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Synthesis, biological activity of newly designed sulfonamide based indole derivative as anti-microbial agent

Khushbu Agrawal*, Tarun Patel and Rajeshree Patel

Abstract

Background In medicinal chemistry, indole and its derivative play an important role. Indole is gaining a lot of importance in medicinal chemistry due to its physiological activity which includes anticancer, antitubercular, antimicrobial, antiviral, antimalarial, anti-inflammatory activities, antileishmanial agents, anti-cholinesterase, and enzyme inhibitory. The spread of antimicrobial resistance becomes a threat to both humans and animals. Antimicrobial resistance has been declared in the top 10 global major health risks by WHO including reported data of 2020 of AMR with 3,106,002 confirmed infections in humans across 70 countries.

Result In this present work some new sulfonamide-based indole derivatives were synthesized by using 1H-indole -2 carboxylic acid as a starting material. The structure of all synthesized sulfonamide-based indole derivatives was confirmed by 1H NMR and LCMS Spectroscopy.

Conclusion All the synthesized compounds were screened for anti-microbial activity against Gram Positive *Staphylococcus aureus, Bacillus megaterium,* and Gram Negative *Klebsiella pneumonia, Escherichia coli, Salmonellatyphiae, Shigella* sp., *Enterobacter aerogenes.* Among gram-positive *Staphylococcus aureus, and Bacillus megaterium*. The compound shows activity against *Staphylococcus aureus,* and among all gram-negative bacteria against *Klebsiella pneumonia* shows good activity.

Keywords Indole, 1H indole-2-carboxylic acid, Antimicrobial activity, Sulfonamide-based indole derivative

Background

Antimicrobial agents are essentially important because of massive microbial infections in today's world [1, 2]. The spread of antimicrobial resistance becomes a threat to both humans and animals [3, 4]. Antimicrobial resistance has been declared in the top 10 global major health risks by WHO including reported data of 2020 of AMR with 3,106,02 confirmed infections in humans across 70 countries [5, 6]. When the microorganism broadens to capacity to defect drug design to kill microbes that time Antimicrobial resistance occurs [7, 8]. We can reduce antimicrobial infection by the proper use of antimicrobials, selecting the required antimicrobial drug regimen, and the proper dose of drugs [9, 10].

Heterocyclic chemistry plays an important role in drug design because a wide range of heterocyclic compounds are clinically active, one of them is "Indole" [11, 12]. Baeyar and knop first prepare indole in 1866 when they were studying the indigo dye [13]. To prepare Indole Baeyar reduced oxindole [14]. The formula of indole is "C_8H_7N" is also known as 1H-benzo[b] pyrrole [15]. The emergence of indole is a colorless crystalline solid with a melting point of 52 °C and a boiling point 253 °C at 762 mm [16]. Indole contains a six-membered benzene ring which is fused to a five-membered pyrrole ring containing

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nitrogen giving it a bicyclic structure [17]. Indole is gaining a lot of importance in medicinal chemistry due to their physiological activity which includes anti-cancer [18, 19], antitubercular [20, 21], antimicrobial [22, 23], antiviral [24, 25], antimalarial [26, 27], anti-inflammatory activities [28, 29], antileishmanial agents [30, 31], anticholinesterase [32, 33], enzyme inhibitory [34, 35]. The important medicinal activities of indole are shown in Fig. 1.

Sulfonamides act as important as biologically active in pharmaceuticals. The basic skeleton of sulfonamide moiety generates sulpha drugs or sulfa drugs [36]. The more potency showed by the sulfonamide functional group help in producing new action toward biologically active scaffolds [37]. The aim of having the best or more potent anti-microbial compounds were reported by substituting the chemistry of sulfonamidee [38] with indole 2-carboxylic acid which provides pharmacological properties and significant biological properties.

In 2022, Yuanyuan and co-workers synthesized para amino benzene sulfonamide indole hybrids and screened them for antibacterial activities against *staphylococcus aureus* and some of the compounds show good activity against *staphylococcus aureus* [39]. In 2022, *S. jagadeesan* and *S. Karpagam* designed a novel series of N-acyl substituted indole-based piperidine, thiazole, and tetrazoles, and after the synthesis, they screened compounds against *Klebsiella* and *Escherichia coli* and all compounds give excellent activity against both bacteria [40]. In 2021, Reem I. Al-wabli and co-workers synthesized new indole-triazole conjugates and screened them for antimicrobial resistance. All the assisted compounds were found as good antimicrobial agents [41]. Synthesis and antimicrobial activity of 3-(1H-indole-3-carbonyl)-2H-chromen-2-one derivatives done by Khadhar Navaz Umar Bashat etc. in 2021. Some of the compounds show potent antimicrobial activity [42]. In 2020, Andre Nehemine Bitombo reported indole alkaloids as a potent antimicrobial agents [43]. In this current work, we synthesized a derivative of Indole -2 carboxylic acid and all the compounds were evaluated for their antimicrobial activity against *staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella.*

Here, we aim to facilitate the current research in designing innovative strategies for the discovery and development of good antimicrobial agents.

