Synthesis of Chiral Fused Heterocyclic Compounds Containing 1,2,4-Triazole Ring

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A series of new chiral (*S*)-3-aryl-6-pyrrolidin-2-yl-[1,2,4]triazolo[3,4-*b*]thiadiazole (**II$_{1-5}$**), (*S*)-1-(3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)-ethylamine (**II$_{6-8}$**) and (*S*)-1,2-bis(3-aryl-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazol-6-yl)-ethylamine (**II$_{9-11}$**) were prepared by the condensation of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles with different L-amino acids in the presence of phosphorus oxychloride and evaluated for their antibacterial activity.

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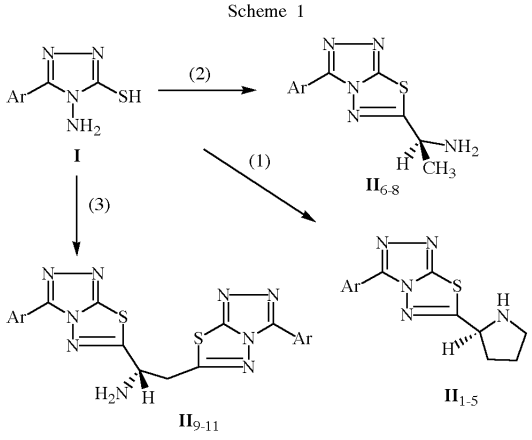
The influence of stereospecificity in the biological activity of enzyme inhibitors and in compounds binding to receptors is a well-known fact in the field of drug action[1]. S-Triazoles and 1,3,4-thiadiazoles are reported to exhibit a broad spectrum of biological activities[2-8]. In recent years bridge head nitrogen heterocycles have received much attention because of their biological activities[9-11]. [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles have been synthesized by Golgolab *et al*.[12]. However, the synthesis of chiral fused heterocyclic compounds containing s-triazole and 1,3,4-thiadiazole has not been reported. In order to study the relationship between stereochemistry and the performance of antibiotics, we have synthesized some new (*S*)-3-aryl-6-pyrrolidin-2-yl-[1,2,4]triazolo[3,4-*b*]thiadiazole (**II$_{1-5}$**), (*S*)-1-(3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)-ethylamine (**II$_{6-8}$**) and (*S*)-1,2-bis(3-aryl-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazol-6-yl)-ethylamine(**II$_{9-11}$**) by the condensation of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles with L-proline, L-alanine and L-aspartic acid in the presence of phosphorus oxychloride (Scheme 1).

Scheme 1



(1). L-Proline (2). L-alanine (3). L-Aspartic acid

Compounds **II** were characterized by IR, ^{1}H-NMR and MS data. In the IR spectra, the SH absorption of (**I**) is not observed in the spectrum corresponding to structure (**II**). The ^{1}H-NMR spectra of (**II**) are in conformity with the assigned structures. Analyzing the MS spectra of **II**, we found that under EI conditions the molecular ion was usually not observed.

Ions of (M+1) were observed for compounds (**II$_{9-11}$**) under FAB conditions. These observations suggest that conjugated systems are present in compounds (**II$_{9-11}$**) whose molecular ions have lower stability. When (**I**) was reacted with L-proline, the molecular ion of the product was of average intensity.

The reaction of (**I**) with L-amino acid was difficult when the aromatic group contained electron-withdrawing groups, but it was easy when the aromatic group

