History of Medicine, 2023, 9(1): 1661–1667
DOI: 10.17720/2409-5834.v9.1.2023.208

Design and synthesis of some novel sulfamethoxazole derivatives bearing β-lactam moiety and evaluate their antibacterial activities

Marwan H. Anowar[1], Ziad T. I. Alkayar[1*]

[1] Department of Chemistry, College of Education for Pure Science, University of Diyala, Iraq
Email: ziadalk15@gmail.com

***Correspondence author:** Ziad T. I. Alkayar (ziadalk15@gmail.com)

Received: 0. H1 s _pw0. 01 **Accepted:** /3 ? npj 0. 01

Citation: Anowar MH, Alkayar ZTI (2023) Design and synthesis of some novel sulfamethoxazole derivatives bearing β-lactam moiety and evaluate their antibacterial activities. History of Medicine 7&' 8/44/ /445, f rmqß-bngmpe-/. ,/550. -02. 7+3612,t 7,/,0. 01,0. 6

Abstract

A series of novel sulfamethoxazole derivatives were synthesized using the appropriate route. The 4-((4-amino-2,5-dimethyiphenyl) diazenyl)-N-(5-meth-ylisoxazol-3-yl) benzene sulfonamide was synthesized using SMX 1 as diazonium component via diazotization reaction by $NaNO_2$/HCl. The diazonium salt thus obtained was coupled, using the standard experimental procedure, to a range of 2,5-dimethylaniline to afford the requisite azo dye in good yield. The Schiff base derivatives were obtained by the condensation reaction of a compound 2 with various aldehydes to give compounds 3a-f, which undergo [2+2] cycloaddition reaction with chloroacetyl chloride to produce substituted β-lactam derivatives 4a-f. Results obtained from spectroscopic (FT-IR, ^{1}H NMR, and ^{13}C NMR) of synthesized compounds were in very good agreement with their chemical structure. The antibacterial activity of some of these compounds was studied in vitro by disk diffusion against two G^+ (Staphylococcus aureus, Streptococcus pneumonia) and two G^- (Escherichia coli, Klebsiella pneumonia).

KeyWords

sulfamethoxazole, cycloaddition, β-lactam, antibacterial.

Scientists and researchers, both chemists and biologists specialists, have been studying antibiotics since discovery of their effect and mechanism of action to kill bacteria,[1,2] and chemically in terms of the active groups they contain, which is the reason for their biological activities, and this interest increased when the emergence of bacterial resistance to antibiotics.[3] This made the study aimed at how to overcome this resistance shown by bacteria by increasing the chemical functional groups with greater biological activity or modifying the biological molecule in addition to a group with good biological activity.[4–7] The antibiotic revolution[8] was launched during the discovery of sulfonamides (SAS) on December 20, 1932 by Domagk when he tried the Prostanil compound for the treatment of streptococci, which gave positive therapeutics reassurances, especially after treating Domagk's daughter with Protonsil after she had a life-threatening infection and after this incident, which is considered a miracle a drug that was discovered at the time, and the drug spread under the name Rubizol.[9]

Sulfomethoxazole (SMX) is a chemical molecule from the class of sulfonamides with a broad spectrum of biological activities and was introduced in the 1960s in the field of clinical treatment of human and animal diseases. SMX is a bactericidal, the basis of its mechanism of action is the inhibition of enzyme dihydro butyrate, which is primarily responsible for the synthesis of folic acid, and the acid is important in the process of growth of bacterial cell walls.[10] The SMX molecule has

functional groups known for its biological activities, which is the isoxazole ring replaced by the methyl group at carbon number 4 and at carbon number 5 linked to the sulfanilamide.[11]

The medical-biological benefit that SMX has gained is to treat bacterial infections, including urinary tract infections and infections of the respiratory and gastrointestinal. The therapeutic prescription that SMX is taken in the form of a combination of sulfamethoxazol-trimethoprim (co-trimoxazole), which is the first developmental step in the field of chemotherapy against bacteria by Hitchings and co-works in October 1968.[12]