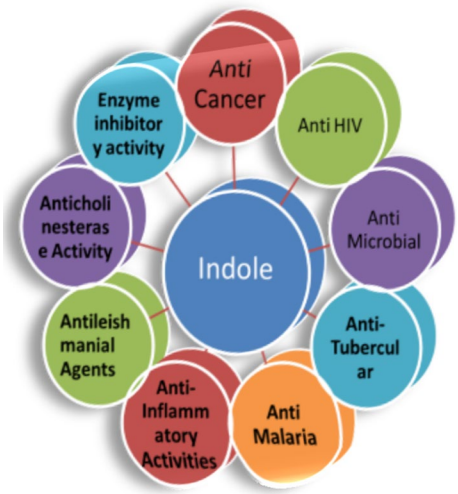


Fig. 1 Different medicinal activity of indole

Method

Materials

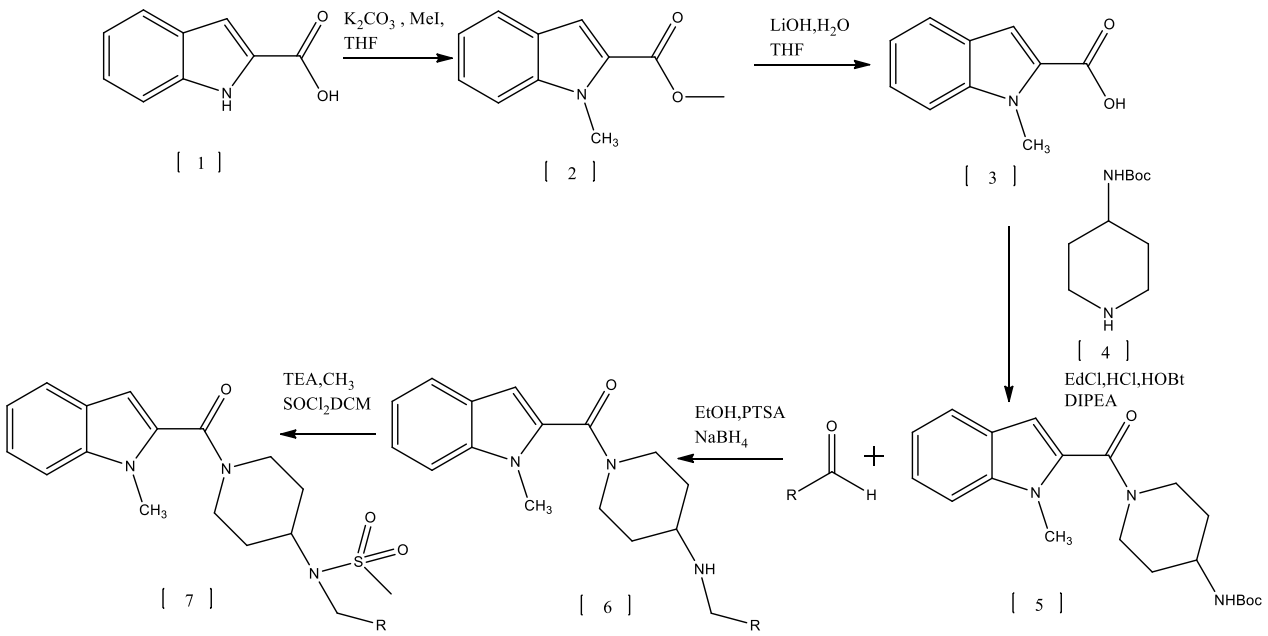
All the chemicals were used without any further purification obtained from sigma Aldrich as well all the solvents were also purchased from sigma Aldrich. Thin layer chromatography (TLC) was performed by using Elutes the gradient of MeOH in MDC on silica gel plates (60F254, 0.2 mm thick, Merck). By taking tetra methyl silane (TMS) as internal standard ^{1}H NMR spectra were carried out in $CdCl_3$ solutions at 400 MHz by Bruker Advance II 400 NMR spectrometer. The δ value in 1 H NMR is calculated in ppm (parts per million).

LCMS data were recorded by WATERS instrument in which 0.15% formic acid in acetonitrile was used as the mobile phase.

