Synthesis of 2-aryl Indoles and Fused Indole Derivatives via Fischer Indolisation and Their Antibacterial Evaluation

Sushanta Kumar Mishra

Sambalpur University

Prajna Parimita Mohanta

Sambalpur University

Ajaya Kumar Behera (✉ ajaykumar.behera@yahoo.com)

Sambalpur University <https://orcid.org/0000-0001-8466-9251>

Research Article

Keywords: Ketone, Hydrazone, Indole, Microwave, cyclization

Posted Date: February 7th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1319618/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

2-aryl indoles and some fused indole derivatives were synthesized from the condensation of 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride with different types of aryl ketones. The target molecules were afforded via hydrazone intermediate formed in situ under one-pot tandem microwave protocol or conventional method using isolated hydrazone intermediate on acid catalyzed cyclization. The antibacterial activity of the synthesized compounds *in vitro* were screened against two Gram-positive and two Gram-negative bacteria *Staphylococcus epidermidis*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Proteus vulgaris* respectively.

Introduction

Indoles are most privileged nitrogen containing heterocycles present widely in biological system which essentially take part in biochemical process. This scaffold encompasses a large number of natural products, pharmaceutical agents and polymer materials [1]. The fascinating chemical properties of indole encourage chemists to fabricate and synthesize diverse indole derivatives [2]. Many simple and direct methods are available for the synthesis of 3-substituted indoles as the 3-position of this scaffold is the preferred site for electrophilic substitution reaction. However, 2-substituted indoles also found in several alkaloids and pharmacologically important substances as potential intermediates.[3–7] The strategies for the preparation of 3-substituted indoles are well established rather, there is still a need for easier access to 2-substituted indoles. The 2-aryl indole moiety included in the structure of diverse bioactive molecules that exhibits antiestrogen [8–9], 5-H-T2A antagonist [10], anti-inflammatory [11–12] and cytotoxic properties [13]. Insertion of an aryl group into the 2- or 3- position of an indole ring is usually accomplished by de novo indole ring construction [14], Fischer indole synthesis [11], or via cross-coupling reactions of 2- or 3-indolyl metal species with an aryl halide [15–19] and related syntheses. These synthetic methods are very common and extensively reviewed [20–21]. Several synthetic routes have been developed for indoles despite; the most common method is the Fischer indole synthesis [22].

Specifically, the Fischer indolisation under microwave has acquired much attention, since it is a very convenient method. The reaction carried under microwave irradiation is rapid, safe and gives better quality of product with high yield as compared to the conventional method of synthesis [23]. In this context, herein we describe the synthesis of 2-aryl and fused indole derivatives using 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride precursor via Fischer indolisation under both microwave irradiation and conventional protocols.

Results And Discussion

Chemistry

The present works aimed at synthesizing 2-aryl and some fused indole derivatives from 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride **1** and different ketones under one-pot microwave

as well as conventional methods. A convenient one-pot reaction of 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride **1** and substituted acetophenones **2a-c** was developed using catalytic amount of acetic acid in ethanol under microwave irradiation protocol (Scheme 1). Here, the desired 2-substituted indole derivatives **4a-c** were afforded up to 93% yields. This experiment was also repeated under conventional method to establish the reaction path properly. The precursor **1** was condensed with substituted acetophenones **2a-c** in presence of acetic acid to achieve corresponding hydrazone intermediates **3a-c**. The intermediates **3a-c** in the next step, were treated with polyphosphoric acid which underwent Fischer indole cyclisation thermally to furnish the desired 2-aryl-indolyl-ethanesulfonamide **4a-c** in 76% yield. The application of microwave energy as a nonconventional activation source enhances the efficiency of the reaction which increases the yield of the target molecules and decreases the reaction time in comparison to the traditional methods. The structures were characterized with the aid of ^1H , ^{13}C NMR and mass spectra.

