https://doi.org/10.31351/vol34iss1pp176-184

Synthesis, Characterization and Preliminary Antimicrobial Study of Some New Ether and Thioether Derivatives of Sulfadiazine

Mohammed Kamil Hadi[1], Maadh Qusay Abdulkadir[1], Mohammed Abdulameer Oleiwi [*,1], Sarah Ahmed[1] and Zainab Dhia Kamms[2]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
[2] AL-Rasheed University College, Baghdad, Iraq.
[*]**Corresponding author**

Received 6/9/2023, Accepted 14/1/2024, Published 29/3/2025

Abstract

A new series of ether and thioether derivatives of sulfadiazine (**T1-T3** and **E\'-E3**) have been synthesized from the reaction of sulfadiazine with chloroacetyl chloride and the resultant compounds treated with different phenols and thiols. The structures of target ether and thioether derivatives were confirmed depending on their analytical and spectral data. The antimicrobial effect of the final products has been tested *in vitro* with gram-positive and gram-negative bacteria and some yeasts – like fungus, such as *candida albicans*. The antibacterial activity of the target compounds after three days of incubation demonstrated that all the evaluated derivatives exhibited superior antibacterial activity in comparison with amoxicillin and ciprofloxacin against all tested bacteria.

Keywords: Antimicrobial Activities, Ether Derivatives, Sulfadiazine, Sulfonamides, Spectral Studies.

Introduction

One of the biggest and most active areas of organic chemistry research is heterocyclic chemistry, which is developing rapidly [(1)]. The heterocyclic containing compounds are vastly distributed in nature and in a variety of non-naturally occurring products. They play a crucial role in the metabolism of all living cells and have numerous applications in industry and in our lives in various ways [(2-4)]. The heterocyclic compounds play a significant role in the field of medicines and drugs. Numerous heteroatom-containing biologically active compounds, such as those containing nitrogen, oxygen, and sulfur have attracted the attention of chemists over the years primarily via their biological significance [(5-7)].The majority of medications introducing pharmacopoeias are heterocyclic substances, including indapamide (diuretic and antihypertensive), guanethidine (antihypertensive), imipramine (antidepressant), chlordiazepoxide (tranquillizer) [(8)]. Many antibiotics such as cephalosporin, penicillins, streptomycin and norfloxacin also contain heterocyclic ring [(9-13)]. Unexpectedly, certain sulfonamides are devoid of antibacterial activities against some microbe species providing the new SAR hypothesis which illustrates the activity-abolished sulfonamide when there is inclusion of heterocyclic N1-based nucleus [(14)]. Replacing 3-carbonyl partially negative oxygen of some isatins with nonaromatic hetero nitrogen had created a powerful octet achieving positive center that played a good role for the new molecules to exert appreciable antimicrobial properties [(15)]. In chemistry, Sulfonamides, also known as sulfa drugs, are a class of medications that are based on the SO_2NH_2 functional group, which is a part of the molecule. The general formula of Sulfonamides (Figure 1) and they are derivatives of 4-aminobenzene sulfonamide [(16)]. The development of chemotherapy began with the discovery of prontosil's (Figure 2) antimicrobial effect in the early 1930s of the 20th century. Gerhard Domagk received the Nobel Prize in Medicine in 1939 in recognition of his discovery. Prontosil is a sulfonamide-structured azo-dye. Cellular enzymes in the human body metabolize prontosil to sulfanilamide [(17)].

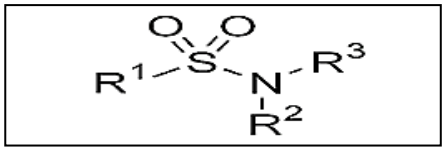


Figure 1. General structure of sulfonamide.

Sulfonamides are the first effectively synthesized selective and toxic antimicrobial drugs [18, 19]. Antibacterial sulfanilamides are a big class of compounds that are structurally similar to 4-aminobenzoic acid [20]. They have a broad variety of pharmacological activities including anti-bacterial, anti-inflammatory, anti-protozoal, anticancer, anti-fungal, diuretic and oral hypoglycemic effects [21-29].

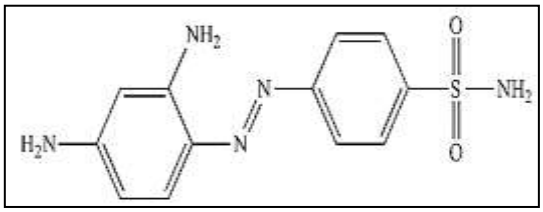


Figure 2. Chemical structure of prontosil.

The application of sulfonamides in the treatment of infections has been limited by the bacterial resistance and side effects, therefore continuous efforts are made to tackle these problems via the development of novel antimicrobial compounds with the sulfonamide moiety. Resistance of E. coli strains to sulphonamides was attributed to their sulfonamides -resistant dihydropteroate synthase. [30] Some novel sulphonamide derivatives containing hydrazine, coumarin, and fused pyrimidine moieties have been synthesized and evaluated for their *invitro* antibacterial activity against Gram-positive bacteria such as (*Streptococcus pneumoniae* and *Bacillus subtilis*) and Gram-negative bacteria such as (*Pseudomonas aeruginosa* and *Escherichia coli*). They were also evaluated for their *invitro* antifungal activity towards a group of fungal strains such as *Aspergillus fumigatus*, and *Candida albicans*, interestingly, the compounds showed similar or better activity in comparison with the reference drug against the selected microorganisms [31] . (Figure 3).The aim of this work was to develop new series of sulfonamide derivatives in an attempt to overcome the bacterial resistance mainly against *E. coli* strains.