Chemistry

As a precursor, commercially available N- unsubstituted indole 2-carboxylic acid (1) was used. Di-methylation at the indole site of N- unsubstituted indole 2-carboxylic acid(1) in presence of MeI and K_2CO_3 lead to the preparation of N-methylated indole ester(2) [44], which undergoes deprotection with lithium hydroxide water ($LiOH.H_2O$) in presence of THF yields 1-methyl-1H-indole-2-carboxylic acid(3) [45]. 1-methyl-1H-indole-2-carboxylic acid(3) further reacts with commercially available reagent 4-boc pieridine amine(4) and a debocking reaction is carried out in presence of EDCl.HCl and HoBt with DIPEA which results (4-aminopiperidin-1-yl) (1-methyl-1H-indol-2-yl)methanone(5) [46].

In Scheme 1 synthesis route of compounds (6a-6o) was shown. All these compounds were derived from (4-aminopiperidin-1-yl) (1-methyl-1H-indol-2-yl) methanone(5) in the presence of various aldehydes via reductive amination in the presence of reducing agent $NaBH_4$ and PTSA with ethanol. All the attached aldehydes are mentioned in Table 1. The synthetic route was shown to afford a series of substituted sulfonamide-based indole derivatives (7a-7o) with different substituents (6a-6o)



Scheme 1 Synthetic route of Sulfonamide-based indole derivatives (R = Aldehyde used)

that were reacted with methyl sulfonamide chloride in the presence of TEA to furnish the sulfonamide-based indole derivatives [47].

Anti-microbial activity

The in vitro antimicrobial potential of new indole derivatives synthesized listed in Table 1 were primarily screened against model Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus megaterium*) and Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella typhiae*, *Shigella* sp., and *Enterobacter aerogenes*). The antibacterial activities of the tested compounds were evaluated by the agar well diffusion method. The solution of each compound is prepared in dimethyl sulfoxide (DMSO) at a final concentration of 0.005% (50 μg ml^{-1}).

The Gram-positive and Gram-negative bacteria were sub-cultured in Mueller Hinton broth (MHB) and incubated overnight on a rotary shaker at 37 °C. Each one ml of overnight grown bacterial culture was inoculated in molten (cooled at 45 °C) Mueller Hinton agar and then poured into the sterile Petri dish. Plates were allowed to solidify and four wells were prepared using a sterile cup borer (6 mm in diameter) into each agar plate. Then, 50 μl of each compound was added to respective wells and the plates were pre-incubated at 4 °C in the refrigerator for 10 min to allow the diffusion of the compound into the agar. For every plate, DMSO was also kept as a negative control. Further, the plates were incubated at 37 °C overnight. The zone of growth inhibition around each well was observed to confirm antimicrobial activity and measured in mm (including the diameter of the wells). In order to determine the minimum inhibitory concentrations (MIC), the concentration was summarized by using agar well diffusion method as reported [48].

The SAR study exposed that the thiophene ring at the R position of moiety exhibits more potency toward the antimicrobial activity. In addition, the present study also showed that due to Mono-substitution on the N1 position of the sulfonamide group with heterocyclic or aromatic ring gives more potent antimicrobial compounds. Investigation performed in the current study by introducing different substituents into core indole. Structure–activity relationship was performed on different synthesized molecules and analyzed that compounds **7a** and **7b** showed good potency against Gram Negative bacteria and more potent towards *Klebsiella pneumonia.* Although compounds **7d** and **7g** are relevant but due to the different modes of attachment in both the compounds, the compounds **7d,** and **7g** showed almost the same potency against Gram-positive *Staphylococcus aureus* and compound **7g** is more potent towards gram-negative *Klebsiella pneumonia* as compared with compound **7d**. On comparing compounds **7j** and **7l**, the increased activity can be seen in **7j** against gram-positive *Staphylococcus aureus* and all gram-negative bacteria due to the increase in no. of an electron-withdrawing group. As **7j** is having more electron-withdrawing groups than **7l**, thus it is more potent towards the anti-microbial organisms.