A tentative mechanism for the formation of the target molecules is proposed. In the first step, corresponding hydrazone derivatives are formed from 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride **1** and substituted acetophenones **2a-c**. Then, the hydrazone intermediates undergo Fischer indolization to afford the 2-aryl indole derivatives. In microwave tandem synthesis, the hydrazone intermediates generated in situ underwent Fischer indolization to furnish 2-aryl indoles.

After successful synthesis of 2-aryl indole derivatives from 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride **1** and substituted acetophenones, we have attempted the same reaction with the precursor **1** and different ketones **5a-c** under similar reaction conditions. In one-pot tandem microwave synthesis, 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride **1** and different ketones **5a-c** furnished subsequent fused indole derivatives **7a-c** (Scheme 2). Moreover, in the conventional procedure, the target fused indole derivatives **7a-c** were formed after isolating the hydrazone intermediates **6a-c** (Scheme 2).

In analogy with this study, the condensation of 2-(4-hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride **1** with 1-hydroxy-propan-2-one **8** and 1-thiophen-2-yl-ethanone **11** did not give the expected target 2-substituted indoles **10** and **13** under both conventional and microwave conditions (Scheme 3). In the individual cases, the reaction stops after forming the hydrazone intermediates **9** and **12**. They failed to undergo Fischer indole cyclisation to afford their corresponding target molecules **10** and **13**.

Anti-microbial activity

All the synthesized compounds were screened for their antibacterial activity *in vitro* against two Gram-positive bacteria *Staphylococcus epidermidis*, *Bacillus subtilis* and two Gram-negative bacteria *Pseudomonas aeruginosa* and *Proteus vulgaris*. The bacterial cultures were obtained from the microbial type culture collection (MTCC) and Gene Bank. The MTCC is a Modern facility housed at the Institute of Microbial Technology (IMTECH), Chandigarh India and maintained in usual laboratory conditions. For preliminary screening the anti-microbial tests were carried out by Agar-diffusion method. The turbidity of bacterial cultures in broth media was adjusted with sterile saline (0.9% w/v) according to 0.5 McFarland

turbidity standards for the preparation of the inoculums. Mueller- Hinton agar medium (Hi-media) previously prepared and sterilized was cooled down to 45-50⁰C. 20 ml of this media were poured into 9 cm sterile glass Petri dishes previously marked suitably at the bottom surface, to a depth of approximately 4 mm. The inoculums were added to the molten agar media in the petri dishes and the plates were swirled gently to disperse the microorganisms homogeneously. The plates were then allowed to solidify. Then well are made with the help of cylinder, the wells are impregnated with each 50 µl test compounds at four different concentration (2.5, 1.2, 0.6, and 0.3 mg/ml) and placed on the solidified surface of the media seeded with respective microorganism. Similarly, vehicle DMSO impregnated in the well were used as negative control. Kanamycin Sulphate (10 µg/disc) were used as a positive reference standard to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37⁰C for 24 hrs for bacteria strains. Anti-microbial activity was evaluated by measuring the diameter of zone of inhibition against tests organisms. The antibacterial activity of compounds against four bacterial strains was initially assessed by agar diffusion method. The results are shown in (Table 1). The compounds showed antibacterial activity against most of the tested bacteria mainly at higher concentrations. The compound **7a** exhibited feeble inhibition against all the bacteria taken. But compounds **4c**, **7b** and **7c** exhibited maximum inhibitory activity to all the test bacteria at highest concentration (2.5 mg/ml). The activities decreased with decrease in concentration. However, compounds **4a** and **4b** exhibited comparable inhibition as that of Kanamycin. All the synthesized compounds were found to possess activity at maximum concentration. The results indicated that compounds **4c**, **7b** and **7c** were more effective than the rest compounds.