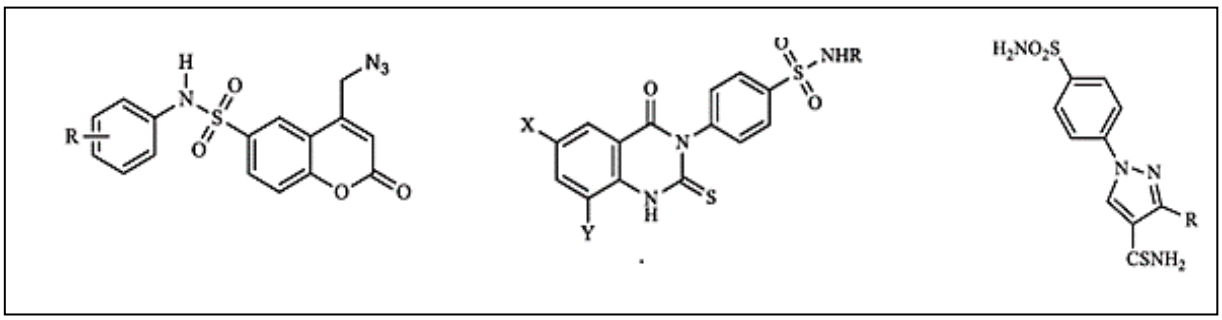


Figure 3. Some of sulfonamide derivatives containing heterocyclic moieties.

Materials and Methods

All of the chemicals and reagents used in this work, in addition to the solvents, were of analytical grade. Melting points were determined (incorrectly) for the target derivatives and their intermediates utilizing melting point apparatus (Thomas Hoover Apparatus). Thin layer chromatography was performed using (n-hexane 5: ethyl acetate 3: methanol 2) solvent system. A Shimadzu FTIR spectrophotometer was used to measure infrared spectra in KBr discs at the College of Pharmacy/ University of Baghdad. The ^{1}HNMR spectra were obtained using a BRUKER model Ultrashield spectrometer (400 MHz) at the College of Science / University of Basrah using dimethyl sulfoxide-d6 as a solvent. ***Synthesis of 2-chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide (II)***

Sulfadiazine (2.07 g, 0083mol) was suspended in 20 mL benzene together with 1.4 mL TEA at ice path for 10 min., chloroacetyl chloride (0.8 mL , 0.0083mol) was then added drop wisely within 20 min. interval, the resultant mixture was left to cool at room temperature within 20 minutes and then allowed to be reflexed with stirring for 3 hrs. Benzene was then evaporated and the residue was washed with 5% Na_2CO_3 solution and water. After drying the residue was washed with ether, cyclohexane, hot ethanol and hot methanol. The product was then recrystallized from dioxane, dried and collected. Yield = 85 %, m.p. (198 ^{o}C). IR (KBr disc), (v cm^{-1}): 3340 (NH) str. of amide, 3070 str. of aromatic (C-H), 2924 (C-H) assymm. str. of CH_2, and 2870 (CH) symm. str. of CH_2, 1627.9 (C=O) str. of amide, 1543-1465 str. of aromatic. (C=C), 1315 assym. 1153 sym. str. of (S=O).

Synthesis of compounds (T1-T3) [32, 33]

Compound II (0.32g, 0.0008mol) was dissolved in a minimum volume of DMF to be added drop wisely during 15 min. onto solution of appropriate thiol (0.0013mol) in 10mL of D.W and 2mL TEA. The mixture was continuously stirred with gentle heating for 2-5 hrs. The solvent was evaporated, and product was solidified with ether, washed with D.W and recrystallized with acetone-water system.

2-(5-ethoxy-1H-benzo[d]imidazol-2-ylthio)-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl) acetamide (T1)

Yield = 70 %, m.p. (214 ºC). Rf = 0.39. FTIR (cm^{-1}): 3255-3296 (NH) strech. of imidazole and amide, 3086: Arom. (C-H) strech., 2978, 2870 (C-H) asymm. and sym. strech. of CH3 and CH2, 1628: (C=O) strech. of amide, 1581 of C=N str., 1543-1465 Aromatic (C=C) str., 1330 assym. 1157sym. (S=O) strech., 1257 (C-O-C) str. ether. ^{1}HNMR (δ, ppm): 12.41 (s, 1H, of imidazole NH) 12.38 (s, 1H, sulfonamide NH), 10.90 (s, 1H, amide NH), 8.51 (s, 1H, pyrimidine CH=N), 6.55-7.95 (9H, m, Aromatic-H), 4.25 (s, 2H, CO-CH_2-S), 4.01(q, 2H, O-CH_2-methyl), 1.29 (t, 3H, CH_2-CH_3).

2-(benzo[d]oxazol-2-ylthio)-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide (T2)

Yield 75 %, mp 179°C. R_f = 0.59 FTIR (υ= cm^{-1}): 3340 (NH) of amide; 3036: str. of aromatic (C-H), 1639: str. of (C=O) amide, 1574 str. of C=N, 1546-1438 Aromatic (C=C) str., 1327 assym. 1153 sym. (S=O). ^{1}HNMR (δ, ppm): 11.17 (s, 1H, NH sulfonamide), 10.87 (s, 1H, NH amide), 8.51 (s, 1H, pyrimidine CH=N), 6.55-8.02 (10H, m, Aromatic-H), 4.43 (s, 2H, CO-CH_2-S).