Table 1 Properties of compounds

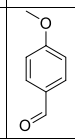
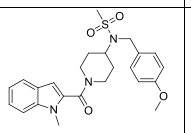
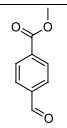
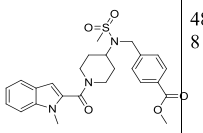
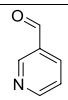
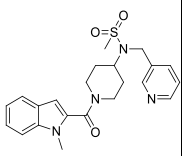
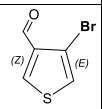
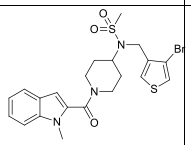
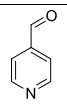
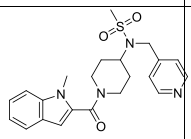
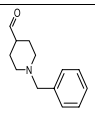
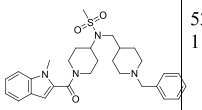
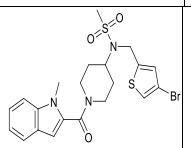
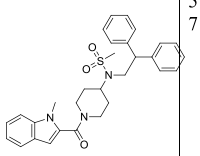
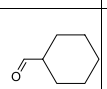
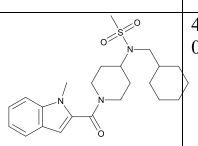
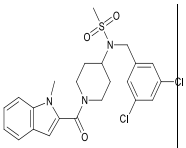
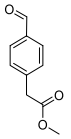
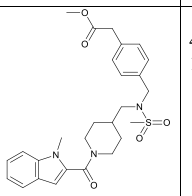
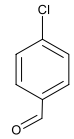
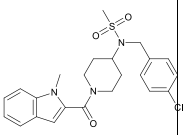
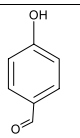
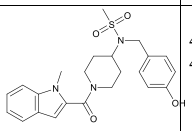
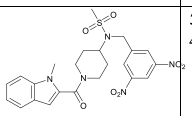
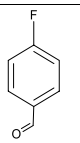
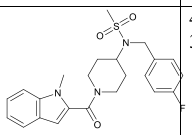
Compound Number	Aldehyde used	Name	Structure	M.W.
7a		N-(4-methoxybenzyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		455.57
7b		methyl 4-((N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methylsulfonamido)methyl)benzoate		483.58
7c		N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)-N-(pyridin-3-ylmethyl)methanesulfonamide		426.54
7d		N-((4-bromothiophen-3-yl)methyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		510.47
7e		N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)-N-(pyridin-4-ylmethyl)methanesulfonamide		426.54
7f		N-((1-benzylpiperidin-4-yl)methyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		522.71
7g		N-((4-bromothiophen-2-yl)methyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		510.47
7h		N-(2,2-diphenylethyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		515.67
7i		N-(cyclohexylmethyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		431.60
7j		N-(3,5-dichlorobenzyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-		494.43

Table 1 (continued)

		yl)methanesulfonamide		
7k		methyl 2-(4-((N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methylsulfonamido)methyl)phenyl)acetate		497.61
7l		N-(4-chlorobenzyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		459.99
7m		N-(4-hydroxybenzyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		441.54
7n		N-(3,5-dinitrobenzyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		515.54
7o		N-(4-fluorobenzyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide		443.53

Result

The biological activity as expressed by the growth inhibition zone (in mm) of the tested microorganism is listed in Table 2. Data represented in Table 2 shows that the synthesized sulfonamide-based indole derivatives under investigation exhibited low antibacterial activity against Gram Positive *Staphylococcus aureus* but failed to inhibit the growth of *Bacillus megaterium* compared with standard Ciprofloxacin. All tested compounds showed the highest antibacterial activity towards Gram-Negative *Klebsiella pneumonia* whereas lower activity against other Gram-negative bacteria. The statistical diagram representing the anti-microbial activity of all compounds is shown in Fig. 2.

Discussion

Preparation of N-methylated indole ester (2)

The synthesis route of desired compounds is illustrated in Scheme 1. In suspension of anhydrous potassium carbonate (3 eq.) and 1H-indole-2-carboxylic acid (1 eq.) methyl iodide (2.5 eq.) was added in dry DMF (10 vol.) with constant stirring at 80 °C, the reaction was then completed by performing TLC. Separation was done with 2–3 washings of ethyl acetate and water. When the temperature of the reaction mixture was allowed to come down to room temperature then ethyl acetate was used to extract the aqueous phase. Under the reduced pressure, the organic layer was dried over $MgSO_4$, and as result we get beige colour solid, and the desired N-methylated indole ester (2) with 96–99% yield.

