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RESEARCH ARTICLE

Design, Synthesis and Biological Evaluation of Some Novel Substituted Thiazolidinone Derivatives as Potent Antihyperglycemic Agents

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ABSTRACT

The main obejcetive of this study is to synthesize 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1-TM_{10}) from 1-acetyl naphthalene. The synthesized compound, characterized on the basis of satisfactory analytical and spectral (IR, H^1NMR, Mass) data, have shown moderate to good antidiabetic activity.

KEYWORDS

Antihyperglycemic activity, 1-Acetylnaphthalene, Thiazoles, Thiazolidinones.

INTRODUCTION

Thiazolidinone are an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. The nucleus is also known as wonder nucleus [1] because it gives out different derivatives with all different types of biological activities. Literature survey reveals that 4-thiazolidinones are usually synthesized starting from thiourea [2-4], thiosemicarbazides [5] and azomethines [6]. Thiazolidinones have been synthesized and screened for possible antimicrobial activity [7-11] moreover; thiazolidinones have a broad spectrum of pharmacological properties like anti HIV [12], antipsychotic [13], anticonvulsant [14] and antitubercular [15] activity. The β-lactams also serve as synthons for many biologically important classes for many biologically important classes of organic compounds [16].

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Due to this, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists.

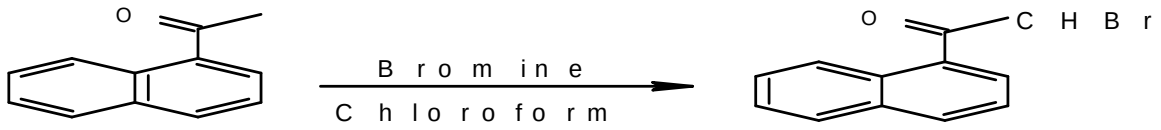
MATERIALS AND METHOD

Chemicals and Reagents

1-acetylnaphthalene, chloroform, bromine, Substituted benzaldehyde thio semicarbazones, ethanol, thiolactic acid, thioglycolic acid, dioxane, zinc chloride.

Method of Synthesis

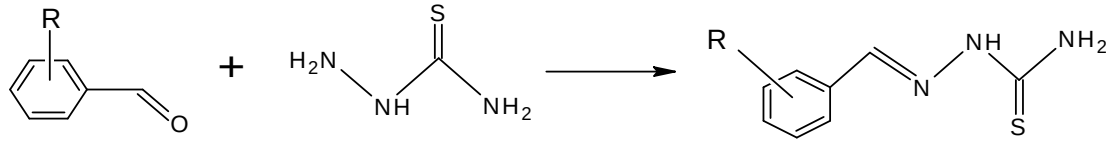
Synthesis of 1-bromoacetyl naphthalene: 1-Acetylnaphthalene (0.02 moles) was taken in 20 mL of chloroform in a 250 mL conical flask. A solution of bromine (0.04 moles) in chloroform was prepared. The bromine solution was added to flask containing 1-acetylnaphthalene solution, drop wise with stirring. The chloroform mixture was distilled on a water bath. The solid obtained was washed with petroleum ether and then recrystallized from benzene yielding 1-bromoacetyl naphthalene.



Synthesis of Substituted Thiosemicarbazone:

A solution of 0.05 mol. Substituted benzaldehyde in warm alcohol (300 ml) and a solution of 0.05 mol thiosemicarbazide in 300 ml water were mixed slowly. The product, which separated, was filtered off after cooling and recrystallised from ethanol. Other thiosemicarbazones were prepared in the same way.

Synthesis of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1-TM_{10}): A mixture of respective thiazole derivative (0.01 mole) and thiomalic acid (0.015 mole) in 25 mL of dioxane was taken in a 100 mL round bottom flask. To this solution 25 mg of $ZnCl_2$ was added and the reaction mixture was refluxed for 6-10 h.



