Synthesis of Some Novel Antibacterial Sulfonamide Reactive Dyes

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Abstract: Several new of sulfonamide based reactive dyes (D1-D4) has been synthesized by coupling reaction of sulfonamide diazonium salt with sulfonamido-cyanurated H-acid. The chemical structure of the synthesized dyes was secured by their spectral data e.g. Elemental analysis, IR, ^{1}HNMR and MS spectroscopy. The principle advantage here for using sulfonamide based moiety is that the activity of antimicrobial is high, short reaction time and reaction procedure is done in few steps, the work up is convenient and thus the starting material can be easily found.

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1. Introduction

Sulfonamides are an essential class of antibacterial drugs used in medicine and veterinary practice. Sulfa drugs are widely used in the treatment of infections, especially for patients intolerant to antibiotics. The vast commercial success of these medicinal agents has made the chemistry of sulfonamides to become a major area of research and an important branch of commercial importance in pharmaceutical sciences. An excellent review of pharmacology and therapeutic use of dapsone (DAP) is given by Uetrecht (Uetrecht, 1989). Comprehensive descriptions of some important sulfa drugs have been reviewed (Rudy& Senkowski, 1973; Orzech, 1976; Woolfenden, 1977; Stober & De witte, 1982). The official method of British Pharmacopoeia (British Pharmacopoeia, 1998) and United States Pharmacopoeia (United States Pharmacopoeia, 2000) describe nitrite titration method for the analysis of sulfa drugs.

In view of the reported biological activities of sulphonamide as well as sulphapyridines **(**Gaffer &Abdel-latif, 2011) efforts have been made to synthesize the first reported moiety of sulfonamide based reactive dyes (D1-D4) were prepared by coupling reaction of sulfonamide diazonium salt with sulfonamido-cyanurated H-acid. Diazotization was carried out according to the literature procedure using sodium nitrite and hydrochloric acid.

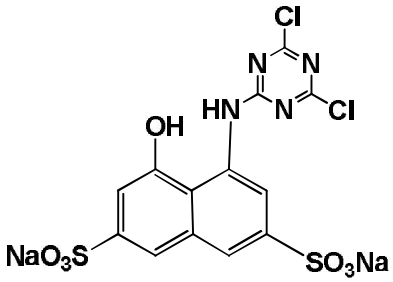
2. Experimental

2.1. General

All melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. UV–visible spectra were recorded with a Perkin-Elmer Lambda 551 S spectrometer, using dichloromethane as the solvent. IR spectra (KBr) were determined on a Mattson 5000 FTIR spectrometer (not all frequencies are reported). The ^{1}H NMR spectra were acquired using a Bruker WP 300 spectrometer at 300 MHz using TMS as an internal standard. Mass spectra were recorded on a Finnigan MAT 212 instrument. Elemental analyses were carried out at the microanalytical unit, Faculty of Science, University of Mansoura, Egypt.

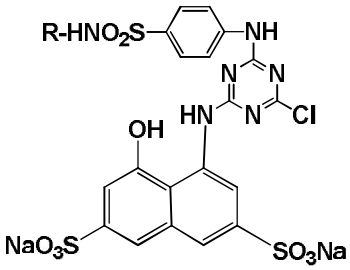
2.2. Synthesis of cyanurated H-acid:

A solution of cyanuric chloride (0.011 mole) in acetone (20 ml) was poured into a vigorously stirred mixture of crushed ice (20 g) and water (20 ml) at a temperature below 5 ˚C for a period of an hour, to the above stirred solution a neutral solution of H-acid (0.01 mole) in aqueous sodium carbonate solution (20% w/v) was then added in small portions for half an hour, maintaining the pH 4 by simultaneous addition of sodium carbonate solution (20% w/v). The reaction mass was stirred continuously at 0–5 ˚C for three hours until clear solution was obtained, the resultant solution was used for the next step without further purification.



2.3. Synthesis of sulfonamido cyanurated H-acid:

The solution of cyanurated H-acid (0.01 mole) was stirred at 40˚C for 15 min, to this well stirred solution, The sulfonamide (0.01 mole) was added drop wise during a period of half an hour, maintaining the pH 6.5 by simultaneous addition of sodium carbonate solution (20% w/v), after addition, the stirring was continued for further 1 hour.



