Asian Journal of Chemistry Vol. 17, No. 4 (2005), 2251–2256

Synthesis and Antimicrobial Activity of Some 2-(4′,5′-Disubstituted Thiazolo)-1H-Isoindole-1,3(2H)-Diones/Succinimides

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4-substituted thiazole (I) derivatives were fused with 2-substituted-1H-isoindole-1,3(2H)-dione/succinic anhydride which converted to 2-(4′-substituted thiazolo)-1H-isoindole-1,3(2H)-dione (II) and 2-(4′-substituted thiazolo)succinimide (III). C-5 carbon of the thiazole nuclei was then blocked by acid chlorides of N-protected amino acids to give the final compound namely 2-[4′-substituted-5′-(2″-alkyl substituted acetylamidophenyl)thiazolo]-5′-(2″-alkyl substituted acetylamidophenyl)thiazolo]-1H-isoindole 1,3(2H)-diones (IV) and 2-[4′-substituted-5′-(2″-alkyl substituted-acetylamido phenyl)thiazolo]succinimides (V). All the synthesized compounds were evaluated for antibacterial and antifungal activities.

Key Words: Synthesis, Antimicrobial activity, Substituted thiazoles.

INTRODUCTION

Compounds of immense pharmaceutical value are synthesized from amino acids taking advantage of biodegradiability and biocompatability of amino acids. Recent literature surveys have revealed that amino acid substituted thiazole derivatives are antimicrobial[1, 2] while thiazole derivatives exhibits antiviral[3, 4], antifungal[5], antibacterial[6, 7], herbicidal[8] and antiinflammatory[9] activities.

These observations prompted us to synthesize some thiazole derivatives incorporated with amino acid residues.

EXPERIMENTAL

The IR spectra were taken on Shimadzu in KBr pellets. PMR was performed on DX X-300 spectrophotometer in $CDCl_3$ with chemical shifts in δ ppm. The melting points were taken in open capillaries and are uncorrected.

Different 4-substituted aminothiazoles (1) were synthesized by previously reported method[10].

Preparation of 2-(4′-methyl thiazolo)-1H Isoindole 1,3-(2H)-Dione (IIa)

4-Methyl-2-amino thiazole (0.004 mol) and of phthalic anhydride (0.006 mol) were taken in a pyrex test tube and immersed the lower part of the tube in an oil bath, which had previously been heated to 180–185°C. The mixture was stirred occasionally during the first 10 min and phthalic anhydride, which sublimed on the walls of the test tube was pushed down into the reaction mixture. The mixture was left undisturbed for 5 min. After 15 min the test tube was removed from the oil bath, when the liquid mass solidified. The solid obtained was then washed with cold water, dried and recrystallized from hot water.

m.p. = 182–184°C; yield = 92%. Anal. (%) Calcd. for $C_{12}H_8N_2O_2S$: C, 59.01; H, 3.72; N, 11.47. Found: C, 58.98; H, 3.68; N, 11.43. IR (KBr, cm^{-1}): 1445 ν(N=C=S), 1790, 1710 ν(>C=O, phthalimido). PMR ($CDCl_3$): 3H, CH_3, δ 2.66 (s), 1H, C_5 carbon 7.26 (s), 4H, ArH, δ 7.59 (s)–8.82 (m).

Preparation of 2-(4′-methyl thiazolo)succinimide (IIIa)

Following the same procedure as in **2a**, 4-methyl 2-amino thiazole (0.004 mol) and succinic anhydride (0.01 mol) were fused together the tube in an oil bath, which had previously been heated to 180–185°C.

m.p. = 189°C; yield = 92%. Anal. (%) Calcd. for $C_8H_8N_2O_2S$: C, 48.97; H, 4.08; N, 14.28. Found: C, 48.95; H, 4.06; N, 14.25. IR (KBr, cm^{-1}): 1445 ν(N=C=S), 1780, 1710 ν(>C=O, succinimido). PMR: 3H, CH_3, δ 2.66 (s), 1H, C_5 carbon δ 7.56 (s), 4H, CH_2—CH_2, δ 3.88 (s, broad).

Other derivatives, *i.e.*, **IIb–IId** and **IIIb–IIId** were synthesized in a similar way. The physical data are given in Table-1.

