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Full Length Research Paper

Physical properties and biological applications of novel substituted biphenyl-sulfonamides

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This study explores the effect of the structural change of novel sulfonamide based-surfactants on the surfactant's behavior and antimicrobial activity. In order, to meet this as our primary goal, three different series, biphenyl-4,4'-disulfonamides (Series A, A_{1-4}), amine acid salts of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series B, B_{1-4}) and their corresponding copper and cobalt complexes (Series C, C_{1-2}), were prepared. The structures of the desired compounds were confirmed by using elemental analysis, Fourier transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (^{1}H NMR) and UV-Vis spectral analysis. In addition to these spectroscopic measurements, compounds C_1 and C_2 (Series C) were subsequently characterized extensively by atomic absorption methods. Also as our secondary goal, we have measured some physical properties as surface tension (γ), critical micelle concentration (cmc), the surface excess concentration (Γ_{max}) and the cross-sectional area per adsorbed surfactant head group (A_{min}). Finally, the investigation has been continued to cover the antibacterial and antifungal screening for all synthesized compounds as well as the antitumor activity for some of them.

Key words: Sulfonamide based-surfactants, surface properties, antimicrobial screening and antitumor activity.

INTRODUCTION

The design of complex molecular architectures based on transition metal atoms and organic ligands is an important goal for synthetic chemistry as it provides the opportunity to control or encode the properties of a material at the molecular level (Scozzafava et al., 2003). Suitable organic ligands favoring structure-specific self-assembly are the bases for the construction of coordination architectures. On the other hand, copper and cobalt halides have been successfully used for the synthesis of uncharged coordination compounds. Various factors, such as the stiochiometric metal-to-ligand ratio, the halide and the nature and substitution of the ligand have been shown to influence the form of the metal-halide motifs and the structures of the resulting coordination compound (Mandloi et al., 2005). Recently, increasing attention has been paid to the use of flexible bridging units in the construction of supramolecular architectures and this approach is attractive because the flexibility and conformation freedoms of such ligands offer the possibility for the construction of unprecedented frameworks with tailored properties and functions (Santos et al., 2006).

Sulfonamides represent an important class of medicinally effective molecules and are known to possess wide varieties of biological activities. Sulfonamides act as antimicrobial agents by inhibiting bacterial growth and activity. Some recent classes of sulfonamides and related sulfonyl derivatives are disclosed as effective antibacterial agents.

Badawi et al. (1980) have synthesized and studied series of cresols disulfonamide derivatives and evaluated their antibacterial activity. The alkylation of these disulfonamides was performed to investigate new compounds possessing more pharmacological activity. More researches regard to different sulfonamides with remarkable antibacterial activity. Thus, series of dihydroxy benzene disulfonamides were prepared and evaluated for their antibacterial activity Joshi et al., 2004. Also, series of acetanilide sulfonyl hydrazides and hydrazones exhibit

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more potent activity against pathogenic bacterial species (Marouan et al., 2008).

In addition to the antibacterial activity, sulfonamides with different substituted groups are considered also, as several types of pharmacological agents. A large number of structurally novel sulfonamide derivatives have ultimately been studied to show substantial antitumor activity in *vitro* and in *vivo* (Fidock et al., 2004; Huanga et al., 2001) also have obtained 2-[N^1-2-Pyrimidyl-aminobenzene-sulfonamido], ethyl-4-bis(2-chloroethyl)-aminophenyl butyrate as potent antitumor agent. Yokoi et al. (2002) have introduced and profiled novel sulfonamide antitumor agents with cell-based phenotypic screens and array-based gene expression analysis.

A recent series of biphenyl sulfonamide derivatives of 2-(biphenyl-4-sulfonyl-amino)-3-methylbutyric acid was prepared and evaluated for their ability to inhibit matrix metalloproteinase, MMP, as effective tumor cell growth inhibitors Zhijian et al., 2008. Another work was concerned with the structure-activity relationships for a series of potent, systemically available as matrix metalloproteinase, MMP by synthesis and evaluation of biphenyl bis-sulfonamide derivatives for the treatment of different types of cancer (Zhijian et al., 2008).

Supuran et al. (2007) have synthesized some of coordination compounds of Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) derived from 1,3,4-thiadiazole-2,5-disulfonamide as ligand and the results indicate that, the metal complexes of sulfonamides behave as very strong carbonic anhydrase inhibitors, and their mechanism of action has also been explained as being due to a dual inhibition, by means of sulfonamide anions and metal ions, formed by dissociation of the complexes in dilute solutions during the enzymatic assay. In studies with structure related sulfonamides, Badawi et al., 1986 have shown that there was a strong correlation between structure of the drugs and their lipophilicity (Badawi et al., 1985; Badawi et al., 1986).

Thus, we report herein the structure relationship of novel biphenyl-4,4'-disulfonamides based ligands (Series A, A_{1-4}), amine acid salts of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)], dianiline (Series B, B_{1-4}) and the corresponding ligand copper and cobalt complexes (Series C, C_{1-2}). These compounds containing nitrogen atoms have extensive and well-documented coordination chemistry. The resulting sulfonamido compounds exhibit enhanced Lewis acidity. Additionally, the sulfonamide linkers are remarkably stable, being resistant to hydrolyzing, oxidizing and reducing conditions (German et al., 2008). The purpose of this paper is to evaluate these compounds for surface properties, antibacterial, antifungal and anticancer activities.

MATERIALS AND METHODS

Materials

All chemicals and solvents were of high purity and used as purchased without any further purification. All solvents were as analytical grade from El Nasr Chemical Co. and ADWIC Labs. Co., Cairo, Egypt. Biphenyl, Orthophenylene diamine, Octanoic, Decanoic, Lauric acids were purchased from El-Nasr Chemical Co. Dipeptide and Tripeptide were supplied from Sigma Chemical Co. Glutamic acid, Anhydrous chloride salts of copper and cobalt (II) metals and Chlorosulfonic acid were supplied from Fluka Co.

Methods

Elemental analysis (C, H, S, X) was performed with a Varian Elemental and in satisfactory agreement with the calculated values. Atomic absorption spectrometer measurements for the copper and cobalt ions were done gravimetrically with Perkin Elmer analyzer. ^{1}H-NMR spectra were recorded on Varian Gemini 200 MHz instrument and the samples were run in deuterated dimethyl sulfoxide (DMSO-d_6, from Cambridge Isotope Laboratories) using tetramethyl silane as internal standard. FT-IR spectra were recorded on a Perkin Elmer-spectrum in one spectrophotometer in the 4,000 - 400 cm^{-1} range using KBr discs. The UV-Vis spectra in the range 200 - 1100 nm were recorded on a Jenway 6505 spectrophotometer in methanol solution. Melting points were recorded on a Haake Bucher apparatus in glass capillary tubes. The surface tension of aqueous surfactant solutions were measured at 25°C by a du-Nouy ring method. Apparent surface tensions were measured about five times for the sample within 2 min interval between each reading. The averages of five measurements were plotted against -log C without any correction. The values of cmc were determined from the plot of surface tension versus concentration.

Antimicrobial activity

Bacterial and fungal strains

The reported compounds were screened against various pathogenic bacteria, Gram-positive bacteria, *Staphylococcus aureus* (NCTC 7447), Gram-negative bacteria, *Escherichia coli* (NCTC 10418), and pathogenic fungi, such as *Aspergillus flavus* and *Candida albicans.* Using the diffusion agar technique by Laboratory Center, Cairo University, Egypt.

Antitumor activity

Human cell lines

The anti-tumor screenings were carried out on three human tumor cell lines namely, HCT116 (colon carcinoma), HEPG2 (liver carcinoma), and MCF7 (breast carcinoma) by National Cancer Institute (NCI), Cairo, Egypt.

