ORIGINAL RESEARCH

ISSN (O): 2349-5332
CODEN: IRJPHY

"SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SOME PYRIDINE DERIVATIVES"

Prabhat Sagar*, Avinash KKondalkar, Munesh Singh Bhadauriya, Muraree Lal, Shankar Singh
SUN INSTITUTE OF PHARMACEUTICAL EDUCATION ANDRESEARCH, LAHAR, BHIND M.P.

Submitted on: 11.03.2023; **Revised on:** 15.03.2023; **Accepted on:** 12.04.2023

ABSTRACT: In an effort to develop new potential molecules for the improving the health condition, a series of novel substituted pyridine analogues having TZD moiety were synthesized.With an orientation to utilize the information produced by the previous works, the synthesis of the novel pyridine derivatives having thiazolidinedione were carried out and the synthesized compounds were evaluated for their hypoglycaemic and hypolipidimic activities.

Characterizations of the synthesized compounds were carried out by determining their melting points, UV absorption maxima, IR spectra, Mass spectra, NMR spectra. The purity was checked by TLC.

The yield of all the synthesised compounds is found to be significant. The structural confirmation of the compounds is done by IR spectra, Mass spectra and NMR spectra.

The compounds were evaluated for antimicrobial activity by serial dilution method against gram positive and gram negative bacteria.

The results obtained may be helpful in designing a new potent molecule for treatment of bacterial infections. A detailed structure activity relationship study would be helpful in obtaining better antibacterial pyridine derivatives.

The general method known as Hantszch pyridine synthesis was used to prepare pyridine-one derivatives. The carboethoxy group of pyridine-one was converted to hydrazide & then this group was converted to an aromatic aldehyde derivative. The methylene group linker between the pyridine and 2-4 thiazolidinedione ring was synthesized by knoevenagel condensation of pyridine-aromatic aldehyde and 2,4-thiazolidinedione ring. Sodium acetate and glacial acetic acid were used as the reagents in this condensation. The Rf, melting point, yield, ^{1}H-NMR spectra, IR spectra & mass spectral values are all listed in the previous section. All the spectral data were in accordance with the presumed structure.

In ^{1}H-NMR spectra protons of pyridine and benzene ring were observed between 8-7 ppm benzylic proton were observed at 4.8-5.1 ppm & 1.2-3ppm. Other protons were also observed at derived values.

KEYWORD:-Norfloxacin**,** Pyridine derivative, Validation, Purification, Preparation, TLC.

Corresponding address: P. Sagar
Email: shankarbhaskar77@gmail.com

Indian Research Journal of Pharmacy and Science; 34(2023)2832-2841;
Journal Home Page: https://www.irjps.in

INTRODUCTION:

Organic chemistry and medicinal chemistry share a venerable common history. Many of the founders of organic chemistry had an intense interest not only in molecules from nature but also in the effects of synthetic compounds on living systems. With the development of series efficacious synthetic medicinal agents, a body of lore evolved concerning the molecular modifications that would most likely lead to biologically active molecules. The operational manipulations were still those of organic chemistry, as indeed were the molecules being modified; the emphasis of the work was subtly changed, however, from that of classic organic chemistry. The overriding goal became the creation of molecules that would alter some process in a living system. Tangentially, then, we approach an organic chemist's working definition of medicinal chemistry.

Role of Biology

Biology helps in understanding the pathophysiology of the disease, in identifying potential targets for therapeutic intervention and evaluation of the potential drug candidates.

Role of Informatics

Informatics plays role in improvement of decision making by identifying and replicating the characteristics of successful drugs and creating databases to predict future clinical success.

A few important commercially important pyridine derivatives include 2-chloropyridine, 2,6-dichloropyridine, 2-bromopyridine, picolinic acid, nicotinic acid, isonicotinic acid, methyl nicotinate, ethyl nicotinate, picolinamide, nicotinamide, 2-cyanopyridine, 3-cyanopyridine, 4-cyanopyridine, 4-pyridylcarbinol, 3-pyridylcarbinol, 2-picolylamine, 4-picolylamine, 2-mercaptopyridine, 4-mercaptopyridine, 2-pyridone, 3-hydroxypyridine, 4-pyridone, 2-aminopyridine, 3-aminopyridine, 4-aminopyridine and 4-dimethylamino-pyridine.

Objective

Due to the rapid resistance developed by microorganisms against the currently available antimicrobial agents, the need for development of antimicrobial agents remains a continuous process worldwide. In an attempt in the ongoing efforts to develop new antimicrobial agents, we have hereby envisaged to synthesize some pyridine derivatives which may be able to possess improvised antimicrobial potential.

