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RESEARCH ARTICLE

Synthesis, Characterization and Biological Activity of New Ester Containing Azo Group Derived From 2-Amino-1, 3, 4-Thiadiazoline Derivatives

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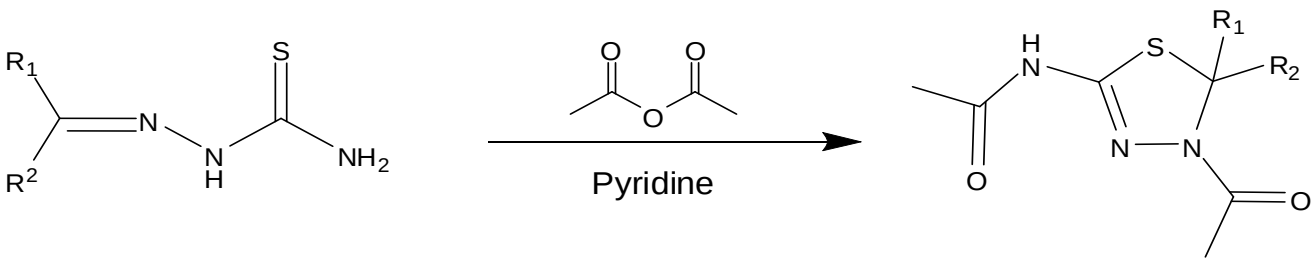
Abstract

New azo compounds derived from 2-amino-1,3,4-thiadiazolines were synthesized. The cyclization reaction of thiosemicarbazones **[I]$_{a,b}$** with the acetic anhydride lead to formation of 1,3,4-thiadiazoline compounds **[II]$_{a,b}$**. Compounds**[II]$_{a,b}$** were converted to 2-amino-1,3,4- thiadiazolines **[III]$_{a,b}$** by hydrolysis of amide group using hydrazine hydrate. The new azo compounds **[IV]$_{a,b}$** were synthesized via converted the amino group of **[III]$_{a,b}$** to diazonium salt, follow by the reaction with 4-hydroxyphenol. Finally the ester compounds **[V]$_{a-f}$** was synthesized from the reaction of azo compounds with suitable carboxylic acid chloride. The synthesized compounds were characterized by elemental analysis, FTIR, ^{1}HNMR and mass spectroscopy. All these compounds were evaluated for antibacterial activity against *Staphylococcus aureus*, *Bacillus Subtilis*, *Escherichia coli* and Pseudomonas *aeruginosa* by disk diffusion method and for antifungal activity against *Aspergillus niger* in Sabouraud's dextrose agar medium. Amoxicillin and fluconazole were used as standard drugs for Gram positive, Gram negative and antifungal activity, respectively. Most of the compounds have shown significant antibacterial and antifungal activity when compared with the standard antimicrobial agents.

Keywords: *1, 3, 4-Thiadiazoline; Ester compounds; Azo compounds; Antibacterial activity; Antifungal activity; Disk diffusion.*

Introduction

The heterocyclic products having wide spectrum of biological and technological applications [1, 2].Three heteroatom in the five member ring have been synthesized in the past decades because of their broad range of pharmacological behaviors. In the literature review, there are various methods available for the synthesis of 1,3,4- thiadiazolines, among them one of the most employed is that of converted thiosemicarbazones to corresponding 1,3,4-thiadiazolines derivatives by cyclization under acetylating conditions [3-5], as in the following reaction [6].



Differently substituted thiadiazoline moieties have been found to have interesting activities such as its anti-inflammatory [7], anticonvulsant [8], antimicrobial [9-13], trypanocidal activity [14] and vitro cytotoxic activity [15]. Azo compounds constitute one of the largest classes of industrially synthesized organic compounds. They are important in dye, drugs and cosmetics and show a variety of interesting biological activities including antibacterial [16, 17], anticancer [18] and pesticidal activities. Another positive

property of azo dyes is their antimicrobial activity. For example, 4-phenylazophenoxyacetic acids revealed antimicrobial activity against two gram-positive bacteria, *Staphylococcus ureus* (bacterium that can causes several serious illnesses such as skin infections, pneumonia, meningitis, osteomyelitis or endocarditic) and *Streptococcus pyogenes* (the causative agent in streptococcal infections, including strep throat) as well as three gram-negative bacteria (*Pseudomonas aeruginosa*, *Proteus vulgaris* and *Escherichia coli*) and one fungi species (*Candida albicans*) [19, 20].

