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Synthesis, characterization and antimicrobial activities of N-substituted indoline derivatives of sultams

S. Harikrishna* and L. K. Ravindranath

Department of Chemistry, Sri Krishnadevaraya University, Anantapur, Andhra Pradesh, India

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ABSTRACT

A new class of N-Substituted Indoline derivatives of Sultams namely (E)-2-benzyl-N'-(N-Substituted-2-oxoindolin-3-ylidene)-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carbohydrazide 1,1-di oxide (10-12) were synthesized through a process of mannich reaction where hydrazone derivative of Sultam (9) get reacted with pipperidine, Morpholine and Methylpipperazine to afford the title compounds. The structure of each novel compound was elucidated on the basis of elemental analysis, IR ^{1}H NMR and Mass spectral Analysis. All the newly synthesized compounds were screened for their antibacterial and antifungal activities. Antimicrobial studies revealed that the pharmacological properties of the synthesized compounds were enhanced by introducing pipperidine, Morpholine, Methylpipperazine substituents.

Key words: Sultams, Antibacterial activity, antifungal activity.

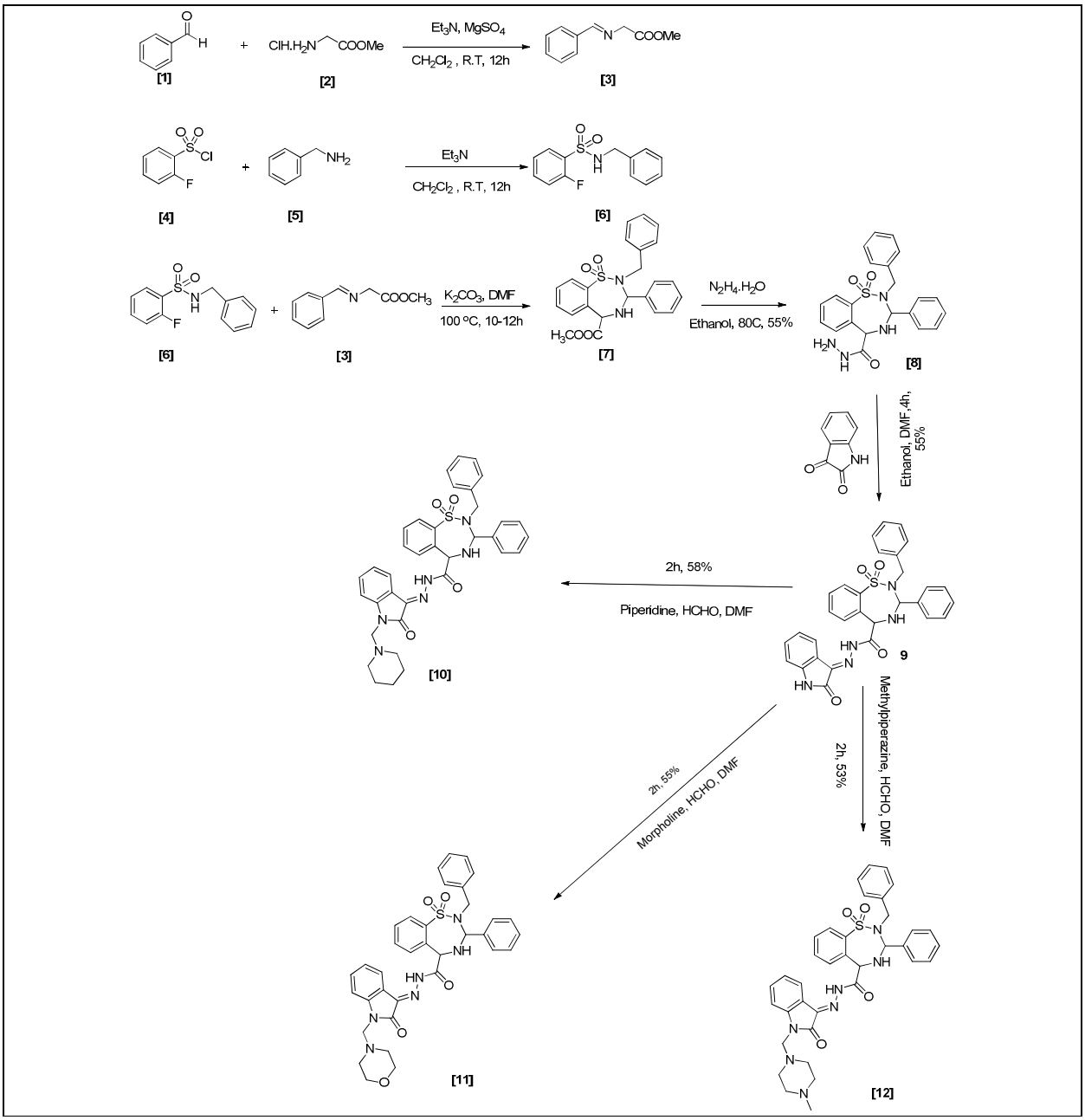
INTRODUCTION

Heterocyclic compounds play vital role in biological activities, Since their introduction, antimicrobials are one of most significant weapons in fighting bacterial infections. They have extremely benefited the health-related quality of human life. Over the past few decades, these health benefits are under threat as many commonly used antibiotics have become less effective against certain illnesses because of their toxic reactions and due to emergence of microbial resistance. Therefore, it is essential to investigate newer drugs with lower resistance [1-2]. Beside this, the lack of new antifungal drugs ascends proportionally to the increasing occurrence of serious infections caused by yeast and fungi mainly in immune compromised or in other way sensitive patients. Primary and opportunistic fungal infections continue to increase rapidly, and as a consequence of this situation, invasive fungal infections constitute a major cause of mortality for such patients. *Candida albicans* is one of the most common opportunistic fungi responsible for these kinds of infections. The current state of pharmacotherapy is briefly drawn out and most of attention is given to newly developed active entities. Established agents do not satisfy the medical needs completely as azoles are fungistatic and vulnerable to resistance, whereas polyenes cause serious host toxicity. Drugs in clinical development include modified azoles and a new class of echinocandins and pneumocandins[3-4]. Benzo[*b*]thiophenes are found to possess various biological activities such as antimicrobial[5-6], antioxidant[7], anti-HIV[8], anticancer[9] and antiviral[10] activities. In light of these interesting biological activities, it was our interest to synthesize some new indole derivatives of Sultams and evaluate their antimicrobial potential.

