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ORIGINAL PAPER

Synthesis and antibacterial activity of new hybrid derivatives of 5-sulfamoyl-1*H*-indole and 4-thiazolidinone groups

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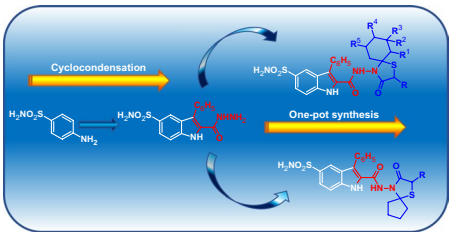
Abstract

The synthesis of a series of new 3-phenyl-5-sulfamoyl-*N*-(7/8/9-(non)substituted-3-oxo-1-thia-4-azaspiro[4.4]non/[4.5]dec-4-yl)-1*H*-indole-2-carboxamide derivatives and their subsequent testing for antibacterial activity is described in this paper. 4-Sulfamoylbenzenediazonium chloride was synthesized from diazotization of sulfanilamide and sodium nitrite in the presence of HCl and was further allowed to condense with ethyl 2-benzylacetoacetate to produce ethyl 2-benzyl-2-(4-sulfamoylphenyl)hydrazonoacetate. This compound was cyclized to ethyl 5-sulfamoyl-3-phenyl-1*H*-indole-2-carboxylate employing the Fischer-indole procedure. The reaction of ethyl 5-sulfamoyl-3-phenyl-1*H*-indole-2-carboxylate with hydrazine hydrate yielded sulfamoyl-3-phenyl-1*H*-indole-2-carbohydrazide. Through a cyclization process, the spirothiazolidinone derivatives were obtained from the reaction of suitable cyclic ketones with 5-sulfamoyl-3-phenyl-1*H*-indole-2-carbohydrazide in the presence of thioglycolic acid/thiolactic acid. Structural elucidation of the novel compounds was achieved with the help of UV, IR, ^{1}H NMR, HSQC, ESI–MS, and as well as elemental analysis. Among all the synthesized compounds tested, four compounds displayed the most promising antibacterial activity. The influence of the substituents and their positions on the antibacterial activity was evaluated.

Graphic abstract



Keywords One-pot synthesis · Spirothiazolidinones · Pharmacophore hybrid · Antibacterial activity · Spectroscopy

Introduction

The indole ring is considered a privileged structure and an attractive scaffold for drug discovery. Indoles can bind to different proteins. This gives it a hallmark of being a constituent of many pharmaceutical drugs [1] and thus, it is considered to be one of the most essential heterocyclic structures in drug discovery. Structural diversity with various and promising biological activities can easily be achieved via ring substitution, particularly, substitution on carbon 2 and 5 [2]. Many bioactive compounds such as the endogenous signaling

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molecules, serotonin (5-HT), and melatonin together with their amino acid precursor, tryptophan, the plant-derived brassinin, the antibacterial indolmycin [3–5], reserpine, vinblastine (alkaloid antineoplastic) [1], and mitomycin (antitumor antibiotic) [2] contain an indole moiety. In addition to these natural compounds, many drugs share this structural feature and examples include the triptans (antimigraine agent), ondansetron (antiemetic used in cancer chemotherapy), indomethacin (non-steroidal anti-inflammatory drug) [6–8], delavirdine (non-nucleoside reverse transcriptase inhibitor) and zafirlukast (leukotriene receptor antagonist used in asthma management) (Fig. 1) [1]. These indole-containing drugs target a variety of receptors and enzymes, such as HIV reverse transcriptase [6–8], the serotonin 5-HT3 receptor [9, 10], the peroxisome proliferator-activated receptor (PPAR) [11–15], kinases [16–20], and HMG-CoA reductase [21].

Furthermore, our group successfully synthesized 3-(substituted)phenyl-5-sulfonamido-1*H*-indole-2-carbohydrazide derivatives that showed selectivity against some carbonic anhydrase (CA) isoforms [22]. In addition, we attained the inhibition of tumor-related hCA IX and hCA XII with 5-sulfonamido-3-substitutedphenyl-1*H*-indole-2-carbohydrazide derivatives incorporated with 2,4,6-trimethylpyridinium moiety [23, 24]. Recently, we communicated a low nanomolar inhibitory activity of novel 3-phenyl-5-sulfonamido-1*H*-indole-2-carbohydrazide hydrazone derivatives against tumor-related hCA IX and hCA XII [25].