Over time, and especially in recent decades, the clinical and medical importance of co-trimoxazole treatments has declined; this is due to the resistance shown by bacteria against the drug and its development towards the mechanism of its elimination. From this point of view, research and experiments continued, and there was a need to synthesize new derivatives of SMX that have known biological functional groups to provide a new and wide range of treatments against bacterial pathogens.[13,14] In the context the synthetic program that we adopted includes the synthesis of derivatives of SMX with heterocyclic four-membered ring. β-lactam (2-Azetidinone) is the four-membered ring composed of three carbon atoms, one of which is a carbonyl group and one nitrogen atom, The importance of this ring emerged after the antibiotic revolution for the discovery of penicillin and its derivatives.[15] The β-lactam ring is included in many antibiotics, as it is considered the main nucleus of the effectiveness of these antibiotics. Hence, it gained its importance in the synthesis of organic chemicals, and clinical and biological treatments.[16] The β-lactam ring is included in many of the most common antibiotics, amounting to half of the global antibiotics.[17] β-lactam have also other pharmaceutical applications such as anti-inflammatory, antifungal, anti-hepatitis, Analgesic properties, antihyperglycemic, LHRH antagonists, cholesterol absorption. Inhibitors, and anticancer agents.[18] In addition, have received significant attention from medical and synthetical chemists because of its importance in organic synthesis as versatile synthetic intermediates and chiral synthons.[19] All of these biological, clinical, and medical activities of these drugs have either been reduced or disappeared in recent years due to the resistance shown by bacteria and viruses towards the mechanism of the drug to eliminate them. Therefore, it has become necessary to develop these drugs by forming functional groups on them that increase their ancient activities against diseases.[20]

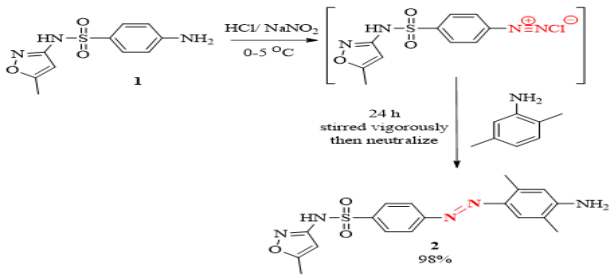
Results and Discussion

Chemical synthesis

In the present study, SMX was used to prepare thirteen novel SMX derivatives accomplished in three steps and was summarized in scheme 1, 2, and 3.

Intermediate was prepared by the diazotization-coupling reaction. SMX was diazotised using sodium nitrite in the presence of HCl followed by coupling with 2,5-dimethyaniline to give good yield (Scheme 1). Compound 2 was confirmed by FT-IR spectra that show absorption bands of the NH_2 groups at 3340 and 3248 cm^{-1}.[21,22] It also shows the azo group of N=N stretching peak at 1411 cm^{-1}.[23]

Next, a series of Schiff bace have been successfully prepared via a feasible chemical modification. In the neutral medium 1.0 equivalent of the amine 2 was dissolved in the methanolic medium, 1.0 equivalent of 2-OH-1-naphthaldehyde was dissolved in ethanol and added drop wise to the previous solution with reflux for 4 h. No desired 3a was observed.

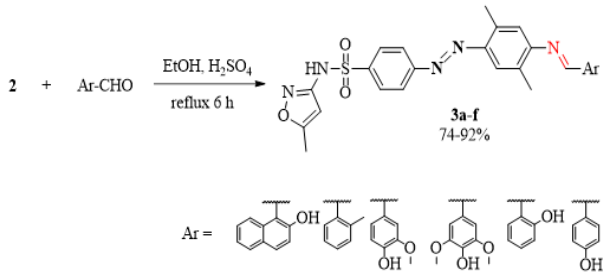


Scheme 1: The synthesis of azo-coupling product

Heating the mixture of amine 2 and 2-OH-1-naphthaldehyde at 78 °C for 6 h, this proceeded unsuccessfully as the reaction mixture. The reaction mixture was then refluxed for 6 h at the base solution using 10% sodium hydroxide NaOH, subsequent TLC silica gel analysis showed many spots on the TLC plant with 55% yield. As a result, the reaction was repeated using drops acetic acid, after 6 h the reaction was cooled to room temperature and a 60% yield of the compound 3a was obtained, and to improve the product, the acid was changed to hydrochloric acid HCl, where the product was 80%, and the acid was changed to sulfuric

acid H_2SO_4 with a reflux time of 6 hours, the solid product was formed in 92% yield.

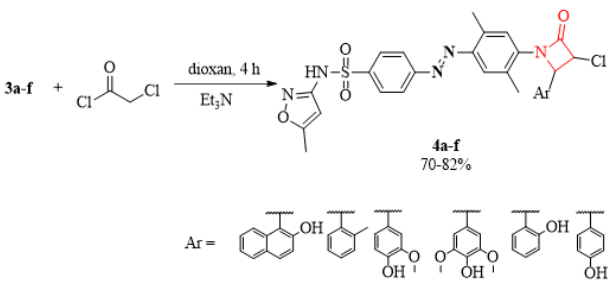
The condensation reaction was optimized and performed to synthesize the other derivatives 3b-f, all synthesized compounds 3a-f resulted in good yield (Scheme 2).



