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Original Article

SYNTHESIS, CHARACTERIZATION AND *IN VITRO* ANTIMICROBIAL EVALUATION OF SOME NEW AMIDES OF THIOMORPHOLINE CARBOXYLATE

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ABSTRACT

Objective: Synthesis and antimicrobial evaluation of some new amides of Thiomorpholine caboxylate.

Methods: A series of new amides of Thiomorpholine caboxylate were synthesized by reacting 4-tert-butyl 2-methyl thiomorpholine-2,4-dicarboxylate 1,1-dioxide with primary amines in presence of Trimethyl aluminum in toluene at ambient temperature in good yields. 4-tert-butyl 2-methyl thiomorpholine-2,4-dicarboxylate 1,1-dioxide was synthesized by reacting tert-butyl thiomorpholine-4-carboxylate 1,1-dioxide with methyl chloroformate in presence of LiHMDS (1M in THF) at -78°C for the first time. The newly synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}C NMR, Mass spectral studies and elemental analysis.

Results: A series of new amides of Thiomorpholine carboxylate were synthesized in good yields and all the compounds were screened for their In-vitro antimicrobial activities.

Conclusion: Preliminary results revealed that the synthesized compounds were showed moderate to good antibacterial and antifungal activity.

Keywords: Antimicrobial activity, Thiomorpholine, Trimethylaluminum, LiHMDS.

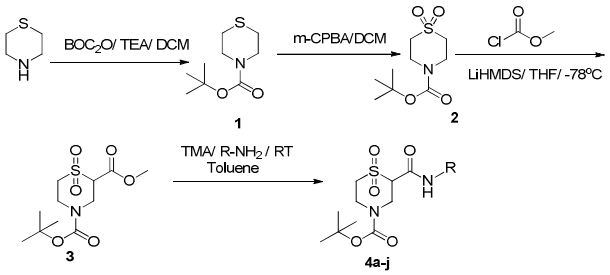
INTRODUCTION

Thiomorpholine units and amides of various heterocyclic compounds have attracted much attention for their remarkable pharmacological activities and have been explored as one of the best pharmacophores. Thiomorpholine derivaties have diverse biological activities that include DPP-IV inhibitors [1], anti-inflammatory [2], antioxidant [3-4], anti-microbial[5], hypertensive [6], anaesthatic [7], antiplatelet[8], antibacterial & Cytotaxin [9], anti-cancer [10], analgesic & hypothertic [11], antimycobacterial [12] and hypnotonic [13]. Considering the above facts and our search on Thiomorpholine linked biologically potent molecules, we herein report the synthesis of some new amides of Thiomorpholine Carboxylate and their microbial activity.

MATERIALS AND METHODS

All reagents and solvents were purchased from commercial suppliers and were purified and dried when necessary by standard techniques. The structures of newly synthesized compounds were established on the basis of, ^{1}H NMR, FTIR, ^{13}C NMR, mass spectral data and elemental analysis. The ^{1}HNMR spectra were recorded on Brucker 300 and 400MHz spectrometer using TMS as internal standard. The Chemical shifts values are given in δ ppm. The FTIR spectra were recorded by using Perkin Elmer FTIR spectrometer using a thin film on KBr pellets and frequencies were expressed in cm^{-1}. The Mass spectra were recorded by the EI process. The elemental analyses were performed on Perkin Elmer CHNS/O analyzer 2400. Melting points were determined on open capillaries using a cintex melting point apparatus and are uncorrected. Follow up of the reactions and checking the purity of the compounds was made by thin layer chromatography (TLC) on silica gel precoated aluminum sheets (Type 60 GF254; Merck; Germany) and the spots were detected by exposure to UV lamp at λ 254 nm for few seconds.

