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Synthesis, Characterization and Biological Evaluation of N-((1-ethyl-5-(substituted phenyl)-1H-indol-3-yl) methyl) Substituted Alkyl/Aryl Carboxamides Derivatives

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ABSTRACT

A series of novel N-((1-ethyl-5-(substituted phenyl)-1H-indol-3-yl) methyl) substituted alkyl/aryl carboxamide derivatives were synthesized for evaluation of their antimicrobial activity. The newly synthesized compounds were characterized by spectroscopic studies such as 1H NMR, Mass spectroscopy. All the synthesized compounds were screened for their in vitro antimicrobial activity. Some of the compounds showed good biological activity.

Keywords: Antimicrobial activity, (1-ethyl-5-(substituted phenyl)-1*H*-indol-3-yl) methanamine.

INTRODUCTION

Indole has a benzene ring and pyrrole ring sharing one double bond. It is a heterocyclic system with 10 electrons from four double bonds and the lone pair from the nitrogen atom. Indole is an important heterocyclic system because it is built into proteins in the form of amino acid tryptophan, because it is the basis of drugs like indomethacin and because it provides the skeleton of indole alkaloids—biologically active compounds from plants including strychnine and LSD. The incorporation of indole nucleus, a biologically accepted pharmacophore in medicinal compounds (Table 1), has made it versatile heterocyclic moiety possessing wide spectrum of biological activities (Table 2).

Table 1

S. No.	Indole Derivative	Biological activity
1	Indomethacin	Anti-inflammatory and analgesic
2	Fendosal	Analgesic
3	Etodolac	Antiarthritis
4	Sumatriptan	Antimigraine
5	Besipirdine	Nootropic
6	Noratriptan	CNS stimulant

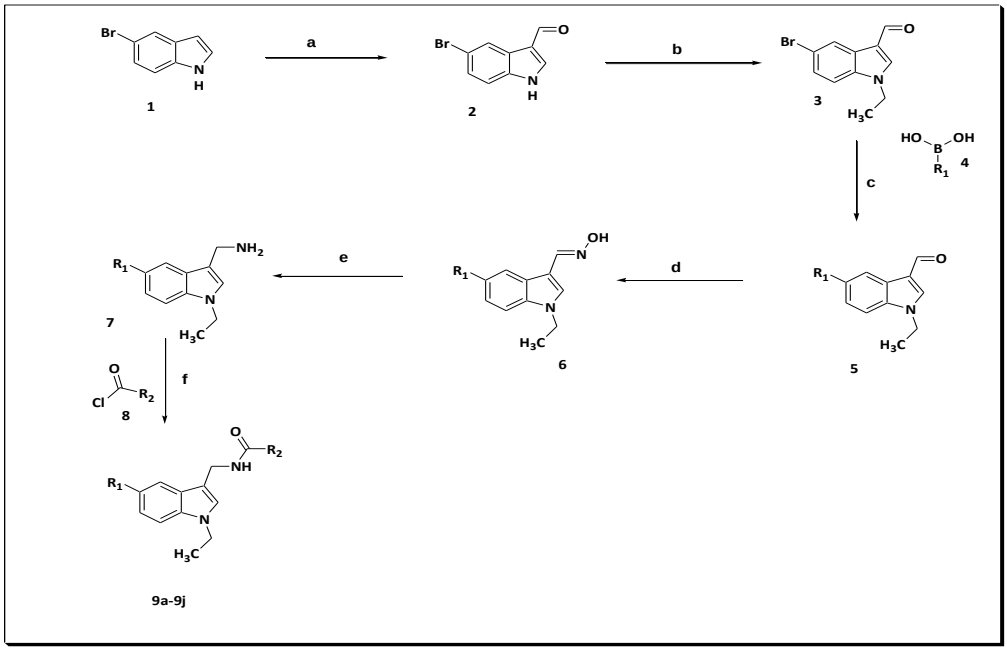
7	Pindolol	Antihypertensive
8	Indolmycin	Antibiotic
9	Indigo carmine	As a dye in functional kidney test and in milk testing
10	Adrenochrome	Hemostatic

