Synthesis, Characterization and Biological Studies on some Derivatives of *N*-(4-Aminobenzenesulphonyl)Morpholine Carrying Amino Acid, Alkoxy and Triazole Moieties

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Abstract: The reaction of *N*-[4-(chloroacetyl)aminobenzenesulphonyl]morpholine (IV) in acetone or dimethyl-formamide with amine derivatives, 4-aminotriazoles (I,II) or sulpha drugs yielded the corresponding *N*-[4-(substituted glycyl)aminobenzenesulphonyl]-morpholine derivatives (V-XV). Moreover, some derivatives of *N*-[4-(alkoxyacetyl)aminobenzenesulphonyl]morpholine (XVI-XXI) were synthesized. The reaction of XI with the requisite aromatic aldehydes in methanol gave Schiff bases (XXII,XXIII). Coupling reaction between (III) and Pht- or Tos-amino acids using the phosphorus oxychloride method furnished the corresponding *N*-[4-(pht- or Tos-aminoacyl)aminobenzenesulphonyl]morpholines (XXIV-XXIX). All the synthesized compounds were characterized by IR, ^{1}H-NMR, MS spectral data and elemental analyses and investigated their antibacterial and antifungal activities.

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1. Introduction:

The present work is a report on the chemistry and preliminary microbiological study of some novel amino acid, Schiff base and alkoxy derivatives of sulfamorpholine. Our target embraced the identification of these compounds that could be important as pharmacologically active agents. The sulfonamides, and their derivatives incorporating morpholine moiety[(1-3)] and glycine unit[(4-7)] have been known to display miscellaneous biological and medicinal activities. The Schiff bases have also been found to possess strong and broad spectrum pharmacological properties[(8-10)].In particular, triazoles and their heterocyclic derivatives have been reported to be used as drugs and to have considerable biological activities[(11-13)]. Keeping in view the biological importance of amino acids, and in continuation of our lab work on structure–activity relationship (*SAR*)[(14-18)], the present paper has been conducted in which the previously mentioned derivatives (I-XXX) have been synthesized and evaluated their antimicrobial activity.

2. Experimental:

Melting points were uncorrected and meassured on electric melting point apparatus SMP1. Thin layer chromatography was run on plastic sheets coated with silica gel-60 (Merck) and developed with *n*-butanol- acetic acid- water (4:1:1 , v/v) and detected under UV light. The infrared spectra (ν_{max} in cm^{-1}) were taken in KBr discs using FTIR-2000 instrument.^{1}H-NMR spectra were measured in DMSO-d_6 or $CDCl_3$ using FX90Q Fourier Transform NMR spectromrter. The mass spectra were performed using Shimadzu-GC-MS-QP 100 Ex by the direct inlet system. Elemental analysis were carried out at Microanalytical Uint, Faculty of Science, Cairo University, Cairo, Egypt. The biological activities were measured in Department of Potany, Faculty of Science, Al-Azhar University, Cairo, Egypt.

1) Synthesis of *N*-(4-amino-5-mercapto-*4H*-[1,2,4]-3-triazolylalkyl)-*p*-toluenesulfonamide derivatives (I,II)

A mixture of equimolar amounts (0.01 mol) of thiocarbohydrazide and tosylamino acid were placed in a Pyrex test tube and heated to 170-179^{o}C in an oil bath for 30 min. During the first ten minutes the mixture was stirred. At the end of the reaction, the test tube was carefully removed and cooled until the liquid solidified. The solid material was recrystallized from ethyl alcohol. The materials were chroma-tographically homogenous when developed under UV light. I, IR(KBr):3389-3250 (broad, NH, NH_2), 3099 (CH, aro.), 2984 (CH, ali.),2298(SH), 1591(C=N), 1341, 1147(SO_2). MS m/e: 299 (M^+, 24.46%), 284 (1.02%), 235 (8.04%), 184 (6.27%), 155 (20.03%), 128 (11.75%), 106 (13.23%), 91 (100%), 65 (33.81%). ^{1}H-NMR: 2.37 (s, 3H, CH_3), 2.48 (s, 2H, CH_2), 7.35-7.68 (m, 4H, Ar-H), 8.17 (hump, 2H, NH_2), 11.2 (s, 1H, SH,

canceled by D_2O). II, IR: 3321-3263(broad, NH, NH_2), 3074(CH and C=C,aro.), 2949,2874 (CH, ali.), 2308(SH), and 1592(C=N).

