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Synthesis, of 3-[3(2-Substituted aryl)-1,3-Thiazolidine-5-one]Thiazolylnaphtha-2H-1-Pyran-2-one as possible antihyperglycemic agents

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Abstract: 3-Acetylnaphtha-2H-1-pyran-2-one(I) was synthesized from 2-hydroxy-1-naphthaldehyde and acetoacetate in presence of catalytic amount of piperidine.The reaction of 3-Acetylnaphtha-2H-1-pyran-2-one with Bromine in chloroform gave 3-Bromoacetylnaphtha-2H-1-pyran-2-one(II).Compound II was refluxed with thiourea in ethanol and amyl alcohol to get 3-[(3-Amino)thiazolylnaptha-2H-1-pyran-2-one (III), which when reacted with eight different aldehydes gave the Schiff's bases of 3-[(3-Arylidiene)]-thiazolylnaphtha-2H-1-pyran-2-one.(IV).These Schiff's bases were then cyclized to get the title compounds by reacting with thioglycollic acid in DMF using zinc chloride.All the synthesized compounds were characterized based on their IR,^{1}H NMR and mass spectral analysis.These compounds were evaluated for their antihyperglycemic activity by *invivo* Alloxan induced diabetic mice model. Only three compounds were showed the antihyperglycemic activity compared to standard Pioglitazone.
Keywords: Synthesisof 3-[3(2-Substituted aryl)-1,3-Thiazolidine-5one]Thiazolylnaphtha-2H-1-Pyran-2-one as possible antihyperglycemic agents.

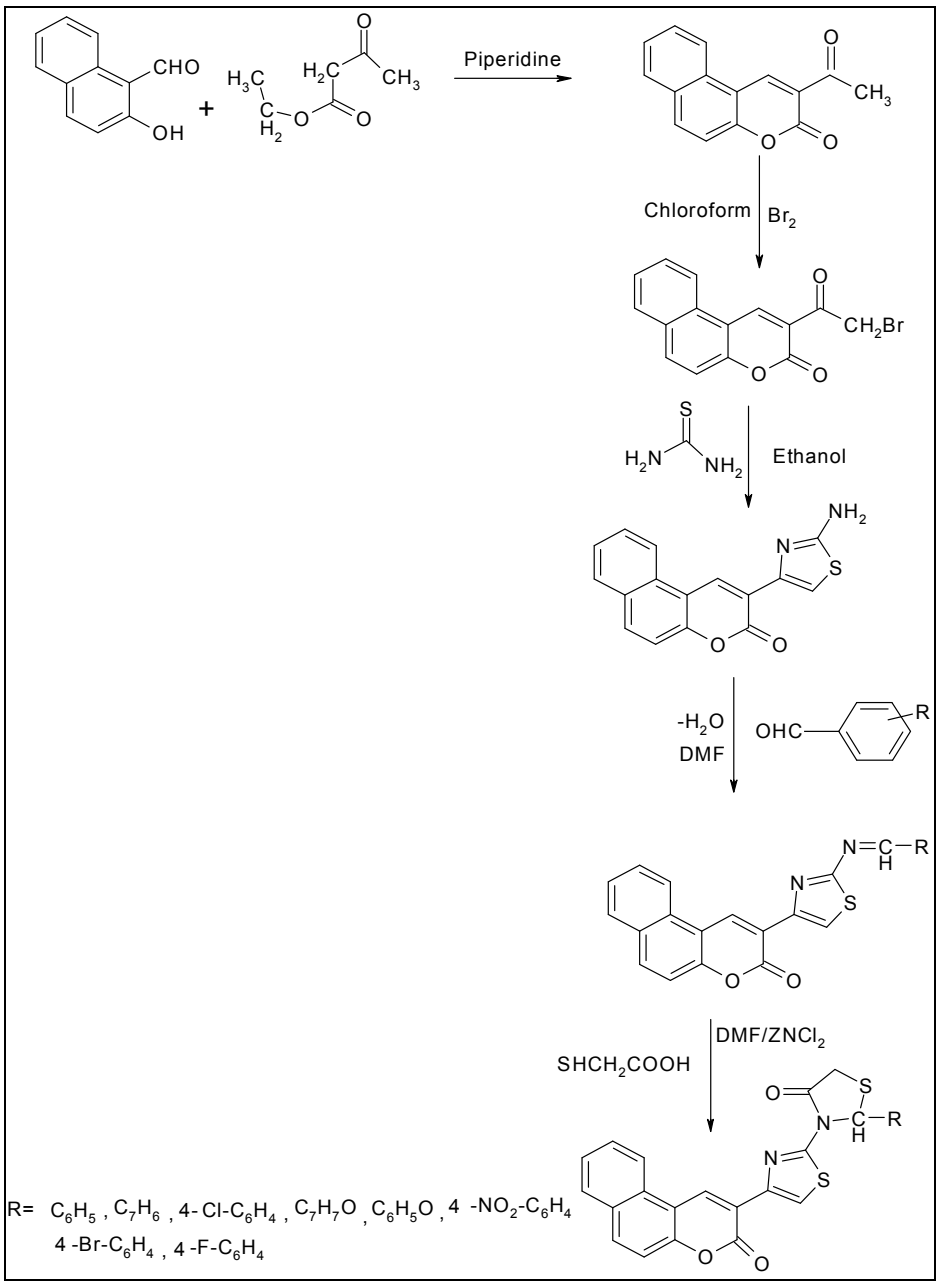
Introduction:

Non-Insulin dependent diabetes mellitus (NIDDM) is a chronic and devastating disease characterized by hyperglycemia, insulin resistance, perturbations in fat, protein and carbohydrate metabolism[1]. Diabetes mellitus is the root cause of several chronic and progressive diseases that adversely affect a number of organs including the nervous and vascular system. Diabetes is a chronic condition described as heterogenous group of disorders characterized by varying degrees of insulin secrection and or insulin insensitivity. Regardless of cause, it is associated with hyperglycemia.

Diabetes is a major and growing public health problem throughout the world, with an estimated worldwide prevalence in 2000 of 150 million people, expected to rise to 220 million people by 2010[2].

Thiazolidinone derivatives have been reported to possees various biological activities such as antibacterial[3], neurotoxicity[4], anticonvulsant[5] and antidiabetic activity[6,7]. With the view to study antihyperglycemic activiwe, have synthesized some thiazolidinone derivatives and screened them for antihyperglycemic activity by *in-vivo* by alloxan induced model. Keeping these facts in view, synthesis of some thiazolidinone bearing Naphtha-pyrazone have been undertaken.

Scheme:



Materials and methods

Chemicals were supplied by E.Merck (Germany) and S.D. fine chemicals (India). Melting point were determined by open tube capillary method and are uncorrected. Purity of the compounds were checked on thin layer chromatography (TLC) plates (Silica gel G) in the solvent system Hexane : Ethyl acetate (1:1), the spots were located under iodine chamber. IR Spectrums were obtained on a Shimadzu 1320 FT-IR spectrometer (KBr pellets). ^{1}H NMR spectra were recorded on DMM X-200 MH_Z Astrazeneca Ind. Ltd cm^{-1} and chemical shift (δ) are reported in parts per million downfield from standard reference Tetramethylsaline(TMS).

Synthesis of 3-Acetylnaphtha-2H-1-pyran-2-one (I)[3]
To a cooled suspension of a mixture of 2-Hydroxy-1-naphthaldehyde(0.5mol) and ethyl acetoacetate (0.5mol) piperidine (10ml) was added with shaking. The mixture was then maintained at freezing temperature overnight in deep freezer. Yellow colored lumps formed were broken in cold ethanol, filtered and

recrystallized from hot glacial acetic acid to get needle shaped crystals.
IR spectrum showed the characteristic Absorption peaks at (cm^{-1}): 3037 (Ar,C-H), 1722 (lactone C=O), 1600 (C=O) and 1211 (C-O-C).

Synthesis of 3-Bromoacetylnaphtha-2H-1-pyran-2-one (II)
To 3-Acetylnaphtha-2H-1-pyran-2-one I (0.1mol) in alcohol free chloroform (40ml), bromine (20ml, 0.3mol) was added with intermittent shaking and warming. The mixture was heated to boiling for fifteen minutes on a waterbath, cooled and filtered. The solid was washed with ether and recrystallized from glacial acetic acid.
IR Spectrum showed the characteristic Absorption peaks at (cm^{-1}) 3012 (Ar, C-H), 1635 (lactone C=O), 1597 (C=O), 1309 (C-O-C) and 792 (C-Br).

Synthesis of 3-[(3-Amino)thiazolylnaphtha-2H-1-pyran-2-one (III)[10]
The 3-Bromoacetylnaphatha-2H-1-pyran-2-one **II**, (0.1mol) was dissolved in hot acetic anhydride (20ml) with thiourea (0.03mol). A mild exothermic reaction took place giving a clear solution that soon deposited crystals. The deposits were removed, washed with ethanol and boiled with water containing sodium acetate which was recrystallized from ethanol. IR Spectrum showed the characteristic Absorption peaks at (cm^{-1}): 3412 (NH_2), 3028 (Ar,C-H), 1720 (lactone C=O), 1691 (C=O), 1554 (C=N), 1213 (C-O-C),and 750 (C-S-C Thiazole). ^{1}H NMR (DMSO-d_6) : 5.1 (S, 2H, NH_2), 6.9 (S, 1H, thiazole) and 7.4-8.3 (m, 7H, Ar H)