Table 2

S.No.	Biological activity	References
1.	Antiinflammatory and analgesic	[1-5]
2.	Anti fungal	[1,6]
3.	Anti microbial	[7,8]
4.	Anti cancer	[1,9-12]
5.	Anti HIV	[1,13]
6.	Anti oxidant	[14,15]
7.	Anti tubercular	[1,16]
8.	Anti viral	[1]
9.	Cardiovascular activity	[1,17]
10.	Anti histaminic	[18]
10.	LXR Receptor Agonist	[19]
11.	ACAT Inhibitor	[20]
12.	Steroid 5α-reductase inhibitor	[21]

MATERIALS AND METHODS

All chemicals were LR grade and used without further purification. The progress of reaction was monitored by Analytical TLC in EtOAc-Hexane or DCM-MeOH solvent system on precoated plates (silica gel 60,F254) and visualized with UV light. Flash chromatography was performed with silica gel 60(60-120 mesh). NMR spectra (1H at 400 MHz) were recorded using CDCl3 OR DMSO-d6 as a solvent. The specifications of the LC/MS are as follows: electrospray (+) ionization, mass range 100-1500 Da, 20-V cone voltage, and Xterra MS C18 column (2.1 mm x 50 mm x 3.5 µm). Melting points were determined using Lab India V10 Thermovar apparatus and were uncorrected.



Scheme-1:

Reagents: **a)**Phosphorous oxychloride, DMF, RT- 80°C; b) Ethyl iodide, Aq. Sodium hydroxide, TBAB, Benzene, RT; c) phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3,Toluene, Ethanol, Water, 80ºC; d)Hydroxylamine hydrochloride, Na_2CO_3, Ethanol, Water, 50°C;e) $NiCl_2$ $6H_2O$, $NaBH_4$, MeOH, Water, 0-10°C; f) TEA, DCM, RT.

Preparation of 5-Bromoindole-3-carbaldehyde (2): Phosphorous oxychloride (10.5 mL, 112 mmol) is added slowly to N,N-dimethylformamide (15 mL) with water bath cooling. To this solution is added a solution of 5-Bromoindole **1** (15 g, 93 mmol) in N,N-dimethylformamide (15 mL) over 15 min causing slight exotherm. Five minutes after the addition, the reaction is placed in an 80ºC bath and heated for 10 minutes. The reaction is cooled to 10°C and water (15 mL) was added drop wise producing a vigorous exotherm. The reaction then heated in a bath temperature of 90°C for 90 min. The reaction was then cooled and then added very slowly to 0.5 N NaOH (500 mL) forming a brown precipitate which was filtered, solid was then dissolved in ethyl acetate (250 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield 5-Bromoindole-3-carbaldehyde **2** (15.0 g, 87.5 %) a reddish solid product.

^{1}H NMR (400 MHz, DMSO-d^6):δ =12.3 (bs,1H), 9.92 (s,1H), 8.34 (d,1H), 8.21(s,1H), 7.49(d,1H), 7.39 (dd,1H).

Preparation of N-ethyl-5-bromoindole-3-carbaldehyde (3): 5-Bromoindole-3-carbaldehyde **2** (15g, 66.95 mmol) and tert-n-butylammonium bromide (2.16g, 6.69 mmol) were taken in benzene (350 mL) at room temperature. 30% sodium hydroxide solution in water (350 mL) was added. The reaction mass was stirred for 10 min at room temperature. Ethyl iodide (9.16 mL, 133.89 mmol) was added to the above reaction mass and stirred it for 4 h at room temperature. After completion of the reaction, layers were separated. Aqueous layer was extracted with benzene (100 mL). Combined organic layers were then washed with water (250 mL) and brine (250 mL). The organic layer was dried over anhydrous sodium sulphate. Distilled under reduced pressure to afford the N-ethyl-5-bromoindole-3-carbaldehyde **3** (15.0g, 88.87 %) as brown solid product. MP: 205-207 °C

