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CSA PROMOTED BY BIO SYNTHESIS N-(5-(3-(1H-INDOL-3-YL) PROPYL)-1, 3, 4-THIADIAZOLES-2- YL)-1-PHENYLMETHANIMINE ANALOGOUS

K. Naveen Kumar[1], V. Narasinga Rao[1], L. Uma Maheswari[1], Krishna Rao*[1]

[1*]Department of Organic Chemistry, PRISM PG and DG College (Affiliated to Andhra University), Andhra Pradesh, Visakhapatnam, India.

ABSTRACT

Extensive computational studies of the N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1-phenylmethanimine from thiazolidine (2) amine and substituted aldehydes in the presence of methanesulphonic acid. The compound (2) can be synthesized from an indole butyric carboxylic acid with thiocemicarbazide in the presence of protic acid. The newly synthesized derivatives were evaluated by advanced spectroscopic data such as FTIR, ^{1}HNMR, ^{13}CNMR and LCMS and the structural determination of the desired compounds were determined by elemental analysis.

KEYWORDS

N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1-phenylmethanimine, Indolebutyric acid, Methane sulphonic acid and Antimicrobial activity.

Author for Correspondence:

Krishna Rao N,

Department of Organic Chemistry,

PRISM PG and DG College (Affiliated by Andhra University), Visakhapatnam, Andhra Pradesh, India.

Email: naallakrishnarao@gmail.com

INTRODUCTION

Schiff's base synthesized from the condemnation between the primary amines and substituted aldehyde which is also important class in organic, medicinally and pharmaceutical compounds. Mostly synthetic organic compounds are containing imines group and also very important significant class of organic synthesis because of their applications in many fields such as biological, inorganic and also analytical chemistry.

Indole derivatives are an important class of organic heterocyclic which have played prominent and vital role in curing so many ailments throughout the history of medicines. Also they are one of the most

attractive frameworks with a wide range of biological and pharmacological activities and one of the most active areas of heterocyclic chemistry which acquiring enormous significance in the field of medicinal chemistry in recent years, particularly due to their natural occurrence and pharmacological activities, There are several thousand indole derivatives known and many of these have important pharmacological activity. Indole derivatives also occur widely in many natural products such as those from plants, fungi and marine organisms. Moreover, a great interest which observed of combination of two or more heterocyclic moieties enhances the biological profile many folds than the parent indole nucleus for these reasons, they have been brought the attentions of organic chemists, medicinal chemists, pharmacists and biologists and encouraged them to compete to synthesise new biologically active substances

Compounds composed of the combination of part of heterocyclic rings which are responsible for exhibit the pharmacological activities. The compound containing five membered heterocyclic rings. The 5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-amine is an important class of their significant biological properties against several virus like influenza, HIV, Herpus (HSV-1) and Epstein-barr[1-3] and 5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-amine moiety present in schiff bases which are show anti-cancer and anti-proliferate properties. N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1-phenylmethanimine is being explored intermediate in the pharmaceutical industries and the N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1-phenylmethanimine derivatives have also been found in the diverse therapeutic applications[4,5]. The versatile core contained in several substances of benzimidazoles derivatives are possess a broad spectrum of pharmacological activities[6-9] in particular, it has been important pharmacopoeia and privileged structure in medicinal chemistry[10,11] encompassing a diverse Schiff bases derived from aromatic primary amines and aryl aldehyde which are also important class of organic compounds. Mostly synthetic organic compounds possess imines group and also very important class of organic compounds because of their applications in many fields such as biological, inorganic and also analytical chemistry. Of biological activities including anti-microbial[12-14], antioxidant[15], anti viral[16,17] antihypertensive[18], antiprotozoal[19], anti-inflammatory[20] and molluscicidal[21] agents. Further mode, benzimidazoles showed anticancer activity against DNA topoisomerase[22,23] and colon cancer cell lines[24].

In this investigation, we synthesized 5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-amine and various P-substituted aromatic aldehyde (Electron donating, an Electron withdrawing and halogen containing) using camphor sulphonic ASA acid catalyst. We aimed to the synthesis of new Schiff's bases using organic acid catalyst due to improved better yield as well as completion of the reaction time is less and also the intermediate of this reaction such as can be synthesized from indole carboxylic acid with semithiocarbazide in the presence of ethanol with concentrated sulphuric acid medium In addition to studied the biological activity.

