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Synthesis and biological evaluation of carbamate and sulfonamide derivatives of carvedilol

Sana Venkata Lakshmi Reddy[a], Sk. Thaslim Basha[a], Kondapalli Naresh[b] and Chamarthi Naga Raju[a]*

[a]*Department of Chemistry, Sri Venkateswara University, Tirupati, India*
[b]*Department of Biochemistry, Sri Venkateswara University, Tirupati, India*

ABSTRACT

The modified structures of Carvedilol as their carbamates and sulfonamides were synthesized by the reaction of Cavedilol with different Chloroformates/sulfonylchlorides in the presence of triethylamine at reflux temperature in THF. The newly synthesized compounds were characterized by IR, NMR (^1H & ^{13}C), LCMS and C, H, N elemental analysis. All the title compounds were screened for their antimicrobial activity.

Key words: Carvedilol, Antimicrobial activity, Carbamate, Sulfonamide

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INTRODUCTION

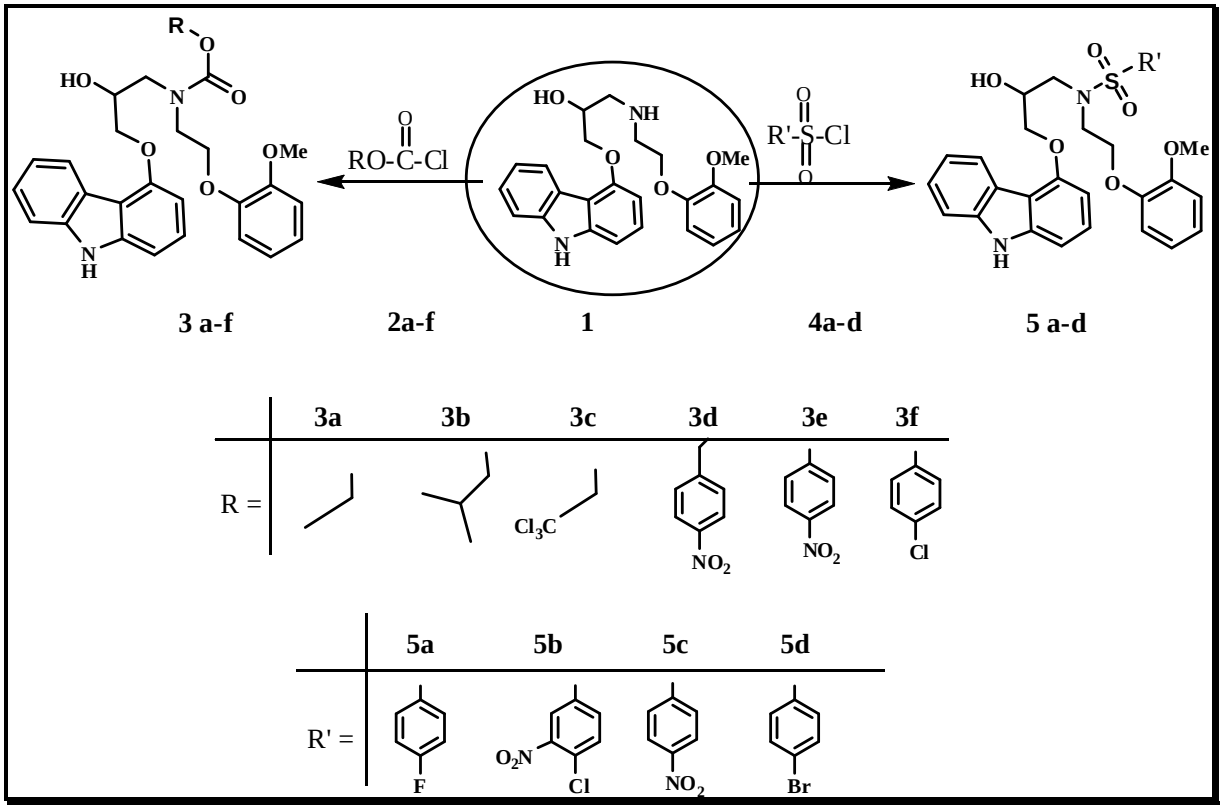
Carvedilol is a non-selective β-blocker devoid of intrinsic sympathomimetic activity with a α_1-adrenergic receptor blocking capability. Carvedilol is administered clinically as a racemic mixture of its R(+)- and S(−)-enantiomers for the treatment of hypertension, ischemic heart disease and heart failure [1]. It is performing as a good antioxidant drug by acting as a β-blocker [2]. Trivial modification of the drug structure will alter the efficiency of the pharmacological activity [3,4]. Based on this study, several drugs are modified in their structure by small amendment of their stereochemistry, functional groups, sulfonation, phosphorylation and by introducing biologically potent groups to the drugs. The prior reports from our laboratory supported the above testimonial [5,6].

