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Synthesis of Some New Substituted Aminoacylthiazoles and Dipeptide Derivatives

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Coupling of N-phthalyl- or N-tosylamino acids with 4-*p*-tolyl- (or 4-*p*-chlorophenyl-) 2-aminothiazole (I-II) using the dicyclohexylcarbodiimide (DCC) method furnishes 2-(N-phthalyl- or N-tosylaminoacyl) amino-4-*p*-tolyl-thiazoles (III-XII) and the corresponding 4-*p*-chlorophenyl-thiazoles (XXIII-XXXII). Hydrazinolysis of 2-(N-phthalylaminoacyl) amino- 4-*p*-tolyl-(or 4-*p*-chloraphenyl-) thiazoles (III-VII and XXIII-XXVIII) in ethanol afforded the desired 2-(aminoacyl) amino-4-*p*-tolyl- or (4-*p*-chlorophenyl-) thiazoles (XIII-XVII and XXXIII-XXXVII). 2-(N-Tosyldipeptidyl) amino-4-*p*-tolyl-(or 4-*p*-chlorophenyl-thiazoles (XVIII-XXII and XXXVIII-XLII) were synthesized via the DCC method. Some of the synthesized compounds were found to be active against a number of micro-organisms.

INTRODUCTION

Reports of the synthesis and pharmacological properties of 2-acetamidothiazole derivatives have been studied extensively for their varied biological activities[1–5]. This led us to synthesize some novel 2-(N-Pht-or N-Tos-aminoacyl or free aminoacyl or N-Tos-dipeptidyl) amino-4-*p*-tolyl- (or 4-*p*-chlorophenyl-) thiazoles (III-XLII), with the hope that the amino acid and dipeptide moieties will enhance the biological activities of these compounds.

RESULTS AND DISCUSSION

Synthesis of 2-(N-Pht-and N-Tos-aminoacyl) amino-4-*p*-tolyl- (or 4-*p*-chlorophenyl-) thiazole derivatives (III-XII and XXIII-XXXII) were achieved through treatment of 4-*p*-tolyl-2-aminothiazole (I) or 4-*p*-chlorophenyl-2-aminothiazole (II) with the appropriate N-Pht- and N-Tos-amino acid in dioxane using the DCC procedure. The products were chromatographically homogeneous and did not respond to ninhydrin reaction.

The IR spectrum of 2-(N-Pht-L-Ala) amino-4-*p*-tolylthiazole (IV) in KBr showed the characteristic bands (in cm^{-1}) at : 3350, 3220, 3060 (NH, —N<, CONH); 2960, 2920 (CH_3); 2880, 2840 (thiazole nucleus); 1750, 1720 (>C=O); 1670, 1560, 1340 (amides I,II and III) and other characteristic bands supporting the structure. UV spectrum of (VI) in ethanol showed λ_{max}(log ϵ) 320nm (3.74), 283nm (3.52). NMR spectrum of (IV) in DMSO-d_6 : δ 2.31 (s, 3H, CH_3–ph); 6.91 (s, 4H, *p*-tolyl aromatic protons);

6.57 (s, 1H, NH); 3.22 (s, 1H, CH); 1.14 (s, 3H, CH_3 and 7.82 (s, 4H, phthalyl aromatic protons).

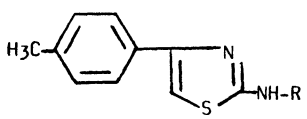
Treatment of 2-(N-Pht-aminoacyl) amino-4-*p*-tolyl-(or 4-*p*-chlorophenyl-) thiazoles (III–VII and XXIII–XXVI) with 0.5 M hydrazine hydrate in ethanol afforded the corresponding 2-(aminoacyl)-4-*p*-tolyl-(or 4-*p*-chlorophenyl-) thiazoles (XIII–XVII and XXXIII–XXXVII). Chromatographic study revealed their homogeneity (positive ninhydrin reaction), and their structures were convincingly supported by the IR, UV and NMR spectral data and their complete acid hydrolysis products.

The IR spectrum of 2-(Gly) amino-4-*p*-chlorophenylthiazole (XXXIII) in KBr showed the characteristic bands (in cm^{-1}) at: 3400, 3350, 3300 (NH_2, >NH and —N<); 2970, 2940 (CH_2); 2870, 2840 (thiazole nucleus); 1750 (>C=O); 1650, 1540, 1320 (amides I, II and III) and other characteristic bands supporting the structure UV spectrum of (XXXIII) in ethanol showed λ_{max} (log ϵ) 315 nm (3.65), 285 nm (3.44). NMR spectrum of compound (XXXIII) in DMSO-d_6: δ2.24 (*s*, 2H, CH_2); 6.20 (*s*, 1H, NH); 8.14 (*s*, 2H, NH_2) and 6.80 (*s*, 4H, aromatic protons).

