World Journal of Chemistry 6 (1): 01-07, 2011
ISSN 1817-3128

Synthesis and Characterization of Some Heterocyclic Derivatives of L-Valine as Antimicrobial Agents

[1]H.M. Hassan, [1]S.A.M. Shedid and [2]M.S. Shaheen

[1]Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City Cairo, Egypt
[2]Department of Flavour and Aromatic, National Research Center, Dokki, Giza, Egypt

Abstract: *N*-(4-Acetylbenzenesulphonyl)-L-valine (II) was prepared by the reaction of *p*-acetophenonesulphonyl chloride (I) with L-valine in sodium hydroxide solution. Reaction of L-valine compound (II) with aromatic aldehydes afforded the corresponding chalcones (V-VII). The latter chalcone (VII) was further brominated and treated with piperidine or morpholine to form the corresponding 2, 3-dipiperidin- or morpholinyl derivatives (IX, X). The substituted chalcones, on condensation with hydrazine hydrate or phenylhydrazine in acetic acid or ethanol provided the desired pyrazolines (XI-XIX). Also, the reaction with hydroxylamine hydrochloride furnished isoxazoles (XX-XXII). The same chalcones made to react with malononitrile in presence of piperidine and ethylcyanoacetate in presence of ammonium acetate gave cyanopyran and pyridine derivatives, respectively (XXIII and XXIV). The structure was confirmed by elemental analyses, IR, NMR and MS spectral studies. Some of the synthesized compounds have been screened for their antimicrobial activity against various strains of bacteria and fungi.

Key words: L-valine · Heterocyclic derivatives · Antimicrobial activity

INTRODUCTION

Chalcones have been very attractive starting compounds in organic chemistry, they are easy to prepare with large variability at the two aromatic rings and the enone provides a bifunctional site for 1, 3-dinucleophiles affording several heterocyclic ring systems [1]. It was found that chalcones have different biological activities including antimalarial [2-4], anticancer [5-7], antimicrobial [8, 9] and ant-inflammatory [10], activities. In addition, several morpholine, piperidine, pyrazolines, isoxazoline, pyran and pyridine derivatives were reported to possess significant biological and medicinal activities [11-22]. In continuation of our work on structure-activity relationship (*SAR*) [23-26], these facts prompted our interest to synthesize some novel L-valine derivatives incorporating with such heterocyclic moieties which are expected to show high biological activities [27]. Thus, L-valine was reacted with *p*-acetophenonesulphonyl chloride (I) in an alkaline medium producing the starting compound, *N*-(4-acetylbenzenesulphonyl)-L-valine (II). The methyl ester derivative (III) and its corresponding hydrazide compound (IV) were easily synthesized via the esterification of (II) with thionyl chloride in excess of absolute methanol at 0°C, followed by hydrazinolysis of the resultant ester with hydrazine hydrate (85%) in ethanol. The structure of (II-IV) was assigned on the basis of their elemental analysis, TLC studies and IR and mass spectra. The IR spectrum of (III) showed the disappearance of the two absorption bands noticed at 3402 and 1724 cm^{-1} characteristic for carboxylic OH and C=O in compound (II) and appearance of vibration at 1736 cm^{-1} attributed to the strong C=O stretching absorption of ester group, while in the IR spectrum of the hydrazide derivative (IV), the NH_2, NH stretching vibrations at 3382 and 3224 cm^{-1}, besides NH bending vibration 1651 cm^{-1} were observed.

When *N*-(4-acetylbenzenesulphonyl)-L-valine (II) was reacted with some aldehydes such as *p*-chloro-, methyl- and methoxybenzaldehyde, in presence of a catalytic amount of a base, this resulted in the formation of *N*-[4-(3-(*p*-substituted)phenyl-2-prop-enoyl) benzenesulphonyl]-L-valine (V-VII). The structure of these unsaturated carbonyl systems was evident from their chemical and spectral analysis (Table 1). The infrared spectra of the chalcone derivatives revealed the appearance of the absorption band C=O stretching at

Corresponding Author: H.M. Hassan, Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City Cairo, Egypt