MATERIALS AND METHODS

All chemicals and reagents were obtained from Merck India Limited. Melting points were determined in open capillary tubes and were uncorrected (in degree Celsius). The infrared spectra of the compounds were recorded in KBr discs on FT-IR (Spectrum ONE) spectrometer manufactured by Perkin-Elmer. The ^{1}H NMR spectra were recorded on a JOEL (300 MHz) spectrometer using TMS as an internal standard (chemical shifts in δ). The Mass spectra were recorded on a mass spectrometer JOEL sx-102 (FAB). Nutrient broth, nutrientagar and 5 mm diameter antibiotic assay discs were obtained from Hi-Media Laboratories Limited, India. The standard bacterial and fungal strains were procured from National Centre for Cell Science (NCCS), Pune, India.

Scheme-1



RESULTS AND DISCUSSION

Sultams bearing Indoline moiety were synthesized by following the procedure as shown in the scheme-1. In the Process, methyl-2-(benzylideneamino)acetate (3) was synthesised by the reaction of benzaldehyde with an amino acid ester in DCM medium using $MgSO_4$ and TEA. The benzylidene ester (3) obtained were reacted with α-fluorosulfonamide derivative (6) which was obtained by the reaction of α-fluorobenzene sulfonyl chloride(4) with benzyl amine(5). The sultam (7) obtained was treated with hydrazine hydrate to remove ester linkage thus resulting a derivative of sultam (8) with an yield of 55%. This hydrazine derivative was reacted with isatin to obtain novel indole derivative of the sultam(9) with an yield of 55%. This compound 9 was treated with pipperidine, Morpholine and Methylpipperazine to afford the reported N-substituted indoline derivatives of sultam (10-12). The synthetic route for preparation of title compounds is given in Scheme-1. The assigned structure and molecular formula of the newly synthesized compounds (10-12) were further confirmed and supported by ^{1}H NMR, IR data, elemental analysis and Mass Spectral data, which was in full agreement with proposed structures. The compounds were screened *in vitro* for their antibacterial and antifungal potential by disc diffusion assay against selected pathogenic bacteria and human pathogenic fungi. The results of antibacterial and antifungal activities are expressed in terms of zone of inhibition and presented in the Table 1. The title compounds were prepared in the following steps.