Preparation of N-ethyl-5-substituted phenyl-1*H*-indole-3-carbaldehyde (5): To a stirred solution of N-ethyl-5-bromoindole-3-carbaldehyde **3** (15g, 59.5 mmol) in toluene (600 mL), substituted phenylboronic acid 4 (65.45 mmol, 1.1 meq) in ethanol (150 mL) and potassium carbonate (20.55g, 148.75mmol) in water (250 mL) were added to the reaction mixture. Degassed the reaction mixture by N_2 for 10 min

followed by the addition of tetrakistriphenylphosphinopalladium (0) (1.88g, 2.97mmol). The reaction mixture was heated to 80°C for 4 h. Water (200 mL) and ethyl acetate (400 mL) were added into the reaction mixture. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (EtOAc/Hexane, 3:7) to yield the N-ethyl-5-substituted phenyl-1*H*-indole-3-carbaldehyde 5 (10.4g, 65.4 % yield) as a yellow solid.MP: 195-197 °C.

Preparation of 1-ethyl-5-substituted phenyl-1*H*-indole-3-carbaldehyde oxime (6): To a stirred cold solution of N-ethyl-5-substituted phenyl-1*H*-indole-3-carbaldehyde 5 (5g, 18.71mmol) in ethanol (80 mL) was added a solution of hydroxylamine hydrochloride (1.95g, 28.06mmol), and sodium carbonate (1.43g, 13.47mmol) in water (10 mL). The reaction mass was heated at 50°C for 20-30 min. Upon completion of reaction, the mixture was concentrated and water (50 mL) was added.The mass was then extracted with ethyl acetate (50 mL x 2). Combined organic layers were washed with water (50 mL) and brine (50 mL). Dried it over sodium sulfate, filtered, and concentrated by rotary evaporation to yield the 1-ethyl-5-substituted phenyl-1*H*-indole-3-carbaldehyde oxime 6 (5g, 94.68 % yield) as a off white solid.MP: **6:** 210-15 °C.

Preparation of (1-ethyl-5-substituted phenyl-1*H*-indol-3-yl)methanamine (7): To a stirred solution of $NiCl_2$ $6H_2O$ in methanol (20 mL) under N_2 atmosphere, sodium borohydride was added in one portion at 0-10°C. 1-ethyl-5-substituted phenyl-1*H*-indole-3-carbaldehyde oxime 6 was added to the above stirred mass at 0-10°C.Stirred the reaction mass for 5 min and additional sodium borohydride was added in a single lot at same temperature. Reaction mass was turned blackish. After 5 min of stirring, the black precipitate was filtered off and filtrate was concentrated under reduced pressure to approx. 1/3 of its original volume and poured into water (20mL) containing 28 % NH_4OH (5 mL). After extraction with ethyl acetate (50 mL x 2), drying the extract with anhydrous sodium sulphate was concentrated under reduced pressure to afford the (1-ethyl-5-substituted phenyl-1*H*-indol-3-yl)methanamine 7 which was taken to the next step without purification instantly.
(Note: Compound **7** was used immediately for next step because of unstable nature)

General Procedure for the Preparation of N-((1-ethyl-5-substituted phenyl)-1*H*-indol-3-yl)methyl) substituted alkyl/aryl amide (9a-j): To a stirred solution of (1-ethyl-5-substituted phenyl-1*H*-indol-3-yl) methanamine 7 (0.2 g, 0.74mmol) in dry DCM (15 mL), triethylamine (0.2 mL, 1.49mmol) was added to the reaction mixture followed by the addition of alkyl/aryl carbonyl chloride 8 (0.76mmol) at room temperature under N2. The reaction mixture was stirred at room temperature for 2 h. The mixture was then concentrated and water (15 mL) and EtOAc (30 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with 1N HCl, followed by saturated aqueous sodium bicarbonate and brine. The combined organic layers were dried over anhydrous sodium sulphate, filtered, and concentrated by rotary evaporation. The crude material was purified by column chromatography (MeOH/DCM, 1:9) to yield the N-((1-ethyl-5-substituted phenyl-1*H*-indol-3-yl)methyl) substituted alkyl/aryl carboxamide (0.112 g, 45 %) as a off-white solid product.
All the compounds were found to be off white solid or brown solid.10 new compounds (9a-j) were synthesized in similar manner and characteristic physical data are shown in Table 3.