Table 1
Physical Constants of Compounds **II$_{1-11}$**

Compd.	Yield (%)	M.P.(°C)	$[\alpha]_D^{20}$ x10^{-3}(g/mL)	Anal. %: Found/(Calcd.) C	H	N
II$_1$	58	114-115	-96.7 (0.21, $CHCl_3$)	57.31(57.54)	4.75(4.83)	26.11(25.81)
II$_2$	45	208(dec.)	+23 (0.37, DMSO)	49.48(49.35)	3.82(3.82)	26.34(26.57)
II$_3$	48	141-142	+15.3 (0.59, DMSO)	57.28(57.12)	5.48(5.43)	21.09(22.21)
II$_4$	30	112-113	-72 (0.21, $CHCl_3$)	55.98(55.79)	4.91(5.02)	23.11(23.24)
II$_5$	28	135-136	+63.5 (0.30, DMSO)	56.03(55.79)	5.13(5.02)	23.38(23.24)
II$_6$	25	193-194	+93 (0.22, DMSO)	52.14(52.35)	4.79(4.76)	25.23(25.44)
II$_7$	40	210(dec.)	+78 (0.19, DMSO)	45.67(45.51)	3.48(3.47)	28.64(28.95)
II$_8$	40	126(dec.)	+26 (0.37, DMSO)	45.38(45.51)	3.59(3.47)	28.61(28.95)
II$_9$	51	138-140	+250 (0.12, DMSO)	45.17(44.85)	2.58(2.45)	29.13(28.77)
II$_{10}$	36	128-130	+90 (0.44, DMSO)	51.97(52.26)	3.76(3.78)	25.17(24.94)
II$_{11}$	44	125-126	+113.6 (0.08, DMSO)	54.17(53.91)	3.44(3.39)	28.56(28.29)

contained electron-donating groups. This is because the electron-donating group may enhance the nucleophilicity of the amino group in (**I**). In the condensation of (**I**) with L-amino acid, the carbonyl of the L-amino acid can be activated by phosphorus oxychloride.

Table 2
Spectral Data of Compounds **II$_{1-11}$**

Compd.	IR (cm^{-1})	^{1}HNMR (δ, ppm)	MS (m/z)
II$_1$	3320, 1619, 1520, 1468, 1249, 690	1.5-2.5(m, 7H, CH, CH_2), 4.2(bs, 1H, NH), 7.8-8.4(m, 5H, ArH)	271(M^+, 32.06), 229 (11.14), 177(11.74), 103(22), 70(100)
II$_2$	3421, 1605, 1480, 1319, 688	1.7-2.6(m, 7H, CH, CH_2), 4.6(bs, 1H, NH), 7.5-8.2(m, 4H, ArH)	316(M^+, 2.04), 286 (21.11), 207(66.12), 192(100)
II$_3$	3432, 1605, 1509, 1254, 680	1.0-1.6(m, 10H, CH, CH_2, CH_3), 3.35-3.65 (q, 2H, J=10Hz, CH_2), 4.0 (bs, 1H, NH), 6.81-8.19 (m, 4H, ArH)	315(M^+, 1.51), 269(3.26), 149 (100)
II$_4$	3422, 1654, 1481, 1260	1.35-2.05(m, 7H, CH, CH_2), 3.86(s, 3H, OCH_3), 4.10(bs, 1H, NH), 6.55-7.45(m, 4H, ArH)	301(M^+, 25.45), 256(68.85), 192 (75.38), 64(100)
II$_5$	3440, 1597, 1493, 1238, 691	1.00-1.35 (m, 7H, CH,CH_2), 4.70 (s, 2H, OCH_2), 5.21 (bs, 1H, NH), 6.65-7.40 (m, 5H, PhH)	301(M^+, 1.5), 256(27.55), 245 (100), 192 (45.26)
II$_6$	3422, 1598, 1493, 1238, 690	0.90-1.10 (d, 3H, J=10.1Hz, CH_3), 2.91-3.22 (m, 1H, CH), 4.65 (s, 2H, OCH_2), 5.51(bs, 1H, NH), 6.71-7.53 (m, 5H, PhH)	275(M^+, 1.5), 245(71.48), 187 (15.53), 94(100)
II$_7$	3434, 1593, 1483, 1318, 685	1.29-1.50 (d, 3H, J=10.1Hz, CH_3), 3.31-3.62 (m, 1H, CH), 5.51(bs, 1H, NH), 7.51-7.23 (m, 5H, ArH)	256 (M+, 7.34), 181(18.37), 91(100)
II$_8$	3422, 1605, 1508, 1311	1.33-1.51 (d, 3H, J=10.2Hz, CH_3), 3.30-3.60 (m, 1H, CH), 6.62 (bs, 2H, NH_2), 7.4-7.8 (m, 4H, ArH)	290 (M^+, 0.4), 232 (4.69), 192 (100), 176 (20.95)
II$_9$	3422, 1608, 1550, 1481, 1260, 690	3.31-3.72 (m, 3H, CH, CH_2), 6.50 (bs, 2H, NH_2), 7.61-8.23 (m, 4H, ArH)	FAB, 535(M^+, 0.2), 457(1.5), 190(8),154 (100)
II$_{10}$	3442, 1606, 1481, 1258, 671	3.12-3.55 (m, 3H, CH, CH_2), 3.80(s, 3H, OCH_3), 4.71(bs, 2H, NH_2), 6.9-7.8 (m, 8H, ArH)	FAB, 506(M+1, 100), 445 (14), 207(12)
II$_{11}$	3424, 1603, 1469, 1250, 689	2.71-3.93 (m, 3H, CH, CH_2), 4.80 (bs, 2H, NH_2), 7.23-8.31 (m, 10H, PhH)	FAB, 446(M+1, 100), 445 (M^+, 14), 307(26)