2-(5-methyl-1,3,4-thiadiazol-2-ylthio)-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl)acetamide (T3)

Yield 78 %, Rf = 0.54, mp 159°C, FTIR (υ= cm^{-1}): 3363 (NH) strech. of amide; 3039: Aromatic (C-H) strech., 2939, 2866 (C-H) asymm. and sym. strech. of CH3, 1633: (C=O) strech. Of amide, 1582 of C=N strech., 1539-1439 of Aromatic (C=C) strech., 1327 assym. 1153 sym. (S=O). ^{1}HNMR (δ, ppm): 11.68 (s, 1H, NH sulfonamide), 10.78 (s, 1H, NH amide), 8.49 (s, 1H, pyrimidine CH=N), 6.58-7.96 (6H, m, Aromatic-H), 4.31 (s, 2H, CO-CH_2-S), 2.45 (s, 3H, -CH_3).

Synthesis of compounds (E1- E3) [34]

Excess amount of appropriate phenol (0.00138mol) is dissolved in 15 mL of dry acetone in presence of excess of potassium carbonate (1gm), compound II (0.32gm, 0.00098mol) was then added. The resultant mixture was left to reflux with stirring for 8 hrs. At the end of reaction, the solvent was evaporated and dilute 0.1N was added until complete acidification obtained. The precipitate was washed several times with DW and then recrystallized from acetone/water.

2-phenoxy-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl)acetamide (E1)

Yield 60 %, mp 137°C, Rf = 0.56, FTIR (υ= cm-1): 3242 (NH) strech. of amide; 3062: Aromatic (C-H) strech., 2924, 2854 (C-H) asymm. and sym. strech. of CH_2, 1626 (C=O) strech. Of amide, 1577 of C=N strech., 1496-1438 of Aromatic (C=C) str., 1335 assym. str. and 1149 symm. str. of (S=O). ^{1}HNMR (δ, ppm): 11.56 (s, 1H, NH sulfonamide), 10.68 (s, 1H, NH amide), 8.57 (s, 1H, pyrimidine CH=N), 7.10-8.06 (11H, m, Aromatic-H), 4.39 (s, 2H, CO-CH_2-O).

2-(4-chlorophenoxy)-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl) acetamide (E2)

Yield 57 %, mp 144°C, R_f = 0.44, FTIR (υ= cm-1): 3325 (NH) strech. of amide; 3109 Aromatic (C–H) strech., 2939, 2859 (C-H) asymm. and sym. strech. of CH_2, 1689 (C=O) strech. of amide,1578 of C=N strech., 1523-1431 of Aromatic (C=C) str., 1338 assymm str. and 1130 symm. str. of (S=O). ^{1}HNMR (δ, ppm): 11.45 (s, 1H, NH sulfonamide), 10.18 (s, 1H, NH amide), 8.08 (s, 1H, pyrimidine CH=N), 7.38-8.08 (10H, m, Aromatic-H), 4.45 (s, 2H, CO-CH_2-O).

2-(2-nitrophenoxy)-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl) acetamide (E3)

Yield 54%, mp153°C, R_f = 0.54, FTIR (υ= cm-1): 3280 (NH) strech. of amide; 3081 Aromatic (C-H) strech., 2969, 2861 (C-H) asymm. and sym. strech. of CH_2, 1693 (C=O) strech. of amide,1581 of C=N strech., 1543-1438 of Aromatic (C=C) str., 1315 assymm str. and 1153 symm. str. of (S=O). ^{1}HNMR (δ, ppm): 11.57 (s, 1H, NH sulfonamide), 11.49 (s, 1H, NH amide), 8.66 (s, 1H, pyrimidine CH=N), 7.17-8.84 (10H, m, Aromatic-H), 4.36 (s, 2H, CO-CH_2-O).

Antibacterial Activity

Resazurin Preparation

The preparation of Resazurin (Alamar Blue) followed the manufacturer's instructions. In 50 mL of sterile, purified water, a tablet was dissolved before being vortexed. The assay was conducted using a total volume ratio of 1 to 10.

Broth Microdilution Assay

Double serial dilutions (125-500 µg / mL) of the synthesized compounds and standards where prepared from a stock (10mg/ mL) in a micro titer plate using Mueller-Hinton broth as diluent. All wells were inoculated with 20µL of bacterial suspension comparable to McFarland standard no.0.5 (1.5×108CFU/mL) except for the negative control wells. Micro-titer plates were incubated for 18 to 20 hrs. at 37°C. 20 µL of the dye resazurin was applied to each well and incubated for 2 hours to check for colour changes. The SUB-MIC Concentrations were measured visually in broth micro dilutions as the lowest concentrations at which the colour of the resazurin broth assay changed from blue to pink [35].

Agar Dilution Assay

Antibacterial activity of the synthesized compounds was determined using the agar well diffusion technique [36]:

1- Each bacterial isolate under study was grown in nutrient broth and incubated for 18-24 hrs. at 37 ºC.

2- Following the incubation time, 0.1 mL of each bacterial suspension was spread on the top of nutrient agar for 24 hrs. at 37 ºC

3- Single colony was added into test tube having 5 mL of normal saline to yield a bacterial suspension

