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Synthesis, spectral characterization and biological evaluation of carbamate and sulfonamide derivatives of *cis*-tramadol

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Abstract: A series of new carbamates and sulfonamide derivatives of *cis*-tramadol **5(a-e**) and **7(a-e)** have been synthesized in high yields by the reaction of *cis*-tramadol with various chloroformates **4(a-e)** and sulfonyl chlorides **6(a-e).** All the newly synthesized compounds were characterized by IR, NMR (^{1}H and ^{13}C), mass and elemental analyses. The synthesized compounds were evaluated for their antibacterial and antifungal activities. Compounds **5a, 5b, 7a and 7c** exhibited potent antibacterial and antifungal activity.

Keywords: *cis*-tramadol; carbonyl chloridates; sulfonyl chlorides; antibacterial; antifungal.

1. Introduction

Nowadays, antibiotics have gained great advancement in treating and controlling of infectious diseases. The usage of antibiotics has become world-wide because of their use as a common medicine in the treatment of various diseases like orthopedics, cancer and transplantation[1,2]. As a result, the bacteria have become resistant to the antibiotics. Investigations of new antimicrobial substances have become essential because there is no medicine for which the bacteria will not become resistant. Hence, considerable attention has been focused on new trends for the development of new, safe and more effective antibiotics with clear mechanism of resistance[3].

Carbamates are the analogues of carbamic acid, where amino and carboxyl termini of carbamates are substituted by a various alkyl, aryl or alkyl-aryl substituents. The –OC(O)NH carbamate moiety has become an important motif in many approved and prodrugs.[4] The use of carbamates in medicinal

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chemistry has been increasing due to its chemical stability and capability to increase permeability across cellular membranes.[5] They are found to possess various pharmacological activities such as anti-cancer, antibacterial, antifungal, antimalarial, antiviral, antiHIV, antiestrogenic, antiosteoporosis, antiprogestational, antiinflammatory, antifilarial, antitubercular, antiobesity, antidiabetic, antihelminthics anticonvulsant, and Alzheimer disease.[6,7]

Sulfonamides are the most commonly used antimicrobial agents in the world because of their low cost, low toxicity and excellent activity against common bacterial diseases. Over the last decades, the usage of sulfonamides was found to be everywhere due to synergetic action of sulfonamides with trimethoprim.[8] The $–SO_2NH_2$ moiety is found in numerous biologically active compounds.[9] Sulfonamides exhibit various biological activities include antimicrobial,[10] antithyroid,[11] antidiabetics,[12] anti-inflammatory,[13] and antihypertensive,[14,15] antileishmanial,[16] activities. Also, these derivatives are used in the treatment of cancer,[17] Alzheimer's disease,[18] osteoporosis,[19] antihepatitis C virus (HCV),[20] and antiproliferative agents.[21] Few examples of sulfonamides and carbamates possessing various activities are shown in Figure 1.