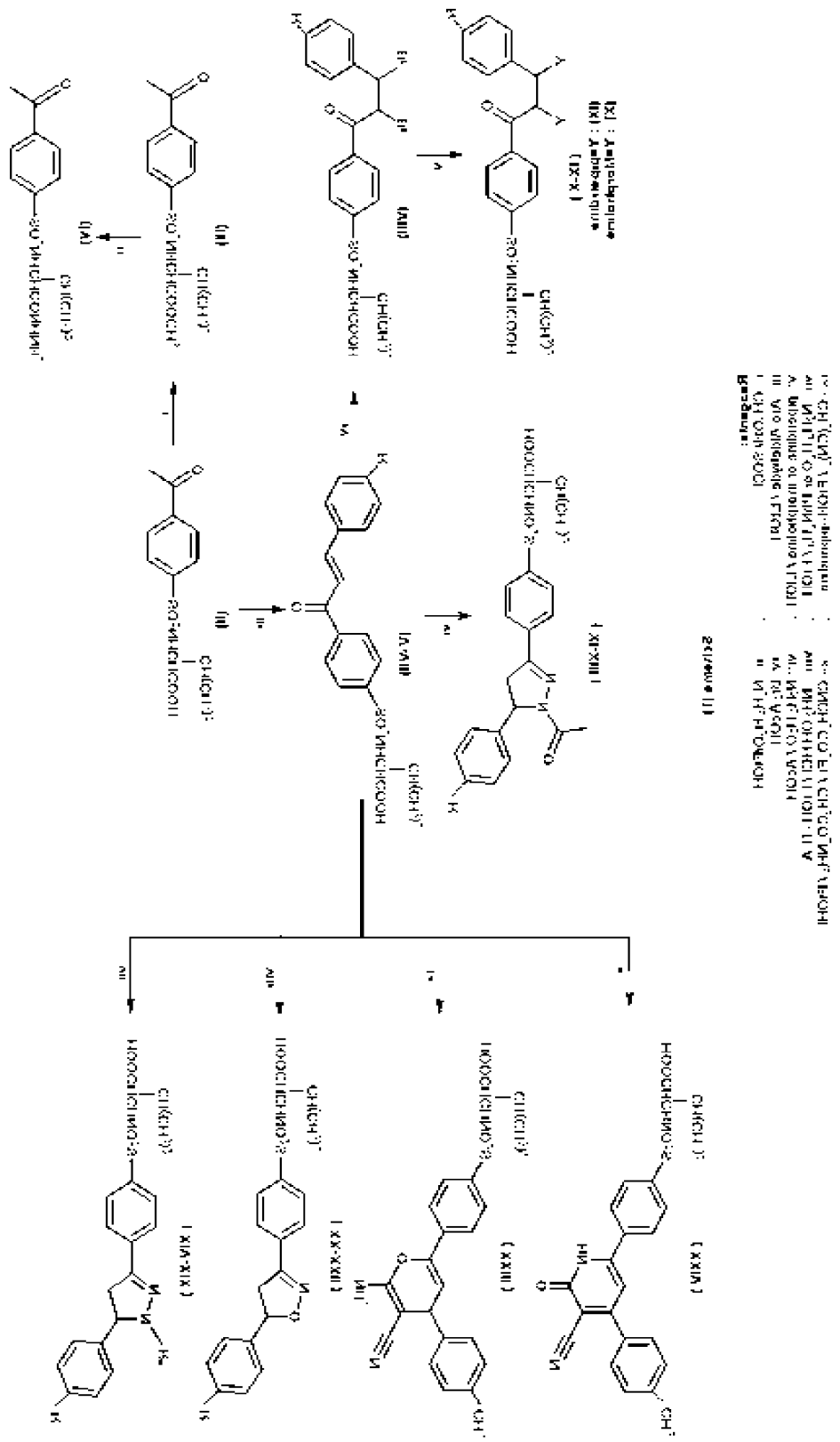
Table 1: The spectral data of the synthesized compounds (II-XXIV)