In view of the above considerations and in continuation of our previous work [21,22] on synthesis and reactions of 1,3,4-thiadiazolines and azo compounds, we report here on the synthesis, characterization and biological activity of new ester compounds containing azo and 1,3,4-thiadiazoline moites.

Experimental

General

All the reagents and solvents used were of analytical grade and were used without further purification unless otherwise mentioned. FTIR spectra (KBr pellets) were recorded with a Shimadzu 8400s spectrophotometer. The ^{1}HNMR spectra were recorded on Bruker AMX-300 spectrometer at 300 MHz, using deutrated DMSO as a solvent with TMS as an internal standard. Elemental analysis was carried out using a Perkin-Elmer model 2400 instrument.

Uncorrected melting points were determined by using a hot-stage Gallen Kamp melting point apparatus. The progress of the reactions was monitored by TLC technique using n-hexane: ethyl acetate (8:2).

Synthesis

All compounds were synthesized according to Scheme 1, and the following procedures:

Synthesis of 4-bromobenzaldehyde Thiosemicarbazone [I]$_a$, 4-bromo-acetophenone thiosemicarbazone [I]$_b$, N-(4-acetyl-5-(4-bromo- phenyl) 5-H-1, 3,4-thiadiazoline)-acetamide [II]$_a$ and N-(4-acetyl-5-(4-bromophenyl)-5-methyl-1,3,4-thiadiazoline)acetamide [II]$_b$

These four compounds were synthesized according to the procedure described in our previous work [21, 22].

General Procedure for the Synthesis of 4-acetyl-2-amino-5-(4-bromophenyl)-5-H-1,3,4-thiadiazoline [III]$_a$ and 4-acetyl-2-amino-5-(4-bromophenyl)-5-methyl -1,3,4-thiadiazoline [III]$_b$.

A mixture of 1, 3, 4-thiadiazolines [II] (10 mmol) and hydrazine hydrate 50% (30 mL) was stirred at 45-50 for 2 h. The resulted precipitate was collected by filtration and recrystallized from ethanol.

4-acetyl-2-amino-5-(4-bromophenyl)-5-H-1, 3, 4-thiadiazoline [III] $_a$

Off-white solid; yield 80 %; m.p 190-192^{0}C.FTIR (KBr, υ, cm^{-1}): 3385-3290 (NH_2 Asy. sy.), 1649 (C=O), 1618 (C=N endocyclic). Anal. calcd. For C_{10} $H_{10}N_3SOBr$: C, 40.0; H, 3.33; N, 14.0; S, 10.66; Found: C, 40.22; H, 3.54; N, 14.46; S, 10.42%.

4-acetyl-2-amino-5-(4-bromophenyl)-5-methyl-1, 3, 4-thiadiazoline [III]$_b$

Off-white; yield 72 %; m.p 140-142^{0}C.FTIR (KBr, υ, cm^{-1}): 3423-3273 (NH_2 asy., sy.), 1654 (C=O), 1630 (C=N endocyclic). ^{1}HNMR (300 MHz, DMSO-*d*6, δ, ppm): 1.88 (s, 3H, CH_3 at C5 of thiadiazoline ring), 2.45 (s, 3H, CH_3CON), 6.51 (s, 2H, NH_2), 7.32-7.52 (dd, J= 6,7 Hz, 4H, CH ar). Anal. calcd. For $C_{11}H_{12}N_3SOBr$: C, 42.03; H, 3.82; N, 13.37; S, 10.19. Found: C, 42.29; H, 3.92; N, 13.08; S, 10.40%.