The synthesis of thiomorpholine moiety was reported by several groups and N-substituted thiomorpholines were reported [14]. The reactions on C's of thiomorpholines are very few. In this work, we are reporting the synthesis of thiomorpholine carboxylate amides for the first time. The synthetic route for thiomorpholine carboxylate and amides is represented in **scheme 1**. The reaction of Compound-2 with methylchloroformate in presence of LiHMDS (1M in THF) resulted thiomorpholine carboxylate in excellent yield (98%). Compound-3 was treated with different amines in presence of Trimethyl aluminum (2M in Toluene) to afford new amide derivatives of thiomorpholine carboxylate **(4a-j)** in good yields.



Scheme 1: Synthetic route for new amides of Thiomorpholine carboxylate

Experimental

Synthesis of N-tert-butyloxycarbonyl thiomorpholine, 1

A solution of BOC_2O (21.16g, 97 mmol) in dichloromethane (100 mL) was added to a solution thiomorpholine (10 g, 97 mmol) and triethylamine (16.23 mL, 116 mmol) in dichloromethane (500 mL). The mixture was stirred for 1 hour at room temperature and monitored by TLC. Ethyl acetate (400 mL) was added and the organic solution was washed with citric acid (3X250 mL, 1M), water (3X250 ml), brine (250 ml), dried over anhydrous sodium sulphate and evaporated in vacuo to afford N-tert-butyloxycarbonyl thiomorpholine, **1** as a colourless solid (19.5g, 99%).

Synthesis of tert-butyl thiomorpholine-4-carboxylate 1,1-dioxide, 2

N-tert-butyloxycarbonyl thiomorpholine (15 g, 73.89 mmol) was dissolved in dichloromethane (500 ml), m-chloroperbenzoic acid (25.49 g, 147.78 mmol) was gradually added while cooled with ice bath. The reaction mixture was stirred at room temperature for 12h. After completion of reaction, was added a saturated aqueous

solution of sodium thiosulfate, extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude. The crude was purified by column chromatography using 30-35% ethyl acetate in hexane as eluent to afford tert-butyl thiomorpholine-4-carboxylate 1,1-dioxide, **2** as off white solid.

Synthesis of 4-tert-butyl 2-methyl thiomorpholine-2,4-dicarboxylate 1,1-dioxide, 3

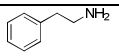
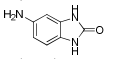
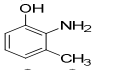
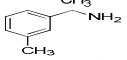
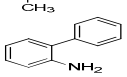
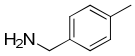
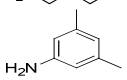
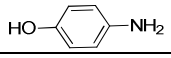
To a stirred solution of tert-butyl thiomorpholine-4-carboxylate 1,1-dioxide (42.55 mmol) in THF (300 mL) was added dropwise 1M solution of LiHMDS (42.55 mmol) at -78^{0}C and the resulting reaction mixture was stirred under the nitrogen atmosphere for 1h. Methylchloroformate (42.55 mmol) was added drop wise to the above reaction mixture and stirred for 2h at -78^{0}C. The reaction mixture was added to NH_4Cl solution (200 mL) and the product was extracted with EtOAc (3 x 150 mL) to obtain crude compound. The crude was recrystalized from diethylether, filtered and dried under vacuum to afford 4-tert-butyl 2-methyl thiomorpholine-2,4-dicarboxylate 1,1-dioxide, **3** as off white solid.

General Method for synthesis of 4a-j [15]

To a stirred solution of alkylamine (0.34 mmol) in Toluene was added Trimethylaluminum (2M in Toluene, 1.02 mmol) at 0^{0}C and allowed to stir for 15 min. A solution of 4-tert-butyl 2-methyl thiomorpholine-2,4-dicarboxylate 1,1-dioxide (0.34 mmol) in toluene was added drop wise to the reaction mixture under N_2 and stirred for overnight at room temperature. The reaction mixture was poured into crushed ice, added 2N HCl, basified to pH 9- 10 with NH_4OH and organic phase was separated.