Scheme 2: The synthesis of Schiff base product

A quite good compatibility was observed in the characterization of experimental and theoretical FT-IR spectral results to structures of the final condensation products 3a-f. The disappeared of NH_2 group in the FT-IR spectra for compounds 3a-f and instead the stretching bond of C=N of azomethine group appeared at rang (1653 − 1627 cm^{-1}),[24–26] also showed characteristic absorption bands of 3b-f at (3525 − 3379 cm^{-1}) which were assigned for the O-H group.[27,28] The N-H stretching vibration could be observed as a sharp medium intensity band (3394 − 3325 cm^{-1}).[29]

The third step included the Staudinger [2+2] cycloadditions of ketenes with iminic systems for the synthesis of heterocyclic systems. The compounds imines 3a-f was treated with chloroacetyl chloride in the presence of TEA as a catalyst in dioxane, readily afforded the corresponding β-lactam derivatives 4a-f in good yield(Scheme 3).



Scheme 3: The synthesis of β-lactam product

The structures of β-lactam 4a-f were characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The observation was confirmed by the synthesis of the β-lactam ring derivatives by FT-IR spectroscopy were recorded sharp strong peaks of the C=O group vibration stretching in the range between 1700-1750 cm^{-1}.[30,31] The bands in the FT-IR spectra of compounds 4a-f at approximately 785 and 760 cm^{-1} can be assigned to the C-Cl stretching bonds.[32] The ^{1}H NMR spectra for all synthesized compounds 4a-f shows peaks for HC-Cl as a doublet in range of 3.90-4.29 ppm, however protons of HC-N gave doublet in range of 4.10-4.36 ppm.[4] Methoxy group (-OCH_3) shows singlet peak between 4.28 and 4.68 ppm for compounds 4c-f. Other aromatic peaks were observed between 6.90 and 8.0 ppm. The proton of the isoxazole ring appeared as singlet in the 6-6.08 ppm range. And singlet at 9.71-10.69 ppm is a proton of the HN-SO_2 group, while the CH_3 protons gave a singlet at 2.16-2.29 ppm.[33]

In the ^{13}C NMR of compounds 4a-f, H_3C-C=C oxazole resonated at 170 ppm, and the characteristic of the C=O in region 165 ppm.[20] The carbon C=N in the oxazole ring was observed at 157 ppm, while carbon attached to azo group C-N=N was observed to peak at 155 ppm. The carbon attached to the OH group confirmed the existence of a chemical shift between 153-147 ppm for compounds 4a, 4c, and 4d. The characteristic of the $C_{aldehyde}$-C_{lactam} signal appeared at around 141 ppm, while the $C_{aniline}$-N_{lactam} appeared to peak at 137 ppm. The twelve carbons of aromatic rings showed a range between 129-117 ppm. The carbons of the β-lactam ring, CH-Cl, CH-N respectively, were showed peaks at 69-66 and 45-43 ppm.[34] Finally, the ^{13}C NMR spectrum showed two carbon as CH_3 of aniline ring were recorded at around 18-17 ppm, and CH_3 for oxazole was observed at 12-11 ppm.[33]

Biological Evaluation

The synthesized compounds 4a-f were evaluated for their antibacterial activity against the Staphylococcus aureus and Streptococcus pneumonia, Klebsiella Pneumonia, and Escherichia coli for their minimum inhibitory concentrations (50 and 100 mg/mL) and the results are provided in Table 2.

Table 2: Antibacterial activity against the Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella Pneumonia, and Escherichia coli (50 and 100 mg/mL)

	S. Aureus	S. Pneumonia	E. coli	K. pneumonia

con.mm/mL	50	100	50	100	50	100	50	100
4a	19	24	24	22	23	25	22	24
4b	24	25	23	25	23	22	22	23
4c	25	26	25	25	25	26	24	25
4d	25	26	23	24	22	22	21	20
SMX	20	21	R	R	R	10	R	11
DMSO	0	0	0	0	0	0	0	0

As evident from table 1, the antibacterial activity of the test compounds 4a-d were gave good-excellent activity. The bacteria S. Pneumonia gave resistance against SMX in

Concentrations 50 and 100 mg/mL, while SMX gave good activity against bacteria S. Aureus, and moderate active observed for SMX against bacteria E. coli and K. pneumonia in concentration 100 mg/mL. When compared to the synthetic 4a-d derivatives, the table shows that the activity of the derivatives against S. aureus bacteria is nearly close to that of the drug in the two concentrations 50 and 100 mg/mL. The compound 4a-d were showed good inhibition zone against bacteria S. Pneumonia in 50 and 100 mg/mL, furthermore activity observed against bacteria E. coli and K. pneumonia in 50 mg/mL. Since the drug gave a moderate activity against bacteria E. coli and K. pneumonia in 100 mg/mL, the effectiveness increased to double for the new synthetic derivatives 4a-f.

Materials and methods

Sulfomethoxazole was supplied from the State Company for the Drugs Industry and medical Appliances / Iraq – Samarra. All the solvents and chemicals involved in synthesis were of analytically grade and used without further purification, which were supplied from different international companies.