Synthesis of (E)-methyl 2-(benzylideneamino)acetate (3):
To the suspension of amino acid ester (1.2 equiv., 12 mmol) and $MgSO_4$ (1.25 equiv., 12.5 mmol) in DCM (15 mL) was added Et_3N (1.2 equiv., 12 mmol). The mixture was stirred at ambient temperature for 1h. Then the corresponding aldehyde (1 equiv., 10 mmol) was added and the mixture was allowed to stir at ambient temperature overnight. The precipitate was removed by filtration and the filtrate was washed with water (15 mL). The aqueous phase was extracted two times with DCM (10 mL) and the combined organic layer was washed once with brine (15 mL), dried over $MgSO_4$ and concentrated. Organic layer concentrated to get crude compound which on further column purification obtained pure desired compound **(3)**.

Synthesis of N-benzyl-2-fluorobenzenesulfonamide (6):
To a vigorously stirred solution of amine (8 mmol, 1.2 equiv.) in CH_2Cl_2 (33.0 mL, 0.2 M) in a round bottom flask was added Et_3N (3 equiv.). A solution of α-fluorobenzenesulfonyl Chloride (6.66 mmol, 1.0 equiv.) was added dropwise, and the reaction was stirred for 4-8 hours. Upon disappearance of sulfonyl chloride, 10% HCl (10 mL) was added and the reaction was stirred for 10 minutes. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO4) and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography (3:1, hexane:EtOAc) to afford the desired N-benzyl-2-fluorobenzenesulfonamide (**6).**

Synthesis of methyl 2-benzyl-4-methyl-3-phenyl-2,3,4,5-tetrahydrobenzo [f][1,2,4] thia diazepine-5-carboxylate 1,1-dioxide (7):
procedure for the synthesis of methyl 2-benzyl-4-methyl-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carboxylate 1,1-dioxide (7) from α-fluorobenzene sulfonamide derivatives. Into a microwave vial (0.5-2.0 mL) was added α-fluorobenzene sulfonamide derivative (0.5 mmol), anhydrous Cs_2CO_3 (1.5 mmol), $BnEt_3NCl$ (0.05 mmol), iminium derivative (0.5 mmol) and dry dioxane/DMF (1:1, 1M). The microwave vial was heated at 110 ºC for 20 minutes, after such time the reaction was purified (directly loading of crude reaction mixture) by flash chromatography (8:2 hexane/EtOAc) to afford the desired sultam (**7).** [11-13]

Synthesis of 2-benzyl-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carbohydrazide 1,1-dioxide (8):
A solution of (7) and hydrazine hydrate in ethanol was refluxed for 5 hours. The progress of the reaction was monitored by TLC with Acetone:Ethylacetate (7:3) as mobile phase. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallised from ethanol to afford 2-benzyl-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carbohydrazide 1,1-dioxide (8). [14-15]

Synthesis of (E)-2-benzyl-N'-(2-oxoindolin-3-ylidene)-3-phenyl-2,3,4,5-tetrahydrobenzo [f][1,2,4] thiadiazepine-5-carbohydrazide 1,1-dioxide (9)
Equimolar quantities (0.01 mol) of Isatin and the corresponding acetohydrazide (8) were dissolved in warm ethanol (40 ml) containing DMF (0.5 ml). The reaction mixture was refluxed for 1-4 hours and then kept at room temperature overnight. The progress of the reaction was monitored by TLC with acetone:ethylacetate (7:3) as

mobile phase. The resulting solid was filtered and washed with ethanol, dried, recrystallised from ethanol to afford compounds (9). The structure of the newly synthesized compound were characterized by spectral data ^{1}H-NMR, ^{13}C-NMR, IR, and Mass. Based on the spectral data the compound was assigned (E)-2-benzyl-N'-(2-oxoindolin-3-ylidene)-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carbohydrazide 1,1-dioxide (9) [16-17].