The aqueous phase was washed with more CH_2Cl_2 the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The crude was chromatographed on silica gel (100-200 mesh), eluting with a gradient mixture of (30-35%) ethylacetate in hexane as eluent, giving (**4a-f)** as pure compounds (**Table 1**).

Table 1: It represents molecular formulas and yields of final compounds (4a-j)

S. No.	Compound	R	Molecular Formula (4a-j)	Molecular Weight	Yield (%)
1	4a		$C_{18}H_{26}N_2O_5S$	382.474	85
2	4b		$C_{17}H_{22}N_4O_6S$	410.445	82
3	4c		$C_{17}H_{24}N_2O_5S$.	368.448	90
4	4d		$C_{17}H_{24}N_2O_6S$	384.44	84
5	4e		$C_{18}H_{26}N_2O_5S$	382.474	88
6	4f		$C_{22}H_{26}N_2O_5S$	430.517	89
7	4g	NH_2-NH_2. H_2O	$C_{10}H_{19}N_3O_5S$	293.340	86
8	4h		$C_{18}H_{26}N_2O_5S$	382.474	88
9	4i		$C_{18}H_{26}N_2O_5S$	382.474	84
10	4j		$C_{16}H_{22}N_2O_6S$	370.421	92

Spectral data

N-tert-butyloxycarbonyl thiomorpholine, **1:** Yield (99%); Offwhite solid: ^{1}HNMR (CDCl3, 300 MHz): 3.71-3.64 (m, 4H), 2.60-2.52 (m, 4H), 1.45 (s, 9H); ESI-MS 148 (M^+- t-Butyl)

tert-butyl thiomorpholine-4-carboxylate 1,1-dioxide, 2: Yield (89%); Off white solid; M. P: 157 - 159 ^{o}C: ^{1}H NMR ($CDCl_3$, 300Mz): δ 4.0 - 3.9 (m, 4H), 3.10 - 2.90 (m, 4H), 1.44 (s, 9H): ESI-MS: 180 (M^+- t-Butyl)

4-tert-butyl 2-methyl thiomorpholine-2,4-dicarboxylate 1,1-dioxide,3: Yield (98%); Off white Solid**;** M. P**:** 110-113^{o}C; ^{1}H NMR (DMSO-d_6, 400MHz): δ 4.37 (br, 1H), 4.11-3.86 (m, 3H), 3.72-3.47 (br, 4H), 3.41- 3.36 (br, 1H), 3.26-3.25(m, 1H), δ 1.41 (s, 9H); ESI-MS: 180 (M^+- t-Butyl)

tert-butyl 2-(phenethylcarbamoyl) thiomorpholine-4-carboxylate 1,1-dioxide, 4a: Offwhite solid; M. P: 95-98^o**C**; FTIR (KBr, cm^{-1});3385, 3072, 1685, 1585, 1273, 1106, 757; **^{1}H NMR (DMSO-d6, 400MHz):** δ 8.40-8.20 (br, 1H), 7.40- 7.10 (m, 5H), 4.18 - 3.90 (m, 2H), 3.80 - 3.50 (m, 5H), 3.20 - 3.10 (m, 2H), 2.80 - 2.60 (m, 2H), 1.41 (s, 9H). **^{13}C–NMR (DMSO, 125Mz):**δ 163.42 (CONH), 153.18 (COBoc), 139.02 (Ar-CH),128.63(2,Ar-CH),128.36(2,Ar-CH), 126.18 (CH), 80.00 (-$(CH3)_3$CO-), 63.01(CH), 50.81(CH_2), 49.25(CH_2), 45.66 (CH_2), 40.58 ($NHCH_2$), 34.85 (Ar-CH_2), 27.79 (CH_3):**EI-MS (m/z):** 327(M^+- t-Butyl); Anal. Cald. for $C_{18}H_{26}N_2O_5S$; C, 56.52; H, 6.85; N, 7.32; O, 20.92; S, 8.38; Found: C, 56.48; H, 6.81; N, 7.36; O, 20.88; S, 8.34