Plan of Work

The design of a novel pyridine TZD derivatives structure came from the pyrrolidine series that had been studied earlier. Some of the partial structure of the substituted moiety were derived from recently reported a novel pyridine and purine TZD derivatives. Therefore, in order to enhance antimicrobial property, I focused my attention on the modification of pyridine moiety having TZD. I describe the design, synthesis and antimicrobial activities of novel substituted pyridine derivatives containing TZD.

EXPERIMENTAL DETAILS

As envisioned from the review of literaturepyridine conjugated thiazolidinedione derivatives were synthesized utilizing the scheme depicted in the figure. 1. The scheme was developed schemes reported by Tripathi et al and Meng et al.

SYNTHESIS OF PYRIDINE DERIVATIVES OF THIAZOLIDINEDIONE

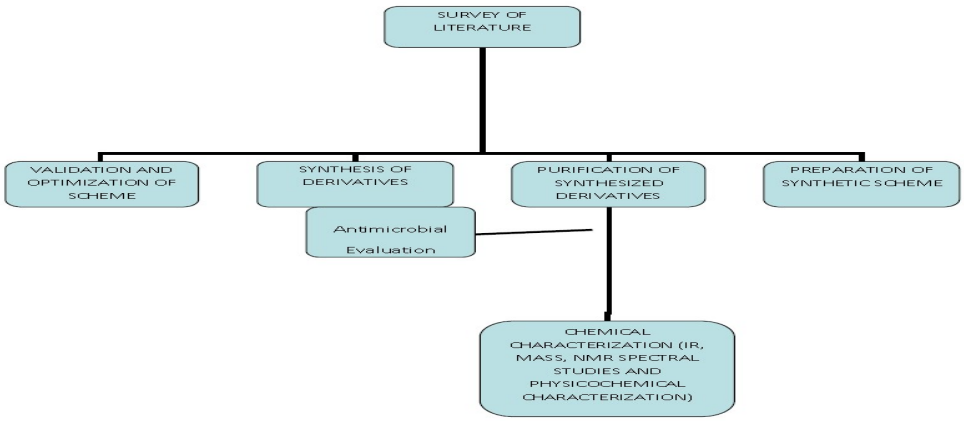
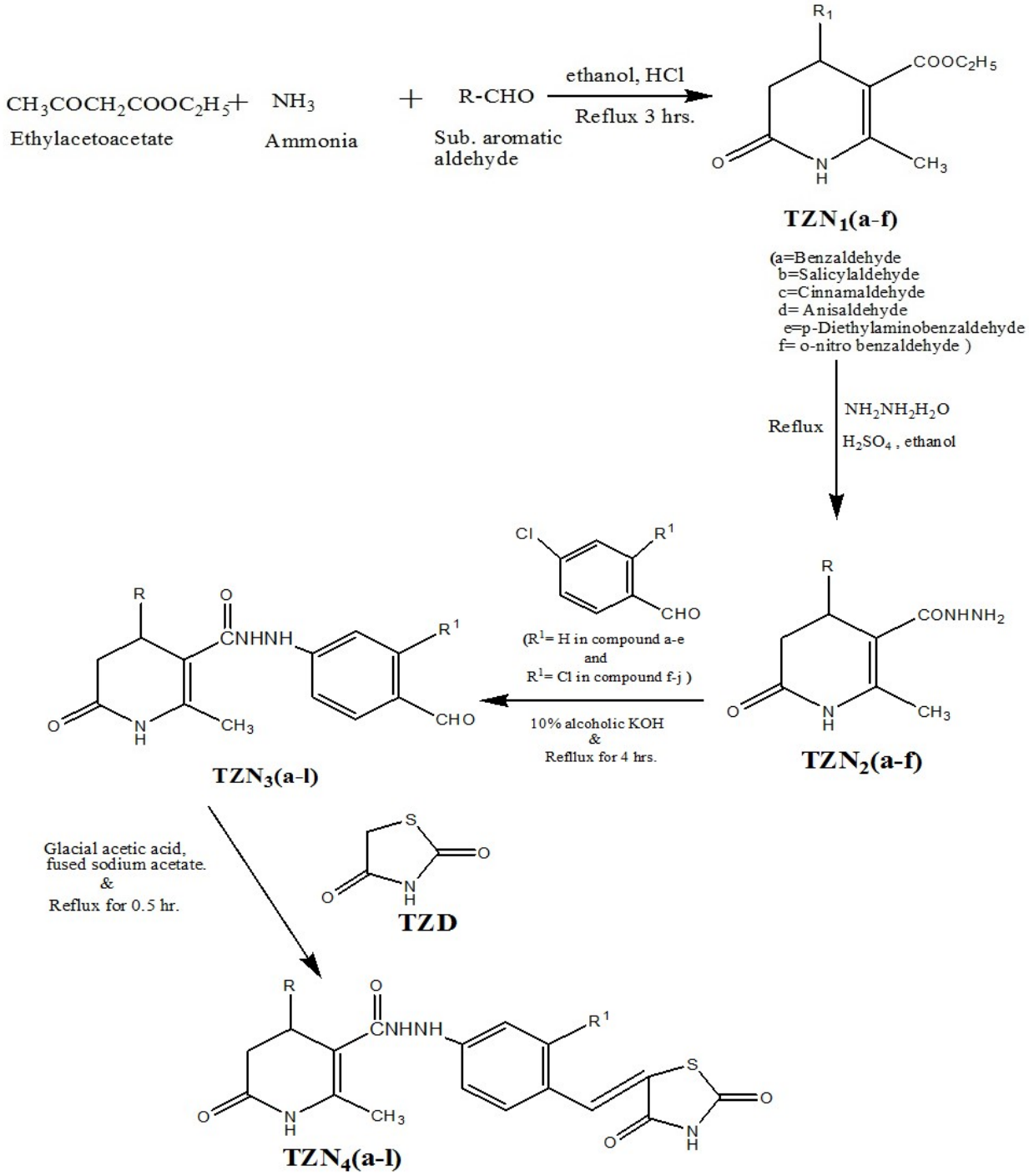


