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Synthetic and antibacterial studies on some new furanopeptides

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Abstract

A series of new furanopeptides (**3**) are prepared by the coupling of arylsubstituted furoic acids (**1**) with amino acid methyl esters, di and tetra-peptide methyl esters using dicyclohexyl carbodiimide (DCC) as coupling agent. Some of the newly synthesized compounds are characterized on the basis of IR, ^{1}H NMR, mass spectral data and elemental analysis. Some of the selected compounds are also tested for their antibacterial properties.

Keywords: Arylfuran derivatives; Coupling agents; Antibacterial activity

1. Introduction

In view of the reported activity of amino acid derivatives of furan [1–4] as potent antibacterial agents and in continuation of our earlier work on the synthesis of arylfuran derivatives of amino acids and peptides [5], we report herein the synthesis of a series of 5-(substituted phenyl)furan-2-carbonyl amino acid methyl esters and peptides (**3**) starting from 5-(substituted phenyl)-2-furoic acids (**1**) and evaluation of the associated antibacterial activity of some selected compounds.

2. Chemistry

For the present work, 5-(3-chloro-4-fluorophenyl) and 5-(2,4-dichlorophenyl)furoic acids (**1**) were synthesized through the Meerwein reaction [6,7] and structures of them were confirmed by spectral data.

For the amino group protection of amino acids di-tert-butyl pyrocarbonate (Boc-O-Boc) was used [8] and the carboxyl group of amino acids was protected by esterification. Dipeptides were prepared from the corresponding amino acid methyl esters and Boc-amino acids using dicyclohexyl carbodiimide (DCC) as a coupling agent and *N*-methylmorpholine (NMM) as a base in dichloromethane (DCM) according to Bodanszky procedure [9]. The Boc group was removed using $CF_3COOH/CHCl_3$ and the methyl ester group was removed using LiOH at room temperature. The tetra peptides were prepared from dipeptides using DCC and NMM after proper deprotection. Amino acid methyl esters, Boc-deprotected dipeptide and tetrapeptide methyl esters were coupled with 5-(substituted phenyl)-2-furoic acids (**1**) using DCC as a coupling agent to get 5-(substituted phenyl)furan-2-carbonyl amino acid methyl esters, dipeptides and tetrapeptide methyl esters (**3**) (Scheme 1). The structures of the newly synthesized compounds were established on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data. The characterization data of the newly synthesized compounds are given in Table 1.

All the synthesized compounds **3a**–**x** gave satisfactory analysis for their nitrogen content. The IR spectrum of the compounds **3a**–**x** showed the absorption band due to –CO–NH, thus confirming the coupling. In addition to this, the absorption bands characteristic of C=O ester and amide are present in the IR spectra of the coupled compounds. IR spectral data of the compounds are given in Table 1.

The coupling of the compounds **1** with amino acid methyl esters was further supported by recording proton magnetic resonance (PMR) spectra of some selected compounds. The PMR spectra of the coupled com-

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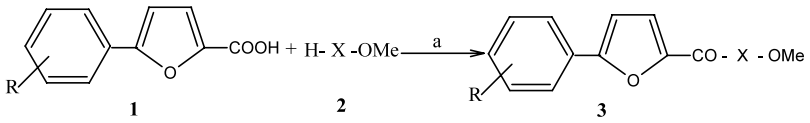


Scheme 1.

pounds showed a peak characteristic of the protons of phenyl group and furan ring. The peak at δ 3.7 clearly indicates the presence of $-OCH_3$ group. Further the PMR spectra of the coupled compounds exhibit peaks corresponding to amino acids and peptides.

The mass spectra of some selected compounds showed the expected molecular ion peaks. The mass spectrum of compound **3b** gave molecular ion peak at *m/z* 401 corresponding to the molecular formula $C_{21}H_{17}NO_4ClF$. The base peak however, was observed at *m/z* 221, which corresponds to 3-chloro-4-flourophenylfuronitrile ion, $C_{11}H_5ClFNO$.