2) *N*-(4-aminobenzenesulphonyl)morpholine (III) was prepared using the procedure described earlier[21] IR: 3436, 3366 (NH_2), 3084, 3006 (CH, aro.), 2970, 2861(CH, ali.), 1592, 1540 (C=C, aro.), 1314, 1154 (SO_2), 828 (*p*-disubstituted benzene).

3) Synthesis of N-[4-(chloroacetyl)aminobenzene-sulphonyl]morpholine (IV)

A suspension of *N*-(4-aminobenzene-sulphonyl)morpholine (III, 0.01 mol) in 30 ml of CH_2Cl_2 was treated with chloroacetyl chloride (0.011mol) gradually with stirring. The reaction mixture was refluxed for 1 h on a water bath and the solvent was then evaporated to dryness under reduced pressure. The crude product was washed several times with CH_2Cl_2 and finally recrystallized from acetone. IR: 3294(NH), 3096, 3052(CH, aro.), 2968, 2922, 2891 (CH, ali.), 1692 (C=O), 1591 (C=C aro.), 1344, 1163 (SO_2), 724(C-Cl).

4) Synthesis of *N*-[4-(substituted glycyl)amino-benzenesulphonyl]morpholine derivatives (V-X)

To a solution of *N*-[4-(chloroacetyl)amino-benzenesulphonyl]morpholine (IV; 0.001 mol) in acetone, excess of ammonia solution or the proper amines (0.0011 mol) was added and the resulting reaction mixture was stirred for 1 hr at r.t., refluxed for 2 h, then left to stand for overnight. The reaction solution was evaporated under reduced pressure and the residual product was washed with cold water, dried, and then recrystallized from the proper solvent. V, IR: 3366(NH_2) 3308 (NH), 3061, 3006 (CH, aro.), 2981, 2920(CH, ali.), 1694 (C=O), 1592, 1540 (C=C, aro.), 1328, 1159 (SO_2). VI, IR: 3288(NH), 3095, 3036(CH, aro.), 2971, 2860 (CH, ali.), 1705 (C=O), 1597 (C=C,aro.), 1346,1162 (SO_2). VII, MS m/e: 327 (M^+, 2.13%), 241(13.43%), 86(C_4H_8NO, 63.04%), 56(C_3H_6N,100%). IX, ^{1}HNMR: 3.01(t, 4H, CH_2-N-CH_2), 3.74 (t, 4H, CH_2-O-CH_2), 4.01 (s, 2H, $COCH_2$), 7.73-7.85 (m, 4H, Ar-H) and 9.34 (s, 1H, NH). X, IR: 3336,3268(OH and NH) ,3061, 3009 (CH, aro.), 2957(CH, ali.), 1722 (C=O, COOH), 1656(C=O), 1592, 1540 (C=C, aro.), 1325 (SO_2).^{1}HNMR: 2.94 (t, 4H, CH_2-N-CH_2), 3.71(t, 4H, CH_2-O-CH_2), 4.30 (s, 2H, $COCH_2$), 7.29-7.85 (m, 8H, Ar-H) and 11.72 (s, 1H, COOH).

5) Synthesis of *N*-[4-(aminoglycyl)aminobenzene-sulphonyl]morpholine (XI)

A mixture of (IV;0.001 mol) dissolved in acetone and hydrazine hydrate 85% (0.003 mol) was stirred at r.t.ºC for 3 h , then left to stand for overnight. The product was filtered off, washed with cold ethanol and then recrystallized from ethanol. MS m/e: 314 ($M^{+\cdot}$ 4.56%), 241 (23.4%, loss of $COCH_2N_2H_3$), 155 (*p*-$NHC_6H_4SO_2$, 4.24%), 86 (C_4H_8NO, 63.04%), 56 (C_3H_6N, 100%).