MATERIAL AND METHODS

Experimental

All the reagents, solvents and chemicals are procured from Sigma Aldrich. The melting points titled compounds measured with Agrawal melting point thermometer and they were uncorrected. IR spectra of the titled derivatives were recorded with a Perkin-Elmer 1430 Spectrophotometer. 1H NM spectra and 13C NMR were obtained on a BRUKER (400 MHz and 100MHz) spectrometer in $CDCl_3$ using TMS as an internal standard and chemical shifts are expressed as δppm. Mass spectra were obtained on a Jeol-JMS 600 spectrometer.

General procedure of 5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-amine

Take dry and clean four necks RBF. The mixture of indole butyric acid and semithiocarbazide dissolved

in the ethanol and catalytic amount of camphor sulfonic acid at RBF at room temperature which is also fitted on the magnetic stirrer containing hot plate. The reaction mixture continuous carried the reaction for 5 hrs at 60^{o}C. The progress of the reaction checked by the TLC (EtOAc: n-hexane = 3:7). After completion of the consumed all reactants, cooled the reaction mixture at RT. The crude dissolved in ethyl acetate and washed with as saturated solution of sodium bicarbonate and separated the ethyl acetate layer and also washed with water separated the organic layer. The organic layer can be distilled off under vacuums and solid compound obtained.

Palered solid; Yield-94%; m.p-221-223^{o}C; IR(KBr) υcm-1): 3057 (C-Haromatic), 3425 (NH), 747. ^{1}HNMR (400MHz, $CDCl_3$) δppm: 10.574 (s, 1H, N-Hindole), 7.582-7.274 (m, 4H, Ar-H), 7.159 (s, 1H, indole), 6.624 (s, 2H, -CH_2-), 2.726 (d, J=7.6Hz, 2H, -CH_2), 2.417 (d, J=8.4Hz, 2H, -CH_2), 1.676 (m, 2H,-CH2); ^{13}CNMR (100MHz, $CDCl_3$): δppm: 169.24, 160.49, 133.36, 128.42, 124.09, 121.96, 120.08, 119.42, 112.57, 29.14, 28.42, 27.72. LCMS (m/z): 258.36(M^+): Molecular formulae: $C_{13}H_{14}N_4S$; Elemental analysis: Calculated C60.44; H-5.46; N-21.69; Obtained: C-60.36; H -5.45; N-21.76%.

General procedure N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1-phenyl methamine

In this project, to of 5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-amine (1mmol) is dissolved in ethanol and camphor sulfonic acid (3mL) was added; the mixture was stirred for two hours in room temperature, then substituted aromatic aldehyde (1mmol) was added to a mixture and was stirred and heated under reflux in conditions an water bath at 70^{o}C. The progress of reaction was monitored by thin layer chromatography (TLC). After the completion of reaction, cold water was added to the mixture. Then solid crystals were formed at the bottom of the beaker and after that, they were filtered. Finally, the solid product was washed with water, ethanol and n-hexane and dried in desiccator in R.T. The pure derivatives were obtained in good yields.

N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1-phenylmethanimine

Palered solid; Yield-85%; m.p-245-246^{o}C; IR (KBr) υcm-1): 3058 (C-Haromatic), 3368 (NH), 1610(CH=N), 747(C–Cl). ^{1}HNMR (400MHz, $CDCl_3$) δppm: 10.274 (s, 1H, N-H indole), 8.746 (s, 1H, =CH), 7.774-7.542 (m, 6H, Ar-H), 7.509 (s, 1H, indole), 7.343-7.281 (m, 7H, Ar-H); 2.656 (d, J=7.6Hz, 2H, -CH_2), 2.328 (d, J=8.8Hz, 2H, -CH_2), 1.674 (m, 2H, -CH_2); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 167.56, 158.74, 135.15, 134.37, 129.88, 129.15, 128.65, 127.66, 124.17, 122.67, 120.64, 118.77, 112.65, 109.12, 30.16, 29.05, 17.96. LCMS (m/z): 347.26: Molecular formulae: $C_{20}H_{18}N_4S$; Elemental analysis: Calculated C-69.34; H-5.24; N-15.17; Obtained: C-69.28; H -5.22; N-16.25%.