SpectralCharacterization:
N-((1-ethyl-5-(*m*-tolyl)-1 *H*-indol-3-yl)methyl)cyclopropane carboxamide (9a): Yield: 60 %. **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.787(s,1H), 7.628-7.592(m,2H), 7.476-7.405(m,2H), 7.169-7.125(m,3H), 5.787(bs,1H), 4.669-4.673(d,2H), 4.221-4.167(q,2H), 2.203(s,3H), 1.521-1.485(t,3H), 1.344-1.271(m,1H), 1.185(3H), 1.035(s,2H), 0.743-0.732(m,2H). ppm; **MS:** m/z 333 $(M+H)^+$

2-(4-chlorophenyl)-N-((1-ethyl-5-(4-fluorophenyl)-1*H*-indol-3-yl)methyl)acetamido (9b): Yield: 65%; **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.564(s,1H), 7.411-7.390(d,1H), 7.250-7.137(m,8H), 6.637-6.631(d,1H), 6.586-6.559(m,1H), 6.085-6.059(m,1H), 4.328-4.315(d,2H), 4.170-4.152(m,2H), 4.234-3.200(m,2H), 2.196(s,3H), 1.357-1.321(t,3H)ppm; **MS:** m/z 417 $(M+H)^+$

N-((5-(2,4-dimethoxyphenyl)-1-ethyl-1*H*-indol-3-yl)methyl)-3-methylbenzamide (9c): Yield: 62 %. **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.787(s,1H), 7.628-7.592(m,2H), 7.536-7.472(m,3H), 7.455-7.405(m,2H), 7.226-7.125(m,3H), 5.318(bs,1H), 4.703-4.673(d,2H), 4.221-4.167(q,2H), 3.780(s,3H), 3.726(s,3H), 1.185(s,3H), 1.521-1.485(t,3H), ppm;**MS:** m/z 429 $(M+H)^+$

N-((1-ethyl-5-(4-fluorophenyl)-1*H*-indol-3-yl)methyl)cyclopropanecarboxamide (9d): Yield: 48%. **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.780(s,1H), 7.621-7.585(m,2H), 7.476-7.400(m,2H), 7.163-7.120(m,3H), 5.777(bs,1H), 4.662-4.666(d,2H), 4.215-4.161(q,2H), 2.210(s,3H), 1.515-1.480(t,3H), 1.335-1.263(m,1H), 1.037(s,2H), 0.735-0.724(m,2H). ppm;**MS:** m/z 337 $(M+H)^+$.

N-((1-ethyl-5-(*m*-tolyl)-1 *H*-indol-3-yl)methyl)-2,4-dimehoxybenzamide (9e): Yield: 77%. **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.791(s,1H), 7.635-7.598(m,2H), 7.539-7.475(m,3H), 7.460-7.410(m,2H), 7.230-7.130(m,3H), 5.325(bs,1H), 4.708-4.680(d,2H), 4.228-4.175(q,2H), 3.788(s,3H), 3.726(s,3H), 1.188(s,3H), 1.526-1.490(t,3H). ppm;**MS:** m/z 429 $(M+H)^+$;

N-((5-(3-chlorophenyl)-1-ethyl-1 *H*-indol-3-yl)methyl)-4-ethylbenzamide (9f): Yield: 70%. **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.788(s,1H), 7.630-7.594(m,3H), 7.537-7.474(m,3H), 7.458-7.408(m,2H), 7.227-7.125(m,3H), 5.320(bs,1H), 4.705-4.675(d,2H), 4.224-4.170(q,2H), 2.732-2.658(q,2H), 1.521-1.485(t,3H), 1.203-1.167(t,3H). **MS:** m/z 417 $(M+H)^+$