6) Synthesis of triazole, sulfamorpholine or sulfadiazine derivatives of *N*-[4-(glycyl)amino-benzenesulphonyl]morpholine (XII-XV)

A mixture of equimolar amounts (0.001mol) of triazole compounds (I or II), sulfa morpholine (III) or sulphadiazine and *N*-[4-(chloroacetyl)amino-benzenesulphonyl]-morpholine (IV) in 20 ml DMF containing (0.0012 mol) of triethylamine was refluxed for 2 hr. The reaction solution was evaporated under reduced pressure and the residual crude product was washed with cold water, dried and recrystallized from the proper solvent. XII, IR: 3268 (NH), 3065, 3036 (CH, aro.), 2918, 2850 (CH, ali.), 1644 (C=O), 1597 (C=C, aro.), 1316, 1159 (SO_2) , 827 (*p*-disubsted benzene).^{1}HNMR: 2.93 (t,4H,CH_2-N-CH_2), 2.63 (s,2H,CH_2-triazole), 4.4 (s,2H,$COCH_2$), 8.52, 8.95 (s,2H,NHCO and $NHSO_2$), 11.12(s, 1H, SH, canceled by D_2O). XV, IR: 3275 (NH), 3099, 3041 (CH, aro.), 2969, 2846 (CH, ali.), 1694 (C=O), 1589, 1527 (C=C, aro.), 1347, 1162 (SO_2).

7) Synthesis of *N*-[4-(alkoxyacetyl)aminobenzene-sulphonyl]morpholines (XVI-XXI)

A solution of *N*-[4-(chloroacetyl)amino-benzenesulphonyl]morpholine (IV; 0.001mol) in 30 ml of dioxane was added portionwisely to a mixture of an alcohol or phenol (0.001 mol) and sodium hydroxide (0.0011mol). The resulting reaction mixture was gently heated on a water-bath for 3-4 h. After cooling, the solution was diluted with water (10 ml) and left to stand for overnight. The crude product was filtered, washed with cold water, dried, and then purified by crystallization from the proper solvent. XVI, ^{1}HNMR: 2.81(t, 4H, CH_2-N-CH_2), 3.57 (t, 4H, CH_2-O-CH_2), 3.76 (s, 3H, OCH_3), 4.21 (s, 2H, $COCH_2$). XVII, IR: 3287 (NH), 3089 (CH, aro.), 2978(CH, ali.), 1694 (C=O), 1587 (C=C, aro.), 1257, 1065 (C-O-C), 1347, 1162 (SO_2). XVIII, MS m/e: 241(M-101, 27.7%, loss of $C_5H_9O_2$), 155(25.2%), 86(100%), 56(98.1%). XIX, IR: 3270(NH), 3034 (CH, aro.), 2980, 2843 (CH, ali.), 1641 (C=O), 1596 (C=C, aro.), 1254, 1105 (C-O-C), 1313, 1153 (SO_2). XX, IR: 3071 (CH, aro.), 2967(CH, ali.), 1701 (C=O), 1230 (C-O-C), 1159 (SO_2). MS m/e: 376 (M^+, 1.32%), 299(M-77(C_6H_5), 17.23%), 226(1.03%), 155(1.56%), 86(100%), 56(76.9%).

8) Synthesis of *N*-[4-(substituted benzalaminoglycyl)-aminobenzenesulphonyl]-morpholine (XXII,XXIII).

Benzaldehyde or *p*-anisaldehyde (0.005 mol) was refluxed with *N*-[4-(aminoglycyl)aminobenzene-sulphonyl]morpholine (XI,0.005 mol) in methanol for 3

h. The solid obtained after cooling, was separated, dried and then recrystallized from ethanol. XXII, IR: 3315 (NH), 3069, 3005 (CH, aro.), 2836 (CH, ali.), 1686 (C=O), 1650 (C=N), 1601 (C=C aro.), 1326(SO_2). XXIII, IR: 3261 (NH), 3068 (CH, aro.), 2920,2857 (CH, ali.), 1697 (C=O), 1649(C=N), 1590 (C=C, aro.), 1345, 1161 (SO_2).^{1}HNMR: 2.98 (t, 4H, CH_2-N-CH_2), 3.80 (t, 4H, CH_2-O-CH_2), 3.91 (s,3H , OCH_3), 4.22 (s,2H,$COCH_2$), 7.02(s,1H,CH=N),7.45-7.90(m,8H,Ar-H).