TABLE-1
CHARACTERIZATION DATA OF SYNTHESIZED COMPOUNDS

Compd. No.	R	m.p. (°C)	Yield (%)	m.f.	% Nitrogen	
					Calcd.	Found
IIa	CH_3	182–184	92	$C_{12}H_8N_2O_2S$	11.47	11.43
IIb	C_6H_5	154	92	$C_{17}H_{10}N_2O_2S$	9.15	9.13
IIc	$C_6H_5CH_2$	165–167	91	$C_{18}H_{12}N_2O_2S$	8.75	8.74
IId	C_6H_4OH	185–186	90	$C_{17}H_{10}N_3O_2S$	8.69	8.70
IIIa	CH_3	189	92	$C_8H_8N_2O_2S$	14.28	14.25
IIIb	C_6H_5	140	93	$C_{13}H_{10}N_2O_2S$	10.85	10.83
IIIc	$C_6H_5CH_2$	204	91	$C_{14}H_{12}N_2O_2S$	10.29	10.26
IIId	C_6H_4OH	180–181	89	$C_{13}H_{10}N_3O_2S$	10.21	10.22

Preparation of 2 [(4′-methyl-5′-acetylamido phenyl)thiazolo]-1H-isoindole-1,3(2H)-dione (IVa)

Benzoyl glycine (0.01 mol) was taken in a dry round-bottomed flask and to this was added 0.01 mol of thionyl chloride. The contents was refluxed for 2 h, the solution was cooled and excess thionyl chloride was distilled off under reduced pressure. To the acid chloride so formed were then added anhydrous potassium carbonate (0.01 mol), dry acetone (15 mL) and 0.01 mol of (**IIa**). The reaction mixture after refluxing for 3–5 h excess solvent was distilled off and the solution was left overnight. The solid so obtained was filtered, dried and recrystallized from acetone.

m.p. > 230°C; yield = 68%. Anal. (%) Calcd. for $C_{21}H_{15}N_3O_4S$: C, 62.33; H, 3.70; N, 10.37. Found: C, 62.20; H, 3.71; N, 10.35. IR (KBr, cm^{-1}): 1450 ν(N═C═S), 1790, 1710 ν(phthalimido), 1680 ν(>C═O, amido), 1620 ν(C═O— stretching aminoacid), 3320 ν(NH— bonded). PMR ($CDCl_3$): 3H, CH_3, δ 2.66 (s), 2H, CH_2, δ 3.18 (d), 1H, NH, δ 6.85 (t), 9H, ArH, δ 7.52–8.11 (m).

Synthesis of 2-[4′-methyl-5′-(2″-methyl)acetylamido phenylthiazolo]-1H-isoindole-1,3(2H)-dione (IVc)

This was synthesized in a similar way as for compound **IVa** except that benzoyl alanine was the N-protected amino acid.

m.p. > 230°C; yield = 52%. Anal. (%) Calcd. for $C_{22}H_{17}N_3O_4S$: C, 63.01; H, 4.05; N, 10.02. Found: C, 63.03; H, 4.04; N, 10.01. IR (KBr, cm^{-1}): 1450 ν(N═C═S), 1790, 1710 ν(>C═O, phthalimido), 1680 ν(>C═O, amido), 1620 ν(>C═O—, stretching amino acid), 3310 ν(NH-bonded). PMR ($CDCl_3$): 3H, CH_3, δ 2.59 (s), 1H, CH—CH_3, δ 4.64 (s, broad), 3H, CH—CH_3, δ 2.09 (d), 1H, NH δ 6.79 (d), 9H, ArH, δ 7.59–8.20 (m).

Preparation of 2-[4′-methyl-5′-(2″-methyl)acetylamido phenyl)thiazolo] succinimide (Ve)

Benzoyl alanine (0.01 mol) was taken in a dry round-bottomed flask and was refluxed for 2 h with 0.01 mol of thionyl chloride. Excess thionyl chloride was distilled off under reduced pressure and to this acid chloride so formed was then added (**IIIa**). The reaction mixture was further refluxed for 3–4 h, in presence of anhydrous potassium carbonate (0.01 mol) and dry acetone (10 mL). Excess solvent was distilled off and the solution was then left overnight. The solid obtained was filtered, washed with ice-cold water, dried and recrystallized from acetone.