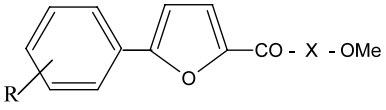
3. Experimental

Melting points were taken in open capillary tubes and are uncorrected. IR spectra (in Kbr pellets) were recorded on Perkin–Elmer infrared spectrophotometer. PMR spectra were recorded in $CDCl_3$ on a Bruker AC-300F (300 MHz) spectrometer using tetramethylsilane as an internal standard. The mass spectra were recorded on a VG micromass mass spectrometer operating at 70 eV. Purity of the compounds was checked by thin layer chromatography on silica gel G plates using chloroform–methanol (9:1, v/v) as eluent.

The substituted arylfuroic acids (**1**) were prepared and coupling with amino acid methyl esters/peptide methyl esters was carried out using DCC according to reported method [5]. All the newly synthesized compounds were recrystallized from ethyl acetate–petroleum ether.

IR (KBr, *v*/cm): **3a**, 3200 (br.s, N–H), 3015 (m, =C–H), 2950 (s, C–H), 1720 (s, C=O ester), 1680 (s, C=O amide), 1590 (s, C=C), 1570 (s, C–N), 1360 (s, C–F), 1090 (s, C–O), 960 (s, C–H), 820 (s, C–H), 690 (s, C–Cl); **3f**, 3280 (br.s, N–H), 3030 (m, =C–H), 2980 (s, C–H), 2940 (s, –C–H), 1730 (s, C=O ester), 1685 (s, C=O amide), 1600 (s, C=C), 1560 (s, C–H), 1320 (s, C–F),

Table 1
Characteristic data of 5-(substituted phenyl)furan-2-carbonyl amino acid methyl esters and peptide methyl esters[**3a**–**x**]



Comp.	R	X	M.p. (°C)	Yield (%)	Mol. formula	*Anal*. %N Found (Calc.)
3a	3-Cl, 4-F	Leu	168–170	76.6	$C_{18}H_{19}NO_4ClF$	3.86 (3.81)
3b	3-Cl, 4-F	Phe	150–152	74.2	$C_{21}H_{17}NO_4ClF$	3.42 (3.49)
3c	3-Cl, 4-F	Trp	155–157	73.0	$C_{28}H_{17}N_2O_4ClF$	6.34 (6.37)
3d	3-Cl, 4-F	Tyr	160–162	79.5	$C_{21}H_{16}NO_5ClF$	3.31 (3.36)
3e	3-Cl, 4-F	Thr–Tyr	163–165	69.9	$C_{25}H_{24}N_2O_7ClF$	5.43 (5.40)
3f	3-Cl, 4-F	Phe–Gly	171–173	71.8	$C_{28}H_{20}N_2O_5ClF$	6.08 (6.11)
3g	3-Cl, 4-F	Val–Leu	118–120	72.0	$C_{28}H_{38}N_2O_5ClF$	5.92 (5.88)
3h	3-Cl, 4-F	Leu–Gly	160–161	79.8	$C_{20}H_{32}N_2O_5ClF$	6.40 (6.45)
3i	3-Cl, 4-F	Ser–Pro–Phe–Leu	168–169	70.2	$C_{35}H_{40}N_4O_7ClF$	8.26 (8.21)
3j	3-Cl, 4-F	Gly–Pro–Leu–Ala	160–161	74.0	$C_{28}H_{34}N_4O_7ClF$	9.46 (9.45)
3k	3-Cl, 4-F	Pro–Phe–Gly–Ile	156–158	73.0	$C_{34}H_{38}N_4O_7ClF$	8.32 (8.38)
3l	3-Cl, 4-F	Gly–Thr–Leu–Pro	148–150	73.8	$C_{29}H_{38}N_4O_8ClF$	9.23 (9.20)
3m	2,4-Cl_2	Ile	149–150	86.0	$C_{18}H_{19}NO_4Cl_2$	3.68 (3.65)
3n	2,4-Cl_2	Pro	152–154	85.4	$C_{17}H_{15}NO_4Cl_2$	3.86 (3.85)
3o	2,4-Cl_2	Gly	142–143	78.3	$C_{14}H_{11}NO_4Cl_2$	4.31 (4.27)
3p	2,4-Cl_2	Val	146–147	81.0	$C_{17}H_{17}NO_4Cl_2$	3.73 (3.78)
3q	2,4-Cl_2	Thr–Tyr	140–141	78.0	$C_{25}H_{24}N_2O_7Cl_2$	5.20 (5.23)
3r	2,4-Cl_2	Phe–Gly	163–165	82.4	$C_{23}H_{20}N_2O_5Cl_2$	5.84 (5.89)
3s	2,4-Cl_2	Val–Leu	149–151	77.2	$C_{23}H_{38}N_2O_5Cl_2$	5.70 (5.68)
3t	2,4-Cl_2	Phe–Trp	147–148	79.4	$C_{32}H_{37}N_3O_5Cl_2$	6.79 (6.84)
3u	2,4-Cl_2	Thr–Tyr–Phe–Gly	163–164	75.0	$C_{36}H_{35}N_4O_9Cl_2$	7.61 (7.59)
3v	2,4-Cl_2	Val–Leu–Leu–Gly	154–155	80.0	$C_{31}H_{41}N_4O_7Cl_2$	8.53 (8.59)
3w	2,4-Cl_2	Gly–Pro–Leu–Ala	159–161	76.0	$C_{28}H_{34}N_4O_7Cl_2$	9.21 (9.20)
3x	2,4-Cl_2	Ser–Pro–Phe–Leu	186–188	77.0	$C_{35}H_{40}N_4O_7Cl_2$	7.97 (8.01)