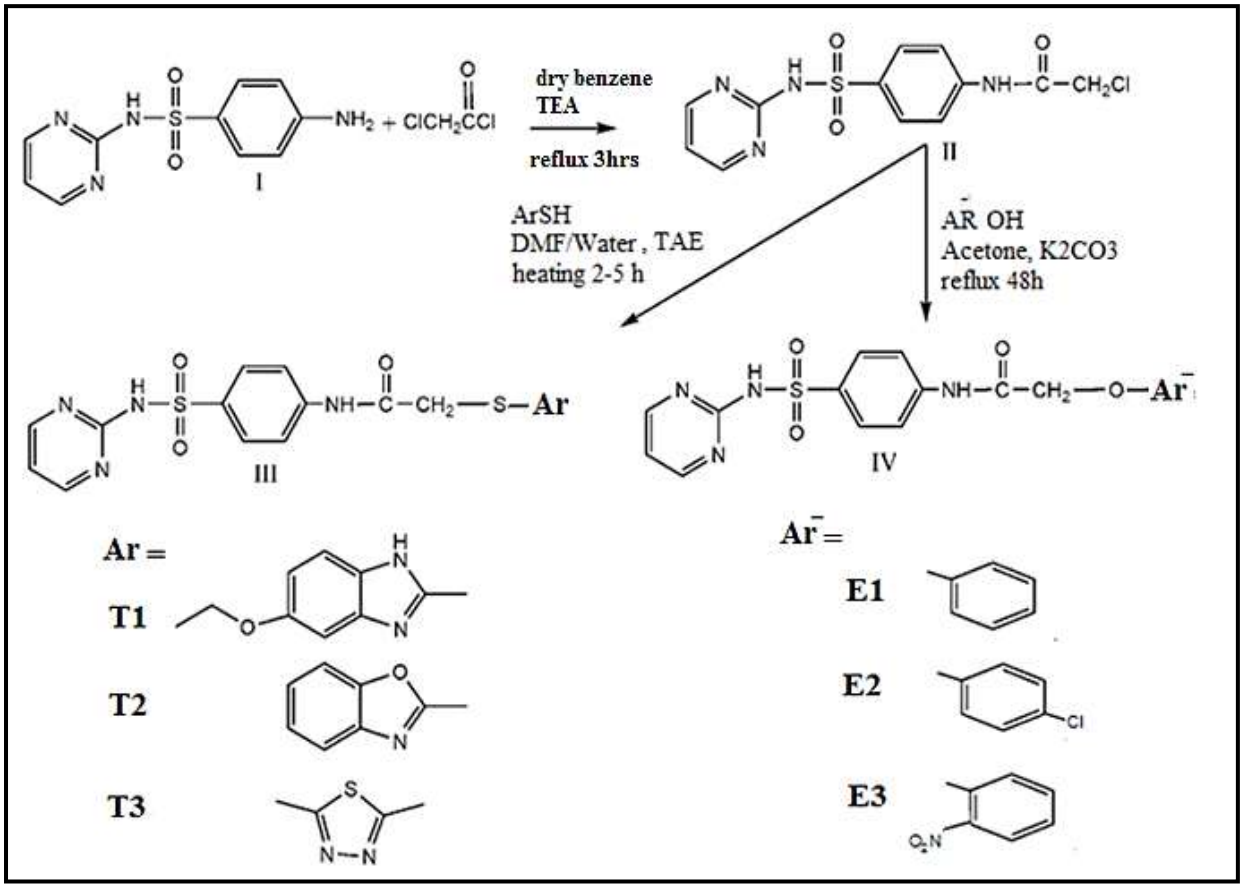
of modest turbidity likened with the standard turbidity solution this nearly equals to 1.5x108 CFU/mL

4- A portion of the bacterial suspension was carefully and consistently spread on Mueller-Hinton agar medium using a sterile cotton swab then it was left for ten minutes.

5- Five millimeter in diameter wells were made in previous agar layer (three wells per plate). The agar discs were removed, 50µL of purified and crud EPS were added to each well by using a micropipette and the DMSO was added to middle well as control plates were incubated at 37 ºC for 18 hrs. and after that, the diameter of inhibition zones was recorded.

Statistical analysis

The values were expressed as the mean ± SEM of the triplicate measurements. The data were analyzed by using the computerized Statistical Package for the Social Sciences (SPSS) program. The statistical significance was determined by one way analysis of variance (ANOVA). $P<0.05$ was considered significant.



Scheme 1. General scheme for the synthesis of the target compounds.

Results and Discussion

The concept of this research is planned in order for hybridizing the properties of two functionalities i.e an antibacterial sulfonamide from side and the microbes-inhibiting thiol-containing heterocyclic or fused heterocyclic rings and phenols from another side to get new derivatives so that the heterocycle is considered substituent to sulfadiazine and vice versa. The obtained modern molecules had been having broader activities against the tested microorganisms in comparison with both the precursors and the standard(ciprofloxacin). Chemically, these compounds are successfully synthesized with two steps method i.e., acylation with chloroacetyl chloride to get the amide derivative of sulfadiazine namely, **sulfadiazine chloroacetate**, and this step was noticed needing heat with reflex distillation otherwise no reaction would happen because of the electron-withdrawing sulfonyl moiety which tend to reduce the nucleophilicity of the para-amino group. The intermediate formed was checked chemically by 0.1N HCl solution test which could not react and solubilize because of the occupation of the 4-amino group with chloroacetate creating a possible unavailability of the nitrogen paired electron to pick a proton. The second step is diverse according to the nucleus intended to be favorably added. The thiol-containing nucleus must be ionized first with triethylamine organic base to be ready for C-S bond formation using aqueous phase at room temperature whereas the C-O linkage needs to apply dry

condition with employing heat under reflex condensation technique and potassium carbonate offers a sufficient basicity necessary for ionization of the phenolic hydroxyl. These two successive steps run as nucleophilic substitution of chloride with more than one nucleophile ranging from nitrogen, sulfur and oxygen. Also the machinery, with which the reaction was preceded, reveals how nucleophilic is the nitrogen and sulfur in comparison with oxygen.

