

Synthesis and Characterization of 1,4-(1,1'-2-aminoaryl bisdithiazolidine-3,3'-aryl) benzene with Insights into Biological Activities

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ABSTRACT

Dithiazolidines are unique kind of five membered heterocyclic compounds which has a special structure which contains two nitrogen and two sulphur atoms in a particular arrangement. They can react to a wide range of substituents because of this arrangement and thus having much capacity to modulate functional behavior as well as their chemical reactivity. Due to this special structure, they represent variety of applications and hence these compounds are matter of interest and attention of the various academic disciplines. These dithiazolidines serve as an effective intermediate in the chemical synthesis and they also facilitate the construction of various complex molecular structures. These dithiazolidine analogs have been of great interest in the field of medicinal chemistry as they have demonstrated promising antibacterial activities and bioactive potential due to their unique mechanisms of action. They are also deemed to be appropriate in material science progress, owing to having donor-acceptor properties and redox-activity, namely in the development of electronic materials, sensors, as well as functional polymers. These dithiazolidines are under investigation and this paper justifies their value in attaining fundamental science and at the same time, effective technologies. In this work, there was synthesis of 1, 4 -bis (R-aminothiocarbonyl) amino) benzene, which were used to determine the structures. Aantimicrobial performance measurement of these compounds were observed and represent moderate or significant effect on a limited number of bacterial strains. This evidence suggests that a dithiazolidine frameworks is being considered in creating antibacterial medication. The significance of dithiazolidines in medicinal chemistry in order to encourage research and further investigation of its applications and functions in medicine is discussed in this work..

Keywords: Dithiazolidines, heterocyclic, biological activity, bioactive, characterization

1. INTRODUCTION

Dithiazolidine is a class of specially-modified heterocyclic compounds which has attracted the attention of scientists. Unique ring structure containing two nitrogen and two sulphur atoms (1) and resulting peculiar geometry of structure makes them a flexible chemical paradigm with molecules having unusual physicochemical as well as biological characteristics may be designed. The substituents are easily added on the dithiazolidine ring which reflects on their stability, reactivity as well as bioactivity. This results in their applications in the field of synthetic organic chemistry, medicinal chemistry and materials science. (2, 7).

Dithiazolidines are useful intermediates in the synthesis of more sophisticated molecular scaffolds and hold way to multifaceted heterocycles, and bioactive scaffolds in the context of organic synthesis (8). Their derivatives have shown good antimicrobial, antifungal, and anticancer property, which is a sign of their

potential therapeutic effects in a wide range of different disease models (5). These compounds have found applications in surfaces science as corrosion inhibitors (11-13) and surface modifiers because of an affinity to engage with metal surfaces and miscellaneous physicochemical characteristics (4). Moreover, they have been regarded as appropriate ligands in process of complexing metals since they can do so (14). This makes it catalytically useful both in coordination chemistry and to widen their application in industrial catalysis (3,15).

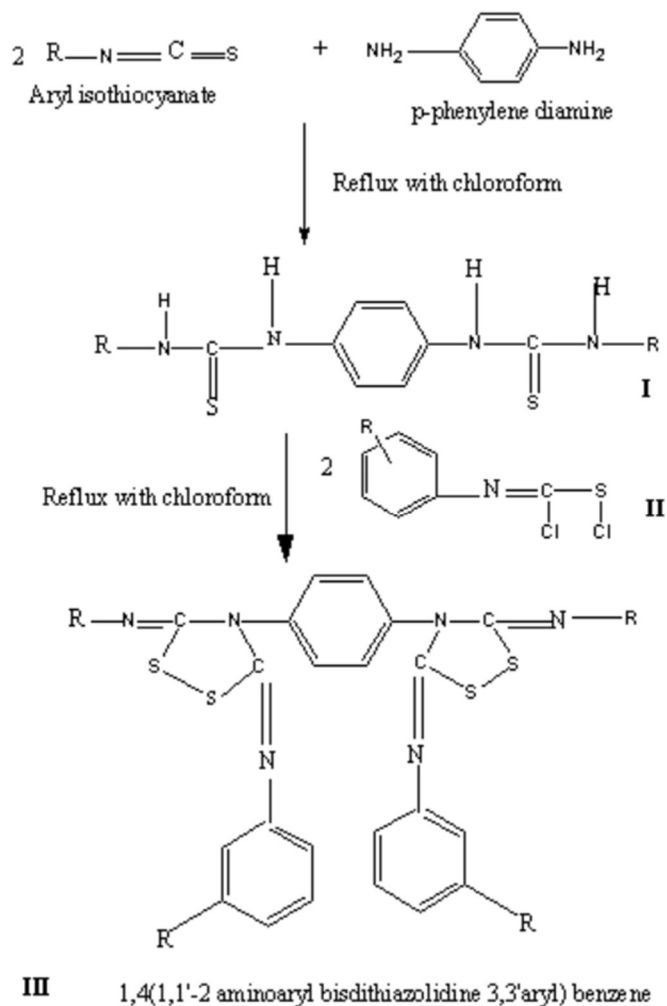
The dithiazolidine ring system is structurally able to accommodate different aryl and functional groups, and essentially this affects the distribution of electrons, as well as, steric interactions. Such studies have been primarily devoted to the synthesis of thiazolidine and diathiazolidine analogs which include varied incorporated aryl groups (16,17) and attempts targeted at both thiazolidine and dithiazolidine analog structurally, with studies of structure-activity relationships (SAR) informing about a variation of substituent-effect on anti-microbial activity (6). Well-developed analysis methods such as IR, NMR and HRMS has significant contribution in the analysis of structural integrity, clarify patterns of reactivity as well as zoning insight of molecular behavior (9).

