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"Synthesis and Antimicrobial activity of Thiazolidinone Derivative"

Research Article

Ruchika Kshatri[1] , Sailendra Singh Chandel[2]
Millennium College Of Pharmacy, Bhopal

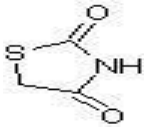
Abstract
Thaizolidone derivative had been taken and their in vitro Antimicrobial Screening had been performed .
Antibacterial activity of novel thiazolidinone derivatives were evaluated by the paper disk diffusion method on Mueller-Hinton agar (MHA) plates. Bacterial cultures were adjusted to 0.5 McFarland turbidity standards and inoculated onto MHA plates (15cm diameter). Sterile filter paper disks (diameter 6 mm) soaked in a known concentration of compounds (100µg/ml per disk) in DMSO were applied over each of the culture plates previously seeded with the 0.5 McFarland and 106 CFU/ml cultures of bacteria. (5)The cultured plates were then incubated at 37°C for 18 h. Paper disks soaked in a known concentration (50µl) of ciprofloxacin in distilled water as standard antimicrobials were used as positive control. Antimicrobial activity was determined by measurement of zone of inhibition around each paper disk. For each thiazolidinone derivatives, three replicate trials were conducted against each organism.
Novel thiazolidinones derivatives were exhibited anti-fungal activity. Against C. Albicans TP-1 has excellent activity, TP-3, TP-4, TP-5 has moderate activity and TP-2 has lower activity. Against A. Niger TP-1 showed excellent activity while rest all has lower activity.
Overall TP-1 was most active compound against both bacterial and fungal strains.

Keyword
Antimicrobial activity ,thiazolidone,heterocyclic compound, Schiff Base

Introduction
Thiazolidinone belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five-member ring. Thiazolidinones are saturated form of thiazole, that have an atom of sulfur at position 1, an atom of nitrogen at position3 and a carbonyl group at position 2, 4, or 5. Substituents in the 2-, 3-, and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position.[1]
Thiazolidinone is a moiety derived from thiazolidine by the replacement of hydrogen by oxygen at the positions 2,4 or 5 in the ring[2]

Chemistry of Thiazolidinone
4- thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4 position[3] . Substitution is possible at 2, 3 and 5 position. Various optical and geometrical isomers are reported in the references10. A series of regioselective isomers has been reported in some works. The carbonyl group of 4-thiazolidinone is highly unreactive. But in few cases 4-thiazolidinone on reaction with Lawesson's reagent gives corresponding 4-thione derivatives.[4] A detail study of tautomerism in 2-imnothiazolidine-4-one has been done by Akerblom E.[5]

Pharmacological uses of 4-thiazolidinones



Structure of thiazolidone
- Anti-HIV activity[6]
- Antimicrobial activity[7]
- Anti-cancer activity, antiproliferative activity [8]
- Anti-inflammatory activity[9]
- CFTR inhibitor
- Antidiabetic[10]
- Antiinflammatory[11]
- Antialzheimer [12]
- Anti-Anxiety[13,14]
- Antipsychotic and Anti-Convulsant[15]
- Antiamoebic[16]
- Antitubercular[17]

Antimicrobials
Antimicrobials are chemicals that kill or inhibit the growth of microorganisms and are used to treat microbial infections. [19] Some are produced naturally by microbes, but many are synthetic. Antimicrobials include antibiotics, antivirals, antifungals, and other drugs such as antimalarials.[20]With increase in the incidence of multidrug-resistant gram-positive and gram-negative bacteria it becomes imperative to continuously search for small molecules as anti-infective agents.36 Multiply resistant organisms render therapy more precarious and costly and sometimes unsuccessful. Individuals may succumb to MDR infections because all available drugs have failed, especially in the developing world.Notable global examples include hospital and community MDR strains of Mycobacterium tuberculosis, Enterococcus faecium, Enterobacter cloacae, Klebsiella pneumoniae, S. aureus, Acinetobacter baumanii and Pseudomonas aerugi. In developing countries, MDR enteric disease agents such as Salmonella enteritidis, Shigella flexneri and Vibrio cholerae threaten and circumvent public health measures.[21,22]

Materials and Methods
Method of in-vitro Antimicrobial Screening of thiazolidinone derivatives
Standardized cultures of bacteria Escherichia coli (ATCC 9637) and Bacillus subtilis (ATCC 9372) and fungi Candida albicans (ATCC 10231) And A. Niger were obtained from the Microbiology Laboratory, NIPRD.

Antibiotic susceptibility testing on bacteria
Antibacterial activity of novel thiazolidinone derivatives were evaluated by the paper disk diffusion method on Mueller-Hinton agar (MHA) plates. Bacterial cultures were adjusted to 0.5 McFarland turbidity standards and inoculated onto MHA plates (15cm diameter). Sterile filter paper disks (diameter 6 mm) soaked in a known concentration of compounds (100µg/ml per disk) in DMSO were applied over each of the culture plates previously seeded with the 0.5 McFarland and 106 CFU/ml cultures of bacteria. The cultured plates were then incubated at 37°C for 18 h. Paper disks soaked in a known concentration (50µl) of ciprofloxacin in distilled water as standard antimicrobials were used as positive control. Antimicrobial activity was determined by measurement of zone of inhibition around each paper disk. For each thiazolidinone derivatives, three replicate trials were conducted against each organism.

Antibiotic susceptibility testing on fungus
Antibacterial activity of novel thiazolidinone derivatives were evaluated by the paper disk diffusion method on Sabroud dextrose agar (SDA) culture media plate. Freshly prepared slants of C. albicans / A. niger were used and washed the slant by using 10 ml of sterile normal saline solution. Sterile filter paper disks (diameter 6 mm) soaked in a known concentration of compounds (100 µg/ml per disk) in DMSO were applied over each of the culture plates previously seeded with the 0.5 McFarland and 106 CFU/ml cultures of fungus. The cultured plates were then incubated at 37°C for 18 h. Paper disks soaked in a known concentration (50µl) of Itraconazole in distilled water as standard antimicrobials were used as positive control. Antimicrobial activity was determined by measurement of zone of inhibition around each paper disk. For each thiazolidinone derivatives, three replicate trials were conducted against each organism.

Statistical Analysis

All the values are expressed as mean standard error of mean (S.E.M.) and analyzed by one way ANOVA and post hoc Tukey multiple comparison test by employing statistical software, Graph Pad in Stat 3. Differences between groups were considered significant at $P < 0.05$ level

General Methods of Synthesis of Thiazolidinones

Prerparation of Schiff Bases

Aniline (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

Schiff base (0.01 mol) and thioglycollic acid (0.02 mol) 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

Equimolar mixture of substituted acetophenone (0.08mol) and substituted benzaldehyde (0.08 mol) 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. [119]

Preparation of Pyrazolines

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

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 hours .The product obtained was filtered and crystallized from appropriate solvent

Result

Characterization and Structural Elucidation of Novel Synthesized Thiazolidone[18]

TP-1

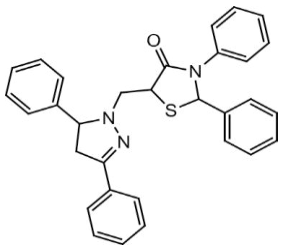
IUPAC Name: 5-((3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl) methyl)-2,3-diphenylthiazolidin-4-one

Molecular formula : **C31H27N3OS**
Molecular weight :**534.63**

Structural Elucidation of TP-1

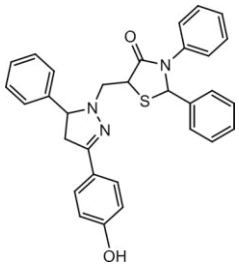
Elemental analysis calculated (Found) % for **C31H27N3OS** : C, 76.04(75.06); H, 5.56(5.42); N, 8.58(8.41); O, 3.02 (3.01); S, 6.55(6.31) **FT-IR (KBr):cm^{-1}** 3051 and 2991**C-H** str. (alkane), 1689 **C=O**, 1651 **C=N** str.(Ar), 1524 **C=C** str. (Ar), 1463 **C-H** str., 1308 **C-N** str. **^{1}H NMR (MeOD, 500 MHz):** δ 7.68(t, 2H, CH), 7.53-7.2(m, 18H, CH), 6.44(s, 1H, CH-Ar), 3.91(t, 1H, =8.05, 3.95, CH), 3.79-3.70(m, 2H, CH), 3.55-3.51(m, 1H, CH), 3.39-3.36 (m, 1H,CH), 3.15- 3.12(m, 1H,CH), ppm.

Physical state : Prism shape Crystalline solid
Color : Yellowish
Melting point : 171^{O}C
Yield : 68.10%,
Solubility : Ethanol, DMSO and Methanol
Rf – Value : 0.42



TP-2

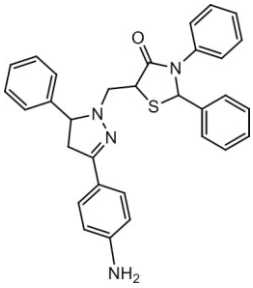
IUPAC Name: 5-((3-(4-nitrophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl) methyl)-2,3- diphenylthiazolidin-4-one



Molecular formula : $C_{31}H_{26}N_4O_3S$
Molecular weight :534.63
Physical state : Crystalline solid
Color : Reddish Yellow
Melting point : 182^{O}C
Yield : 62.72%,
Solubility : Ethanol, DMSO and Methanol
Rf – Value : 0.42

Structural Elucidation of TP-2

Elemental analysis calculated (Found) % for **C31H26N4O3S**: C, 69.64(69.32); H, 4.90(4.83); N, 10.48(10.31); O, 8.98(8.84); S, 6.00(5.91). **FT-IR (KBr):cm^{-1}** 3052, 2931 and 2871 **C-H** str.(alkane), 1682 **C=O**, 1651 **C=N** str.(Ar), 1592 **NO2,** 1524 **C=C** str. (Ar), 1455 **C-H** str., 1308**C-N** str. **^{1}H NMR (MeOD, 500 MHz):** δ 8.33(d, 2H, CH), 8.10(d, 2H, CH), 7.52-7.24(m, 15H,CH), 6.44(s, 1H, CH-Ar), 3.91(t, 1H, CH), 3.80(m, 1H, CH), 3.72(m, 1H, CH), 3.55-3.51(m, 1H, CH), 3.38-3.35 (m, 1H,CH), 3.14-3.11(m, 1H,CH), ppm.

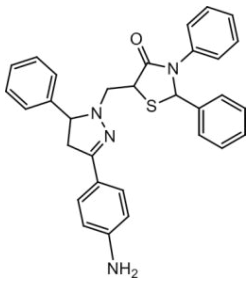


TP -3

IUPAC Name: 5-((3-(4-aminophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl) methyl)-2,3-diphenylthiazolidin-4-one

Molecular formula : **C31H28N4OS**
Molecular weight **: 504.65**
Physical state : Crystalline solid
Color : Yellowish
Melting point : 192^{O}C
Yield : 65.52%,
Solubility : Ethanol, DMSO and Methanol
Rf – Value : 0.64

Elemental analysis calculated (Found) % for **C31H28N4OS**: C, 73.78(73.64); H, 5.59(5.48); N, 11.10(11.02); O, 3.17(3.11); S, 6.35(6.21). **FT-IR (KBr):cm^{-1}** 3372 **N-H** str.(Amino), 1682 **C=O**, 1607 **C=N** str.(Ar), 1544 **C=C** str. (Ar), 1462 **C-H** str., 1332 **C-N** str. **^{1}H NMR (MeOD, 500 MHz):** δ 7.60(d, 2H, CH), 7.51-7.24(m, 15H, CH), 6.70(d, 2H, CH), 6.44(s, 1H, CH-Ar), *6.27(s, 2H, NH2), 3.90(t, 1H, CH), 3.80(t, 1H, CH), 3.71(t, 1H, CH), 3.55-3.52(m, 1H, CH)3.39-3.36(m, 1H,CH), 3.14-3.12(m, 1H,CH), ppm.*



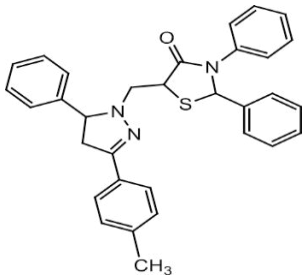
TP-4

IUPAC Name: 5-((3-(4-hydroxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl) methyl)-2,3-diphenylthiazolidin-4-one

Molecular formula : C31H27N3OS
Molecular weight :505.63
Physical state : Crystalline solid
Color : Dark Yellowish
Melting point : 184-186^{O}C
Yield : 69.32%,
Solubility : Ethanol, DMSO and Methanol
Rf – Value : 0.56

Structural Elucidation of TP- 4

Elemental analysis calculated (Found) % for **C31H27N3O2S:** C, 73.64(73.47); H, 5.38(5.26); N, 8.31(8.26); O, 6.33(6.19); S, 6.34(6.14). **FT-IR (KBr):cm^{-1}** 3366 **O-H** str. (alcohol), 3013 and2930 **C-H** str., 1674 **C=O** str., 1648 **C=N** str.(Ar), 1556 **C=C** str. (Ar), 1405 **C-H** str. **^{1}H NMR (MeOD, 500 MHz):** δ 7.86(d, 2H, CH), 7.52-7.24(m, 15H, CH), 6.86(d, 2H, CH), 6.45(s, 1H,CH-Ar), 5.35(s, 1H, OH), 3.90(t, 1H, CH), 3.81(t, 1H, CH), 3.72(t, 1H, CH), 3.55-3.52(m, 1H, CH), 3.39-3.36(m, 1H,CH), 3.16-3.13(m, 1H,CH), ppm.



TP- 5

IUPAC Name 2,3-diphenyl-5-((5-phenyl-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl) methyl)thiazolidin-4-one
Molecular formula : C32H29N3OS
Molecular weight :505.66
Physical state : Crystalline solid
Color : Off- white
Melting point : 174-176^{O}C
Yield : 70.51%,
Solubility : Ethanol, DMSO and Methanol
Rf – Value : 0.62

Structural Elucidation of TP- 5

Elemental analysis calculated (Found) % for **C32H29N3OS:** C, 76.31(76.15); H, 5.80(5.79); N, 8.34(8.28); O, 3.18(3.11); S, 6.37(6.02). **FT-IR (KBr): cm^{-1}** 3072 **C-H** str. (alkane), 1682 **C=O** str., 1607 **C=N** str. (Ar), 1576 **C=C** str. (Ar), 1400 **C-H** str., **^{1}H NMR (MeOD, 500 MHz):** δ 7.72(d, 2H, CH), 7.50-7.24(m, 17H, CH), 6.44(s, 1H, CH-Ar), 3.91(t, 1H, CH), 3.79(t, 1H, CH),3.72(t, 1H, CH), 3.55-3.51(m, 1H, CH), 3.41-3.38(m, 1H, CH), 3.15-3.12(m, 1H, CH), 2.36(s,3H, CH3), ppm.

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Antibacterial activity and Antifungal activity has been shown in the table 01 and 02 and figure represent graphical representation respectively of noble synthesized thiazolidone derivatives.

Discussion

Novel synthesized thiazolidinones derivatives were exhibited excellent anti-bacterial activity. Against B. subtilis, TP-2, TP-3, TP-4 and TP-5 were possessed moderate activity while TP-1 possessed lower activity. Against **E. coli** TP-2, TP-3, TP-5 possessed lower activity while TP-4 has moderate activity and TP-1 possessed equal to standard.

Novel synthesized thiazolidinones derivatives were exhibited anti-fungal activity. Against C. Albicans TP-1 has excellent activity, TP-3, TP-4, TP-5 has moderate activity and TP-2 has lower activity. Against A. Niger TP-1 showed excellent activity while rest all has lower activity.

Overall TP-1 was most active compound against both bacterial and fungal strain.

Conclusion

Novel thiazolidinones derivatives were exhibited excellent anti-bacterial activity. Against B. subtilis, TP-2, TP-3, TP-4 and TP-5 were possessed moderate activity while TP-1 possessed lower activity. Against **E. coli** TP-2, TP-3, TP-5 possessed lower activity while TP-4 has moderate activity and TP-1 possessed equal to standard.

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Overall TP-1 was most active compound against both bacterial and fungal strains.

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Table No.01 : Antibacterial activity of Thiazolidinones

Sample applied	Diameter of zone of inhibition (mm)	
	B. subtilis	*E. coli*
TP-1	8(25)	25(6.25)
TP-2	15(25)	11(6.25)
TP-3	15(6.25)	12(6.25)
TP-4	13(6.25)	20(6.25)
TP-5	12(6.25)	12(6.25)
Control **(C)**	-	-
Ciprofloxacin **(S)**	20(6.25)	25(6.25)

Table No.02 : Anti-fungal activity of thiazolidinones

Sample applied	Diameter of zone of inhibition (mm)	
	C. Albicans	*A. Niger*
TP-1	20(6.25)	25(12.5)
TP-2	8(6.25)	8(12.5)
TP-3	16(6.25)	10(12.5)
TP-4	13(6.25)	9(12.5)
TP-5	10(6.25)	9(12.5)
Control (C)	-	-
Itraconazole (S)	22(6.25)	27(12.5)

Figure no.1: Anti-bacterial activity of thiazolidinones

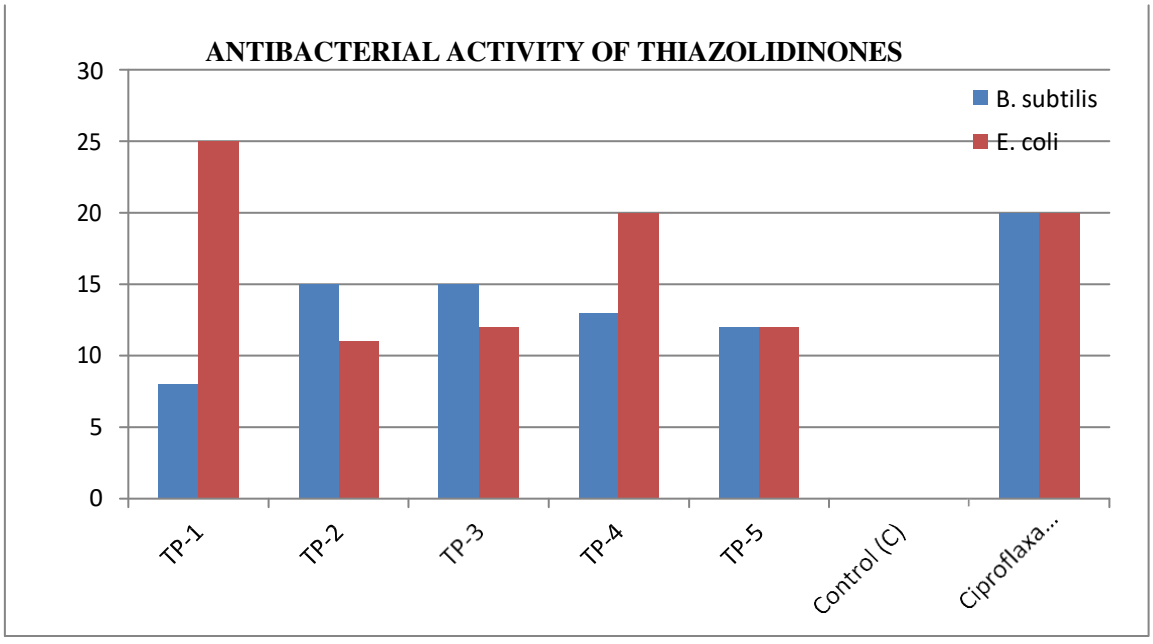

Figure no.2: Anti-fungal activity of thiazolidinones