Instrumentation

All synthesized compounds were confirmed using ^{1}H and ^{13}C NMR spectra, recorded on a Bruker AV 400 MHz spectrometer, the synthesized compounds were dissolved with DMSO-d_6 in the laboratories of the Department of Chemistry, University of Tehran, Iran. The FT-IR spectra were recorded as pressed thin films on KBr disks, using SHIMADZU, 8400S spectrophotometer in the region of 4000-400 cm^{-1}, and melting points were measured on a Stuart SMP3 apparatus by open capillary tube method and are uncorrected, in the laboratories of the Department of Chemistry, University of Diyala, Iraq. The purity and monitoring of the synthesis reactions of the synthesized compounds were ascertained by thin layer chromatography TLC silica gel.

Synthesis and characterization

The synthetic route includes the azo-coupling reaction of SMX with 2,5-dimethylaniline, followed by a condensation reaction with some benzaldehyde derivatives to give the desired product of azomethine derivatives (dipolarophiles) that could participate in cycloaddition reactions with 1,3-dipolar compounds, namely, chloroacetyl chloride to synthesize novel derivatives of sulfamethoxazole that containing heterocyclic four-membered ring called β-lactam.

General Procedure for the synthesis of compound (2)

SMX 1 (1.0 g, 3.94 mmol) was added to a solution of 37% HCl 5.0 mL and 5.0 mL of distilled water and thoroughly stirred at room temperature for 30 min. Then rapidly cooled in an ice bath to 0 °C. $NaNO_2$ (0.29 g, 4.33 mmol) dissolved in 5.0 mL cold distilled water, and added over 15 min into the mixture, and stirred for 1 h at 0 °C. The resulted diazonium salt solution was continuously added to the solution of 2,5-dimethylaniline (3.94 mmol) in water 10 mL at 0 °C. The coloured mixture was stirred at room temperature for 24 h and neutralized with saturated NaOH solution. The product was filtered, washed with cold water (3x25 mL), dried, and crystallized from diethyl ether.

4-((4-amino-2,5-dimethyiphenyl) diazenyl)-N-(5-meth-yliso xazol-3-yl)benzenesulfonamide 2

The product was obtained as a dark orange solid (1.5 g, 98%). Molecular formula ($C_{18}H_{19}N_5O_3S$), M. wt = 385 g/mol. m.p = 220-222 °C. R_f 0.37 [Petroleum ether-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3340-3248 (NH_2), 3116 (N-H), 3032 (C=C-H Ar), 2962 (C-C-H aliphatic), 1620 (C=N oxazole), 1543-1411 (C=C Ar),

1465 (N=N), 1334-1257 (S=O asy), 1165-1095 (S=O sy), 933 (S-O).

General Procedure for the synthesis of compounds (3a-f)

To a suspension of compound of 2 (0.50 g, 1.30 mmol) in ethanol 10 mL, 5 drops of concentrated sulfuric acid was added, and stirred for 20 min. Benzyl aldehyde derivatives (1.30 mmol) were dissolved in 5 mL ethanol and added drop wise to the mixture and heated under reflux. After 6 h the reaction monitored with TLC silica gel, ice water is poured into the mixture and was left overnight at room temperature until a solid appeared. The product was filtered, washed with cold water (3x25 mL), dried, and crystallized from diethyl ether.

4-(4-(2-hydroxynaphthalen-1-yl) methylene) amino)-2,5-dimethylphenyl) diazenyl)-N-(5-methylisoxazol-3-yl) benzenesulfonamide 3a

The product was obtained as a red solid (0.64 g, 92%). Molecular formula ($C_{29}H_{25}N_5O_4S$), M. wt = 539 g/mol. m.p = 235-237 °C. R_f 0.34 [Petroleum ether-EtOAc (6:4)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3479 (O-H), 3371 (N-H), 3040 (C=C-H Ar), 2970 (C-C-H aliphatic), 1643 (C=N imine), 1604 (C=N oxazole), 1543-1404 (C=C Ar), 1465 (N=N), 1342-1303 (S=O asy), 1249-1172 (S=O), 972 (S-C).

4-((2,5-dimethyl-4-((2-methylbenzylidene) amino) phen yl) d iazenyl)-N-(5-methylisoxazol-3-yl) benzenesulfona mide 3b

The product was obtained as a light red solid (0.47 g, 75%). Molecular formula ($C_{26}H_{25}N_5O_3S$), M. wt = 487 g/mol. m.p = 220-222 °C. R_f 0.39 [Petroleum ether-EtOAc (5:5)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3394 (N-H), 3124 (C=C-H Ar), 2985 (C-C-H aliphatic), 1643 (C=N imine), 1604 (C=N oxazole), 1543-1404 (C=C Ar), 1465 (N=N), 1334-1257 (S=O asy), 1165-1095 (S=O sy), 933 (S-C).