One of the major health problems facing the world today is microbial resistance and the diathiazolidine derivatives are the ones that would solve the problem. They are believed to be good future therapeutic development prospects, since they have unusual structure as well as the selectivity in acting on the Gram-positive bacteria. Biological testing of strains that are resistant to drugs should be applied in future studies, attainment of minimum-inhibitory concentrations (MICs) and computational methods, including molecular docking and SAR modelling, to exhaust the potential. It will also be useful in the study of the substituent effect in dithiazolidines (10).

In this work, 1, 4(1,17 2 aminoaryl bisdithiazolidine 3,37aryl) benzene (III) was produced using Aryl groups a) o -tolyl b) p -tolyl c) phenyl d) o -anisyl. Such studies as IR, NMR and HRMS were used in characterization of synthesized compounds. There were also antimicrobial research studies on synthesized compounds.

2. MATERIALS AND METHODS:

2.1. Synthesis: Aryl Isothiocyanates were synthesized with the help of already known procedures (18). Aryl isothiocyanate (0.02M) and p-phenylene diamine (0.01M) were refluxed using chloroform as a solvent to produce 1, 4-bis ((R-aminothiocarbonyl) amino) benzene (I). Using CHCl₃ as a solvent was refluxed and then subjected to cyclization reaction to make 1,4(1,1 2 aminoaryl bisdithiazolidine 3,3 aryl) benzene (III). Incorporated aryl groups are 2-tolyl a) 4-tolyl b) phenyl and 2-anisyl d).



Where R in (III) 1,4(1,1'-2 aminoaryl bisdithiazolidine-3,3'aryl) benzene is 2-tolyl (III-a), 4-tolyl (III-b), phenyl (III-c) and 4-anisyl (III-d).

2.2. Characterization: The structures of newly synthesized compounds were ascertained using IR, ^1H -NMR, ^{13}C -NMR and HRMS study.

(III-a) 1,4(1,1'-2 amino 2-tolyl bisdithiazolidine-3,3' 2-tolyl) benzene

IR (KBr) ν max cm^{-1} : 3229(N-H), 2851.88(C-H aromatic), 1621.34(C=N), 1509.96(C=C Aromatic ring stretch), 1339.15(C-N), 753.26(C-S), 503.89(S-S). ^1H NMR (CDCl_3) δ_{H} ppm: 8.07-6.8 (m, 28H, Ar-H), 2.50(s, 6H, Ar-CH₃). ^{13}C NMR (CDCl_3) δ_{C} ppm: 161.195 (2C, C=N dithiazolidine ring carbon), 141.744 - 116.309 (42C, Aromatic ring carbons), 16.243-16.521 (4C, Ar-CH₃ carbon). MS(m/z): Aromatic core (107), thiazole + side chain (209), di-thiazolidine (244). The molecular formula of III-a was established as $\text{C}_{50}\text{H}_{40}\text{N}_6\text{S}_4$. Molecular weight 852. Colour: Black.