m.p. > 220°C; yield = 57%. Anal. (%) Calcd. for $C_{18}H_{17}N_3O_4S$: C, 58.22; H, 4.58; N, 11.32. Found: C, 58.24; H, 4.53; N, 11.30. IR (KBr, cm^{-1}): 1460 ν(N═C═S), 1780, 1720 ν(>C═O, phthalamido), 1620 ν(C═O, amino acid), 1675 ν(>C═O, amido), 3320 ν(—NH, stretching bonded), PMR ($CDCl_3$): 3H, CH_3, δ 2.60 (s), 1H, CH—CH_3 δ 4.52 (s, broad), 3H, CH—CH_3, δ 2.15 (d), 4H, CH_2—CH_2, δ 3.88 (s, broad), 1H, NH, δ 6.82 (d), 5H, ArH, δ 7.72–8.25 (m).

Other compounds were synthesized in a similar way. The physical data are given in Table-2.

Antimicrobial Activity

The compounds were screened for their antibacterial and antifungal activity using the Kirby-Bauer disc diffusion technique[11, 12]. The antibacterial activity was done at 250 μg/disc with *Staphylococcus aureus, Psuedomonas, Klebsiella* species, *Proteus vulgaris* and *Escherichia coli* as the test strains (Table-3).

TABLE-2
CHARACTERIZATION DATA OF SYNTHESIZED COMPOUNDS

Compd.	R	R′	m.p. (°C)	Yield (%)	m.f.	% Nitrogen	
						Calcd.	Found
IVa	CH_3	H	> 230	68	$C_{21}H_{15}N_3O_4S$	10.37	10.35
IVb	C_6H_5	H	> 215	62	$C_{26}H_{17}N_3O_4S$	8.99	8.96
IVc	$C_6H_5CH_2$	H	190	65	$C_{26}H_{17}N_3O_5S$	8.73	8.72
IVd	C_6H_4OH	H	> 230	64	$C_{26}H_{17}N_3O_5S$	8.28	8.25
IVe	CH_3	CH_3	> 230	52	$C_{22}H_{17}N_3O_4S$	10.02	10.01
IVf	C_6H_5	CH_3	> 230	58	$C_{27}H_{19}N_3O_4S$	8.73	8.74
IVg	$C_6H_5CH_2$	CH_3	> 240	51	$C_{28}H_{21}N_3O_4S$	8.48	8.46
IVh	C_6H_4OH	CH_3	> 230	54	$C_{27}H_{19}N_3O_5S$	8.45	8.43
Va	CH_3	H	> 230	69	$C_{17}H_{15}N_3O_4S$	11.76	11.75
Vb	C_6H_5	H	183–184	64	$C_{22}H_{17}N_3O_4S$	10.02	10.01
Vc	$C_6H_5CH_2$	H	198–201	65	$C_{23}H_{19}N_3O_4S$	9.69	9.67
Vd	C_6H_4OH	H	95–97	62	$C_{22}H_{17}N_3O_5S$	9.65	9.63
Ve	CH_3	CH_3	> 220	57	$C_{18}H_{17}N_3O_4S$	11.32	11.30
Vf	C_6H_5	CH_3	225–227	53	$C_{23}H_{19}N_3O_4S$	9.69	9.68
Vg	$C_6H_5CH_2$	CH_3	189–190	56	$C_{24}H_{21}N_3O_4S$	9.39	9.35
Vh	C_6H_4OH	CH_3	160	60	$C_{23}H_{19}N_3O_5S$	9.37	9.35

TABLE-3
ANTIBACTERIAL ACTIVITY

Compd. No.	*E. coli*	*S. aureus*	*P. vulgaris*	*Pseudomonas*	*Klebsiella*
IVa	±	±	–	–	–
IVb	±	±	±	–	–
IVc	±	±	±	±	±
IVd	±	±	±	±	±
IVe	±	±	–	±	–
IVf	±	±	±	–	–
IVg	±	±	±	±	±
IVh	±	±	±	±	±
Va	–	–	–	–	–
Vb	–	–	–	–	–
Vc	±	±	–	–	–
Vd	±	±	–	±	–
Ve	–	–	–	–	–
Vf	–	–	–	–	–
Vg	±	±	–	–	–
Vh	±	±	±	±	–

Concentration = 250 μg/disc
– = < 8 mm
± = 8–12 mm (maximum zone of inhibition)
Standard drugs = ampicillin, streptomycin (> 20 mm)
Incubation = 24 h, 37°C

The antifungal activity was done at 50 μg/disc against *Candida albicans*, *Aspergillus niger* and *Penicillium* (Table-4).