Carbamates are playing the vital role in the human life with different applications like the synthesis of so many pharmacological drugs and insecticides. They can act as good antioxidants [7], antimicrobial [8], antiviral, anti-diabetic [9], anticancer [10] and antitumor [11] agents. The importance of sulfonamides is not inferior to carbamates, which having the equivalent biological importance in our existence such as antioxidants, antimicrobial, antiviral, anticancer [12] and anti-diabetic [13] drugs.

In our studies, we focused on the slight structural modification of Carvedilol as its carbamates and sulfonamide derivatives by reacting with different chloroformates and sulfonylchlorides. All the title compounds were screened for their antimicrobial activity.

MATERIALS AND METHODS

Chemicals were procured from Sigma–Aldrich and Merck were used without further purification. All solvents used in experimental conditions are reagent grade and purified by literature methods [14]. Melting points (mp) were determined using a calibrated thermometer by Guna Digital Melting Point apparatus and are uncorrected. Infrared spectra (IR) were obtained on a Perkin-Elmer 281-B spectrophotometer using KBr disks. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The ^{1}H and ^{13}C chemical shifts were expressed in parts per million (ppm) with reference to tetramethylsilane (TMS) and LCMS were recorded on a Jeol SX 102 DA/600 mass spectrometer.



Scheme 1. Synthesis of Carbamate and sulfonamide derivatives of Carvedilol

Synthesis of ethyl 3-(9H-carbazol-4-yloxy)-2-hydroxypropyl(2-(2-methoxyphenoxy)ethyl) carbamate (3a)

To a stirred solution of Carvedilol (**1**) (0.001 mol) in THF (10 mL), ethylchloroformate (**2**) (0.001 mol) was added drop wise in the presence of triethylamine at 0 ^{o}C and raised the temperature to 40 ^{o}C and continued the stirring for 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, $Et_3N.HCl$ was removed by filtration and the solvent was evaporated under rota-evaporator and the crude carbamate derivative **(3a)** was isolated by addition of 20 mL of DCM and extracting with 10% of aq HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to obtain ethyl 3-(9H-carbazol-4-yloxy)-2-hydroxypropyl(2-(2-methoxyphenoxy)ethyl) carbamate **(3)** in high yield 78%. All the carbamate derivatives (**3b-f**) were prepared using the same procedure by the reaction of various alkyl/aryl chloroformates (**2b-f**) with Carvedilol **(1)**.

Synthesis of N-(3-(9H-carbazol-4-yloxy)-2-hydroxypropyl)-4-fluoro-N-(2-(2-methoxy phenoxy)ethyl) benzene sulfonamide (5a)

To a stirred solution of Carvedilol (**1**) (0.001 mol) in 10 mL of THF, a solution of 4-fluorobenzene sulfonyl chloride (**4a)** (0.001mol) in THF (10 mL) was added slowly at 0 ^{o}C in the presence of Et_3N (0.001 mol). After the completion of the addition, the reaction mixture was stirred for 3 h at 50 ^{0}C. The progress of the reaction was

monitored by TLC. After completion of the reaction, $Et_3N.HCl$ was removed by filtration and solvent was evaporated in rota-evaporator. The crude product was purified by column chromatography using 30% ethyl acetate and n-hexane as eluent to afford N-(3-(9H-carbazol-4-yloxy)-2-hydroxypropyl)-4-fluoro-N-(2-(2-methoxyphenoxy)ethyl)benzenesulfonamide (**5a**). All the sulfonamide derivatives (**5b-d**) were prepared using the same procedure by the reaction of various arylsubstituted sulfonylchlorides with Carvedilol (**1**).

All the title compounds are characterized by their IR, NMR, Mass spectral data and elemental analysis.

