(d, 1H, J=10Hz, Ar-H of phenyl ring); 6.92-6.90 (d, 1H, J=10Hz, Ar-H of furan); 6.44-6.43 (d, 2H, J=5Hz, Ar-H of furan); 6.15 (s,1H, -CH-N of thiazolidine-4-one); 3.49 (s, 1H, S-CH_2-CO of thiazolidine-4-one); 3.24(s, 1H, S-CH_2-CO of thiazolidine-4-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.2; 151.6; 142.1; 141.2; 130.5; 129; 123.5; 121.1; 113.6; 110.8; 106.7; 57.7; 31.2. MS (*m/z*): 312.97 (100%); 314.99(68.5%).

3-(3,4-Difluorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vf)

Yield: 78%; Melting Point: 192-193^{0}C; IR (KBr, υ_{max}/cm^{-1}): 1698(C=O); 1315 (C-N); 1011 (C-F). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.36-7.34 (d,1H,J=10Hz,Ar-H of phenyl ring); 7.00-6.98 (d,1H, J= 10Hz, Ar-H of phenyl ring); 6.79 (s, 1H, Ar-H of phenyl ring); 6.79-6.75 (d, 1H, J=20Hz, Ar-H of furan); 6.44-6.40 (d, 2H, J=20Hz, Ar-H of furan); 6.15 (s, 1H, -CH-N of thiazolidine-4-one); 3.59 (s, 1H, S-CH_2-CO of thiazolidine-4-one); 3.44(s, 1H, S-CH_2-CO of thiazolidine-4-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 174.2; 153.9; 149.7; 145.1; 142.1; 138.9; 118.8; 117.3; 110.6; 106.5; 57.6; 31.9. MS (*m/z*): 281.03(100%); 282.04 (14.2%).

3-(2-Fluoro-4-nitrophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vg)

Yield: 71%; Melting Point: 186-187^{0}C; IR (KBr, υ_{max}/cm^{-1}): 1671(C=O); 1553(C-NO_2); 1300(C-N); 1013(C-F). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 8.01(s, 1H, Ar-H of phenyl ring); 7.93-7.91(d, 1H, J=10Hz, Ar-H of phenyl ring); 7.43-7.41(d, 1H, J=10Hz, Ar-H of phenyl ring); 7.28-7.26 (d, J= 6Hz 1H, Ar-H of furan); 6.24-6.22 (d, 2H, J=6Hz,Ar-H of furan); 6.15 (s,1H, -CH-N of thiazolidine-4-one); 3.49 (s,1H,S-CH_2-CO of thiazolidine-4-one); 3.24(s,1H,S-CH_2-CO of thiazolidine-4-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.9; 163.9; 151.6; 145.6; 142.1; 133.9; 124.1; 116.8; 110.6; 106.7; 57.7; 31.2. MS (*m/z*): 308.03 (100%); 309.04 (15.2%).

3-(3-Chloro-4-fluorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vh)

Yield: 73%; Melting Point: 195-196^{0}C; IR (KBr, υ_{max}/cm^{-1}): 1750(C=O); 1334(C-N); 1013(C-F); 789(C-Cl). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.27-7.25 (d, 1H, J= 10Hz, Ar-H of phenyl ring); 7.09 (s, 1H, Ar-H of phenyl ring); 6.96-6.94 (d, 1H, J= 10Hz, Ar-H of phenyl ring); 6.9-6.88 (d, 1H, J=10Hz, Ar-H of furan); 6.24-6.22 (d, 2H, J=10Hz, Ar-H of furan); 6.15 (s, 1H, -CH-N of thiazolidine-4-one); 3.49 (s, 1H, S-CH_2-CO of thiazolidine-4-one); 3.24 (s, 1H, S-CH_2 -CO of thiazolidine-4-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.5; 158.4; 151.8; 142.3; 138.7; 123.6; 121.3; 121; 117.1; 110.8; 106.7; 67.7; 31.2. MS (*m/z*): 297(100%); 299.04 (36.2%).