4-((4-((4-hydroxy-3-methoxybenzylidene)amino)-2,5-dimethylphenyl)diazenyl)-N-(5-methylisoxazol-3-yl)be nzenesul fonamide 3c

The product was obtained as a red solid (0.53 g, 80%). Molecular formula ($C_{26}H_{25}N_5O_5S$), M.wt = 519 g/mol. m.p = 200-202 °C. R_f 0.36 [Petroleum ether-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1} υ_{max}: 3502 (O-H), 3325 (N-H), 3124 (C=C-H Ar), 2978 (C-C-H aliphatic), 1643 (C=N imine), 1597-1419 (C=C Ar), 1535 (N=N), 1334-1257 (S=O asy), 1165-1095 (S=O sy), 1026 (C-O) cm^{-1}.

4-((4-((4-hydroxy-3,5-dimethoxybenzylidene)amino)-2,5-dimethylphenyl)diazenyl)-N-(5-methylisoxazol-3-yl)benzeneeulfonamide 3e

The product was obtained as a red solid (0.61 g, 86%). Molecular formula ($C_{27}H_{27}N_5O_6S$), M.wt = 549 g/mol. m.p = 157-159 °C. R_f 0.35 [Petroleum ether-EtOAc (5:5)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3525 (O-H), 3340 (N-H), 3062 (C=C-H Ar), 2978 (C-C-H aliphatic), 1635 (C=N imine), 1604 (C=N oxazole), 1535-1419 (C=C Ar), 1442 (N=N), 1396-1327 (S=O asy), 1280-1249 (S=O sy), 1219 (C-O).

4-((4-(2-hydroxybenzylidene)amino)-2,5-dimethylphe nyl)diazenyl)-N-(5-methylisoxazol-3-yl)benzenesulfon amide 3d

The product was obtained as a red solid (0.47 g, 74%). Molecular formula ($C_{25}H_{23}N_5O_4S$), M.wt = 489 g/mol. m.p = 217-219 °C. R_f 0.34 [Petroleum ether-EtOAc (6:4)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3448 (O-H), 3178 (N-H), 3047 (C=C-H), 2939 (C-C-H aliphatic), 1658 (C=N imine), 1604 (C=N oxazole), 1550-1419 (C=C Ar), 1496 (N=N), 1327-1265 (S=O asy), 1203-1149 (S=O sy), 987 (C-S).

4-((4-((4-hydroxybenzylidene)amino)-2,5-dimethylphe nyl)diazenyl)-N-(5-methylisoxazol-3-yl)benzenesulfo nami de 3f

The product was obtained as a red solid (0.51 g, 81%). Molecular formula ($C_{25}H_{23}N_5O_4S$), M. wt = 489 g/mol. m.p = 191-193 °C. R_f 0.34 [Petroleum ether-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) υ: 3441 (O-H), 3325 (N-H), 3186 (C=C-H Ar), 2978 (C-C-H aliphatic), 1651 (C=N imine), 1604 (C=N oxazole), 1543-1427 (C=C Ar), 1481 (N=N), 1334-1257 (S=O asy), 1203-1157 (S=O sy), 933 (C-S).

General Procedure for the synthesis of β-Lactam derivatives (4a-d)

To a well-stirred solution of compounds 3a-d (0.35g, 0.60 mmol) with triethylamine (0.65 mmol) in dioxane 5 mL. The chloroacetyl chloride (0.60 mmol) in 5 mL dioxane was added drop wise at 0-5 °C. The solution was heated under reflux for 4 h. Then, the solvent was evaporated under vacuum pressure. Ice water was added to the products, filtered, washed with cold water, and crystallized from dimethyl ether.

4-((4-(3-chloro-2-(2-hydroxynaphthalen-1-yl)-4-oxoazet idin-1-yl)-2,5-dimethylphenyl)diazenyl)-N-(5-ethylisoxaz ol-3-yl)benzenesulfonamide 4a

The product was obtained as a red solid (0.3 g, 82%). Molecular formula ($C_{31}H_{26}ClN_5O_5S$), M.wt = 616 g/mol. m.p = 179-181 °C. R_f 0.38 [Petroleum ether-EtOAc (5:5)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3479 (O-H), 3340 (N-H), 3178 (C=C-H Ar), 2958 (C-C-H aliphatic), 1720 (C=O), 1627 (C=N oxazole), 1581-1458 (C=C Ar), 1535 (N=N), 1396-1327 (S=O asy), 1249-1165 (S=O sy), 925 (C-S), 786 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm), 10.69 (s, 1H, O-H), 9.77 (s, 1H, SO_2NH), 8.02-6.90 (m, 12H, ArH), 5.99 (s, 1H, oxazol ring), 4.32 (d, 1H, HC-Cl), 4.15 (d, 1H, HC-N), 2.59, 2.48 (s, 6H, $2CH_3$ aniline ring), 2.34 (s, 3H, CH_3 oxazole ring). ^{13}C NMR (100 MHz, DMSO-d_6), 170 (H_3C-C=C)$_{oxazole}$, 165 (C=O), 157 ($C_{oxazole}$=N), 155 (C-OH), 153 (C-N=N), 145 (N=N-C), 141 ($C_{aldehyde}$-C_{lactam}), 138 (C-SO_2), 137 ($C_{aniline}$-N_{lactam}), 129-120 (12$C_{aromatic}$-H), 95 (C=C-CH_3)$_{oxazole}$, 66 (C-Cl)$_{lactam}$, 43 (C-N)$_{lactam}$, 17 ($2CH_3$)$_{aniline}$, 12 (CH_3)$_{oxazole}$.