Sulforhodamine B (SRB) assay

Potential cytotoxicity of the reported compounds was tested using the method of Patrick et al., 2002. The tumor cell lines were plated in 96-multiwell plates for 24 h before treatment with the tested compounds to allow attachment of the cells to the wall of the plate. Different concentrations of the compound under test (0, 1, 2.5, 5, and 10 g/ml) were added to the cell - monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37°C in an atmosphere of 5% CO_2. After 48 h, the cells were fixed, washed, and stained with Sulforhodamine B stain. Excess stain was washed off with acetic acid and the attached stain was recovered with Tris-EDTA buffer. Color intensity was measured in an ELISA reader. The relationship

between the surviving fraction and the drug concentration was plotted to get the survival curve of each tumor cell line after the specific compound was added. Inhibitions of cell proliferation (IC_{50}) for tested compounds (µg sample/L) were recorded.

EXPERIMENTAL

Synthesis of biphenyl-4,4'-disulfonyl chloride (A)

A flat container was charged with 5.4 ml (80 mmol) of chlorosulfonic acid and 40 ml of methylene chloride under cold condition, and then 6.2 g (40 mmol) of biphenyl were added gradually with stirring. After the addition was completed, stirring was continued for 6 h at room temperature. The mixture obtained was poured onto ice to hydrolyze the excess of chlorosulfonic acid and to precipitate the water insoluble biphenyl-4,4'-disulfonyl chloride, then washed thoroughly with distilled water and the deposited white insoluble product was removed by suction filtration. Since the small amount of product was possible to be remained, the residue was washed well with methylene chloride Novotny et al., 2006. The collected crude product was recrystallized by chloroform to give white crystals.

Synthesis of series A

2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (A_1)

With maintenance of the temperature at about 10°C and with vigorous stirring, 0.5 g (1.4 mmol) of biphenyl-4,4'-disulfonyl dichloride was added to a solution of o-phenylene diamine (0.5 g, 4.3 mmol) in 30 ml of 1:1 aqueous ethanol in small portions during 2 h (Claudiu et al., 2001). The reaction mixture was stirred continuously for 1 h at room temperature then 10 ml of 2 N hydrochloric acid was added for acidification of the medium. The mixture was filtered to remove the unreacted sulfonyl chloride residue and the filtrate was neutralized with slow addition of solid sodium bicarbonate forming the solid product.

The precipitate was washed thoroughly with cold deionized water and then filtered. The collected very pale yellow precipitate was recrystallized in ethanol (95%) to give colourless crystals. This procedure was repeated through 0.6923 g (6.408 mmole) (instead of 0.4615 g 4.273 mmole) of o-phenylene diamine. This increase, enlarged the amount of product to 0.4171 g to yield 59.24% (instead of 46.3%). This is due to o-phenylene diamine, since it have two amino groups which lead to a basic medium of the reaction by acting as proton acceptor.

Synthesis of compounds A_2, A_3 and A_4

Biphenyl-4,4'-disulfonyl-bis-L-glutamic acid (A_2), biphenyl-4,4'-disulfonyl-bis-valinyl leucine dipeptide (A_3), and biphenyl-4,4'-disulfonyl-bis-glycyl-glycyl arginine tripeptide (A_4)

The selected amino acid or peptide (0.9 mmol) was taken in 100 ml conical flask and sodium hydroxide solution (5N) was added slowly until all contents were dissolved, and the mixture became distinctly alkaline to phenolphthalein indicator. The reaction mixture was stirred on a magnetic stirrer and the temperature was maintained at 70°C using water path. Biphenyl-4,4'-disulfonyl chloride (0.4 mmol) was added in small portions with continuous stirring and then sodium hydroxide (5 N) was added to keep the reaction mixture alkaline. After the addition was completed, the reaction mixture was refluxed for 1 h (Noaman et al., 1999). The reaction was continued until a clear homogenous solution was formed. Then, it was cooled to room temperature and filtered to separate the residue. The filtrate was acidified with concentrated hydrochloric acid for just neutralization. The formed white precipitate was collected and washed with an amount of ice-cold methanol and then filtered.

Synthesis of Series B

2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium dioctanoate ($B_1$), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didecanoate (B_2), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didodecanoate ($B_3$), and 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium diglutaminate (B_4)

2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (A_1) (0.4 mmol) were dissolved in a minimum amount of methanol with heating. The solution was cooled to room temperature and added to fatty acid / methanol solution. This mixture was refluxed for 1 h and allowed to cool to room temperature (Shane et al., 2004).

The formed precipitate was collected and washed with a little amount of ice-cold methanol and then filtered giving white precipitate.

Synthesis of Series C

Copper Complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline ($C_1$), and cobalt complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_2)

To 10 ml of 0.02 M metal chloride solution in a 100 ml a flask equipped with a magnetic stirrer, 20 ml of buffer solution (40 ml of 2.0 N aqueous ammonia, 320 gram of ammonium acetate, 30.0 g of sodium potassium tartarate and 850 ml of distilled water) were added. 10 ml of 0.02 M of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (A_1) in ethanol was gradually added over 5 to 10 min time with stirring at room temperature.

The stirring was continued for 30 min after the addition of chelating agent solution was completed. If needed, 100 ml of distilled water was added to ensure complete precipitation of the chelate and then the mixture was stirred for additional 15 min; the colored precipitate, which had formed was collected and washed thoroughly with distilled water, acetone or 1:1 aqueous acetone, distilled water again (Rosen et al., 1999). The precipitate was collected after being at room temperature.

RESULTS AND DISCUSSION

Reaction screening

Structure of the synthesized compounds was confirmed by elemental analysis which was satisfactorily for C, H, N, S and Cl Table 1. Also their IR measurements Table (2) showed the characteristic bands and Table 3 showed ^{1}H-NMR measurements of the investigated compounds. The most important bands, presented in Table 2, show that the formation of series B salts and series A sulfonamide linkages which confirmed by the presence of a medium intensity band at 3400 corresponding to v ($^+NH_3$) and sharp bands in the range of 1190-1150 cm^{-1} due to v (SO_2) respectively.

Biphenyl-4,4'-disulfonylchloride (A) was synthesized by the reaction of cold chlorosulfonic acid with biphenyl in the presence of methylene chloride upon stirring for 6 h at room temperature. The structure was evidenced by ^{1}H-

Table 1. Physical properties and elemental data of synthesized compounds.

Series	Comp.	R	Colour	Molecular formula	M. Wt.	M.P °C	Yield %
Start		Biphenyl-4,4'-disulphonyl chloride	White ppt	$C_{12}H_8C_{l2}O_4S_2$	351.23	205	58.0
A	A_1	O-phenylenediamine	Colourless crys.	$C_{24}H_{22}N_4O_4S_2$	494.59	245	46.3
	A_2	Glutamic acid	White ppt	$C_{22}H_{24}N_2O_{12}S_2$	572.56	>300	81.3
	A_3	Val-leuc dipeptide	White ppt	$C_{34}H_{50}N_4O_{10}S_2$	738.91	>300	76.8
	A_4	Gly-Gly-Arg tripeptide	White ppt	$C_{32}H_{46}N_{12}O_{12}S_2$	854.91	>300	90.6
B	B_1	$CH_3(CH_2)_6COO^-$	White ppt	$C_{40}H_{54}N_4O_8S_2$	783.01	240	76.8
	B_2	$CH_3(CH_2)_8COO^-$	White ppt	$C_{44}H_{62}N_4O_8S_2$	839.12	238	78.6
	B_3	$CH_3(CH_2)_{10}COO^-$	White ppt	$C_{48}H_{70}N_4O_8S_2$	895.22	234	60.4
	B_4	Glutaminate	Colourless crys.	$C_{34}H_{42}N_8O_{10}S_2$	786.87	139	46.6
C	C_1	Copper ion	Olive green ppt	$C_{24}H_{22}Cl_4Cu_2N_4O_4S_2$	763.49	>300	62.94
	C_2	Cobalt ion	Brown ppt	$C_{24}H_{22}Cl_4Co_2N_4O_4S_2$	754.26	>300	70.42

Table 1. Contd.