Spectral data

Ethyl 3-(9H-carbazol-4-yloxy)-2-hydroxypropyl(2-(2-methoxyphenoxy)ethyl)carbamate(3a)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 1335 (-C-N), 1747 (-C=O), 1266 (C-O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ8.51-6.74 (11H, m, Ar), 3.81 (2H, d, H-10), 3.04-3.02 (2H, m, H-12), 3.19-3.16 (2H, t, H-13), 4.05-4.03 (2H, t, H-14), 4.12-4.06 (1H, m, H-11), 3.53 (3H, s, OMe), 3.91 (2H, m, H-1'), 1.21 (3H, t, H-2'), 10.63 (1H, s, N-H); ^{13}C NMR (100 MHz DMSO-d_6): δ15.6, 45.2, 49.5, 55.8, 59.4, 62.9, 66.3, 73.1, 94.7, 103.5, 109.4, 110.3, 111.6, 118.4, 119.7, 120.8, 121.4, 121.5, 122.3, 127.9, 129.3, 134.9, 142.5, 148.6, 149.4, 150.2, 152.3; LC MS (%): m/z 479.3 (100%) [$MH^{+\bullet}$]; Anal. Calcd. for $C_{27}H_{30}N_2O_6$: C 67.77; H 6.32; N 5.85; Found: C 67.52; H 6.24; N 5.74;

Isobutyl 3-(9H-carbazol-4-yloxy)-2-hydroxypropyl(2-(2-methoxyphenoxy)ethyl)carbamate (3b)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 1330 (-C-N), 1742 (-C=O), 1260 (C-O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ8.54-6.72 (11H, m, Ar), 3.84 (2H, d, H-10), 3.07-3.05 (2H, m, H-12), 3.18-3.14 (2H, t, H-13), 4.08-4.05 (2H, t, H-14), 4.14-4.08 (1H, m, H-11), 3.57 (3H, s, OMe), 3.78 (2H, d, H-1'), 1.76-1.67 (1H, m, H-2'), 1.12-1.09 (6H, d, H-3'), 10.83 (1H, s, N-H); ^{13}C NMR (100 MHz DMSO-d_6): δ21.5, 29.7, 45.6, 49.4, 55.2, 62.5, 66.7, 69.2, 73.6, 94.2, 103.6, 109.1, 110.4, 111.9, 118.1, 119.5, 120.9, 121.7, 121.3, 122.8, 127.3, 129.1, 134.2, 142.8, 148.3, 149.1, 150.9, 152.6; LC MS (%): m/z 507.4 (100%) [$MH^{+\bullet}$]; Anal. Calcd. $C_{29}H_{34}N_2$: C 68.76; H 6.76; N 5.53; Found: C 68.65; H 6.67; N 5.28.

2,2,2-Trichloroethyl 3-(9H-carbazol-4-yloxy)-2-hydroxypropyl(2-(2-methoxyphenoxy)ethyl) carbamate (3c)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 1345 (-C-N), 1758 (-C=O), 1271 (C-O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ8.55-6.79 (11H, m, Ar), 3.89 (2H, d, H-10), 3.05-3.04 (2H, m, H-12), 3.16-3.14 (2H, t, H-13), 4.03-4.01 (2H, t, H-14), 4.15-4.08 (1H, m, H-11), 3.55 (3H, s, OMe), 5.03 (2H, s, H-1'), 10.6 (1H, s, N-H); ^{13}C NMR (100 MHz DMSO-d_6): δ45.6, 49.7, 62.3, 55.5, 66.3, 71.2, 73.8, 94.3, 96.3, 103.6, 109.8, 110.5, 111.3, 118.9, 119.7, 120.8, 121.6, 121.3 122.7, 127.3, 129.8, 134.4, 142.3, 148.9, 149.7, 150.3, 152.7; LC MS (%): m/z 582.3 (100%) [$MH^{+\bullet}$]; Anal. Calcd. for $C_{27}H_{27}Cl_3N_2O_6$: C 55.73; H 4.68; N 4.81; Found: C 55.62; H 4.55; N 4.71.

4-Nitrobenzyl 3-(9H-carbazol-4-yloxy)-2-hydroxypropyl(2-(2-methoxyphenoxy)ethyl) carbamate (3d)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 1335 (-C-N), 1748 (-C=O), 1264 (C-O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ8.59-6.58 (15H, m, Ar), 3.85 (2H, d, H-10), 3.01-3.00 (2H, m, H-12), 3.15-3.12 (2H, t, H-13), 4.04-4.02 (2H, t, H-14), 4.14-4.10 (1H, m, H-11), 3.57 (3H, s, OMe), 5.16 (2H, s, H-1'), 10.72 (1H, s, N-H); ^{13}C NMR (100 MHz DMSO-d_6): δ44.9, 49.9, 62.3, 55.3, 66.6, 73.8, 94.4, 103.1, 109.3, 110.9, 111.5, 118.6, 119.3, 120.7, 121.2, 121.7, 122.1, 125.9, 127.3, 128.6, 129.6, 134.7, 142.4, 143.5, 145.4, 148.8, 149.3, 150.3, 152.2; LC MS (%): m/z 586.4 (100%) [$MH^{+\bullet}$]; Anal. Calcd. for $C_{32}H_{31}N_3O_8$: C 65.63; H 5.34; N 7.18; Found: C 65.52; H 5.28; N 7.09.