4-((4-(3-chloro-2-oxo-4-(o-tolyl)azetidin-1-yl)-2,5-dimet hylphenyl)diazenyl)-N-(5-methylisoxazol-3-yl)ben zenesu lfonamide 4b

The product was obtained as a red solid (0.23 g, 70%). Molecular formula ($C_{28}H_{26}ClN_5O_4S$), M.wt = 564 g/mol. m.p = 130-132 °C. R_f 0.34 [Petroleum ether-EtOAc (3:7)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3356 (N-H), 3170 (C=C-H Ar), 2924 (C-C-H aliphatic), 1712 (C=O), 1620 (C=N oxazole), 1573-1465 (C=C Ar), 1535 (N=N), 1396-1334 (S=O asy), 1334-1249 (S=O sy), 933 (C-S), 748 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm), 9.80 (s, 1H, SO_2NH), 8.01-7.52 (m, 10H, ArH), 6.08 (s, 1H, oxazol ring), 4.36 (m, 1H, HC-N), 4.30 (m, 1H, HC-Cl). 2.89, 2.54 (s, 6H, $2CH_3$ aniline ring), 2.20 (s, 3H, CH_3 aldehyde ring), 2.17 (s, 3H, CH_3 oxazole ring). ^{13}C NMR (100 MHz, DMSO-d_6), 170 (H_3C-C=C)$_{oxazole}$, 165 (C=O), 157 ($C_{oxazole}$=N), 155 (C-N=N), 147 (N=N-C), 141 ($C_{aldehyde}$-C_{lactam}), 140 (C-SO_2), 137 ($C_{aniline}$-N_{lactam}), 129-122 (10$C_{aromatic}$-H), 96 (C=C-CH_3)$_{oxazole}$, 69 (C-Cl)$_{lactam}$, 45 (C-N)$_{lactam}$, 17 (CH_3)$_{aldehyde}$, 17-16 ($2CH_3$)$_{aniline}$, 11 (CH_3)$_{oxazole}$.

4-((4-(3-chloro-2-(4-hydroxy-3-methoxyphenyl)-4-oxo azetidin-1-yl)-2,5-dimethylphenyl)diazenyl)-N-(5-meth ylisoxa zol-3-yl)benzenesulfonamide 4c

The product was obtained as a red solid (0.26 g, 75%). Molecular formula ($C_{28}H_{26}ClN_5O_6S$), M.wt = 596 g/mol. m.p = 125-127 °C. R_f 0.32 [Petroleum ether-EtOAc (5:5)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3417 (O-H), 3263 (N-H), 3147 (C=C-H Ar), 2939 (C-C-H aliphatic), 1728 (C=O), 1620 (C=N oxazole), 1581-1465 (C=C Ar), 1535 (N=N), 1396-1334 (S=O asy), 1257-1172 (S=O sy), 1134 (C-O) 933 (C-S), 794 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm), 10.70 (s, 1H, O-H), 9.66 (s, 1H, SO_2NH), 7.96-67.07 (m, 12H, ArH), 6.09 (s, 1H, oxazol ring), 4.29 (s, 3H, OCH_3), 4.21 (d, 1H, HC-Cl), 3.97 (d, 1H, HC-N), 2.57, 2.20 (s, 6H, $2CH_3$ aniline ring), 2.16 (s, 3H, CH_3 oxazole ring). ^{13}C NMR (100 MHz, DMSO-d_6), 170 (H_3C-C=C)$_{oxazole}$, 165 (C=O), 157 ($C_{oxazole}$=N), 155 ($C_{aldehyde}$-O, C-OH), 147 (C-N=N, N=N-C), 141 ($C_{aldehyde}$-C_{lactam}), 140 (C-SO_2), 137 ($C_{aniline}$-N_{lactam}), 129-117 (9$C_{aromatic}$-H), 95 (C=C-CH_3)$_{oxazole}$, 66 (C-Cl)$_{lactam}$, 43 (C-N)$_{lactam}$, 18-17 ($2CH_3$)$_{aniline}$, 12 (CH_3)$_{oxazole}$.