TABLE-4
ANTIFUNGAL ACTIVITY

Compd. No.	*Candida albicans*	*Penicillin* sp.	*Aspergillus niger*
IVa	–	+	–
IVb	±	++	–
IVc	±	+	–
IVd	±	+	–
IVe	–	±	–
IVf	±	±	–
IVg	±	++	–
IVh	±	±	–
Va	–	+	–
Vb	–	++	–
Vc	–	+	–
Vd	–	±	–
Ve	–	±	–
Vf	–	±	–
Vg	–	±	–

Concentration = 50 μg/disc
++ = strongly active (no fungal colony)
+ = moderately active (one colony)
± = active (two colonies)
– = inactive (heavy colony)
Standard Drugs = griseofulvin, gentamycin (no fungal colony)
Incubation = 72 h, 37°C

RESULTS AND DISCUSSION

The IR spectra of compound **IVa** showed extra vibrations at 1620 and 1680 cm^{-1}, which are characteristic of carbonyl groups present as an amido group and as part of an amino acid. A higher frequency band at 3320 cm^{-1} was accounted for a bounded NH group. This confirmed the blockage of C-5 carbon of the thiazole nuclei with an N-protected amino acid. Similar vibrations were observed for the other derivatives, *i.e.*, **IVc** and **Ve.** The PMR spectra of compound **IVa** gave a singlet at δ 2.66 for the three protons of the methyl group at C-4 carbon while a doublet at δ 3.18 for $—CH_2$ and a triplet at δ 6.85 confirmed C-4 in the presence of $—CH_2NH$ group. Such a linkage can arise by the presence of glycine as the amino acid, which enters at C-5 carbon of the thiazole nuclei. Multiplet between δ 7.52–8.11 were nine aromatic protons.

The PMR spectra of compound **Vc** gave a broad singlet at δ 4.64 for a single proton and a doublet at δ 2.09 for the three methyl protons. The NH proton also appeared as a doublet at δ 6.79 indicating the presence of $—NH—CH(CH_3)—$ group. A multiplet between δ 7.59–8.20 was of the nine aromatic protons.

2-[4'-methyl-5'-(2''-methyl)acetyamidophenyl)thiazolo]succinimide (**Ve**) in which position C-5 was blocked with N-benzoyl alanine, signals at δ 2.15 as a doublet and a broad singlet at δ 4.52 were of the —$CH(CH_3)$— group while a singlet at δ 2.60 were the three protons of the methyl group. The singlet proton of —NH appeared as a doublet at δ 6.82. A very down field signal at δ 3.88 as a broad singlet were of the four protons of the —CH_2—CH_2 linkage of the succinimido group. Presence of this signal further confirmed the formation of this derivative. Multiplet between δ 7.72–8.25 were of the five aromatic protons.

Biological Activity

Most of the compounds showed moderate activity against all the bacterial strains with zone size between 8–12 mm while compounds **Va, Vb, Ve** and **Vf** were inactive after 24 h incubation at 37°C.

However, the derivatives were more effective against the fungi. Maximum inhibition, *i.e.*, no fungal colony was observed by compounds **IVb, IVg** and **Vb** against *Penicillium* while **IVa, IVc, IVd** and **Vb** were also active with growth of a single colony. Other derivatives showed lesser inhibition (**IVe, IVf** and **Vd–Vf**).

Against *C. albicans,* six compounds namely **IVb, IVc, IVd, IVg** and **IVh** were moderately active. Rest of the compounds were inactive. Inactivity was also observed against *A. niger.*

A correlation between structure and biological activity reveals that compounds with R = C_6H_5—, $C_6H_5CH_2$— and C_6H_4OH showed better results than a methyl substituent.

ACKNOWLEDGEMENTS

The authors are thankful to the Director, CDRI, Lucknow for the spectral analysis and Head, Department of Microbiology, S.N. Medical College for the antimicrobial activity. Thanks are also duw to the Head, Department of Chemistry for providing necessary facilities.

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(*Received*: 11 September 2004; *Accepted*: 13 June 2005) AJC-4245