Compd. No.	Spectral data
II	IR (ί in cm^{-1}): 3402 (broad OH), 3342(NH), 3068, 1602(aro.CH and C=C), 2987, 2865 (ali.CH), 1724 (carboxylic C=O), 1682 (acetyl C=O), 1356, 1157 (SO_2) and 833 (*p*-disubstituted benzene)
III	IR: 3321(NH), 3075, 3008, 1597(aro.CH and C=C), 2972, 2843 (ali.CH), 1736 (ester C=O), 1687 (acetyl C=O), 1340, 1161 (SO_2). Ms: m/z 298 (M-15) is compatible with its proposed structure and a base peak at m/z 254 (100%) due to the fragment $C_7H_2N_2O_2S$.
IV	IR: 3382, 3224, 1651 (NH_2 and NH), 3064, 1605 (aro.CH and C=C), 2979 (ali.CH), 1685 (C=O), 1354, 1171 (SO_2).
V	IR: 3309(NH), 3041, 1592(aro.CH and C=C), 2982, 2876(ali.CH), 1711 (acid, C=O), 1665 (C=O), 1329, 1159 (SO2), 712 (C-Cl). ^{1}HNMR at ä(ppm):0.81 (d,6H,2CH_3), 2.31(h,1H,CH(CH$_3$)$_2$), 3.81 (d,1H, CHCO), 7.67(d,1H, trans CH), 7.19-8.22 (m,8H,aro-H), 8.33 (d,1H, cis CH), 8.68(s,1H,$NHSO_2$), 12.53 (s,1H,COOH, D_2O-canceled).
VII	IR: 3487 (broad OH), 3263(NH), 3062, 1597(aro.CH and C=C), 2970 (ali.CH), 1706 (acid, C=O), 1659 (C=O), 1335, 1165 (SO_2).
VIII	IR: 3367 (broad OH interfered with NH), 3037, 1593 (CH and C=C, aromatic), 2932 (ali.CH), 1728, 1674 (carboxylic acid and acetyl C=O), 1327, 1157 (SO_2), 840 (*p*-disubstituted benzene), 609 (C-Br).
IX	IR: 3286(NH), 3057, 1602(aro. CH and C=C), 2970, 2864 (ali.CH), 1736 (carboxylic C=O), 1669 (C=O), 1335, 1165 (SO_2).
X	IR: 3392(broad OH), 3233(NH), 3032, 1597 (aro.CH and C=C), 2955, 2862 (ali.CH), 1736(C=O), 1666 (C=O), 1327(SO2) and 817 (*p*-disubstituted benzene). ^{1}HNMR at ä(ppm): 0.83(d,6H,2CH_3), 2.29 (h,1H,CH(CH_3)$_2$), 2.46 (s,3H, CH_3), 2.69 (t,4H,CH_2-N-CH_2), 3.75 (t,4H,CH_2-O-CH_2), 5.02 (d,1H, α -CHCO), 7.23-8.29(m,8H,aro-H), 8.73(s,1H,$NHSO_2$),11.78 (s,1H,COOH, D_2O-canceled).
XI	IR: 3279 (NH), 3051, 1598 (aro.CH and C=C), 2970, 2884 (ali.CH), 1728 (C=O), 1666 (C=O), 1496 (C=N), 1327, 1134 (SO_2), 832 (*p*-disubsted benzene). ^{1}HNMR: 0.79 (d, 6H, 2CH_3), 1.85 (d, 2H,CH_2-pyrazoline), 2.31(s, 3H, $COCH_3$), 3.79 (d,1H,CHCO), 5.10(t,1H,CH-pyrazoline), 6.86-7.91(m,8H,aro-H), 8.46 (s,1H,NH). 11.56 (s, 1H, COOH, D2O-canceled).
XIII	IR: 3314 (NH), 3078 (aro.CH), 2989, 2836 (ali.CH), 1724 (C=O), 1673 (C=O), 1493 (C=N), 1337, 1118 (SO_2).
XIV	IR: 3421 (broad OH), 3271 (NH), 3039, 1591 (aro.CH and C=C), 2931, 2839 (ali.CH), 1735 (C=O), 1504 (pyrazolines), 1341, 1167 (SO_2), 712(C-Cl).
XVI	IR: 3256 (NH), 3031, 1597 (aro.CH and C=C), 2932 (ali.CH), 1728 (C=O), 1489 (C=N), 1242 (etheral C-O) and 1335, 1142 (SO_2). ^{1}HNMR: 0.82 (d, 6H, 2CH_3), 1.87 (d, 2H,CH_2-pyrazoline), 3.68 (d,1H,CH-CO), 5.00 (t,1H,CH-pyrazoline), 5.85(s,1H,NH-pyrazoline), 6.86-7.91(m,8H,aro-H), 11.39 (s,1H,COOH, D_2O-canceled).
XVII	^{1}HNMR: 0.81 (d, 6H, 2CH_3), 1.89 (d, 2H,CH_2-pyrazoline), 3.62 (d,1H,CH-CO), 5.02(t,1H,CH-pyrazoline), 6.87-7.94(m,13H,aro-H), 8.43(s,1H,$NHSO_2$),12.13 (s,1H,COOH, D_2O-canceled).
XVIII	IR: 3361 (broad OH interfered with NH), 3011(aro.CH), 2991, 2852 (ali.CH), 1731 (C=O), 1511 (C=N), 1341, 1149 (SO_2).
XX	IR: 3271 (NH), 3023, 1597 (aro.CH and C=C), 2970, 2878 (ali.CH), 1720 (C=O), 1626, 1509 (isoxazoline), 1339, 1165(SO_2), 696 (C-Cl).
XXI	^{1}HNMR:0.82(d,6H,2CH_3), 3.66(d,1H,CHCO),3.75(d,2H,CH_2-isoxazoline), 4.41(t,1H,CH-isoxazoline),6.87-8.01(m,8H,aro-H),8.52(s,1H,$NHSO_2$), 11.89(s,1H,COOH, D_2O-canceled).
XXII	IR: 3467 (broad OH), 3271 (NH), 3011 (aro.CH), 2931 (ali.CH), 1735 (C=O), 1621, 1512 (isoxazoline), 1327(SO2) and 810 (*p*-disubstituted benzene).
XXIII	IR: 3255(NH), 3054, 1589 (aro.CH and C=C), 2970, 2931 (ali.CH), 2214 (C=N), 1728 (C=O), 1485 (C=N), 1335, 1165 (SO_2) and 817 (*p*-disubsted benzene). Ms: m/z 467, 468(M and M+1) is compatible with its proposed structure and a base peak at m/z 105 (100%).
XXIV	IR: 3401 (broad OH), 3240(NH), 3010 (aro.CH), 2964, 2870 (ali.CH), 2219 (C=N), 1719 (C=O), 1612, (C=N), 1347, 1136(SO_2). Ms: m/z 391 (23%) due to loss of fragments CO_2 and 2CH_3 of L-Valine moiety and is compatible with its proposed structure and a base peak at m/z 109 (100%).