Synthesis of (E)-2-benzyl-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)-3-phenyl-2,3,4,5-tetra hydrobenzo[f][1,2,4]thiadiazepine-5-carbohydrazide 1,1-dioxide (10):
A mixture of **(9)** (0.1 mol), piperidine (0.15 mol) and water 20 mL was stirred to obtain a clear solution. To this solution, HCHO (0.05 mol) and DMF were added in ice-cold condition and stirred for 2 hours in an ice-bath and left overnight at room temperature. The obtained white solid was isolated and crystallized from ethanol to give Compound (10).

Synthesis of (E)-2-benzyl-N'-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carbohydrazide 1,1-dioxide (11):
A mixture of **(9)** (0.1 mol), Morpholine (0.14 mol) and water 20 mL was stirred to obtain a clear solution. To this solution, HCHO (0.05 mol) and DMF were added in ice-cold condition and stirred for 2.5 hours in an ice-bath and left overnight at room temperature. The obtained white solid was isolated and crystallized from ethanol to give Compound (11).

Synthesis of (E)-2-benzyl-N'-(1-((4-methylpiperazin-1-yl)methyl)-2-oxoindolin-3-ylidene)-3-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine-5-carbohydrazide 1,1-dioxide (12):
A mixture of **(9)** (0.1 mol), N-methylpiperazine (0.16 mol) and water 20 mL was stirred to obtain a clear solution. To this solution, HCHO (0.05 mol) and DMF were added in ice-cold condition and stirred for 3 hours in an ice-bath and left overnight at room temperature. The obtained white solid was isolated and crystallized from ethanol to give Compound (12).

Characterization of [3]:
Molecular formula: $C_{10}H_{11}NO_2$, yield: 65%; element found% (calculated%): C 67.14(67.24); H 6.20 (6.14); N 7.77 (7.82), IR max in cm−1 (Group): 3050 (Ar-H); 2980 (aliphatic CH2); 1740 (> C=O of Ester), 1610(-C=N); MS: m/z 177 (M+), ^{1}H NMR (300 MHz, DMSO-d6) _ ppm: 3.68(s, 3H,O-CH_3), 4.51(s, 2H, N-CH_2), 7.52-7.83(m, Ar-H), 8.65(s,1H, =C-H).

Characterization of [6]:
Molecular formula: $C_{13}H_{12}FNO_2S$, yield: 64%; element found% (calculated%): C 59.04(59.09); H.4.57 (4.54); N 5.25 (5.30), MS: m/z 265 (M+), IR max in cm−1(Group):3287(N-H), 1600(C=C), 2960(C-H), ^{1}HNMR (300 MHz, DMSO-d^{6}) _ ppm: 3.95(s, 2H,CH2-NH-), 7.72(broad,1H,NH-), 7.22-7.829(m, 8H, Ar-H)

Characterization of [7]:
Molecular formula: $C_{23}H_{22}N_2O_4S$, yield: 61%; element found% (calculated%): C 65.36(64.40); H.5.17 (5.19); N 6.56 (6.61), MS: m/z 422 (M+), IR max in cm^{-1}(Group):3286(N-H), 1600(C=C), 2960(C-H), 1740(-C=O), ^{1}HNMR (300 MHz, DMSO-d^{6})_ ppm: 3.95(s, 2H,CH2-NH-), 7.72(broad,1H,NH-), 7.22-7.82(m, 8H, Ar-H)

Characterization of [8]:
Molecular formula: $C_{22}H_{22}N_4O_3S$, yield: 55%; element found% (calculated%): C 62.49(62.53); H.5.20 (5.24); N 13.21 (13.25), MS: m/z 422 (M+),IR max in cm^{-1}(Group): 1600(C=C), 2960(C-H), 3180(N-H), 3300(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^{6})_ ppm: 2.0(s,1H, N-H), 2.01(s,2H,NH_2), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H,N-CH-N), 7.23-7.74(m, 8H, Ar-H), 8.0(s, 1H, -CO-NH)

Characterization of [9]:
Molecular formula: $C_{30}H_{25}N_5O_4S$, yield: 55%; element found% (calculated%): C 65.27(65.31); H.4.54 (4.57); N 12.64 (12.69), MS: m/z 551 (M+); IR max in cm^{-1}(Group): 1600(C=C),1610(C=N), 2950(C-H), 3340(N-H), 1640(-C=O), ^{1}HNMR (300 MHz, DMSO-d^{6})_ ppm: 2.0(s,1H, N-H), 4.42(s,2H,N-CH_2), 4.85(s,1H,-CH-NH), 5.04(s,1H, N-CH-N), 7.0(s, O=C-NH-N), 7.23-7.74 (m, 16H, Ar-H), 7.81(d,1H,Isatin-H), 7.86 (d, 1H, Isatin-H), 8.0(s, 1H, Isatin -CO-NH-).