General Procedure for the Synthesis of 4-acetyl-2-(4-hydroxy-phenyl) azo-5-(4-bromophenyl)-5-H-1, 3, 4- thiadiazoline [IV]$_a$ and 4-acetyl-2-(4-hydroxyphenyl) azo-5-(4-bromophenyl)-5-methyl-1,3,4-thiadiazoline[IV]$_b$

Amine compound [III] (1.7 mmol) was dissolved by heating and stirring in 8 mL of 85% phosphoric acid. The solution was cooled to 0 in an ice bath, and then concentrated nitric acid 4 ml and a solution of sodium nitrite (0.10 g, 1.7 mmol) in 2 ml of water were added. The mixture was stirred vigorously and maintained at below 5 for10 min. Afterwards phenol (0.15 g , 1.7 MMOL) in 0.5 ml water was added drop wise with stirring.

The brown solid was filtered, washed several times with water, then dissolved in 30 ml 10% Na OH, the solution filtered, the crude product precipitated during neutralization with 10% HCl then filtered and washed with water several time and recrystallized from ethanol.

4-acetyl- 2-(4- hydroxyphenyl) azo- 5-(4-bromo-phenyl)-5H- 1, 3, 4-- thiadia-zoline [IV]$_a$

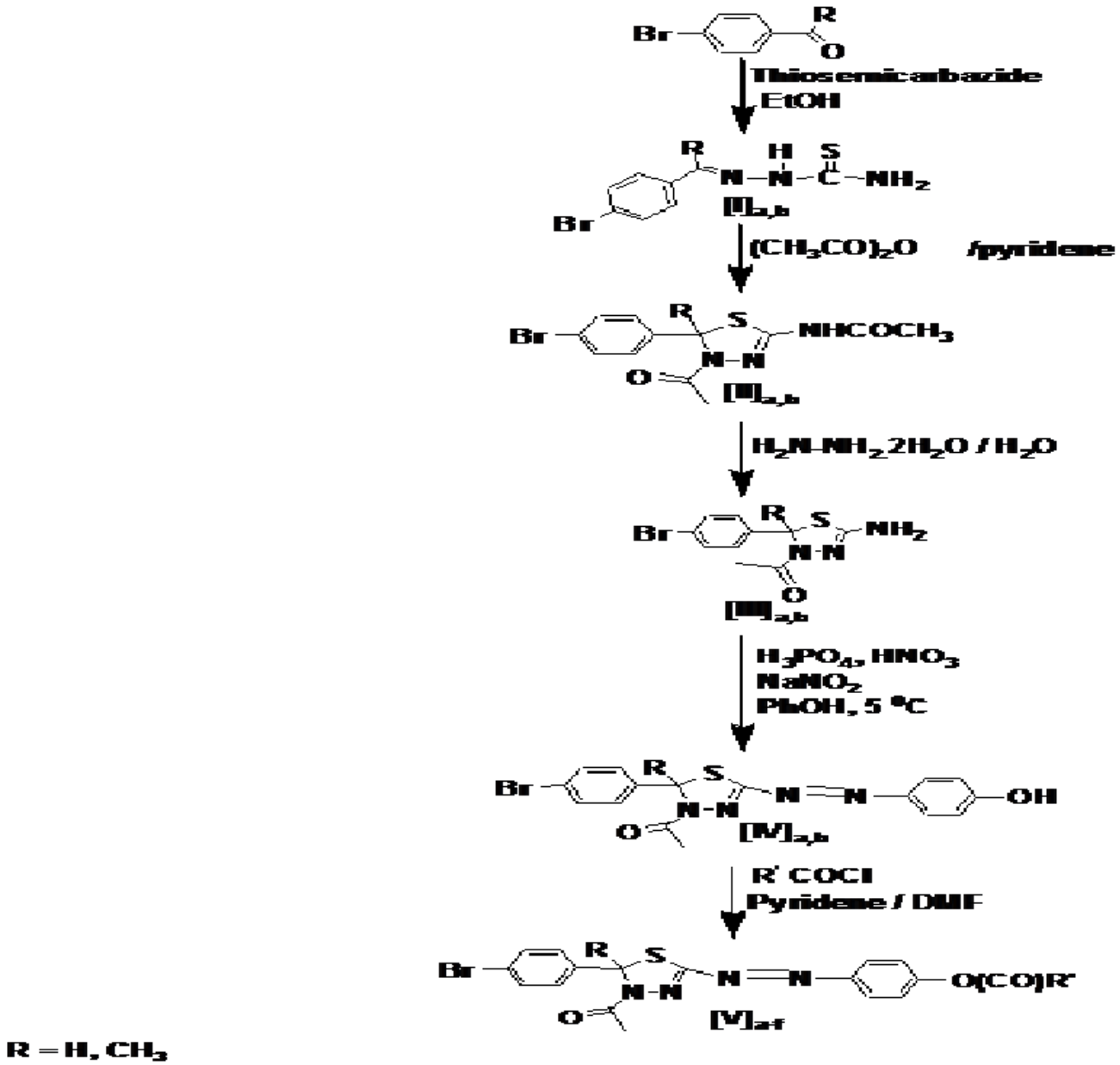
Orange solid; yield 78 %; m.p 196-198°C. FTIR (KBr, υ, cm^{-1}): 3460 (OH), 1697 (C=O), 1626 (C=N endocyclic), 1480 (N=N). MS (EI, *m/z* (%)): 406 $[M+H]^+$. Anal. calcd. For $C_{16}H_{13}N_4SO_2Br$: C, 47.40; H, 3.20; N, 13.82; S, 7.90; Found: C, 47.65; H, 3.42; N, 13.99; S, 7.66%.