(E)-4-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)imino) methyl) phenol

Palered solid; Yield-92%. m.p-248-250^{o}C; IR(KBr) υ(cm-1): 3055 (C-Haromatic), 3368 (NH), 1609 (CH=N), ^{1}HNMR (400MHz, $CDCl_3$) δppm: 10.126 (s, 1H, NH indole), 9.237 (s, 1H, -OH); 8.762 (s, 1H, =CH), 7.512 (s, 1H, indole), 7.262-6.845 (m, 7H, Ar-H); 2.656 (d, J=7.6Hz, 2H, -CH2), 2.328 (d, J=8.8Hz, 2H, -CH_2), 1.674 (m, 2H, -CH_2); 13CNMR (100MHz, CDCl3) δppm: 169.25, 158.75, 155.74, 137.69, 129.75, 128.96, 128.74, 124.26, 120.68, 119.25, 118.46, 117.65, 111.25, 30.54, 29.12, 28.62. LCMS (m/z): 363.12 (M+H): Molecular formulae: $C_{20}H_{18}N_4OS$. Elemental analysis: Calculated C-66.28; H- 5.01; N- 15.46; Obtained: C- 66.35; H -5.00; -N 15.54%.

(E)-N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1methoxyphenyl) methanimine

Palered solid; Yield-85%. m.p-256-258^{o}C. IR (KBr) υ (cm-1): 3050 (C-Haromatic), 3376 (NH), 1608 (CH=N), 755 (C–Cl). ^{1}HNMR (400MHz, $CDCl_3$) δppm: 10.326 (s, 1H, NH indole), 8.656 (S, 1H, =CH), 7.746-7.584 (m, 2H, Ar-H); 7.502-7.045 (m, 5H, Sr-H), 7.508 (s, 1H, Indole), 7.021-6.924 (m, 2H, Ar-H), 2.844 (d, J=7.8Hz, 2H, -CH2), 2.312 (d, J=7.6Hz, 2H, -CH2), 1.745 (m, 2H, -CH_2), ^{3}CNMR (100MHz, $CDCl_3$) δppm: 169.72, 158.09, 155.24,

135.65, 130.62, 128.43, 122.6, 121.45, 120.84, 118.77, 115.33, 110.65, 54.63, 30.14, 29.62, 28.35. LCMS (m/z): 377.45(M+H); Molecular formule: $C_{21}H_{20}N_4OS$; Elemental analysis: Calculated: C-66.91; H- 5.34; N-14.94; Obtained: C-66.85; H -5.33; N-15.04%.

(E)-N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1-(3, 4, 5-trimethoxyphenyl) methanimine

Palered solid; Yield-85%. m.p-266-268^oC. IR(KBr) υ (cm-1) 3050 (C-Haromatic), 3376 (NH), 1608 (CH=N), 755(C–Cl). ^{1}HNMR (400MHz, $CDCl_3$) δppm=10.321 (s, 1H, NH indole), 8.756 (S, 1H, =CH), 7.502 (s, 1H, indole), 7.312-7.273 (m, 4H, indole), 7.128-7.012 (m, 2H, Ar-H), 3.712 (s, 3H, -OCH3), 3.582 (s, 6H, (OCH3)2), 2.486 (t, J=8.4Hz, 2H,-CH2), 2.584 (t, J=8.0Hz, 2H, -CH2), 1.872-1.623 (m, 2H, -CH2-),; 13CNMR (100MHz, CDCl3) δppm: 1167.94, 159.04, 151.45, 140.22, 135.72, 132.65, 128.81, 128.96, 122.81, 120.56, 119.75, 117.64, 111.42, 110.56, 60.08, 55.72, 29.56, 28.54, 27.65. LCMS (m/z); 437.27 (M+H); Molecular formule: $C_{23}H_{24}N_4O_3S$; Elemental analysis: Calculated C-63.28. H- 5.54; N- 12.83; Obtained: C- 63.20; H -5.53; -N -12.95%.

(E)-N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1-(4-chlorophenyl) methanimine

Palered solid; Yield-89%. m.p-265-267^oC; IR (KBr) υ (cm-1); 3050 (C-H aromatic), 3376(NH), 1608 (CH=N), 755 (C–Cl). ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 10.456 (s, 1H, NH indole), 8.755 (S, 1H, =CH), 7.816 (m, 2H, Ar-H); 7.592-7.512 (m, 2H, Sr-H), 7.508 (s, 1H, Indole), 7.256-7.096 (m, 4H, indole), 2.534 (t, J=7.6Hz, 2H, -CH2), 2.428 (t, J=8.4Hz, 2H, -CH2), 1.651 (m, 2H, -CH2), 13CNMR (100MHz, CDCl3) δppm: 167.65, 151.38, 137.21, 132.09, 131.05, 129.45, 128.17, 127.44, 123.09, 122.16, 120.39, 118.46, 112.62, 110.08, 29.41, 28.09, 27.62. LCMS (m/z): 382.16 (M+2); Molecular formule: C20H17ClN4O. Elemental analysis: Calculated C-63.07; H- 4.50; N- 14.71; Obtained: C- 63.01; H -4.48; N-14.77.