Figure : 1.1 Scheme of the synthesis f pyridine derivatives of thiazolidinedione.

Synthesis of 4-phenyl-5-carboethoxy-6-methyl-3,4-dihydropyridine-2-one

The synthesis of 3, 4-dihydropyridine was performed by using substituted aromatic aldehyde, ammonia and ethylacetoacetate as depicted in the section below.

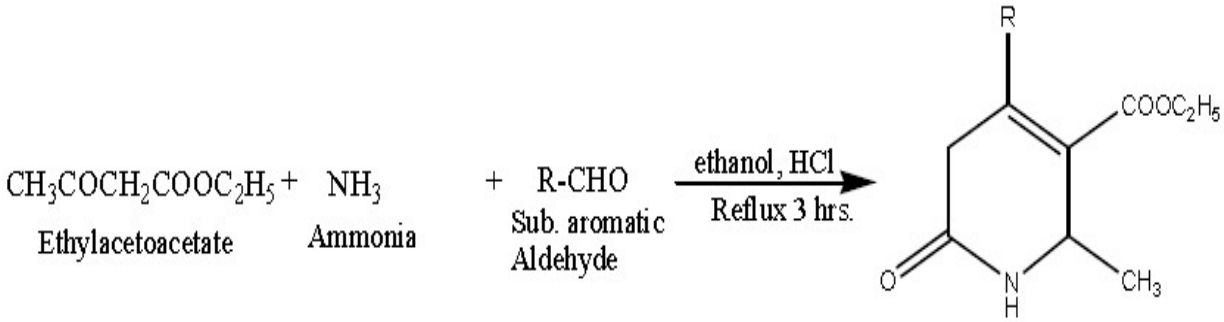


HANTZSCH PYRIDINE SYNTHESIS

General

This method is an acid catalyzed multi-component reaction of an aldehyde, a β- keto ester and ammonia in presence of ethanol with a catalytic amount of concentrated hydrochloric acid at reflux temperature.

Mechanism



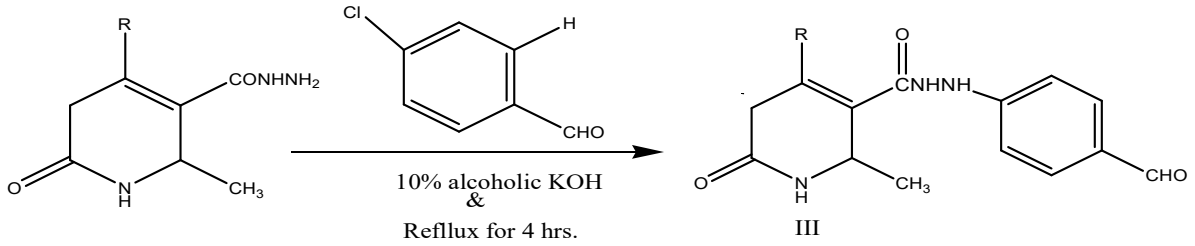
TZN_1(a-f)

The experiments revealed that the key step in this sequence of reactions involves the acid- catalyzed formation of N-acylinium ion intermediate of type from the aldehyde and ammonia precursors. Retainment of the iminium ion by ethylacetoacetate, probably through its enol tautomer, produces an open chain ureide which subsequently cyclizes to hexahydropyridine.