Elemental analysis Calc (found) %					
C	**H**	**N**	**S**	**Cl**	**M**
41.04 (41.17)	2.32 (2.83)	********	18.26 (18.39)	20.19 (19.97)	********
58.28 (57.78)	4.48 (4.37)	11.33 (11.08)	12.97 (13.78)	********	********
46.15 (47.52)	4.22 (4.58)	4.89 (5.38)	11.2 (10.89)	********	********
55.27 (57.18)	6.82 (7.44)	7.58 (7.89)	8.68 (8.77)	********	********
44.96 (45.37)	5.42 (5.87)	19.66 (20.45)	7.5 (7.01)	********	********
61.36 (62.18)	6.95 (7.22)	7.16 (7.24)	8.19 (8.58)	********	********
62.98 (63.55)	7.45 (7.87)	6.68 (6.95)	7.64 (7.55)	********	********
64.4 (65.8)	7.88 (7.98)	6.26 (6.41)	7.16 (6.87)	********	********
51.9 (52.7)	5.38 (5.82)	14.24 (13.59)	8.15 (7.8)	********	********
37.76 (38.68)	2.9 (3.19)	7.34 (7.08)	8.4 (7.98)	18.57 (19.14)	16.65 (16.37)
38.22 (39.45)	2.94 (3.22)	7.43 (7.16)	8.5 (7.14)	18.8 (19.3)	15.63 (15.8)

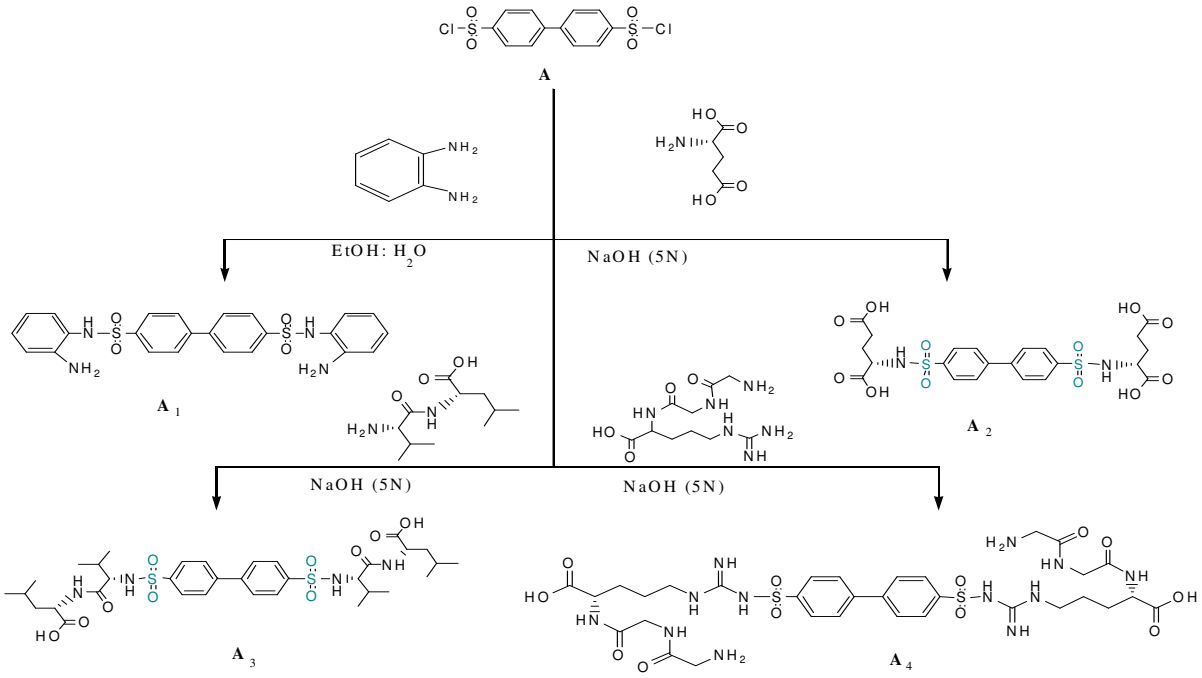
Table 2. Selected FT-IR frequencies (cm^{-1}) of synthesized compounds.

Abbr.	Start	A_1	A_2	A_3	A_4	B_1	B_2	B_3	B_4	C_1	C_2
Aromatic (=C–H)	3103	3071	3063	3061	3063	3071	3092	3038	3009	3031	3065
v $(SO_2)_{asym}$	1369	1326	1244	1239	1249	1326	1326	1326	1323	1280	1318
v $(SO_2)_{sym}$	1169	1180	1193	1189	1189.1	1161	1161	1161	1154	1190	1182
v (N–H)	----------	3264	3252.7	3340.7	3340	3265	3266	3265	3167	3166	3258
v (NH_2)	----------	3476-3377	----------	----------	3453.6-3322.3	----------	----------	----------	3315-3209	3255-3302	3386 - 3287
v (C=O)	----------	----------	1646	1634	1740	1637	1638	1637	1689	----------	----------
v $(C–H)_{asym}$	----------	----------	2924	2961.6	2924	2933	2945	2918	2978	----------	----------
v $(C–H)_{sym}$	----------	----------	2840	2875.4	2841	2806	2816	2850	2869	----------	----------
v $(^+NH_3)$	----------	----------	----------	----------	----------	3390	3400	3483	3400	----------	----------
v (O–H)	----------	----------	3470.9	3453.6	3450.9	----------	----------	----------	----------	----------	----------
v (M-N)	----------	----------	----------	----------	----------	----------	----------	----------	----------	582	596
v (C=N)	----------	----------	----------	----------	1657	----------	----------	----------	----------	----------	----------

NMR data, Table 3, which shows two doublet signals at σ7.4 corresponding to 4 biphenyl protons and σ7.8 corresponding to other 4 biphenyl protons. To an aqueous / ethanol solution of o-phenylene diamine, biphenyl-4,4'-disulfonylchloride (A) was added. The mixture reaction was stirred for half an hour at room temperature. As a

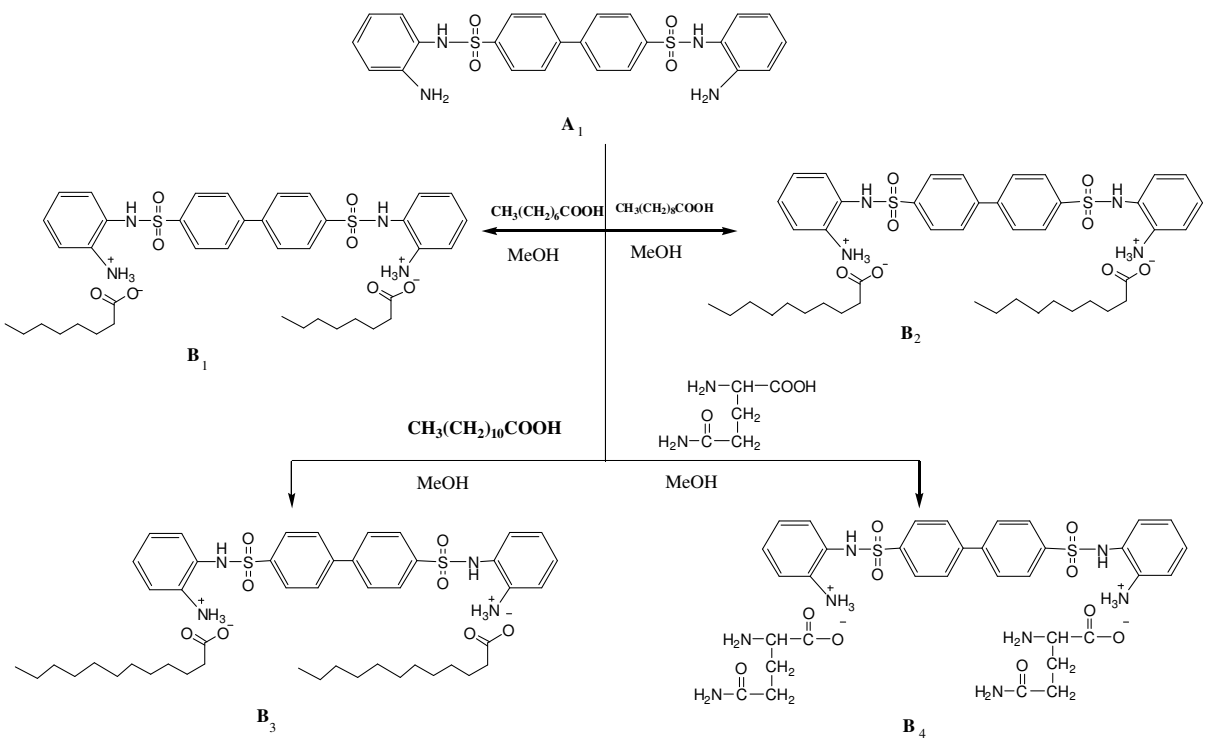
Table 3. σ Values of ^{1}H NMR of synthesized compounds.