tert-butyl 2-((2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl) carbamoyl) thiomorpholine -4-carboxylate 1,1-dioxide, 4b; Offwhite solid. **M. P:** 258- 260^o**C**; **FTIR (KBr, cm^{-1}):** 3388, 2978, 1693,1566, 1295, 868, 710; **^{1}H NMR (DMSO-D_6, 400MHz)**: δ 10.62 (s, 1H), 10.55 (s, 1H), 10.22-10.18(br, 1H), 7.46 (s, 1H), 7.02-6.85 (br, 1H), 6.87-6.85 (d, *j*= 8.0Hz, 1H), 4.40-4.20 (br, 2H), 4.02 -3.90(m, 1H), 3.80-3.70 (m, 1H), 3.70-3.55 (m, 1H), 3.42.-3.30 (m, 1H), 3.22-3.16 (m, 1H), 1.41 (s, 9H). **EI-MS (m/z):** 355(M^+- t-Butyl); Anal. Cald. for $C_{17}H_{22}N_4O_6S$: C, 49.75; H, 5.40; N, 13.65; O, 23.39; S, 7.81;Found; C, 49.68; H, 5.46; N, 13.60; O, 23.32; S, 7.78

tert-butyl 2-(benzylcarbamoyl)thiomorpholine-4-carboxylate 1,1-dioxide, 4c: Offwhite solid; **M. P**: 85-90^{o}C; **FTIR (KBr, cm^{-1}):** 3345, 3088, 1687,1609,1267,1100, 833, 751: **^{1}H NMR (DMSO-D_6, 400MHz):** δ 8.80-8.65 (br, 1H), 7.4-7.2(m, 5H), 4.5-4.1 (br, 4H), 3.95-3.85 (m, 1H), 3.80-3.50 (m, 3H), 3.20-3.10 (m, 1H), 1.35(s, 9H). **EI-MS (m/z):** 313 (M^+- t-Butyl); Anal. Cald. for $C_{17}H_{24}N_2O_5S$; C, 55.42; H, 6.57; N, 7.60; O, 21.71; S, 8.70; Found; C, 55.39; H, 6.50; N, 7.58; O, 21.61; S, 8.65.

tert-butyl 2-[(2-hydroxy-6-methylphenyl) carbamoyl] thio morpholine-4-carboxylate 1,1-dioxide, 4d; Light yellow solid; **M. P**; 90- 92; **FTIR (KBr, cm^{-1}):** 3601, 3341,3064, 1693,1601,1521,1203, 850, 711 ^{1}H NMR (DMSO-d_6, 400MHz): δ 9.44(s, 1H), 9.35-9.18(b, 1H), 6.98 (t, *j*= 7.6Hz, *j*= 8Hz,1H), 6.71-6.64 (dd, *j*= 7.6Hz, *j*= 8.0Hz, 2H), 4.40-4.30(m, 1H), 4.25-4.15 (m, 2H), 4.00-3.70 (m, 2H), 3.55-3.40 (m, 2H), 3.20-3.10 (m, 1H) 2.08 (s, 3H),1.5-1.25 (br, 9H); **EI-MS (m/z):**329(M^+- t-Butyl); Anal. Cald. for

$C_{17}H_{24}N_2O_6S$; C, 53.11; H, 6.29; N, 7.29; O, 24.97; S, 8.34;Found; C, 53.08; H, 6.26; N, 7.27; O, 24.94; S, 8.30

tert-butyl 2-(m-tolylcarbamoyl)thiomorpholine-4-carboxylate 1,1-dioxide, 4e: Brownsolid: **M. P;** 82- 84^oC; **FTIR (KBr, cm^{-1}):** 3376, 3068, 1696,1606,1270,1099, 847, 751: ^1H NMR (DMSO-d_6, 400 MHz): δ 8.80-8.60 (br, 1H), 7.25 (s, 1H), 7.20-7.00 (m, 3H), 4.50-4.11 (m, 3H), 4.10-3.80 (m, 2H), 3.80-3.50 (m, 1H), 3.20-3.10 (m, 2H), 2.25 (s, 3H), 1.40 (s, 9H); **EI-MS (m/z):**327(M^+- t-Butyl); Anal. Cald. for $C_{18}H_{26}N_2O_5S$**; C, 56.52;** H, 6.85; N, 7.32; O, 20.92; S, 8.38; Found: C, 56.48; H, 6.80; N, 7.28; O, 20.94; S, 8.34.