The compounds were effective against most gram-positive and gram-negative bacteria tested, thereby indicating a broad spectrum of activity. However, the results revealed that the gram-positive bacteria were in general, more sensitive to this compound. In this investigation the agar disk diffusion method was employed to serve as initial antibacterial screening procedure. The diameter of zone of inhibition is a function of initial concentration (in the well), solubility and diffusion rate of the antibacterial compounds present in the exact through the agar media and thus not a true measure of effectiveness. Many physical and chemical factors unrelated to antibacterial activity affect the rate of diffusion of compounds through bacteria seeded solid media. Therefore, it is not possible to measure the antibacterial activity of a new compound in terms of another antibiotic as standard by comparing the diameter zone of inhibition produced by agar diffusion, hence in the present study no antibiotic standard was employed while agar diffusion method was used to assess the antibacterial activity where the compounds were diluted serially in a sequence of decreasing concentration and inoculated with test bacteria. The smallest concentration of the extract that prevented visible growth (turbidity) was called the minimum inhibitory concentration (MIC). Here, a reference broad spectrum antibiotic Kanamycin sulphate was employed as standard. Furthermore, some MIC values obtained for Kanamycin sulphate were roughly in agreement with literature values [24–29]. Therefore, the standard antibiotic was employed not only for the comparison but also to ensure the bacteria used in the study and the experimental conditions were appropriate and acceptable. Present investigation is the first experimental demonstration of any biological activity as well as broad spectrum antibacterial efficacy compounds. The results of the anti-microbial screening are

given in Table 1. From the results obtained, it is obvious that most of the compounds showed promising activity against bacteria.

Table 1
In vitro antibacterial activity of 4a-c, 7a-c (mg/ml) by agar diffusion method

Compd.	Conc. (mg/ml)	Zone of inhibition(mm)			
		Gram-positive bacteria		Gram-negative bacteria	
		Staphylococcus epidermidis	Bacillus subtilis	Pseudomonas aeruginosa	Proteus vulgaris
4a	2.5	20	25	15	20
	1.2	15	20	10	18
	0.6	12	10	12	10
	0.3	-	-	-	-
4b	2.5	29	32	14	24
	1.2	23	27	13	18
	0.6	17	23	-	10
	0.3	15	19	-	-
4c	2.5	33	38	27	29
	1.2	29	30	25	25
	0.6	22	27	15	20
	0.3	20	25	12	15
7a	2.5	20	25	15	20
	1.2	18	23	14	18
	0.6	17	21	12	15
	0.3	12	18	10	12
7b	2.5	40	40	25	35
	1.2	30	35	20	30
	0.6	20	25	15	25
	0.3	14	17	12	14

^a Kanamycin Sulphate (10 µg/disc) were used as a positive reference standard to determine the sensitivity of each microbial species tested.

Compd.	Conc. (mg/ml)	Zone of inhibition(mm)			
		Gram-positive bacteria		Gram-negative bacteria	
		Staphylococcus epidermidis	Bacillus subtilis	Pseudomonas aeruginosa	Proteus vulgaris
7c	2.5	36	35	25	25
	1.2	30	25	20	23
	0.6	25	20	15	22
	0.3	22	15	12	22
Kanamycin sulphate ^a		30	33	15	25
^a Kanamycin Sulphate (10 µg/disc) were used as a positive reference standard to determine the sensitivity of each microbial species tested.					

Conclusions

In summary, we have synthesized 2-aryl and fused indole derivatives using 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride precursor via Fischer indolisation under both microwave irradiation and conventional protocols. All the synthesized compounds were screened for their antibacterial activity *in vitro* against two Gram-positive bacteria *Staphylococcus epidermidis*, *Bacillus subtilis* and two Gram-negative bacteria *Pseudomonas aeruginosa* and *Proteus vulgaris*. The results indicated that compounds **4c**, **7b** and **7c** were more effective than the rest compounds. However, compounds **4a** and **4b** exhibited comparable inhibition as that of Kanamycin.