Comp.	Start	A_1	C_1	C_2	A_2
4 CH of biphenyl	7.74 (d, 4H)	7.81 (d, 4H)	7.81 (d, 4H)	7.81 (d, 4H)	7.74 (d, 4H)
4 CH of biphenyl	7.79 (d, 4H)	7.94 (d, 4H)	7.89 (d, 4H)	7.89 (d, 4H)	7.79 (d, 4H)
2 amino groups	----------	5.10 (s, 4H)	3.52 (s, 4H)	3.52 (s, 4H)	----------
2 CH of benzene ring	----------	6.45 (t, 2H)	6.41 (t, 2H)	6.42 (t, 2H)	----------
2 CH of benzene ring	----------	6.62 (t, 2H)	6.65 (t, 2H)	6.65 (t, 2H)	----------
2 CH of benzene ring	----------	6.71 (t, 2H)	6.76 (t, 2H)	6.76 (t, 2H)	----------
2 CH of benzene ring	----------	6.89 (t, 2H)	6.89 (t, 2H)	6.81 (t, 2H)	----------
2 NH group	----------	9.30 (s, 2H)	9.31 (s, 2H)	9.31 (s, 2H)	9.66 (s, 2H)
2 CH_2 groups	----------	----------	----------	----------	1.45 (t, 4H)
2 CH_2 groups	----------	----------	----------	----------	1.66 (m, 4H)
2 CH groups	----------	----------	----------	----------	2.26 (t, 2H)
4 COOH groups	----------	----------	----------	----------	12.26 (s, 4H)



Scheme 1. Sulfonamides

result, 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (A_1) was obtained with high purity. The reaction of A with L-glutamic acid, valinyl leucine dipeptide or glycyl-glycyl arginine tripeptide in the presence of 5N sodium hydroxide, was carried out to give 4,4´-disulfonyl-bis-L-glutamic acid A_2, 4,4´-disulfonyl-bis-valinyl-leucine dipeptide A_3, or 4,4´-disulfonyl-bis-glycyl-glycyl arginine tripeptide A_4, respectively. The reactions proceeded via nucleophilic displacement S_N^2 of two chloride ions by two amino groups at both sides of sulfonyl chlorides via loss of two molecules of HCl and formation of the corresponding sulfonamides (Scheme 1). Modification of sulphonamides was proceeded by amine acid saltation upon reaction with fatty acids and glutamine in order to improve their surface properties, they are also important in the pharmaceutical cosmetics, and agrochemical industries (John et al., 2003) Thus, when sulfonamide A_1 was refluxed in methanol with the selected fatty acids (octanoic acid, decanoic acid and dodecanoic acid), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium dioctanoate ($B_1$), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didectanoate (B_2), and 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didoctanoate ($B_3$) were formed. Refluxing of sulfonamide $A_1$ and glutamine in methanol afforded 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium diglutaminate (B_4),



Scheme 2.

[Scheme 2]. FT-IR spectral charts of the resulted precipitate could prove the product. Complexation of sulfonamides as bidentate ligands sulphamido and heterocyclic atoms was used also for modification of sulfonamides. However coordination metal complexes are gaining increasing importance in the design of respiratory, slow release and long acting drugs. The efficiencies of therapeutic drugs are known to increase upon coordination, where some metal complexes do have remarkable antitumor, antiviral and special biological activities (El-Sharkawy, 2007).

Thus, when sulfonamide A_1 was complexed with 0.02 M solutions of $CuCl_2$ and $CoCl_2$ at pH = 8.2 by using a buffer solution upon stirring at room temperature, the copper complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline ($C_1$) and the cobalt complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_2). Atomic absorption spectrometer (AAS) measurements for copper and cobalt ions were done in which the percentage weights of copper and cobalt ions were 0.005 g/20 ml and 0.003 g/20 ml [Scheme 3].

UV-Vis spectral data for A_1 and series C, (C_1 and C_2)

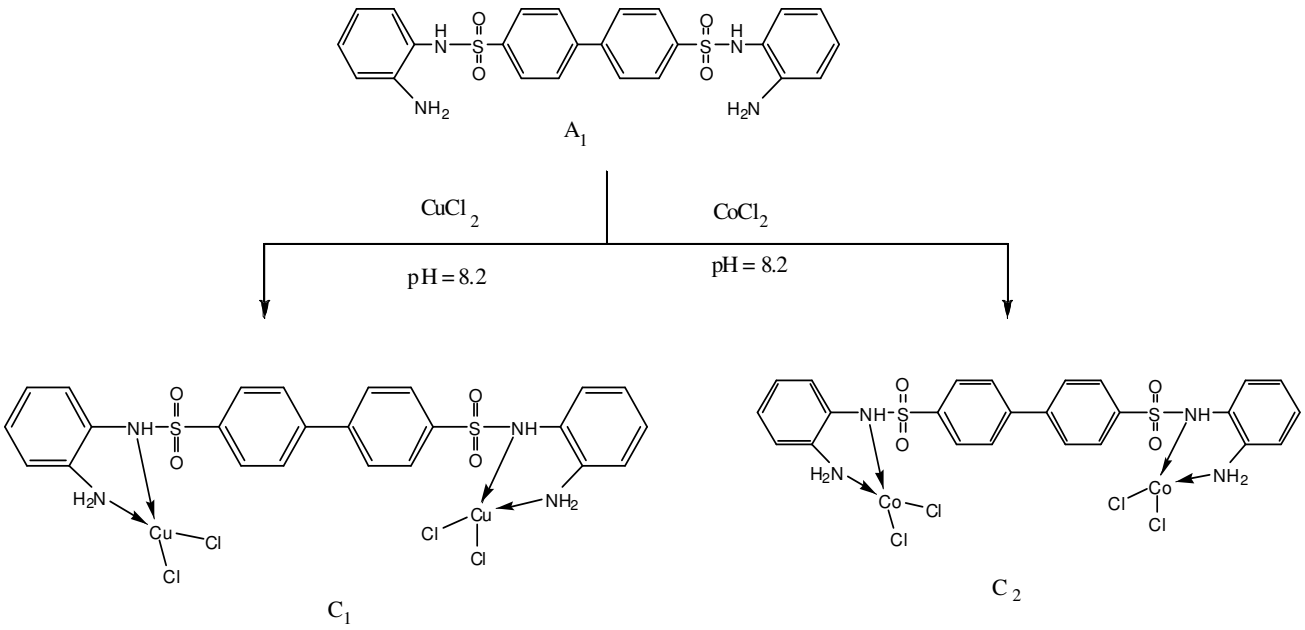
The UV-visible absorption spectra has been concerned only for 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (ligand) and its copper and cobalt complexes (C_1 and C_2), which could be given an evidence for the complexation. Additionally, the spectral data have been confirmed as the configuration of the complexes.