Thiazolidinone, on the contrary, is derived from a saturated thiazole and has a carbonyl group at positions 2, 4, or 5 [26, 27]. However, 4-thiazolidinone (with carbonyl at position 4) derivatives have gained considerably the interest of medicinal chemists due to their diverse pharmacological activities such as anticancer, antibacterial, antidiabetic, antifungal, anticonvulsant, and antiepileptic [28]. Some of the current commercial drugs that carry the thiazolidinone scaffold are ralitoline (anticonvulsant) and etozoline (loop diuretic) [29]. The antibacterial, antifungal, antimycobacterial [30–37], and anti-influenza virus activities of 4-thiazolidinones as well as their spiroheterocyclic hybrids have been reported in many studies [38]. Moreover, Gududuru and co-workers have recorded the antiproliferative activity of 2-aryl-4-oxothiazolidin-3-yl amides in prostate cancer [39].

Deductively, the combination of these two essential scaffolds leads to a promising hybrid pharmacophore with a wider range of pharmacological activities. A series of novel

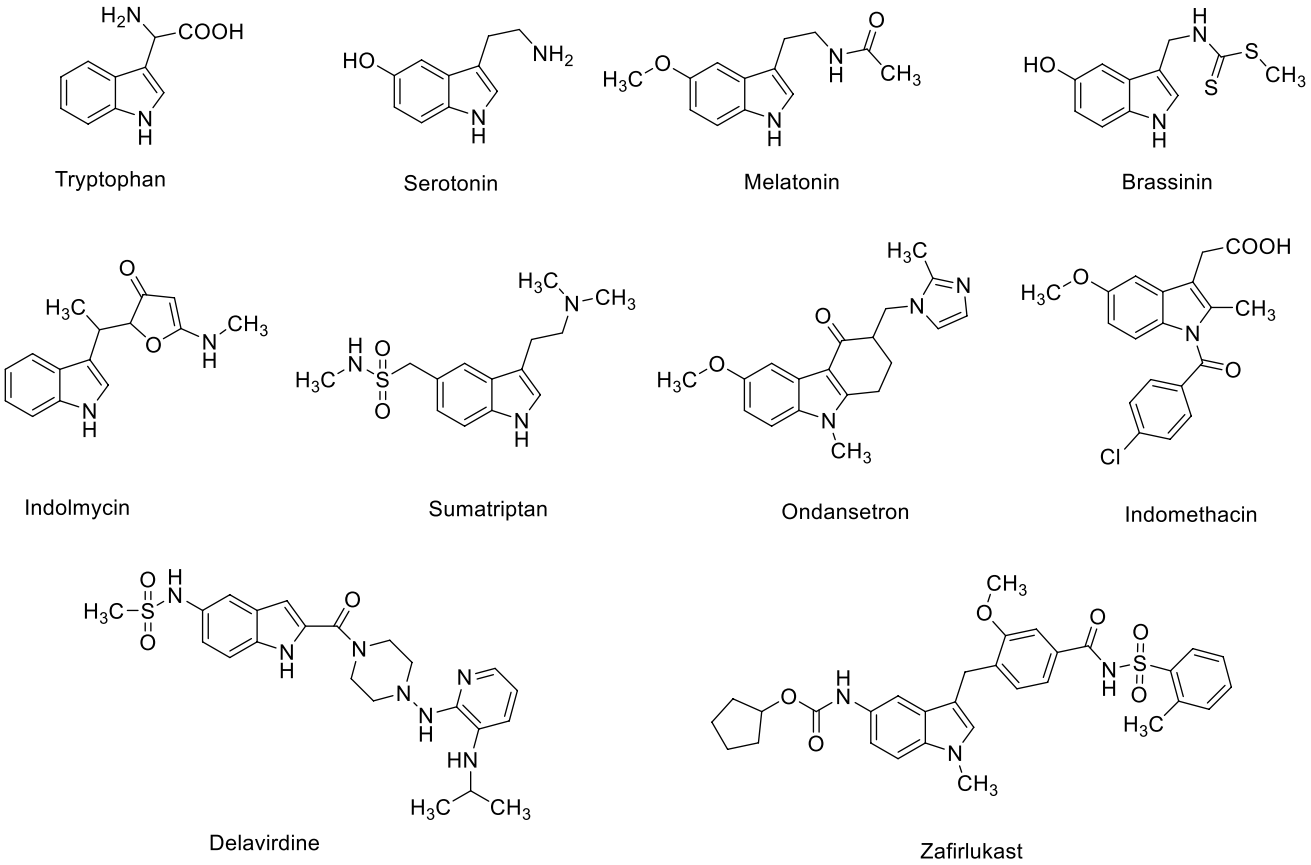


Fig. 1 Indole-containing endogenous compounds and drugs

compounds containing indole-4-thiazolidinone hybrid were reported to have superior cytotoxicity than Sunitinib against three different human cancer cells [28]. Also, a hybrid of indole and spirothiazolidinone derivatives exhibited both antimycobacterial and anticancer activity [40].