Experimental Section

General Information

Melting points were recorded on an Electro thermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrometer as pellets on KBr discs. The ¹H and ¹³C NMR spectra were recorded on Bruker ADVANCE II spectrometer (400 and 100 MHz, respectively). Chemical shifts were reported in ppm downfield from TMS as internal standard (Chemical shifts in δ, ppm). The mass spectra were recorded on a Varian Mat CH-7 at 70 eV. All of the chemicals were purchased from Sigma, Fluka, Hi-media and Merck Co. The reaction were monitored by thin layer chromatography (TLC) using glass plates coated with silicagel-G containing 13% calcium sulphate as binder. The two Gram-positive bacteria *Staphylococcus epidermidis*, *Bacillus subtilis* and two Gram-negative bacteria *Pseudomonas aeruginosa*, *Proteus vulgaris* culture were obtained from the microbial type culture collection (MTCC) and Gene Bank. The MTCC is a modern facility housed at the Institute of Microbial Technology (IMTECH), Chandigarh, India and maintained in usual laboratory conditions.

Synthetic procedures

General procedure for 2-aryl indole 4a-c and fused indole 7a-c derivatives

Method A (Conventional).

General procedure for hydrazone derivatives of 2-(4-Hydrazino-aryl)-ethanesulfonic acid methylamide hydrochloride (**3a-c**, **6a-c**).

To the solution of 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride **1** (0.11 mmol) in ethanol (30 ml), a catalytic amount of acetic acid was added which was then stirred for 10 min followed by addition of different aryl ketones **2a-c**, **5a-c** (0.13 mmol) at room temperature. The mixture was stirred for another 2 hrs at room temperature. The precipitated solid was filtered and washed with ethanol and dried under vacuum at 50 °C to give the hydrazone derivatives of 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride **3a-c**, **6a-c**.

General procedure for 2-(2-aryl-1H-indol-5-yl)-ethanesulfonic acid methylamide (**4a-c**, **7a-c**). The hydrazone derivatives **3a-c**, **6a-c** (0.0065 mol) were added to preheated polyphosphoric acid at 80 °C and stirred for 1 hrs at 70-80 °C. After completion of the reaction (monitored by TLC) water was added to the reaction mass to get a clear solution which was then extracted with ethyl acetate. The organic layer was washed with 10% potassium carbonate solution. The organic layer was dried over sodium sulphate and distilled out under vacuum at 50 °C to give a residue which was then crystallized with isopropyl ether to give corresponding indole derivatives (**7a-c**).

Method B (Microwave).

To a mixture of 2-(4-Hydrazino-phenyl)-ethanesulfonic acid methylamide hydrochloride **4** (0.11 mmol) (30 ml) and aryl ketones (0.13 mmol) in ethanol, a catalytic amount of acetic acid was added at room temperature. The reaction mixture was then subjected to microwave irradiation at 80 °C, 300w for 10 min. The progress of the reaction was monitored by TLC. After completion of the reaction the precipitated solid cooled and was filtered to give corresponding indole derivatives (**7a-c**).

2-{4-[N'-(1-Phenyl-ethylidene)-hydrazino]-phenyl}ethanesulfonic acid methylamide (**3a**)

Brown solid; Yield: 78%; Melting point: 186-188 °C; FTIR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3329, 3061 (-NH), 1617 (-C=N); ESI-MS m/z calculated for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+1]^+$: 331.4325, found: 332.1388.

2-{4-[N'-[1-(3-Methoxy-phenyl)-ethylidene]-hydrazino]-phenyl}-ethanesulfonic acid methylamide (**3b**)

Brown solid; Yield: 81%; Melting point: 191-193 °C; FTIR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3427, 2940 (-NH), 1724 (-C=N); ESI-MS m/z calculated for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$ $[\text{M}+1]^+$: 361.4585, found: 362.1494.

2-{4-[N'-[1-(4-Methoxy-phenyl)-ethylidene]-hydrazino]-phenyl}-ethanesulfonic acid methylamide (**3c**)

Brown solid; Yield: 84%; Melting point: 196-198°C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3420, 3310 (-NH), 1603 (-C=N); ESI-MS m/z calculated for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$ $[\text{M}+1]^+$: 361.4585, found: 362.1464.

2-[4-(N'-Cyclohexylidene-hydrazino)phenyl]-ethanesulfonic acid methylamide (6a)

Brown solid; Yield: 74%; Melting point: 196-198°C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3210, 3037(-NH), 1586(-C=N); ESI-MS m/z calculated for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+1]^+$: 309.4270, found: 310.1545.