3-(2-Fluorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vi)

Yield-71%; Melting Point: 177-179^{0}C; IR (KBr, υ_{max}/cm^{-1}): 1751(C=O); 1344 (C-N); 1010C-F). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.28-7.26 (d, 2H, J=10Hz, Ar-H of phenyl ring); 7.22-7.20 (d, 2H, J=10Hz, Ar-H of phenyl ring); 7.08-7.02(m, 1H, Ar-H of phenyl ring); 7.00-6.98 (d, 1H, J=10Hz, Ar-H of furan); 6.24-6.22 (d, 2H, J=10Hz, Ar-H of furan); 6.18 (s, 1H, -CH-N of thiazolidine-4-one); 3.49 (s, 1H, S-CH_2-CO of thiazolidine-4-one); 3.24 (s, 1H, S-CH_2-CO of thiazolidine-4-one). ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.8; 163.9; 151.6; 142.1; 127.8; 126.9; 124.6; 123.2; 115.7; 110.8; 106.7; 57.7; 31.2. MS (*m/z*): 263.04 (100%); 264.04 (15.2%).

3-(3-Methyl-4-nitrophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vj)

Yield: 72%; Melting Point: 178-179^{0}C; IR (KBr, υ_{max}/cm^{-1}): 2950(CH_3); 1731(C=O); 1540 (C-NO_2); 1324(C-N). ^{1}H-NMR (DMSO-d_6, 500 MHz, δ/ppm): 7.25-7.22(d, 1H, J=15Hz, Ar-H of phenyl ring); 7.17-7.15(d, 1H,J=10Hz, Ar-H of phenyl ring); 7.1(s, 1H, Ar-H of phenyl ring); 6.24-6.23 (d, 2H, J=5Hz, Ar-H of furan); 6.18-6.17 (d, 2H, J=5Hz, Ar-H of furan); 6.18 (s, 1H, -CH-N of thiazolidine-4-one); 3.59 (s, 1H, SCH_2CO of thiazolidine-4-one); 3.24 (s, 1H, SCH_2CO of thiazolidine-4-one); 2.35 (s, 3H, -CH_3) ^{13}C-NMR (DMSO-d_6, 500 MHz, δ/ppm): 171.9; 151.6; 147.7; 144.7; 142.1; 136.5; 122.2; 121.2; 118.5; 110.8; 106.7; 57.7; 31.2; 15.7. MS (*m/z*): 304.05 (100%); 305.06(15.4%).

DISCUSSION

Chemistry

The present work involved cyclization of Schiff bases to azetidine-2-one and thiazolidine-4- ones derivatives. The Schiff bases (IIIa-j) were obtained by the reaction between electrophillic carbon atom of furfuraldehyde and nucleophillic nitrogen atom of amines. The methodology involves two steps synthesis followed by two different protocols resulted azetidine-2-one and thiazolidine-4-one respectively. Azetidine-2-one derivatives (IVa-j) were obtained by reaction between imines and monochloro acetyl chloride using 1, 4-dioxan as solvent. It was a base catalysed reaction where triethyl amine was used as base catalyst. Tertiary amine counter balance between nucleophilicity and basicity, which was considered as key factor for efficient completion of reaction. On the other hand, preparation of thiazolidine-4-one (Va-j) was preceded by nucleophilic attack of sulphur of thioglycolic acid on imine carbon followed by intramolecular cyclization in the presence of $SnCl_2$. During reaction one mole of water was eliminated. The most important factor which complete the reaction in shorter duration and good percentage yield in presence of eco-benign tin chloride dehydrate $SnCl_2.2H_2O$ at 45ºC. The $SnCl_2$, $2H_2O$ was acted as acid catalyst which counters balance between nucleophilicity and acidity for completion of reaction. The substitutions on aromatic amine have great significance on yield value. The substitution with electron donating group at para and meta position of ring increases percentage yield where as it decreases in case of ortho substitution due to steric effect. Purification of compounds were done using benzene and chloroform (1:20 v/v) for azetidine-2-one and petroleum ether and chloroform (2:8 v/v) for thiazolidine-4-ones by column chromatography.