Based on the above-mentioned data and our continuous research on potential biologically active heterocyclic compounds, we herein report the preparation and antibacterial activity of new 3-phenyl-5-sulfamoyl-*N*-(7/8/9-(non) substituted-3-oxo-1-thia-4-azaspiro[4.4]non/[4.5]dec-4-yl)-1*H*-indole-2-carboxamide derivatives. Analytical and spectral analysis were employed in the structural elucidation of the synthesized compounds.

Results and discussion

Chemistry

In a one-pot reaction, using a Dean–Stark water separator, 2-(hydrazinecarbonyl)-3-phenyl-1*H*-indole-5-sulfonamide (obtained from a multistep-reaction) [41] was refluxed in anhydrous toluene with a suitable cyclic ketone in the presence of thioglycolic acid/thiolactic acid to give 3-phenyl-5-sulfamoyl-*N*-(3-oxo-1-thia-4-azaspiro[4.4]non/[4.5]-dec-4-yl)-1*H*-indole-2-carboxamide and 3-phenyl-5-sulfamoyl-*N*-(2-methyl-3-oxo-1-thia-4-azaspiro[4.4]non/[4.5]-dec-4-yl)-1*H*-indole-2-carboxamide derivatives, respectively (compounds **6**–**23**, Scheme 1).

Structural determination of the compounds was achieved with IR, ^{1}H NMR, HSQC, electrospray ionization mass spectrometry (ESI–MS), and elemental analysis.

In the IR spectra, bands observed between 3219–3313 cm^{-1} and 1641–1670 cm^{-1} regions correspond to the N–H and C=O bonds, respectively, and these bands validate the presence of the common CONH functional group of compounds **6**–**23** [42]. The formation of the amide functional group is a hallmark feature for these compounds and substantiates a successful desired cyclization of compounds **6**–**23** [32, 33].

^{1}H NMR spectroscopic data revealed the spirononane C_2–H_2 of compounds **6**–**15** between $\delta = 3.48$ and 3.94 ppm,