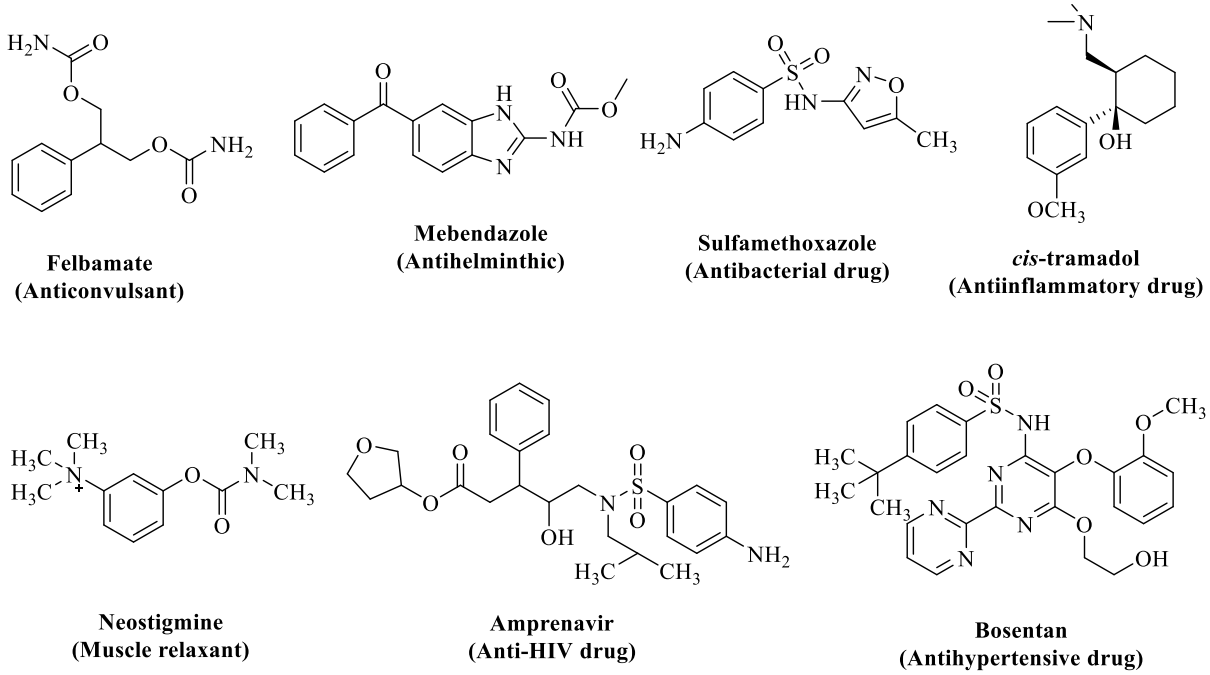


Figure 1. Some examples of carbamates and sulfonamides drugs

tramadol is an analgesic drug acts mainly on the central nervous system and has unique pharmacokinetic and pharmacodynamic properties relative to other opioid. It is used in the treatment of treatment of rheumatoid arthritis, restless legs syndrome, motor neurone disease and fibromyalgia. [22] Led by the above facts, herein we report the synthesis of carbamate and sulfonamide derivatives of *cis*-tramadol and evaluated their biological activity.

2. Experimental

2.1. General

All the required chemicals were purchased from Sigma-Aldrich and Merck and were used as such without further purification. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 0.2 mm thick aluminum plates. The plates were visualized under an UV-lamp at a wavelength of 254 nm or TLC visualization was made with iodine chamber. Column chromatography was performed on silica gel (60–120 mesh). The melting points of the compounds were determined on Guna digital melting point apparatus with Digital Imaging Processing Technology of Stanford Research Systems using open capillary method and are uncorrected. The Infrared spectra were recorded on Perkin-

Elmer Model 281-B spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker FT-NMR 100 MHz in $CDCl_3$ solvent and the spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in $CDCl_3$. Tetramethylsilane (TMS) was used as an internal standard in the recording of ^{1}H and ^{13}C NMR spectra. The chemical shift (δ), coupling constant (J) were expressed in ppm and Hertz respectively. The following abbreviations were used s, d, t and m as singlet, doublet, triplet and multiplet. The mass spectra were recorded on Joel SX 102 DA/600 Mass spectrometer. The CHN analysis was carried out Flash EA 1112 instrument.

*2.2. General procedure for the synthesis of carbamate and sulfonamide derivatives of cis-tramadol **5(a-e)** and **7(a-e)***

To a stirred solution of *cis*-tramadol **1** (0.001 mol, 0.263 g) dissolved in THF (10 mL), 2-bromoethan-1-amine **2** (0.001 mol, 0.122 g) was added in presence of a base dimethyl piperazine (1 mL) at 50-55 ^{o}C for 1h resulted the formation for the intermediate compound **3.** To the intermediate compound **3** (0.001 mol, 0.306 g) dissolved in THF (10 mL), 4-nitrophenyl carbonochloridate **4b** (0.001 mol, 0.201 g) was added in presence of dimethyl piperazine (1 mL) at 20-40^{o}C for 2h resulted the formation of crude compound. The progress of the reaction was monitored by TLC. After the completion of reaction, the crude reaction mixture was concentrated under rota-evaporator and purified by column chromatography using ethyl acetate and hexane (2:1) to obtain 4-nitrophenyl-2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy) ethylcarbamate **5b**.

The same experimental procedure was adopted for the synthesis of remaining target compounds **5a, 5(c-e)** and **7(a-e)** using various corresponding substituted chloroformates and sulfonyl chlorides.

*2.2.2. Spectral data for the synthesized carbamate and sulfonamide derivatives of cis-tramadol **5(a-e)** and **7(a-e)***