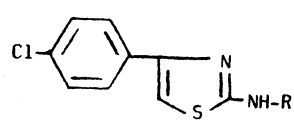
The dipeptide derivatives (XVIII–XXII and XXXVIII–XLII) were prepared by the DCC method. Coupling of N-Tos-L-serine with 2-(aminoacyl) amino-4-*p*-tolylthiazoles (XIII–XVII) and similarly N-Tos-L-alanine with 2-(aminoacyl) amino-4-*p*-chlorophenylthiazoles (XXXIII–XXXVII) in DMF using the DCC technique furnished the dipeptides (XVIII–XXII and XXXVIII–XLII respectively) which were isolated, purified and obtained in good yields (Table 1).

The IR spectrum of 2-(N-Tos-L-Ser-L-Ala) amino-4-p-tolylthiazole (XIX) in KBr showed the characteristic bands (in cm^{-1}) at: 3370, 3260, 3100 (NH, CONH, N, SO_2NH); 2970, 2930 (CH_3, CH_2); 2885, 2850 (thiazole nucleus); 1740, 1715 (>C=O); 1660, 1565, 1330 (amides I, II and III) and other characteristic bands supporting the structure. UV spectrum of (XIX) in ethanol showed λ_{max} (log ϵ) 320 nm (3.70), 280 nm (3.49). NMR spectrum of (XIX) in DMSO-d_6: δ 3.22 (*s*, 2H, 2CH-); 2.33 (*s*, 6H, $2CH_3$-ph); 1.12 (*s*, 3H, CH_3); 3.52 (*s*, 2H, CH_2); 4.21 (*s*, 1H, OH); 6.73 (*s*, 3H, 3NH); 6.82–7.23 (s, aromatic protons).

The IR, UV and NMR spectra, chromatograpic studies and elemental analysis of compounds (III–XLII) were consistent with their assigned structures.



Compounds of Type (A)
(III–XXII)



Compounds of Type (B)
(XXIII–XLII)

EXPERIMENTAL

Samples for analysis were dried at 70/10° mm, over anhyd. P_2O_5 for 24 hrs. Melting points were determined on a Gallen-Kamp melting points apparatus and are uncorrected. All thin-layer chromatograms (R_f value) were made on Silica Gel-G using benzene-ethyl acetate (1 : 1) as solvent system and iodine-potassium iodide (20%) as detection reagent. Benzidine, ninhydrin and hydroxamate reactions were used for detection of amino acid derivatives on Whatman No. 1 paper chromatograms (spot reaction). Optical rotations were taken in a Bellingham Stanley polarimeter, 1 dm tube (c=5) in ethanol (Table 1). The UV spectra were measured with Unicam SP 8000 and the IR spectra (KBr, ν_{max} in cm^{-1}) with a Unicam SP 1200. The ^1H-NMR data were determined with Varian T-60A spectrophotometer and shifts are reported in (δ) ppm relative to internal TMS.

4-*p*-Tolyl-2-aminothiazole(I) and 4-*p*-chlorophenyl-2-aminothiazole(II) were prepared according to the procedure described in literature[6].

General Procedure for the Synthesis of 2-(N-Pht- or N-Tos-aminoacyl) amino-4-*p*-tolyl- (or 4-*p*-chlorophenyl-) thiazoles (III–XII and XXIII–XXXII)

N-Phthalyl- or N-tosylamino acid (0.007 mole) and 4-*p*-tolyl-2-aminothiazole or 4-*p*-chlorophenyl-2-aminothiazole (I and II, 0.007 mole) were dissolved in dioxane (40 ml). The mixture was cooled to −5°C, dicyclohexylcarbodiimide (1.40 g, 0.007 mole) added and the mixture stirred for 2 hrs at 0°C and left for 24 hrs at 0°C and for another 24 hrs at room temperature. The dicyclohexylurea was filtered off and the filtrate evaporated in vacuo. The residual solid was recrystallized from dioxan. The products (III–XII and XXIII–XXXII) were soluble in EtOH, DMF, DMSO and insoluble in ether and petroleum ether. The products were chromatographically homogeneous when developed with benzidine and iodine solution.