N-((5-(3-chlorophenyl)-1-ethyl-1*H*-indol-3-yl)methyl)-2,4-dimethylbenzamide (9g): Yield: 69%. **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.785(s,1H), 7.626-7.590(m,2H), 7.534-7.470(m,3H), 7.451-7.401(m,2H), 7.225-7.125(m,3H), 5.316(bs,1H), 4.700-4.670(d,2H), 4.218-4.164(q,2H), 2.500(s,3H), 2.184(s,3H), 1.520-1.484 (3H). **MS:** m/z 418 $(M+H)^+$

N-((1-ethyl-5-(4-methoxyphenyl)-1 *H*-indol-3-yl)methyl)-2-methoxy-4-methyl benzamide (9h): Yield: 55 %. **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.787(s,1H), 7.628-7.592(m,2H), 7.536-7.472(m,3H), 7.455-7.405(m,2H), 7.226-7.125(m,3H), 5.318(bs,1H), 4.703-4.673(d,2H), 4.221-4.167(q,2H), 3.780(s,3H), 3.726(s,3H), 1.185(s,3H), 1.521-1.485(t,3H),. ppm;**MS:** m/z 429 $(M+H)^+$

3-chloro-N-((1-ethyl-5-(4-ethylphenyl)-1 *H*-indol-3-yl)methyl)benzamide (9i): Yield: 83%. **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.787(s,1H), 7.622-7.592(m,3H), 7.530-7.470(m,3H), 7.459-7.405(m,2H), 7.220-7.124(m,3H), 5.318(bs,1H), 4.700-4.670(d,2H), 4.218-4.164(q,2H), 2.730-2.656(q,2H), 1.520-1.484(t,3H), 1.200-1.164(t,3H). **MS:** m/z 417 $(M+H)^+$

3-chloro-N-((5-(2,4-dimethylphenyl)-1-ethyl-1*H*-indol-3-yl)methyl)benzamide (9j): Yield: 74%. **^{1}H NMR (400 MHz, DMSO-d^6):**δ = 7.777(s,1H), 7.618-7.581(m,2H), 7.527-7.463(m,3H), 7.445-7.396(m,2H), 7.216-7.115(m,3H), 5.308(bs,1H), 4.695-4.663(d,2H), 4.213-4.158(q,2H), 2.500(s,3H), 2.200(s,3H), 1.511-1.475 (3H). **MS:** m/z 418 $(M+H)^+$

RESULTS AND DISCUSSION

Chemistry: 5-Bromoindole-3-carbaldehyde 2 has been prepared by reaction of 5-Bromoindole 1 with Vielsmayer Heck reaction condition. 5-Bromoindole-3-carbaldehyde 2 was furtheralkylated by ethyl iodidein a biphasic solution of water and benzene using sodium hydroxide base and tetra butyl ammonium bromide as a phase transfer catalyst yielding the N-ethyl-5-bromoindole-3-carbaldehyde 3. It was then

reacted with mono or disubstituted phenylboronic acid 4 by means of Suzuki coupling reaction to afford the N-ethyl-5-substituted phenyl-1*H*-indole-3-carbaldehyde 5. N-ethyl-5-substituted aryl indole-3-carb aldehyde 5 has been further convertedto oxime intermediate 6 by hydroxylamine hydrochloride. Oxime intermediate 6 has been then reduced to amino compound 7 by in situ prepared nickel borohydride from nickel chloride hexahydrate and sodium borohydride in methanol. Amino compound 7 was reacted with various aryl or acyl chlorides 8 in the presence of triethyl amine to yield corresponding amide derivatives (9a-j). These new compounds were purified by column chromatography using 2-3 % methanol in DCM as the eluent. All the reactions were smooth, and provided the products in the range of 48-83% yield.

Table 3: Characteristic physical data of amide derivatives 9a-j.