4-((4-(3-chloro-2-(4-hydroxy-3,5-dimethoxyphenyl)-4-oxoazetidin-1-yl)-2,5-dimethylphenyl) diazenyl)-N-(5-methyliso xazol-3-yl)benzenesulfonamide 4e

The product was obtained as a red solid (0.27 g, 80%). Molecular formula ($C_{29}H_{28}ClN_5O_7S$), M. wt = 625 g/mol. m.p = 200-202 °C. R_f 0.39 [Petroleum ether-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3387 (O-H), 3232 (N-H), 3147 (C=C-H Ar), 2924 (C-C-h aliphatic), 1751 (C=O), 1620 (C=N oxazole), 1535-1396 (C=C Ar), 1465 (N=N), 1334-1257 (S=O asy), 1172-1087 (S=O sy), 1002 (C-O), 914 (C-S), 740 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm), 10.61 (s, 1H, O-H), 9.72 (s, 1H, SO_2NH), 7.95-7.41 (m, 8H, ArH), 6.08 (s, 1H, oxazol ring), 4.69, 4.58 (s, 6H, $2OCH_3$), 4.30 (d, 1H, HC-Cl), 4.10 (d, 1H, HC-N), 2.54, 2.42 (s, 6H, $2CH_3$ aniline ring), 2.16 (s, 3H, CH_3 oxazole ring). ^{13}C NMR (100 MHz, DMSO-d_6), 170 (H_3C-C=C)$_{oxazole}$, 165 (C=O), 157 ($C_{oxazole}$=N), 155 ($C_{aldehyde}$-O, C-OH), 147 (C-N=N, N=N-C), 141 ($C_{aldehyde}$-C_{lactam}), 140 (C-SO_2), 137 ($C_{aniline}$-N_{lactam}), 129-117 (9$C_{aromatic}$-H), 95 (C=C-CH_3)$_{oxazole}$, 66 (C-Cl)$_{lactam}$, 43 (C-N)$_{lactam}$, 18-17 ($2CH_3$)$_{aniline}$, 12 (CH_3)$_{oxazole}$.

4-((4-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)-2,5-dimethylphenyl)diazenyl)-N-(5-methylisoxazo l-3-yl)benz enesulfonamide 4d

The product was obtained as a red solid (0.24 g, 73%). Molecular formula ($C_{27}H_{24}ClN_5O_5S$), M.wt = 566 g/mol. m.p = 219-221 °C. R_f 0.33 [Petroleum ether-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3410 (O-H), 3255 (N-H), 3147 (C=C-H Ar), 2924 (C-C-H aliphatic), 1743 (C=O), 1612 (C=N oxazole), 1535-1396 (C=C Ar), 1465 (N=N), 1334-1249 (S=O asy), 1165-1087 (S=O sy), 918 (C-S), 748 (C-Cl).

4-((4-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)-2,5-dimethylphenyl)diazenyl)-N-(5-methylisoxazol -3-yl)be nzenesulfonamide 4f

The product was obtained as a red solid (0.26 g, 77%). Molecular formula ($C_{27}H_{24}ClN_5O_5S$), M.wt = 566 g/mol. m.p = 181-183 °C. R_f 0.37 [Petroleum ether-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) υ_{max}: 3456 (O-H), 3317 (N-H), 3093 (C=C-H Ar), 2924 (C-C-H aliphatic), 1751 (C=O), 1620 (C=N oxazole), 1581-1458 (C=C Ar), 1535 (N=N), 1404-1334 (S=O asy), 1257-1165 (S=O sy), 972 (C-S), 732 (C-Cl).

Conclusion

In this study new azo dye, new Schiff base and 2-azetidinone derivatives have been designed and synthesized starting from sulfamethoxazole. All products were characterized by spectroscopic data (FT-IR, ^{1}H NMR, and ^{13C} NMR). The results of biological studies (antibacterial) for some products were also reported.

References

P. Hammann, L. Halby, P. B. Arimondo, P. Glaser, B. Aigle, H. B. Bode, O. Genilloud, A. W. Truman, K. J. Weissman, M. Graz, S. Donadio, L. Fraisse, L. J. V Piddock, I. H. Gilbert, H. E. Moser, *Nat. Rev. Chem.* **2021**, *5*, 726–749.

F. C. Tenover, *Am. J. Med.* **2006**, *119*, DOI 10.1016/j.amjmed.2006.03.011.

D. Rodr, M. Pernas, A. Rodr, E. Colcho, *J. Med. Chem.* **2020**, *63*, 1859–1881.

R. Kaur, R. Singh, A. Kumar, S. Kaur, N. Priyadarshi, N. K. Singhal, K. Singh, *Heliyon* **2020**, *6*, e04241.

D. Abdelhamid, **n.d.**, DOI 10.1016/j.bmcl.2009.01.104.

P. K. Prabhakar, **n.d.**, DOI 10.1007/s00044-010-9342-1.

S. M. Hell, C. F. Meyer, G. Laudadio, A. Misale, M. C. Willis, T. Noël, A. A. Trabanco, V. Gouverneur, *J. Am. Chem. Soc.* **2020**, *142*, 720–725.