2-{4-[N'-(1-Methyl-piperidin-4-ylidene)-hydrazino]-phenyl}-ethanesulfonic acid methyl-amide (6b)

Brown solid; Yield: 75%; Melting point: 201-203°C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3331, 3062 (-NH), 1617 (-C=N); ESI-MS m/z calculated for $\text{C}_{15}\text{H}_{24}\text{N}_4\text{O}_2\text{S}$ $[\text{M}+1]^+$: 324.4417, found: 325.4132.

2-{4-[N'-(1-Benzyl-piperidin-4-ylidene)-hydrazino]-phenyl}-ethanesulfonic acid methyl- amide (6c)

Brown solid; Yield: 78%; Melting point: 207-209°C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3427, 2940 (-NH), 1724 (-C=N); ESI-MS m/z calculated for $\text{C}_{21}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$ $[\text{M}+1]^+$: 400.5376, found: 401.3725.

N-methyl-2-(2-phenyl-1H-indol-5-yl)ethanesulfonamide (4a)

Yield: 93%; Melting point: 145-148°C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3433 (-NH), 1597, 1571 (S=O); ^1H NMR (400 MHz, DMSO- d_6): δ 2.23-2.24 (s, 3H), 3.04-3.08 (m, 2H), 3.82-3.84 (m, 2H), 6.80-6.81 (q, 1H), 6.98-6.99 (m, 1H), 7.00-7.01 (m, 1H), 7.28-7.36 (m, 5H), 7.58-7.62 (m, 2H), 11.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 28.5, 29.5, 51.8, 106.9, 110.7, 114.2, 116.2, 120.5, 125.7, 127.8, 128.5, 132.7, 134.7; Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 65.77; H, 6.57; N, 10.96; found: C, 65.60; H, 6.50; N, 10.71; ESI-MS m/z $[\text{M}+1]^+$: calculated: 314.4020, found: 315.4998.

2-(2-(3-methoxyphenyl)-1H-indol-5-yl)-N-methylethanesulfonamide (4b)

Yield: 89%; Melting point: 159-163°C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3383, 3294 (-NH); 1307, 1230 (S=O); ^1H NMR (400 MHz, DMSO- d_6): δ 1.03-1.05 (d, 3H), 2.63 (s, 3H), 2.98-3.04 (m, 2H), 3.27-3.34 (m, 2H), 3.84 (bs, 1H), 6.87 (dd, 1H), 7.33-7.36 (m, 1H), 7.39-7.42 (m, 2H), 7.45 (m, 4H), 11.48 (bs, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 28.6, 32.2, 50.8, 51.6, 111.2, 114.8, 118.3, 118.5, 121.1, 122.6, 124.9, 125.5, 126.0, 127.0, 127.4, 129.9, 135.1, 144.4; Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$: C, 62.77; H, 5.85; N, 8.13; found: C, 62.69; H, 6.45; N, 8.95; ESI-MS m/z $[\text{M}+1]^+$: calculated: 344.4280, found: 345.4696 .

2-(2-(4-methoxyphenyl)-1H-indol-5-yl)-N-methylethanesulfonamide (4c)

Yield: 92%; Melting point: 155-160°C; FTIR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3404, 3294 (-NH), 1602, 1183 (S=O); ^1H NMR (400 MHz, DMSO- d_6): δ 2.63 (d, J= 6.84 Hz, 3H), 2.90-2.94 (m, 2H), 3.13-3.17 (m, 2H), 3.39 (s, 3H), 6.53 (d, J= 8.0 Hz, 2H), 6.74 (d, J= 8.0 Hz, 1H), 7.19 (d, J= 8.0 Hz, 2H), 7.22-7.26 (m, 3H), 10.60 (s, 1H); ^{13}C NMR

(100 MHz, DMSO- d_6): δ 28.6, 32.2, 50.8, 51.6, 111.2, 114.8, 118.3, 118.5, 121.1, 122.6, 124.9, 125.5, 126.0, 127.0, 127.4, 129.9, 135.1, 144.4; Anal. Calcd. for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13; found: C, 62.60; H, 5.84; N, 8.11; ESI-MS m/z $[M+1]^+$: calculated: 344.4280, found: 345.4996.