Table 2: Physical data of derivatives (II-XXIV)

Compound								Elemental Analysis calculated / found					
No	R	R^1	Cryst. solv*	M.P.°C	Yield %	R_f	Mol. Formula	C%		H%		N%	
II	---	---	A	200-202	70	0.86	$C_{13}H_{17}NO_5S$ 299	52.17	52.20	5.68	5.51	4.68	4.62
III	---	---	A	130-132	54	0.66	$C_{14}H_{19}NO_5S$ 313	53.67	53.73	6.07	6.21	4.47	4.42
IV	---	---	B	102-105	62	0.78	$C_{13}H_{21}N_5O_3S$	47.70	47.92	6.42	6.76	21.40	21.78
V	Cl	---	B	215-217	70	0.78	$C_{20}H_{20}ClNO_5S$ 421.5	56.93	56.89	4.74	4.81	3.32	3.24
VI	CH_3	---	C	222-224	80	0.88	$C_{21}H_{23}NO_5S$ 401	62.84	62.90	5.7	35.69	3.49	3.41
VII	OCH_3	---	B	190-192	82	0.89	$C_{21}H_{23}NO_6S$ 417	60.43	60.48	5.51	5.53	3.35	3.52
VIII	CH_3	---	C	130-132	75	0.62	$C_{21}H_{23}Br_2NO_5S$ 561	44.91	44.81	4.09	4.00	2.49	2.54
IX	CH_3	---	D	189-191	60	0.60	$C_{31}H_{43}N_3O_5S$ 567	65.37	65.72	7.55	7.83	7.38	7.49
X	CH_3	---	D	176-178	46	0.72	$C_{29}H_{39}N_3O_7S$ 573	60.73	60.89	6.80	6.71	7.32	7.62
XI	Cl	---	C	182-184	70	0.89	$C_{22}H_{24}ClN_3O_5S$ 477.5	55.28	55.42	5.02	5.23	8.79	8.39
XII	CH_3	---	A	195-197	69	0.81	$C_{23}H_{27}N_3O_5S$ 457	60.39	60.73	5.90	6.21	9.19	8.87
XIII	OCH_3	---	A	252-254	64	0.87	$C_{23}H_{27}N_3O_6S$ 473	58.35	58.98	5.71	5.48	8.88	9.01
XIV	Cl	H	C	98-99	70	0.72	$C_{20}H_{22}ClN_3O_4S$ 435.5	55.10	55.00	5.05	5.19	9.64	9.70
XV	CH_3	H	B	135-137	74	0.76	$C_{21}H_{25}N_3O_4S$ 415	60.72	60.84	6.02	5.71	10.12	9.70
XVI	OCH_3	H	D	185-186	61	0.71	$C_{21}H_{25}N_3O_5S$ 431	58.47	58.64	5.80	5.66	9.74	9.87
XVII	Cl	C_6H_5	B	250-252	64	0.88	$C_{26}H_{26}ClN_3O_4S$ 511.5	60.99	61.02	5.08	5.13	8.21	8.35
XVIII	CH_3	C_6H_4	C	176	45	0.87	$C_{20}H_{18}ClN_3O_3S$ 416.5	57.76	57.81	4.33	4.07	10.11	10.27
XIX	OCH_3	C_6H_5	C	108-110	50	0.87	$C_{27}H_{29}N_3O_5S$ 507	63.90	63.84	5.71	5.84	8.28	8.44
XX	Cl	---	A	188-190	75	0.82	$C_{20}H_{21}ClN_2O_5S$ 436.5	54.98	54.79	4.81	4.89	6.41	6.72
XXI	CH_3	---	A	147-149	63	0.86	$C_{21}H_{24}N_2O_5S$ 416	60.57	60.10	5.76	4.78	6.73	6.95
XXII	OCH_3	---	D	120-122	60	0.84	$C_{21}H_{24}N_2O_6S$ 432	58.33	58.70	5.55	5.76	6.48	6.34
XXIII	CH_3	---	B	120	79	0.95	$C_{24}H_{25}N_3O_5S$	61.67	61.62	5.35	5.73	8.99	8.72
XXIV	CH_3	---	B	>300	62	0.87	$C_{24}H_{22}N_3O_5S$	61.93	62.48	4.94	4.76	9.03	9.26

*Cryst. solv.: A= Methanol, B= Ethanol, C= AcOH-H_2O, D= Ethanol– benzene, E = Dioxane.