About these soon compounds, para sulfonamide is still maintained on unsubstituted benzene and these two factors might impact in reserving both the antibacterial activity and the possible receptor interaction since N4 may carry a negative charge at physiological and this anion may be the best situation for our compounds' action via ionic attraction forces with a possible cationic, partially positive or electron deficient center on the targeted biomolecule inside the bacterium cell. Additionally, benzene ring and the heterocycles might offer an additional hydrophobic-hydrophobic with a hydrocarbon side within the receptor. At last, the electron density on N1 might be possibly lowered by both the partial participation with benzene ring resonance and the particular inductive effect reasoned by the electron-withdrawing electronegative oxygen or sulfur. This may create a dipole-like axis along the acetate arm and this might introduce a dipole-dipole-resembling electrostatic forces with the similar counterpart on the receptor. Alternatively, the N1 hydrogen and the ether heteroatoms may perform hydrogen forces with suitable atoms on the positions of interested action and this might inforce the formation of drug-receptor complex or binding preferably with the specific key goal and this is the essential for anti-infective objects. Table 1 displays the results of the agar dilution and resazurin broth micro-dilution tests (Figure 4) used to determine the antibacterial Minimum Inhibitory Concentration (MIC). The result showed that the synthesized derivatives displayed significant antibacterial and antifungal effects in comparison with ciprofloxacin (Figure 6). Table 2 showed the result of the antibacterial activity of the compounds after 18 hrs. of incubation. All the examined derivatives demonstrated superior antibacterial effect in comparison with amoxicillin and ciprofloxacin against all tested bacteria.

Table 1. The Sub-Minimum Inhibitory Concentration (SUB-MIC) of the synthesized compounds on the selected bacteria using the agar and resazurin broth dilution assay.

Isolates	T1		T2		T3		E1		E2		E3		AX.		CIP.	
	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB
Staph.	250	125	250	125	250	125	250	125	500	250	250	125	---	---	250	125
Strepto.	250	125	250	125	500	250	250	125	500	250	500	250	---	---	250	125
E.coli	500	250	500	250	500	250	250	125	500	250	500	250	---	---	500	250
Pseudo.	500	250	500	250	500	250	500	250	500	250	500	250	---	---	500	250
Candida	250	125	250	125	250	125	250	125	500	250	250	125	---	---	250	125

AX: Amoxicillin, CIP: Ciprofloxacin

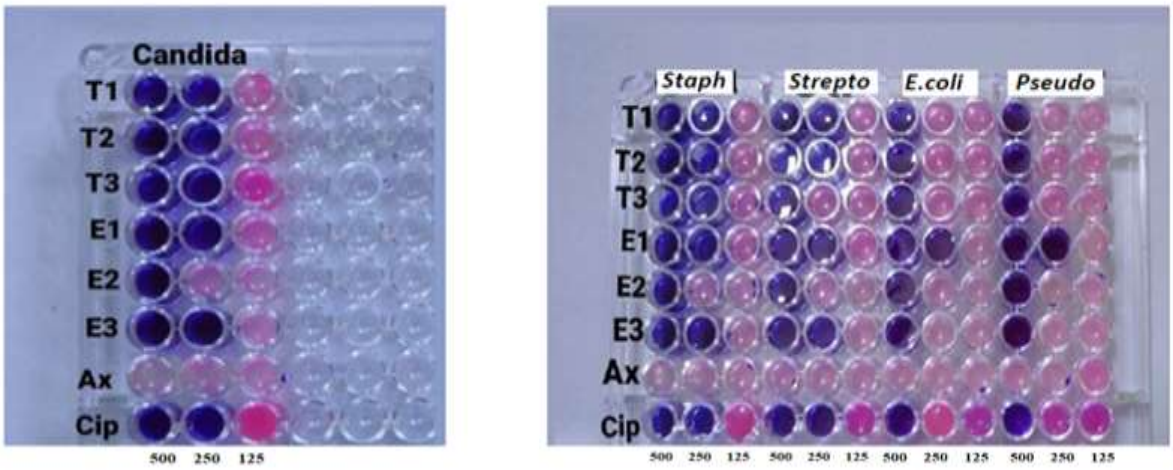


Figure 4. A schematic representation of the 96-well resazurin broth microdilution model. The blue coloration indicates inhibition of growth; pink indicates that organisms are active.

Table 2. Values of the inhibition zone (mm) of the synthesized compounds

Zone of inhibition (mm)								
Isolates	**T1**	**T2**	**T3**	**E1**	**E2**	**E3**	**AX.**	**CIP.**
Staph.	23	15	17	19	12	15	-----	10
Strepto.	16	25	24	10	10	14	-----	11
E.coli	24	13	17	22	18	15	10	15
Pseudo.	20	17	15	14	18	10	-----	10
Candida	17	10	12	19	16	10	-----	10

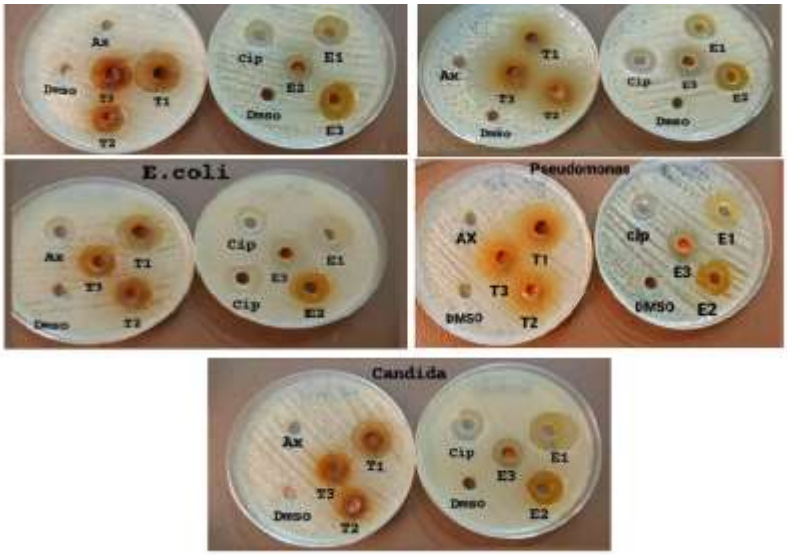


Figure 5. The inhibition zone (mm) of the tested compounds against *Escherichia Coli, Staphylococcus aureus, Streptococcus pyogens, Pseudomonas aeurogenosa* and *candida albicans.* DMSO (10% v\v) is the negative control, AX: Amoxicillin, CIP: Ciprofloxacin.