*4-Nitrobenzyl2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy) ethylcarbamate (**5a**)*: Yield: 82 %; Yellow, M.p.: 132-134 ^{o}C. IR (KBr) νmax (cm^{-1}): 1734 (-C=O), 3218 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36-2.14 (m, 8H, -CH_2), 2.19 (d, J = 5.4 Hz, 2H, -CH_2), 2.26 (s, 6H, $(CH_3)_2$), 2.34 (m, 1H, -CH), 3.12 (t, J = 4.8 Hz, 2H, -CH_2), 3.62 (d, J = 5.2 Hz, 2H, -OCH_2), 3.64 (s, 3H, -OCH_3), 5.12 (s, 2H, -CH_2-Ar), 5.61 (t, J = 6.0 Hz, 1H, -NH-C=O),7.48-6.86 (m, 4H, Ar-H), 8.19-7.62 (m, 4H, Ar'-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6 (C-11), 22.8 (C-12), 33.4 (C-9), 40.4 (C-18), 42.3 (C-13), 46.2 (C-15 and C-16), 54.2(C-14), 55.4 (C-7), 65.2 (C-17), 66. 2 (C-20), 76.1 (C-8), 110.4 (C-2), 113.2 (C-6), 119.4 (C-4), 124.2 (C-3'and C-5'), 128.2 (C-5), 128.4 (C-2'and C-6'), 128.6 (C-10), 141.2 (C-1'), 146.2 (C-4'), 147.2 (C-3), 151.6 (C-19), 160.1 (C-1); LC-MS: *m/z:* 485 [100, M+.]. Anal. Calcd. for $C_{26}H_{35}N_3O_6$: C 64.31, H 7.27, N 8.65. Found: C 64.31, H 7.21, N 8.57.

*4-Nitrophenyl2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy) ethylcarbamate (**5b**)*: Yield: 90 %; White, Solid, M.p.: 144-146 ^{o}C. IR (KBr), νmax (cm^{-1}): 1736 (-C=O), 3242 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47-2.15 (8H, m, -CH_2), 2.25 (s, 6H, -CH_3), 2.35 (m, 1H, -CH), 2.46 (d, J = 5.6 Hz, 2H, -CH_2), 3.51 (t, J = 4.8 Hz, 2H, -CH_2), 3.71 (t, J = 5.0 Hz, 2H, -OCH_2), 4.03 (s, 3H, -OCH_3), 5.72 (t, J = 5.2 Hz, 1H, -NH-C=O), 8.16-6.98 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4 (C-11), 22.6 (C-12), 33.2 (C-9), 40.2 (C-18), 42.5 (C-13), 46.4 (C-15 and C-16), 53.2 (C-7), 54.0 (C-14), 65.0 (C-17), 76.0 (C-8), 112.8 (C-6), 111.4 (C-2), 118.2 (C-4), 124.6 (C-3'andC-5'), 128.0 (C-5), 128.4 (C-10), 128.6 (C-2' and C-6'), 141.4 (C-1'), 146.4 (C-3), 146.6 (C-4'), 155 .2 (C-19),161.2 (C-1); LC-MS: *m/z:* 471 [100, M+.]. Anal. Calcd. for $C_{25}H_{33}N_3O_6$: C 63.68, H 7.05, N 8.91. Found: C 64.61, H 7.01, N 8.87.

*2,2,2-Trichloroethyl2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy) ethylcarbamate (**5c**)*: Yield: 85 %; Yellow, M.p.: 135-137 ^{o}C. IR (KBr), νmax (cm^{-1}): 1748 (-C=O), 3236 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34-2.10 (m, 8H, -CH_2), 2.14 (d, J = 4.8 Hz, 2H, -CH_2), 2.26 (s, 6H, -$(CH_3)_2$), 2.34 (m, 1H, -CH), 3.12 (t, J = 5.0 Hz, 2H, -CH_2), 3.60 (d, J = 5.2 Hz, 2H, -OCH_2), 3.64 (s, 3H, -OCH_3), 4.62 (s, 2H, -O-CH_2), 5.58 (t, J = 5.4 Hz, 1H, -NH-C=O), 7.38-6.91 (m, 4H, Ar-

H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5 (C-11), 22.8 (C-12), 33.6 (C-9), 40.4 (C-18), 42.3 (C-13), 46.2 (C-15 and C-16), 53.6 (C-7), 54.1 (C-14), 65.4 (C-17), 71.2 (C-20), 76.2 (C-8), 94.2 (C-21), 111.7 (C-2), 112.2 (C-6), 118.4 (C-4), 128.2 (C-10), 128.4 (C-5),146.0 (C-3), 153.4 (C-19), 161.6 (C-1); LC-MS: *m/z: m/z:* 481 [100, M+.]. Anal. Calcd. for $C_{21}H_{31}Cl_3N_2O_4$: C 52.35, H 6.49, N 5.81. Found: C 52.20, H 6.45, N 5.63.