4-acetyl--2-(4--hydroxyphenyl) azo-- 5--(4-bromophenyl)-- 5- methyl- 1,3,4-thiadiazo- line [IV]$_b$

Orange solid; yield 74 %; m.p 214-215 . FTIR (KBr, υ, cm-1): 3465 (OH), 1680 (C=O), 1626 (C=N endocyclic), 1483 (N=N). 1HNMR (300 MHz, DMSO-d6, δ, ppm): 2.0 (s, 3H, CH3 at C5 of thiadiazole ring), 2.33 (s, 3H, CH3CON), 6.97–8.01 (m, 8H, CH ar), 8.61 (s, H, OH). Anal. calcd. For C16 H15N4SO2Br: C, 48.68; H, 3.57; N, 13.36; S, 7.63; Found C, 48.55; H, 3.69; N, 13.58; S, 7.89%.

General Procedure for Synthesis of Ester [V]$_{a-f}$

Acetyl chloride, benzoyl chloride or 4-methoxybenzoyl chloride (10 mmol) was added to a stirred solution of azo compound [IV] (10 mmol) in dry pyridine (1 ml) and dry dimethylformamide (DMF) (10 ml) at (5-10). Stirring was continued for 3 h at the same temperature. The resulting mixture was poured onto 100 mL of 5% HCl. The precipitate was filtered and washed with solution of 10% NaHCO3 and water for several times, dried and recrystalized from ethanol.



Scheme 1: Synthetic route for compounds $[I]_{a,b}$, $[II]_{a,b}$, $[III]_{a,b}$, $[IV]_{a,b}$ and $[V]_{a-f}$

4-((4-acetyl-5-(4-bromophenyl)-5-H-1, 3, 4-thiadia-zoline) diazenyl) Phenyl acetate [V]a

Orange powder; yield 92 %; m.p 209-210°C.FTIR (KBr, υ, cm^{-1}): 1770 (C=Oester), 1689 (C=O), 1624 (C=N endocyclic), 1495 (N=N). ^{1}HNMR (300 MHz, DMSO-*d*6, δ, ppm): 5.7 (s, 1H, at C5 of thiadiazoline ring), 2.27 (s, 6H, $\underline{CH_3}CON$), 3.08 (s, 3H, CH_3COO), 6.97-8.2(m, 12H, CH ar). Anal. Cal cd. For $C_{18}H_{15}N_4SO_3Br$: C, 48.32; H, 3.35; N, 12.52; S, 7.15; Found: C, 48.54; H, 3.39; N, 12.62; S, 7.49%.