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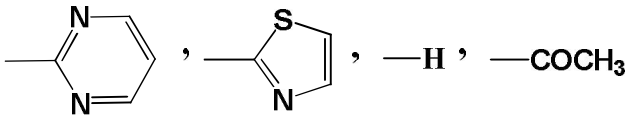


2.4. Diazotization of Sulfonamide:

The sulfonamide (0.01 mole) was stirred in hydrochloric acid (6 ml), the mixture was gradually heated up to 70˚C, till clear solution obtained then the solution was gradually cooled to 0–5˚C in an ice bath, a solution of sodium nitrite (0.01 mole) in water (4 ml), previously cooled to 0˚C, was then added over a period of 15 min with stirring the stirring was continuous for half an hour, the clear diazo solution at 0– 5˚C was used for subsequent coupling reaction.

2.5. Coupling of the sulfonamide diazonium salt with the coupling component:

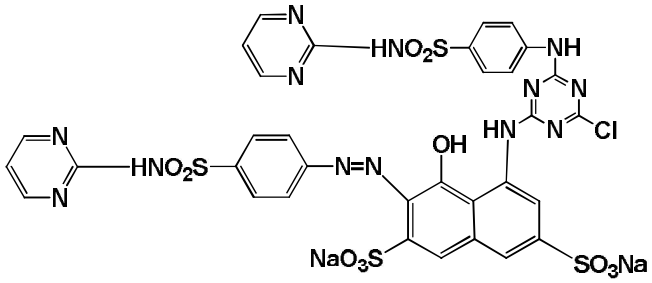
To an ice cold and stirred solution of the coupling component (0.01 mol), a freshly prepared diazo solution (0.01 mole) was added drop-wise over a period of 15 min, the pH was maintained at 7.5–8.5 by simultaneous addition of sodium carbonate solution (20% w/v), the stirring was continued for 3 h, maintaining the temperature below 5˚C, the pH was adjusted to about 6.8.

The reaction mixture was reach to room temperature and sodium chloride (15%) of the total solution used added during a period of half an hour, then the solution was cooled to 0–5˚C in an ice bath, the stirring was continuous for half an hour, remain overnight, filtered and dried at 40˚C under vacuum.

2.6. Sodium 5-((4-chloro-6-((4-(pyrimidine-2-sulfonamido) phenyl) amino)-1, 3, 5-triazin-2-yl) amino) -4-hydroxy-3-((4-(pyrimidine 2bsulfonamido) phenyl) diazenyl) naphthalene-2, 7-disulfonate (D1)

Yield = 54%. **IR (v/cm^{-1}):** 3354- 3332 and 3265 (NH_2 and NH), 2937 (=C-H), 1647 (C=N), 1596 (C=C), 1504 (N=N) and 1156, 1084(SO_2) cm-1. **^{1}H NMR (DMSO):** δ/ppm = 6.68-6.94 (d.d, 4H, NH-Ar-NH), 6.98-7.28 (d.d, 4H, NH-Ar-N=N), 7.76, 7.87, 7.88 (s, 3H, naphthoic Ar H), 8.43-8.47 (m, 6H, two pyrimidine rings), 14.11 (s, 1H, SO_2NH). **MS (EI):** m/z (%) = 986 (100), 625(46), 510(51), 261(72), 81(47).

2.6.1.Analysis:				
$C_{33}H_{22}O_{11}N_{13}ClS_4Na_2$(986.30)	Calcd. % :	C, 40.19;	H, 2.25;	N, 18.46
	Found % :	C, 40.07;	H, 2.18;	N, 18.51

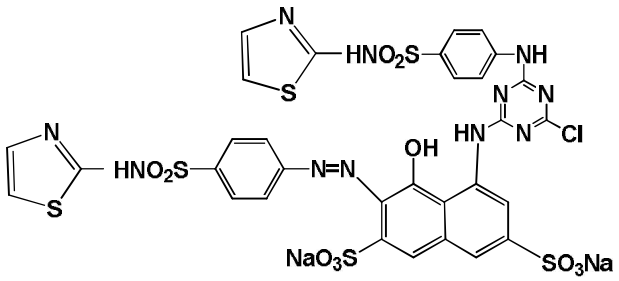


2.7. Sodium 5-((4-chloro-6-((4-(thiazole-2-sulfonamido) phenyl) amino)-1, 3, 5-triazin-2-yl) amino) -4-hydroxy-3-((4-(thiazole-2 sulfonamido) phenyl)diazenyl)naphthalene-2,7-disulfonate (D2)

