Characterization and Biological Activity of Some New Derivatives Derived from Sulfamethoxazole Compound

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Abstract:
A new series of Sulfamethoxazole derivatives was prepared and examined for antifibrinolytic and antimicrobial activities. Sulfamethoxazole derivatives bear heterocyclic moieties such as 1,3,4-thiadiazine, pyrazolidine-3,5-diol, 6-hydroxy-1,3,4-thiadiazinan-2-thione, and [(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazeyl]. Their structures were elucidated by spectral methods (FT-IR, H¹-NMR). Physical properties are also determined for all compound derivatives. Recently prepared compounds were tested for their antimicrobial activity in the laboratory. Each screened compound showed good tendency to moderate antimicrobial activity.

Key words: Biological activity, Characterization, Sulfamethoxazole, Synthesis.

Introduction:
Sulfamethoxazole (SMZ or SMX) IUPAC is chemically labeled as 4-Amino-N-(5-methylisoxazol-3-yl) - benzenesulfonamide is a wide board antibiotic. It was approved in the United States in 1961. At present, it is mostly used in combination with trimethoprim (abbreviated SMX-TMP). It is also referred to as sulfamethalazole, sulfisomezole, and sulfamethazole. It is used for many bacterial diseases and is effective against both germs positive and negative. (1) In the recent years, a great number of sulfamethoxazole derivatives were synthesized, characterized, tested and used for the treatment of many infections. (2) A large number of Sulfamethoxazole derivatives are currently designed based on heterocyclic moieties, they are widely used in clinical medicine exhibits as pharmacological agents with a wide range of biological procedures such as anti-cancer treatment, antiviral agents, anti-fungal, antimycobacterial, and anti-tubercular uses (8). In the light of the facts and due to the huge development in antimicrobial activities of sulfamethoxazole derivatives, a series of heterocyclic rings such as 1,3,4-thiadiazine, pyrazolidine-3,5-diol, 6-hydroxy-1,3,4-thiadiazinan-2-thione compounds are designed and synthesized.

The chemical structure of Sulfamethoxazole is 4-Amino-N-(5-methylisoxazol-3-yl) – benzenesulfonamide.

Materials and Methodologies:
All the chemicals used in this work were of highest purity available and supplied without further purification in Layer Chromatography (TLC) was checked by pro-coated sheets with silica –gel as immobile phase Appropriate solvent(ethanol) as mobile phase (Melting points) was specified by Stuart melting point SMP10 Spectr (FT-IR) were via KBr disk on SHIMADZU FT-IR-8300 spectrophotometer in Ibn Sina Company and College of Sciences for Women in University of Baghdad. H¹-NMR measurements were achieved from Moscow University of Russia, operated at 500MHZ in DMSO-d₆.
Synthesis methods 2- chloro- N-[(4- (2-chloroacetamido) phenyl)sulfonyl] - N-(5-methylisoxazol-3-yl)acetamide compound (1) preparation (9)

To a stirred solvent of 4-amino-N-(5-methylisoxazol-3-yl) benzenesulfonamide (3.27 g, 1 mmol.) in (20 ml) dimethyl formamide, a chloroacetyl chloride (3 ml, 3 mmol.) were added drop by drop. The reaction carried out by refluxing the reaction mixture for (6 hrs.). The resulting solid product then has been filtered, dried, and recrystallized from ethanol. compound as listed in Table (1).

Synthesis methods 2-hydrazineyl-N-[(4- (2-hydrazineylacetamido)phenyl)sulfonyl]-N-(5-methylisoxazol-3-yl) acetamide compound (2) preparation (10)

A mixture of a 2-chloro-N-[(4-(2-chloroacetamido)phenyl)sulfonyl]-N-(5-methylisoxazol-3-yl) acetamide (1) (4.8 g, 1 mmol.) and hydrazine hydrate 99% (2 ml, 2 mmol) has been refluxed to (3hrs.). Resulting solids were collected, washed, and recrystallized from ethanol. compound as listed in Table (1).

Synthesis methods N-[5-methylisoxazol-3-yl]-N-[(2-(phenylamino)-4H,1,3,4-thiadiazinan-6-yl)-4-(2(phenyl amino) -4H-1,3,4-thiadiazinan-6-yl)amino]benzenesulfonamide compound (3) preparation (11)

To a solution of 2-hydrazineyl-N-[(4-(2-hydrazineylacetamido)phenyl)sulfonyl]-N-(5-methylisoxazol-3-yl)acetamide compound (2) (3.54 g, 1 mmol) in absolute ethanol (20ml) p-chlorophenylisocyanate (5.46 g, 2 mmol) has been added and refluxed for 4 hrs. and checked by TLC. The reaction was cooled and the soluble matter was filtered, dried and recrystallized from ethanol. compound as listed in Table (1).