Sr. No	Comp. Code	R_1	R_2	M.P(°C)	Yield(%)
1	9a	3-methylphenyl	Cyclopropyl	204-206	60
2	9b	4-fluorophenyl	4-chlorobenzyl	212-213	65
3	9c	2,4-dimethoxyphenyl	m-tolyl	219-220	62
4	9d	4-fluorophenyl	cyclopropyl	199-201	48
5	9e	3-methylphenyl	2,4- ıoxyphenyl	205-206	77
6	9f	3-chlorophenyl	4-ethylphenyl	241-242	70
7	9g	3-chlorophenyl	2,4-dimethylphenyl	222-223	69
8	9h	4-methoxyphenyl	2-methoxy-4-methyl phenyl	232-233	55
9	9i	4-ethylphenyl	3-chlorophenyl	202-203	83
10	9j	2,4-dimethylphenyl	3-chlorophenyl	252-253	74

All compounds are either crystalline or amorphous solid.

Biological activities

Antibacterial and antifungal activities: The newly synthesized derivatives were evaluated for their in vitro antibacterial activity against gram positive Staphylococcus aureus and Bacillus subtilis, gram negative Escherichia coli & Pseudomonas aeruginosa, and antifungal activity against Aspergillus niger & Aspergillus flavus by micro broth dilution method [22-24]. The standard drugs used for antibacterial activity were ampicillin and streptomycin and nystatin for antifungal activity. Mueller Hinton Broth was used as nutrient medium for bacteria and Sabouraud Dextrose Broth for fungal to grow. Inoculums size for test strain was adjusted to 10^5CFU mL^{-1} by comparing the turbidity. The serial dilutions were prepared in primary and secondary screening. The target compounds and standard drugs were dissolved in DMSO-water at a concentration of 2.0 mgmL^{-1}. In primary screening1000µg mL^{-1}, 500µg mL^{-1}, 250µg mL^{-1}, 125µg mL^{-1}, 62.5µg mL^{-1}concentrations of the synthesized drugs were taken. Data were not taken for the initial solution because of the high DMSO concentration (10%). The actively synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. In secondary screening, the drugs found active in primary screening were similarly diluted to obtain 100 µg mL^{-1}, 50 µg mL^{-1}, and 25 µg mL^{-1}, 12.5 µg mL^{-1}, and 6.25 µg mL^{-1} concentrations. The inoculated wells were incubated overnight at 37ºC in a humid atmosphere overnight. The highest dilution showing at least 99% inhibition zone is taken as MIC.

The MIC values revealed that some of the newly synthesized compounds showed moderate to good inhibition. Compound 9b showed moderate activity against bacillus subtilis and both of the fungal strains. Compound 9e shows good activity against S. aureus, E. coli and A. flavus strains, while Compound 9f shows good to excellent activity against both the fungal strains. Compound 9h showed moderate activity against gram positive and gram negative bacterial strains. Compound 9j showed overall good activities against bacillus subtilis and E.coli bacterial strains. All other compounds showed poor activities against all bacterial and fungal strains.

Table 4: Antibacterial and antifungal activity of sulfonamidederivatives **9a-j.**

	Antibacterial MIC (µg mL^{-1})				*Antifungal MIC (µg mL^{-1})*	
Compounds	***Bacillus subtilis***	***Staphylococcus aureus***	***Escherichia coli***	***Pseudomonas aeruginosa***	***Aspergillus niger***	***Aspergillus flavus***
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
9a	1000	1000	1000	1000	1000	1000
9b	500	1000	1000	1000	500	500
9c	1000	1000	1000	1000	1000	1000
9d	1000	1000	1000	1000	250	1000
9e	1000	250	250	1000	1000	250
9f	1000	1000	1000	1000	500	125
9g	1000	1000	1000	1000	1000	1000
9h	125	500	500	500	1000	1000
9i	1000	1000	1000	500	500	1000
9j	250	1000	250	1000	500	1000

APPLICATIONS

In the present study, the derivatives which we have synthesized were screened for their antimicrobial activity, which are promising as active pharmacophore. Further studies are undergoing to explore the scope of the various biological activities.

CONCLUSIONS

An efficient method for preparation of N-((1-ethyl-5-substituted phenyl)-1*H*-indol-3-yl)methyl) substituted alkyl/aryl amide derivatives was described and the structure of synthesized compounds was determine by ^{1}H NMR, and LC-Mass spectroscopic analysis and evaluated there in vitro antimicrobial activity by broth dilution method.

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