tert-butyl 2-([1,1'-biphenyl]-2-ylcarbamoyl)thiomorpholine-4-carboxylate 1,1-dioxide, 4f: Offwhite solid; **M. P**: 148-150; **FTIR (KBr, cm^{-1}):** 3359, 3072, 1695,1588,1269,1098,1008, 759: **1H NMR (DMSO-d6, 300MHz**): δ 9.65-9.58 (br, 1H), 7.7-7.50(br, 1H), 7.50-7.30 (m, 8H), 4.4-4.0 (br, 3H), 3.80-3.40 (br, 3H), 3.29-3.10 (m, 1H), 1.4 (s, 9H); **EI-MS (m/z):**375 (M^+- t-Butyl); Anal. Cald. for $C_{22}H_{26}N_2O_5S$; C, 61.38; H, 6.09; N, 6.51; O, 18.58; S, 7.45; Found; C, 61.30; H, 6.15; N, 6.50; O, 18.52: S, 7.42.

tert-butyl 2-(hydrazinecarbonyl)thiomorpholine-4-carboxylate 1,1-dioxide, 4g: Offwhite solid; **M. P;** 120- 125; **FTIR (KBr, cm^{-1}):** 3348, 2933, 1689, 1590, 1426, 1298, 875, 611: ^1H NMR (DMSO-d_6, 400MHz): δ 9.50- 9.30 (b, 1H), 4.50-4.30 (m, 2H), 4.20-4.00 (b, 1H), 4.00-3.90 (b, 1H), 3.80-3.60 (m, 2H), 3.60-3.40 (m, 2H), 3.15-3.10 (m, 1H), 1.40 (s, 9H), **EI-MS (m/z):** 238 (M^+- t-Butyl); Anal. Cald. for $C_{17}H_{24}N_2O_6S$; C, 53.11; H, 6.29; N, 7.29; O, 24.97; S, 8.34;Found; C, 53.08; H, 6.26; N, 7.27; O, 24.94; S, 8.30

tert-butyl 2-((4-methylbenzyl)carbamoyl)thiomorpholine-4-carboxylate 1,1-dioxide, 4h: Offwhite solid; **M. P**; 98- 100; **FTIR (KBr, cm^{-1}):** 3333, 3068, 1696,1511, 1456, 1256, 847, 769: ^1H NMR (DMSO-d_6, 400MHz): δ 8.60-8.80 (b, 1H), 7.35 (d, J=8.2 Hz, 2H), 7.05 (d, J=8.2 Hz, 2H), 4.40-4.11 (m, 3H), 4.10-3.80 (m, 2H), 3.80-3.50 (m, 2H), 3.20-3.10 (m, 2H), 2.25 (s, 3H), 1.40 (s, 9H): **EI-MS (m/z):** 327(M^+- t-Butyl); Anal. Cald. for $C_{17}H_{24}N_2O_6S$; C, 53.11; H, 6.29; N, 7.29; O, 24.97; S, 8.34;Found; C, 53.08; H, 6.26; N, 7.27; O, 24.94; S, 8.30