Scheme 1:

lower frequency due to its conjugation with α, β-double bond of chalcone moiety. ^{1}HNMR signals of duch compounds noticed at δ ~ 7.67 and 8.33 ppm characteristic for the trans and cis hydrogen protons of α, β-double bond of chalcone moiety. Addition reaction of the latter chalcone (VII) with bromine in AcOH afforded N-[4-(2, 3-dibromo 3-*p*-tolylpropionyl) benzenesulphonyl]-L-valine (VIII). Its IR spectrum exhibited the following bands in support of its proposed structure: 3367 (broad OH interfered with NH), 1728, 1674 (carboxylic acid and acetyl C=O) and 609cm^{-1} (C-Br). Nucleophilic replacement reactions of this compound with piperidine or morpholine produced the respective dipiperidinyl- or morpholinyl derivatives (IX, X). The structure of these products was assigned on the basis of their elemental analysis, TLC studies and spectral analysis.

The presence of α, β-unsaturated ketonic group in the synthesized chalcones (V-VII), prompted us to interact it with hydrazine hydrate in glacial acetic acid or ethanol to yield the corresponding *N*-[4-(1-acetyl-5-*p*-substituted phenyl-4, 5-dihydro-1*H*-3-pyrazolyl) benzenesulphonyl]-L-valine derivatives (XI–XIII). Moreover, when this reaction was carried out with hydrazine hydrate, phenylhydrazine or hydroxylamine hydrochloride in abs. ethanol containing a catalytic amount of an organic base, the novel products; *N*-[4-(1-substituted-5-(*p*-substituted phenyl)-4,5-dihydro-*(1H)*-3-pyrazolyl)benzenesulphonyl]- or *N*-[4-(5-(*p*-substituted phenyl)-4,5-dihydro-3-isoxazolyl)benzenesulphonyl]-L-valine derivatives (XIV-XIX or XX-XXII) were isolated respectively. Finally, the condensation reaction of chalcone (VII) with malononitrile in abs. ethanol containing few drops of piperidine or ethylcyanoacetate in the presence of ammonium acetate yielded *N*-[4-(2-amino-3-cyano-4-*p*-tolyl-4*H* pyran-6-yl)benzenesulphonyl]- or *N*-[4-(5-cyano-6-oxo-4-*p*-tolyl-1,6-dihydro-2-pyridinyl)benzenesulphonyl]L-valine (XXIII) and (XXIV) respectively. The formation of all above derivatives (XI–XXIV) seems to proceed by a nucleophilic addition on the carbonyl group followed by cyclization. The structure of these systems was substantial by elemental analysis, TLC studies and spectral data listed in Tables 1, 2. The above reactions were summarized in Scheme 1.

MATERIALS AND METHODS

Melting points were uncorrected and measured on electric melting point apparatus SMP1. Thin layer chromatography (tlc, R_f) 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 and also using iodine / KI (20%) solution as spraying agent. 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 analyses were carried out at Microanalytical Unit, Faculty of Science, Cairo University and Cairo, Egypt. Antimicrobial screening was carried out at Botany Department, Faculty of Science and Al-Azhar University.

Synthesis of N-(4-acetylbenzenesulphonyl)-L-valine (II): A solution of L-valine (0.05 mol) in 80 ml. of 1*N* NaOH was treated with a solution of *p*-acetophenonesulphonyl chloride (I, 0.051mol) in 100 ml Et_2O, added in small portions, with stirring over a half-hour period. The reaction mixture was stirred for additional 3 h and then the organic layer was removed in vacuo and 40 ml of water added. The resulting solution was cooled and acidified with 2N HCl. The crude product was collected, washed with water, dried and recrystallized from methanol.

Synthesis of N-(4-acetylbenzenesulphonyl)-L-valine Methyl Ester (III): A solution of *N*-(4-acetylbenzenesulphonyl)-L-valine (II, 0.002 mol) in abs. methanol was cooled to –5°C and pure thionyl chloride (0.0021 mol) was added dropwise, with stirring over a half-hour period. The reaction mixture was stirred for additional 3 h at 5-10°C, kept overnight at room temperature and then the solvent was removed in vacuo. Methanol was added and reevaporated several times. The residual product was recrystallized from methanol.