Procedure

0.5 moles of ammonia, 0.75 moles of ethylacetoacetate and 0.5 moles of substituted aromatic benzaldehyde were mixed in 25 ml of ethanol. Catalytic amount of concentrated hydrochloric acid (5 drops) was added to the mixture and the mixture was refluxed until the completion of the reaction (approximately 3 hours). On cooling, a solid separated which was filtered and recrystallised using ethanol to give the product $TZN_{1(a-f)}$. Completion of the reaction was monitored by TLC.

Synthesis of 4-subsituted-carboxyhydrzide-N-benzaldehyde-6-methyl-3,4-Dihydro -pyridine-2-one derivatives



III

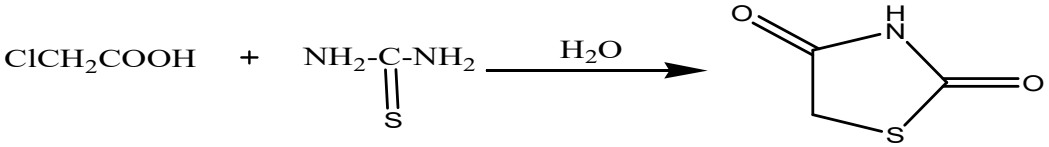
The Synthesis of 4-subsituted-carboxyhydrzide-N-benzaldehyde-6-methyl-3, 4-dihydro-pyridine-2-one derivatives was achieved by condensation of the hydrazide derivative and chloro-benzaldehyde in the presence of alcoholic potassium hydrochloride solution.

Procedure

To 1 mole of product TZN 2(a-f) in 15 ml of 10% alcoholic potassium hydroxide, was added of 1 mole of para-chlorobenzaldehyde. The reaction mixture was refluxed until the completion of the reaction (approximately 4 hours). On cooling, a solid separated, which was recrystallized from chloroform: ether (1:1) to give the product TZN 3(a-f).

Synthesis of thiazolidinedione

The thiazolidinedione was synthesized by the condensation of chloroacetic acid and thioammonia in the presence of water.



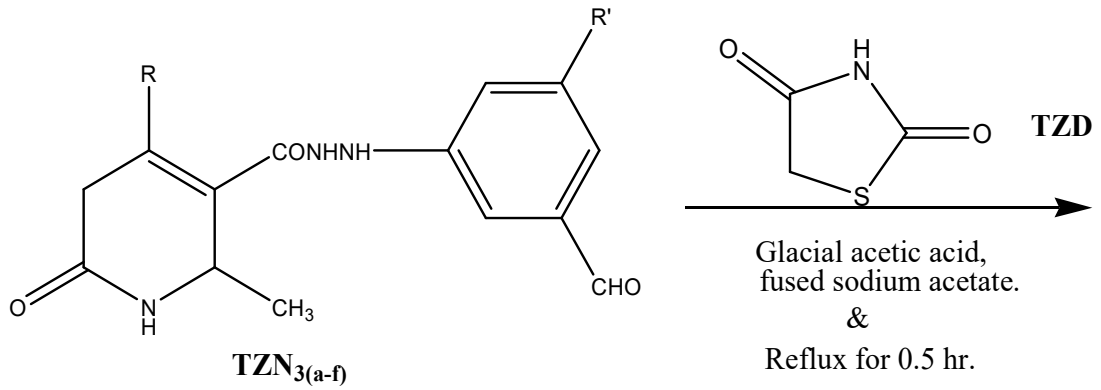
ChloraceticacidThioammonia**TZD**

Procedure

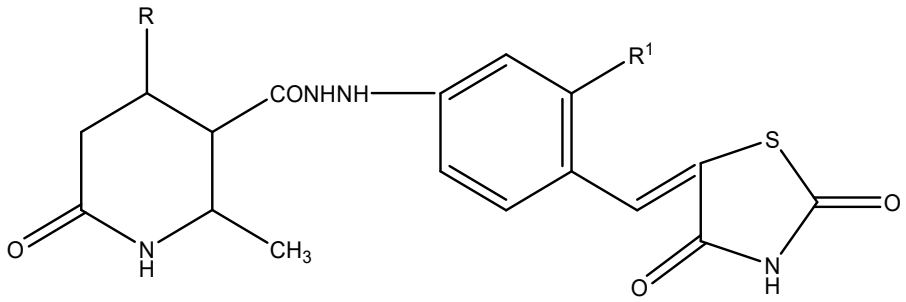
To 0.6 mole of chloroacetic acid in 60 ml of water, was added of 0.6 mole of thioammonia. The reaction mixture was stirred until white ppt was formed, (approximately 15 min.) and refluxed until the completion of the reaction (approximately 40 hours). On cooling, a solid separated, which was recrystallized from ethyl alcohol to give the product TZD.