The copper complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_1) shows a sharp band at 255 nm and the corresponding cobalt complex (C_2) shows a sharp band at 271 nm as well as the disappearance of the band characteristic of the ligand A_1 at 283 nm has been observed.

The band of free ligand (283 nm) was shifted to lower wavelengths in the spectra of the corresponding complexes due to the formation of the deprotonated di-negative anion. This can be attributed to the stabilization of the ground state of the more polar complex by extensive solvation relative to the corresponding less polar complexes. Spectral data served as confirmation that our reactions were successful and our products were present (El-Sharkawy and Surfact, 2007)

Evaluation of surface properties

The surface activity of biphenyl-4,4'-disulfonyl-bis-valinyl leucine dipeptide (A_3), biphenyl-4,4'-disulfonyl-bis-glycyl glycyl arginine tripeptide (A_4), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium dioctanoate ($B_1$), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didecanoate (B_2), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didodecanoate ($B_3$), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium



Scheme 3.

Table 4. Surface parameters of tested compounds

Series	Abbr.	γ mN/m	CMC × 10 $^{-3}$ mol/L	Γ_{max} × 10^{-4} mol/cm^2	A $_{min}$ nm^2
A	A3	36	13.50	1.510	1.104
	A4	47	11.70	1.185	1.406
B	B1	37	6.30	1.441	1.157
	B2	36	5.90	1.312	1.270
	B3	34	2.50	0.759	2.195
	B4	46	4.30	1.547	1.078
C	C2	38	2.00	1.029	1.619

diglutaminate (B_4) and the cobalt complex of 2,2`-[biphenyl-4, 4'-diylbis (sulfonylimine)] dianiline (C_2) were evaluated in terms of surface parameters and collected in Table 4. The surface parameters include surface tension (γ), critical micelle concentration (cmc), the surface excess concentration (Γ_{max}), and the cross-sectional area per adsorbed surfactant head group (A_{min}).

Surface-activity relationships

Surface tension (γ) and critical micelle concentration (cmc)

Figures 1 and 2 represent the variations of surface tension (γ) as a function of the logarithm of concentrations of series A, series B, and series C sulfonamides at 25°C. An almost linear decrease in surface tension (γ) and a clear break with the absence of a minimum change of surface tension (γ) at cmc according to previous literature reports. The critical micelle concentration (cmc) values were taken as the molar concentration at the intersection of two linear parts of the relationship in (equation 1) above and below is the discontinuity El-Sharkawy et al., 2008.

$$\gamma = f (\text{Log } C) \quad (1)$$

The surface tension of the studied surfactant series ranging from 34 to 47 mN/m revealed a high surface activity. These sulfonamide derivatives possess good surface properties due to the presence of amino acid chain (series A), long alkyl chain (series B) and metal formulation (series C) which ensure hydrophobic

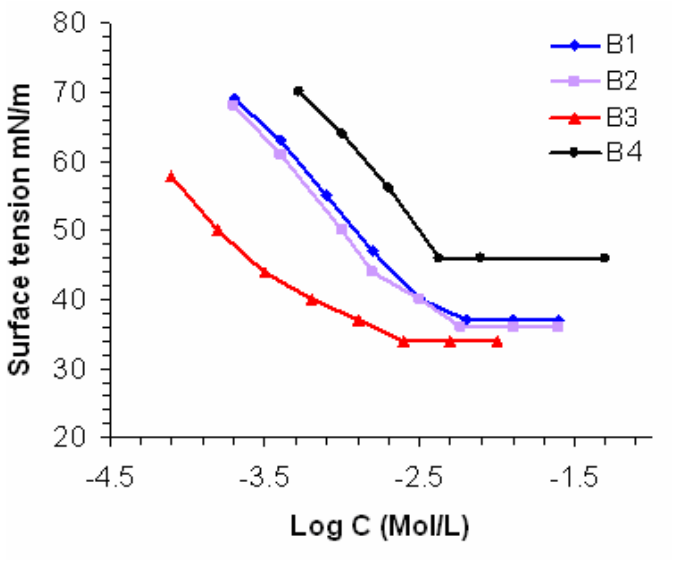


Figure 1. Surface tension measurements of compounds B_1, B_2, B_3, B_4

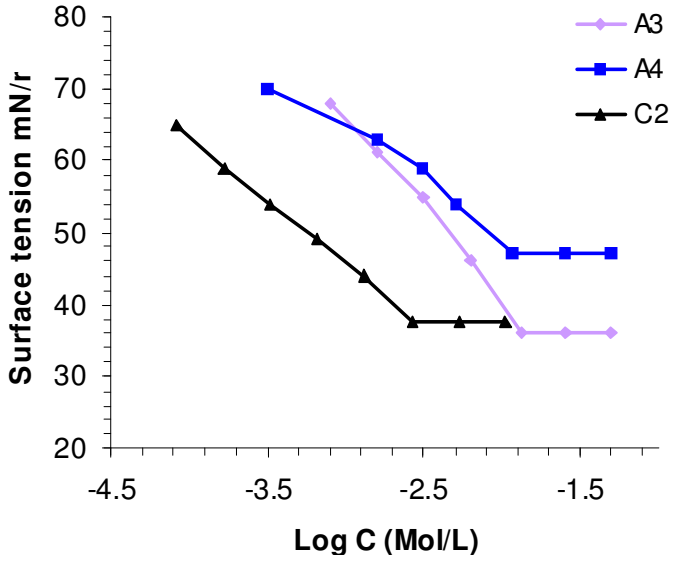


Figure 2. Surface tension measurements of compounds A_3, A_4, C_2

character as well as the sulfonamide function which ensure hydrophilic character. Another consideration which can be taken into account is the cmcs of surfactants with nonionic heads are greater than those with ionic heads; the results are also in good agreement with literature data El-Sharkawy et al., 2008. Analyzing the surface tension (γ(and the cmc data (Table 4) indicated that the surface activity of all syn-thesized surfactants is greatly enhanced in the aqueous and the magnitude of the effect follows the order : $A_4 > B_4 > C_2 > B_1 > B_2 = A_3 > B_3$ and the cmc values increase with: $C_2 < B_3 < B_4 < B_2 < B_1 < A_4 < A_3$.

From surface tension (γ) values, 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didodecanoate (B_3) is more effective compound to reduce surface tension (γ) of water but biphenyl-4,4'-disulfonyl-bis-glycyl-glycyl arginine tripeptide (A_4) is the least effective one.

This behavior is explained by the fact that primary deriving force in favor of micelle formation is the energy gain due to reduction of water – hydrophobe interaction, while the effect of the ionic group, beyond its impact on water solubility, works against the aggregation process. According to series A (A_3 & A_4) results, biphenyl-4,4'-disulfonyl-bis-valinyl leucine dipeptide (A_3) lower the surface tension of water efficiently compared with biphenyl-4,4'-disulfonyl-bis-glycyl glycyl arginine tripeptide (A_4) leading to a surface tension of about 47 mN/m, and that of sulfonamide A_3 leading to the lowest surface tension value of about 36 mN/m.