Synthesis of *N*-[(4-(1-hydrazonoethyl) benzenesulphonyl)]-L-valine Hydrazide (IV): *N*-(4-Acetylbenzenesulphonyl)-L-valine methyl ester (III, 0.001 mol) was dissolved in methanol and hydrazine hydrate (0.006 mol, 85 %) was heated for one hour and then kept overnight at room temperature. The crude product was filtered, washed with water, dried and purified by recrystallization from ethanol.

General Procedure for the Synthesis of *N*-[4-(3-[*p*-substituted phenyl]-2-prop-enoyl) benzenesulphonyl]-L-valine (V-VII): A mixture of equimolar amounts (0.01mol) of *N*-(4-acetylbenzenesulphonyl)-L-valine (II) and *p*-substituted Benzaldehyde in ethanol containing 0.2 g. of NaOH was stirred for 4h at room temperature and then acidified. The separated solid product was filtered, washed with few ml. of ethanol, dried and then recrystallized from the proper solvent.

Table 3: Antimicrobial activities of some synthesized derivatives

	S.aureus		*B. cereus*			
Compd. No.		MIC		MIC	*E. coli*	*A.. niger*
II	-	-	++	125	-	-
VI	+	250	-	-	-	-
X	-	-	-	-	-	-
XII	+	250	-	-	-	-
XV	-	-	-	-	-	-
XVIII	+	250	+++	75	-	-
XX	-	-	-	-	-	-
XXII	++	125	+	250	-	-
XXIII	+++	75	++	125	-	-
XXIV	+	250	-	-	-	-

General Procedure for the Synthesis of N-[4-(2, 3-dibromo3*p*-tolylpropionyl)-benzenesulphonyl]-L-valine (VIII): Compound VI (0.003 mol) was dissolved in 10 ml. of acetic acid and to it was added bromine (0.0031 mol) and the mixture was stirred at room temperature for 3h. The crude dibromo compound obtained was recrystallized from dil. acetic acid.

General Procedure for the Synthesis of N-[4-(2, 3-dipiperidin-or morpholin-1or 4-yl -3-*p*-tolylpropionyl) benzenesulphonyl]-L-valine (IX, X): A mixture of VIII (0.001 mol) and piperidine or morpholine (0.0022 mol) in abs. Ethanol was refluxed for 8h. The reaction mixture was concentrated in vacuum and then cooled. The separated solid was filtered, dried and recrystallized from ethanol- benzene.

General Procedure for the Synthesis of *N*-[4-(1-acetyl-5-(*p*-substituted phenyl)-4, 5-dihydro-1*H*-3-pyrazolyl) benzenesulphonyl]-L-valine (XI-XIII): To a solution of chalcone derivatives (V-VII, 0.001 mol) in glacial acetic acid, hydrazine hydrate (0.0015mol) was added and the reaction mixture refluxed for 6-8h. The solid that separated upon concentrating the reaction mixture was filtered and recrystallized from the proper solvent.

General Procedure for the Synthesis of N-[4-(1-substituted-5-(*p*-substituted phenyl)-4, 5-dihydro-1*H*-3-pyrazolyl) benzenesulphonyl]-L-valine (XIV-XIX): A mixture of chalcone derivatives (V-VII, 0.001 mol) and hydrazine hydrate or phenyl hydrazine (0.0015 or 0.0011 mol, respectively) in abs. Ethanol containing few drops of piperidine as a catalyst was refluxed for 6-8h. The resulting crude product filtered off, dried and recrystallized from the proper solvent.

General Procedure for the Synthesis of N-[4-(5-(*p*-substituted phenyl)-4, 5-dihydro-3-isoxazolyl) benzenesulphonyl]-L-valine (XX-XXII): An ethanolic solution of chalcone (V-VII, 0.001 mol) was refluxed with hydroxylamine hydrochloride (0.0011mol) in the presence of excess of triethylamine as a catalyst for 6-8h. The reaction mixture was concentrated under reduced pressure and left to cool. The separated product was filtered, dried and recrystallized from the proper solvent.

General Procedure for the Synthesis of N-[4-(2-amino-3-cyano-4-*p*-tolyl-4*H*-pyran-6-yl) benzenesulphonyl]-L-valine (XXIII): A mixture of chalcone compound (VI, 0.001 mol) and malononitrile (0.0011 mol) in abs. ethanol containing few drops of piperidine as a catalyst was refluxed for 8h. The resulting crude product filtered off, dried and recrystallized from ethanol.

General Procedure for the Synthesis of N-[4-(5-cyano-6-oxo-4-*p*-tolyl-1, 6-dihydropyridin-2-yl) benzenesulphonyl]-L-valine (XXIV): Equimolar ratio of ethanolic solution of (VI) and ethylcyanoacetate in the presence of ammonium acetate was refluxed for 8h. The reaction mixture was allowed to cool. The precipitated product was filtered, washed with cold water, dried and then crystallized from ethanol. The physical data of derivatives (II-XXIV) were summarized in Table 2.