N-methyl-2-(6,7,8,9-tetrahydro-5H-carbazol-3-yl)ethanesulfonamide (7a)

Yield: 91%; Melting point: 148-151°C; FTIR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3278 (-NH), 1317, 1273 (S=O); ^1H NMR (400 MHz, DMSO- d_6): δ 1.79-1.85 (t, 4H), 2.51-2.52 (t, 2H), 2.64 (d, J = 8.0 Hz, 3H), 2.70-2.71 (t, 2H), 3.01-3.06 (m, 2H), 3.21-3.25 (m, 2H), 3.59 (q, 1H), 6.85 (dd, 1H), 6.91-6.94 (q, 1H), 7.18 (s, 1H), 10.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 20.6, 22.8, 23.0, 28.6, 29.5, 51.9, 107.8, 110.5, 116.4, 120.4, 127.5, 127.5, 134.4, 134.8; Anal. Calcd. for $C_{15}H_{20}N_2O_2S$: C, 61.23; H, 6.85; N, 9.93; found: C, 61.19; H, 6.18; N, 9.71; ESI-MS m/z $[M+1]^+$: calculated: 292.3965, found: 293.4028.

N-methyl-2-(2-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-6-yl)ethanesulfonamide (7b)

Yield: 94%; Melting point: 163-166°C; FTIR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3278 (-NH), 1317, 1273 (S=O); ^1H NMR (400 MHz, DMSO- d_6): δ 2.46 (s, 3H), 2.62 (d, J =8.0 Hz, 3H), 2.71-2.74 (m, 2H), 2.79-2.81 (m, 2H), 3.00-3.09 (m, 2H), 3.12-3.20 (m, 2H), 3.53 (s, 2H), 6.84-6.90 (m, 2H), 7.16-7.20 (m, 2H), 10.54 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): 22.6, 28.5, 29.5, 45.6, 51.4, 51.8, 52.1, 106.9, 110.7, 116.2, 120.5, 125.7, 127.8, 132.7, 134.7; Anal. Calcd. for $C_{15}H_{21}N_3O_2S$: C, 58.61; H, 6.89; N, 13.67; found: C, 58.60; H, 6.50; N, 13.65; ESI-MS m/z $[M+1]^+$: calculated: 307.4111, found: 308.4537.

2-(2-benzyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-6-yl)-N-methylethanesulfonamide (7c)

Yield: 95%; Melting point: 146-149°C; FTIR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3336 (-NH), 1313, 1151 (S=O); ^1H NMR (400 MHz, DMSO- d_6): δ 2.50 (d, J = 8.0 Hz, 3H), 2.70 (t, 4H), 2.83-2.89 (m, 2H), 3.12-3.18 (m, 2H), 3.46 (s, 2H), 3.64 (s, 2H), 6.79-6.84 (m, 2H), 7.06-7.11 (m, 2H), 7.18 (m, 1H), 7.20-7.31 (m, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): 23.6, 28.6, 29.4, 49.4, 50.0, 51.7, 61.8, 106.9, 110.7, 116.3, 120.6, 125.8, 126.7, 127.9, 128.0, 128.5, 133.1, 134.8, 138.7; Anal. Calcd. for $C_{21}H_{25}N_3O_2S$: C, 65.77; H, 6.57; N, 10.96; found: C, 65.60; H, 6.53; N, 10.71; ESI-MS m/z $[M-1]^+$: calculated: 383.5071, found: 382.4354.

Declarations

Acknowledgements

The authors thank UGC (DRS-SAP), New Delhi for financial support, FIST-DST for providing infrastructural research facility, SAIF (Punjab University, Chandigarh) and Institute of Microbial Technology (IMTECH), Chandigarh for recording NMR and Mass spectra and screening antibacterial activity.

Compliance with ethical standards

Conflict of interest

The authors declare no competing interests.