9) Synthesis of *N*-[4-(Pht- or Tos-aminoacyl)amino-benzenesulphonyl]morpholine derivatives (XXIV-XXIX).

A mixture of Pht- or Tos-amino acid (0.001mol), and *N*-[4-aminobenzenesulphonyl]-morpholine (III, 0.001 mol) was suspended in 20 ml of anhydrous THF and cooled to -15 ^{o}C with stirring for 15 minutes. The mixture was then treated with (0.001 mol) of purified phosphorus oxychloride and directly with (0.002 mol) of triethylamine. After the reaction mixture has stood for 1 h at -15^{o}C; 20 ml of water was added and the mixture was evaporated in vacuo in order to remove THF. The residual material was treated with 20 ml of water and extracted two times with 20 ml portions of ethyl acetate. The combined ethyl acetate extracts were washed three times with 5 ml portions of water, several portions of 5 % sodium bicarbonate solution, and finally with water. After being dried with anhydrous sodium sulfate, the ethyl acetate fraction was evaporated in vacuo. The residual crude product was recrystallized from the proper solvent. XXIV,IR: 3301(NH), 3069 (CH, aro.),2974,2858(CH, ali.), 1756, 1702(C=O, phthalyl and amide),1598(C=C, aro.), 1158 (SO_2). ^{1}HNMR: 2.96 (t, 4H, CH_2-N-CH_2), 3.74 (t, 4H, CH_2-O-CH_2), 4.64 (s, 2H, $COCH_2$), 7.27-7.92 (m, 8H, Ar-H), 8.21 (s, 1H, NHCO). XXV, IR: 3269 (NH), 3004 (CH, aro.), 2981, 2850 (CH, ali.), 1778, 1716 (C=O, phthalyl and amide), 1595 (C=C, aromatic). MS m/e: 443 (M^+, 7.82%), 174($C_{10}H_8NO_2$, 100%),159(0.98%), 46(2.64%),86(21.74%),56(47.21%). XXVI, IR: 3249(NH), 3013(CH, aro.), 2923, 2872 (CH, ali.), 1776, 1719 (C=O, phthalyl and amide), 1593 (C=C, aro.), 843 (*p*-disubstituted benzene). MS m/e: 469 (M-2, 10.06%), 202(5.11%), 173(19.6%), 155 (12.8%) , 146(3.67%), 86(100%), 56(61.67%). XXVII, IR: 3316(NH), 3069, 3008 (CH, aro.), 2943, 2835 (CH, ali.), 1686 (C=O), 1590,1517 (C=C, aro.), 1345, 1161 (SO_2). ^{1}HNMR: 2.35(s,3H, *p*-CH_3), 4.42(s,2H,$COCH_2$), 7.45-8.0 (m,8H,Ar-H), 8.29,9.08 (s,2H,NHCO and $NHSO_2$). XXIX, IR: 3307(NH), 3023 (CH, aro.), 2989, 2923 (CH, ali.), 1709, 1633 (amide I and II), 1597 (C=C, aro.), 1367(SO_2), 822 (*p*-disubstituted benzene). ^{1}HNMR: 2.41(s, 3H, *p*-CH_3), 3.02 (t, 4H, CH_2-N-CH_2), 3.16(h, 1H, isopropyl-CH), 3.80 (t, 4H, CH_2-O-CH_2), 5.01 (d, 1H, COCH), 7.27-7.62 (m, 8H, Ar-H).

10) Synthesis of *N*-[4-(succinimido) benzene-sulphonyl]-morpholine (XXX).

A mixture of (III, 0.001 mol), succinic anhydride (0.0011 mol) and glacial acetic acid (30 ml) was refluxed for 8 h at 120 ^{o}C. The reaction mixture was cooled and the formed solid product was collected, washed with water and recrystallized from dil.acetic acid. IR: 3297(NH), 3032 (CH, aro.), 2972, 2865 (CH, ali.), 1762, 1711 (C=O), 1593 (C=C, aro.).