Ethyl2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy)ethylcarbamate (***5d***): Yield: 80 %; White, M.p.: 141-143 ^{o}C. IR (KBr), *ν*max (cm^{-1}): 1742 (-C=O), 3252 (-NH); 1H-NMR (400 MHz, $CDCl_3$): δ 1.34 (t, *J* = 4.8 Hz, 3H, -CH_3), 1.32-2.08 (m, 8H, -$(CH_2)_2$), 2.10 (d, J = 4.8 Hz, 2H, -CH_2), 2.22 (s, 6H, -$(CH_3)_2$), 2.32 (m, 1H, -CH), 3.10 (d, *J* = 5.2 Hz, 2H, -CH_2), 3.61 (d, J = 5.6 Hz, 2H, -OCH_2), 3.62 (s, 3H, -OCH_3), 4.64 (s, 2H, -O-CH_2), 5.68 (t, *J* = 5.8Hz, 1H, -NH-C=O), 7.44-6.94 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (C-21), 22.1 (C-12), 22.7 (C-11), 33.2 (C-9), 40.2 (C-18), 42.4 (C-13), 46.4 (C-15 and C-16), 53.2 (C-7), 54.2 (C-14),61.4(C-20),65.1(C-17), 76.0 (C-8), 111.4(C-2), 112.5 (C-6), 118.2 (C-4), 128.2 (C-5), 128.5 (C-10), 146.2 (C-3), 154.2 (C-19), 160.2 (C-1). Anal. Calcd. for $C_{21}H_{34}N_2O_4$: C 66.64, H 9.05, N 7.40. Found: C 66.58, H 9.01, N 7.32.

iso-Butyl2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy) ethylcarbamate (***5e***): Yield: 76 %; White, M.p.: 151-153 ^{o}C. IR (KBr), *ν*max (cm^{-1}):1745 (-C=O), 3268 (-NH);^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38-1.22 (q, 6H, -CH_3), 1.32-2.08 (m, 8H, -CH_2), 1.92 (m, 1H, -$CH(CH_3)_2$, 2.10 (d, *J* = 5.2 Hz, 2H, -CH_2), 2.22 (s, 6H, -$(CH_3)_2$), 2.32 (m, 1H,-CH), 3.10 (s, 2H, -CH_2), 3.61(d, *J* = 4.8 Hz, 2H, -OCH_2), 3.62 (s, 3H, -OCH_3), 4.64 (s, 2H, -O-CH_2), 5.64 (t, *J* = 5.6 Hz, 1H, -NH-C=O), 7.38-6.96 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 (C-22 and C-23), 22.1 (C-12), 22.7 (C-11), 26.6 (C-21), 33.2 (C-9), 40.2 (C-18), 42.4 (C-13), 46.4 (C-15 and C-16),53.2(C-7),54.2(C-14), 65.1 (C-17), 71.4 (C-20), 76.0 (C-8), 111.4 (C-2), 112.5 (C-6), 118.2 (C-4), 128.2 (C-5), 128.5 (C-10), 146.2 (C-3), 152.7 (C-19), 160.2 (C-1); LC-MS: *m/z:* 406 [100, M+.]. Anal. Calcd. for $C_{23}H_{38}N_2O_4$: C 67.95, H 9.42, N 6.89. Found: C 67.89, H 9.36, N 6.83.

N-(2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy)ethyl)-4-nitro benzenesulfonamide (***7a***): Yield: 88%; Yellow, M.p.: 121-123^{o}C. IR (KBr), *ν*max (cm^{-1}):1328 (-S=O), 3245 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58-1.32 (m, 4H, -CH_2), 1.62 (t, *J* = 5.0 Hz, 2H, -CH_2), 2.17 (d, *J* = 5.4 Hz, 2H,-CH_2), 2.22 (t, *J* = 5.2 Hz, 2H, -CH_2), 2.24 (s, 6H, -$(CH_3)_2$), 2.38 (d, *J* = 5.8 Hz, 1H, -CH), 3.10 (s, 2H, -CH_2), 3.22 (t, *J* = 5.2 Hz, 1H, -NH-SO_2), 3.60 (d, *J* = 5.0 Hz, 2H, -OCH_2), 3.62 (s, 3H, -OCH_3), 8.20-7.82 (m, 4H, Ar'-NH), 7.46-6.87 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2 (C-11), 22.4 (C-12), 33.6 (C-9), 40.8 (C-18), 42.2 (C-13), 46.4 (C-15 and C-16), 54.0 (C-14), 55.6 (C-7), 65.1 (C-17), 76.2 (C-8), 161.2 (C-1), 110.2 (C-2), 113.4 (C-6), 119.2 (C-4), 124.5 (C-3 'and C-5'), 128.3 (C-2' and C-6'), 128.6 (C-5), 128.8 (C-10), 147.5 (C-3), 148.2 (C-4'), 150.4 (C-1'); LC-MS: *m/z:* 491 [100, M+.]. Anal. Calcd. for $C_{24}H_{33}N_3O_6S$: C 67.95, H 9.42, N 6.89. Found: C 67.90, H 9.38, N 6.82.