4-Nitrophenyl 3-(9H-carbazol-4-yloxy)-2-hydroxypropyl(2-(2-methoxyphenoxy)ethyl) carbamate (3e)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 1333 (-C-N), 1747 (-C=O), 1261 (C-O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ8.62-6.63 (15H, m, Ar), 3.82 (2H, d, H-10), 3.04-3.03 (2H, m, H-12), 3.16-3.13 (2H, t, H-13), 4.04-4.02 (2H, t, H-14), 4.17-4.11 (1H, m, H-11), 3.58 (3H, s, OMe), 10.75 (1H, s, N-H); LC MS (%): m/z 572.5 (100%) [$MH^{+\bullet}$]; Anal. Calcd. for $C_{31}H_{29}N_3O_8$: C 65.14; H 5.11; N 7.35; Found: C 65.02; H 5.05; N 7.24.

4-Chlorophenyl 3-(9H-carbazol-4-yloxy)-2-hydroxypropyl(2-(2-methoxyphenoxy)ethyl) carbamate (3f)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 1338 (-C-N), 1748 (-C=O), 1264 (C-O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ8.65-6.65 (15H, m, Ar), 3.83 (2H, d, H-10), 3.07-3.06 (2H, m, H-12), 3.15-3.12 (2H, t, H-13), 4.05-4.03 (2H, t, H-14), 4.12-4.06 (1H, m, H-11), 3.59 (3H, s, OMe), 10.68 (1H, s, N-H); LC MS (%): m/z 562.5 (100%) [$MH^{+\bullet}$]; Anal. Calcd. for $C_{31}H_{29}ClN_2O_6$: C 66.37; H 5.21; N 4.99; Found: C 66.25; H 5.13; N 4.92.

N-(3-(9H-Carbazol-4-yloxy)-2-hydroxypropyl)-4-fluoro-N-(2-(2-methoxy phenoxy)ethyl) benzenesulfonamide (5a)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 911 (-S-N), 1348 (S=O), 1318 (S-C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ8.48-6.69 (15H, m, Ar), 3.86 (2H, d, H-10), 3.06-3.04 (2H, m, H-12), 3.14-3.11 (2H, t, H-13), 4.05-4.03 (2H, t, H-14), 4.19-4.13 (1H, m, H-11), 3.59 (3H, s, OMe), 10.69 (1H, s, N-H); ^{13}C NMR (100 MHz DMSO-d_6): δ45.5, 49.3, 62.1, 55.9, 66.7, 73.5, 94.3, 103.2, 109.7, 110.5, 111.3, 114.3, 118.7, 119.8, 120.3, 121.2, 121.5, 122.7, 127.5, 129.2, 131.2, 134.5, 136.1, 142.3, 148.7, 149.3, 150.6, 152.9, 168,4; LC MS (%): m/z 565.7 (100%) [$MH^{+\bullet}$]; Anal. Calcd. for $C_{30}H_{29}FN_2O_6S$: C 63.82; H 5.18; N 4.96; Found: C 63.77; H 5.09; N 4.85.

N-(3-(9H-Carbazol-4-yloxy)-2-hydroxypropyl)-4-chloro-N-(2-(2-methoxyphenoxy)ethyl)-3-nitrobenzene sulfonamide (5b)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 908 (-S-N), 1352 (S=O), 1310 (S-C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ8.51-6.72 (14H, m, Ar), 3.85 (2H, d, H-10), 3.02-2.99 (2H, m, H-12), 3.11-3.09 (2H, t, H-13), 4.02-4.00 (2H, t, H-14), 4.12-4.07 (1H, m, H-11), 3.58 (3H, s, OMe), 10.63 (1H, s, N-H); ^{13}C NMR (100 MHz DMSO-d_6): δ45.4, 49.8, 62.6, 55.4, 66.9, 73.5, 94.6, 103.3, 109.7, 110.5, 111.7, 118.2, 119.3, 120.4, 121.7, 121.9, 122.6, 125.1, 128.3, 129.3, 130.9,131.4, 133.7, 134.6, 135.4, 142.8, 146.2, 148.4, 149.2, 150.7, 152.6; LC MS (%): m/z 527.3 (100%) [$MH^{+\bullet}$]; Anal. Calcd. for $C_{30}H_{28}ClN_3O_8S$: C 57.55; H 4.51; N 6.71; Found: C 57.45; H 4.42; N 6.65.