tert-butyl 2-((3,5-dimethylphenyl)carbamoyl)thiomorpholine-4-carboxylate 1,1-dioxide, 4i: Offwhite solid; **M. P;** 105-108; **FTIR (KBr, cm^{-1}):**3364, 3092, 1696,1608,1455,1211, 867, 697: ^1H NMR (DMSO-d_6, 400MHz): δ 9.00 (s, 1H), 7.30 (s, 2H), 6.70(s, 1H), 4.40-4.30(m, 1H), 4.25-4.15 (m, 2H), 4.00-3.70 (m, 2H), 3.55-3.40 (m, 1H), 3.20-3.10 (m, 1H) 2.25 (s, 6H),1.41 (s,9H); **EI-MS (m/z):** 327(M^+- t-Butyl); Anal. Cald. for $C_{17}H_{24}N_2O_6S$; C, 53.11; H, 6.29; N, 7.29; O, 24.97; S, 8.34;Found; C, 53.08; H, 6.26; N, 7.27; O, 24.94; S, 8.30

tert-butyl 2-((4-hydroxyphenyl)carbamoyl)thiomorpholine-4-carboxylate 1,1-dioxide, 4j: Offwhite solid; **M. P**; 95-98; **FTIR (KBr, cm^{-1}):** 3625, 3385, 3084,1674,1482, 1451, 981, 741: ^1H NMR (DMSO-d_6, 400MHz): δ 9.50(s, 1H), 9.40-9.20(b, 1H), 7.33 (d, *J*=6.8 Hz, 2H), 6.67 (d, *J*=6.9 Hz, 2H), 4.40-4.00 (m, 3H), 4.00-3.60 (m, 2H), 3.55-3.40 (m, 1H), 3.20-3.10 (m, 1H), 1.42(s, 9H); **EI-MS (m/z):** 315(M^+- t-Butyl); Anal. Cald. for $C_{17}H_{24}N_2O_6S$; C, 53.11; H, 6.29; N, 7.29; O, 24.97; S, 8.34;Found; C, 53.08; H, 6.26; N, 7.27; O, 24.94; S, 8.30.

Table 2: Zone of inhibition (mm) data of synthesized compounds (4a-j)

S. No.	Compound	B. subtilis	S. aureus	E. coli	S. typhi	A. niger	C. albicans
1	4a	8	7	7	6	10	8
2	4b	11	10	12	11	13	11
3	4c	9	6	8	4	9	6
4	4d	7	5	9	6	11	9
5	4e	9	4	8	6	10	8
6	4f	7	5	6	4	12	8
7	4g	9	7	10	7	8	6
8	4h	7	6	9	8	10	8
9	4i	8	7	9	6	11	8
10	4j	8	6	8	4	12	7
11	Control	-	-	-	-	-	-
12	A	16	15	19	16	-	-
13	B	-	-	-	-	19	17

Control=DMSO, **A**=Ciprofloxacin and B=Ketoconazole

RESULTS AND DISCUSSION

Antibacterial activity

The antibacterial activity of all the synthesized compounds (**4a-j**) was examined against different Gram-positive (Bacillus subtilise and Staphylococcus aureus) and Gram-negative (Escherichia coli and Salmonella typhii) organisms by measuring zone of inhibition. The antibacterial activity was performed by Agar diffusion method at the concentration level of 250µg/ml. Ciprofloxacin was used as the standard drug at a concentration of 250µg/ml. Nutrient agar was used as culture media and DMSO was used as the solvent control. The results of the antibacterial activity are shown in **Table 2.**

Antifungal activity

The antifungal activity of all the synthesized compounds (**4a-j**) was examined against *Aspergillus niger* and *Candida albicans* by measuring zone of inhibition. The antifungal activity was performed by Agar diffusion method at the concentration level of 250µg/ml. Ketoconazole was used as a standard drug at a concentration of 250µg/ml. Sabouraud dextrose agar was used as culture media and DMSO was used as solvent control. The results of the antifungal activity are shown in **Table 2.**

CONCLUSION

In accordance with the data obtained from antimicrobial activity, **4b** showed good antimicrobial activity against the tested microbes among all the synthesized amides and rest of the compounds showed moderate antimicrobial activity against tested microbes.

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