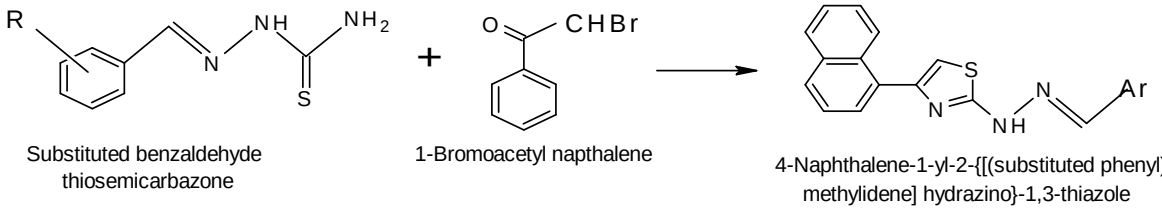
Substituted Benzaldehyde | Thiosemicarbazide | Substituted benzaldehyde thiosemicarbazone

Synthesis of 4-naphthalen-1-yl-2-{2-[(substituted phenyl) methyl idene] hydrazino}-1, 3- thiazole: Equimolar quantities (0.01 mole) of 1- bromoacetylnaphthalene and substituted benzaldehyde thiosemicarbazones were dissolved in 50 mL of ethanol in a 100 mL round bottom flask. The reaction mixture was refluxed for 1-2 h. A solid was separated during refluxing which was hot filtered, dried and recrystallized from ethanol yielding 4-naphthalen-1-yl-2-{2- [(substituted phenyl) methylidene] hydrazino}- 1,3-thiazole.

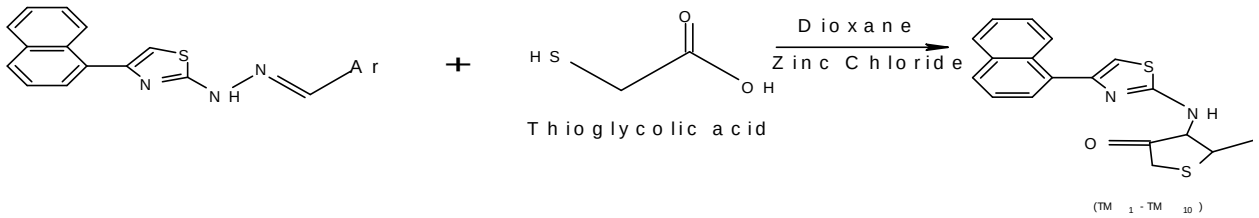
The mixture was then poured on crushed ice and solid so obtained was filtered, washed with water, dried and recrystallized from dioxane.

The purity of the compounds was established on the basis of TLC.

Compound [TM_1]: Preparation of 2-(4-nitrophenyl)-3-[(4-(1naphthyl) -1, 3-thiazol-2-yl} amino]-5-methyl-1, 3- thiazolidin-4-one. **IR Spectra:** 3243.54 (N-H), 1697.68 (C=O), 1613.32 (C=N), 1543.84 (C=C), 1512.04, 1441.30 and 1042.02 (Characteristic of thiazole



Substituted benzaldehyde thiosemicarbazone | 1-Bromoacetyl napthalene | 4-Naphthalene-1-yl-2-{[(substituted phenyl) methylidene] hydrazino}-1,3-thiazole



Thioglycolic acid

(TM_1 - TM_{10})

nucleus). **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3), 4.79 (q, 1H, -CH-S-), 6.45 (s, 1H, -N-CH-), 7.35 (s, 1H, Ar-H), 7.42 (d, J=12Hz, 2H, Ar-H), 7.56 (m, 2H, Ar-H), 7.67 (m, 4H, Ar-H), 7.97 (d, J=12Hz, 1H, Ar-H), 8.07 (d, J=12Hz, 1H, Ar-H), 8.21 (d, J=12Hz, 1H, Ar-H), 8.92 (s, 1H, NH). **Mass (m/z):** 462(M^+, $C_{23}H_{18}N_4O_3S_2$), 181 (100%, $C_7H_5N_2O_2S$), 154 ($C_{11}H_8N$), 70 (C_3H_4NO), 57 (C_3H_5O).

Compound [TM$_2$]: Preparation of 2-(3-chlorophenyl)-3-[{4-(1naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3- thiazolidin-4-one **IR Spectra:** 3251.03 (N-H), 1696.48 (C=O), 1617.56 (C=N), 1539.30 (C=C). 1516.60. 1440.04 and 1037.94. **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3) 4.79 (q, 1H, -CH-S-), 6.69 (s, 1H. -N-CH-), 7.24 (m, 4H, Ar-H), 7.66 (m, 5H, Ar-H), 7.94 (d, J=12Hz, 1H, Ar- H), 8.11 (d, J=12Hz, 1H, Ar-H), 8.21 (d, J=12Hz, 1H, Ar-H), 8.97 (s, 1H, NH).