Table 9: Fasting blood glucose level (mg/dl) by synthesized compounds

Treatment (mg/kg body wt)	0 days	7 days	14days	21days
Control	91±1.00	115.7±3.9	114±6.8	100±2.47
Diabetic control	244.7±2.96	281.3±2.51	311±3.99	336±2.12
Standad	311.3±3.99	247.8±7.4	126.7±5.8	106.5±1.9
Compound IVa (10)	285.3±5.28	195±6.58	152±7.66	108.17±1.35***
Compound IVb (10)	293.5±4.35	191±6.79	150.5±7.55	115.5±1.76***
Compound IVe (10)	283.2±1.19	190±3.73	157±6.09	110.81±2.8***
Compound IVf (10)	293.5±6.99	158.2±3.20	127.3±2.01	117.33±0.5***5
Compound IVh (10)	285.2±4.79	149.8±2.89	129±1.88	98.33±0.76***
Compound Va (10)	301.7±3.07	152.5±1.2	132.2±1.65	97.83±0.87***
Compound Vb (10)	285±4.8	136.7±2.04	124.5±1.60	95.33±1.33***
Compound Ve (10)	301.7±3.07	123.2±0.94	119.5±1.04	90.12±2.26***
Compound Vf (10)	250.3±8.51	132.8±3.19	124.5±1.29	87±3.48***
Compound Vh (10)	286.5±1.19	193±3.73	120±1.89	96.11±2.26***

Table 10: Change in Bodyweight (gm) by synthesized compounds

Treatment (mg/kg body wt)	0 days	7 days	14days	21days
Control	160±0.6	169±0.5	166±0.8	163±0.2
Diabetic control	178.5±0.99	190±0.69	215±0.56	253±0.12
Standad	171±0.39	144.5±0.67	141±0.60	169±0.6
Compound IVa (10)	163.3±0.61	215.2±0.69	187±0.89	178±0.9***
Compound IVb (10)	174±0.49	133±0.57	127.8±0.27	167±0.61***
Compound IVe (10)	167.7±0.49	143±0.57	129.8±0.55	169.2±0.46***
Compound IVf (10)	166±0.36	142±0.36	125±0.83	160±0.69***
Compound IVh (10)	167±0.41	131±0.5	127±0.56	163±0.26***
Compound Va (10)	168±0.51	141±0.6	137±0.4	162±0.3***
Compound Vb (10)	169±0.66	132±0.25	142±0.7	156±0.2***
Compound Ve (10)	165±0.6	158±0.7	153±0.46	158±0.2***
Compound Vf (10)	170±0.21	161±0.4	155±0.3	168±0.2***
Compound Vh (10)	168±0.4	123±0.61	141±0.52	159±0.67***