3. Results and Discussion:

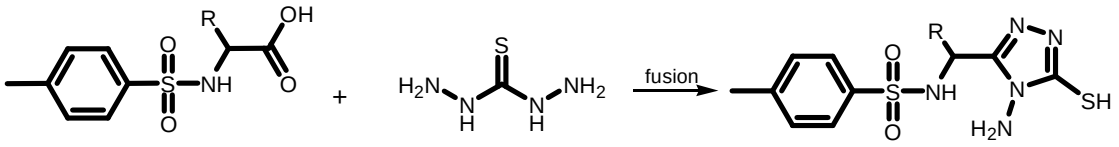
Thus, *N*-(4-Amino-5-mercapto-4*H*-[1,2,4]-triazol-3-yl) *p*-toluenesulfonamide derivatives (I and II) were formed by fusion of thiocarbohydrazide and tosylamino acids at 170-179^{0}C[(11)]. The products were recrystallized from ethyl alcohol. The structure was confirmed by IR spectra which revealed not only the absence of C=O band but also the presence of both strong SH and C=N stretching bands at about 2298 and 1591cm^{-1} respectively (Scheme 1).

Table 1: The physical data of the synthesized derivatives (I-XXX).

Compd. No.	R	R_f	Yield %	Cryst. Solv.*	M. P. [ºC]	Mol. formula	Elemental analysis** N%
I	H	0.80	75	a	193	$C_{10}H_{13}N_5O_2S_2$	23.41 23.39
II	-$CH_2C_6H_5$	0.66	73	a	198	$C_{17}H_{19}N_5O_2S_2$	17.99 17.92
III	---	0.79	91	b	193-195	$C_{10}H_{14}N_2O_3S$	11.57 11.67
IV	---	0.74	79	b	140-143	$C_{12}H_{15}ClN_2O_4S$	8.79 8.58
V	-H	0.83	93	a	130-133	$C_{12}H_{17}N_3O_4S$	14.04 13.87

VI	$-CH_3$	0.85	79	c	95-97	$C_{13}H_{19}N_3O_4S$	13.42 13.40
VII	$-(CH_3)_2$	0.69	80	c	98-101	$C_{14}H_{21}N_3O_4S$	12.84 12.82
VIII	1-piperidinyl	0.68	73	b	220-222	$C_{17}H_{25}N_3O_4S$	11.44 11.62
IX	4-morpholinyl	0.72	79	b	190-192	$C_{16}H_{23}N_3O_5S$	11.38 11.55
X	*p*-$C_6H_4CO_2H$	0.80	70	c	230-233	$C_{19}H_{21}N_3O_6S$	10.02 10.00
XI	$-NH_2$	0.78	82	a	110-115	$C_{12}H_{18}N_4O_4S$	17.83 17.81
XII	-H	0.73	80	d	210-213	$C_{22}H_{27}N_7O_6S_3$	16.86 16.95
XIII	$-CH_2C_6H_5$	0.76	82	d	249-251	$C_{29}H_{33}N_7O_6S_3$	14.60 14.56
XIV	4-morpholinyl	0.79	77	a	188-191	$C_{23}H_{28}N_3O_7S_2$	8.01 8.13
XV	2-pyrimidinyl	0.66	70	d	269-271	$C_{22}H_{24}N_6O_6S_2$	15.79 15.98
XVI	$-CH_3$	0.86	88	c	145-148	$C_{13}H_{18}N_2O_5S$	8.91 8.89
XVII	$-CH_2CH_3$	0.84	83	c	149-151	$C_{14}H_{20}N_2O_5S$	8.53 8.74
XVIII	$-CH_2CH_2CH_3$	0.89	79	c	211-213	$C_{15}H_{22}N_2O_5S$	8.18 8.16
XIX	$-CH(CH_3)_2$	0.87	77	c	159-160	$C_{15}H_{22}N_2O_5S$	8.18 8.05
XX	C_6H_5-	0.81	81	a	220-222	$C_{18}H_{20}N_2O_5S$	7.44 7.41
XXI	*o*-ClC_6H_4-	0.83	74	a	179-182	$C_{18}H_{19}ClN_2O_5S$	6.82 6.79
XXII	-H	0.85	91	a	119-121	$C_{19}H_{22}N_4O_4S$	13.93 13.90
XXIII	$-OCH_3$	0.82	79	a	208-201	$C_{20}H_{24}N_4O_5S$	12.96 12.91
XXIV	Pht-Gly	0.76	83	b	113-116	$C_{20}H_{19}N_3O_6S$	9.79 9.92
XXV	Pht-L-Ala	0.71	85	b	150-153	$C_{21}H_{21}N_3O_6S$	9.48 9.45
XXVI	Pht-L-Val	0.79	84	b	110-113	$C_{23}H_{25}N_3O_6S$	8.91 8.74
XXVII	Tos-Gly	0.83	69	a	184-186	$C_{19}H_{23}N_3O_6S_2$	9.27 9.46
XXVIII	Tos-L-Ala	0.74	71	c	111-113	$C_{20}H_{25}N_3O_6S_2$	8.99 9.08
XXIX	Tos-L-Val	0.83	78	a	149-151	$C_{22}H_{29}N_3O_6S_2$	8.48 8.46
XXX	---	0.77	91	c	213-216	$C_{14}H_{16}N_2O_5S$	8.64 8.80