4-Bromo-N-(2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy)ethyl) benzenesulfonamide (***7b***): Yield: 86 %; Brown, M.p.: 128-130 ^{o}C. IR (KBr), *ν*max (cm^{-1}): 1356 (-S=O), 3232 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57-1.31 (m, 4H, -CH_2), 1.64 (t, *J* = 5.2 Hz, 2H,-CH_2), 2.16 (d, *J* = 5.0 Hz, 2H,-CH_2), 2.28 (s, 6H, -$(CH_3)_2$), 2.34 (d, *J* = 5.4 Hz, 1H, -CH), 3.14 (s, 2H, -CH_2), 3.18 (t, *J* = 5.8 Hz, 1H, -NH-SO_2), 3.64 (d, *J* = 5.0 Hz, 2H, -OCH_2), 3.68 (s, 3H, -OCH_3), 7.42-7.34 (m, 4H, Ar'-NH), 7.32 (t, *J* = 5.2 Hz, 2H, -CH_2), 7.18-6.89 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6 (C-11), 22.8 (C-12), 33.2 (C-9), 40.2 (C-18), 42.4 (C-13), 46.1 (C-15 and C-16), 54.2 (C-14), 55.7 (C-7), 65.4 (C-17), 76.4 (C-8), 113.2 (C-6), 110.3 (C-2), 119.6 (C-4), 123.2 (C-3' and C-5'), 126.4 (C-4'),128.4(C-5),127.2 (C-2' and C-6'), 128.2 (C-10), 143.4 (C-1'), 147.4 (C-3), 161.5 (C-1). Anal. Calcd. for $C_{24}H_{33}BrN_2O_4S$: C 54.85, H 6.33, N 5.33. Found: C 54.81, H 6.28, N 5.28.

4-Chloro-N-(2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy)ethyl)-3-nitrobenzenesulfonamide (***7c***): Yield: 85 %, White, M.p.: 132-134 ^{o}C; IR (KBr), *ν*max (cm^{-1}): 1346 (-S=O), 3228 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54-1.38 (m, 4H, -CH_2), 1.42 (t, *J* = 5.0 Hz, 2H, -

CH_2), 2.12 (t, *J* = 4.8 Hz, 2H, -CH_2), 2.14 (s, 6H, -$(CH_3)_2$), 2.18 (d, *J* = 5.0 Hz, 2H,-CH_2), 2.37 (d, *J* = 5.2 Hz, 1H, -CH), 3.12 (2H, s, -CH_2), 3.16 (t, *J* = 4.8 Hz, 1H, -NH-SO_2), 3.52 (s, 3H, -OCH_3), 3.58 (d, *J* = 5.4 Hz, 2H, -OCH_2), 7.43-6.89 (m, 4H, Ar-H), 8.12-7.82 (m, 3H, Ar'-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.4 (C-9), 22.2 (C-12), 22.8 (C-11), 40.8 (C-18), 42.7 (C-13), 46.2 (C-15 and C-16), 54.6 (C-14), 55.2 (C-7), 65.6 (C-17), 76.6 (C-8), 110.4 (C-2), 113.4 (C-6), 119.2 (C-4), 123.1 (C-3'), 124.6 (C-6'), 126.4 (C-4'),127.7 (C-2'), 128.5 (C-5), 128.6 (C-10), 133.2 (C-1'), 147.1 (C-3), 147.2 (C-5'), 161.1 (C-1); LC-MS: *m/z:* 526 [100, M+.], 528 [33, M+2]. Anal. Calcd. for $C_{24}H_{33}BrN_2O_4S$: C 54.80, H 6.13, N 7.99. Found: C 54.74, H 6.08, N 7.92.

*3-Chloro-N-(2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy)ethyl)-4-fluorobenzenesulfonamide (**7d**)*: Yield: 90%; White, M.p.: 122-124 ^oC; IR (KBr), *ν*max (cm^{-1}):1336 (-S=O), 3262 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 5.0 Hz, 2H, -CH_2), 1.78-1.61 (m, 4H, -CH_2), 2.04 (d, *J* = 5.4 Hz, 2H,-CH_2), 2.18 (t, *J* = 5.2 Hz, 2H, -CH_2), 2.24(s, 6H,-$(CH_3)_2$), 2.52 (d, *J* = 5.2 Hz, 1H,-CH), 2.94 (s, 2H, -CH_2), 3.17 (t, *J* = 5.6 Hz, 1H,-NH-SO_2), 3.52 (d, *J* = 4.8 Hz, 2H,-OCH_2), 3.58 (s, 3H,-OCH_3), 7.46-6.92 (m, 4H, Ar-H), 8.21-7.52 (m, 3H, Ar'-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4 (C-11), 22.6 (C-12), 33.1 (C-9), 40.2 (C-18), 42.8 (C-13), 46.0 (C-15 and C-16), 54.2 (C-14), 55.4 (C-7), 65.4 (C-17), 76.2 (C-8), 110.6 (C-2), 113.5 (C-6), 116.6 (C-3'), 118.6 (C-4), 120.6 (C-5'), 124.2 (C-6'), 127.2 (C-2'), 128.2 (C-10), 128.7 (C-5), 136.5 (C-1'), 146.2 (C-3), 160.2 (C-1), 161.2 (C-4'); LC-MS: *m/z:* 499 [100, M+.], 501[33, M+2]. Anal. Calcd. for $C_{24}H_{32}ClFN_2O_4S$: C 57.76, H 6.46, N 5.61. Found: C 57.63, H 6.41, N 5.56.