Scheme 1

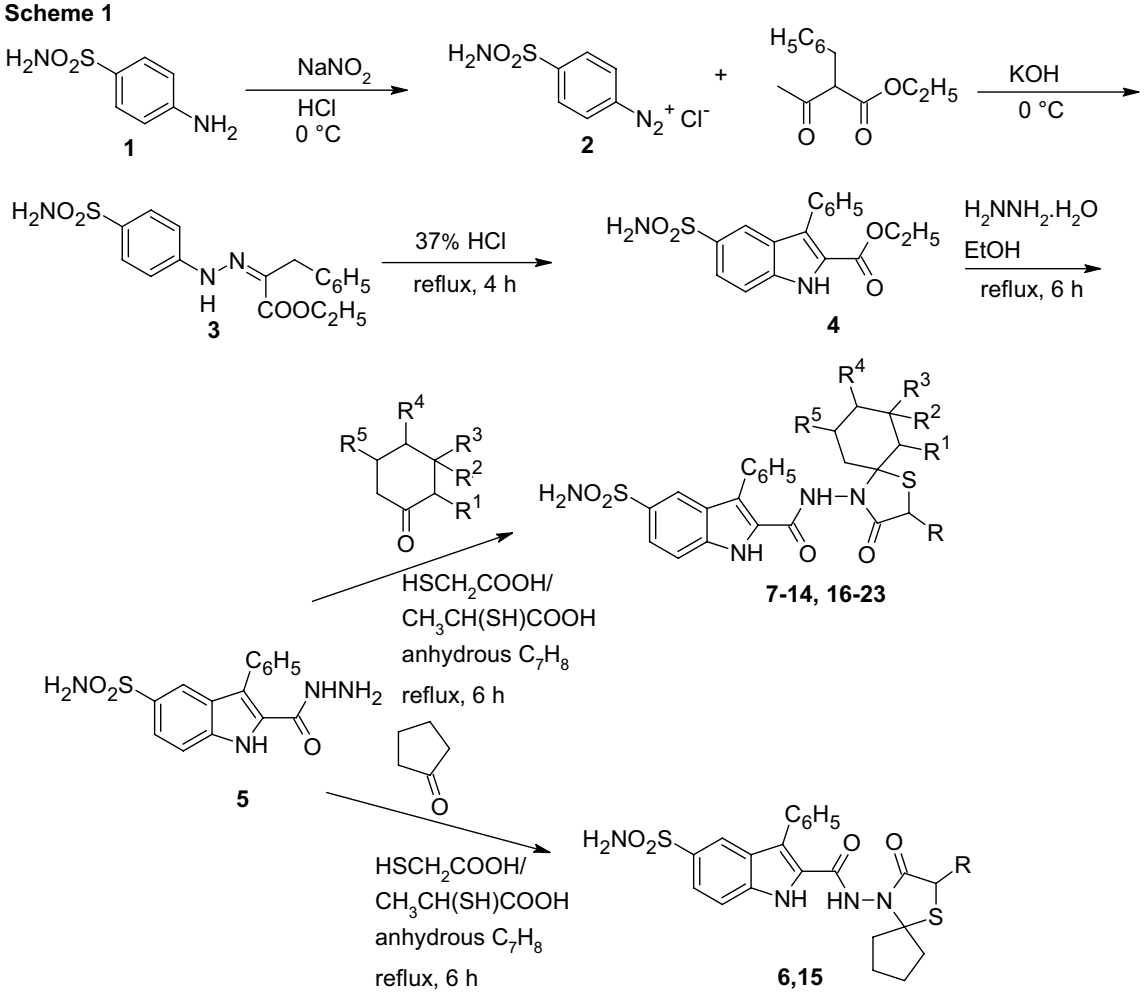
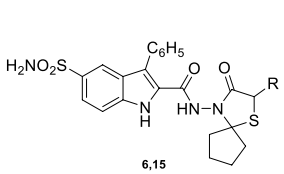
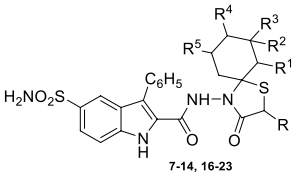


Table 1 Antimicrobial activities of compounds **6–23**





Compounds	*R*	R^1	R^2	R^3	R^4	R^5	MIC[a] /μg cm^{-3}		
							S. epidermidis ATCC 12228	*S. aureus* ATCC 33951 (MRSA)	*S. aureus* ATCC 29213 (MSSA)
6	H	–	–	–	–	–	> 2500	1250	> 2500
7	H	H	H	H	H	H	> 2500	1250	> 2500
8	H	H	CH_3	H	H	H	> 2500	1250	> 2500
9	H	H	H	H	CH_3	H	> 2500	1250	> 2500
10	H	H	H	H	C_2H_5	H	> 2500	625	> 2500
11	H	H	H	H	C_3H_7	H	625	625	> 2500
12	H	H	H	H	*tert*-C_4H_9	H	625	156.25	> 2500
13	H	H	CH_3	CH_3	H	CH_3	> 2500	1250	> 2500
14	H	H	H	H	C_6H_5	H	> 2500	1250	> 2500
15	CH_3	–	–	–	–	–	> 2500	1250	> 2500
16	CH_3	H	H	H	H	H	> 2500	1250	> 2500
17	CH_3	CH_3	H	H	H	H	> 2500	625	78.125
18	CH_3	H	CH_3	H	H	H	> 2500	19.53	78.125
19	CH_3	H	H	H	CH_3	H	> 2500	39.06	19.53
20	CH_3	H	H	H	C_2H_5	H	> 2500	78.12	9.765
21	CH_3	H	H	H	C_3H_7	H	> 2500	78.12	9.765
22	CH_3	H	H	H	*tert*-C_4H_9	H	625	78.12	625
23	CH_3	H	H	H	C_6H_5	H	> 2500	78.12	39.06
Reference compound							Vancomycin 2	Cefuroxime 9.8	Cefuroxime Na 1.2

[a]*MIC* Minimum inhibitory concentration of the compounds required to suppress a visible growth

whereas spirodecane C_2-H of compounds **16–23** appeared between 3.87 and 3.94 ppm [33, 43, 44]. The signals of the remaining protons on the spirononane/spirodecane ring and the alkyl substituent on the ring were observed between 0.73 and 2.05 ppm. The SO_2NH_2 protons resonated at 7.12–7.21 ppm. Chemical shifts assigned to the indole protons appeared in the anticipated regions [25, 42].