Table 11: Change in biochemical parameter of rat by synthesized compounds

Treatment (mg/kg body wt)	Cholesterol (mg/dl)	Triglycerides (mg/dl)	Creatinin (mg/dl)	Urea (mg/dl)	HDL Cholesterol (mg/dl)	Total Protein (g/dl)
Control	148±1.5	83.3±4.6	0.6±0.4	22±0.4	34.1±1.8	8.3±1.7
Diabetic control	290±1.9	258±9.8	2±1.9	80±3.2	28±1.8	4±3.2
Standad	119±2.8	101±5.2	0.41±1	32.2±3.1	63±2.9	8.4±0.4
Compound IVa(10)	150±2.49***	120.5±3.6***	0.63±0.09***	31±0.44***	46±1.41***	7.6±1.1***
Compound IVb(10)	164.7±2.71***	136.5±1.4***	0.58±0.01***	34.83±0.87***	57±0.85***	8.7±0.9***
Compound IVe(10)	179.8±2.18***	135.7±1.54***	0.53±0.02***	34.5±0.99***	42.5±0.42***	5.4±1.7***
Compound IVf (10)	156.8±0.6***	143±2.09***	0.47±0***	35.5±0.42***	45±2.46***	5±2***
Compound IVh(10)	167.2±0.6***	134.3±1.33***	0.6±0.01***	32.0±0.73***	41.67±3.8***	4.9±1.6***
Compound Va (10)	136.8±0.7***	137±1***	0.77±0.1***	25.67±0.61***	32.33±2.41***	4.7±0.8***
Compound Vb (10)	144.5±0.8***	138±1***	0.47±0.01***	23.67±0.42***	36.17±0.94***	4.6±0.3***
Compound Ve (10)	143.8±1.2***	123±1.11***	0.63±0.01***	24.17±1.02***	38.5±2.34***	5.2±0.1***
Compound Vf (10)	149.8±1.19***	125.5±1.6***	0.56±0.06***	26.17±0.03***	33.83±1.53***	5.3±0.1***
Compound Vh (10)	150.5±2.23***	152±2.5***	0.55±0.08***	23.17±0.7***	30.86±3.10***	4.8±1.3***

The physical and analytical datas were determined for synthesized compounds. In view of establishment of structure spectral analysis has been performed by IR, ^{1}HNMR, ^{13}CNMR and MS. The formation of compound 4-Chloro-N-(Furan-2-ylmethylene) benzimine (IIIa) was confirmed by characteristic IR peaks at 1709 (C=N), 742 (C-Cl) cm $^{-1}$ and ^{1}H-NMR peak at δ value 7.50 (s, 1H,-N=CH- of imine). After completion of reactions the formation of compound 1-(4-Chlorophenyl)-4-(furan-2-yl) azetidin-2-one (IVa) was confirmed by IR peaks at 1690(C=O); 1280(C-N); 1201 (C-C) cm $^{-1}$ and ^{1}H-NMR peak at δ value for 5.08(s, 1H, -CH-N-); 3.49 (s,1H,-CH_2-CO) and 3.24(s,1H,-CH_2-CO) for azetidin-2-one nucleus. Similarly 3-(4-Chlorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Va) was justified by characteristic IR at peaks 1691(C=O); 1284 (C-N) cm $^{-1}$ and ^{1}H-NMR peak at δ value 6.15 (s, 1H, -CH-N); 3.49 (s, 1H,S-CH_2-CO), 3.24 (s, 1H, S-CH_2-CO) of thiazolidine-4-one. The ^{1}HNMR data also confirmed aromaticity of the compounds. ^{13}CNMR spectral data also give characteristic peak according to proposed structure. From the mass spectral it was found that *m/z* peaks according to calculated molecular mass of the synthesized compounds. Like this spectral data confirmed formation of all the synthesized compounds as per proposed Scheme 1. The formation of compound also justified by elemental analysis (C, H, N analysis) showed in table 1and table 2.

Biological activity

In-vitro anti-microbial activity against different strains of bacteria and fungi at 100, 150, and 250µg/mL showed in the tables 3, 4. From the anti-microbial data it was found that compounds IVa, IVb, IVe, IVf, IVh, Va, Vb, Ve, Vf andVh were showed more zone of inhibition compare to standard. Compounds with meta and para substitution was showed more antimicrobial activity. Similarly *in-vitro* antioxidant activity was determined by DPPH method. The compounds IVa, IVb, IVe, IVf, IVh, Va, Vb, Ve, Vf and Vh was showed more potency. But from the IC_{50} value it was found that thiazolidine-4-one derivatives have more activity compared to azetidine-2-one.

The acute toxicity study was performed. The study was showed that at 10 mg/kg body weight the compounds were nontoxic. After fixation of dose the analgesic activity (hot immersion), CNS depressant activity (Actophotometer) and antidiabetic activity (STZ induced method) were determined.