Compound [TM$_3$]: Preparation of 2-(4-chlorophenyl)-3-[{4-(1naphthyl)-1,3-thiazol-2-yl} amino]-5-methyl-1,3- thiazolidin-4-one **IR Spectra:** 3252.84 (N-H), 1700.02 (C=O), 1613.66 (C=N), 1541.92 (C=C), 1515.15, 1452.48 and 1040. 10. **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3), 4.78 (q, 1H, -CH-S-), 6.45 (s, 1H, -N-CH-), 7.28 (m, 5H, Ar-H), 7.59 (m, 4H, Ar-H), 7.95 (d, J=12Hz, 1H, Ar-H), 8.11 (d, J=12Hz, 1H, Ar-H), 8.22 (d, J=12Hz, 1H, Ar-H), 8.90 (s, 1H, NH). **Mass (m/z):** 452 ($M^{+\cdot}$, $C_{23}H_{18}N_3S_2OCl$), 453 (M^+ +1), 170 (100%, C_7H_5NSCl), 155 (C_7H_4SCl), 127 ($C_{10}H_7$), 99 ($C_3H_3N_2S$).

Compound [TM$_4$]: Preparation of 2-(2, 4-dichlorophenyl)-3-[{4- (1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1,3-thiazolidin-4-one. **IR Spectra:** 3248.44 (N-H), 1694.06 (C=O), 1617.74 (C=N), 1542.92 (C=C), 1515.16, 1452.78 and 1038.66. **^{1}HNMR [δ ppm]:** 1.36 (d, J=8Hz, 3H, CH_3), 4.79 (q, 1H, -CH-S-), 6.75 (s, IH, -N-CH-), 7.08 (d, J-12Hz, 2H, Ar-H), 7.33 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.58(m, 4H, Ar-H), 7.92 (d, J=12Hz, 1H, Ar-H), 8.12 (d, J=12Hz, 1H, Ar-H), 8.22 (d, J=12Hz, 1H, Ar-H), 8.96 (s. 1H, NH).

Compound [TM$_5$]: Preparation of 2-(2, 6-dichloro phenyl)-3-[{4- (1 -naphthyl) - 1, 3-thiazol-2-yl} amino] -5 -methyl – 1, 3-thiazolidin-4-one. **IR Spectra:** 3248.04 (14-H), 1693.88 (C=O), 1610.65 (C=N), 1541.06 (C=C), 1515.15, 1438.64 and 1040.25 **^{1}HNMR [δ ppm]**: 1.36 (d, J=8Hz, 3H, CH_3), 4.76 (q, 1H, -CH-S-), 6.77 (s, 1H. -N-CH-), 7.54 (m, 8H, Ar-H), 7.95 (d. J=12Hz, 1H, Ar-H), 8.12 (d, J=12Hz, 1H, Ar-H), 5.24 (d, J=12Hz, 1H, Ar-H), 8.95 (s, 1H, NH).

Compound [TM$_6$]: Preparation of 2-(3-fluorophenyl)-3-[{4-(1-naphthyl)-1,3-thiazol.-2-yl} amino], -5-methyl-1, 3- thiazolidin-4-one. **IR Spectra:** 3251.66 (N-H), 1694.83 (C=O), 1615.18 (C=N), 1542.56 (C=C), 1514.20, 1451.92 and 1039.08. **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3), 4.79 (q, 1H, -CH-S-), 6.50 (s, 1H, -N-CH-), 6.89 (s, 1H, Ar-H), 7.16 (m, 2H, Ar-H), 7.32 (s, 1H, Ar-H), 7.62 (m, 5H, Ar-H), 7.96 (d, J= 12Hz, 1H, Ar-H), 8.08 (d, J= 12Hz, 1H, Ar-H), 8.23 (d, J=12Hz, 1H, Ar-H), 8.92 (s, 1H, NH).