*N-(2-((1R)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexyloxy)ethyl)-1,1,1-trifluoromethanesulfonamide (**7e**)*: Yield: 76 %; Yellow, M.p.: 122-124 ^oC; IR (KBr), *ν*max (cm^{-1}):1352 (-S=O), 3238 (-NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52-1.46 (m, 4H, -CH_2), 1.58 (t, *J* = 5.0 Hz, 2H, -CH_2), 2.06 (t, *J* = 5.2 Hz, 2H, -CH_2), 2.17 (d, *J* = 5.0 Hz, 2H,-CH_2), 2.21 (s, 6H, -$(CH_3)_2$), 2.34 (d, *J* = 5.2 Hz, 1H, -CH), 3.17 (2H, s, -CH_2), 3.19 (t, *J* = 5.2 Hz, 1H, -NH-SO_2), 3.56 (d, *J* = 4.8 Hz, 2H, -OCH_2), 3.58 (s, 3H, -OCH_3), 7.45-6.94 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4 (C-12), 22.8 (C-11), 33.4 (C-9), 40.8 (C-18), 42.0 (C-15 and C-16), 42.2 (C-13), 54.1 (C-14), 55.1 (C-7), 62.1 (C-17), 76.5 (C-8), 110.8 (C-2), 113.2 (C-6), 118.7 (C-4), 127.4 (C-5), 128.6 (C-10), 141.5 (-CF3), 146.4 (C-3),161.5 (C-1); LC-MS: *m/z:* 438 [100, M+.]. Anal. Calcd. for $C_{19}H_{29}F_3N_2O_4S$: C 52.04, H 6.67, N 6.39. Found: C 51.92, H 6.60, N 6.35.

2.3. Biological Activity

2.3.1.Antibacterial Activity

In vitro antibacterial activities of the newly synthesized compounds were evaluated for their antibacterial activity against two gram positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus*, two gram negative bacteria such as *Klebsiella pneumoniae* and *Escherichia coli* using disc diffusion method.[23-25] Ciproflaxacin was used as a standard drug. The bacterial cultures used are Gram positive *Staphylococcus aureus*, *Bacillus subtilis* and Gram-negative bacteria *Escherichia coli* and *Klebsiella pneumoniae*. The bacterial cultures were grown in nutrient agar media and subcultured for the better growth (log phase cultures) in a liquid nutrient broth medium and further sub cultured onto the Petri plates for the experiments. The broth cultures were diluted with sterilized saline to bring the final size of inoculums approximately to 10^5–10^6 CFU/mL. The compounds were diluted in acetone, DMSO and diethyl ether for biological assays. Among the three solvents diethyl ether is taken as the best solvent than the remaining two solvents. The bacterial culture inoculums were placed on the media and incubated at 37^{o}C for 24 h to 48 h along with the chemical discs dipped and placed over the media. The zone of bacterial growth inhibition was measured using the diameter of the zone as a unit to measure the anti-bacterial activity. All the experiments were carried out in triplicates and the results were expressed as Zone of Inhibition in mm. The results were compared with the activity of the standard antibiotic ciprofloxacin (150 µg/mL). For disc diffusion method, the test compound was introduced onto the disc and then allowed to dry. Once the disc was completely saturated with the test compound and then it was introduced onto the upper layer of the medium containing the bacterial inoculums. The petri

dishes were incubated overnight at 37 °C for 24 h. Bioactivity was determined by measuring Diameter of Inhibition Zones (DIZ) in mm and the results are represented in Table 1.