4-((4-acetyl-5-(4-bromophenyl)-5-H-1, 3, 4-thiadiazoline) diazenyl) Phenyl benzoate [V]b

Pale orange powder; yield 85%; m.p 265°C. FTIR (KBr, υ, cm^{-1}): 1738 (C=O ester), 1687 (C=O amide), 1622 (C=Nendocyclic), 1489 (N=N). MS (EI, *m/z* (%)): 510 $[M+H]^+$. Anal. calcd. For $C_{23}H_{17}N_4SO_3Br$: C, 54.22; H, 3.33; N, 11.00; S, 6.28; Found: C, 54.39; H, 3.54; N, 10.66; S, 6.14%.

4-((4-acetyl-5-(4-bromophenyl)-5-H-1, 3, 4-thiadiazoline) diazenyl) phenyl 4-methoxybenzoate [V]c

Pale orange powder; yield 86 %; m.p 178-180°C.FTIR (KBr, υ, cm^{-1}): 1760 (C=O ester), 1685 (C=O amide), 1618 (C=N endocyclic), 1481 (N=N). ^{1}HNMR (300 MHz, DMSO-*d*6, δ, ppm): 2.24 (s, 3H, $\underline{CH_3}CON$), 5.5 (s, 1H, at C5 of thiadiazoline ring), and 6.96-8.20 (m, 12H, CH ar). Anal. calcd. For $C_{24}H_{19}N_4SO_4Br$: C, 53.43; H, 3.52; N, 10.38; S, 5.93; Found: C, 53.19; H, 3.64; N, 10.49; S, 6.12%.

4-((4-acetyl-5-(4-bromophenyl)-5-methyl-1, 3, 4-thiadiazoline) diazenyl) phenyl acetate [V]d

Yellow powder; yield 88 %; m.p 170-172.FTIR (KBr, υ, cm-1): 1774 (C=O ester), 1674 (C=O amide), 1610 (C=Nendocyclic), 1487 (N=N). 1HNMR (300 MHz, DMSO-d6, δ, ppm): 1.87 (s, 3H, CH3 at C5 of thiadiazoline ring), 2.22 (s, 6H, CH3CON), 2.9 (s,3H, CH3COO), 6.92-7.71 (m,12H, CH ar). Anal. calcd. For C19H17N4SO3Br: C, 49.45; H, 3.68; N, 12.14 S, 6.94; Found: C, 49.14; H, 3.52; N, 12.44; S, 6.80%.

4-((4-acetyl-5-(4-bromophenyl)- 5-methyl-1, 3, 4-thiadiazoline) diazenyl- phenyl benzoate [V]e

Pale yellow powder; yield 82 %; m.p 188-190^{0}C. FTIR (KBr, υ, cm^{-1}): 1745 (C=O ester), 1683 (C=O amide), 1614 (C=Nendocyclic), 1489 (N=N). ^{1}HNMR (300 MHz, DMSO-*d*6, δ, ppm): 1.7 (s, 3H, CH_3 at C5 of thiadiazole ring), 2.1 (s, 3H, $\underline{CH_3}CON$), and 6.93-7.85 (m, 13H, CH ar). Anal. calcd. For $C_{24}H_{19}N_4SO_3Br$: C, 55.06; H, 3.63; N, 10.70; S, 6.11; Found: C, 55.29; H, 3.52; N, 10.55; S, 6.24%.