Yield = 62%. **IR (ν/cm^{-1}):** 3349- 3333 and 3271 (NH_2 and NH), 2946 (=C-H), 1616 (C=N), 1562 (C=C), 1509 (N=N) and 1146, 1076(SO2) cm-1. **^{1}H NMR (DMSO):** δ/ppm = 6.67-6.82 (d.d, 4H, NH-Ar-NH), 6.90-7.43 (d.d, 4H, NH-Ar-N=N), 7.76, 7.85, 7.88 (s, 3H, naphthoic Ar H), 8.74-6.56 (d, 4H, two thiazole rings), 14.11 (s, 1H, SO_2NH). **MS (EI):** m/z (%) = 994 (100), 650(54), 522(23), 210(67), 99(77), 83(34).

2.7.1.Analysis:

$C_{31}H_{20}O_{11}N_{11}ClS_6Na_2$(996.42)	Calcd. % :	C, 37.37;	H, 2.02;	N, 15.46
	Found % :	C, 37.21;	H, 1.98;	N, 15.39

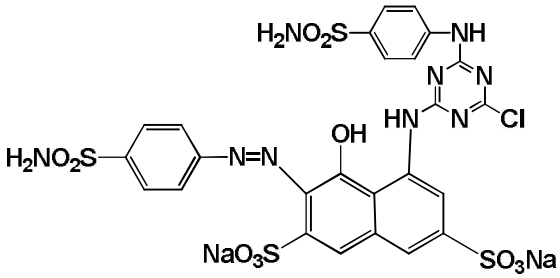


2.8. Sodium 5-((4-chloro-6-((4-(phenylsulfonamido) phenyl) amino)-1, 3, 5-triazin-2-yl) amino)-4-hydroxy-3-((4 (phenylsulfonamido) phenyl)diazenyl)naphthalene-2,7-disulfonate (D3)

Yield = 64%. **IR (ν/cm^{-1}):** 3341- 3338 and 3258 (NH_2 and NH), 2952 (=C-H), 1627 (C=N), 1562 (C=C), 1507 (N=N) and 1141, 1056(SO_2) cm^{-1}. **^{1}H NMR (DMSO):** δ/ppm = 5.4 (s, 2H, NH_2), 6.66-6.82 (d.d, 4H, NH-Ar-NH), 6.88-7.55 (d.d, 4H, NH-Ar-N=N), 7.64, 7.75, 7.79 (s, 3H, naphthoic Ar H), 11.11 (s, 2H, SO_2NH_2). **MS (EI):** m/z (%) = 829 (100), 568(54), 453(23), 281(67).93(61).

2.8.1.Analysis:

$C_{25}H_{18}O_{11}N_9ClS_4Na_2$(830.16)	Calcd. % :	C, 36.17;	H, 2.19;	N, 15.19
	Found % :	C, 35.99;	H, 2.03;	N, 15.06

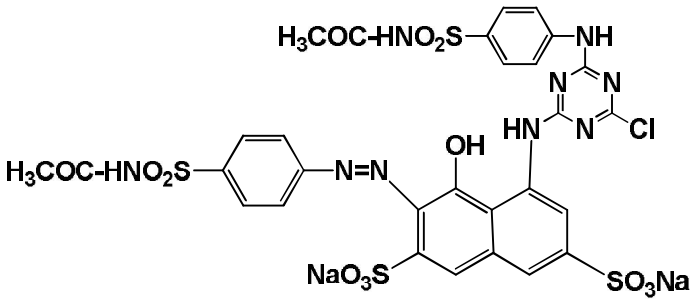


2.9. sodium 5-((4-((4-(N-acetylsulfamoyl)phenyl)amino)-6-chloro-1,3,5-triazin-2-yl)amino) -3-(4-(N-acetylsulfamoyl)phenyl)diazenyl)-4-hydroxynaphthalene-2,7-disulfonate (D4)

