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SYNTHESIS AND CHARACTERISATION OF SOME NOVEL MANNICH BASES OF THIAZOLIDINONES DERIVED FROM PYRAZOLINES

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ABSTRACT

The main approach of medicinal chemistry is to synthesize compounds that show promising activity as therapeutic agents with lower toxicity. Thiazolidinone and Pyrazoline derivatives may show different activities such as analgesic, anti-inflammatory, antitubercular activitiesetc. Mannich base derivatives of Thiazolidinones from Schiff bases have been synthesized by reacting them with previously prepared Pyrazolines from Chalocnes, with the yield ranging from 56% to 71%. The identification and characterization of the synthesized compounds were carried out by melting point, TLC and FT-IR to ascertain that all prepared compounds were of different chemical nature than the respective parent compound.

KEY WORDS: Thiazolidinone, Pyrazoline, Mannich Base, Schiff Bases, Chalcones.

INTRODUCTION

One of the main objectives of organic and medicinal chemistry is the design, synthesis andproduction of molecules having value as human therapeutic agents[1]. There are numerous biologically active molecules with five membered rings, containing two heteroatoms among which is the 4-thiazolidinone ring system which is a core structure in various synthetic compounds and an important scaffold known to be associated with several biological activities such as hypnotic activity[2], antitubercular[3], anticonvulsant[4], antibacterial[5],

anticancer[6], antihistaminic[7], antifungal[8], anti-inflammatory[9], antiviral[10] and cardiovascular effects[11].Thiazolidinone is a moiety derived from thiazolidine by the replacement of hydrogen by oxygen at the positions 2,4 or 5 in the ring.

Pyrazoline is five-membered heterocyclic having two adjacent nitrogen atoms within the ring. It has only one endocyclic double bond and is basic in nature.Pyrazoline derivativeswere found to have potential antipyretic-analgesic, tranquillizing, muscle relaxant, psycho analeptic, antiepileptic, antidepressant, anti-inflammatory, insecticidal and antimicrobial and antihypotensive activities. Their derivatives were also found to exhibit cytotoxic activity, inhibitory activity of platelet aggregation, herbicidal activity and cannabinoid CB1-receptor modulators. Pyrazoline interest extended to dyes and dye couplers too[12].

Pyrazoline ring is an important part of Losartan structure which is a well known Angiotensin II blocking agent. Pyrazolines have been studied, since the introduction of angiotensin II blockers in the antihypertensive therapy, for their antihypertensive activity and have been found potent blockers. In the recent years, the potency of Thiazolidinones for angiotensin II blocking action was studied and found out to be worthwhile investigating but they were found to be less potent as compared to Pyrazolines.The present work involves the synthesis of various mannich bases by the combination of thiazolidinones and pyrazolines.

MATERIALS AND METHODS

The melting points were recorded on technico apparatus and are uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel G (Merck). The instrument used for Infra red spectroscopic data was IR: Perkin Elmer spectrophotometer (KBr) with diffuse reflectance method.

Prerparation of Schiff Bases (1)[13]

Sulfanilamide (25 mmol) was dissolved in 40 ml boiling ethanol and aromatic aldehyde (25 mmol) was added to this solution. This mixture was refluxed for 3-4 hrs and was then cooled. The solid obtained was filtered, dried and crystallized from 95% ethanol.

Preparation of Thiazolidinones (A) [14]

0.01 mol Schiff base and 0.02 molthioglycollic acid were dissolved in 30 ml glacial acetic acid. This mixture was refluxed for 4-5 hrs. The reaction mixture was then poured in an ice cool saturated solution of sodium bicarbonate. It was then kept overnight at refrigeration. The

product obtained was washed with cold water to remove alkali and crystallized with appropriate solvent.

Preparation of Chalcones (2)[15]

Equimolar mixture of substituted acetophenone (0.08mol) and substituted benzaldehyde (0.08mol) was added to a mixture of 4.2g sodium hydroxide in 40ml water and 25ml ethanol. The resulting mixture was stirred for 3-4 hrs in an ice bath. The stirred mix was kept under refrigeration overnight. The product was filtered and was crystallized from 95% ethanol.

Preparation of Pyrazolines (B) [16]

Chalcone (0.01 mol) and hydrazine hydrate (0.02 mol) were taken in 20ml glacial acetic acid and the mixture was refluxed for 10-12 hrs. The reaction mixture was poured in 300ml ice cold water and was kept aside for 12 hrs. The product obtained was filtered and crystallized from 95% ethanol.

Preparation of Mannich Bases (FP1-FP5)[17]

An equimolar mixture of thiazolidinone (0.005mol) and pyrazoline (0.005mol) in an appropriate solvent was refluxed for 4-5-hrs. The reaction mixture was poured in 200-300 ml ice cold water and was kept aside for 12 hrs. The product obtained was filtered and crystallized from appropriate solvent.

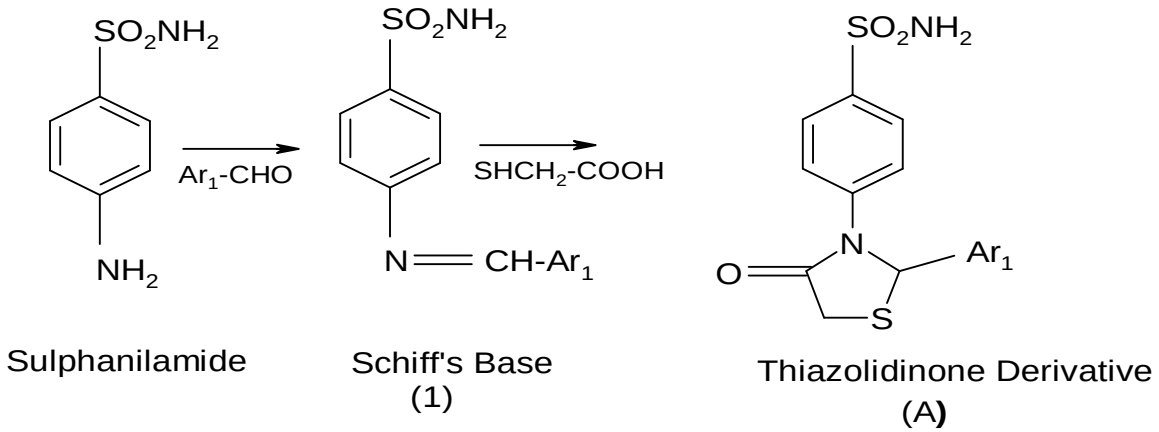


Fig: 1 Scheme for the synthesis of Thiazolidinone Derivatives(A)

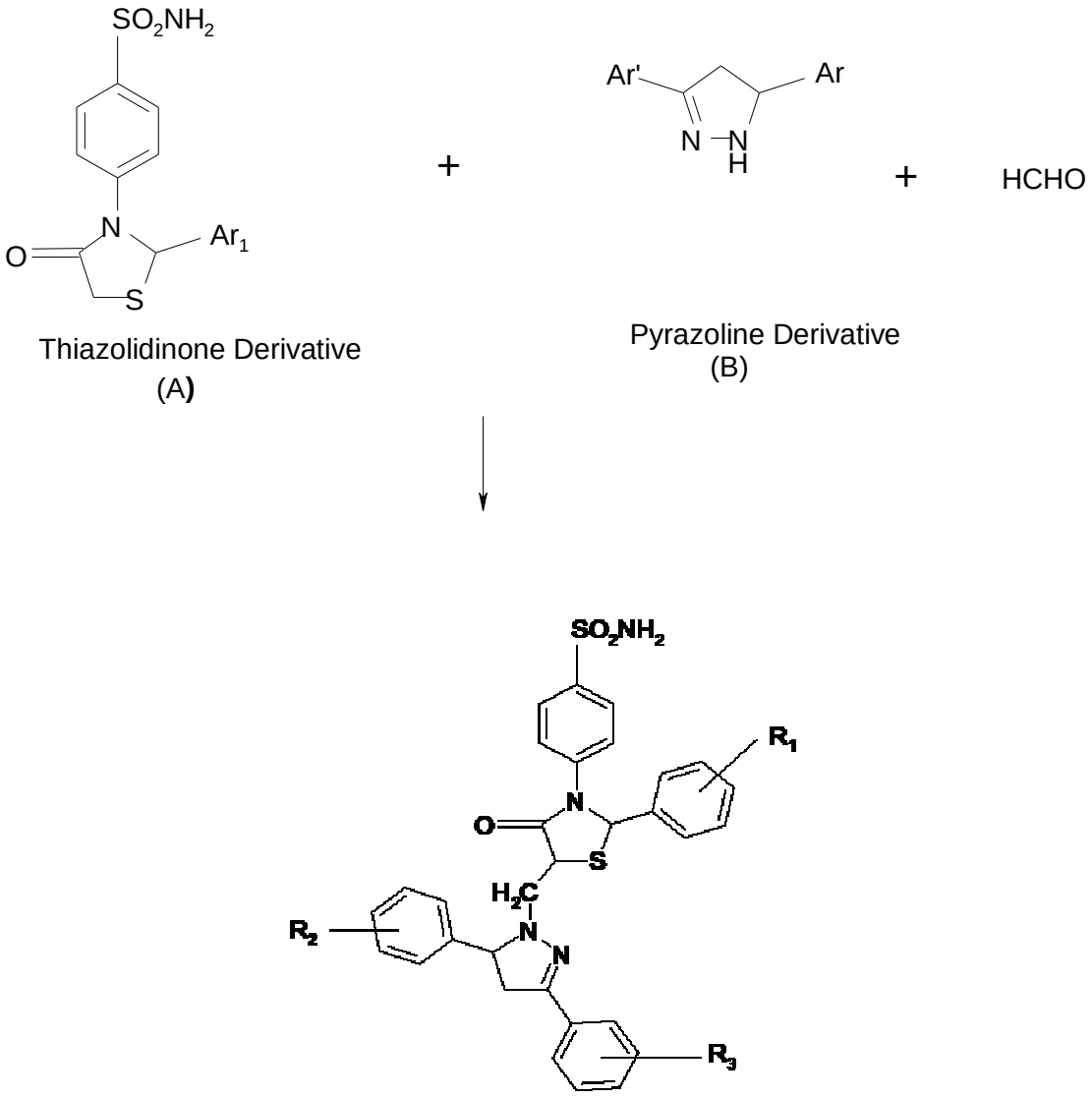


Fig: 2 Scheme for the synthesis of Pyrazoline Derivatives (B)

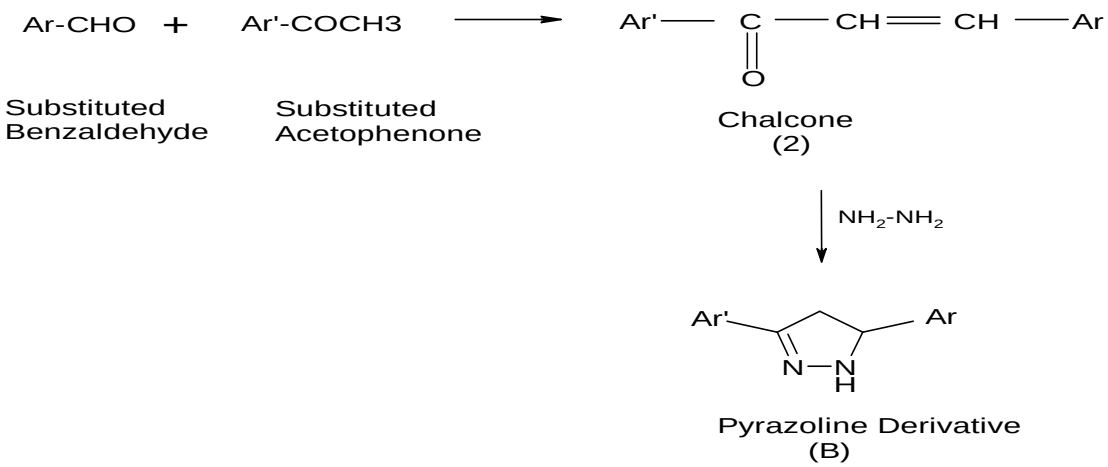


Fig: 3 Scheme for the synthesis of Mannich bases of thiazoldinones with pyrazolines

RESULTS AND DISCUSSION

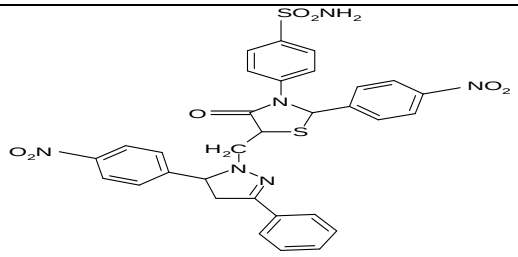
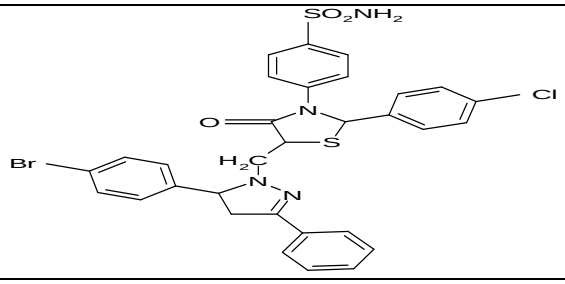
During the present work, an effort is made to combine two important angiotensin II blockers, i.e. thiazolidinone and pyrazoline rings. In the present work, some Thiazolidinone derivatives were synthesized from Schiff bases derived from different aromatic amines and aldehydes. They were synthesized by the classical method. Further Schiff bases on reacting with thioglycollic acid yielded the corresponding Thiazolidinone derivatives. Meanwhile, some Pyrazoline derivatives were also synthesized from Chalcones derived from aromatic aldehydes and acetophenones. Further chalcones were reacted with hydrazine hydrate which yielded the corresponding pyrazoline derivative. Mannich condensation is very useful method which acts as a bridge to combine two different moieties. The Thiazolidinones were made to combine with pyrazolines, the yields were optimum. All the synthesized compounds were tested for their purity by TLC (in Table No: 1) and the characterizationof the synthesized mannich bases were done by IR spectroscopic analysis (in Table No: 3).

Mobile Phase used for TLC was Benzene: Chloroform in the ratio of 4.5: 0.5

Table No 1: Physico- chemical data of the synthesised Mannich bases of thiazoldinones with pyrazolines

SL.NO.	Comp. Code	R_1	R_2	R_3	Mol. Formula	% Yield	M.P. (˚C)	R_f
1.	FP1	4- NO_2	4- NO_2	H	$C_{31}H_{26}O_7N_6S_2$	71	146	0.72
2.	FP2	4- Cl	4- Br	H	$C_{31}H_{26}O_3N_4S_2ClBr$	56	110	0.45
3.	FP3	4-CH_3	4-CH_3	4-OH	$C_{33}H_{32}O_4N_4S_2$	49	180	0.30
4.	FP4	4- $N(CH_3)_2$	4- OCH_3	4-Cl	$C_{34}H_{34}O_4N_5S_2Cl$	58	118	0.59
5.	FP5	4- Br	4- OCH_3	4- OCH_3	$C_{33}H_{31}O_5N_4S_2$	64	110	0.75

Table No 2: Structure and IUPAC names of the synthesised Mannich bases of thiazoldinones with pyrazolines

Compound Code	Structure	IUPAC Name
FP1		4-{2-(4-nitrophenyl)-5-[(3-phenyl-5-(4-nitrophenyl))-1,2-pyrazolidin-1-yl)methyl]-4-oxo-thiazolidin-3-yl}benzene sulphonamide
FP2		4-{2-(4-chlorophenyl)-5-[(3-phenyl-5-(4-bromophenyl)-1,2-pyrazolidin-1-yl) methyl]-4-oxo-thiazolidin-3-yl}benzene sulphonamide

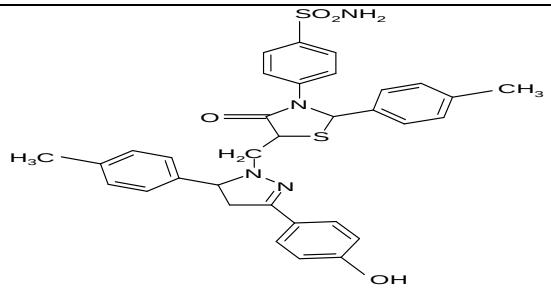
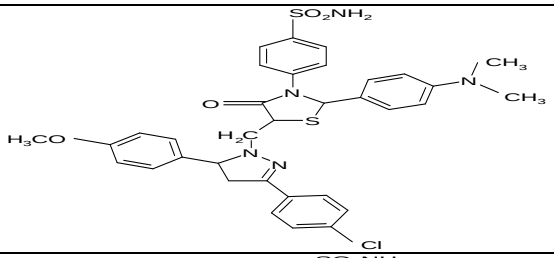
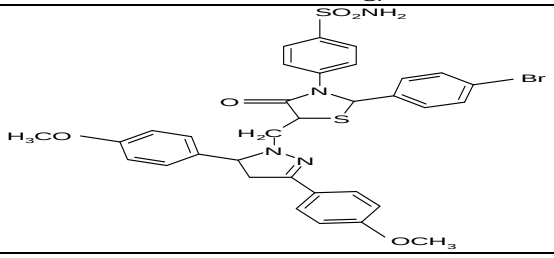
FP3		4-{2-(4-chlorophenyl)-5-[(3-(4-hydroxyphenyl)-5-(4-methylphenyl)-1,2-pyrazolidin-1-yl) methyl]-4-oxo-thiazolidin-3-yl}benzene sulphonamide
FP4		4-{2-[4-(N,N-dimethylaminophenyl)]-5-[(3-(4-chlorophenyl)-5-(4-methoxyphenyl)-1,2-pyrazolidin-1-yl) methyl]-4-oxo-thiazolidin-3-yl}benzene sulphonamide.
FP5		4-{2-(4-bromophenyl)-5-[(3,5-(4,4'-dimethoxyphenyl)-1,2-pyrazolidin-1-yl) methyl]-4-oxo-thiazolidin-3-yl}benzene sulphonamide.

Table No 3: IR Spectroscopical data of the synthesized Mannich bases of Thiazoldinones with Pyrazolines

Compound Code	Type of Stretch	Wave number (cm^{-1})
FP1	-NH str	3430
	C=N str.	1570
	C=O str	1710
	C-N str.	1014.56
	-N-O	1508.53
	S=O str	1448
	$-NO_2$ str.	1363.67
	-C-S	690.52
FP2	-NH str	3242.34
	C=N str.	1590.76
	C=O str	1645.28
	C-N str.	1163.08
	S=O str	1496.76
	-C-S	833.25
	-C-Cl	750.31
	-C-Br	617.22
FP3	-OH	3145.90
	-NH str	3126.54
	-C-H	2814.14
	C=N str.	1575.84
	C=O str	1803.44
	C-N str.	1022.27
	S=O str	1442.75
	-C-S	1336

FP4	-NH str -CH str. C=O str. C=N str. S=O str. C-O str. C-N C-Cl	3331.07 3255.84 1658.78 1595.13 1444.48 1251.80 1155.36 1024.20
FP5	-OH str. -NH str. C-H str. C=O str. S=O str. C-O C-N C-Br	3257.77 3022.45 2937.59 1907.60 1444.68 1089.78 1024.20 827.46

CONCLUSION

Thiazolidinones and Pyrazolines are interesting groups of heterocyclic compounds exhibiting diverse pharmacological activities.Structure based drug design too gives an emphasis on thiazolidinone and pyrazoline moiety. We thought that these models as such for synthesis give good opportunities to look for discovering ideal lead for anti-hypertensive activity.

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