Characterization of [10]:
Molecular formula: $C_{36}H_{36}N_6O_4S$, yield: 58%; element found% (calculated%): C 66.60(66.65); H 5.54 5.59); N 12.91(12.95) MS: m/z 648 (M+), IR max in cm^{-1}(Group): 1602(C=C),1611(C=N), 2948(C-H), 3345(N-H). ^1H NMR (300 MHz, DMSO-d^6) ppm: 1.53-1.59(m, 6H, CH2 of Pipperidine), 2.0(s,1H, N-H), 2.45(t, 4H, N-Adj.CH2 of Pipperidine), 4.05(s, 2H, N-CH2-N), 4.42(s,2H,N-CH_2-Ph), 4.85(s, 1H, N-CH-C=O) 5.04(s,1H,-CH-NH), 7.0(s, 1H, NH), 7.23-7.86 (m, 18H, Ar-H).

Characterization of [11]:
Molecular formula: $C_{35}H_{34}N_6O_5S$, yield: 55%; element found% (calculated%): C 64.56 (64.60); H 5.23 5.27); N 12.86 (12.91) MS: m/z 650 (M+), IR max in cm^{-1}(Group): 1599(C=C),1608(C=N), 2932 (C-H), 3350(N-H). ^1H NMR (300 MHz, DMSO-d^6) ppm: 2.0(s,1H, N-H), 2.45(t, 4H, N-Adj.CH2 of Morpholine), 3.65(t, 4H, O-Adj.CH2 of Morpholine), 4.05(s, 2H, N-CH2-N), 4.42(s,2H,N-CH_2-Ph), 4.85(s, 1H, N-CH-C=O) 5.04(s,1H,-CH-NH), 7.0(s, 1H, NH), 7.23-7.86 (m, 18H, Ar-H).

Characterization of [12]:
Molecular formula: $C_{36}H_{37}N_7O_4S$, yield: 53%; element found% (calculated%): C 65.08(65.14); H 5.57 5.62); N 14.72(14.77) MS: m/z 663 (M+), IR max in cm^{-1}(Group): 1602(C=C),1611(C=N), 2948(C-H), 3345(N-H). ^1H NMR (300 MHz, DMSO-d^6) ppm: 2.0(s,1H, N-H), 2.26(s, 3H, N-CH_3 of N-methylpiperazine), 2.35(s, 8H, N-Adj.CH2 of N-Methyl Pipperazine), 4.05(s, 2H, N-CH2-N), 4.42(s,2H,N-CH_2-Ph), 4.85(s, 1H, N-CH-C=O) 5.04(s,1H,-CH-NH), 7.0(s, 1H, NH), 7.23-7.86 (m, 18H, Ar-H).

CONCLUSION

Some novel Indole derivatives of sultams (10-12) have been synthesized and evaluated for antimicrobial activities. The results of antimicrobial studies of newly synthesized compounds reveal that the compounds possess significant antibacterial and moderate antifungal activities. Compounds with N-Substituents were found to be most potent compounds with antibacterial activity higher than that of standard drug i.e., ciprofloxacin against *S. aureus* and *B. subtilis*. Compound 9 with no N-substituents showed moderate activities against *S. aureus* and *B. subtilis*. The outstanding properties of this new class of antibacterial substances deserve further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure-activity relationship and to optimize the effectiveness of this series of molecules.

Table-1: Antimicrobial activity-sensitivity testing of compounds

Compound No.	*Zone of Inhibition in mm*					
	Antibacterial Activity				*Antifungal activity*	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
No N-Substituent(9)	18	19	12	15	10	11
Morpholine derivative(11)	29	26	14	18	9	11
Pipperidine derivative(10)	28	25	12	17	8	10
N-Methyl Pipperazine(12)	26	25	13	16	9	10
Ciproflaxacin	26	25	28	25	-	-
Fluconazole	-	-	-	-	26	25

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