Yield = 57%. **IR (ν/cm^{-1}):** 3344- 3336 and 3258 (NH_2 and NH), 2941 (=C-H), 1692 (C=O), 1628 (C=N), 1507 (N=N) and 1141, 1056(SO2) cm-1. **^{1}H NMR (DMSO):** δ/ppm = 2.32 (s, 3H), 5.3 (s, 1H, NH), 6.66-6.80 (d.d, 4H, NH-Ar-NH), 6.86-7.55 (d.d, 4H, NH-Ar-N=N), 7.58, 7.75, 7.78 (s, 3H, naphthoic Ar H), 14.02 (s, 1H, SO_2NH). **MS (EI):** m/z (%) = 914 (100), 553(68), 438(64), 224(48).43(55).

2.9.1.Analysis:

$C_{29}H_{22}O_{13}N_9ClS_4Na_2$(914.23)	Calcd. % :	C, 38.10;	H, 2.43;	N, 13.79
	Found % :	C, 38.02;	H, 2.36;	N, 13.65



2.10. Antibacterial activity

The synthesized sulphonamide derivatives affects their antibacterial activity, we evaluated the in vitro antibacterial activity of the synthesized compounds was investigated against several pathogenic representative Gram-negative bacteria (*P. aeruginosa*, *P. mirabilis*), Gram-positive bacteria (*E. faecalis*, *S. aureus*). MB and L strains were obtained from our collection. The minimal inhibitory concentrations (MICs) were determined by agar plate dilution method. Mueller–Hinton Agar (BBL) and Sabouraud Dextrose Agar (Difco) were employed for bacterial growth. Stock solutions of tested compounds were prepared in N, N-dimethylformamide (DMF). Inocula containing 105–106 cfu/ mL of bacteria was prepared from broth cultures in log phase growth. Bacterial plates were made in triplicate and incubated at 37 and 28ºC for 48 and 72 h, respectively.

3. Results and Discussion

3.1. Spectral analyses

The IR spectrum of **(D1-D4)**, is characterized by the presence of strong absorption bands of NH at 3341 cm^{-1}, C=N group at 1627 cm^{-1} , (N=N) azo group at 1507 cm^{-1} and SO_2 at 1141, 1056cm^{-1}. The ^1H NMR spectrum of the same compound is characterized by the presence of singlet signal at δ = 2.10 and 2.30 corresponding to two methyl protons, singlet at δ = 4.31 for amidic proton, multiplet at δ = 7.20-7.80 for four aromatic protons in p-position, in addition to one singlet signal at δ = 13.40 for two SO_2NH protons.

3.2 Antibacterial activity

The *in vitro* antimicrobial activity of the synthesized compounds D1–D4 was investigated against several pathogenic representative Gram-negative bacteria (*Pseudomonas aeruginosa* and *Proteus mirabilis*) and Gram positive bacteria (*Enterococcus faecalis* and *Staphylococcus aureus*): all MIC values for the Gram-negative bacteria tested were >100 mg/mL, as well as high MIC values, ranging from 75 to >100 mg/mL, were found for the Gram-positive bacteria (Table 1). Sulphonamide derivatives D1–D4 showed a better spectrum of activity than the reference drug **Amoxicillin**.

Table 1. Minimum Inhibitory Concentration (MIC) against Gram–positive and Gram–negative bacteria

Compound	Bacteria tested MIC(mg/mL)			
	Pseudomonas aeruginosa	***Proteus mirabilis***	***Enterococcus faecalis***	***Staphylococcus aureus***
Amoxicillin	10	5	3.5	1.5
D1	>100	>100	>100	100
D2	>100	>100	>100	100
D3	>100	>100	>80	76
D4	>100	>100	>100	100

These changes resulted in the preparation of compounds with good activity against Gram-negative organisms. Various substituents were also placed on the sulphonamide moieties in order to study their effects on an antibacterial activity in vitro. Differences in activity showed strongly on suitable changes in the electronic character of the overall sulphonyl system. pyrimidinyl **1**, thiazolyl **2** and acetyl **4** derivatives generally led to dramatic improvements in activity against both Gram-positive and Gram-negative bacteria.

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