Synthesis methods 2-(3,5-dihydroxyprazolidin-1-yl)-N-[(4-(2-(3,5-dihydroxyprazolidin-1-yl)acetamide] phenyl)sulfonyl]-N-(5-methylisoxazol-3-yl)acetamide compound (4) preparation (12)

Amixtureof2-hydrazineyl-N-[(4-(2-hydrazineylacetamido)phenyl)sulfonyl]-N-(5-methylisoxazol-3-yl) acetamide compound (2) (3.54 g, 1 mmol), ethylacetoacetate (1 mmol) respectively and absolute ethanol (15ml) was mixed carefully, refluxed for (3 hrs.). The reaction mixture is then concentrated and cooled with crushed ice to form the solid product, which is eventually filtered and re-crystallized from ethanol. compound as listed in Table (1).

Synthesis methods N-(6-hydroxy-2-thioxo-1,3,4-thiadiazinan-6-yl)-4-[(6-hydroxy-2-thioxo-1,3,4-thiadiazinan-6-yl)amino]N-(5-methylisoxazol-3-yl)benzenesulfonamide compound (5) preparation (13)

To a stirred ethanolic solution of KOH (1.12 g, 2 mmol) in (20 ml), 2-hydrazineyl-N-[(4-(2-hydrazineylacetamido)phenyl)sulfonyl]-N-(5-methylisoxazol-3-yl)acetamide compound (2) (3.54 g, 1 mmol), carbon disulfide (2 ml, 2 mmol) was added slowly and refluxed for (3 hrs.). The solid precipitate was filtered, washed with ether, and dried and crystallized from ethanol. Compound as listed in Table (1).

Synthesis methods 4-(N-(5-methylisoxazol-3-yl)sulfamoyl)benzene diazonium chloride compound (6) preparation (14)

(0.69 g, 1 mmol) Sodium nitrite is gently added to (5 mL) of concentrated hydrochloric acid at less than 5 ° C. and then (3.27 g, 1 mmol) of 4-amino-N-(5-methylisoxazol-3-yl) benzenesulfonamide [sulfamethoxazole] it was slowly added to the solution over an hour. The reaction mixture was stirred for one more time for (2 hrs.).The reaction mixture was stirred for more time (2 hrs. 0-5 C°), compound as listed in Table (1).

Synthesis methods Ethyl 2-[(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)diazeyl]-3-oxobutanoate compound (7) preparation (15)

The clear solution of diazonium salt compound (6) (3g, 1 mmol) was added to solution of ethyl acetocacete (1.3g, 1mmol.) in sodium hydroxide (0.4g, 1mmol.). Mixture of reaction was refluxed for (3 hrs.). The solid product is filtered, washed with a little hot water, dried and purified from ethanol. compound as listed in Table (1).

Synthesis methods 4-[(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazeyl]-N-(5-methylisoxazol-3-yl) benzene sulfonamide compound (8) preparation (16)

To (3.9g, 1 mmol.) of ethyl 2-[(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)diazeyl]-3-oxobutanoate compound (7) hydrazine hydrate99% (3.6g, 1mmol.) gently added. The reaction mixture was reactivated for (3 hrs.) and then cooled to room temperature. The solid precipitate is formed washed, dried, and crystalized from ethanol. compound as listed in Table (1)

Result and Discussion:

Artificial pathways of newly prepared derivatives sulfamethoxazole are presented in Scheme (1)
FTIR spectrum for compound(1) showed new band at (3263 cm$^{-1}$) were assigned to the v(N-H)sym. stretching symmetry. Besides the appearances of v(C=O) stretching band attributable to amide group at (1693 cm$^{-1}$) and stretching band at (2881cm$^{-1}$) back to v(CH$_2$) and at (1600 cm$^{-1}$) for (C=N) isoxazole are best proof for the structure give to intended compound as listed in Table (2). FTIR spectrum of hydrazine carboxamide showed remarkable stretching bands in (3321 cm$^{-1}$) and (3267 cm$^{-1}$) which were assigned to the v (-NHN$_2$) group frequency stretch proved the formation of compound (2). On the other hand, disappearance of v(-NHNH$_2$) (CH$_2$) and (C=O) group stretching frequency for thiadiazine ring is considered a good proof of formation of compound (3) FTIR spectrum for pyrazolidine-3,5-diol compound (4) gives starching bands for v(O-H) at (3365cm$^{-1}$) and v(CH$_2$) at (2835cm$^{-1}$). While pyrazolone compound (5) shows starching bands for v(C=S) 1165 beside starching bands for v(O-H) at (3363cm$^{-1}$) and v(CH$_2$) at (2835cm$^{-1}$).
Other sulfamethoxazole derivatives attached with pyrazolidine-3,5-diol rings, 6-hydroxy-1,3,4-thiadiazine-2-thione moieties compounds (4) and (5) respectively were prepared by condensation of compound (2) with ethylacetocetate in absolute ethanol to offered compounds (4). On the other hand, intensification of the compound (2) with carbon dioxide in the base medium of potassium hydroxide gives compound (5) as shown in the Scheme (2).
The $^1$H-NMR spectrum of sulfamethoxazole compounds (1-3), shows the important characteristics of chemical shifts (DMSO-d$_6$, ppm) as listed in Table (3). It displayed signals attributed to sulfamethoxazole attached to thiadiazine moiety compound (3), methyl group attached to isoxazole ring, for 2-CH groups of thiadiazine ring, (CH) isoxazole ring, fourteen aromatic ring protons, one proton of secondary amine (NH), two protons of amines attached to phenyl group, two proton for amine group of thiadiazine respectively as shown in Table (3). $^1$H-NMR spectrum of pyrazolone compound (5) detected significant characteristics of chemical shifts and showed suggested signals, the attribution of the CH$_3$ linked to isoxazole ring, four protons for methylene groups of thiadiazinane rings, two protons of hydroxyl groups –OH, one proton of CH isoxazole, four aromatic ring protons, four proton of NH thiadiazinane, and one proton of Ph-NH-C thiadiazinane ring respectively as shown in the Table 3.
Diazotization reaction of start sulfamethoxazole with sodium nitrite with hydrochloric acid yield the diazonium chloride derivative of sulfamethoxazole compound (6). Diazonium salt (4) then it was treated with ethyl acetoacetate in the presence of sodium hydroxide to give derivative (7). Final product of rings attached with sulfamethoxazole compound (8) were obtained in good yield from condensation of compound (7) with hydrazine hydrate. The synthetic routes for preparation of mentioned compounds (6-8) are shown in Scheme (3).