2.3.2. Antifungal Activity

The antifungal activity of titled compounds was tested against three pathogenic fungi, *Fusarium oxysporum*, *Aspergillus niger* and *Aspergillus flavus* using poison plate technique.[26,27] Clotrimazole was used as a standard drug. Test compounds were dissolved in diethyl ether (10 mL) before mixing with Potato Dextrose Agar medium (PDA, 90 mL). The final concentration of compounds in the medium was maintained at 250 µg/mL. Above mentioned types of fungi were incubated in PDA at 25±1 °C for 3-4 days to get good mycelium growth for antifungal assay, then a mycelia disk of approximately 0.45 cm diameter cut from the culture medium was picked up with a sterilized inoculation needle and inoculated in the center of PDA plate. The inoculated plates were incubated at 25±1°C for 5 days. Diethyl ether in sterilized distilled water used as control, while clotrimazole were used as positive controls for all the treatment, three replicates was performed. The radial growth of the fungal colonies was measured on the fourth day and the data were statistically analyzed. The *in vitro* inhibition effects of the test compounds on the fungi were calculated by the given formula CV =A-B/A, where A represents the diameter of fungi growth on untreated PDA, B represents the diameter of fungi on treated PDA, and CV represents the rate of inhibition. The diameter of zone of inhibition was shown in Table 2.

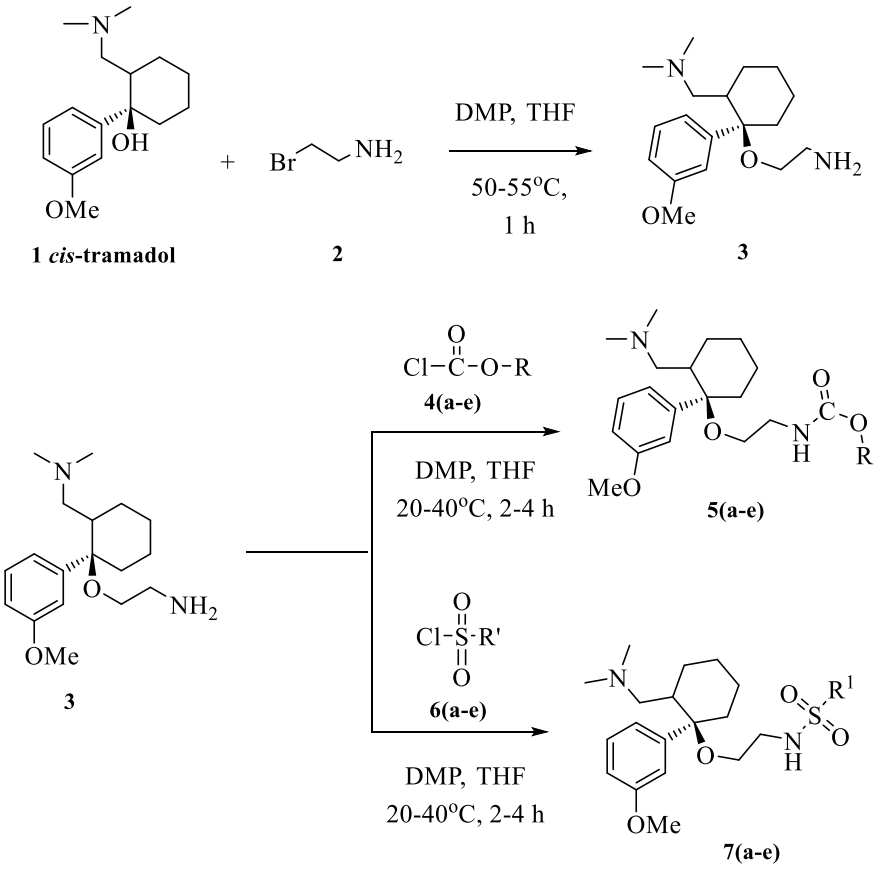
3. Results and Discussion

3.1. Chemistry

The newly synthesized carbamate and sulfonamide derivatives of *cis*-tramadol **5**(**a-e**) and **7**(**a-e**) were represented in Scheme1.

Carbamate and sulfonamide derivatives of *cis*-tramadol **5**(**a-e**) and **7**(**a-e**) were synthesized in two steps. In the first step, *cis*-tramadol was reacted with 2-bromoethan-1-amine in the presence of DMP, THF at 50-55^{o}C for 1 h resulted the formation of intermediate. In the second step, the intermediate was reacted with various chloroformates and sulfonyl chlorides in presence of DMP, THF at 20-40^{o}C for 2-4 h resulted the formation of crude compound. The progress of the reaction was monitored by TLC. After the completion of the reaction, the crude reaction mixture was concentrated under rota-evaporator and purified by column chromatography using ethyl acetate and hexane (2:1) as an eluent to obtain pure title compounds **5**(**a-e**) and **7**(**a-e**).