General Procedure for the Synthesis of 2-(free aminoacyl)-amino-4-*p*-tolyl-(or 4-*p*-chlorophenyl-) thiazoles (XIII–XVII and XXXIII–XXXVII)

2-(N-Pht-aminoacyl) amino-4-*p*-tolyl-(or 4-*p*-chlorophenyl-) thiazoles (III–VII and XXIII–XXVII, 0.015 mole) were dissolved in ethanol (100 ml) and then treated with 0.5 M hydrazine hydrate in ethanol (10 ml). The reaction mixture was refluxed for 2 hrs. The residue obtained after evaporation of the solvent was treated with 2N HCl (50 ml) for 25 min at 50°C. The reaction mixture was cooled and the insoluble phthalylhydrazide filtered off. The filtrate was evaporated in vacuo and the residual material dissolved in ethyl acetate (120 ml) and triethylamine

TABLE 1

PHYSICAL DATA OF VARIOUS 2-(N-Pht-or N-Tos-aminoacyl or free aminoacyl or N-Tos-dipeptidyl) amino-4-*p*-tolyl-(or 4-*p*-chlorophenyl-)thiazoles (III-XLII)

Comp. no.	R	Yield %	m.pt. °C	R_f	$[\alpha]_D^{20}$ EtOH	Molecular formula	Elemental analysis % Calcd. C	H	N	Found C	H	N
					Compounds (III-XXII) of the Type (A)							
III	Pht-Gly	62	181–183	0.56	—	$C_{28}H_{15}N_3O_3S$	63.66	3.98	11.14	63.48	3.95	11.08
IV	Pht-L-Ala	65	163–165	0.51	+56.5	$C_{21}H_{17}N_3O_3S$	64.45	4.35	10.74	64.21	4.32	10.65
V	Pht-L-Val	58	155–156	0.45	+44	$C_{23}H_{21}N_3O_3S$	65.87	5.01	10.02	65.65	5.00	9.88
VI	Pht-L-Leu	55	184–185	0.62	+49.5	$C_{24}H_{23}N_3O_3S$	66.51	5.31	9.70	66.33	5.29	9.66
VII	Pht-L-Phe	67	194–196	0.55	—33.2	$C_{27}H_{21}N_3O_3S$	69.38	4.50	8.99	69.17	4.48	8.89
VIII	Tos-Gly	70	215–217	0.54	—	$C_{19}H_{19}N_3O_3S_2$	56.86	4.74	10.47	56.67	4.72	10.40
IX	Tos-L-Ala	68	187–189	0.66	+61.6	$C_{20}H_{21}N_3O_3S_2$	57.83	5.06	10.12	57.64	5.03	10.08
X	Tos-L-Val	65	190–192	0.60	+29.4	$C_{22}H_{25}N_3O_3S_2$	59.59	5.64	9.48	59.38	5.62	9.43
XI	Tos-L-Leu	62	211–213	3.59	—55.3	$C_{23}H_{27}N_3O_3S_2$	60.39	5.91	9.19	60.22	5.89	9.09
XII	Tos-L-Phe	59	201–203	0.48	—22.8	$C_{26}H_{25}N_3O_3S_2$	63.54	5.09	8.55	63.40	5.05	8.49
XIII	Gly	64	240–241	0.57	—	$C_{12}H_{13}N_3OS$	58.30	5.26	17.06	58.08	5.25	17.02
XIV	L-Ala	60	232–234	0.52	+38.3	$C_{13}H_{15}N_3OS$	59.77	5.75	16.09	59.61	5.74	16.04
XV	L-Val	65	217–219	0.44	+50.4	$C_{15}H_{19}N_3OS$	62.28	6.57	14.53	62.19	6.55	14.50
XVI	L-Leu	58	210–212	6.64	+68.7	$C_{16}H_{21}N_3OS$	63.37	6.93	13.86	63.20	6.90	13.81
XVII	L-Phe	56	245–247	0.62	+36	$C_{19}H_{19}N_3OS$	76.81	4.04	8.94	76.66	4.01	8.92
XVIII	Tos-L-Ser-Gly	52	222–224	0.52	+29.3	$C_{22}H_{24}N_4O_5S_2$	54.10	4.92	11.48	54.29	4.95	11.51
XIX	Tos-L-Ser-L-Ala	49	260–261	0.42	—63.5	$C_{23}H_{26}N_4O_5S_2$	54.98	5.18	11.16	84.83	5.16	11.11
XX	Tos-L-Ser-L-Val	58	234–236	0.48	+44.8	$C_{25}H_{30}N_4O_5S_2$	56.60	5.66	10.57	56.75	5.68	10.60
XXI	Tos-L-Ser-L-Leu	60	215–217	0.43	+36.6	$C_{26}H_{32}N_4O_5S_2$	57.35	5.88	10.29	57.22	5.85	10.26
XXII	Tos-L-Ser-L-Phe	55	237–239	0.56	—69.1	$C_{29}H_{30}N_4O_5S_2$	60.21	5.19	9.69	60.01	5.16	9.65

