Asian Journal of Chemistry Vol. 4, No. 3 (1992), 629–635

Synthesis and Biological Activity of Some New Substituted 2-(aminoacyl) Aminobenzoxazoles and Dipeptide Derivatives

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The synthesis of 2-(N-Pht-aminoacyl) aminobenzoxazoles (VI–IX) and 2-(N-Pht-aminoacyl) amino-5-chloro-(or 6-bromo- or 5-chloro-6-bromo-5-nitro-) benzoxazoles (X–XXV) has been achieved via the carbodiimide (DCC) method. Hydrazinolysis of the N-phthalyl derivatives (VI–XXV) affords the free aminoacyl derivatives (XXVI–XLV). Some Pht-dipeptide derivatives (XLVI–LV) has been synthesized using the DCC method. Many of the prepared compounds were found to be active against a number of microorganisms.

INTRODUCTION

Several of the heterocyclic compounds such as quinoxalines, thiazoles and benzoxazoles were observed to possess biological and pharmacological properties[1–4]. In view of the marked antibacterial activity of the benzoxazole derivatives and in continuation of our previous work[5–8], we had synthesized a new class of 2-(aminoacyl) aminobenzoxazoles (VI–LV). These compounds were tested for their biological activities.

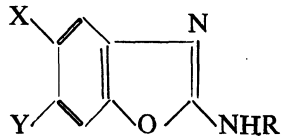
RESULTS AND DISCUSSION

For preparation of 2-(N-phthalylaminoacyl) aminobenzoxazoles (VI–IX) or the corresponding 2-amino-5-chloro- (or 6-bromo- or 5-chloro-6-bromo- or 5-nitro-) benxoxazoles (X–XXV), the appropriate N-phthalyl-amino acid was reacted with 2-aminobenzoxazole (I) or 2-amino-5-chloro-(or 6-bromo- or 5-chloro-6-bromo- or 5-nitro-) benzoxazoles (II–V) in dioxane using the dicyclohexylcarbodiimide (DCC) procedure. All the products (VI–XXV) were obtained in crystalline form in 56–83% yield.

Hydrazinolysis of the N-phthalyl derivatives (VI–XXV) with hydrazine hydrate in ethanol under reflux for 2 hrs afforded the free aminoacyl derivatives (XXVI–XLV) which were obtained in 46–62% yield. Chromatographic studies revealed their homogeneity (positive ninhydrin reaction).

2-(N-Phthalyldipeptidyl) aminobenzoxazoles (XLVI and XLVII) or the corresponding 2-amino-5-chloro- (or 6-bromo- or 5-chloro-6-bromo- or 5-nitro-) benzoxazoles (XLVIII–LV) were prepared by coupling of N-phthalylamino acid with 2-(free aminoacyl) derivatives (XXVI–XLV) in dioxane containing triethylamine using the DCC technique. All the dipeptides (XLVI–LV) were isolated, recrystallized and obtained in 53–72% yield.

The IR, UV and PMR spectra, chromatographic studies and elemental analysis of compounds (VI–LV) were constant with their structures.



Compounds VI–LV

Biological Screening

The antimicrobial activity of the synthesized compounds (VI–LV) were tested using the hole plate and filter paper disc methods[9,10]. The results were tested against gram-positive, gram-negative microorganisms and fungi, and the results were compared with the parent 2-aminobenzoxazoles (I–V).

In the series of 2-aminobenzoxazole, 2-(Pht-L-Leu)aminobenzoxazole (VIII) showed moderate activity against *Bacillus subtilis* and *B. megaterium*, and the activity enhanced against *B. cereus* and *Candida utilis*. 2-(L-Leu)aminobenzoxazole (XXVIII) was found to give promising activity against *Staphylococcus aureus* only. These results led to the conclusion that removal of the phthalyl group leads to markable decrease of the activity towards some microorganisms and cancels their activities towards others.