Preparation of 1-methyl-1H-indole-2-carboxylic acid (3)

For the desired 1-methyl-1H-indole-2-carboxylic acid (3), $LiOH{\cdot}H_2O$ in water (3 eq.) was added to a solution of N-methylated indole ester (2) (1 eq.) in THF (3 ml) at room temperature. The ensuing residue was neutralized with 2 N HCl with constant stirring of 3 h and the solvent was completely evaporated under reduced pressure. To get desired corresponding acids with EtOAc (20 ml × 2), a solution was extracted by performing filtration, and

Table 2 Antibacterial activity of tested compounds as a zone of inhibition in mm and MIC (μg/mL^{-1}) of synthesized compound

Compound number	*Staphylococcus aureus* (Gram+)	*Bacillus megaterium* (Gram+)	*Escherichia coli* (Gram−)	*Klebsiella pneumonia* (Gram−)	*Salmonella typhiae* (Gram−)	*Shigella* sp. (Gram−)	*Enterobacter aerogenes* (Gram−)
7a	7.0 (6.0)	–	8.0 (5.0)	9.0 (4.0)	8.0 (5.0)	7.0 (5.0)	7.0 (4.0)
7b	9.0 (4.0)	–	7.0 (6.0)	9.0 (4.0)	8.0 (5.0)	8.0 (5.0)	7.0 (4.0)
7c	7.0 (5.0)	–	7.0 (5.0)	8.0 (6.0)	7.0 (6.0)	7.0 (6.0)	8.0 (4.0)
7d	8.0 (5.0)	–	8.0 (5.0)	8.0 (6.0)	7.0 (6.0)	8.0 (4.0)	7.0 (6.0)
7e	7.0 (4.0)	–	7.0 (5.0)	7.0 (5.0)	8.0 (4.0)	8.0 (5.0)	8.0 (5.0)
7	7.0 (4.0)	–	8.0 (5.0)	8.0 (5.0)	8.0 (5.0)	7.0 (4.0)	8.0 (4.0)
7g	8.0 (5.0)	–	–	10.0 (4.0)	7.0 (4.0)	–	7.0 (5.0)
7h	7.0 (5.0)	–	8.0 (5.0)	7.0 (5.0)	–	8.0 (4.0)	8.0 (5.0)
7i	7.0 (5.0)	–	7.0 (6.0)	8.0 (5.0)	8.0 (6.0)	7.0 (4.0)	8.0 (4.0)
7j	8.0 (4.0)	–	8.0 (5.0)	10.0 (4.0)	9.0 (4.0)	8.0 (5.0)	8.0 (5.0)
7k	8.0 (4.0)	–	–	9.0 (4.0)	7.0 (5.0)	8.0 (6.0)	7.0 (5.0)
7l	7.0 (5.0)	–	7.0 (5.0)	9.0 (4.0)	7.0 (5.0)	7.0 (4.0)	7.0 (4.0)
7m	7.0 (5.0)	–	8.0 (5.0)	8.0 (5.0)	8.0 (6.0)	7.0 (4.0)	–
7n	8.0 (4.0)	–	7.0 (5.0)	7.0 (6.0)	8.0 (6.0)	8.0 (5.0)	7.0 (5.0)
7o	7.0 (5.0)	–	–	8.0 (6.0)	7.0 (5.0)	7.0 (4.0)	8.0 (4.0)
Ciprofloxacin	11.0 (4.0)	12.0 (4.0)	10.0 (4.0)	12.0 (4.0)	11.0 (4.0)	10.0 (5.0)	10.0 (4.0)

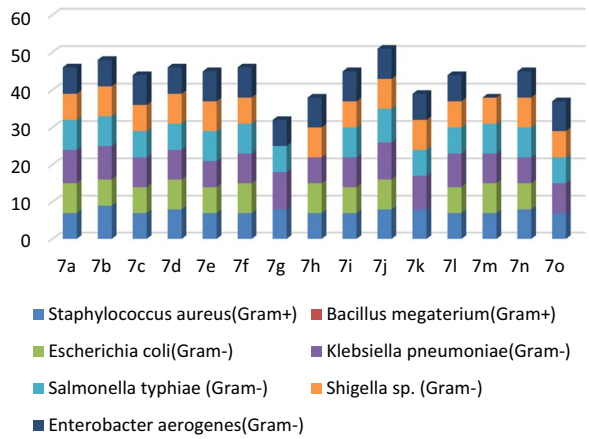


Fig. 2 Statistical diagram of antimicrobial activity

then dried over Na_2SO_4 and excess solvent was evaporated under reduced pressure. We get brown solid residue with 85% yield.

Preparation of (4-aminopiperidin-1-yl)(1-methyl-1H-indol-2-yl)methanone (5)

In a round-bottomed flask first add reagent 4-amino bocpiperidine (4) (1.2 eq.) then add 1-methyl-1H-indole-2-carboxylic acid (3), in the presence of dry DMF. The colloid was allowed to stir overnight with the addition of a measured quantity of EDCl-HCl (1.5 eq.), HOBt (1.5 eq.), and DIPEA (2 eq.) at room temperature. Into a Separating funnel, pour the stirred solution which contains ethyl acetate and water. By using of separator funnel, the aqueous phase was separated as well as extracted three times. The collected residue was dried using Na_2SO_4. After filtration, the residue was concentrated in vacuo and further purified by using column chromatography (CH_2Cl_2:MeOH with a ratio of 9:1) to get the desired product (4-aminopiperidin-1-yl)(1-methyl-1H-indol-2-yl)methanone (5).