(III-b) 1,4(1,1'-2 amino 4-tolyl bisdithiazolidine-3,3' 4-tolyl) benzene

IR (KBr) ν max cm^{-1} : 3429.52 (N-H), 2852.55 (C-H aromatic), 1630.20 (C=N), 1509.27 (C=C Aromatic ring stretch), 1313.15 (C-N), 751.47 (C-S), 502.95 (S-S). ^1H NMR (DMSO) δ_{H} ppm: 7.89 - 7.02 ^{13}C NMR (DMSO) δ_{C} ppm:

161.727 (2C, C=N dithiazolidine ring carbon) 130.786-122.437 (42C, Aromatic ring carbons), 16.808-16.248 (2C, Ar-CH₃ carbon). MS(m/z):- Aromatic core (107), di-thiazolidine (223-224). The formula of III-b was determined to be C₅₀H₄₀N₆S₄. Molecular weight 852. Colour: Black.

(III-c) 1,4(1,1'-2 amino phenyl bisdithiazolidine-3,3' phenyl) benzene

IR(KBr) ν max cm⁻¹: 3203.73(N-H), 2850.78(C-H aromatic), 1621.69(C=N), 1550.31(C=C Aromatic ring stretch), 1333.24(C-N), 756.34(C-S), 491.59(S-S). ¹H NMR(CDCl₃) δ ppm: 8 -1 0 - 7.95 C13 NMR(CDCl₃) δ ppm: 161.516 (2C, C=N dithiazolidine ring carbon), 140.413 -122.389(42C, Aromatic ring carbons). MS(m/z): Fragments of thiazoles (mid-range 227-244). The C₄₆H₂₈N₆S₄ molecule formula was determined to be III-c. Molecular weight 792. Colour: Black.

(III-d) 1,4(1,1'-2 amino 2-anisyl bisdithiazolidine-3,3' 2-anisyl) benzene

IR (KBr) ν max cm⁻¹: 3215.01(N-H), 3012.67(C-H aromatic), 1613.16(C=N), 1536.89(C=C Aromatic ring stretch), 1330.60(C-N), 1180.91(C-O), 718.97(C-S), 518.02(S-S). ¹H NMR (DMSO) δ ppm: 7.656-6.890 (m, 28H, Ar-H), 3.7428 (Ar-OCH₃). C¹³ NMR (DMSO) δ ppm: 179.679 (2C, C=N dithiazolidine ring carbon), 139.226 - 122.829 (42C, Aromatic ring carbons), 156.480(Ar-OCH₃). MS(m/z): Strong di-thiazolidine (240), extended scaffold (287). The molecular formula of III-d was established as C₅₀H₄₀N₆S₄O₄. Molecular weight 916. Colour: Grey.

2.3. Antimicrobial Studies: Antimicrobial activity of these synthesized compounds was screened. As per standard procedure, the antibacterial screening was done. (19, 20).

3. RESULTS AND DISCUSSION

3.1. Synthesis, characterization of molecules

1,4(1,1'-2 aminoaryl bisdithiazolidine-3,3' aryl) benzene was synthesized with derivatives (III-a-III-d) as per scheme. The structures of newly synthesized molecules were assessed through FT-IR, ¹³C-NMR, ¹H-NMR, and HRMS studies and elemental analysis.

The IR spectra were recorded on a FTIR Shimadzu (Affinity) Elmer spectrum RXI (8300 to 350 cm⁻¹) FT IR spectrometer. ¹H NMR were obtained on a JOEL, ECZR Series 600 MHz NMR spectrometer for a sample in DMSO/CDCl₃ solution with TMS as an internal reference. The mass spectra were recorded on Maldi-TOF Synapt XS HD Mass Spectrometer.

The IR spectra displayed characteristic absorption bands corresponding to incorporated functional groups. All compounds exhibited strong N-H stretching bands (3200-3430 cm⁻¹), confirming the presence of amino functionalities. For diagnostic dithiazolidine ring system the C=N stretching vibrations (~1610-1630 cm⁻¹) were observed. Similarly, C-S (~750 cm⁻¹) and S-S (~500 cm⁻¹) stretches consistently validated the thiazolidine framework. Substituent-specific signals were observed for III-a and III-b, typical aromatic C-H stretches (~2850 cm⁻¹). An additional C-O stretch (~1180 cm⁻¹) observed in III-d confirming anisyl substitution

The ¹H-NMR spectra further validated the structures of all synthesized compounds. Substituent signals were observed for III-a at δ 2.50 ppm and for III-b at δ 2.20 ppm indicating Ar-CH₃ bonding. III-d at δ 3.74 ppm showed diagnostic Ar-OCH₃ for anisyl substitution.