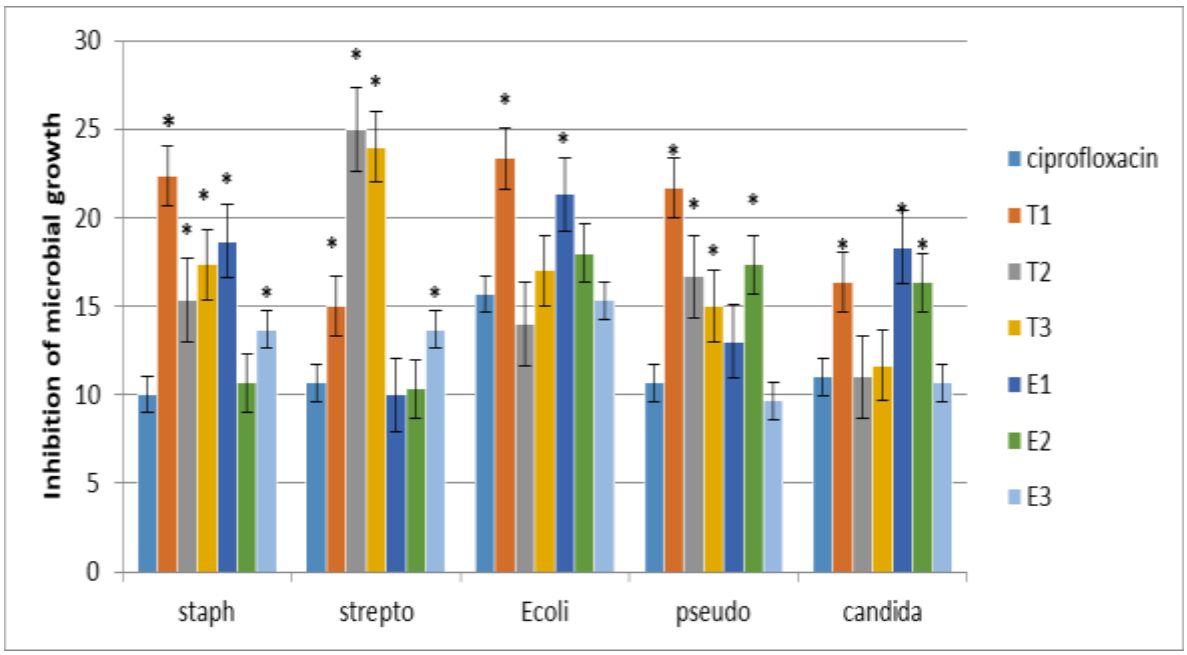


Figure 6. Histogram showing the growth inhibition effects of the tested compounds against G (+ve), G (-ve) bacteria and *candida albicans*. (Values are represented by the mean ± SEM of triplicate measurements, P < 0.05 is statistically significant (*) (relative to reference drug (ciprofloxacin)).

Conclusion

Derivation of amino with acetamido-linked hetero atoms like sulfur or oxygen had reduced the polarity by decreasing the tendency of hydrogen bond formation at sulfadiazine yielding ethers or thio-ethers that are possibly with improved physico-chemical properties, namely higher lipophilicity, over the parent nucleus enabling them to penetrate bacterial outer cell membrane via partition through the lipid barrier and this conflicts with the well results obtained of the two series of synthesized molecules. As shown with the values, there were approximated observations and this is interpreted as that the difference in the atomic size or electronic liability (created by the presence of either oxygen or sulfur) will never make a tangible or perceptible effect on the biological activity. Therefore, this isosterism is expected to be a mere change but without making a real hindrance against mechanism of drug action whether achieving intracellular effective concentration or introducing the ligand to the receptor of importance. Although acylated, the free amino N4 is now occupied with a new functionality which is represented as heteroatom-bearing acetate which would form, with the para-acidic sulfonated N1moiety, a unique dual pharmacophoric armed-molecule or what can be described as **bi-pharmacophoric functionality** exerting an additional antipseuodomonal and anticandidal potencies that are not appeared with the classical sulfonamides. This wide range may be accompanied with further possible variable activities resembling a mutual prodrug and this must be checked in the future scanning.

Abbreviations

DMF: Dimethylformamide. **CFU**: Colony Forming Unit. **SEM**: Standard Error of the Mean.**EPS**: Exopolysaccharides. **TEA**: Triethylamine. **Rf:** Retention factor.

Acknowledgment

The authors are grateful to the department of pharmaceutical chemistry in the college of pharmacy, University of Baghdad for providing the research facilities.

Conflicts of Interest

There is no conflict of interest regarding the publication of this manuscript.

Funding

The authors received no financial support for this research publication from any institution.