General procedure of compound (6a-6o)

The solution of (4-aminopiperidin-1-yl)(1-methyl-1H-indol-2-yl)methanone (5) (50 mg, 0.194 mmol) in MeOH (2 ml) was cooled at 0 °C. In the reaction mixture at 0 °C dropwise addition of TEA (0.582 mmol) was done. At 0 °C for 20 min. the reaction was allowed to stir for 1 h at 60 °C after the addition of aldehyde. To the ice-cold resulting mixture $NaCNBH_3$ (0.582 mmol) was added and allowed to stir for 16 h at room temperature. After the dilution of the resulting mixture with ethyl acetate(50 ml), washed with sat. $NaHCO_3$ solution and water. The organic layer was dried over sodium sulphate and under the vaccum crude product was extracted. Purification of this crude product was done by column chromatography using 12% MeOH in MDC to give off a white solid.

General procedure of compound (7a-7o)

The mixture of compound (6a-6o) with methanol (2 ml) was cooled down at 0 °C. After this reaction at 0 °C TEA (0.430 mmol)was added and stirred for 20 min.

Then at room temperature reaction mixture was stirred for 3 h after the addition of methane sulfonyl chloride (0.253 mmol). Extraction of crude product was done under vacuum, column chromatography was used to purify and the product was eluted in 1–5% MeOH in MDC to obtain a white solid as the desired compound.

Methyl4-((N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methylsulfonamido)methyl)benzoate (7b)

^{1}H NMR: δ 0.85–1.86 (4H, m, 0.90 (d, *J* = 13.4 Hz), 1.28 (d, *J* = 13.4 Hz), 1.30 (d, *J* = 13.4 Hz), 1.86 (d, *J* = 13.4 Hz)), 2.07–2.92 (8H, m, 2.07 (s), 2.13 (d, *J* = 15.6 Hz), 2.56 (d, *J* = 15.6 Hz), 2.90 (s)), 3.77–3.79 (4H, m, 3.77 (d, *J* = 15.2 Hz), 3.77 (d, *J* = 15.2 Hz), 3.78 (d, *J* = 15.2 Hz), 3.78 (d, *J* = 15.2 Hz)), 3.94 (3H, s), 4.13–4.15 (2H, 4.11 (t, *J* = 10.3 Hz), 4.11 (d, *J* = 6.7 Hz)), 4.50–4.67 (2H, 4.55 (s)), 6.54–7.37 (6H, m, 6.55 (d, *J* = 7.9 Hz), 7.16 (d, *J* = 8.1 Hz), 7.28 (d, *J* = 7.9 Hz), 7.34 (d, *J* = 8.1 Hz), 7.35 (d, *J* = 8.5 Hz)), 7.50–7.62 (2H, d, *J* = 8.5 Hz).LCMS m/z Cal. $[M\text{-}H]^+$483.18 found $[M\text{-}H]^+$483.23.

N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)-N-(pyridin-4-ylmethyl)methanesulfonamide (7C)

^{1}HNMR δ 1.29–1.91 (4H, m, 1.45 (d, *J* = 13.4 Hz), 1.90 (d, *J* = 13.4 Hz)), 3.16 (3H, s), 3.21–3.69 (4H, m, 3.53 (d, *J* = 15.2 Hz), 3.53 (d, *J* = 15.2 Hz)), 3.82 (3H, s), 4.00 (1H, t, *J* = 10.3 Hz), 4.92 (2H, s), 6.78 (1H, d, *J* = 1.0 Hz), 7.31–7.36 (5H, q, 7.31 (d, *J* = 8.0 Hz), 7.31 (t, *J* = 7.7 Hz), 7.35 (d, *J* = 8.0 Hz), 7.35 (d, *J* = 7.8 Hz), 7.36 (d, *J* = 8.0 Hz)), 7.66 (1H, d, *J* = 8.0 Hz), 8.73–8.77 (2H, d, 8.76 (d, *J* = 4.7 Hz), 8.76 (d, *J* = 1.9 Hz)). LCMS m/z Cal. $[M\text{-}H]^+$426.17 found $[M\text{-}H]^+$427.28.