Compounds (XXIII-XLII) of the Type (B)

XXIII	Pht-Gly	64	205–207	0.52	—	$C_{19}H_{12}N_3O_3SCl$	57.36	3.02	10.57	57.47	3.04	10.61
XXIV	Pht-L-Ala	68	221–223	0.56	+46.4	$C_{20}H_{14}N_3O_3SCl$	58.32	3.40	10.21	58.12	3.39	10.18
XXV	Pht-L-Ser	58	191–193	0.63	+33.8	$C_{20}H_{14}N_3O_4SCl$	56.14	3.27	9.82	56.39	3.29	9.86
XXVI	Pht-L-Val	63	211–213	0.68	+42.9	$C_{22}H_{18}N_3O_3SCl$	60.07	4.10	9.56	60.20	4.11	9.59
XXVII	Pht-L-Leu	65	224–226	0.51	+55.2	$C_{23}H_{20}N_3O_4SCl$	60.86	4.41	9.26	60.68	4.40	9.24
XXVIII	Tos-Gly	67	195–197	0.47	—	$C_{18}H_{16}N_3O_3S_2Cl$	51.31	3.80	9.96	51.19	3.78	9.94
XXIX	Tos-L-Ala	62	204–206	0.44	+40.2	$C_{19}H_{18}N_3O_3S_2Cl$	52.35	4.13	9.64	52.46	4.14	9.66
XXX	Tos-L-Val	57	214–216	0.58	+51.3	$C_{21}H_{22}N_3O_3S_2Cl$	54.37	4.74	9.06	54.21	4.72	9.02
XXXI	Tos-L-Leu	55	188–190	0.62	−42	$C_{22}H_{24}N_3O_3S_2Cl$	55.29	5.03	8.80	55.01	5.03	8.78
XXXII	Tos-L-Phe	61	202–204	0.43	−69.4	$C_{25}H_{22}N_3O_3S_2Cl$	58.65	4.30	8.21	58.49	4.29	8.18
XXXIII	Gly	62	232–234	0.66	—	$C_{11}H_{10}N_3OSCl$	49.35	3.74	15.70	49.17	3.74	15.68
XXXIV	L-Ala	58	214–215	0.61	+73.8	$C_{12}H_{12}N_3OSCl$	51.15	4.26	14.92	51.38	4.28	14.96
XXXV	L-Ser	55	205–206	0.72	+55.6	$C_{12}H_{12}N_3O_2SCl$	48.40	4.03	14.12	48.28	4.02	14.09
XXXVI	L-Val	64	236–238	0.65	+30.9	$C_{14}H_{16}N_3OSCl$	54.28	5.17	13.57	54.03	5.15	13.53
XXXVII	L-Leu	59	226–227	0.70	+47.5	$C_{15}H_{18}N_3OSCl$	55.64	5.56	12.98	55.49	5.54	12.95
XXXVIII	Tos-L-Ala-Gly	51	247–249	0.51	+60.3	$C_{21}H_{21}N_4O_4S_2Cl$	51.17	4.26	11.37	50.94	4.25	11.33
XXXIX	Tos-L-Ala-L-Ala	54	255–257	0.53	+45.4	$C_{22}H_{23}N_4O_4S_2Cl$	52.12	4.54	10.06	51.99	4.54	10.05
XL	Tos-L-Ala-L-Ser	61	241–243	0.48	−66.8	$C_{22}H_{23}N_4O_5S_2Cl$	50.52	4.40	10.72	50.38	4.39	10.69
XLI	Tos-L-Ala-L-Val	58	261–263	0.55	−70.7	$C_{24}H_{27}N_4O_4S_2Cl$	53.88	5.05	10.48	53.67	5.04	10.45
XLII	Tos-L-Ala-L-Leu	52	270–272	0.46	+52.4	$C_{25}H_{29}N_4O_4S_2Cl$	54.69	5.29	10.21	54.79	5.30	10.24

(10 ml) added. The mixture was stirred for 20 min at room temperature then cooled to 0°C and the precipitated triethylammonium chloride filtered off and the solution washed successively with water, $NaHCO_3$ (3%), water and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residual material recrystallized from ethanol-water (1 : 1) mixture. The products (XIII–XVII and XXXIII–XXXVII) gave positive ninhydrin reaction.