Synthesis of thiazolidinedione derivatives of pyridine

The thiazolidinedione derivatives of pyridine derivatives were synthesized by the condensation of the product $TZN_{3(a-f)}$ derivatives and thiazolidinedione in the presence of glacial acetic acid and fused sodium acetate.



$TZN_{3(a-f)}$



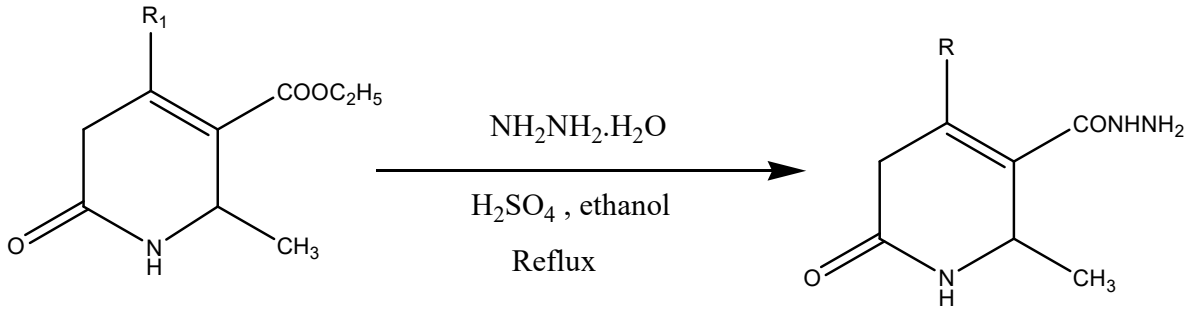
R'=H—$TZN_{4(a-f)}$

Procedure

To 0.25 mole of product $TZN_{3(a-f)}$ in 50 ml of hot glacial acetic acid, 0.25 mole of thiazolidinedione (TZD) and 1.8 gm of fused sodium acetate were added. The reaction mixture was refluxed until the completion of the reaction (approximately 1 hour) with occasional shaking. Mixture was poured in water (500 ml). Product was filtered and washed with water, alcohol and ether. On cooling, a solid separated, which was recrystallized from glacial acetic acid to give the product TZN $_{4(a-f)}$.

Synthesis of 4-phenyl-5-carboxyhydrazide-6-methyl-3,4-dihydroprimidinedione 2-one

The hydrazide derivative of the dihydropyridine- 2-one was synthesized by the product of TZN_1 by hydrazine hydrate in presence of ethanol with catalytic amount of concentrated sulfuric acid.



TZN $_{1(a-f)}$ **TZN $_{2(a-f)}$**

Mechanism

The reaction proceeds by the way of ammonolysis of esters. The mechanism involves nucleophilic attack on the electron deficient carbon atom of the ethoxy group, $-OC_2H_5$, by hydrazine hydrate. The alkoxy group gets replaced by $–NHNH_2$ to yield the product, hydrazide derivative.

Procedure

To 0.1 mole of the product TZN $_{1(a-f)}$ in 20 ml ethanol, 0.1 mole of hydrazine hydrate was added. To the mixture, catalytic amount of concentrated sulfuric acid was added. The mixture was refluxed until the completion of the reaction (approximately 2 hours). On cooling, a solid separated, which was recrystallized from ethanol to give the product TZN $_{2(a-f)}$.

The characterization of the physicochemical properties of these compounds was done as follows:-

(1) The **melting points** were determined by open capillary method and are uncorrected.

(2) The purity and homogeneity of the compounds was determined by **thin layer chromatography**(TLC), using silica gel G as the stationary phase on glass plates. Iodine vapors were use for development of the chromatogram. The solvent system used for running the compounds was hexane: chloroform in the ratio 7:3.