References

1. Gribble GW. Pyrroles and benzo derivatives: applications; In Comprehensive Heterocyclic Chemistry II. Katritzky AR, Rees CW, Scriven EFV. (Eds.) Pergamon Press: New York, Oxford. **1996**; Vol. 2: pp. 207-256.
2. Gribble, GW. Recent developments in indole ring synthesis-methodology and applications. J. Chem. Soc. Perkin Trans. 1. **2000**; 1045-1047.
3. Kuehne ME, Podhorez DE, Mulamba T, Bornmann WG. Biomimetic alkaloid syntheses. 15. Enantioselective syntheses with epichlorohydrin: total syntheses of (+)-, (-)- and (+-)-vindoline and a synthesis of (-)-vindorosine. J. Org. Chem. **1987**; 52:347-353. <https://doi.org/10.1021/jo00379a006>
4. Hashimoto C, Husson HP. **Synthetic and structural studies in the goniomitine alkaloid series: A new reductive cyclization reaction in the indole field.** Tetrahedron Lett. **1988**; 29: 4563-4566. [https://doi.org/10.1016/S0040-4039\(00\)80547-X](https://doi.org/10.1016/S0040-4039(00)80547-X)
5. Leon P, Garbay-Jaureguiberry C, Barsi MC, Le Pecq JB, Roques BP Modulation of the antitumor activity by methyl substitutions in the series of 7H-pyridocarbazole monomers and dimmers. J. Med. Chem. **1987**; 30: 2074-2080. <https://doi.org/10.1021/jm00394a024>
6. Sundberg RJ. In The Chemistry of Indoles. Blomquist AT. Ed.; Academic: New York, **1970**.
7. Brown RK, In Houlihan WJ. Ed. Heterocyclic Compounds; Wiley-Interscience: New York, **1972**; Vol. 25.
8. Ismail MF, Shmeiss NAMM, El-Diwani HI, Arbid MS. Synthesis and pharmacological activity of some 2, 3-diphenylindole derivatives. Indian J. Chem. Sect. B: Org. **1997**; 36B: 288-292. <http://nopr.niscair.res.in/handle/123456789/57067>
9. Medarde M, Ramos AC, Caballero E, De Clairac RPL, Lopez JL, Gravalos DG, Feliciano AS. Synthesis and pharmacological activity of diarylindole derivatives. Cytotoxic agents based on combretastatins. Bioorg. Med. Chem. Lett. **1999**; 9: 2303-2308. [https://doi.org/10.1016/S0960-894X\(99\)00370-4](https://doi.org/10.1016/S0960-894X(99)00370-4)
10. Colletti SL, Li C, Fischer MH, Wyvratt MJ, Meinke PT. Tryptophan-replacement and indole-modified apicidins: synthesis of potent and selective antiprotozoal agents. Tetrahedron Lett. **2000**; 41: 7825-7827. [https://doi.org/10.1016/S0040-4039\(00\)01363-0](https://doi.org/10.1016/S0040-4039(00)01363-0)
11. Von Angerer E, Knebel N, Kager M, Ganss B. 1-(Aminoalkyl)-2-phenylindoles as novel pure estrogen antagonists. J. Med. Chem. **1990**; 33: 2635-2640. <https://doi.org/10.1021/jm00171a045>
12. Biberger C, Von Angerer E. 1-Benzyl-2-phenylindole- and 1,2-diphenylindole-based antiestrogens. Estimation of agonist and antagonist activities in transfection assays. J. Steroid Biochem. Mol. Biol. **1998**; 64: 277-281. [https://doi.org/10.1016/S0960-0760\(97\)00197-0](https://doi.org/10.1016/S0960-0760(97)00197-0)
13. Stevenson G I, Smith AL, Lewis S, Michie SG, Neduvélil JG, Patel S, Marwood R, Castro JL. 2-Aryl tryptamines: selective high-affinity antagonists for the h5-HT_{2A} receptor. Bioorg. Med. Chem.