(E)-N-(5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-yl)-1-(4-nitrophenyl) methanimine

Paleredsolid; Yield-87%. m.p-251-253^oC; IR (KBr) υ (cm-1) 3065 (C-H aromatic), 1609 (CH=N), 765(C–Cl). ^{1}HNMR (400MHz, $CDCl_3$) δppm: ^{1}HNMR (400MHz, $CDCl_3$) δppm: 10.512 (s, 1H, NH indole), 8.894 (S, 1H, =CH), 8.312-8.045 (m, 4H, Ar-H); 7.523 (s, 1H, indole), 7.312-7.273 (m, 3H, indole), 2.615 (t, J=8.0Hz, 2H, -CH2), 2.452 (t, J=8.4Hz, H,-CH2), 1.618 (m, 2H, -CH_2): 13CNMR (100MHz, $CDCl_3$) δppm: 169.45, 161.12, 148.26, 141.56, 135.34, 128.15, 127.46, 123.65, 122.84, 121.15, 119.08, 117.77, 111.84, 29.65, 28.46, 27.19. LCMS (m/z): 347.26; Molecular formule: $C_{20}H_{18}N_4S$; Elemental analysis: Calculated C-69.34; H- 5.24; N- 16.17; Obtained: C- 69.28; H -5.22; -N-16.25.

Biology

Antibacterial activity

Antibacterial activity was evaluated by the paper disc method. The Muller-Hinton agar (beef infusion, casein hydrolyte, starch and agar) and 5 mm diameter paper discs of Whatman No.1 were used. The compound was dissolved in DMSO. The filter paper discs were soaked in different solutions of the compounds, dried and then placed in the petriplates previously seeded with the test organisms *E. coli and S. aureus*. The plates were incubated for 30 hours at 28±2°C and the inhibition zone around each disc was measured.

Antifungal screening:

The antifungal activity of the compounds was evaluated against *A.Niger and C. albicans* by the agar plate technique. The Sabouraud dextrose agar (dextrose, peptone, and agar) and 5mm diameter paper discs of Whatman No.1 were used. The compounds were dissolved in DMSO and then were mixed with in the medium. These petriplates were wrapped in the polythene bags containing a few drops of alcohol and were placed in an incubator at 25±2°C. The activity was determined after 96 hours of incubation at room temperature (25°C).

RESULTS AND DISCUSSION

Chemistry

All newly titled derivatives can be prepared 70^{o}C and also cooler product. In this reaction, we got the percentage of the yield 85-92%. These titled derivatives can be synthesized, we used to camphor sulfonic acid. This acid catalyst can be used to develop the reaction conditions and reaction is completed maximum 3 hours. The rate of reaction developed by using this acid catalyst. The catalyst used due to emerging as a powerful nature, inexpensive, eco-friendly, readily available, economical and water soluble compound. We used various P-substituted aromatic aldehydes having electron donating group of aldehydes and electron withdrawing group of aldehydes. Hence ,electron donating group of aldehydes react with 5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-amineto give more yield and rate of reaction increases and completion of the reaction before 90 min compared to that of electron withdrawing group of aldehyde react with5-(3-(1H-indol-3-yl) propyl)-1, 3, 4-thiadiazol-2-amine. We are using camphor sulphonic acid, the reaction workup is easily. (Scheme No.1).

1H NMR

The bonding patterns of these compounds are further supported by the proton magnetic resonance spectral studies in (400 MHz) $CDCl_3$. The compounds exhibit a singlet at δ 6.624ppm due to NH_2 and singlet at δ 2.726-2.147ppm due to CH_2. This compound shows multiplet in the region at δ 7.746- 7.584ppm attributable to the aromatic protons. Another singlet appearing at δ 8.746ppm due to the (=CH) and singlet at δ 10.512ppm due to NH-imidazole. A singlet due to the -OH group appears around δ 9.237ppm. Mass spectra of the base peak m/z appeared at 382.21 of derivatives "4e".