4-((4-acetyl-5-(4-bromophenyl)-5-methyl-1, 3, 4-thiadiazoline) diazenyl phenyl-4-methoxybenzoate [V]f

Pale yellow powder; yield 90 %; m.p. 132-134°C.FTIR (KBr, υ, cm^{-1}): 1762 (C=O ester), 1685 (C=O amide), 1618 (C=N endocyclic), 1510 (N=N). ^{1}HNMR (300 MHz, DMSO-*d*6, δ, ppm): 1.75 (s, 3H, CH_3 at C5 of thiadiazole ring), 2.15 (s, 3H, $\underline{CH_3}CON$), and 6.90-8.26 (m, 12H, ,CH ar). Anal. cal cd. For $C_{25}H_{21}N_4SO_4Br$: C, 54.24; H, 3.79; N, 10.12; S, 5.78; Found: C, 53.89; H, 3.74; N, 10.42; S, 5.86%.

Biological Assay

All the compounds have been screened for both antibacterial and antifungal activities (in vitro) using cup-plate agar diffusion method [23] by measuring the inhibition zone in mm. Amoxicillin (1 µg/ml) was used as standard drug for antibacterial activity, and Fluconazole (1µg/ml) as a standard drug for antifungal activity. The compounds were screened for antibacterial activity against, Staphylococcus aureus, Bacillius Subtilis, Escherichia coli and Pseudomonas aerugenosa in nutrient agar medium, and for antifungal activity against Aspergillus niger in Sabouraud's dextrose agar medium.

All the synthesized compounds (1µg/mL) were placed serially in the cavities with the help of micropipette and allowed to diffusion for 1 h, DMSO was used as solvent for all compounds, and as control. These plates were incubated at 37 for 24 hrs and 28 for 72h, for antibacterial and antifungal activities, respectively. The zone of inhibition observed around the cups after respective incubation was measured and percent inhibition of the compounds was calculated.

Results and Discussion

The synthesis of thiosemicarbazones was achieved by the condensation reaction of thiosemicarbazide and equimolar amount of suitable aldehyde or ketone. The structural assignments of the thiosemicarbazones **[II]** are based on elemental analysis and their spectral data of FTIR and ^{1}HNMR spectroscopy.

The data of FTIR, and ^{1}H-NMR spectrum along with elemental analyses data confirmed the structural formula of the synthesized compounds.

The resulted thiosemicarbazones [I] were cyclized to 1, 3, 4-thiadiazolines [II]a,b under acylation condition (pyridine, acetic anhydride). The progress of the reactions was monitored by TLC technique until the disappearances of thiosemicarbazones. The data of FTIR, and 1HNMR spectrum along with elemental analyses data confirmed the structural formula of the synthesized compounds. Treatment of the product [III] with hydrazine hydrate (50%) at room temperature lead to formation amino group at position 2 of 1, 3, 4-thiadiazoline ring; 4-acetyl-2-amino-5- (4- bromophenyl)-5 methyl (H)-1,3,4-thiadiazolines [III].

The structural assignments of this compound [III] is based on it is elemental analysis and spectral data. The percentages of C, H, N and S from the elemental analysis were in good agreement with the calculated values for these compounds. FTIR spectra, showed two absorption bands at (3423-3273 cm-1) for asymmetrical and symmetrical (NH2) group. The 1HNMR spectrum of compound [III]b showed two singlet signals at δ (2.45 ppm and 1.88 ppm) due to six protons of two (CH3) groups at NCOCH3 and C-5. Two protons of NH2 group appeared as a singlet at δ (6.51 ppm). The four aromatic protons of 4-substituted benzene ring appeared as two doublets in the region δ (7.32 –7.52 ppm).

Diazonium coupling reactions are typical electrophilic aromatic substitutions in which the positively charged diazonium ion in the electrophile that reacts with the electron-rich ring of a phenol. This reaction usually occurs at the para position. The azo compounds [IV]a,b was synthesized by coupling diazonium salt of compound [III] with phenol at 0-4 . The structural assignments of azo derivatives [IV] a,b were based on elemental analysis and their spectral data of FTIR, and 1HNMR spectroscopy or mass spectroscopy.