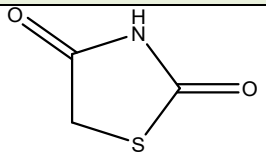
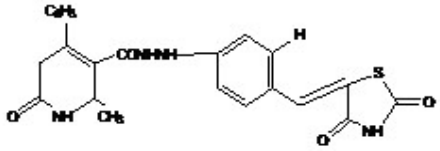
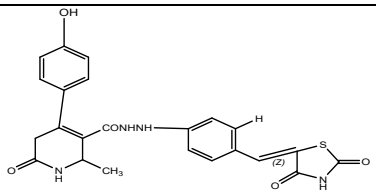
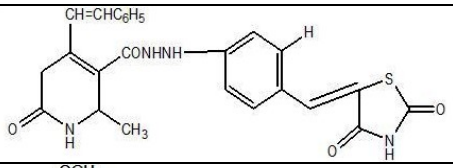
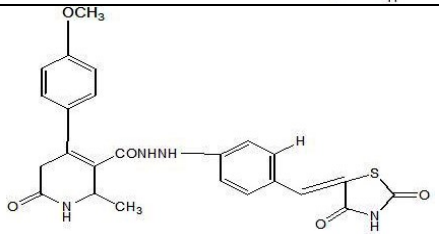
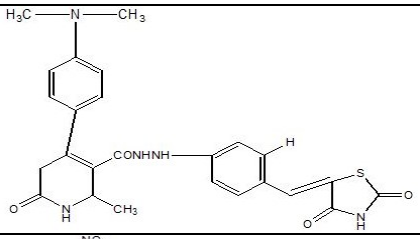
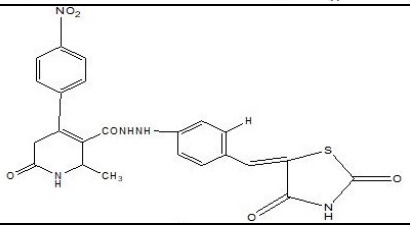
(3) **UV-Absorption studies**: Ultra violet (UV) absorption studies of the synthesized compounds were carried using the solution of the compounds in the ethanol. The compounds were scanned in the region of 200 to 400 nm, using Shimadzu spectrophotometer, Pharmaspec UV-1700. The absorption maximum of the compounds was determined.

(4) **Infrared spectroscopy**: The I.R. spectra of the synthesized compounds were obtained using FT-IR spectrophotometer, Bruker alpha.

RESULTS

Synthesis of the desired compounds was carried out by utilizing the optimized scheme. The Rf value obtained from TLC, the melting point and percent yield of the synthesized compounds is depicted in –

Table 1.1.

Compound code	Structure	$R_f$value R P	Melting Point	% Yield
TZD		**0.18 0.83**	**110-115**	**72**
$TZN_{4(a)}$		**0.2 0.38**	**134-140**	**63**
$TZN_{4(b)}$		**0.49 3.2**	**230-232**	**66**
$TZN_{4(c)}$		**0.46 0.40**	**210-215**	**79**
$TZN_{4(d)}$		**0.54 0.22**	**140-142**	**72**
$TZN_{4(e)}$		**0.46 0.85**	**112-117**	**5**
$TZN_{4(f)}$		**0.32 0.39**	**185-190**	**78**

Calculated molecular weight, percent nitrogen content and the determined λmax of the final synthesized derivatives (physical properties of the synthesized compounds)

Table 1.2

Compound Name	Molecular Formula	Molecular Weight (calculated)	%Nitrogen (calculated)	Absorption Maximum (λ_{max}) Order			
				0	I	II	III
TZD	$C_4H_7NO_2S$	133.17	10.52				
$TZN_{4(a)}$	$C_{24}H_{26}N_5O_4S$	480.56	14.57	307	283	326	-
$TZN_{4(b)}$	$C_{24}H_{26}N_5O_5S$	496.54	14.10	355	342	207	-
$TZN_{4©}$	$C_{26}H_{28}N_5O_4S$	506.60	13.82	305	291	206	-
$TZN_{4(d)}$	$C_{25}H_{28}N_5O_5S$	510.59	13.72	307	291	206	-
$TZN_{4(e)}$	$C_{26}H_{31}N_6O_4S$	523.21	16.05	230	285	206	-
$TZN_{4(f)}$	$C_{24}H_{25}N_6O_6S$	525.56	15.99	302	297	203	-

Table : 1.3 Antibacterial activity of the synthesized compounds

Compound	MIC (µg/mL)			
	Proteus mirabilis	***Pseudomonas aeruginosa***	***Staphylococus aureus***	***Bacillus subtilis***
TZN_{4a}	130	110	85	90
TZN_{4b}	70	50	50	60
TZN_{4c}	110	120	85	90
TZN_{4d}	130	110	120	150
TZN_{4e}	70	50	60	50
TZN_{4f}	60	60	60	60
Norfloxacin	06	05	04	08