Antibacterial activity

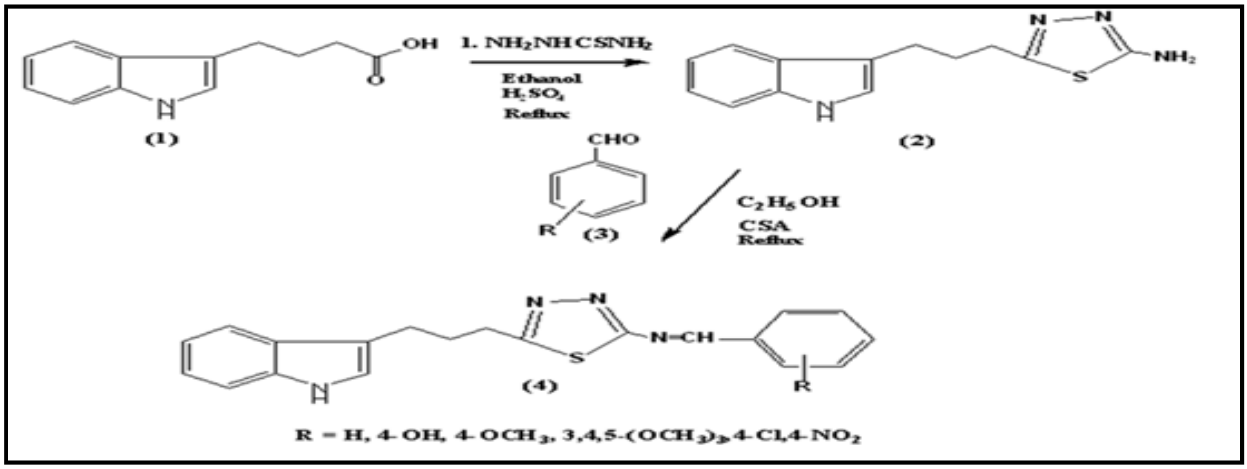
Amongst all the synthesized derivatives were examined for their antibacterial activity against Escherichia coli, Pseudomona aeruginosa, as Gram-(-Ve) bacteria, *Bacillus subtilis, Staphylococcus aureus* as Gram-(+Ve) bacteria and the antifungal activity was examined against yeast *C.albicans, A. Niger*. The inhibitory zones (in mm) were evaluated by using agar well method (cup plate method). Antibiotic, streptomycin and Ketonozole were used as standard drug controls against bacteria and fungi activity respectively. In all tests compounds were represented and determined in duplicate and results were reports submitted as mean of at least three determinations. Table No.1 showed that all the tested compounds showed moderated to good to excellent antibacterial activity. Compounds "4c and 4d" showed significant inhibition against all the bacteria tested. In compounds 4a and 4f were poor effect of activating or deactivating substituents on the aryl ring in their inhibitory activity and observed to be less potent than the other compounds tested. Moreover, these derivatives such as 4a and 4f were low active against the tested bacteria. The significant inhibition showed by the compounds "4e" might be due to the presence of chloro group on the para position of their corresponding.

Antifungal activity

The investigation of antifungal activity newly derivatives were examined data from Table I represented that the all tested compound evaluated moderate to good fungal inhibition. Compounds 4e were active against all the fungal species. The 5-fluro and 5-bromo phenyl derivatives exhibited excellent inhibitory activity against all the two fungal strains than the corresponding 4b, 4c derivatives.

Table No.1: Antimicrobial activity screening activity synthesized scaffold

S.No	Entry	*Zone of inhibition in (mm)					
		Bacteria				Fungi	
		P. aeruginosa	*E.coli*	*S. typhi*	*B.substills*	*A. niger*	*C. albicans*
1	3a	07	09	06	07	08	07
2	3b	20	21	18	20	18	17
3	3c	21	22	21	23	17	21
4	3d	22	20	20	23	17	14
5	3e	24	23	21	23	21	22
6	3f	16	07	04	06	04	06
7	Streptomycin	30	30	28	28	NA	NA
8	Ketoconazole	NA	NA	NA	NA	25	25
9	DMSO	---	----	---	---	---	---



Scheme No.1: Chemistry

CONCLUSION

The reaction condition carried at room temperature for all the newly synthesized compounds. The yield of the titled compounds obtained from 85-92%. The compound possesses electron donating group gives maximum yield than that of the compound possesses electron withdrawing group. The rate of reaction developed by using camphor sulfonic acid catalyst. All the compounds tested by anti-microbial activity against gram positive, gram negative and fungal. The compound having electron donating group showed excellent active potential. Otherwise the compounds having halogens which showed better active potential than that of the electron with drawing group.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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