- Lett. **2000**; 10: 2697-2699. [https://doi.org/10.1016/S0960-894X\(00\)00557-6](https://doi.org/10.1016/S0960-894X(00)00557-6)
14. Gribble GW. Recent developments in indole ring synthesis—methodology and applications. J. Chem. Soc. Perkin Trans. 1 **2000**; 1045-1047. <https://doi.org/10.1039/A909834H>
 15. Newcastle GW, Katritzky AR. Adv. Heterocycl. Chem. **1993**; 56: 155.
 16. Hudkins RL, Diebold JL, Marsh FD. Synthesis Of 2-Aryl- and 2-Vinyl-1H-indoles via Palladium-Catalyzed Cross-Coupling of Aryl and Vinyl Halides with 1-Carboxy-2-(tributylstannyl)indole. J. Org. Chem. **1995**; 60: 6218-6220. <https://doi.org/10.1021/jo00124a048>
 17. Amat M, Hadida S, Pshenichnyi G, Bosch J. Palladium(0)-Catalyzed Heteroarylation of 2- and 3-Indolylzinc Derivatives. An Efficient General Method for the Preparation of (2-Pyridyl)indoles and Their Application to Indole Alkaloid Synthesis. J. Org. Chem. **1997**; 62: 3158-3175. <https://doi.org/10.1021/jo962169u>
 18. Kawasaki I, Yamashita M, Ohta S. Total Synthesis of Nortopsentins A-D, Marine Alkaloids. Chem. Pharm. Bull. **1996**; 44: 1831-1837. <https://doi.org/10.1248/cpb.44.1831>
 19. Johnson CN, Stemp G, Anand N, Stephen SC, Gallagher, T. Palladium(0)-Catalysed Arylations using Pyrrole and Indole 2-Boronic Acids. Synlett. **1998**; 1025-1027. <https://10.1055/s-1998-1834>
 20. Sundberg RJ. Pyrroles and benzo derivatives: synthesis; In Comprehensive Heterocyclic Chemistry II. Katritzky AR, Rees CW, Scriven EFV (Eds.); Pergamon Press: New York, Oxford, **1996**; vol. 2, pp. 119-206,
 21. Sundberg RJ. Indoles; Academic Press: London, **1996**.
 22. Robinson B. **1982**; The Fischer Indole Synthesis, Wiley: Salisbury.
 23. Liu G, Yang S, Song B, Xue W, Hu D, Jin L, Lu P. Microwave Assisted Synthesis of N-Arylheterocyclic Substituted-4-aminoquinazoline Derivatives. Molecules. **2006**; 11(4): 272-278. <https://doi.org/10.3390/11040272>
 24. Anonymous. Wealth of india, raw materials. Vol. XI. New delhi: council of scientific and industrial research. **1976**; p.24.
 25. Seeley HW, Vandemark PJ. Microbes in action, A laboratory manual in microbiology, Bombay: D.B. Teraporevala sons & co. pvt. Ltd. **1975**; 163-164.
 26. Prescott LM, Herley JP, Klein DA. Microbiology. Oxford: Wm. C. Brown publishers, **1993**; 328-330.
 27. Cyantia H, Callaghan O. Assessment of a new antibiotic in. Hugo WB, Russel, AD. editors. Pharmaceutical microbiology. Oxford: Blackwell scientific publications. **1983**; 122-134.
 28. Anhalt JP. JA II Washington. Antimicrobial susceptibility tests of aerobic and facultative anaerobic. In: Washington JA, editors. Procedures in clinical microbiology. New York, Heidelberg, Berlin and Tokyo: Springer-verlag, **1985**; 281-305.
 29. Reeves DS, White LO. Principle and methods of assaying antibiotics. In: Hugo WB, Russel AD. editors. Pharmaceutical microbiology. Oxford: Blackwell scientific publication. **1983**; 140-148.

Scheme

Schemes 1, 2 and 3 are available in the Supplemental Files section.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Scheme1.jpg](#)
- [Scheme2.jpg](#)
- [Scheme3.jpg](#)
- [SupportingInformation.docx](#)