This can be explained in part by branching chain effect of surfactant which increase the thermal stability of the molecules between them and leads to higher surface tension values (El-Sharkawy and Badawi, 2008).it is well known also, that it leads to a decrease in their cmc's. This may also be attributed to a difference in steric packing of molecules, which causes a different arrangement of the alkyl amine and chain at the surface and causes particularly looser packing of the surfactant molecules at the interface.The values of (γ) and (cmc) within series B (B_1, B_2, B_3 & B_4) decreased with the increasing of the tails. This is due to increasing of the hydrophobic group length, causes an increase in the hydrophobic nature of the surfactant and decreases the stability of the surfactant in water. This behavior is consistent with the closer packing of the surfactant molecules at the interface. Furthermore, the presence of the aromatic nucleus in the hydrophobic part permits more loosely packed. Moreover, series B com-pounds exhibit powerful surface activity because of the strong electrostatic attraction between two species, the interaction starts at very low surfactant concentration forming hydrophobic aggregates (El-Sharkawy 2007). This may be in terms of the reason that series B sulfonamide has two functional groups (amine and carboxylic groups) and it causes the increase of distortion of water structure that leads to the greater surface activity of this compound. Even though these functional groups are present in water, the hydrophobic part of surfactant can bend and become part of the micelle hydrophobic core, and thus decrease the free energy that probably explains the decrease in cmc value. This is obviously shown in 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium diglutaminate (B_4) which is more surface active than the other fatty carboxylic acid salts (B_1, B_2, B_3) and this also may be due to that the Glutamine acid has more polar sites which increases the stability of surfactant in water and increase the ability to form micelles. It is found that the cmc value of cobalt complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_2)

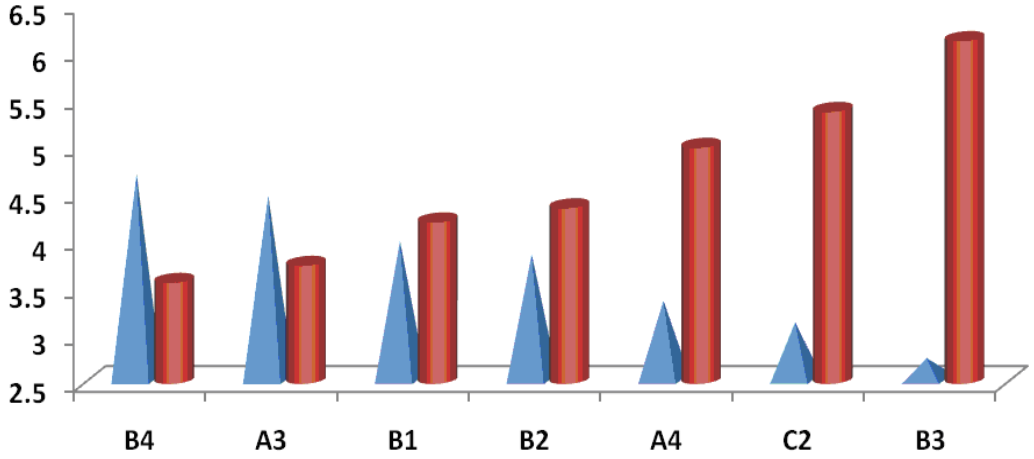


Figure 3. Correlation between Γ_{max} (pyramid) and A_{min} (cylinder) of compounds B_1, B_2, B_3, B_4, A_3, A_4 & C_2.

(series C) is smaller than the cmc values of series B and much lower than those of series A. This gives an evidence for the complexation should result in a decrease in the free energy and cmc value. In contrast, the structure stability of cobalt complex of bis (2-aminophenyl) biphenyl-4,4'-disulfonamide (C_2) causes an increase in distortion of water structure and thus leads to the greater surface activity of this metal surfactant complex.

Furthermore, the presence of long hydrophobic molecule has two sites whose coordinationally linked with two metal ions which enhance the adsorption and aggregation properties, by strengthening the inter- or intra- molecular hydrophobic interaction, which leads to more repulsion in the bulk of aqueous solution and increasing adsorption onto the surface (Maloy et al., 2008).

Adsorption studies

Surface excess concentration (Γ_{max}) and cross-sectional area (A_{min})

An important objective of this work was to evaluate how surfactant adsorption is affected when adding an ionic and nonionic surfactant, series A, B and C, on a microbe surface. On this basis, the adsorption amount of surfactants (Γ_{max}) and the minimum surface area per adsorbed surfactant molecule (A_{min}) of the titled sulfonamides were calculated in Table 4 and illustrated in Figure 3.

Due to the fact that the cross-sectional area per molecule adsorbed (A_{min}) is an inversely proportional to the maximum surface adsorption (Γ_{max}). Figure 3 results are in agreement with this fact, since the results indicate that the adsorption amount of surfactant values (Γ_{max}) of series A, B and C increase with decreasing the minimum surface area per adsorbed surfactant molecule (A_{min}) values. The magnitude of Γ_{max} following the order: $B_4 > A_3 > B_1 > B_2 > A_4 > C_2 > B_3$ and that of A_{min} is: $B_4 < A_3 < B_1 < B_2 < A_4 < C_2 < B_3$. Increasing the kinetic motion of water molecules makes the hydration process for surfactant faster and equilibrium is soon reached. The increase of Γ_{max} values was enough to make the surfactant molecule crowded at the interface which causes a decrease in A_{min} values (El-Sharkawy, 2007).

Evaluation of antimicrobial activity data

The antimicrobial activity of all synthesized compounds was used to compare between compounds of every series and evaluate, how the modification of sulfonamides could improve the biological activity of these compounds. The selected strains of Gram-positive bacteria, Gram-negative bacteria and fungi were chosen since these microorganisms are widely distributed in nature, where they are found in aquatic environments, and used extensively as an indicator of pollution. Secondly, the commonly used strains were used in this work for assays of antimicrobial agents (Krungkrai et al., 2005). The antimicrobial screening of biphenyl-4,4'-disulfonamides (Series A), amine acid salts of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series B) and their copper and cobalt complexes (Series C) against various pathogenic strains, Gram-positive bacteria, *Staphylococcus aureus* (NCTC 7447), Gram-negative bacteria, *Escherichia coli* (NCTC 10418) and pathogenic fungi, such as *Aspergillus flavus* and *Candida albican*. All antimicrobial results were shown in Table 5.

Inhibition zone values refer that the activity of compounds are: (i) not active (0-6 mm),(ii) slight active (7-8 mm), (iii) moderate active (9-11 mm) and (iv) active

Table 5. Diameter of inhibition zone of the synthesized compounds.

Series	Comp.	*E. coli*	*S.. Aureus*	*A.. Flavus*	*C. albicans*
Control sample		**0**	**0**	**0**	**0**
Tetracycline		29	23	********	********
Diflucan®		********	********	14	**18**
A	A_1	13	14	0	0
	A_2	16	13	0	0
	A_3	16	13	0	0
	A_4	12	12	0	0
B	B_1	22	21	14	16
	B_2	19	20	13	15
	B_3	15	20	13	13
	B_4	10	10	0	0
C	C_1	11	15	0	0
	C_2	10	11	0	0

Inhibition zone values refer that the activity of compounds are: i) not active (0-6 mm), ii) slight active (7-8 mm), iii) moderate active (9-11 mm) and iv) active (12-15 mm) and v) high active (≥ 16 mm), Tetracycline is the reference antibiotic and DIFLUCAN ® is the reference antifungal.

12-15 m) and (v) high active (≥ 16 mm), Tetracycline is the reference antibiotic and DIFLUCAN ® is the reference antifungal.

Antibacterial activity

The data shown in Table 5 indicated that:

- Biphenyl-4,4'-disulfonamides (Series A) remarkably have high activity against both Gram-positive and Gram-negative bacteria, both biphenyl-4,4'-disulfonyl-bis-L-glutamic acid (A_2) and biphenyl-4,4'-disulfonyl-bis-valinyl leucine dipeptide (A_3) are the more effective in series A against *E. coli*. Biphenyl-4,4'-disulfonyl-bis-glycyl glycyl arginine tripeptide (A_4) is the least effective one. Whereas, all of them have nearly the same activity towards *S. aureus*.

- An outstanding character of the A_3 and A_4 structures impart the possibility of chelation effects through the free amino group and imine group. Beside, the carboxylate moiety of A_2 structure is orientated almost perpendicular to the surface which increase the biological compatibility and degradability of A_1, A_2, A_3 and A_4 compounds and act as powerful antibacterocides. This suggestion is proved by strong evidence that A_1 which has two free amino groups displayed low activity than A_2 and A_3.