1090 (s, C–O), 950 (s, C–H), 710 (s, C–H), 680 (s, C–Cl); **3j**, 3600–3400 (br.s, N–H), 3300 (s, NH), 3040 (m, =C–H), 2940 (s, C–H), 1710 (s, C=O ester), 1690 (s, C=O amide), 1650 (s, C=O amide), 1610 (s, C=C), 1530 (s, C–N), 1470 (s, C–H), 1340 (s, C–F), 1090 (s, C–O), 800 (s, C–H), 720 (s, C–Cl); **3m**, 3080 (m, =C–H), 2900 (s, –C–H), 2850 (s, –C–H), 1715 (s, C=O ester), 1690 (s, C=O amide), 1600 (s, C=C), 1560 (s, C–N), 1480 (s, C–H), 1220 (s, C–O), 830 (s, C–H), 650 (s, C–Cl).

^{1}H NMR ($CDCl_3$): **3a**, δ 7.6 (1H, m, Ar C_2–H), 7.35 (1H, m, Ar C_6–H), 7.15 (1H, $J = 3.6$ Hz, Furyl C_3–H), 7.05 (1H, m, Ar C_6–H), 6.85(1H, $J = 3.6$ Hz, Furyl C_3–H), 6.6 (1H, br.s, NH), 4.25–4.15 (1H, m, α-CH), δ 3.7 (3H, s, $-OCH_3$), 2.0–1.7 (2H, m, β-CH_2) 1.3–1.1 (1H, m, γ-CH), 0.95 (6H, d, $J = 7.0$ Hz, $CH(CH_3)_2$); **3b**, δ 7.65 (1H, m, Ar C_2H), 7.5–7.1 (7H, m, ArH and Ar′H), 7.0 (1H, d, $J = 3.6$ Hz, Furyl C_4–H), 6.8 (1H, d, $J = 3.6$ Hz, Furyl C_3–H), 6.4 (1H, br.s, NH), 4.5–4.3 (1H, m, α-CH), δ 3.7 (3H, s, $-OCH_3$), 3.1–3.0 (2H, m, β-CH_2); **3f**, δ 8.9 (1H, br.s, NH), 7.6 (1H, m, Ar C_2–H), 7.5–7.2 (7H, m, ArH, Ar′H), 7.1 (1H, d, $J = 3.6$ Hz, Furyl C_3–H), 6.90 (1H, $J = 3.6$ Hz, Furyl C_4–H), 6.2 (1H, br.s, –NH), 4.6–4.3 (1H, m, α-CH), 4.1–3.9 (2H, m, $-CH_2$), 3.65 (3H, s, $-OCH_3$), 3.0–2.8 (2H, m, β-CH_2); **3j**, δ 7.6 (1H, m, Ar C_2–H), 7.4 (1H, m, Ar C_6–H), 7.15 (1H, d, $J = 3.6$ Hz, Furyl C_3–H), 7.0 (1H, m, Ar C_5–H), 6.9 (1H, d, $J = 3.6$ Hz, Furyl C_4–H), 6.4 (2H, br.s, NH), 6.2 (1H, br.s, –NH), 4.5–4.3 (2H, m, α-CH), 4.2–4.0 (3H, m, CH_2 and α-CH), 3.7 (3H, s, $-OCH_3$), 3.4–3.2 (2H, m, N–CH_2), 2.3–1.6 (6H, m, $-CH_2-CH_2$ and $-CH_2$), 1.3–1.1 (4H, m, –CH and $-CH_3$), 0.95 (6H, d, $J = 6.5$ Hz, $CH(CH_3)_2$); **3m**, δ 7.82 (1H, d, $J = 8.4$ Hz, Ar C_6–H), 7.46 (1H, s, Ar C_3–H), 7.3 (1H, m, Ar C_5–H), 7.15 (1H, d, $J = 3.6$ Hz, Furyl C_4–H), 6.75 (1H, d, $J = 3.6$ Hz, Furyl C_4–H), 4.2–4.1 (1H, m, α-CH), 3.7 (3H, s, $-OCH_3$), 3.6–3.4 (2H, m, N–CH_2), 2.2–1.6 (4H, m, $-CH_2-CH_2$); **3n**, δ 7.7 (1H, d, $J = 8.5$ Hz, Ar C_6–H), 7.5 (1H, s, Ar C_3–H), 7.3 (1H, m, Ar C_5–H), 7.1 (1H, d, $J = 3.6$ Hz, Furyl C_3–H), 6.8 (1H, d, $J = 3.6$ Hz, Furyl C_4–H), 6.3 (1H, br.s, –NH), 4.1–4.0 (1H, m, α-CH), δ 3.75 (3H, s, $-OCH_3$), 1.8–1.6 (1H, m, β-CH), 1.3–1.2 (2H, m, γ-CH_2), 0.9 (6H, m, $(CH_3)_2$); **3s**, δ 7.6 (1H, d, $J = 9$ Hz, Ar C_6–H), 7.5 (1H, s, Ar C_3–H), 7.25 (1H, m, Ar C_5–H), 7.05 (1H, d, $J = 3.6$ Hz, Furyl C_3–H), 6.9 (1H, d, $J = 3.6$ Hz, Furyl C_5–H), 6.3–6.1 (2H, br.s NH), 4.3–3.9 (2H, m, α-CH), δ 2.3–1.7 (3H, m, β-CH_2 and β-CH), 1.3–1.1 (1H, m, γ-CH), 0.9 (6H, m, $-CH(CH_3)_2$).

Mass:**3b**, m/z 401 [M^+, 1.2%], m/z 221 (3-chloro-4-fluorophenylfuronitrile, 100%), m/z 195 (3-chloro-4-fluorophenylfuryl cation, 11.8%), m/z 132 (3-chloro-4-fluorophenylcyclopropyl cation, 40.6%), m/z 95(tropylium ion, 9.4%); **3n**, m/z 383 [M^+, 1.8%], m/z 237 (2, 4-dichlorophenylfuronitrile, 100%), m/z 209 (2, 4-dichlorophenylfuryl cation, 26.5%), m/z 145 (2, 4-dichlorophenyl cation, 6.5%).

Table 2
Antibacterial activity of 5-arylfuran-2-carbonyl amino acid methyl esters and peptide methyl esters (minimum inhibitory concentration (mg/ml))

Comp.	*S. aureus*	*E. coli*	*P. aeruginosa*	*g. Bacillus*
3b		25		12.5
3c		12.5		6
3f	12.5		25	
3h	25			
3l	25			12.5
3j	12.5			
3n	6.0		12.5	
3o			25	
3s		25	12.5	
3t		25	12.5	
3w			12.5	
3x		12.5	25	
Furacin	12.5	6.0	12.5	12.5

4. Antibacterial activity

Twelve selected synthesized compounds were screened for their in vitro antibacterial activities against *g. Bacillus*, *P. aeruginosa*, *E. coli* and *S. aureus* according to the serial dilution method [10]. Furacin was used as a standard drug for comparison. The results of the screening studies are given in Table 2.

5. Conclusion

From the above data it is evident that, most of the 5-arylfuran-2-carbonyl amino acid methyl esters and peptide methyl esters showed antibacterial activities lower than that observed for the reference drug, furacin. However, **3c** showed antibacterial activity against *g. Bacillus* and **3n** against *S. aureus* to a higher degree when compared to the standard drug.

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