N-((4-bromothiophen-3-yl)methyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide (7d)

^{1}H NMR: δ 1.61–1.94 (4H, m, 1.78 (d, *J* = 13.5 Hz), 1.87 (d, *J* = 13.5 Hz)), 2.98 (3H, s), 3.42–3.86 (4H, m, 3.45 (d, *J* = 15.0 Hz), 3.75 (d, *J* = 15.2 Hz)), 4.09 (3H, s), 4.40 (1H, t, *J* = 10.3 Hz), 6.61 (1H, d, *J* = 1.0 Hz), 7.18–7.67 (6H, m, 7.20 (d, *J* = 1.5 Hz), 7.30 (d, *J* = 1.5 Hz), 7.32 (d, *J* = 8.0 Hz), 7.33 (t, *J* = 7.7 Hz), 7.41 (d, *J* = 7.8 Hz), 7.65 (d, *J* = 8.0 Hz)). LCMS m/z Cal. $[M+H]^+$511.04 found $[M+H]^+$509.76.

N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)-N-(pyridin-4-ylmethyl)methanesulfonamide (7e)

^{1}HNMR: δ 1.30–2.52 (4H, m,1.47 (d, *J* = 13.4 Hz), 2.09 (d, *J* = 13.4 Hz)), 3.07 (3H, s), 3.25–3.69 (4H, m, 3.30 (d, *J* = 15.2 Hz), 3.30 (d, *J* = 15.2 Hz)), 3.86 (3H, s), 4.18 (1H, t, *J* = 10.3 Hz), 4.72 (2H, s), 6.86 (1H, d, *J* = 1.0 Hz), 7.19–7.77 (6H, m, 7.20 (d, *J* = 4.8 Hz), 7.31 (d, *J* = 8.0 Hz), 7.35 (t, *J* = 7.7 Hz), 7.39 (d, *J* = 7.8 Hz), 7.54 (d, *J* = 8.0 Hz)), 8.76 (2H, d, *J* = 4.8 Hz). LCMS m/z Cal. $[M\text{-}H]^+$526.17 found $[M\text{-}H]^+$526.82.

N-((4-bromothiophen-2-yl)methyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide (7g)

^{1}H NMR: δ 1.30–2.15 (15H, m,1.30 (d, *J* = 13.2 Hz), 1.43 (d, *J* = 13.2 Hz), 1.50 (d, *J* = 13.0 Hz), 1.51 (d, *J* = 12.9 Hz), 1. 51 (d, *J* = 12.9 Hz), 1.65 (d, *J* = 13.0 Hz), 1.68 (d, *J* = 13.1 Hz), 1.73 (d, *J* = 13.1 Hz), 1.76 (d, *J* = 13.4 Hz), 1.77 (d, *J* = 13.4 Hz), 1.89 (d, *J* = 13.4 Hz), 1.96 (d, *J* = 13.4 Hz), 1.99 (d, *J* = 13.6 Hz), 2.02 (d, *J* = 13.6 Hz), 2.02 (d, *J* = 9.6 Hz)), 2.93 (3H, s), 3.03 (3H, s), 3.28–3.55 (5H, q, 3.28 (d, *J* = 9.9 Hz), 3.28 (d, *J* = 15.2 Hz), 3.50 (d, *J* = 15.2 Hz), 3.55 (d, *J* = 15.2 Hz), 3.55 (d, *J* = 15.2 Hz)), 3.78 (1H, *J* = 7.4 Hz), 4.02 (1H, t, *J* = 10.3 Hz), 4.62 (2H, 4,62(s)), 7.05 (1H, d, *J* = 1.9 Hz), 7.67 (1H, d, *J* = 1.9 Hz). LCMS m/z Cal. $[M\text{-}H]^+$511.04 found $[M\text{-}H]^+$512.02.

N-(2,2-diphenylethyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide (7h)

^{1}H NMR: δ 1.23–1.29 (4H, m, 1.26 (d, *J* = 13.4 Hz), 1.29 (d, *J* = 13.4 Hz)), 1.64 (3H, s), 2.25–2.89 (4H, m, 2.57 (d, *J* = 15.2 Hz), 2.88 (d, *J* = 15.2 Hz)), 2.90–3.99 (5H, q, 3.86 (d, *J* = 6.1 Hz), 3.99 (s)), 4.00 (1H, tt, *J* = 10.3 Hz), 4.30 (1H, t, *J* = 6.1 Hz), 6.67 (1H, d, *J* = 0.9 Hz), 7.19–7.80 (14H, m, 7.19 (tt, *J* = 7.7, 1.3 Hz), 7.23 (d, *J* = 7.8 Hz), 7.30 (m, *J* = 7.7 Hz), 7.35 (m, *J* = 7.8 Hz), 7.37 (d, *J* = 8.0 Hz), 7.77 (d, *J* = 8.0 Hz), 7.79 (d, *J* = 7.8 Hz)). LCMS m/z Cal. $[M\text{-}H]^+$515.22 found $[M\text{-}H]^+$516.24.