In the compounds containing 2-amino-5-chlorobenzoxazole moiety, the phthalyl derivatives of L-Ala and L-Leu (XXX and XXXII) exhibited moderate activities against all the tested microorganisms except *B. cereus*. 2-(N-Aminoacyl) derivatives (XXX–XXXIII) showed highly antimicrobial action towards *B. subtilis*, *S. aureus* and *B. megaterium*. The dipeptides (XLVIII and XLIX) exhibited high activity against all the tested microorganisms except *C. utilis*. These results led to the conclusion that introduction of chlorine atom in 5-position of the benzoxazole moiety ring gave aminoacyl or dipeptide derivatives of interesting biological properties.

In the series of 2-amino-6-bromobenzoxazole, the Pht-derivative of L-Ala (XIV) and the free aminoacyl derivatives (XXXIV–XXXVII) showed moderate activities against *B. subtilis*, *B. megaterium* and *S. aureus*.

In the case of 2-amino-5-chloro-6-bromobenzoxazole, all the Pht-derivatives (XVIII–XXI) showed moderate activities against *B. subtilis*, *B. megaterium* and *S. aureus*. 2-(N-Aminoacyl)derivatives (XXXVIII–XLI) showed high activities against all the tested microorganisms except *E. coli*. These results led to the conclusion that incorporating of the chlorine and bromine atoms in the benzoxazole nucleus in combination with amino acid moieties gave new derivatives of enhanced biological activities.

In the series of 2-amino-5-nitrobenzoxazole, the Pht-L-Ala derivative (XXII) showed high activity against *B. subtilis*, *B. cereus* and *B. mega-*

terium and inactive against the remaining microorganisms. The free aminoacyl derivatives (XLII–XLV) were found to be highly active against all the tested microorganisms except *E. coli*. Furthermore, the dipeptide derivatives (LIV and LV) were possessing moderate activities only against *B. subtilis* and *B. megaterium* and were inactive against the other microorganisms.

EXPERIMENTAL

All melting points are uncorrected. Thin-layer chromatography (R_f) was made on Silica Gel-G (BDH) using benzene-ethyl acetate (4 : 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 $[\alpha]_D^{20}$ were taken in a Bellingham Stanley polarimeter, 1 dm tube (C=5) in ethanol (Table 1). The UV spectra were measured with a Unicam SP 8000, the IR spectra (KBr, ν_{max} in cm^{-1}) with a Unicam SP 1200 and PMR data were determined on Varian EM 360L spectrophotometer in DMSO-d_6 and chemical shifts are reported in (δ) ppm relative to TMS as the internal standard. 2-Aminobenzoxazole (I), 2-amino-5-chlorobenzoxazole (II), 2-amino-6-bromobenzoxazole (III), 2-amino-5-chloro-6-bromobenzoxazole (IV) and 2-amino-5-nitrobenzoxazole (V) were prepared according to the procedure described in literature[11,12].

General procedure for synthesis of 2-(N-Pht-aminoacyl)amino-benzoxazoles (VI–IX) and the corresponding derivatives of 2-amino-5-chlorobenzoxazole (X–XIII); 2-amino-6-bromobenzoxazole (XIV–XVII); 2-amino-5-chloro-6-bromobenzoxazole (XVIII–XXI) and 2-amino-5-nitrobenzoxazole (XXII–XXV)

N-Pht-amino acid (0.005 mole) and 2-aminobenzoxazole (I) or its derivatives (II–V, 0.005 mole) were dissolved in dioxane (30 ml). The mixture was cooled to 0°C and dicyclohexylcarbodiimide (1.03 g., 0.005 mol) added, and the mixture was stirred for 3 hrs. at 5°C. The precipitated dicyclohexylurea was filtered off, the filtrate evaporated in vacuo. The residue was recrystallized from ethanol-water (1 : 1) mixture. The products (VI–XXV) were chromatographically homogeneous and did not respond to ninhydrin reaction.