Locomotor activity was considered as basic parameter for CNS acting drug which was an index of wake fullness of mental activity. CNS depressant activity was measured by actophotometer. usuing chlorpromazine as standard. The analgesic activity of the compounds were determined using morphine as standard but out of all the compounds IVa, IVb, IVe, IVf, IVh, Va, Vb, Ve, Vf and Vh was showed more potent CNS depressant and analgesic activity.

The antidiabetic activity was performed by using STZ induced model in Rat. Blood glucose level in rats administered with 2g/kg glucose was significantly decreased by test compounds with in 1 hour as compare to standard glibenclamide. Treatment with compounds showed that there was significant fall of blood glucose level compared to standard glibanclamide on 21 day of study. Diabetes was also characterized by severe loss of body wt. On 21 day of treatment it was found that there was significant gain of body wt. specially the rat treated with test compounds. The biochemical parameter was investigated for synthesized compound. From the study it was found that serum cholesterol, triglyceride, creatinine, urea levels are decreased significantly where as the HDL level and total protein levels are found to increase after 21 days treatment. But out of all the compounds tested IVa, IVb, IVe, IVf, IVh, Va, Vb, Ve, Vf and Vh was more significant hypoglycemic effect but there was no significant effect found in case of normoglycemic rat.

As per proposed Scheme1 there was around 20 compounds synthesized. From the antimicrobial, antioxidant and pharmacological investigation it was found that out of all the compounds IVa, IVb, IVe, IVf, IVh, Va, Vb, Ve, Vf and Vh was more active. The furan molecule itself did not show any biological efficacy where compound IVa-j and Va-j was showed good efficacy. This may be due to presence of azetidine-2-one and thiazolidine-4-one nucleus. Again from the biological structure it was also found that phenyl ring substitutions have great effect on biological activity. In compounds IVa, IVb, IVe, IVf, IVh, Va, Vb, Ve, Vf and Vh substitution on phenyl ring at meta and para position with electron donating group showed potent activity, especially anti-microbial, antioxidant, analgesic and CNS depressant activity. But in respect to anti-diabetic activity the compounds Va, Vb, Ve, Vf and Vh was showed more potent anti-diabetic profile, due to presence of thiazolidine-4-one nucleus as well as para and meta substitution of phenyl ring.

CONCLUSION

The synthesis of 4-(furan-2-yl)-1-phenylazetidin-2-ones (IVa-j) and 4-(furan-2-yl)-1-phenyl thiazolidine-4-ones (Va-j) were confirmed by spectral and elemental analysis From the antimicrobial, antioxidant and pharmacological investigation it was found that out of all the compounds 1-(4-Chlorophenyl)-4-(furan-2-yl)azetidin-2-one (IVa); 1-(4-Bromophenyl)-4-(furan-2-yl) azetidine-2-one (IVb);1-(3, 4-Dichloro phenyl)-4-(furan-2-yl)azetidin-2-one (IVe);1-(3,4-Difluoro phenyl)-4-(furan-2-yl)azetidin-2-one (IVf);1-(3-Chloro-4-fluorophenyl)-4-(furan-2-yl)azetidin-2-one (IVh);3-(4-Chlorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Va);3-(4-Bromophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vb); 3-(3,4-Dichlorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Ve); 3-(3,4-

Difluorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vf);3-(3-Chloro-4-fluorophenyl)-2-(furan-2-yl)-thiazolidine-4-one (Vh) were biologically active. This may be due to presence of azetidine-2-one and thiazolidine-4-one nucleus present along with furan ring. Again from the biological evaluation it was also found that substitution on phenyl ring at meta and para position was showed potent activity especially anti-microbial, antioxidant, analgesic and antidepressant activity. But compounds with thiazolidine-4-one nucleus were showed more potent anti diabetic profile compared to azetidin-2-one nucleus containg compounds.

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REFERENCES

Arslan S, Log Glu F and Oktermer A (2006). Anti-microbial activity studies on some piperidine and pyrrolidine substituted halogenobenzene derivatives. *J. Enzyme Inhib. Med. Chem.,* **21**: 211-214.