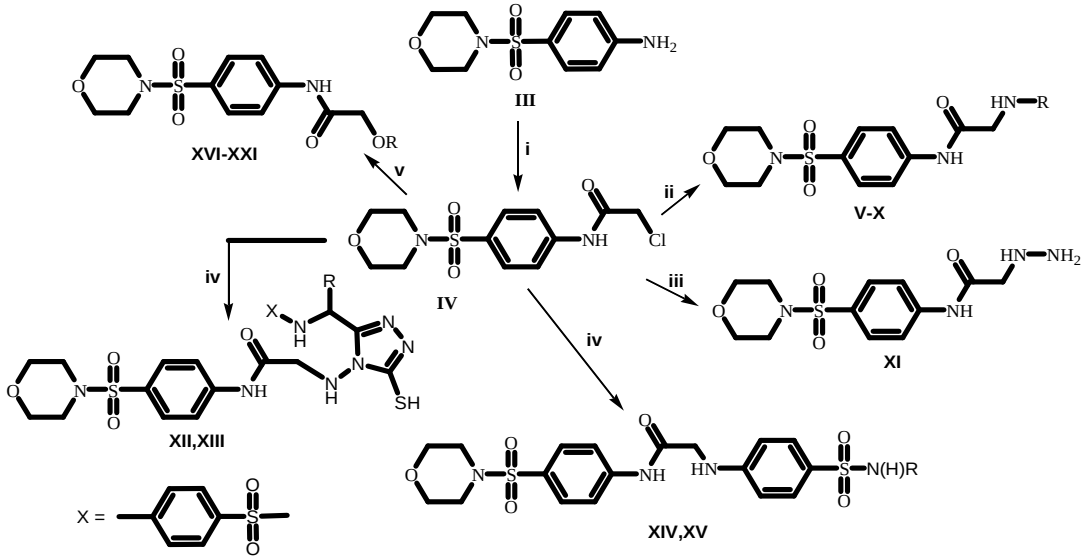
*Crystallization solvent: (a) ethanol, (b) acetone, (c) acetic acid-water, and (d) dioxane-water.
**All compounds gave satisfactory C and H analysis (calc./found)