Table 3
Results of Antibacterial Activity of **II$_{1-11}$**

Compd.	Ar substituent	E. *coli*	B. *subilis*	S. *aureus*
II$_1$	H	++	-	-
II$_2$	*m*-NO_2	+	-	-
II$_3$	*p*-EtO	++	+	++
II$_4$	*o*-MeO	+	+	++
II$_5$	1-OCH_2	++	+	++
II$_6$	1-OCH_2	++	+	+
II$_7$	*m*-NO_2	+	-	-
II$_8$	*p*-NO_2	+	-	+
II$_9$	*p*-NO_2	+	-	+
II$_{10}$	*o*-MeO	++	+	++
II$_{11}$	H	++	-	-
Penicillin		-	++	++
Gentamicin		++	++	+

antibacterial activity: "++", strong; "+", medium strong; "-", no inhibition.

EXPERIMENTAL

Melting points were recorded on a X_4 microscopic melting point apparatus and are uncorrected. Elemental analyses were obtained on PE-240C instrument. IR spectra on VECTOR-22 or FTS-40 (potassium bromide). The ^{1}H NMR spectra were recorded on EM-60MHZ or Bruker AC100MHz spectrometer in DMSO-d_6 with TMS as internal reference. The MS data were recorded on FABMS-NBA or HP5989(EI) instrument. The optical rotations were measured in a 1-dm cell with WZZ-1 polarimeter. 3-Aryl-4-amino-5-mercapto-1,2,4-triazoles(I) were prepared by the known procedure[13].

General Procedure for the Preparation of Compounds **II**.

A mixture of 3-aryl-4-amino-5-mercapto-1,2,4-triazole (2 mmol), L-amino acid (2.5 mmol) and phosphorus oxychloride (18 ml) was reacted for 3-4 hours in oil bath at 90-95 °C. The excess phosphorus oxychloride was removed under reduced pressure and the remaining mixture poured into ice water. The solid was separated from the mixture, washed with sodium bicarbonate solution and then with water, recrystallized from ethyl acetate/-triethylamine/methanol to yield compounds **II**. Their physical properties and analytical results are listed in Table 1 and Table 2.

Antibacterial Activity.

All compounds **II$_{1-11}$** were tested for antibacterial activity against E. *coli*, B. *subilis* and S. *aureus* by plate technique. The concentration of the test compounds was 200 ppm. Their antibacterial activities were compared with standard Penicillin and Gentamicin. It was found that **II$_3$**, **II$_5$** and **II$_{10}$** are more active than the others and comparable to that of Penicillin and Gentamicin (Table 3).

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