N-(3-(9H-Carbazol-4-yloxy)-2-hydroxypropyl)-N-(2-(2-methoxyphenoxy)ethyl)-4-nitro benzene sulfonamide (5c)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 902 (-S-N), 1354 (S=O), 1312 (S-C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ8.49-6.71 (15H, m, Ar), 3.81 (2H, d, H-10), 3.03-3.01 (2H, m, H-12), 3.19-3.16 (2H, t, H-13), 4.07-4.05 (2H, t, H-14), 4.13-4.07 (1H, m, H-11), 3.58 (3H, s, OMe), 10.72 (1H, s, N-H); ^{13}C NMR (100 MHz DMSO-d_6): δ46.4, 49.1, 63.2, 56.2, 66.7, 73.8, 94.2, 103.8, 109.7, 110.8, 111.9, 118.7, 119.4, 120.3, 120.9, 121.1, 122.5, 125.6, 127.7, 128.2, 129.6, 134.6, 142.8, 144.9, 148.1, 149.7, 150.7, 151.3, 152.8; LC MS (%): m/z 592.5 (100%) [$MH^{+\bullet}$]; Anal. Calcd. for $C_{30}H_{29}N_3O_8S$: C 60.90; H 4.94; N 7.10; Found: C 60.82; H 4.89; N 7.03.

N-(3-(9H-Carbazol-4-yloxy)-2-hydroxypropyl)-4-chloro-N-(2-(2-methoxyphenoxy)ethyl) benzenesulfonamide (5d)

Yield: 75%; mp: 167-169 ºC; IR (KBr): 914 (-S-N), 1349 (S=O), 1312 (S-C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ8.48-6.54 (15H, m, Ar), 3.81 (2H, d, H-10), 3.07-3.05 (2H, m, H-12), 3.16-3.13 (2H, t, H-13), 4.04-4.02 (2H, t, H-14), 4.16-4.09 (1H, m, H-11), 3.58 (3H, s, OMe), 10.69 (1H, s, N-H); LC MS (%): m/z 626.3 (100%) [$MH^{+\bullet}$]; Anal. Calcd. for $C_{30}H_{29}BrN_2O_6S$: C 57.60; H 4.67; N 4.48; Found: C 57.56; H 4.60; N 4.41;

Antimicrobial activity

Preparation of test samples

The test solutions of the samples were prepared in dimethylformamide (DMF). The antibiotic Ciprofloxacin was used as standard for antibacterial screening and Ketoconazole was used as a standard for antifungal screening. The antibacterial standard was dissolved in sterile distilled water. The antifungal standard was dissolved in buffered 70% propanol.

Antibacterial screening test: The antibacterial activity of the synthesized compounds **3a-f** and **5a-d** were studied against different Gram-positive [*Bacillus subtilis* (MTCC 2274) and *Staphylococcus aureus* (ATCC 9144)] and Gram-negative [*Escherichia coli* (ATCC 9637) and *Proteus vulgaris* (MTCC 0426)]. For detection of antibacterial activity the filter paper disc diffusion method [15] was employed. Nutrient agar (NA) was used as the basal medium for test bacteria. These agar media were inoculated with 0.5 mL of the 24 hr liquid cultures containing 1×10^7 cells/mL. The diffusion time was 24 hr at 5ºC and the incubation time was 12 hr at 37ºC for bacteria. Discs with only DMSO were used as control. The diameter (in mm) of the observed inhibition zones were taken as a measure of inhibitory activity.