Ethics Statements

This research was approved by the scientific and ethical committees in the College of Pharmacy/ University of Baghdad.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Mohammed Kamil Hadi; Mohammed Abdulameer Oleiwi; data collection: Zainab Dhia Kamms; analysis and interpretation of results: Mohammed Kamil Hadi; Maadh Qusay Abdulkadir; Sarah Ahmed; draft manuscript preparation: Mohammed Abdulameer Oleiwi; Maadh Qusay Abdulkadir. All authors reviewed the results and approved the final version of the manuscript.

References

1. Kawkab Y. Saour , Ridha I. Al-Bayati and Mohammed K. Hadi Synthesis of New Coumarin and 2-quinolone Derivatives with Expected Biological Activities Iraqi J Pharm Sci, 2012; 21(2): 42-50.
2. T. Eicher and S. Hauptmann; "The Chemistry of Heterocycles: Structure, Reactions, Synthesis, and Aplications." Wiley-VCH 2nd ed. 2003; 159-165.
3. Tanzeela Q., Andleeb A , Praveen Kumar S., Ishtiaq J. and Hitoshi A. A Review on Medicinally Important Heterocyclic Compounds. The Open Medicinal Chemistry Journal. 2022; 16:1-34.
4. Luiza H. Martins, Jhonatas R. Barbosa, Sabrina B. da Silva, P. Wender. Microbial Degradation of Heterocycles. A Review. Journal of Science & Sustainable Engineering (JSSE) 2023;(1); 1-6
5. Abduljabbar TT, Hadi MK. Synthesis, Characterization and Antibacterial Evaluation of Some Coumarin Derivatives. Iraqi Journal of Pharmaceutical Sciences, 2021, 30(1):249-257.
6. Sahib HA, Dakhel ZA, Hadi MK. Synthesis and Preliminary Antimicrobial Activity Evaluation of New Amide Derivatives of 2-aminobenzothiazole. International Journal of Drug Delivery Technology. 2021; 11(4):1258-1261.
7. Ritu S., Dhara P., and Dhananjay M. Recent developments of heterocyclic chemistry in some drug discovery scaffolds synthesis. Journal of Medicinal and Chemical Sciences 2020; (3): 71-78.
8. Harshita S., Jaya M., and Anjali G. Indole Derivatives as Potential Anticancer Agents: A Review . J. Chil. Chem. Soc. 2020; 65 (3):
9. A. Fleming; On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenza." Br. J. Exp. Pathol. 1929 ; 10(31), 226-36.
10. C. H. Dash; "Penicillin allergy and the cephalosporins." J. Antimicrob.Chemother. 1975; 1(3), 107-18.
11. E. Goldstein; "Norfloxacin, a fluoroquinolone antibacterial agent, Classification, mechanism of action and in vitro activity" Am. J. Med . 1987, 82(6B), 3-17.

12. R. Lavanya; "Sulphonamides: A Pharmaceutical Review" International Journal of Pharmaceutical Science Invention. 2017, 6(2): 1-3.

13. Ana T., Vesna N., Ljubiša N., and Ivan S.; Antimicrobial Sulfonamide Drug. Advanced technologies. 2017, 6(1): 58-71.

14. May M.J.Al-Mudhafar, Maadh Q. Abdulkadir, et.al., Synthesis and microbiological Study of New Sulfonamides, International Journal of Comprehensive Pharmacy, 2012, 3 (6),1-4.

15. Maadh Q. Abdulkadir, Abdulhafeedh H. Abdulwahab, May M. J. Al-Mudhafar, synthesis and evaluating the antimicrobial activities of various adducts prepared from isatins and proline, International Journal of Drug Delivery Technology, 2022;12(2):682-687.

16. Neu .H. C, Gootz T. D, in Medical Microbiology, S. Baron Ed., The University of Texas Medical Branch at Galveston, Galveston 1996.

17. Van Meter K. C., Hubert R. J, Microbiology for the Healthcare Professional, Elsevier, China. 2016; 214- 232.

18. Gringause A.,Mechanism of drug action., An Introduction to medicinal chemistry: how drugs act and why, Gringause A.(ed), 1st edition, New York wiley-VCH Inc. 1997; 64-7.

19. Kanda Y., Kawanishi Y., Oda K., Sakata T., Mihara S., Asakura K., KanemasaT., Ninomiya M., Fujimoto M., Kanoike T.: Synthesis and structure-activity relationships of potent and orally active sulfonamide ETB selective antagonists. Bioorg. & Med. Chem. 2001; 9, 897.

20. Stokes S. S., Albert R., Buurman Ed T., Andrews B., Shapiro A. B., GreenO. M., McKenzie A. R., Otterbein L. R.: Inhibitors of the acetyltransferase domain of N-acetylglucosamine-1-phosphate-uridylyltransferase/glucosamine-1-phosphate acetyl transferase (GlmU). Part 2: Optimization of physicalproperties leading to antibacterial aryl sulfonamides. Bioorg. & Med. Chem.Lett. 2012; 22, 7019.

21. Chuang Zhao, K.P. Rakesh, L. Ravidar, Wan-Yin Fang, Hua-Li Qin. Pharmaceutical and medicinal significance of sulfur (SVI)-Containing motifs for drug discovery: A critical review.
European Journal of Medicinal Chemistry, 2019: (162); 679-734

22. Yichao W., Guoqing F., Hongjuan C., Xu D. , Zilong T. Sulfonamide derivatives as potential anti-cancer agents and their SARs elucidation. European Journal of Medicinal Chemistry, 2021: (226): 113837

23. Fangcheng H., Jing S., Yanju W., Shaobo W., Jixiang C., Xiuhai G., Baoan S., and Deyu H. Synthesis, Antiviral Activity, and Mechanisms of Purine Nucleoside Derivatives Containing a Sulfonamide Moiety. J. Agric. Food Chem. 2019, 67, 31, 8459–8467.