Compound [TM$_7$]: Preparation of 2-(2-hydroxy-4-bromophenyl) - 3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5- methyl- 1,3-thiazolidin-4-one. **IR Spectra:** 3418.44 (O-H), 3239.96 (N-H), 1697.82 (C=0), 1616.38 (C=N), 1543.72 (C=C), 1515.15, 1440.02 and 1043.82. **^{1}HNMR [δ ppm]:** 1.34 (d, J=8Hz, 3H, CH_3), 4.79 (q, 1H, -CH-S-), 6.53 (s. 1H, -N-CH-), 7.12 (m, 3H, Ar-H), 7.33 (s, 1H, Ar-H), 7.59 (m, 4H, Ar-H), 7.97 (d, J=12Hz, lH, Ar-H), 8.13 (d, J=12Hz, 1H, Ar-H), 8.24 (d., J=12Hz, 1H, Ar-H), 8.97 (s, 1H, NH), 10.98 (s, 1H, OH). **Mass (m/z):** 512 ($M^{+\cdot}$, $C_{23}H_{18}N_3S_2O_2Br$), 514(M^- +2), 287 ($C_{10}H_9NO_2SBr$), 259 (C_9H_9NOBrS), 215 (C_7H_5NSBr), 57 (C_3H_5O).

Compound [TM$_8$]: Preparation of 2-(2-hydroxy-4-chlorophenyl) - 3-[{14-(1-naphthyl)-1,3-thiazol-2-yl}amino]-5- methyl-1,3-thiazolidin-4-one. **IR Spectra:** 3418.06 (O-H), 3249.50 (N-H). 1798.02 (C=0), 1616.20 (C=N), 1538.93 (C=C). 1509.48, 1436.88 and 1040.10. **^{1}HNMR [δ ppm]:** 1.37 (d. J=8Hz, 3H, CH_3), 4.77 (q, 1H, -CH-S-), 6.53 (s, 1H, -N-CH-), 6.98 (m, 3H, Ar-H), 7.35 (s, 1H, Ar-H), 7.62 (m, 4H,

Ar-H), 7.95 (d, J=12Hz- 1H, Ar-H), 8.09 (d, J=12Hz, 1H, Ar-H), 8.23 (d. J=12Hz, 1H, Ar-H), 8.99 (s, 1H, NH), 10.97 (s, 1H, OH).

Compound [TM_9]: Preparation of 2-(4-dimethylaminophenyl)-3- [{4-(1-naphthyl)-I, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-one. **IR Spectra:** 3247.88 (N-H), 1698.04 (C=0), 1616.42 (C=N), 1543.30 (C=C), 1515.15, 1440.80 and 1043.76. **^{1}HNMR [δ ppm]:** 1.33 (d. J=8Hz, 3H, CH_3), 3.01 (s, 6H, CH_3), 4.79 (q. 1H, -CH-S-), 6.39 (s, 3H, Ar-H, -N-CH-), 7.10 (d, J=12Hz, 2H, Ar-H), 7.35 (s, 1H, Ar-H), 7.62 (m, 4H, Ar-H), 7.95 (d, J=12Hz, 1H, Ar-H), 8.08 (d, J=12Hz, 1H, Ar-H), 8.26 (d, J= I 2Hz, 1H, Ar-H), 8.93 (s, 1H, NH). **Mass (m/z):** 460 (M^+, $C_{25}H_{24}N_4OS_2$), 164 ($C_9H_{10}NS$), 154 (100%, $C_{11}H_8N$), 120 ($C_8H_{10}N$), 88 (C_3H_6NS), 44 (C_2H_6N).

Compound [TM_{10}]: Preparation of 2-(4-methoxyphenyl)-3-[{4-(1-naphthyl)-1,3-thiazol-2-yl}amino]-5-methyl-1,3- thiazolidin-4-one. **IR Spectra:** 3247.72 (N-H), 1697.42

(C=O). 1613.82 (C=N), 1548.50 (C=C), 1515.13, 1441.35 and 1040.10. **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3), 1.65 (s, 3H, OCH_3), 4.80 (q, 1H, -CH-S-), 6.44 (s, 1H, -N-CH-), 7.24 (m, 5H, Ar-H), 7.58 (m, 4H, Ar-H), 7.93 (d, J=12Hz, 1H, Ar-H), 8.09 (d, J=12Hz, 1H, Ar-H), 8.25 (d, J= 12Hz, 1H, Ar-H), 8.95 (s, 1H, NH).

General Procedures: Melting points were determined in open capillaries and all uncorrected. IR spectra (KBr pellet technique) were recorded using a Perkin-Elmer 237 spectrophotometer. ^{1}HNMR spectra were recorded on bruker AM 400 instrument (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as a solvent. Chemical shifts are given in parts per million(ppm). Splitting patterns are designated as follows: S-Singlet, d-doublet, t-triplet, q-quartet and m-multiplet. Mass spectra (MS) were recorded on Shimadzu GC-MS operating at 70eV. All the synthesized compounds were purified by recrystallization. The reaction were followed up and the purity of compounds was monitored on pre-coated TLC plates and visualizing the spots in ultra violet light.