The characteristic FTIR absorption bands showed the disappearance of absorption bands due to NH2 stretching of compound [III] together with the appearance of a stretching broad band around 3460 cm-1 due to vO-H group.

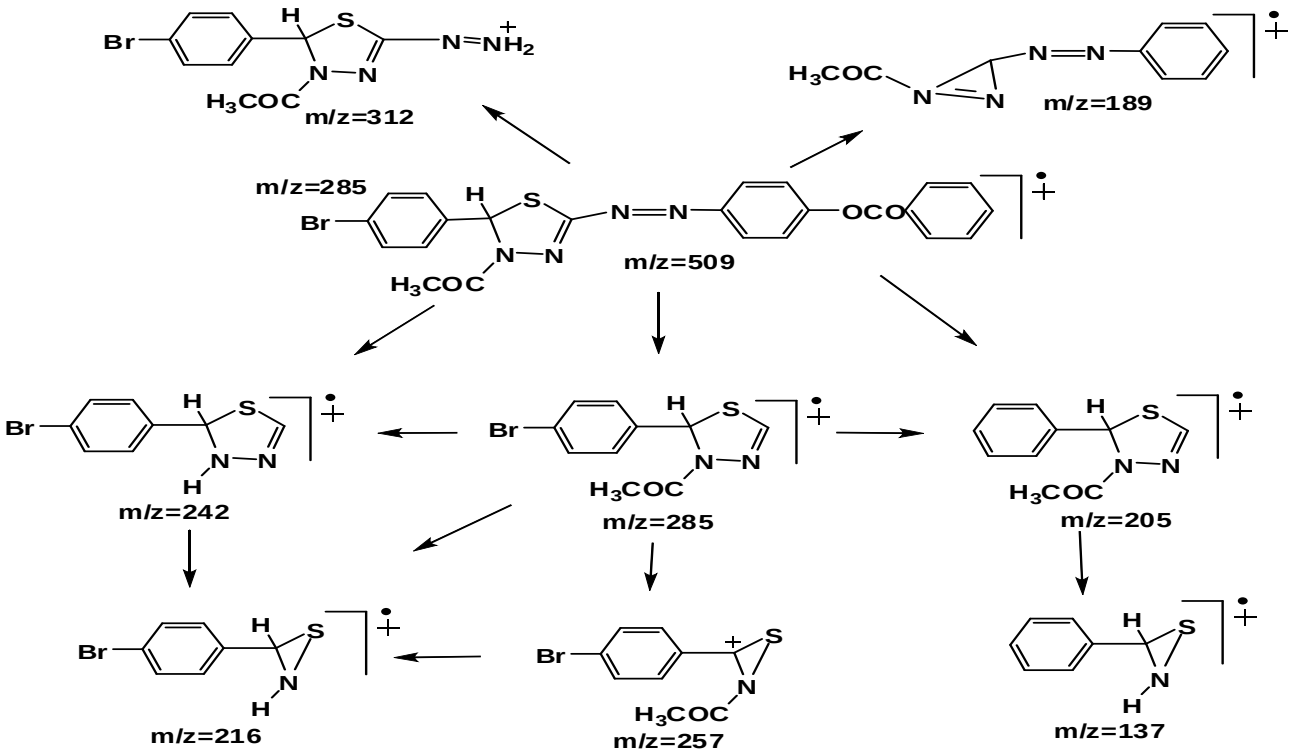
It also shows a band around 1483 cm-1 which is due to the vN=N group. The 1HNMR spectrum of compound [IV]b showed a good singlet signal at δ 8.61 ppm due to OH proton, multiplate at δ (6.97-8.01 ppm) that could be attributed to the eight protons of tow aromatic ring. Two singlet signals at δ 2.0 ppm and δ 2.33 ppm due to six protons of CH3 at C5 of thiadiazole ring and CH3CON groups, respectively.