To further substantiate the structures of compounds **6**, **7**, **10**, **11**, and **13** by explicitly assigning chemical shifts for proton and carbon, a 2D NMR spectrum (HSQC) was carried out which proved the expected cyclization and confirmed the characteristic resonances of spirodecane C_2, C_3 (lactam C=O), and C_5 at $\delta = 28.52–29.98$, 168.00–168.14, and 72.08–76.64 ppm, respectively. The CONH resonance was observed at about 162.22–162.30 ppm [33, 44, 45].

Electrospray ionization mass spectrometry (ESI–MS) was employed to confirm the accurate weights of compounds **6–14**. Analysis of compounds **6**, **9**, and **12** was performed under negative-ion ESI conditions, whereas compounds **7**, **8**, **10**, **11**, **13**, and **14** were analyzed in positive-ion mode. The calculated molecular weights of compounds **6–14** were authenticated with $[M\text{-}H]^-$ and $[M+H]^+$ ions observed in the ESI–MS. Detailed spectral data are provided in the supplementary information.

Antibacterial activity

All the compounds were evaluated for their antibacterial activity against *Staphylococcus aureus* ATCC 33951 (MRSA), *Staphylococcus aureus* ATCC 29213 (MSSA), and *Staphylococcus epidermidis* ATCC 12228 (Table 1).

The antibacterial activities of these compounds were evaluated using cefuroxime-Na, vancomycin, and cefuroxime as

references. All the compounds exhibited no activity against *Staphylococcus epidermidis* ATCC 12228, except compounds **11** (with a propyl at position 8 on the spirothiazolidinone system), **12** and **22** (with a *tert*-butyl at position 8 on the spirothiazolidinone system). An alkyl (not smaller than propyl) substitution at position 8 of the spirothiazolidinone system elicited an impact on the activity against *S. epidermidis* ATCC 12228. Compounds **18**–**23** showed optimum activity against *S. aureus* ATCC 33951 with **18** (with a methyl at position 2 and 7 of the spirothiazolidinone system) being the most active against *S. aureus* ATCC 33951 (MRSA). Except for compound **22**, compounds **17**–**23** showed promising activity against *S. aureus* ATCC 29213 (MSSA). Compounds **20** (with a methyl and an ethyl at positions 2 and 8, respectively) and **21** (with a methyl and a propyl at positions 2 and 8, respectively) were observed to have the highest antibacterial activity against *S. aureus* ATCC 29213 (MSSA) with 99% inhibition at 9.765 μg/cm^3. Generally, the attachment of a methyl group and an alkyl group at positions 2 and 8, respectively, yielded compounds with promising antibacterial activity.

Conclusion

A new series of 5-sulfamoyl-*N*-(3-oxo-1-thia-4-azaspiro[4.4.]non / [4.5]-dec-4-yl)-3-phenyl-1*H*-indole-2-carboxamide derivatives were successfully synthesized with moderate yields and were in concordance with the obtained spectral data. The biological targets of these compounds have not been established; however, compound **18**, with a methyl substituent at position 7 on the spirothiazolidinone system, displayed the highest inhibition against *Staphylococcus aureus* ATCC 33951 (MRSA) which is an important nosocomial pathogen resistant to many antibiotics. Compounds **20** and **21**, with an ethyl and a propyl at position 8 on the spirothiazolidinone system consecutively, showed potent activity against *Staphylococcus aureus* ATCC 29213 (MSSA). An in-depth Structure Activity Relationship (SAR) study and structural modifications on compounds **18**, **20**, and **21** can lead to the emergence of new compounds with potential antibacterial activity.