N-(cyclohexylmethyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide (7i)

^{1}H NMR: δ 0.90–1.94 (10H, m, 0.92 (d, *J* = 12.1 Hz), 0.94 (d, *J* = 12.1 Hz), 1.25 (d, *J* = 12.8 Hz), 1.29 (d, *J* = 12.8 Hz), 1.37 (d, *J* = 13.3 Hz), 1.48 (d, *J* = 13.3 Hz)), 1.67–1.94 (5H, q, 1.68 (d, *J* = 13.5 Hz), 1.79 (t, *J* = 10.3 Hz), 1.85 (d, *J* = 13.5 Hz)), 2.92 (3H, s), 3.00–3.04 (4H, m, 3.028 (d, *J* = 15.2 Hz), 3.028 (d, *J* = 15.2 Hz)), 3.77–3.85 (5H, q, 3.77 (d, *J* = 5.7 Hz), 3.85 (s)), 4.00 (1H, tt, *J* = 10.3 Hz), 6.67 (1H, d, *J* = 1.0 Hz), 7.20–7.70 (4H, m, 7.21 (d *J* = 8.0 Hz), 7.33 (t, *J* = 7.7 Hz), 7.42 (d, *J* = 7.8 Hz), 7.69 (d, *J* = 8.0, 1.2, 0.5 Hz)). LCMS m/z Cal. [M + H] + 431.22 found [M + H] + 431.19.

N-(3,5-dichlorobenzyl)-N-(1-(1-methyl-1H-indole-2-carbonyl)piperidin-4-yl)methanesulfonamide (7j)

^{1}HNMR: δ 0.90–1.87 (4H, m, 1.45 (d, *J* = 13.4 Hz), 1.64 (d, *J* = 13.4 Hz)), 2.92 (3H, s), 2.97–3.00 (4H, m, 2.98 (d, *J* = 15.2 Hz), 2,98 (d, *J* = 15.2 Hz)), 3.17 (3H, s), 3.82 (1H, t, *J* = 10.3 Hz), 4.40 (2H, s), 6.58 (1H, d, *J* = 1.0, 0.5 Hz), 7.18 (2H, d, *J* = 1.6 Hz), 7.30–7.66 (5H, q, 7.30 (t, *J* = 1.6 Hz), 7.34 (d, *J* = 8.0 Hz), 7.36 (t, *J* = 7.7 Hz),

7.41 (d, $J = 7.8$ Hz), 7.64 (d, $J = 8.0$ Hz)). LCMS m/z Cal. $[M\text{-}H]^+$ 493.10 found $[M\text{-}H]^+$494.10 (Additional file 1).

Conclusion

In Conclusion, Sulfonamide based indole derivatives are synthesized and discovered as antimicrobial agents. The biological assay showed that all the synthesized compounds showed good activity towards Gram Positive *Staphylococcus aureus* and inactive towards *Bacillus megaterium*. Among all Gram-negative bacterial organisms, all the synthesized compounds showed good activity towards Gram-Negative and are highly potent towards *Klebsiella pneumonia*. This study helps for further research in indole-containing derivatives.

Abbreviations

AMR	Antimicrobial resistance
WHO	World Health Organization
MeI	Methyl iodide
THF	Tetra hydro furan
EDCI.HCl	1-Ethyl-3-(3-dimethyl amineopropyl) carbodilimide
HoBt	Hydroxy benzotrizole
DIPEA	N,N-Diisopropylethylamine
PTSA	P-toluen sulfonic acid
TLC	Thin layer chromatography
MeOH	Methanol
MDC	Methylene chloride
TMS	Tri methyl silane
NMR	Nuclear magnetic resonance
PPM	Parts per million
LCMS	Liquid chromatography mass spectrometry
DMF	Dimethylformamide
DCM	Dichloromethane
TEA	Triethanolamine

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43094-023-00466-4.

Additional file 1. Spectral data of NMR and LCMS Spectroscopy of Synthesised Compound.

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Author contributions

KA, Dr. TP Contributed to design of the research, Material preparation, writing the manuscript, editing, designed the table and figures done by KA, Antimicrobial activity was performed and written by Dr. RP. Sample characterization with spectroscopy was done by KA, Dr. TP. Dr. TP was involved in supervision of all work. All authors read and approved the final manuscirpt.

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Availability of data and materials

Data and materials are available upon request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The authors declare no completing financial interest.

Competing interests

There are no competing interests to declare for all authors.

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