24. Halah A. Sahib, Mohammed K. Hadi, Maadh Qusay Abdulkadir. Synthesis, and Antimicrobial Evaluation of New hydrazone Derivatives of (2,4-dinitrophenyl) hydrazine. Research Journal of Pharmacy and Technology. 2022; 15(4):1743-8.

25. Demir Yazıcı, K., Yılmaz, F.N.., Özbek Çelik, B., & Güzel Akdemir, Ö. Evaluation of some o-benzenedisulfonimido–sulfonamide derivatives as potent antimicrobial agents. Istanbul Journal of Pharmacy, 2022:52(3); 297-301.

26. Skocovska M, Ferencik M, Svoboda M, Svobodova Z (2021): Residues of selected sulfonamides, non-steroidal anti-inflammatory drugs and analgesics-antipyretics in surface water of the Elbe river basin (Czech Republic). Vet Med-Czech, 2021:(66); 208–218.

27. Arafa, F.M.; Said, H.; Osman, D.; Rezki, N.; Aouad, M.R.; Hagar, M.; Osman, M.; Elwakil, B.H.; Jaremko, M.; Tolba, M.M. Nanoformulation-Based 1,2,3-Triazole Sulfonamides for Anti-Toxoplasma In Vitro Study. Trop. Med. Infect. Dis., 2023, 8, 401.

28. Haq, F., Siraj, A., Ameer, M., Hamid, T., Rahman, M., Khan, S., Khan, S. and Masud, S. (2021) Comparative Review of Drugs Used in Diabetes Mellitus—New and Old. Journal of Diabetes Mellitus, 2021 :(11);115-131.

29. Zhuang H., Chuanchao L., Yichuang L., Miao Z., Yitong W., Zhanfang F., Chun G., Bin L., and Yang L. Design, synthesis and biological evaluation of carbohydrate-based sulphonamide derivatives as topical antiglaucoma agents through selective inhibition of carbonic anhydrase II, J Enzyme Inhib Med Chem. 2020; 35(1): 383–390.

30. Thomas G Medicinal Chemistry, 2nd edition. John Wiley and Sons; 2007.

31. Mohamed S. A. El-Gabya, Yousry A. Ammarb, Mohamed I.H. El-Qalieia, Ahmed M. Alia , Modather F. Husseina, Faraghally A. Faraghallya. Sulfonamides: Synthesis and The Recent Applications in Medicinal Chemistry. Egyptian Journal of Chemistry. 2020; 63(12): 5289 – 5327.

32. Mohammed Abdulameer Oleiwi and Munaf H. Zalzala. Synthesis, Molecular Docking Study and Cytotoxicity Evaluation of some

Quinazolinone Derivatives as Nonclassical Antifolates and Potential Cytotoxic Agents**,** Iraqi J Pharm Sci. 2022, 31 (2),283-296.

33. Kamms ZD, Hadi MK. Synthesis, Characterization and Preliminary Antimicrobial and Anti-inflammatory Evaluation of New Ibuprofen Hydrazide Derivatives. International Journal of Drug Delivery Technology. 2023; 13(1):376-38.

34. Abdulraheem SS, Hadi MK. Synthesis and Characterization of New Coumarin Derivatives as Possible Antimicrobial Agents. International Journal of Drug Delivery Technology. 2021; 11(4):1484-1490.

35. Ohikhena, F. U., Wintola, O. A., & Afolayan, A. J. Evaluation of the antibacterial and antifungal properties of Phragmanthera capitata (Sprengel) Balle (Loranthaceae), a mistletoe growing on rubber tree, using the dilution techniques. The Scientific World Journal, 2017:(2017);1-8

36. Lewus, C. B., Kaiser, A. L. A. N., & Montville, T. J. Inhibition of food-borne bacterial pathogens by bacteriocins from lactic acid bacteria isolated from meat. Applied and Environmental Microbiology, 1991: 57(6), 1683-1688.

تحضير، توصيف ودراسة أولية لمضادات الميكروبات لبعض مشتقات الأيثر والثيوإيثر الجديدة من السلفاديازين

محمد كامل هادي[١]، معاذ قصي عبد القادر[١]، محمد عبد الامير عليوي[١]، سارة احمد[١] و زينب ضياء خماس[٢]

[١] فرع الكيمياء الصيدلانية، كلية الصيدلة،جامعة بغداد،بغداد، العراق.

[٢] كلية الرشيد الجامعة، بغداد، العراق.

الخلاصة

تم تصنيع مجموعة من مشتقات الايثر والثايوايثر للسلفاديازين من خلال تفاعل السلفاديازين مع كلوريد الكلورواستيل وتم معاملة المركبات الناتجة مع الفينولات والثيولات المختلفة. تم التأكد من بنية مشتقات الايثر والثايوايثر المستهدفة بالاعتماد على البيانات التحليلية والطيفية الخاصة بها. تم اختبار التأثير المضاد للميكروبات للنواتج النهائية في المختبر باستخدام البكتيريا إيجابية الجرام وسالبة الجرام وبعض الخمائر الشبيهه بالفطر مثل المبيضات البيضاء. أظهر النشاط المضاد للبكتيريا للمركبات المستهدفة بعد ثلاثة أيام من الحضانة أن جميع المشتقات التي تم تقييمها أظهرت نشاطًا مضادًا للبكتيريا متفوقًا مقارنة بالأموكسيسيلين والسيبروفلوكساسين ضد جميع البكتيريا التي تم اختبارها.

الكلمات المفتاحية: النشاط المضاد للميكروبات، مشتقات الايثر، السلفاديازين، السلفونامايد، الدراسات الطيفية.