Pharmacological Studies

Table 1: Antihyperglycemic activity of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1-TM_{10}) in SLM model

Compound	%age blood sugar lowering activity ± SEM in SLM model (1000 $mgkg^{-1}$)	
	1hr	4hr
Pioglitazone	100.00 ± 9.54*	100.00 ± 6.00
TM_1	106.91 ± 6.64**	115.37 ± 8.55***
TM_2	93.26 ± 9.76	104.39 ± 7.72
TM_3	95.74 ± 9.44*	102.48 ± 7.83
TM_4	111.218 ± 10.18*	117.82 ± 9.22**
TM_5	109.06 ± 07.07**	116.37 ± 8.13**
TM_6	105.04 ± 8.34**	110.53 ± 7.16**
TM_7	88.68 ± 8.43*	95.00 ± 5.90*
TM_8	110.93 ± 7.52**	115.34 ± 7.52**
TM_9	83.38 ± 8.126	92.17 ± 12.23
TM_{10}	101.97 ± 9.21*	107.23 ± 7.29*

*p<0.05, **p<0.01, ***p<0.001

Table 2: Antihyperglycemic activity of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1-TM_{10}) in alloxan model

Compound	%age blood sugar lowering activity ± SEM in Alloxan model (50 $mgkg^{-1}$)			
	24 Hr	72 Hr	120 Hr	168 Hr
Pioglitazone	100.00±19.74	100.00±18.54	100.00±18.09	100.00± 28.27
TM_1	106.52±44.19	113.82±39.57	132.11±16.99*	143.50±41.85***
TM_2	149.98±25.52	152.12±6.83**	180.88±3.65***	185. ±1.10***
TM_3	49.46±24.65	59.79±57.76	87.69±27.45	98.91±24.38
TM_4	106.52±21.67	110.63±19.18	131.95±23.29*	143.87±28.22
TM_5	41.31±18.915	56.38±28.37	84.62±20.12	95.59±19.05**
TM_6	134.24±28.40	141.69±10.83*	170.44±7.33***	180.79±2.69
TM_7	120.08±18.46	126.58±12.91*	156.41±8.38*	169.49±6.50***
TM_8	52.17±23.52	62.76±28.49	88.63±26.86	99.34±23.89
TM_9	117.38±16.48	121.70±7.00	154.14±4.88**	164.54±3.79***
TM_{10}	33.16±18.28	54.05±28.33	84.22±19.94	93.77±17.28

*p<0.05, **p<0.01, ***p<0.001

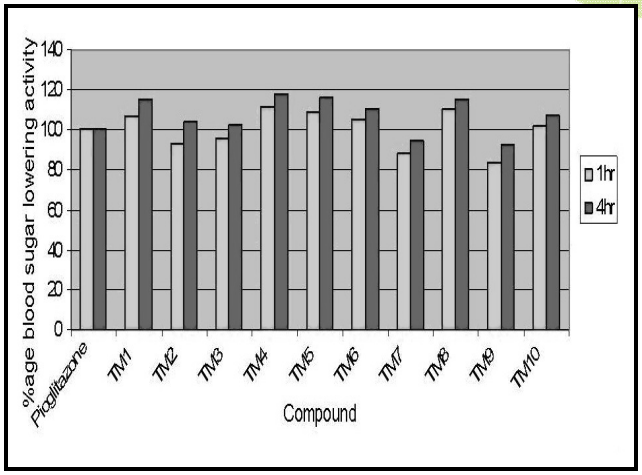


Figure 1: Antihyperglycemic activity of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1-TM_{10}) in SLM model