Experimental

Sulfanilamide (**1**), ethyl 2-benzyl-3-oxobutanoate, cyclic ketones, and thioglycolic acid/thiolactic acid were obtained from commercial sources. Compounds **2**–**5** were synthesized as previously reported [41]. Open capillary tubes were used in the estimation of melting points with a Buchi 540 apparatus. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 elemental analyzer. IR spectra were recorded on KBr discs, using a Perkin-Elmer Model 1600 FT-IR spectrometer. ^{1}H NMR, ^{1}H-decoupled ^{13}C NMR, and HSQC-2D spectra were obtained on Varian UNITY INOVA 500, BRUKER NEO AVANCE 500 MHz, and Varian Mercury (Agilent, Palo Alto, CA, USA) 400 MHz FT-NMR spectrometers using DMSO-d_6. Mass spectra were determined on an AGILENT 1100 MSD instrument. Spn and spd were used to describe spirononane and spirodecane, respectively.

Synthesis of 3-phenyl-5-sulfamoyl-*N*-(3-oxo-1-thia-4-azaspiro[4.4]non/[4.5]dec-4-yl)-1*H*-indole-2-carboxamide derivatives 6, 15, and 7–23

To a mixture of 1.65 g of compound **5** (5 mmol) and the suitable cyclic ketone (5 mmol, 1 equiv) in 20 cm^3 anhydrous toluene, thioglycolic acid/thiolactic acid (20 mmol) was added, and with the help of a Dean-Stark water separator, the reaction was refluxed for 5–6 h. The mixture was evaporated under reduced pressure to eliminate excess toluene. The residue formed was treated with a saturated $NaHCO_3$ until the evolution of CO_2 stopped. The reaction mixture was left to stand overnight and sometimes, refrigerated until solidified. The crude solid was washed with H_2O, air-dried, and recrystallized from ethanol.

3-Phenyl-5-sulfamoyl-*N*-(3-oxo-1-thia-4-azaspiro[4.4]-non-4-yl)-1*H*-indole-2-carboxamide (6, $C_{22}H_{22}N_4O_4S_2$) White powder (31%); m.p.: 332–335 °C; IR (KBr): $\overline{\nu}$ = 3294, 3223 (NH), 1710, 1645 (C=O), 1330, 1145 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.57–1.64 (4H, m, spn $C_{7/8}$-H), 1.70–1.75 (2H, m, spn $C_{6/9}$–Hax), 1.90 (2H, s, spn $C_{6/9}$-Heq), 3.65 (2H, s, spn C_2–H), 7.17 (2H, s, SO_2NH_2), 7.39 (1H, tt, J = 7.32, 1.46 Hz, 3-phenyl C_4-H), 7.47 (2H, t, J = 7.32 Hz, 3-phenyl $C_{3/5}$-H), 7.52 (2H, dd, J = 8.05, 1.46 Hz, 3-phenyl $C_{2/6}$-H), 7.62 (1H, d, J = 8.78 Hz, indole C_7-H), 7.72 (1H, dd, J = 8.54, 1.46 Hz, indole C_6-H), 8.03 (1H, d, J = 1.46 Hz, indole C_4-H), 10.12 (1H, s, CONH), 12.34 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.58 (spn C_7/C_8), 29.26 (spn C_2), 38.10 (spn C_6/C_9), 76.64 (spn C_5), 113.49 (indole C_7), 119.41 (indole C_4), 120.37 (indole C_3), 122.15 (indole C_6), 126.19 (indole C_{3a}), 127.90 (3-phenyl C_4), 128.77 (indole C_2), 129.09 (3-phenyl C_3/C_5), 130.78 (3-phenyl C_2/C_6), 133.36 (indol C_5), 137.19 (3-phenyl C_1), 137.99 (indole C_{7a}), 162.23 (CONH), 168.14 (spn C_3) ppm; ESI–MS: m/z (%) = 469.3 ([M−H]$^-$, 100).

3-Phenyl-5-sulfamoyl-*N*-(3-oxo-1-thia-4-azaspiro[4.5]-dec-4-yl)-1*H*-indole-2-carboxamide (7, $C_{23}H_{24}N_4O_4S_2$) White powder (31%); m.p.: 343–345 °C; IR (KBr): $\overline{\nu}$ = 3294, 3230 (NH), 1708, 1645 (C=O), 1328, 1145 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.02–1.05 (1H, m, spd C_8-Hax), 1.38 (2H, dd, J = 12.69, 3.17 Hz, spd $C_{7/9}$-Hax), 1.54 (2H, d,