J. Davies, *Microbiologia* **1996**, *12*, 9–16.

S. B. Christensen, *Molecules* **2021**, *26*, 1–32.

G. Prasannamedha, P. S. Kumar, *J. Clean. Prod.* **2020**, *250*, 119553.

S. Kumar Verma, R. Verma, F. Xue, P. Kumar Thakur, Y. R. Girish, K. P. Rakesh, *Bioorg. Chem.* **2020**, *105*, 104400.

D. C. Wallace Jr, Richard J and Septimus, Edward J and Williams Jr, Temple W and Conklin, Richard H and Satterwhite, Terry K and Bushby, Margaret B and Hollowell, *Rev. Infect. Dis.* **1982**, *4*, 196–236.

F. Eugene-Osoikhia, T.T., Aleem, A. O and Ayeni, *FUDMA J. Sci.* **2020**, *4*, 217–232.

P. Eliopoulos, G. M., & Huovinen, *Clin. Infect. Dis.* **2001**, *32*, 1608–1614.

S. Hosseyni, A. Jarrahpour, *Org. Biomol. Chem.* **2018**, *16*, 6840–6852.

M. W. Grinstaff, A. S. Balijepalli, J. H. McNeely, A. Hamoud, *J. Org. Chem.* **2020**, *85*, 12044–12057.

R. B. Hamed, J. R. Gomez-Castellanos, L. Henry, C. Ducho, M. A. McDonough, C. J. Schofield, *Nat. Prod. Rep.* **2013**, *30*, 21–107.

R. Heiran, S. Sepehri, A. Jarrahpour, C. Digiorgio, H. Douafer, J. M. Brunel, A. Gholami, E. Riazimontazer, E. Turos, *Bioorg. Chem.* **2020**, *102*, DOI 10.1016/j.bioorg.2020.104091.

V. Mehra, P. Singh, N. Manhas, V. Kumar, *Synlett* **2014**, *25*, 1124–1126.

A. Mermer, H. Bayrak, S. Alyar, M. Alagumuthu, *J. Mol. Struct.* **2020**, *1208*, 127891.

S. Y. and F. K. NESRIN SENER, IZZET SENER, *Asian J. Chem.* **2015**, *27*, 3658–3662.

F. Cuenú, N. Muñoz-Patiño, J. E. Torres, R. Abonia, R. A. Toscano, J. Cobo, *J. Mol. Struct.* **2017**, *1148*, 557–567.

I. H. R. Tomi, A. H. R. Al-Daraji, R. R. T. Al-Qaysi, M. M. Hasson, K. H. D. Al-Dulaimy, *Arab. J. Chem.* **2014**, *7*, 687–694.

S. Özkınalı, M. Gür, N. Şener, S. Alkın, M. S. Çavuş, *J. Mol. Struct.* **2018**, *1174*, 74–83.

O. Bekircan, H. Bektas, *Molecules* **2008**, *13*, 2126–2135.

A. N. Kursunlu, E. Guler, H. Dumrul, O. Kocyigit, I. H. Gubbuk, *Appl. Surf. Sci.* **2009**, *255*, 8798–8803.

M. Özil, H. T. Balaydın, M. Şentürk, *Bioorg. Chem.* **2019**, *86*, 705–713.

S. Imran, M. Taha, N. H. Ismail, K. M. Khan, F. Naz, M. Hussain, S. Tauseef, *Molecules* **2014**, *19*, 11722–11740.

H. Aziz, A. Mahmood, S. Zaib, A. Saeed, H. R. El-Seedi, J. Pelletier, J. Sévigny, J. Iqbal, *J. Biomol. Struct. Dyn.* **2021**, *39*, 6140–6153.

H. Lal, N. Sharma, T. P. Agarwal, N. Sharma, *J. Appl. Pharm. Sci.* **2012**, *2*, 104–112.

N. Borazjani, M. Behzadi, M. Dadkhah Aseman, A. Jarrahpour, J. A. Rad, S. Kianpour, A. Iraji, S. M. Nabavizadeh, M. M. Ghanbari, G. Batta, E. Turos, *Med. Chem. Res.* **2020**, *29*, 1355–1375.

A. Bishnoi, K. Srivastava, S. Singh, C. M. Tripathi, *Eur. J. Chem.* **2011**, *2*, 359–364.

V. Akbary Moghaddam, V. Kasmaeifar, Z. Mahmoodi, H. Ghafouri, O. Saberi, A. Mohammadi, *Int. J. Biol. Macromol.* **2021**, *189*, 194–205.

N. Berber, M. Arslan, Ç. Bilen, Z. Sackes, N. Gençer, O. Arslan, *Bioorg. Khim.* **2015**, *41*, 468–474