Bair MJ, Robinson RL, Katon W and Kroenke K (2003). Depression and pain comorbidity: A literature review. *Arch. Intern. Med.,* **163**: 2433-2445,

Bakker J, Gommers FJ, Nieuwenhuis I and Wynberg H (1979). Photoactivation of the nemat ocidal compound alpha-terthienyl from roots of marigolds (tagetes species) possible singlet oxygen role. *J. Biol. Chem.,* **254**: 1841-1844.

Beers SA, Malloy EA, Wu W, Wachter M, Ansell J, Singer M, Steber M, Barbone A, Kirchner T, Ritchie D and Argentieri D (1997). N-(5-Substituted Thiophene-2-alkyl sulfona mide as potent inhibitors of 5-lipoxygenase. *Bioorganic and Medicinal Chemistry Letters,* **5**: 779-786.

Brand Willams W, Cuvelier ME and Berset C (1995). Use of a free radical method to evaluate anti-oxidant activity. *Lebensmittel-Wissenschaft and Technologie*, **28**: 25-30.

Burstein M, Scholnick HR and Morfin R (1970). Rapid method for the isolation of lipoprotein from human serum by precipitation with polyamines. *J. Lipid Res*., **11**: 583-595.

Chan GFQ, Towers GHN and Mitchell JC (1975). Ultraviolet-mediated anti-obiotic activity of thiophene compounds of Tagetes. *Phytochemistry*, **14**: 2295-2296.

Dalvie DK, Kalgutkar AS, Khojasteh Bakht CS, Scott Obach R and Donnell PO (2002). Biotransformation reactions of five membered aromatic heterocyclic rings. *Chem. Res. Toxicol.,* **15**: 269-299.

Dhingra D and Sharma A (2006). Antidepressant like activity of Glycyrrhiza glabra. *Progress in Neuropsycho pharmacol and Biological Psychiatry,* **30**: 449-454.

Espin JC, Soler Rivas C and Wichers HJ (2000). Characterization of total free radical scavenger capacity of vegetableoils and oil fraction using 2, 2-diphenyl-1picrylhydrazyl radical. *J. Agric. Food Chem.,* **48**: 648-656.

Fajans SS, Cloutier MC and Crowther RL (1997). Clinical and etiological heterogeneity of idiopathic diabetes mellitus (Banting Memeoral Lecture). *Daibetes,* **7**: 1112-1125.

Hudson JB, Graham EA, Miki N, Towers GHN, Hudson LL, Rossi R, Carpita A and Neri D (1989). Photoactive anti-viral and cytotoxic activities of synthetic thiophenes and their acetylenic derivatives. *Chemosphere,* **19**: 1329-1343.

Ira J. Goldberg (2001). Diabetic Dyslipidemia: Causes and Consequences The Journal of Clinical Endocrinology & Metabolism. *JCEM*., **86**: 965-971.

Iyengar S, Arnason JT, Philogene BJR, Murand P, Werstink NH and Timmins G (1987). Toxicokinetics of the phototoxicallelo chemical alpha-terthienyl in 3 herbivorous Lepidoptera. *Pestic. Biochem. Phys.,* **29**: 1-9.

Joshi Nirmal MD, Gregory M and Caputo MD (1999). Primary care: Infections in with diabetes mellitus. *N. Engl. J. Med.,* **341**: 1906-1912.

Kadnur SV and Goyal RK (2005). Comparitive antidiabetic activity of methanolic extract and ethyl acetate extract of Zingiber officinale Roscoe. *Indian J. Pharm. Sci.,* **67**: 453-457.

Keay BA and Dibble PW (1996). *In Comprehensive Heterocyclic Chemistry*. Pergamon Oxford, **2**: 395-436.

Li Y, Yang ZS, Zhang H, Cao BJ and Wang FD (2003). Artemisinin Derivatives Bearing Mannich Base Group: Synthesis and Antimalarial Activity. *Bio. Org and Med. Chem.*, **11**: 4363-4368.