The structures of all the newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analyses. The details are provided in the experimental section. In IR spectra, the absorption bands in the region 1328-1356, 1734-1748 and 3218-3268 cm^{-1} were assigned to -S=O, –C=O and -NH stretching frequencies. In ^{1}H NMR spectra, the chemical shift in the region δ 2.32 to 2.52 ppm resonated as a multiplet and doublet and it corresponds to aliphatic CH and CH_2 protons. The chemical shift in the region of δ 3.16-3.22 ppm appeared as a triplet and it corresponds to -$NHSO_2$ protons. A doublet was observed in the region of δ 3.52-3.71 ppm and is assigned to -OCH_2 protons. The chemical shift in the region of δ 3.62-4.03 ppm appeared as a singlet and it corresponds to -OCH_3 protons. The aromatic protons were resonated as multiplets in the region of δ 6.86 to 8.16 ppm. Further, the structural confirmation of the synthesized compounds **5**(**a-e**) and **7**(**a-e**) was confirmed ^{13}C NMR by the corresponding mass and elemental analyses.



compound	R	compound	R^1
5a	O_2N—C_6H_4—CH_2—	**7a**	O_2N—C_6H_4—
5b	O_2N—C_6H_4—	**7b**	Br—C_6H_4—
5c	Cl_3CH_2C—	**7c**	Cl, O_2N—C_6H_3—
5d	H_3CH_2C—	**7d**	F, Cl—C_6H_3—
5e	$(H_3C)_2HCH_2C$—	**7e**	F_3C—

Scheme 1. Synthesis of carbamate and sulfonamide derivatives of *cis*-tramadol

3.2. *Biological Activity*

3.2.1 Antibacterial Activity

All the newly synthesized compounds were evaluated for their antibacterial activity against two-gram positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus*, two-gram negative bacteria

such as *Klebsiella pneumoniae* and *Escherichia coli* using disc diffusion method. Ciproflaxacin was used as a standard drug. Compounds **5a**, **5b**, **7a** and **7c** have exhibited potent antibacterial activity against all the tested microorganisms. This might be due to the presence of nitro and chloro substituents on the benzene ring. The diameter of zone of inhibition was presented in Table 1.

Table 1. Antibacterial activity of the newly synthesized carbamate and sulfonamide derivatives of *cis*-tramadol **5**(**a-e**) and **7**(**a-e**)

Compounds	*B. subtilis*	*S. aureus*	*K. pneumoniae*	*E.coli*
5a	20	22	20	22
5b	18	20	18	19
5c	11	9	10	12
5d	13	13	14	10
5e	9	11	12	11
7a	21	19	18	20
7b	8	5	6	5
7c	20	18	19	19.5
7d	11	14	12	12
7e	14	10	10	14
Ciprofloxacin	22	24	23	24
Control	-	-	-	-

* The zone diameters measured at the concentration of 150 µg/mL

3.2.2 Antifungal Activity

In vitro antifungal activities of the newly synthesized compounds were tested against three fungal strains *Aspergillus niger*, *Aspergillus flavus* and *Fusarium oxysporum* using poison plate technique. Clotrimazole was used as a standard drug. Compounds **5a**, **5b**, **7a** and **7c** have exhibited potent antifungal activity against all the fungal strains, due to the presence of nitro and chloro substituents on the benzene ring. The diameter of zone of inhibition was shown in Table 2.

Table 2. Antifungal activity of the newly synthesized carbamate and sulfonamide derivatives of *cis*-tramadol **5(a-e)** and **7(a-e).**

Compound	*A.niger*	*A.flavus*	*F.oxysporum*
5a	15.8	13.6	17.5
5b	14.6	12.9	15.1
5c	2.5	6.1	4.2
5d	8.7	6.2	7.9
5e	8.1	9.2	4.7
7a	16.2	13.3	15.2
7b	7.8	7.8	6.8
7c	15.8	14.2	16.5
7d	8.4	9.2	8.7
7e	6.5	5.7	6.9
Clotrimazole	17.3	16.7	18.2
Control	-	-	-

* The zone diameters measured at the concentration of 150 µg/mL

4. Conclusion

We have synthesized a series of new carbamates and sulfonamide derivatives of *cis*-tramadol **5**(**a-e**) and **7**(**a-e**) by reacting the *cis*-tramadol with various chloroformates and

sulfonyl chlorides in presence of DMP, THF at 20-40ºC for 2-4 h with good yields. All the newly synthesized compounds were characterized by the spectral analyses. The newly synthesized compounds were screened for their antibacterial and antifungal activities. Compounds **5a**, **5b**, **7a** and **7c** have exhibited potent antibacterial and antifungal activities against the tested strains. On the basis of biological results, it is concluded that, these compounds may prove useful antimicrobial agents in future.

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