Table 3. $^1$H-NMR spectral data (δppm) for selected prepared compounds

| Comp. No. | Compound structure | $^1$H-NMR parameters (δppm) |
|-----------|--------------------|-----------------------------|
| 1         | ![Image of compound 1](image1.png) | 1.19 (s, 3H, CH$_3$), 4.67 (s, 4H, CO-CH$_2$-Cl), 6.07 (s, 1H, C-H), 6.92-7.96 (m, 4H, Ar-H), 12.39 (s, 1H, NH-CO). |
| 2         | ![Image of compound 2](image2.png) | 1.18 (s, 3H, CH$_3$ isoxazole), 3.83 (s, 4H, NH$_2$), 4.65 (s, 2H, CO-CH$_2$-NH), 4.96 (s, 2H, NH), 6.22 (s, 1H, C-H), 6.85-7.38 (m, 4H, Ar-H), 12.22 (s, 1H, NH-CO). |
| 3         | ![Image of compound 3](image3.png) | 1.19 (s, 3H, CH$_3$), 4.67 (s, 2H, C-H thiazadine), 5.39 (s, 1H, C-H), 6.92-7.93 (m, 10H, Ar-H), 8.26 (s, 2H, NH-Ph), 8.40(s, 1H, Ph-NH-C thiazadine), 8.88(s, 2H NH thiazadine). |
| 4         | ![Image of compound 4](image4.png) | 1.22 (s, 3H, CH$_3$), 1.87 (t, 4H, C-H pyrazolidine), 3.35 (s, 4H, CO-CH$_2$-N), 4.11 (s, 2H, N-H pyrazolidine), 4.67 (s, 4H, CH$_2$ pyrazolidine), 5.44 (s, 1H, C-H ), 5.81 (s,4H, OH), 6.92-7.46 (m, 4H, Ar-H), 7.93 (s,1H,Ph-NH-CO). |
| 5         | ![Image of compound 5](image5.png) | 1.19 (s, 3H, CH$_3$ i, 4.67 (s, 4H, CH$_2$ thiazadinean), 5.52 (s, 1H, OH), 6.34 (s, 1H, C-H isoxazole), 6.46 - 7.83 (m, 4H, Ar-H), 7.99 (s,4H, NH thiazadinean), 8.21 (s, 1H, Ph-NH-C thiazadinean). |
| 6         | ![Image of compound 6](image6.png) | 1.62 (s, 3H, CH$_3$), 1.93 (t, 3H, CH$_3$ isoxazole), 3.52 (q, 2H, CH$_2$), 4.30 (s, 1H, C-H), 5.25 (s, 1H, CH), 6.96-7.97 (m, 4H, Ar-H), 9.32 (s, 1H, SO$_2$-NH-C), |
| 7         | ![Image of compound 7](image7.png) | 1.24 (s, 3H, CH$_3$), 1.88 (s, 3H, CH$_3$ pyrazole), 2.08 (s, 1H, CH, pyrazole), 5.52 (s, 1H, C-H), 6.92-7.65 (m, 4H, Ar-H), 9.26 (s, 1H, SO$_2$-NH-C), 12.16 (s, 1H, NH pyrazole). |
FTIR spectrum for compounds (7) showed the characteristic stretching band for ν(N-H) at 3267 cm⁻¹ beside ν(CH₂) at 2877 cm⁻¹ and ester group at (1670 cm⁻¹). While pyrazole compound (8) showed stretching band for ν(N-H) at 3217 cm⁻¹ beside ν(C=O) at (1724 cm⁻¹).

¹H-NMR spectrum of sulfamethoxazole derivatives (7 and 8), showed the characteristic chemical shifts (DMSO-d₆, ppm) as listed in Table (3). It displayed signals attributed for sulfamethoxazole linked to pyrazole moiety compound (8), CH₃ isoxazole ring, pyrazole ring, one proton of –CH- pyrazole ring, one proton of –CH- isoxazole ring, four aromatic ring protons, one proton of SO₂-NH-C and one proton of NH pyrazole ring respectively as shown in Table 3.

**The Antimicrobial Activity:**

The inhibition zone of the newly synthesized sulfamethoxazole derivatives (1-5) were observed and measured. The biological activates of some prepared compounds (C₁, C₂, C₃, C₄, C₅, C₆) were tested against bacterial strains and fungi. Escherichia coli, staphylococcus aureus and candida alb(ican) were well diffused using ager method. The results of this study are summarized in Table 4 and shown in Figs 1, 2 and 3 respectively.

| No. inhibition zone | Compound No. | 1000 ppm | E.coli | Staphylococcus aureus | Candida albicans |
|---------------------|--------------|----------|--------|-----------------------|----------------|
| A₁                  | Cl           | Nil      | 12     | Nil                   | 10             |
| A₂                  | C₂           | Nil      | 12     | 10                    |                |
| A₃                  | C₃           | 10       | 14     | 20                    |                |
| A₄                  | C₄           | 18       | 20     | 25                    |                |
| A₅                  | C₅           | 10       | Nil    | 10                    |                |
| Control- (A₆)       | 0            | 0        | 0      | 0                     |                |

![Scheme 3. Prepared derivatives sulfamethoxazole 6,7,8](image-url)
Table 4 shows anti-bacterial and anti-fungal results which were interpreted in terms of the diameter of inhibition zone for antibacterial activity showed medium biological effect against Staphylococcus aureus and against E.coli, although it showed high effect forward Candida albicans.

**Conclusion:**

This paper reports the changes in various physical properties associated with the derivatization of sulfamethoxazole. The properties studied include by FTIR, and $^1$H-NMR spectroscopies that derivatization substantially changed the pharmaceutical properties antibacterial activities of these compounds against Gram-positive bacteria (Staphylococcus aureus), Gram-negative bacteria (Escherichia coli,) and yeast-like fungi (Candida albicans).
Figure 6. FT-IR, $^1$H NMR spectrum of compound 4

Figure 7. FT-IR, $^1$H NMR spectrum of compound 8

Author's declaration:
- Conflicts of Interest: None.
- I hereby confirm that all the Figures and Tables in the manuscript are mine. Besides, the Figures and images, which are not mine, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

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