Lopez F, Jett M, Muchowski JM, Nitzan D and Yang C (2002). Synthesis and biological evaluation of Keterolac analogs. *Heterocycles*, **56**: 91-97.

Mac Donald RP (1953). *Standard methods of clinical chemistry*. New York, Academic press, 215-222.

Malmstrom J, Jonsson M, Cotgreave IA, Hammarstro ML, Sjodin M and Engmann L (2001). The anti-oxidant profile of 2, 3dihydrobenzo[b]furan-5-ol and its 1-thio, 1-seleno and 1-telluro analogues. *J. Am. Chem. Soc.,* **123**: 3434-3440.

Matsuura H, Saxena G, Farmer SW, Hancock REW and Towers GHN (1996). Anti-bacterial and anti-fungal polvine compounds from Glehnia littoralis ssp. *leiocarpa. Planta Med.,* **62**: 256-259.

Mazze RS, Lucido D and Shamoon H (1984). Psychological and social correlates of glycemic control. *Diabetes Care,* **7**: 360-366.

Meotti FC, Silva DO, Santos ARS, Zeni G, Rocha JBT and Nogueira CW (2003). Thiophenes and furans derivatives: A new class of potential pharmacological agents. *Environmental Toxicology and Pharmacology,* **37**: 37-44.

OECD. Guidelines No. 423 for the testing of chemicals revised draft guideline 423 (acute oral toxicity). Paris: *OECD*; 2000.

Patel R, Shervington A, Pariente JA, Martinez-Burgos MA, Salido GM, Adeghate E and Singh J (2006). Mechanism of exocrine pancreatic insufficiency in streptozotocin-induced type 1 diabetes mellitus. *Annals of the New York Academy of Sciences,* **1084**: 71-88.

Rifaci N, Bachorik PS and Albers JJ (1999). Lipid, lipoprotein and apolipoprotein. *ln*: Burtis CA and Ashwood ER, *Tretz text book of clinical chemistry,* third edition, WB Saunder company, Philadolphia. Pp.809-861.

Sadhu SK, Okuyama E, Fujimoto H and Ishibashi M (2003). Separation of Leucas aspera, a medicinal plant of Bangladesh, guided by prostaglandin inhibitory and antioxidant activities. *Chem. Pharm. Bull.*, **51**: 595-598.

Sewell RDE and Spencer PSJ (1976). Anti-nociceptive activity of narcotic agonist and partial agonist analgesics and other agents in the tail-immersion test in mice and rats. *Neuropharmacology*, **15**: 683-688.

Testa MA and Simonson DC (1998). Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus. *JAMA*, **280**: 1490-1496.

Thomas L (1998). Clinical Laboratory Dragnostics, TH book Verlasgesell schaft 1st edition, Frankfurt, pp.208-214, 366-374.

Toshihiro Suwa, Ikuya Shibata, Keita Nishino and Akio Baba (1999). Synthesis of nitrogen heterocycles by intramolecular Michael Type of amination via reduction of imines with Di-n-butyliodotin Hydride (n-Bu2SnIH), *Org. Lett.*, **1**:1579-1581.

Tretz NW (1986). *Text book of clinical chemistry*, WB Saumder Company, 3rd edition Philadelphia, p.579.

Varley H, Gowenlock AH and Masvice B (1993). Practical *clinical biochemistry. Heinemann medical book.* London: William Heinemann Medical Books, pp.625-685.

Wilkinson JH, Boutwell JH and Winston S (1969). Evaluation of a New system for the kinetic measurement of serum alkaline phosphatase. *Clin. Chem.,* **15**: 487-495.

Yu L (2001). Free radical scavenging properties of conjugated linoleic acids. *J. Agric Food Chem.,* **49**: 3452-3456.

Zeni G, Lqdtke DS, Nogueira CW, Panatieri RB, Braga AL, Silveira CC, Stefani HA and Rocha JBT (2001). New aceylenic furan derivatives: Synthesis and anti-inflammatory activity. *Tetrahedron Letters*, **42**: 8927-8930.