All amine acid salts of 2,2`-[biphenyl-4,4'-diylbis (sulfonylimine)] dianiline (Series B) have high activity against Gram-positive and Gram-negative bacteria. 2,2`-[Biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium dioctanoate (B_1) has a powerful activity against *E. coli* and *S. aureus*. The order of activities against *E. coli* decreases from 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium dioctanoate ($B_1$) to 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didecanoate (B_2) to 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didodecanoate ($B_3$) by increasing the chain length of the attached carboxylic acid. In series B, amine carboxylic acid salts of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline have nearly the same activity towards *S. aureus*. 2,2`-[Biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium diglutaminate (B_4) was less effective against both *S. aureus* and *E. coli* having the same value of the diameter of the zone of inhibition (10 m).

On the other hand, the metal complexes of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series C) have moderate activity against both Gram-positive and Gram-negative bacteria. Copper complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_1) and cobalt complex of 2,2`-[biphenyl-4,4'-diylbis (sulfonylimine)] dianiline (C_2) have nearly the same activity against *E. coli,* while the first (C_1) is more effective against *S. aureus* than the cobalt complex (C_2).

By overview on the whole data of antibacterial activity, we remark that the amine acid salts of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series B) were powerfully effective series against both pathogenic bacteria, Gram-positive bacteria, *S. aureus* and Gram-negative bacteria, *E. coli*, but the metal complexes of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series C) were less effective group. Therefore, the modification of sulfonamides by amine acid saltation was useful to improve the antibacterial activity on these pathogenic bacteria.

Antifungal activity

The data presented in Table 5 indicate that all synthesized compounds, series A, B and C, have strongly

different activities against both *A. flavus* and *C. albican*. The amine carboxylic acid salts of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline of Series B were successful to inhibit the growth of both pathogenic fungi *A. flavus* and *C. albican* but unfortunately, biphenyl-4,4'-disulfonamides (Series A) and the copper and cobalt complexes of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series C) didn't have any activity against both *A. flavus* and *C. albican*. 2,2`-[Biphenyl-4,4'-diylbis (sulfonylimine)] dianilinium dioctanoate ($B_1$), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didecanoate (B_2) and 2,2`-[biphenyl-4,4'-diylbis (sulfonylimine)] dianilinium didodecanoate ($B_3$) have high activity against both *Aspergillus flavus* and *Candida albican*.2,2`-[Biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium dioctanoate (B_1) has a powerful activity against *C. albican*. The order of activities against *C. albican* decrease from 2,2`-[biphenyl-4,4'-diylbis (sulfonylimine)] dianilinium dioctanoate ($B_1$), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didecanoate (B_2) to 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium didodecanoate (B_3), respectively, by increasing the chain length of the attached carboxylic acid. Through Series B, all amine carboxylic acid salts of bis (2-aminophenyl) biphenyl-4,4'-disulfonamide have nearly the same activity towards *A. flavus.* On the other hand, 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianilinium diglutaminate ($B_4$) didn't have any activity against both *A. flavus* and *C. albican.* By comparing the DIFLUCAN® results, the amine carboxylic acid salts of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline of Series B are within range of the already-used antifungal in market.

This comparison proved an interesting result that all amine carboxylic acid salts of 2,2`-[biphenyl-4, 4'-diylbis(sulfonylimine)] dianiline of Series B have the same activity with already-used antifungal product in market but had slightly less activity against *C. albican.*By overview on the whole data of antifungal activity, we remark that only the carboxylic acid salts of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series B) was powerfully effective series against both pathogenic fungi species, *A. flavus* and *C. albican*, but the metal complexes of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series C) and biphenyl-4,4'-disulfonamides (Series A) didn't have any activity against both *A. flavus* and *C. abdicant.* Therefore, the modification of sulfonamides by amine acid saltation was useful to establish new compounds having antifungal activity on these pathogenic fungal species (Krungkrai et al., 2007).

Biological activity correlation with surface properties

The hydrophilicity of all synthesized sulfonamides shows high antibacterial activities of these surfactants against *S. aureus* and *E. coli*. In contrast, the antifungal properties were only observed for B_1, B_2 and B_3 compounds, meanwhile, the other sulfonamides were found to be inactive against the tested fungi species, *A. flavus* and *C. albican*. It is interesting to note that similar trends in the maximum surface excess, the concentration of surfactant molecules at the interface per unit area, (Γ_{max}) obtained for this type of compounds. The surface properties and hydrophilicity of these surfactants showed a tendency towards adsorption at the interfaces, which facilitate their role of adsorption at the bacterial cell membrane. It is assumed that synthesized compounds inhibit the growth of organisms by forming an electrostatic attraction with the cell wall and this effects permeability of protein formation, by cross-linking outer proteins of cell (Melina et al., 2008). The antibacterial activity data reflect on the fact that, the biological effects caused by the surfactant action on the cell membrane or the bacterial surface, respectively, are favoured by low hydrophilicity of the synthesized sulfonamides, with the exception of B_4, C_1 and C_2 compounds. The antibacterial activity was decreased to a moderate extent in the case of B_4, C_1 and C_2 surfactants. This decrease could be explained by their higher solubility which is acquired from the hydrophobic nature of such molecules which decreases the stability of the surfactant in water. This demonstrated that compounds B_1, B_2 and B_3 have elevated inhibition of bacterial and fungal growth. In such case of ionic surfactants, the micelle with hydrocarbon inclusion can be readily adsorbed at the negatively charged surface, so an increase in inhibition zone diameter can be achieved (Maloy et al., 2008). At high concentration of nonionic surfactant, A_1, A_2, A_3 and A_4, the diffusion of surfactant solution could take place. Therefore, the cell membrane is directly exposed to the solution, and has to accommodate for all osmotic pressure differences which could led to the essential cellular functions that are disrupted, the cell dies (cell lysis). This leads to the important conclusion that the size of the surfactant head group is a determining factor for the efficacy by which a surfactant is able to perforate a cell membrane Krungkrai et al., 2007

Evaluation of anticancer activity data

Selected compounds were screened for their cytotoxic activity according to SRB assay (El-Sharkawy and Surfact, 2007). The cytotoxicity results of biphenyl-4,4'-disulfonyl-bis-L-glutamic acid (A_2), biphenyl-4,4'-disulfonyl-bis-valinyl leucine dipeptide (A_3), 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dailies didodecanoate ($B_3$), 2,2`-[biphenyl-4,4'-diylbis-(sulfonylimine)] dianiline diglutaminate (B_4) and their copper and cobalt complexes are shown in Table 6.The relationship between the surviving fraction and the drug concentration was plotted to get the survival curve of each tumor cell line after the specific compound was added. Control sample of the used solvent (DMSO) was performed giving negative results. The data of the anticancer activity show that newly synthesized

Table 6. Inhibition of cell proliferation (IC_{50}, µg sample /L) for compounds A_2, A_3, B_3, B_4, C_1 and C_2

Series	Comp.	Colon cancer	Liver cancer	Breast cancer
Control sample (DMSO)		-ve	-ve	-ve
A	A_2	0.47	0.67	2.55
	A_3	1.21	0.74	2.01
B	B_3	0.47	0.74	0.47
	B_4	2.55	0.40	2.28
C	C_1	1.01	0.47	1.74
	C_2	0.87	0.54	1.67

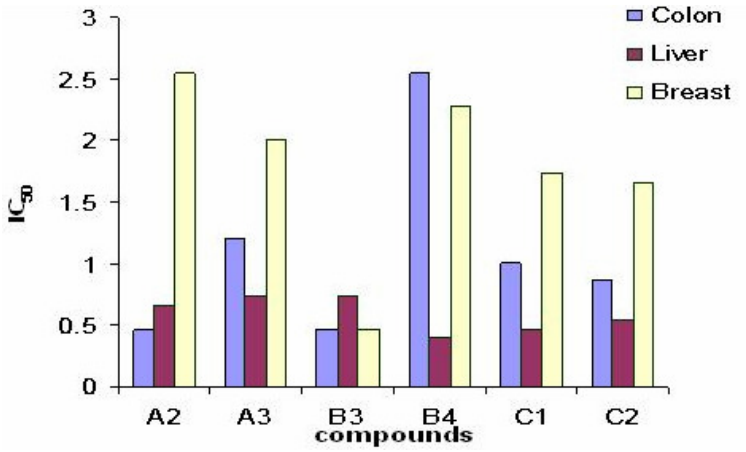


Figure 4. Cytotoxic activity of the investigated compounds on different three types of cell lines.

compounds, A_2, A_3, B_3, B_4, C_1 and C_2, have high activity against HCT116 (colon carcinoma), HEPG2 (liver carcinoma), and MCF7 (breast carcinoma).