The IR spectrum of 2-(N-Pht-L-Val) aminobenzoxazole (VII) in KBr showed the characteristic bands at: 3320 (CONH); 2960 (CH_3); 1780, 1730 ($\rangle C=O$); 1680, 1540, 1380 (amides I, II and III) and other characteristic bands supporting the structure. The UV spectrum of (VII) in EtOH showed λ_{max} at 212 nm, 253 nm and 293 nm characteristic of the benzo-

xazole moiety. The PMR spectrum in DMSO showed: δ1.25 (s, 6H, $2CH_3$); δ3.22 (s, 1H, CH); δ6.61 (s, 1H, NH) and δ8.1 (s, aromatic protons).

General procedure for synthesis of 2-(N-aminoacyl)aminobenzoxazoles (XXVI–XXIX) and the corresponding derivatives of 2-amino-5-chlorobenzoxazole (XXX–XXXIII); 2-amino-6-bromobenzoxazole (XXXIV–XXXVII); 2-amino-5-chloro-6-bromobenzoxazole (XXXVIII–XLI) and 2-amino-5-nitrobenzoxazole (XLII–XLV)

2-(N-Pht-aminoacyl)aminobenzoxazole (VI–IX, 0.005 mole) or its derivatives (X–XXV) were dissolved in ethanol (20 ml) and hydrazine hydrate (0.8 ml) added. The reaction mixture was refluxed for 2 hrs and left for 24 hrs at room temperature. The residue obtained after evaporation of the solvent was acidified with acetic acid till (pH 6), heat for 1 h on a steam bath and the suspension was diluted with 25 ml of water, cooled to room temperature and filtered off, the filterate was evaporated in vacuo. The residue was recrystallized from ethanol-water. The products (XXVI–XLV) gave positive ninhydrin reaction.

The IR spectrum of 2-(N-L-Ala)amino-5-chloro-6-bromobenzoxazole (XXXVIII) in KBr showed the characteristic bands at: 3340, 3320, 3290 (NH_2, NH, N); 2850, 1460 (CH_3); 1760, 1710 (>C=O) and other bands due to the benzoxazole moiety. The UV spectrum of (XXXVIII) in EtOH showed λ_{max} at 215, 240 and 290. The PMR spectrum of (XXXVIII) in DMSO showed: δ1.85 (s, 3H, CH_3); δ4.2 (s, 1H, CH); δ6.43 (s, 1H, NH); 8.12 (s, 2H, NH_2) and 7.85 (s, aromatic protons).

General procedure for synthesis of 2-(N-Pht-dipeptidyl)aminobenzoxazoles (XLVI–XLVII) and the corresponding derivatives of 2-amino-5-chloro-benzoxazole (XLVIII and XLIX); 2-amino-6-bromobenzoxazole (L and LI); 2-amino-5-chloro-6-bromobenzoxazole (LII–LIII) and 2-amino-5-nitrobenzoxazole (LIV–LV)

N-Pht-amino acid (0.005 mole) and 2-(N-aminoacyl)amino-benzoxazole (XXVI–XXIX, 0.005 mole) or its derivatives (XXX–XLV) were dissolved in dioxane (30 ml). The mixture was cooled to 0°C and DCC (1.03 g, 0.005 mole) added. The mixture was stirred for 2 hrs at 0°C and for 2 hrs at room temperature, then worked up as described for synthesis of (VI–XXV). The dipeptides (XLVI–LV) were recrystallized from ethanol-water (1 : 1) mixture. All the dipeptides (XLVI–LV) gave negative ninhydrin reaction and were chromatographically homogeneous.

The IR spectrum of 2-(N-Pht-L-Val-L-Val)amino-6-bromo-benzoxazole (L) in KBr showed the characteristic bands at 3350 (CONH); 3000 (CH_3); 1760, (>C=O) and other bands confirming the structure. The UV spectrum

of (L) in EtOH showed λ_{max} at 210 nm, 235 nm and 280 nm. PMR spectrum of (L) in DMSO showed: δ1.68 (s. 6H, $2CH_3$); δ4.67 (s, 2H, 2CH); δ8.75 (s, 2H, 2NH); and 7.63 (s, aromatic protons).

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(*Received*: 15 May 1991; *Accepted*: 15 June 1991) AJC-321