General Procedure for the Synthesis of 2-(N-Tos-dipeptidyl)-amino-4-*p*-tolyl-(or 4-*p*-chlorophenyl-) thiazoles (XVIII–XXII and XXXVIII–XLII)

N-Tos-L-serine (0.01 mole) with 2-(aminoacyl)amino-4-*p*-tolylthiazoles (XIII–XVII, 0.01 mole), and N-Tos-L-alanine (0.01 mole) with 2-(aminoacyl)amino-4-*p*-chlorophenylthiazoles (XXXIII–XXXVII, 0.01 mole) were dissolved in DMF (50 ml). The mixture was cooled to −5°C and DCC (0.013 mole) added. The mixture was stirred for 1 h at 0° and for 2 hrs. at 20°C, then left overnight at room temperature and then worked up as described for synthesis of (III–XII). The dipeptides (XVIII–XXII and XXXII–XLII) were recrystallized from ethanol-water (1 : 1) mixture. Most of the dipeptides were easily soluble in alcohols, DMF, dioxane and DMSO and insoluble in water and ether. All dipeptides (XVIII–XXII and XXXVIII–XLII) were chromatographically homogeneous (TLC-pure) when developed with iodine solution or benzidine and showed negative ninhydrin, silver nitrate and hydroxamate reactions. Complete acid hydrolysis of (XVIII) (6N HCl, 24 h) followed by subsequent chromatograpy afforded L-serine and glycine (two positive spots with ninhydrin).

Biological Screening Results

The antimicrobial activity of synthesized compounds was determined using the hole plate and filter paper disc methods[7–10]. Compounds (III–XLII) were tested against different types of gram-positive, gram-negative microorganisms and fungi, *e.g. Bacillus subtilis* (ICC-strain), *B. mycoid* (USSR), *B. cereus* (NRRL-B-569), *Escherichia coli* (NRLL-B-210), *Salmonella typhosa* (NRRL-B-573) and *Penicillum chrysogenum.*

2-(N-Tos-aminoacyl) amino-4-p-tolyl-(or 4-*p*-chlorophenyl-) thiazoles (X, XI and XXXI), 2-(N-Tos-L-Ser-L-Val)-amino-4-p-tolylthiazole (XX) and 2-(L-Ser) amino-4-p-chlorophenylthiazole (XXXV) showed maximum activity (at MIC 25–50 μg/ml) against *B. subtilis, B. mycoids, B. cereus, E. coli* and inactive against *Salm. typhosa* and *Pen. chrysogenum.*

2-(Aminoacyl) amino-4-*p*-tolyl-(or 4-*p*-chlorophenyl-) thiazoles (XIV, XV and XXXVI) and 2-(N-Tos-L-Ser-L-Leu)-4-*p*-tolylthiazole (XXI) were found to be active against *B. subtilis, B. mycoids, B. cereus* and *Pen. chrysogenum* (at MIC 75–100 μg/ml). 2-(L-Leu) amino-4-p-tolyl- (or 4-p-chlorophenyl-) thiazole (XVI and XXXVII) and 2-(N-Tos-dipeptidyl)

amino-4-*p*-chlorophenylthiazoles (XL–XLI) were found to be active (at MIC 125–150 μg/ml) against *B. subtilis*, *B. mycoids* and inactive against the other types of tested micro-organisms. The remaining compounds were inactive.

The present investigation revealed that introduction of N-Tos-amino acid or free aminoacyl or N-Tos-dipeptide residues in combination with 4-*p*-tolyl-2-aminothiazole or 4-*p*-chlorophenyl-2-aminothiazole moieties gave compounds of novel, specific and improved biological properties. Removing the phthalyl group of 2-(N-Pht-aminoacyl) amino-4-*p*-tolyl-(or 4-*p*-chlorophenyl-) thiazoles by hydrazinolysis produced biologically active compounds.

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