$J = 12.69$ Hz, spd $C_{7/9}$-Heq), 1.61–1.65 (5H, m, spd $C_{6/10}$-H, C_8-Heq), 3.57 (2H, s, spd C_2-H), 7.12 (2H, s, SO_2NH_2), 7.39 (1H, t, $J = 7.32$ Hz, 3-phenyl C_4-H), 7.49 (2H, t, $J = 7.32$ Hz, 3-phenyl $C_{3/5}$-H), 7.54 (2H, d, $J = 7.32$ Hz, 3-phenyl $C_{2/6}$-H), 7.62 (1H, d, $J = 8.79$ Hz, indole C_7-H), 7.72 (1H, dd, $J = 8.79$, 1.46 Hz, indole C_6-H), 8.03 (1H, d, $J = 1.47$ Hz, indole C_4-H), 10.12 (1H, s, CONH), 12.34 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 23.55$ (spd C_7/C_9), 24.51 (spd C_8), 28.52 (spd C_2), 37.32 (spd C_6/C_{10}), 72.87 (spd C_5), 113.46 (indole C_7), 119.40 (indole C_4), 120.26 (indole C_3), 122.10 (indole C_6), 126.21 (indole C_{3a}), 127.86 (3-phenyl C_4), 128.97 (indole C_2), 129.17 (3-phenyl C_3/C_5), 130.85 (3-phenyl C_2/C_6), 133.48 (indole C_5), 137.16 (3-phenyl C_1), 137.47 (indole C_{7a}), 162.29 (CONH), 168 (spd C_3) ppm; ESI–MS: *m/z* (%) = 485 ($[M+H]^+$, 100).

3-Phenyl-5-sulfamoyl-*N*-(7-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (8, $C_{24}H_{26}N_4O_4S_2$) White powder (41%); m.p.: 335–340 °C; IR (KBr): $\overline{\nu} = 3275$, 3226 (NH), 1712, 1647 (C=O), 1328, 1145 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.74$–0.78 (1H, m, spd C_8-Hax), 0.85 (3H, d, $J = 5.86$ Hz, spd 7-CH_3), 1.20–1.35 (1H, m, spd C_7-Hax), 1.43 (1H, t, $J = 13.18$ Hz, spd C_9-Hax), 1.54 (4H, d, $J = 10.73$ Hz, spd $C_{6/10}$-Hax, $C_{8/9}$-Heq), 1.70 (2H, s, spd $C_{6/10}$-Heq), 3.56 (2H, s, spd C_2-H), 7.16 (2H, s, SO_2NH_2), 7.39 (1H, t, $J = 7.32$ Hz, 3-phenyl C_4-H), 7.48 (2H, t, $J = 7.32$ Hz, 3-phenyl $C_{3/5}$-H), 7.52 (2H, d, $J = 7.32$ Hz, 3-phenyl $C_{2/6}$-H), 7.62 (1H, d, $J = 8.78$ Hz, indole C_7-H), 7.71 (1H, dd, $J = 8.54$, 1.46 Hz, indole C_6-H), 8.01 (1H, d, $J = 1.47$ Hz, indole C_4-H), 10.08 (1H, s, CONH), 12.34 (1H, s, indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.96$ (7-CH_3), 22.39 (spd C_9), 27.91 (spd C_2), 29.50 (spd C_7), 37.48 (spd C_{10}), 36.07 (spd C_8), 72.13 (spd C_5), 112.77 (indole C_7), 118.69 (indole C_4), 119.56 (indole C_3), 121.40 (indole C_6), 125.54 (indole C_{3a}), 127.18 (3-phenyl C_4), 128.30 (indole C_2), 128.53 (3-phenyl C_3,C_5), 130.20 (3-phenyl C_2,C_6), 132.83 (indole C_5), 136.44 (3-phenyl C_1), 136.77 (indole C_{7a}), 161.65 (CONH), 167.24 (spd C_3) ppm; ESI–MS: *m/z* (%) = 499 ($[M+H]^+$, 100).