Antimicrobial Screening Results: Ten compounds were screened *In vitro* for their antimicrobial activities against three strains of bacteria *Staphylococcus aureus* (*TCC25923*), *Bacillus cereus* (*NCTC10400*), Escherichia coli (*ATCC25922*) and one strain of fungi *Aspergillus niger* by the filter paper disc method [28]. After 24h of incubation at 30°C for bacteria and 48h of incubation at

28°C for fungi, the activity was recorded. Ampicillin and Mycostatine used as a reference for antibacterial and antifungal activities respectively. The minimal inhibitory concentration (*MIC*) of some of the tested compounds was measured. The results of screening indicated that the following three compounds (XVIII, XXII and XXIII) were found to possess weak to moderate activities only against gram positive bacteria while the remaining derivatives were biologically inactive against all the tested microorganisms (Table 3).

REFERENCES

1. Powers, D.G., D. Fokas, W.J.J. Ryan and D.I. Coffen, 1998. Automated parallel synthesis of chalcone-based screening libraries", Tetrahedron, 54: 4085-4096.
2. Liu, M. and P. Wilairat, 2001. Antimalarial alkoxylated and hydroxylated chalcones: Structure-activity relationship analysis. J. Med. Chem., 44(25): 4443-4452.
3. Dominguez, J.N., C. Leon, J. Rodrigues, N. Gamboa de Dominguez, J. Gut and P.J. Rosenthal, 2001. Synthesis and evaluation of new antimalarial phenylurenyl chalcone derivatives", J. Med. Chem., 48(10): 3654-3658.
4. José, N.D., L. Caritza, R. Juan, G. Jiri and J.R. Philip, 2005. Synthesis and antimalarial activity of sulfonamide chalcone derivatives; Il Formica, 60(4): 307-311.
5. Kumar, S.K., E. Hager, C. Pettit, H. Gurulingappa, N.E. Davidson and S.R. Khan, 2003. Design, synthesis and evaluation of novel boronic-chalcone derivatives as antitumor agents, J. Med. Chem., 46(14): 2813-2815.
6. Tatsuzaki, J., K.F. Bastow, K. Nakagawa-Goto, S. Nakamura, H. Itokawa and K. Lee, 2006. Dehydrozingerone, chalcone and isoeugenol analogues as in vitro anticancer agents, J. Nat. Prod., 69(10): 1445-1449.
7. Chin, Y.W., H.A. Jung, Y. Liu, B.N. Su, J.A. Castoro, W.J. Keller and A.D. Kinghorn, 2007. Antioxidant constituents of the roots and stolons of Licorice (*Glycyrrhiza glabra*), J. Agric. Food Chem., 55(12): 4691-4697.
8. Svetaz, L., A. Tapia, S.N. Lopez, R.L.E. Furlan, E. Petenatti, R. Pioliand S.A. Zacchino, 2004. Antifungal chalcones and new caffeic acid esters from *Zuccagnia punctata* acting against soybean infecting fungi" J. Agric. Food Chem., 52(11): 3297-3300.
9. Zhao, P.L., C.L. Liu, W. Huang, Y.Z. Wang and G.F. Yang, 2007. Synthesis and fungicidal evaluation of novel chalcone-based strobilurin analogues. J. Agric. Food Chem., 55(14): 5697-5700.
10. Meng, C.Q., L. Ni, Z. Ye, M.D. Weingarten, J.E. Simpson, J.W. Skudlarek, E.M. Marino, K.L. Suen, A. Souder, R.B. Howard and C.L. Sundell Sikorski, 2007. Carboxylated, heteroaryl-substituted chalcones as inhibitors of vascular cell adhesion molecule-1 expression for use in chronic inflammatory diseases. J. A. J. Med. Chem., 50(6): 1304-1315.
11. Chiara, B.V., R. Carlo, A. Elisa and M. Donatella, 2007. Synthetic pyrazole derivatives as growth inhibitors of some phytopathogenic fungi. J. Agric. Food Chem., 55(25): 10331-10338.
12. Barceló, M., E. Raviña, C.F. Masaguer, F.M. Areias, J. Brea and M.L. Loza, 2007. Synthesis and binding affinity of new pyrazole and isoxazole derivatives as potential atypical antipsychotics, Bioorg. Med. Chem. Lett., 17(17): 4873-487.
13. John, W.S. and B. Alfred, 1973. 3, 5-Dialkyl-4-(phthalimidomethyl) isoxazoles, pyrazoles and isothiazoles Novel antiandrogens. J. Med. Chem., 16(5): 512-516.
14. Klaus, H. and Y.B. Cyril, 2004. Polypeptides. XLVII. Effect of the pyrazole-imidazole replacement on the biological activity of thyrotropin-releasing hormone. J. Med. Chem., 13(6): 1099-110.
15. Reviriego, F., M.I. Rodriguez-Franco, P. Navarro, E. Garcia-Espana, M. Liu-Gonzalez, B. Verdejo and A. Domenech, 2006. The sodium salt of diethyl 1*H*-pyrazole-3, 5-dicarboxylate as an efficient amphiphilic receptor for dopamine and amphetamines. crystal structure and solution studies, J. Am. Chem. Soc., 128(51): 16458-16459.
16. Stefano, M., B. Rita, G. B. Pier, G. Mario, S. Daniele, E.M. Maria, P. Alessandra, C. Paolo and T. Enzo, 1992. Pyrazole-related nucleosides. Synthesis and antiviral/ antitumor activity of some substituted pyrazole and pyrazolo [4,3-d]-1,2,3-triazin-4-one nucleosides. J. Med. Chem., 35(5): 917-924.
17. Hari, G.G. and P.S. Prem, 1970. Potential antidiabetics.VI. 3-Methyl-4-aryl-hydrazono-2-isoxazolin-5-ones and 3-methyl-4-arylazo-5-(methyl phenyl)-isoxazoles J. Med. Chem., 13(6): 1250-1251.
18. Liu, M.C., T.S. Lin, J.G. Cory and A.H. Cory, 1996. Synthesis and biological activity of 3- and 5-amino derivatives of pyridine-2-carboxaldehyde thiosemicarbazone, J. Med. Chem., 39(13): 2586-2593.