Scheme 1

I,II

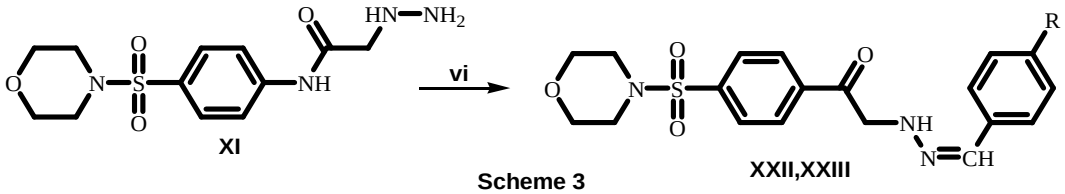
Treatment of *N*-(4-aminobenzenesulphonyl)-morpholine (III) with chloroacetyl chloride gave *N*-[4-(chloroacetyl)aminobenzenesulphonyl]morpholine (IV) that reacted, in acetone or DMF, with ammonia, hydrazine hydrate, substituted amines, 4-amino-triazoles (I,II) or sulpha drugs to afford the corresponding *N*-[4-(substituted glycyl)-aminobenzenesulphonyl]-morpholine derivatives (V-XV). The products were isolated, purified and obtained in good yield. Moreover, preparation of *N*-[4-(alkoxyacetyl)aminobenzene-sulphonyl]-morpholine derivatives **(XVI-XXI)** was achived by the action of sodium salt of the requisite alcohol or phenol on a solution of **(IV)** in dioxane. The products were precipitated on cooling, purified and obtained in 74-88% yield. The mechanism of formation of *N*-[4-(chloroacetyl)aminobenzene-sulphonyl]-morpholine (IV) could be rationalized in terms of electrophilic attack on nucleophilic center, the acyl group of chloroacetyl chloride by the lone pair on N^4 of sulfamorpholine (III) accompained by loss of Cl^- and H^+ to afford (IV). Further, nucleophilic substitution reactions with amine or hydroxyl containing compounds produce the corresponding derivatives mentioned above. The IR spectra showed the disappearance of the absorption band noticed at 724 cm^{-1} characteristic for C-Cl in compound (IV), and the appearance of vibrations at ~ 1257 and 1065 cm^{-1} attributed to the strong (C-O-C) band in compounds (XVI-XXI). In addition, ^{1}H-NMR signals that noticed at δ ~ 3.76 ppm characteristic for alkoxy (OR) supports the proposed structure of these derivatives (Scheme 2).



Scheme 2

Reagents:
i) $ClCOCH_2Cl$ / CH_2Cl_2
ii) NH_3 or 1° or 2° amine / acetone , **iii)** $NH_2NH_2.H_2O$ / acetone
iv) aminotriazole (I,II) or sulfa drug / DMF-TEA
(v) =R(Ar)OH/ dioxane-NaOH

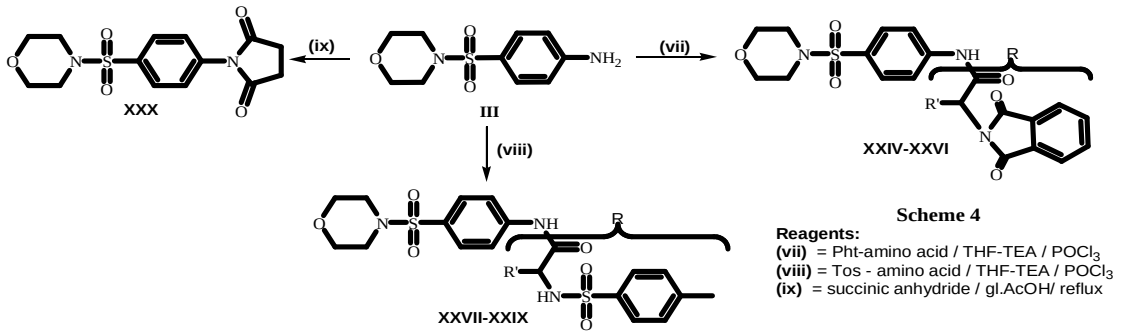
Schiff bases, *N*-[4-(substituted benzal-aminoglycyl)- aminobenzenesulphonyl]-morpholines derivatives (XXII,XXIII) were easily obtained by the condensation reaction of XI with one equivalent of benzaldehyde or *p*-anisaldehyde in abs. methanol. Complete condensation of all amino group was confirmed by the presence of strong C=N stretching band in IR at about 1649 cm^{-1}. This conclusion is also supported by the ^{1}H-NMR data which verified the presence of CH=N hydrogen resonance at about 7.02 ppm (Scheme 3).