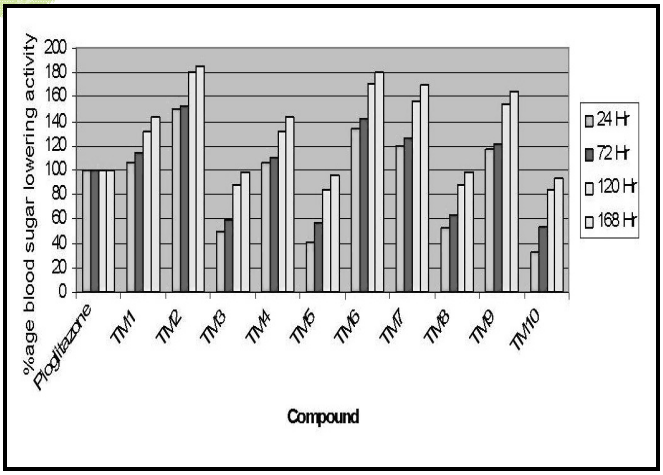
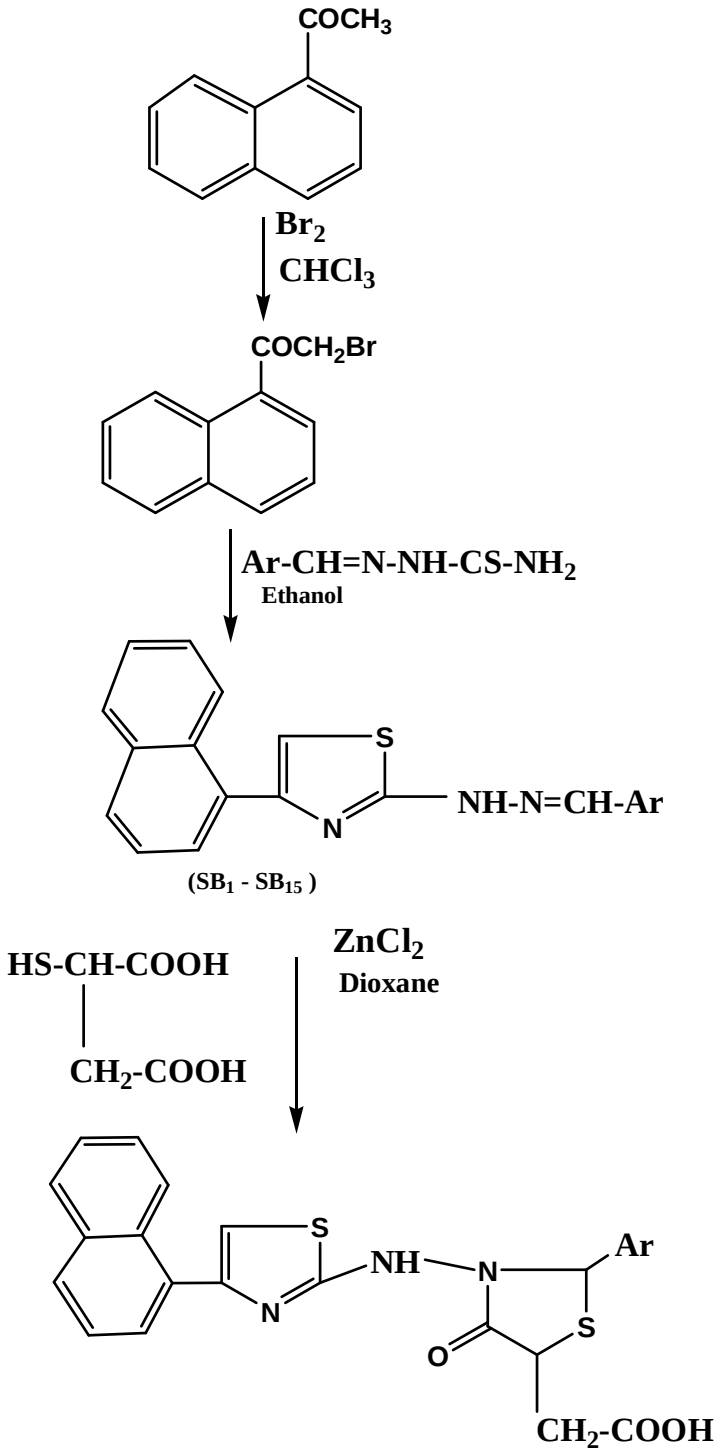


Figure 2: Antihyperglycemic activity of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1-TM_{10}) in alloxan model

REACTION SCHEME:



(TA_1- TA_{10})

Ar = Phenyl / Substitutedphenyl ring

RESULTS AND DISCUSSION

All the synthesized compounds were characterized on the basis of their IR, 1H NMR and elemental analysis. The study was aimed at evaluating the anticonvulsant effect of compounds on mice.