In the mass spectrum of compound [IV]a, the molecular ion peak (m/Z=406) is prominent which corresponds to the molecular weight of the structure suggested to this compound. The compounds ester [V]a-f was synthesized by reaction of one mole of compounds [IV] with one mole of different acid chloride in presence of dry pyridine as acceptor. The structures of these compounds were characterized by elemental analysis, FTIR, 1HNMR and mass spectroscopy. The FTIR and 1HNMR spectra showed that the disappeared OH group of azo compounds.

The FTIR and 1HNMR spectral data of functional group which are characteristic of these ester compounds are given in the experimental procedures. The elemental analysis data, signals in 1HNMR spectra and two carbonyl bands in FTIR spectra were utilized to confirm the structure of these ester compounds. Mass spectra of this heterocyclic compound [V]b as a representative example resemble one another as regards the observed rupture pattern, although the relative abundance and the m/z relationship are characteristic for this compound, in agreement with that observed for 1,3,4-thiadiazoline moiety [24]. The proposed fragmentation model is presented in Scheme 2.

Antiviral and Antimicrobial Evaluation

Microbial growth inhibitory activities against standard strains of pathogenic microorganisms including *Staphylococcus aureus, Bacillius Subtilis, Escherichia coli and Pseudomonas aerugenosa* in nutrient agar medium, and for antifungal activity against *Aspergillus niger* in Sabouraud's dextrose agar medium were investigated. The results are summarized in Table 1. All the synthesized compounds were screened for their antimicrobial activity against *Staphylococcus aureus, Escheriochia coli*, *Candida albicans* and a clinical isolate of *Candida albicans*.



Scheme 2: The proposed fragmentation model of 1, 3, 4-thiadiazoline

The azo derivatives **[IV]**$_{a,b}$ showed good antibacterial activity against bacterial and fungal when compared with the ester derivatives. The compounds **[V]**$_b$ and **[V]**$_e$ did not show any activity against *E. coli*, also the two compounds **[V]**$_b$ and **[V]**$_e$ showed the lowest activity against all the bacterial and fungal under examined. Rest of the ester derivatives showed moderate to good antibacterial against *Staphylococcus aureus, Bacillius Subtilis and Pseudomonas aerugenosa* and antifungal against *Aspergillus niger*. On the other hand all synthesized ester compounds **[V]**$_{a-f}$ showed moderate to low antibacterial activity against *E. coli* type. Finally, all the synthesized compounds showed good activity against *Aspergillus niger*. The antibacterial activity data, as in Table 1, may be explained depending on the molecular structure and nature of the substituted group. Also, we can observe differences in the biological activity of the synthesized compounds against different types of bacteria that could be due to cell membrane permeability or other genetic factor [25].

Table 1: Inhibition zones of titled compounds [IV] a, b and [V]$^{a-f}$

Compound	Inhibition zone (mm.)				
	Staphylococcus aureus	*Bacillius Subtilis*	*E. Coli*	*Pseudomonas aeruginosa*	*Aspergillus niger*
	Gram Positive (+)		Gram negative (-)		
[IV]$_a$	14	11	13	14	16
[IV]$_b$	12	14	12	13	15
[V]$_a$	11	12	8	12	13
[V]$_b$	10	8	_	8	11
[V]$_c$	13	14	8	14	13
[V]$_d$	11	15	9	12	13
[V]$_e$	9	8	_	9	11
[V]$_f$	13	12	8	11	12
Amoxicillin	4	4	4	5	_
Fluconazole	_	_	_	_	5
Control (DMSO)	–	–	–	–	–

Conclusion

A new biologically significant ester containing azo group derived from 2-amino-1, 3, 4-thiadiazoline derivatives were synthesized and structurally characterized by elemental analysis and spectroscopic techniques (FTIR, ^{1}HNMR and mass spectroscopy). All the compounds are potentially active against microorganisms. It is evident from the

microbial screening results, that most of the compounds exhibited good to excellent specific activities against each strain of bacteria and a strain of fungi.

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