DISCUSSION

The general method known as Hantszch pyridine synthesis was used to prepare pyridine-one derivatives. The carboethoxy group of pyridine-one was converted to hydrazide & then this group was converted to an aromatic aldehyde derivative. The methylene group linker between the pyridine and 2-4 thiazolidinedione ring was synthesized by knoevenagel condensation of pyridine-aromatic aldehyde and 2,4-thiazolidinedione ring. Sodium acetate and glacial acetic acid were used as the reagents in this condensation. The Rf, meiting point, yield, ^{1}H-NMR spectra, IR spectra & mass spectral values are all listed in the previous section. All the spectral data were in accordance with the presumed structure.

In ^{1}H-NMR spectra protons of pyridine and benzene ring were observed between 8-7 ppm

benzylic proton were observed at 4.8-5.1 ppm & 1.2-3ppm. Other protons were also observed at derived values.

Table 4.5: Concentration of the synthesized compounds in the nutrient broth

Test tube No.	Synthesized compound stock solution (mL)	Nutrient Broth (mL)	Concentration of the synthesized compound (µg/mL)
1	0.1	9.9	10
2	0.2	9.8	20
3	0.3	9.7	30
4	0.4	9.6	40

SUMMARY AND CONCLUSION

In an effort to develop new potential molecules for the improving the health condition, a series of novel substituted pyridine analogues having TZD moiety were synthesized.The Overall Synthesis of the Pyridine substituted Thiazolidinedione is as Follows.