Antihyperglycemic Activity

The antihyperglycemic activity of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1-TM_{10}) was aimed at evaluating the antihyperglycemic effect of compounds on diabetic rats. Male Wistar albino rats weighing between 200-250 gm, 6 per group were used for study. All the drugs, including the standard drug pioglitazone were administered i.p. at 50 $mgkg^{-1}$ doses. The study was divided into two phases.

Phase-1 involved evaluation of blood glucose lowering ability of 2- (substituted phenyl)-3–[{4-(1 -naphthyl)- 1,3-thiazol-2-yl} amino]-5-methyl-1,3- thiazolidin-4 -ones (TM_1-TM_{10}) in normal rats in sucrose loaded model. It was observed that all the compounds exhibited very good antihyperglycemic activity by SLM. The compound TM_4 (Ar = 2, 4-dichlorophenyl) displayed highest antihyperglycernic activity by SLM model followed by TM_5 (Ar = 2,6-dichlorophenyl), TM_1 (Ar = 4-nitrophenyl) and TM_8 (Ar = 4-chloro-2- hydroxyphenyl).

Phase-II: Phase-II included the evaluation of blood sugar by alloxan model. It was observed that all the compounds showed more antihyperglycemic activity than pioglitazone on 7th day (168 hr) of study. It was also observed that blood glucose lowering effects were more pronounced and stronger in alloxan model. Two compounds, TM_2 (Ar = 3-chlorophenyl) and TM_6 (Ar = 3-fluorophenyl) displayed highest antihyperglycemic activity by alloxan model. It was followed by TM_7 (Ar = 4-bromo-2-hydroxyphenyl), TM_9 (Ar = 4-dimethylaminophenyl), TM_1 (Ar = 4-nitrophenyl) and TM_4 (Ar = 2, 4-dichlorophenyl).

CONCLUSION

From the above result it has been concluded that 2-(substituted phenyl)-3-[{4-(1-naphthyl) - 1, 3 -thiazo 1-2 –yl} amino] - 5 -methyl- 1, 3-thiazolidin-4 -ones (TM_1-TM_{10}) may be used as lead compounds for antihyperglycemic and may further be evaluated for toxicological profile.

REFERENCES

1. Mulay A, Ghodke M, Pratima NA, “Exploring potential of 4- thiazolidinone: A brief review”, International Journal of Pharmacy and Pharmaceutical Science, 2009, 1(1), 47-64.
2. Kalluraya B, Rahiman AM, David B, Isloor AM, Ganesh R, Indian J Het Chem 2000, 9, 217.
3. Ingale VS, Sawale AR, Ingale RD, Mane RA, Indian J Chem, 2001, 40B, 124.
4. Singh SR, J Indian Chem Soc, 1975, 52, 734.
5. Bhatt AH, Parikh KA, Parikh AR, Indian J Chem, 1999, 38B, 628.
6. Gadaginamath GS, Shyadigeri AS, Kavali RR, Indian J Chem, 1999, 38B, 156.
7. Dinesh B, Chirag S, Shweta S, Vijaykumar S, Talesara GL, Indian J chem., 2009, 48B, 1006.
8. Patil SG, Bagul RR, Swami MS, Hallale SN, Kamble VM, Kotharkar NS, Darade K, J. Chem. Pharm. Res., 2011, 3(3), 69.
9. Vagdevi HM, Vaidya VP, Latha KP, Padmashali B, Indian J Pharm Sci, 2006, 68(6), 719.
10. Patel D, Kumari P, Patel N, J. Chem. Pharm. Res., 2010, 2(5), 84.
11. Ahirwar M, Shrivastava SP, E-Journal of chemistry, 2011, 8(2), 931.
12. Barreca ML, Chimirri A, Luca L De, Monforte AM, Monforte P, Rao A, Zappala M, Balzarini J, Clercq E De, Pannecouque C, Witvrouw M, Bioorg. Med Chem Lett, 2001, 11, 1793.

13. Harib NJ, Jurcak JG, Bregna DE, Burgher KL, Hartman IB, Kafka S, Kerman LL, Kongsamut S, Roehr JE, Szewczal MR, Woods Kettelberger AT, Corbett R, J Med Chem, 1996, 39, 4044.
14. Gursoy A, Terzioglu N. Turk J Chem, 2005, 29, 247.
15. Ilango K, Aruankumar S, Rasayan J. Chem, 2010, 3(3), 493.
16. Singh GS, Mini-Rev. Med. Chem, 2004, 4, 93.