The ¹³C-NMR spectra showed characteristic bands around δ 161-180 ppm suggesting for C=N carbons of dithiazolidine ring. Aromatic carbons were distributed between δ 116-141 ppm (CDCl₃) or δ 122-139

ppm (DMSO). Substituent-specific peaks observed around $\delta \sim 16$ ppm specific for Ar-CH₃ in III-a & III-b. Methoxy substitution was confirmed around $\delta \sim 156$ ppm for Ar-OCH₃ for III-d.

HRMS data provided major fragment ions and molecular ion peaks which are consistent with various proposed structures of the compound. All compounds showed a common aromatic core fragment ($m/z \sim 107$). Thiazolidine-related fragments appeared in the range m/z 223–244, which varies with substituents present. III-d displayed extended scaffold fragments (m/z 240, 287), consistent with anisyl substitution.

The synthesized compounds were assessed for elemental composition and physical properties which are summarized in the Table. The range observed for molecular weights is from 852 to 916 g/mol which appears to be correlating with the calculated values. Synthesized compounds varies in color from grey to black.

Molecular weight and Molecular Formula

	Name	Molecular Weight	Molecular Formula	Colour
III-a	1,4(1,1'-2 amino 2-tolyl bisdithiazolidine-3,3' 2-tolyl) benzene	852	C ₅₀ H ₄₀ N ₆ S ₄	Black
III-b	1,4(1,1'-2 amino 4-tolyl bisdithiazolidine-3,3' 2-tolyl) benzene	852	C ₅₀ H ₄₀ N ₆ S ₄	Black
III-c	1,4(1,1'-2 amino phenyl bisdithiazolidine-3,3' phenyl) benzene	792	C ₄₆ H ₂₈ N ₆ S ₄	Black
III-d	1,4(1,1'-2 amino 2-anisyl bisdithiazolidine-3,3' 2-anisyl) benzene	916	C ₅₀ H ₄₀ N ₆ S ₄ O ₄	Grey

The combined IR, NMR, and MS data confirm the successful synthesis of dithiazolidine derivatives with varying aromatic substituents. Due to methyl substitution (III-a, III-b), with ortho vs para positioning which influences chemical environment, slightly shifted NMR signals were observed. Simplest spectral profile with reduced molecular weight was observed in Phenyl substitution (III-c) attributed to due to absence of alkyl/alkoxy substituents. Distinct IR and NMR signals were observed due to Methoxy substitution (III-d). I also increased molecular weight and altered colour from grey to black, likely due to electronic effects of the -OCH₃ group. Subtle spectral shifts were observed due to substituents modulating electron density across the aromatic core and dithiazolidine rings. Enhanced conjugation and altered optical properties attributed due to Methoxy groups (III-d) which are electron-donating. While compounds III-a to III-c are black and III-d is grey which suggests modification of electronic transitions, possibly reducing π - π stacking or altering charge-transfer interactions due to anisyl substitution,

3.2. Antimicrobial Activity

Newly synthesized dithiazolidines were assessed for antibacterial sensitivity against the selected Gram-negative strain as *Escherichia coli* and Gram-positive strain as *Staphylococcus aureus*. The comparative study for inhibition zones produced is as per table.

Compound Name	Active Against <i>E. coli</i>	Active Against <i>S. aureus</i>	Max Zone (mm)	Dose Response
1,4(1,1'-2 amino 2-tolyl bisdithiazolidine-3,3' 2-tolyl) benzene	NZI	6.66 -11.5 mm	11.5	Moderate

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Compound Name	Active Against <i>E. coli</i>	Active Against <i>S. aureus</i>	Max Zone (mm)	Dose Response
1,4(1,1'-2 amino 4-tolyl bisdithiazolidine-3,3'-2-tolyl) benzene	NZI	7.33 - 13.5 mm	13.5	Strong
1,4(1,1'-2 amino phenyl bisdithiazolidine-3,3' phenyl) benzene	7.67 - 12.5 mm	8.00 - 12.17 mm	12.5	Strong
1,4(1,1'-2 amino 2-anisyl bisdithiazolidine-3,3' 2-anisyl) benzene	8.67 - 13.33 mm	9.83 - 12.67 mm	13.33	Strong