19. Moustafa, O.S. and R.A. Ahmad, 2003. Synthesis and antimicrobial activity of some new cyanopyridines, isoxazoles, pyrazoles and pyrimidines bearing sulfonamide Moiety, Phosphorus, Sulfur Silicon Relat. Elem., 178(3): 475-484.
20. Fabien J., L. Xavier, M. Catherine, R. Jean-François, W. Jean-Yves, M. Jean-Louis, D. Jacques, D. Jean-Michel and P. Bernard, 2004. Design, synthesis and pharmacological evaluation of pyridinic analogues of nimesulide as cyclooxygenase-2 selective inhibitors. J. Med. Chem., 47(27): 6749-6759.
21. Chan, W.N., J.M. Evans, M.S. Hadley, H.J. Herdon, J.C. Jerman and H.K.A. Morgan, 1996. Synthesis of novel *trans*-4-(substituted benzamido)-3, 4-dihydro-2*H*-benzo[*b*]pyran-3-ol derivatives as potential anticonvulsant agents with a distinctive binding profile. J. Med. Chem., 39(23): 4537-4539.
22. Adolf, P., J. Ivo and R.M. Rene, 1980. Synthesis and antiallergic properties of some 4H,5H-pyrano[3,2-c][1]benzopyran-4-one, 4H,5H-[1] benzothiopyrano [4,3-b]pyran-4-one and 1,4-dihydro-5H-[1]benzothiopyrano[4,3-b]pyridin-4-one-derivatives., J. Med. Chem., 23(12): 1372-1376.
23. Flematti, G.R., E.D. Goddard-Borger, D.J. Merritt, E.L. Ghisalberti and K.W. Dixon, 2007. Preparation of 2*H*-Furo [2, 3-*c*] pyran-2-one Derivatives and Evaluation of Their Germination-promoting-activity. J. Agric. Food Chem., 55(6): 2189-2194.
24. Hassan, H.M., 1998. Synthesis and antibacterial activity of some novel *p*-(*N*-benzoyl) amino benzoic acid derivatives. J. Serb. Chem. Soc., 63(2): 117-123.
25. Hassan, H.M. and S.A.M. Shedid, 1998. Synthesis and antimicrobial activity of some new Mannich bases, *N*-(2-hydroxy-1-naphthyl) amino acid, methyl ester and hydrazide derivatives. J. Serb. Chem. Soc., 63(2): 125-130.
26. Hassan, H.M., 2004. Synthesis and antimicrobial activity of some new imidazoline and quinazoline amino acid and peptide derivatives. Al-Azhar Bull. Sci., 15(2): 163-170.
27. Hassan, H.M., S.A.M. Shedid, F.A. Kora and R.M. Eisway, 2007. Synthesis of novel 3, 6-dichlorobenzo[b]thiophene-2-carbonylamino acid derivatives as potential antimicrobial agents. Al-Azhar Bull. Sci., 18(2): 37-46.
28. Wood, S.J. and S. Shadomy, 1983. Disk diffusion susceptibility tests with norfloxacin: confirmation of proposed interpretive criteria. Eur. J. Clin. Microbiol., 2(3): 242-244.