Synthesis of 3-[(3-Arylidine)]thiazolylnaphtha-2H-1-pyran-2-one (IV)[11]
The compound **III** (0.01 mol) was dissolved in DMF and various aryl aldehydes (0.01mol) were added and heated under reflux for 8hr, cooled and poured into crushed ice to yield compound **IV**.The crude product that seperated out was filtered anr recrystallised from ethanol. IR Spectrum showed the characteristic Absorption peaks at (cm^{-1}) : 3068 (Ar,C-H), 1718 (lactone C=O), 1684 (C=O), 1556 (C=N), 1236 (C-O-C), 762 (C-S-C Thiazole).
^{1}H NMR (DMSO- d_6) : 7.0(S,1H, Thiazole), 7.6-8.6 (m, 12H, ArH) and 8.7 (S, 1H, CH = N)

Synthesis of 3-[(2-Substituted aryl)1, 3-thiazolidine-5-one] thiazolylnaphtha-2H-1-pyran-2-one. (V)[12]
1ml(0.01mol) of Thioglycolic acid and a catalytic amount of dry Zinc chloride was added to a solution of arylidene in DMF (15ml). The reaction mixture was refluxed for 10 hr, cooled and poured into sodium bicarbonate solution to remove unreacted thioglycollic acid. The residue was filtered dried and recrystallized from ethanol.
IR Spectrum showed the characteristic Absorption peaks at (cm^{-1}): 3199 (Ar,C-H), 1718 (lactone C=O), 1691 (C=O), 1554 (C=N), 1228 (C-O-C) and 750 (C-S-C Thiazole). ^{1}H NMR (DMSO- d_6) 3.3(d,1H, -CH-), 4.1(S, 2H,-CH_2-), 7.0 (S, 1H, Thiazole) and 7.3-8.5 (m,7H,ArH).

Table-1: Physical and analytical data of 3-[3(2-Substituted Aryl)-1, 3-thiazolidine-5--one]thiazolynaptha-2H-1-pyran-2-one.

Cpd. No.	Substituents (Ar)	Molecular Formula	MP (^oC)	Yield (%)
A	C_6H_5	C_7H_6O	232	70.2
B	C_7H_6	C_9H_8O	239	67.1
C	C_6H_4Cl	C_7H_5ClO	230	69.3
D	C_7H_7O	$C_8H_8O_2$	222	72.1
E	C_6H_5O	$C_7H_6O_2$	236	71.2
F	$C_6H_4NO_2$	$C_7H_5NO_3$	145	65.4
G	C_6H_4Br	C_7H_5BrO	150	68.1
H	C_6H_4F	C_7H_5FO	>250	64.7

ANTIHYPERGLYCEMIC ACTIVITY

Table : 2

Percentage change in SG level of 1a-1h in alloxan induced diabetic rats

Percentage change in SG at hr					
Comp	**0 hr**	**2 hr**	**4 hr**	**6 hr**	**24 hr**
Control	94.83±3.13	98.67±1.76	96.33±2.70	96.67±3.33	97.5±2.12
Pioglitazone	408.3±41.18	297±30.43**	218.3±8.72**	183.3±10.54**	81.33±15.31**
1a	366.7±43.18	403.3±50.51	421.7±44.45	443.3±37.83	495.0±39.73
1b	431.7±57.47	458.3±53.75	493.3±50.57	516.7±39.47	536.7±33.33
1c	443.3±39.30	333.3±30.64**	232.7±15.16**	134.0±12.06**	90.50±4.03**
1d	419.8±30.57	317.0±29.82**	227.7±9.52**	175.2±7.74**	96.0±4.20**
1e	465.2±40.07	463.3±40.88	450.0±31.52	495.0±32.94	550.0±15.92
1f	405.8±77.46	461.7±24.42	475.8±11.86	490.0±12.91	520.0±25.43
1g	468.3±31.98	357.5±22.20**	270.0±18.93**	173.3±15.63**	93.50±4.43**
1h	426.7±36.94	458.3±27.62	495.0±26.04	533.3±21.71	565.0±16.28

All values are expressed as means ± S.E.M

*significance compared to 0hrs p<0.05, p<0.01, p<0.00

Results and Discussion.

The synthesized compounds were evaluated to determine their ability to decrease serum glucose(SG) level by alloxan induced diabetic rat model[8,9] at different time intervals. Albino rats of either sex (130-150gm) were used for the screening of antidiabetic activity and were suggested into control, standard and test groups, of six animals each. The test compounds and the standard drug were administered orally to the animals and the results were expressed as percentage change in SG level and compared with that of 0hr reading.

The test compounds (homogenized suspension in 1% acacia) and standard (pioglitazone solution) were administered orally to the animals. The readings were taken at different intervals by using blood Glucose Meter (Lifescan Inc.Milpitas, CA 95035,0336,USA, One Touch Horizon) and compared with pioglitazone with 0 hr readings (Table-2). Compounds 1a, 1b, 1e, 1f and 1h did not show decrease in SG levels, while Compounds 1c, 1d and 1g exhibited significant decrease in SG levels significantly ($p<0.01$ for 100mg/kg).

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