Table 1. Antibacterial Zone of inhibition of title compounds 3a-f and 5a-d

Compound	Zone of inhibition (in mm) at conc. 200µg/mL after 24 hours			
	B. subtilis (MTCC-2274)	*S. aures* (ATCC-9144)	*E. coli* (ATCC-9637)	*P. vulgaris* (MTCC-0426)
3a	18.5	17	20	21
3b	16	18	17.5	16.5
3c	15.5	17.5	16	18
3d	17	16	19	18.5
3e	21	20	22	21.5
3f	18.5	16.5	15.5	16
5a	16.5	18	14.5	15.5
5b	20	19.5	18	19
5c	19	17.5	18.5	16.5
5d	17.5	19	16.5	18
Ciprofloxacin	25	27	27	25

Antifungal screening test: The antifungal activity of compounds were **3a-f** and **5a-d** were evaluated towards two plant pathogenic and mold fungi, *viz*., *Aspergillus niger* (MTCC 1881) and *Aspergillus fumigates*. The antifungal activity was assessed by poisoned food technique [16] with some modifications. Potato dextrose agar (PDA) was used as basal medium for test fungi. Glass petri dishes were sterilized and 15 mL of sterilized melted PDA medium (~ 45ºC) was poured into each petri dish (90 mm). After solidification of the medium small portions of mycelium of each fungus were spread carefully over the center of each PDA plate with the help of sterilized needles. Thus each fungus was transferred to a number of PDA plates. The PDA plates were then incubated at (25 ± 2ºC) and after five days of incubation they were ready for use. The prepared discs of test samples were placed gently on the solidified agar plates freshly seeded with the test organisms with sterile forceps. Control discs were also placed on the test plates to compare the effect of solvents, respectively. The plates were then kept in a refrigerator at 4ºC for 24 hr in order that the materials had sufficient time to diffuse to a considerable area of the plates. Afterwards the plates were incubated at 37.5ºC for 72 hr.

Table 2. Antifungal Zone of inhibition of title compounds 3a-f and 5a-d

Compound	Zone of inhibition (in mm) at 200µg/mL	
	A. niger	*A. fumigates*
3a	17.5	18.5
3b	15.5	19.5
3c	22	21
3d	13.5	16
3e	19	22.5
3f	16.5	19
5a	14	18.5
5b	24	20
5c	20.5	17
5d	18	20.5
Ketoconazole	27	28

RESULTS AND DISCUSSION

Chemistry

Various alkyl/aryl chloroformates (**2a-f**) in THF were added dropwise to Carvedilol in the presence of triethylamine at 0 ^{o}C and raised the temperature to 40-45 ^{o}C and continued the stirring for 2-3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, $Et_3N.HCl$ was removed by filtration and concentrated by rota-evaporator and the crude carbamate derivative **(3a-f)** was isolated by addition of 20 mL of DCM and extracting with 10% of aq HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to obtain title compounds **(3-f**) in high yield 78-85%. Similarly four different aryl sulfonyl chlorides (**4a-d**) in THF were added dropwise to Carvedilol in the presence of triethylamine at 0 ^{o}C and raised the temperature to 50-55 ^{o}C and continued the stirring for 2-3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, $Et_3N.HCl$ was removed by filtration and concentrated in a rota-evaporator to obtain the crude carbamate derivatives **(5a-d).** The crude product was purified by column chromatography using 30% ethyl acetate and n-hexane as eluent to afford title compounds **5a-d** in high yield 72-77%.

Structures of all the synthesized compounds were established by their spectral analysis. In ^{1}H NMR spectra, disappearance of aliphatic NH proton signal confirms the formation carbamate/sulfonamides. IR spectral values 1330-1345 and 1742-1758 cm^{-1} of O=C-N and C=O represent the formation of carbamates. Presence of 902-914 and 1348-1354 cm^{-1} of C-S and S=O bands confirm the formation of sulfonamides. The ^{13}C NMR values are observed in their expected regions.

All the title compounds **(3a-f & 5a-d)** were screened *in vitro* for their antibacterial against different Gram-positive [*Bacillus subtilis* (MTCC 2274), *Staphylococcus aureus* (ATCC 9144)] and Gram-negative [*Escherichia coli* (ATCC 9637), *Proteus vulgaris* (MTCC 0426)] and antifungal activities against *Aspergillus niger* (MTCC 1881) and *Aspergillus fumigates* and compared their activities with standard compounds. The title compounds showed moderate activity. Especially, **3a**, **3e, 3f, 5b** and **5c** exhibited good zone of inhibition on gram positive bacteria than on gram negetive bacteria. When compared to carbamates, sulfonamides showed better activity. When compared to aliphatic and aromatic carbamate derivatives of Carvedilol, aromatic substituents exhibited good activity. Nitro substituted compounds exhibited better antibacterial activity. The compounds **3c, 5b** and **5c** showed good antifungal activity. All the remaining compounds showed moderate antifungal activity.

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