Activity against colon cancer

The activity of tested compounds against HCT116 (colon carcinoma) shown in Figure 4 illustrates that the order of their activities is $A_2 = B_3 > C_2 > C_1 > A_3 > B_4$. Both of biphenyl-4,4'-disulfonyl-bis-L-glutamic acid (A_2) and 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline didodecanoate ($B_3$) are more potent while 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline diglutaminate (B_4) is the least effective one against HCT116 (colon carcinoma). Cobalt complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_2) is slightly more effective than the corresponding copper complex. On the other hand, biphenyl-4,4'-disulfonyl-bis-L-glutamic acid (A_2) (as amino acid sulfonamide) is more effective than biphenyl-4,4'-disulfonyl-bis-valinyl leucine dipeptide (A_3) (as dipeptide sulfonamide).It is revealed that the metal complexes of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series C), biphenyl-4,4'-disulfonamides $A_2$ and $A_3$, and the amine dodecanoic acid salt of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (B_3) were powerfully effective compounds against HCT116 (colon carcinoma), while 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline diglutaminate (B_4) was the less effective compound. Therefore, the modification of sulfonamides by single amino acid sulfonamide, amine carboxylic acid saltation and complexation were useful to produce new compounds having anti-colon cancer activity (Philippe et al.,2006).

Activity against liver cancer

Fortunately, all tested compounds are powerfully effective against HEPG2 (liver carcinoma) and their data shown in Figure (4) illustrates that the order of their activities is $B_4 > C_1 > C_2 > A_2 > A_3 = B_3$. 2,2`-[Biphenyl-4,4'-diylbis(sulfonylimine)] dianiline diglutaminate ($B_4$) was very successful one to inhibit the growth of liver cancer while both of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline didodecanoate (B_3) and biphenyl-4,4'-disulfonyl bis-valinyl leucine dipeptide (A_3) have less activity. Both the copper and cobalt complexes of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series C) have high potent activity. Cytotoxic activity of the copper complex of

2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_1) is slightly better than that of the corresponding cobalt complex. Therefore, the modification of sulfonamides by complexation and amine acid saltation were extremely useful to create new compounds having anti-liver cancer activity.

Activity against breast cancer

The activity of some selected compounds against MCF7 (breast carcinoma) shown in Figure 4 illustrates that the order of their activities is $B_3 > C_2 > C_1 > A_3 > B_4 > A_2$. Unfortunately, with the exception of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline didodecanoate ($B_3$), all tested compounds displayed low activity against MCF7. Just both the copper and cobalt complexes of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series C) exhibit the best results. However, the cobalt complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline ($C_2$) is slightly better than the copper complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_1) while biphenyl-4,4'-disulfonyl-bis-L-glutamic acid (A_2) was the worst one. Therefore, the modification of sulfonamides by complexation and amine dodecanoic acid salt of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline ($B_3$) were very useful to improve the anticancer activity of sulfonamide molecule against breast cancer. By over viewing the whole data of anticancer activity, It is remarkable that the metal complexes of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (Series C) were powerfully effective series against three tumor cell lines used in the present study, including HCT116 (colon carcinoma), HEPG2 (liver carcinoma) and MCF7 (breast carcinoma). Specially, the cobalt complex of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_2) shows excellent cytotoxic activity against several tumor cell lines and under very low concentration, it reduces the survival to 50%. Figure 4 shows cytotoxic activity of the investigated compounds on different three types of cell lines. This comes from the fact that the cobalt complexes have a capacity to reduce the energy status in tumors as well as enhance the tumor hypoxia which also influences their antitumor activities. It may be also concluded that the level of cellular damage inflicted by these complexes depends on the nature of their axial ligands. There is evidence that the cobalt complexes cause significant changes in metabolism, namely activation of lipid peroxidation, DNA damage and reduction of the bioenergetic status tumor tissues. In general, the high selectivity of action by redox - active cobalt complexes upon tumors is due to their specific reactivity (Krungkrai et al., 2007). Moreover, copper complex also show very good cytotoxic activity against all selected tumor cell lines. This may be due to the oxidative reaction of Cu^{2+} and site-directed mutagenesis of the putative catalytic base inhibiting both serine and tyrosine protein kinase activity which suggests that one active site is involved in both activities which leads to suppress resistance of tumor cell against cytotoxic agents. In general, copper complexes exhibit superoxide dismutase like activity, which is used as anti-inflammatory agent and lipid soluble. This property enables the compound to penetrate membranes and become inter-cellular (Melagraki et al., 2006). On the other hand, amine carboxylic acid saltation was useful to inhibit the growth of all tumor cell lines successfully. Biphenyl-4,4'-disulfonyl-bis-L-glutamic acid (A_2), biphenyl-4,4'-disulfonyl-bis-valinyl leucine dipeptide (A_3) of biphenyl-4,4'-disulfonamides (Series A), the copper and cobalt complexes of 2,2`-[biphenyl-4,4'-diylbis(sulfonylimine)] dianiline (C_1) and (C_2) exhibit more remarkable activity against both of HCT116 (colon carcinoma) and HEPG2 (liver carcinoma). Therefore, the modification of sulfonamides by amine carboxylic acid saltation and complexation generally was useful to improve the anticancer activity against all selected tumor cell lines.

Anticancer activity correlation with surface properties

All selected sulfonamides display high anticancer activities of these surfactants against HCT116 (colon carcinoma) and HEPG2 (liver carcinoma), in the mean-time, moderate activity against MCF7 (breast carcinoma). These sulfonamides behave differently with their surface properties. In case of colon and breast cancer, highest activities may be achieved with great cross-sectional area of surfactant head group, A_{min}. In contrast, by different trends in the maximum surface, excess concentration of surfactant molecules at the interface per unit area, (Γ_{max}) is obtained for this type of compounds. The surface properties of these surfactants showed low tendency towards adsorption at the inter-faces. It is clearly illustrated in B_3 compound. Therefore, the great effect of these surfactants may be accoplished by the massive attack towards target colon or breast cancer cells. This leads to the important conclusion that the size of the surfactant head group is a determining factor for the efficacy by which a surfactant is able to face a cell membrane (Melagraki et al., 2006). On the other hand, in case of liver cancer, high effect was achieved with similar trends in the concentration of surfactant molecules at the interface per unit area, (Γ_{max}) obtained in this type of compounds. The surface properties of these surfactants showed a tendency towards adsorption at the interfaces, which facilitate their role of adsorption at the membrane of cancer cell. It is assumed that tested compound attack tumor cells by accumulation around the cancer cell wall which effects permeability of protein formation and vital cellular functions by cross-linking outer proteins of cell. It is clearly illustrated in B_4 compound. This leads to the important conclusion that the maximum surface excess of surfactant is a deter-mining factor for the efficacy by which a surfactant is able to face a cell membrane

(Melina et al., 2008; Osinsky et al., 2004).

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