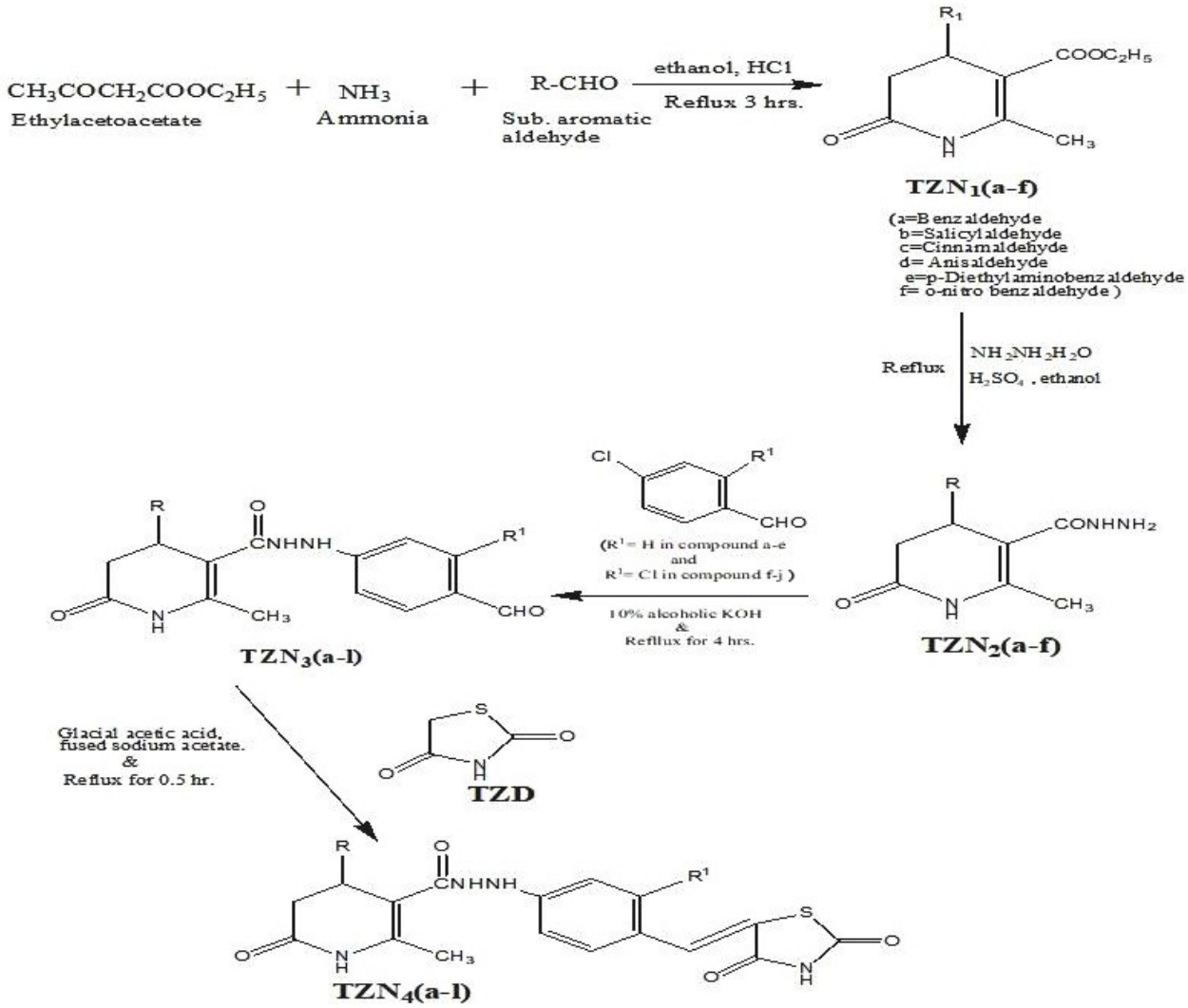


Figure : 1.2 Scheme of the synthesis f pyridine derivatives of thiazolidinedione.

REFERENCES

1. Lednicer, D. Introduction. In *Organic chemistry of drug synthesis*, Vol. 1; Wiley Interscience: New York, **1977**; pp 01-03.
2. Kar, A. Introduction. In *Pharmacognosy and pharmacobiotechnolog*; New Age International: New Delhi, **2003**; pp 01-45.
3. Vogel, G. H.,Ed. Strategies in drug discovery and evaluation. In *Drug discovery and evaluation: Pharmacological assays*; Springer-Verlag: Berlin, **2002**; pp 01-22.
4. Charifson, P. S.; Kuntz, I. D. Recent successes and continuing limits in CADD. In *Practical Applications of CADD*, Charifson, P.S., Ed.; Marcel Dekker Inc.: New York, **1997**; pp 01-37.
5. Nadendla, R. R.; Babu, S. P.; Narendra, A. Trinath, V. S. K. Microwave assisted organic synthesis. *The Indian Pharmacist*, **2003**; 12, 38-42.
6. Abdullah jawadkadhim. Synthesis and characetization of some pyridine derivatives. Iraqui National Journal of Chemistry, **2012**, 47, 378-390
7. Mojarrad JS, Zamani Z, Hazemiych H, Ghasemi S, Asgari D. Synthesis of novel 1,4-dihydropyridine derivatives bearing biphenyl-2'-tetrazole substitution as potential dual angiotensin II receptors and calcium channel blockers. Advanced Pharmaceutical Bulletin, **2011**,1 (1), 1-9
8. SihamAbdulRahman Al-Issa. Synthesis of new series of pyridine and fused pyridine derivatives. Molecules, **2012**, 17, 10902-10915
9. Ali KA. A new convenient synthesis of some novel 2,6-disubstituted –pyridine derivatives. ARKIVOC, **2010**, xi, 55-63
10. Rajput CS, Sharma S, Yashovardhan. Synthesis of new pyridine derivatives as potential antifungal agents. International Journal of Pharma and Bio Sciences, **2011**, 2 (3), 201-209
11. Nowicka A, Liszkiewickz H, Nawrocka WP, Wietrzyk J, Zubiak A, Kolodziejczyk W. Synthesis and antiproliferative activity *in vitro* of new 2-thioxoimidazo[4,5-*B*]pyridine derivatives. ActaPolaniaePharmaceutica-Drug Research, **2015**, 72 (1), 101-111
12. Thirumurugan P, Mahalaxmi S, Perumal P. Synthesis and anti-inflammatory activity of 3-indolyl pyridine derivatives through one-pot multi component reaction. Journal of Chemical Science, **2010**, 122 (6), 819-832
13. Hassan AY, Sarg MT, Said MM, El-Sebaey SA. Utility of thieno[2,3-b]pyridine derivatives in the synthesis of some condensed heterocyclic compounds with expected biological activity. Universal Organic Chemsitry, **2013**, 1, 1-15
14. Mathi VN, Suresh AJ, Bala SC. Eco-friendly one-pot synthesis and characterization of 1,4-dihydropyridine derivatives. International Journal of Pharmacy and Pharmaceutical Sciences, **2012**, 4 (3), 651-654
15. Bhargava S, Choudhary A. Ionic liquid promoted synthesis of 2-phenylimidazo[1,2-a]pyridine derivatives and their antibacterial screening. International Journal of Pharmacy and Pharmaceutical Sciences, 2014, 6 (6), 553-557

CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED