RESEARCH ARTICLE

Synthesis and Biological Activity of New Derivatives of Thiazolidine and Oxazepine-Linked to Pyridine Moieties

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ABSTRACT

This research includes reaction and condensation between substituted 4-aminopyridine and 4-(N, N-dimethyl amino benzaldehyde) to produce Schiff base derivative (3), the compound (3) was selected to react with a different compound such as Thioglycolic acid, Phthalic anhydride, and maleic anhydride, to produced new ring of Thiazolidine derivatives and oxazepine derivatives structures (4,5,6,7,8,9,10,11,12), respectively. The final compound was characterized the structure by Fourier transform-infrared spectroscopy, H-Nuclear magnetic resonance (H-NMR) in addition to the Carbon, Hydrogen, Nitrogen (CHN) analyzer. Biological activity has been considered for the final structures and achievements of multi drugs.

Keywords: Oxazepine, Pyridine, Schiff base, Thiazolidine

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INTRODUCTION

Organic compound $(CH_2)_3(NH)S$, thiazolidine, is a heterocyclic compound Thioether and amine groups are located at positions 1 and 3, respectively, in this 5-member structure ring. Oxazolidine is a sulfur analog of this. The structure of thiazolidine is devoid of color.[1]

Thiazolidines, a derivative, have been identified. The thiazolidine ring is found in, for example, pioglitazone. Penicillin, an antibiotic with a thiazolidine ring, is another option.[2]

Thiazolidine is made by combining cysteamine and formaldehyde as it was in its first known preparation.[3] Similar reactions can yield other thiazolidines. The 4-carboxy thiazolidine derivative of formaldehyde and cysteine is noteworthy. To speed up the vulcanization of chloroprene rubbers, N-Methyl-2-thiazolidinethione is used as a catalyst.[1-3]

Thiazolidinediones, which are thiazolidinediones functionalized with carbonyls at positions 2 and 4, are drugs used to treat type 2 diabetes.[4] Bioactive Rhodanine contains both carbonyl and thiocarbonyl groups.[5,6]

There are seven atoms in an oxazepineheterocycle,[7] with nitrogen replacing a carbon at one location and oxygen replacing a carbon at another location. It has been shown that several pyridine derivatives play an essential role in biological systems.[1]

Niacin is an organic compound and a form of vitamin B_3, an essential human nutrient. Plants and animals can manufacture it from the amino acid tryptophan is found in bacteria, fungi, and mammals, but it's biological synthesis is not finished.[8] The amino acid tryptophan is oxidized in mammals to produce kynurenine, a pyridine derivative[9] that is the starting point for synthesizing nicotinic acid. On the contrary, Escherichia coli and mycobacterium tuberculosis produce nicotinic acid through the condensation of glyceraldehyde 3-phosphate and aspartic acid.[9]

New structures made in the lab were synthesized, and the biological activity of these new derivatives, thiazolidine and oxazepine, linked to pyridine moieties and their structure, was validated.

MATERIALS AND METHODS

Chemicals were supplied by Merck, Sigma-Aldrich, BDH, and Fluka and used as received.

Apparatus

The compounds' melting point was measured using Gallen kamp melting point. The elemental analysis was performed using the Euro EA3000. Using tetramethyl silane as an internal standard and DMSO as a solvent, ^{1}H-NMR spectra were collected on a JNM-model Joal 400 MHZ. At sapala organics private, measurements were taken (India). Fourier-transform spectroscopy (FT-IR) spectra were recorded on an FT-IR 8400s, Shimadzu- spectrophotometer, and KBr discs were utilized to measure FT-IR spectra in the region of wavenumber 4000–200 cm^{-1}.

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Compound (3abc)

Equal amounts were mixed in the stirring mixture of substituted 4-amino pyridine (1-mmol), 25 mL Absolute C_2H_5OH, and p-(N, N-dimethylamino) benzaldehyde (1-mmol) at room temperature. That prepared in the present study was added to the mixture was refluxed for 24 hours at 78°C. The reaction mixtures was neutralization with acetic acid and filtration to purification the precipitate, then the precipitate washed with ethanol to yield compound (3a) with 82% m.p. (124–126°C),FT-IR (in KBr): azomethine group (1645 cm^{-1}), $C_{aromatic}$ (1610 cm^{-1}), C-H (3030 cm^{-1}) $^1HNMR_{DMSO\text{-}d6}$; (7.34–7.37 δ, m, Aromatic-H), (8.12–8.62 δ, 3H, pyridine) and ^{13}C-NMR(108-139 δ for $C_{aromatic}$) and (30-35 δ) for CH_3 and compound (3b) in 78% m.p. (134-136 °C); FT-IR (in KBr): Schiff group C=N(1642 cm^{-1}), C=$C_{aromatic}$ (1615 cm^{-1}), C-H(3010 cm^{-1}) $^1HNMR_{DMSO\text{-}d6}$; (7.44-7.85 δ, m, Aromatic-H), (8.31-8.66 δ, 3H, pyridine) and ^{13}C-NMR(111-142 δ for $C_{aromatic}$) and (50-55 δ) for C-Br and compound (3c) in 81% m.p (141-143 °C); FT-IR (in KBr): Schiff group C=N(1637 cm^{-1}), C=$C_{aromatic}$ (1621 cm^{-1}), C-H(3020 cm^{-1}) $^1HNMR_{DMSO\text{-}d6}$; (7.12-7.92 δ, m, Aromatic-H), (8.33-8.69 δ, 3H, pyridine) and ^{13}C-NMR(115-145 δ for $C_{aromatic}$) and (40–45 δ) for C-Cl.

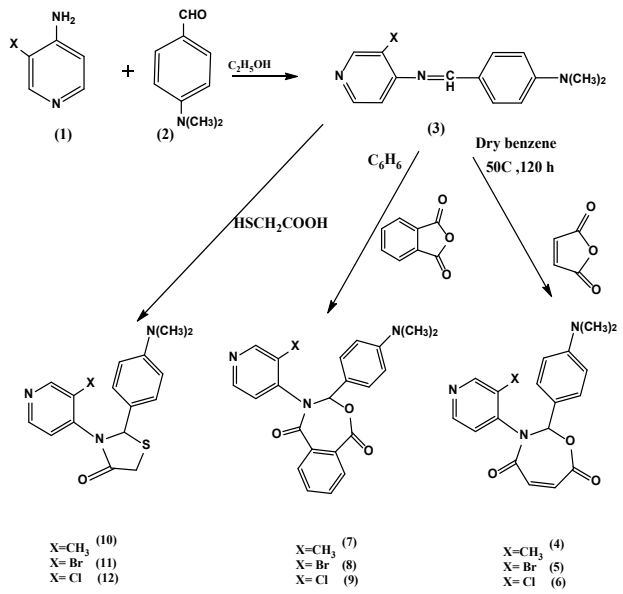
Oxazepine Derivative (4)

Compound (3a) (2 mmol) was dissolved in dry benzene (30 ml); in the stirring mixture, added maleic anhydride (2 mmol). The mixed compound was heated at 60°C for 40 hours The final structure was cooled, separation, and filtration with recrystallization in ethanol to yield (4) as crystal (solid) in 72% m.p (186-188°C) ;FT-IR (in discs of KBr) : (O-C=O lactone(1689 cm^{-1}), (N-C=O lactam(1627 cm^{-1}), C=$C_{aromatic}$ (1620 cm^{-1}), C-H(3020 cm^{-1}) $^1HNMR_{DMSO\text{-}d6}$; (7.32-7.67 δ, m, Aromatic-H), (8.22-8.67 δ, 3H, pyridine) and ^{13}C-NMR (115–145 δ for $C_{aromatic}$) and (32-36 δ) for CH_3.

The analytical calculation for structure (4) MF=$C_{19}H_{19}N_3O_3$, found. C 71.03, H 5.92, N 13.08; finding, C 71.02, H 5.95, N 13.13

Table 1: Antibacterial effects of the different synthetic structures

Comp. No.	*Conc.g/mlμ*	*Gram-(-ve) bacteria*			*Gram-(+ve) bacteria*		
		Escherichia coli	*Enterobacter*	*Shigella*	*Streptococci*	*Bacilli*	*Clostridia*
	30	10	5	6	-	-	6
4	20	11	8	7	12	5	12
	10	-	3	5	1	2	4
	30	5	14	-	-	-	11
5	20	3	8	7	6	4	8
	10	-	-	-	-	-	-
	30	8	7	11	12	9	8
6	20	9	5	3	9	7	3
	10	2	5	2	7	6	-
	30	11	8	12	9	14	5
7	20	7	9	4	5	6	10
	10	-	3	5	2	-	7
	30	12	9	11	12	9	14
8	20	11	8	7	10	8	9
	10	1	3	-	-	-	5
	30	14	10	12	9	12	10
9	20	10	9	12	8	11	13
	10	-	3	-	2	-	-
	30	14	10	14	9	12	10
10	20	10	9	12	8	11	13
	10	-	3	-	2	-	-
	30	14	10	14	9	12	10
11	20	10	9	12	8	11	13
	10	-	3	-	2	-	-
10	30	15	10	14	8	12	10
13	20	10	9	12	8	10	13
-	10	-	3	-	2	-	-
Ciprofloxacin		9	5	8	9	9	11



Scheme (1): Shows the preparation of the Heterocyclic compounds (4-12)

Oxazepine Derivative (5)

Compound (3b) (2 mmol) was dissolved in dry benzene (30 mL); in the stirring mixture, added maleic anhydride (2 mmol). The mixed compound was heated at 60 ºC for 40 hours The resulting structure was cold, filtrated, and recrystallization in ethanol to give (5) as crystal (solid) in 70% m.p (133-135 ºC) ;FT-IR (in KBr) : FT-IR (in KBr): (O-C=O lactone(1685 cm^{-1}), (N-C=O lactam(1622 cm^{-1}), C=$C_{aromatic}$ (1614 cm^{-1}), C-H(2985 cm^{-1}) $^{1}HNMR_{DMSO\text{-}d6}$; (7.32–7.86 δ, m, Aromatic-H), (8.27–8.69 δ, 3H, pyridine) and ^{13}C-NMR (111–142 δ for $C_{aromatic}$) and (45-55 δ) for C-Br.

The analysis calculation for structure (5) MF=$C_{18}H_{16}N_3O_3Br$, was found. C 56.10, H 4.16, N 10.91; finding, C 56.14, H 4.12, N 10.88

Oxazepine Derivative (6)

Compound (3c) (2 mmol) was dissolved in dry benzene (30 mL), and in the stirring mixture added, maleic anhydride(2 mmol). The mixed compound was heated at 60 ºC for 40 hours, and the compound was chilled, filtration, and purified with recrystallization in ethanol to get (6) as solid crystal in 66% m.p (108–109 ºC); FT-IR (in KBr): (O-C=O lactone(1692 cm^{-1}), (N-C=O lactam(1621 cm^{-1}), C=$C_{aromatic}$ (1645 cm^{-1}), C-H(2984 cm^{-1}) $^{1}HNMR_{DMSO\text{-}d6}$; (7.34–7.91 δ, m, Aromatic-H), (8.11–8.62 δ, 3H, pyridine) and ^{13}C-NMR(112–146 δ for $C_{aromatic}$) and (42–45 δ) for C-Cl

The analytical calculation for the structure (6) MF=$C_{18}H_{16}N_3O_3Cl$, was calculated. C 63.25, H 4.69, N 12.30; result, C 63.31, H 4.63, N 12.42

Oxazepine Derivative (7)

Compound (3a) (2 mmol) was dissolved in dry benzene (30 mL); in the stirring mixture, added phthalic anhydride (2 mmol). The mixture compound was refluxed at 60ºC for 40 hr. Then the resulting compound was cooled, filtration, and the recrystallization in ethanol to give (7) as solid crystal in 68% m.p (112-114 ºC) ;FT-IR (in KBr) : (O-C=O lactone(1705 cm^{-1}), (N-C=O lactam(1626 cm^{-1}), C=$C_{aromatic}$ (1585 cm^{-1}), C-H(2988 cm^{-1}) $^{1}HNMR_{DMSO\text{-}d6}$; (7.017.62 δ, m, Aromatic-H), (8.15-8.64 δ, 3H, pyridine) and ^{13}C-NMR(112-148 δ for $C_{aromatic}$) and (35-39 δ) for CH_3.

The analysis calculations for structure (7) MF=$C_{23}H_{21}N_3O_3$was found. C 71.32, H 5.43, N 10.85; resulting in, C 71.36, H 5.61, N 10.66

Oxazepine Derivative (8)

Compound (3b) (2 mmol) was dissolved in dry benzene (30 mL); in the stirring mixture, added phthalic anhydride (2 mmol) the mixture compound was refluxed at 60 ºC for 40 hours Then the resulting structure was cooled, filtration, and the recrystallization in ethanol to get (8) as crystal (solid) in 81% m.p (134-136 ºC) ;FT-IR (in KBr) : (O-C=O lactone(1710 cm^{-1}), (N-C=O lactam (1620 cm^{-1}), C=$C_{aromatic}$ (1598 cm^{-1}), C-H(2970 cm^{-1}) $^{1}HNMR_{DMSO\text{-}d6}$; (7.37-7.98 δ, m, Aromatic-H),

Table 2: The antifungal properties of the synthesized compounds

Comp. No.	*Conc.g/mLμ*	*Aspergillus flavus*	*Penicillium*
	30	7	11
4	20	9	10
	10	-	1
	30	8	7
5	20	6	4
	10	3	-
	30	8	12
6	20	10	9
	10	4	3
	30	12	7
7	20	8	10
	10	7	-
	30	14	8
8	20	11	9
	-	-	5
	30	12	9
9	20	5	6
	10	4	-
	30	12	7
10	20	8	10
	10	6	-
	30	10	7
11	20	9	9
	10	7	-
	30	12	8
12	20	8	10
	10	6	2
Clotrimazole		10	8

(8.26–8.89 δ, 3H, pyridine) and ^{13}C-NMR(112–155 δ for $C_{aromatic}$) and (42–51 δ) for C-Br.

The analytical calculation for the structure (8) MF=$C_{22}H_{18}N_3O_3Br$, was found. C 58.65, H 3.69, N 10.31; result, C 58.39, H 3.62, N 10.38

Oxazepine Derivative (9)

Compound (3c) (2 mmol) was dissolved in dry benzene (30 mL); in the stirring mixture, added phthalic anhydride (2 mmol) was. The mixed compound was refluxed at 60 ºC for 40 hours The final structure was chilled, filtration, and the recrystallization in ethanol to yield (9) as solid crystal in 82% m.p (127–129 ºC) ;FT-IR (in KBr) : (O-C=O lactone(1708 cm^{-1}), (N-C=O lactam(1622 cm^{-1}), C=$C_{aromatic}$ (1601 cm^{-1}), C-H 2956 cm^{-1}) ^{1}HNMR$_{DMSO\text{-}d6}$; (7.32–7.96 δ, m, Aromatic-H), (8.13-8.68 δ, 3H, pyridine) and ^{13}C-NMR(118–149 δ for $C_{aromatic}$) and (40–44 δ) for C-Cl

Analytical calculation of the structure (9) MF=$C_{22}H_{18}N_3O_3Cl$, found. C 64.79, H 4.42, N 10.31; resulting in, C 63.98, H 4.53, N 10.45

Thiazolidine Derivative (10)

Compound (3a) (2 mmol) was added to thioglycolic acid (2 mmol) in 1,4-Dioxane (25 mL) and added to the mixture Zinc chloride anhydrous, and the mixed compound was refluxed for 24 hours in 55ºC. The final product was cooled, filtration, and the recrystallization in ethanol to give (9) as crystal (solid) in 74% m.p (131–132 ºC) ;FT-IR (in KBr) : C=O (1681 cm^{-1}), C=$C_{aromatic}$ (1580 cm^{-1}), C-H(2945 cm^{-1}) ^{1}HNMR$_{DMSO\text{-}d6}$; (CH-N, 3.6 δ), (CH_2-S, 3.3 δ), (7.51–7.89 δ, m, Aromatic-H), (8.26–8.69 δ, 3H, pyridine) and ^{13}C-NMR(105–148 δ for $C_{aromatic}$) and (31–35 δ) for CH_3.

The analytical calculation for the compound (10) MF=$C_{17}H_{19}N_3OS$was found. C 65.18, H 6.07, N 13.42; resulting in, C 65.58, H 6.51, N 13.45

Thiazolidine Derivative (11)

Compound (3b) (2 mmol) was added to thioglycolic acid (2 mmol) in 1,4-Dioxane (25 mL) and added to the mixture Zinc chloride anhydrous, and the mixed compound was refluxed for 24 hours in 55ºC. The resulting product was left to be cold, filtration, and recrystallization in ethanol to yield (11) as a crystal (solid) in 67% m.p (155–157 ºC), FT-IR (in KBr): C=O (1688 cm^{-1}), C=$C_{aromatic}$ (1593 cm^{-1}), C-H (2945 cm^{-1}) ^{1}HNMR$_{DMSO\text{-}d6}$; (CH-N, 3.3 δ), (CH_2-S, 3.1 δ),(7.31–7.92 δ, m, Aromatic-H), (8.23–8.85 δ, 3H, pyridine) and ^{13}C-NMR (115–152 δ for $C_{aromatic}$) and (41–45 δ) for C-Br.

The analytical calculation for the compound (11) MF=$C_{16}H_{16}N_3OSBr$, was found. C 50.93, H 4.24, N 11.14; resulting in, C 50.98, H 4.33, N 11.65.

Thiazolidine Derivative (12)

Compound (3c) (2mmol) was added to thioglycolic acid (2 mmol) in 1,4-Dioxane (25 mL) and added to the mixture Zinc chloride was anhydrous, and the mixed compound was 24 hours at 55ºC. The final compound was chilled, filtration, and purification with recrystallization in ethanol to yield (9) as solid crystal in 69% m.p (145–147 ºC) ;FT-IR (in KBr) : C=O (1684 cm^{-1}), C=$C_{aromatic}$ (1595 cm^{-1}), C-H (2946 cm^{-1}) ^{1}HNMR$_{DMSO\text{-}d6}$; (CH-N, 3.8 δ), (CH_2-S, 3.5 δ), (7.38–7.90 δ, m, Aromatic-H), (8.23-8.56 δ, 3H, pyridine) and ^{13}C-NMR (114–146 δ for $C_{aromatic}$) and (42–46 δ) for C-Cl

The analytical calculation for compound (12) MF=$C_{16}H_{16}N_3OSCl$, was found. C 57.57, H 4.80, N 12.59; rsulting in, C 57.68, H 4.83, N 12.48

RESULTS AND DISCUSSION

To obtain Thiazolidine and oxazepine derivatives, we take compound (3) that was prepared by reaction of substituted benzaldehyde (2) with various substituted aminopyridine (1) shown in Scheme 1. The various Schiff base was identified by FT-IR in different peaks between (1624–1665 cm^{-1}) that indicated the formation of azomethine groups CH=N with proton NMRof it that appeared in 8-8.5 δ in and (7.13–7.28 δ, m, Aromatic-H) in ^{1}HNMR$_{DMSO\text{-}d6}$: Schiff group C=N(1642 cm^{-1}), C=$C_{aromatic}$ (1615 cm^{-1}), C-H(3010 cm^{-1}) ^{1}HNMR$_{DMSO\text{-}d6}$; (7.00–7.99 δ, m, Aromatic-H), (8.00-8.66 δ, 3H, pyridine) and ^{13}C-NMR (100–142 δ for $C_{aromatic}$) for compounds a, b and c.

It was refluxing the azomethine compound (3) with maleic anhydride to give oxazepine derivative(4-6); the Spectro data that identify produced oxazepine that disappearance of azomethine group and produced lactone data shown for compound (4) FT-IR (in KBr discs): (O-C=O lactone(1689 cm^{-1}), (N-C=O lactam(1627 cm^{-1}), C=$C_{aromatic}$ (1620 cm^{-1}), C-H (3020 cm^{-1}) ^{1}HNMR$_{DMSO\text{-}d6}$; (7.32–7.67 δ, m, Aromatic-H), (8.22–8.67 δ, 3H, pyridine) and ^{13}C-NMR(115–145 δ for $C_{aromatic}$) and (32–36 δ) for CH_3.

Reaction and Refluxing of the azomethine compound (3) with phthalic anhydride to give oxazepine derivative(7-9) from various Spectro data that shown disappearance of Schiff base group and produced of new bond for example compound (8); FT-IR (in KBr): (O-C=O lactone(1710 cm^{-1}), (N-C=O lactam(1620 cm^{-1}), C=$C_{aromatic}$ (1598 cm^{-1}), C-H (2970 cm^{-1}) ^{1}HNMR$_{DMSO\text{-}d6}$; (7.37–7.98 δ, m, Aromatic-H), (8.26–8.89 δ, 3H, pyridine) and ^{13}C-NMR (112–155 δ for $C_{aromatic}$) and (42–51 δ) for C-Br.

To prepare Thiazolidine derivative (9-12) from thioglycolic acid that dissolved in 1,4-Dioxane that added to mixture Zinc chloride anhydrous is refluxed for one day, various Spectro data that shown disappearance of Schiff base group and produced of new bond (CH-N), (CH_2-S) and carbonyl group for example compound(12):FT-IR (in KBr): C=O (1684 cm^{-1}), C=$C_{aromatic}$ (1595 cm^{-1}), C-H (2946 cm^{-1}) ^{1}HNMR$_{DMSO\text{-}d6}$; (CH-N, 3.8 δ), (CH_2-S, 3.5 δ), (7.38–7.90 δ, m, Aromatic-H), (8.23–8.56 δ, 3H, pyridine) and ^{13}C-NMR(114-146 δ for $C_{aromatic}$) and (42–46 δ) for C-Cl.

Antibacterial and the Antifungals Activity Study

Various bacterial and fungicidal properties in 5- and 7-membered heterocyclic compounds and pyridine moieties are linked to the same condition's different biological activity.11-16

These six newly synthesized heterocyclic compounds were used in this study to combat the bacteria *Clostridium* (negative), *E. coli*, *Shigella*, *Streptococcus,* and *Enterobacter, Bacillus,* and at concentrations of (1, 0.2 0.3 0) μg/cm^3 as explained in Table 1 and the fungi *Penicillium and Aspergillus flavus* at the exact concentration conditions (Table 2).

CONCLUSION

According to the findings, new structures made in the lab were synthesized, and their structure was validated using Fourier transform-infrared (FTIR) spectroscopy, H-Nuclear magnetic resonance (HNMR) in addition to elemental analysis. Biological activity has been considered for the final structures and tested on Gram-negative and Gram-positive bacteria and fungi. The results showed that these structures are active and could be used to treat these microorganisms in the future since they were linked to the drugs Clotrimazole and Ciprofloxacin utilized to disinfect these microbes. A percentage of the synthetic structures has been found to be an active treatment.

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AUTHORS' CONTRIBUTIONS

All authors contributed towards data analysis, drafting and revising of the paper and agreed to be responsible for all the aspects of this work.

CONFLICT OF INTEREST

We have no conflicts of interest to disclose.

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