Scheme 3

Reagents: (vi) = ArCHO / CH_3OH

Some new derivatives of *N*-[4-(Pht- or Tos-amino-acyl)aminobenzene-sulphonyl]morpholine (XXIV-XXIX) were prepared using the phosphorus oxy-chloride method[19]. The desired pure products were obtained upon treatment of a mixture of *N*-(4-aminobenzenesulphonyl]morpholine (III), phthalyl-(Pht-) or tosyl-(Tos-)amino acids in anhydrous THF containing two molar equivalents of triethylamine at -15°, with phosphorus oxychloride $POCl_3$. The phosphorus oxychloride method led to high yields and the products were isolated in a high degree of analytical purity prior to crystallization. The succinimido derivative **(XXX)** was synthesized by refluxing (III) with succinic anhydride in gl.AcOH for 8 h at 120 °C (Scheme 4). The spectral data are found to be consistent with the formualations shown below.



Scheme 4

Reagents:
(vii) = Pht-amino acid / THF-TEA / $POCl_3$
(viii) = Tos - amino acid / THF-TEA / $POCl_3$
(ix) = succinic anhydride / gl.AcOH/ reflux

Antimicrobial activities of the prepared compounds: Sensitivity of microorganisms to antimicrobial compounds:

For testing the antimicrobial activity of the prepared compounds, we used more than one test organisms as Gram positive bacteria: *Bacillus subtilis* (ATCC-6051), *Staphylococcus aureus* (ATCC-12600) ,and Gram negative bacteria: Escherichia coli *(ATCC-11775)* and *Pseudomonas aeruginosa* (ATCC-10415) and selscted fungi: Candida albicans, *and* Aspergillus niger to increase the range of antibiotic detection in the tested materials by using filter paper disc method[20]. A filter paper discs must be of uniform thickness and size and containing an equal and graded amount of the agent to be tested for its antimicrobial activity. The method was performed by dissolving 5 mg of the sample in one ml. of solvent solution, *N*,*N*-dimethylformamide (DMF), then a sterile filter paper discs were dipped into this solution . After absorption, the discs were dried and placed on test organisms seeded plates to be tested for their antimicrobial activity. The inhibition zone was measured in millimeters at the end of incubation period. The activity of the compounds was compared with the activity of *N*-(4-aminobenzene-sulphonyl)morpholine (III) that showed a weak to moderate activity aganist *B.subtilis S.aureus, P.aeruginosa and Candida albicans* with inhibition zone (6, 6, 7, 12 mm respectively) *and was biologically inactive against E.coli and Aspergillus niger*. From the data recorded in Table 1, we could conclude that most of the synthesized derivatives (I-XXX) were found to be biologically inactive towards the test organisms except (XIII) which exhibited a moderate to high antimicrobial activity aganist *B.subtilis S.aureus, E.coli, P.aeruginosa and Candida albicans* with inhibition zone (12, 10, 12, 13, 13 mm respectively) and was *completely inactive against Aspergillus niger*. This study revealded that the incorporation of *N*-(4-aminobenzenesulphonyl)-morpholine (III) with a triazole moiety may improve and verify the antimicrobial activity of the synthesized derivatives of such type. On the other hand, the incorporation of (III) with amines, alcohols, phenols, pht- and Tos-amino acids led to decrease or completely abolish the antimicrobial activity of the synthesized derivatives.

Table 2: In-Vitro Antimicrobial Activities of Synthetic Compounds.

Compd. No.	Gram –positive				Gram–negative				Fungi			
	B. subtilis		*S. aureus*		*E. coli*		*P. aeruginosa*		*Candida albicans*		*A. niger*	
I	-	-	-	-	-	-	-	-	-	-	-	-
II	-	-	-	-	-	-	-	-	-	-	-	-
III	+	6	+	6	-	-	+	7	++	12	-	-
IV	-	-	-	-	-	+	-	-	++	10	-	-
IX	-	-	-	-	-	-	-	-	-	7	-	-
X	+	6	+	6	+	6	+	7	+	7		-
XII	+	7	++	8	+	7	+	7	++	10		
XIII	++	12	++	10	+++	12	+++	13	+++	13	-	-
XXII	+	8	+	7	++	10	++	9	+++	15	-	-
XXIII	-	-	-	-	-	-	++	9	-	-	-	-
XXVI	-	-	-	-	-	-	-	-	+	7	-	-
XXIX	-	-	-	-	-	-	-	-	+	7	-	-

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