Distinct structure–activity relationship was observed on comparative evaluation of the synthesized dithiazolidine derivatives. The tolyl-substituted derivatives (2-tolyl and 4-tolyl) exhibited a lack of efficacy toward Gram-negative bacteria and hence no measurable activity observed against *E. coli*. However, both compounds demonstrated moderate to strong inhibition against Gram-positive *S. aureus*. It was also observed that the 2-tolyl derivative consistently outperformed the 4-tolyl derivative. This suggests that the position of the substituent on the aromatic ring of heterocycles plays an important role in regulating antibacterial potency against Gram-positive strains.

In contrast, broad-spectrum activity was displayed by phenyl and 2-anisyl derivatives, effectively. Among these, the 2-anisyl derivative, producing the largest zone of inhibition (13.33 mm against Gram-negative *E. coli* at 2x concentration), thereby highlighting its superior efficacy.

4. Conclusion

It is a synthesis and characterization of a series of new methodologies of aryl substituted dithiazolidines that provides a contribution to the accolade of literature on heterocyclic chemistry and a continuation of the previous studies which solely looked at thiazolidines, and dithiazolidines. Structural variation was strictly checked with the help of IR, NMR and HRMS of various aromatic substituents (o tolyl, p tolyl, phenyl and o anisyl). The dithiazolidine structures are continually confirmed in this study, and substituent-site-specific signatures (methyl, phenyl, anisyl) are also sufficient to obtain a definitive structural variation. The results point out the fine-tuning ability of structural, electronic and physical characteristics using substituent variation on the dithiazolidine backbone. This tunability can indicate possible applications in the synthesis of functional materials or bioactive molecules in which electronic control is required. This work puts a strong and pronounced connection between the type of the substituents and the spectral/physical features underpinning the need to use dithiazolidine derivatives as a starting point to research more within material science and medicinal chemistry.

On biological screening, clear structure -activity relationship (SAR) was observed. The tolyl derivatives were selective activity towards *Staphylococcus aureus* and not towards *Escherichia coli*. Para tolyl derivative was more active in comparison to the ortho tolyl derivative. It was found that phenyl and o anisyl derivatives had on clear zone of inhibition with both Gram negative and Gram-positive strains on the other activity. The o anisyl derivative which was majorly giving the greatest zone inhibition (13.33 mm with Gram-negative *E. coli* at 2X concentration, and 12.67 mm at 2X concentration with *S. aureus*). Such increased efficacy could be explained by the electron donating nature of the anisyl substituent that could be responsible of increased lipophilicity that predetermines more effective interactions with microbial targets. The dose dependence inhibition zones were found across all the active compounds with particular

impact in *S. aureus* with significant findings in the reproducibility and pharmacological appeal of these scaffolds.

What is more, their multidisciplinary nature is also observed because of their antimicrobial potential. They are regarded as an appealing target to drug discovery as well as a material science (as building block to functional materials) and coordination chemistry (as ligands to metal-based catalysts). This is highly explained by heterocyclic structure and diversity of substituents. They have the potential to make contributions in the areas of biomedical and industrial innovation because they have a versatile nature.

5. Limitations and Future Outlook

With these positive outcomes, it is necessary to note that there are certain limitations. Elucidation through mechanistic studies to become aware of precise mode of action was beyond the current scope. The biological screening was limited to few bacteria and fungi strains. Thus, the future research should be mostly occupied by mechanical studies aimed at explaining the interactions between the target, SAR-directed structural modifications, and more general antimicrobial testing on a wide range of pathogens. Pharmacokinetic profiling, computational docking and validation in vivo will further better the translational potential of these types of scaffolds. Their role in resistant micro strains can also provide a valuable clue how to combat antibiotic resistance in case of their study into their operation.

6. Final Perspective

All these discoveries would place aryl-substituted dithiazolidines as good lead structures to be utilized as a foundation and base of antibacterial drugs in the future. Due to their wide spectrum effect, selective characteristics and chemical versatility, they are regarded as a rather promising candidate to be studied in the future. The combination of medical chemistry, materials science and catalysis also highlights the interdisciplinary importance of modern-day synthetic chemistry with these heterocyclic structures uniting these disciplines. The urgent need of new antimicrobials and functional material is only one of the urgent global problems that will necessitate the further research of the dithiazolidines.

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