3-Phenyl-5-sulfamoyl-*N*-(8-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (9, $C_{24}H_{26}N_4O_4S_2$) White powder (51%); m.p.: 342–345 °C; IR (KBr): $\overline{\nu} = 3280$, 3226 (NH), 1712, 1647 (C=O), 1328, 1145 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.88$ (3H, d, $J = 6.35$ Hz, spd 8-CH_3), 1.08–1.11 (2H, m, spd $C_{7/9}$-Hax), 1.30 (1H, s, spd C_8-Hax), 1.60–1.85 (6H, m, spd $C_{6/10}$-H, spd $C_{7/9}$-Heq), 3.57 (2H, s, spd C_2-H), 7.16 (2H, s, SO_2NH_2), 7.38 (1H, tt, $J = 7.57$, 1.46 Hz, 3-phenyl C_4-H), 7.47 (2H, t, $J = 7.56$ Hz, 3-phenyl $C_{3/5}$-H), 7.54 (2H, dd, $J = 7.56$, 1.46, Hz, 3-phenyl $C_{2/6}$-H), 7.62 (1H, d, $J = 8.78$ Hz, indole C_7-H), 7.72 (1H, dd, $J = 8.78$, 1.95 Hz, indole C_6-H), 8.04 (1H, s, indole C_4-H), 10.10 (1H, s, CONH), 12.34 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 22.37$ (8-CH_3), 30.80 (spd C_2), 31.70, 32.12 (spd C_7/C_9), 37.02, 37.21 (spd C_6/C_{10}), 37.86 (spd C_8), 71.16 (spd C_5), 113.22 (indole C_7), 119.20 (indole C_4), 120.05 (indole C_3), 121.90 (indole C_6), 126.00 (indole C_{3a}), 127.63 (3-phenyl C_4), 128.68 (indole C_2), 128.93 (3-phenyl C_3,C_5), 130.47, 130.64 (3-phenyl C_2/C_6), 133.22 (indole C_5), 136.93 (3-phenyl C_1), 137.24 (indole C_{7a}), 162.02 (CONH), 170.47 (spd C_3) ppm; ESI–MS: *m/z* (%) = 497.5 ($[M-H]^-$, 100).

3-Phenyl-5-sulfamoyl-*N*-(8-ethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (10, $C_{25}H_{28}N_4O_4S_2$) White powder (43%); m.p.: 365–368 °C; IR (KBr): $\overline{\nu} = 3277$, 3223 (NH), 1712, 1647 (C=O), 1327, 1145 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.88$ (3H, t, $J = 7.32$ Hz, spd 8-$CH_2\mathbf{CH_3}$), 1.05 (3H, br s, spd C_8-H, $C_{7/9}$-Hax), 1.06–1.22 (2H, m, spd 8-$\mathbf{CH_2}CH_3$), 1.69 (6H, br s, spd $C_{7/9}$-Heq, C6/10-H), 3.57 (2H, s, spd C_2-H), 7.17 (2H, s, SO_2NH_2), 7.38 (1H, td, $J = 7.80$, 0.97 Hz, 3-phenyl C_4-H), 7.47 (2H, t, $J = 7.56$ Hz, 3-phenyl $C_{3/5}$-H), 7.54 (2H, dd, $J = 7.80$, 0.97 Hz, 3-phenyl $C_{2/6}$-H), 7.62 (1H, d, $J = 8.80$ Hz, indole C_7-H), 7.72 (1H, dd, $J = 8.53$, 1.95 Hz, indole C_6-H), 8.03 (1H, s, indole C_4-H), 10.16 (1H, s, CONH), 12.38 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 12.17$ (spd 8-$CH_2\mathbf{CH_3}$), 29.46 (spd 8-$\mathbf{CH_2}CH_3$), 28.55 (spd C_2), 29.63 (spd C_7/C_9), 37.07 (spd C_6/C_{10}), 37.68 (spd C_8), 73.01 (spd C_5), 113.47 (indole C_7), 119.41 (indole C_4), 120.33 (indole C_3), 122.10 (indole C_6), 126.23 (indole C_{3a}), 127.83 (3-phenyl C_4), 128.94 (indole C_2), 129.14 (3-phenyl C_3/C_5), 130.85 (3-phenyl C_2/C_6), 133.52 (indole C_5), 137.15 (3-phenyl C_1), 137.48 (indole C_{7a}), 162.22 (CONH), 168.05 (spd C_3) ppm; ESI–MS: *m/z* (%) = 513.3 ($[M+H]^+$, 100).

3-Phenyl-5-sulfamoyl-*N*-(3-oxo-8-propyl-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (11, $C_{26}H_{30}N_4O_4S_2$) White powder (63%); m.p.: 366–369 °C; IR (KBr): $\overline{\nu} = 3278$, 3223 (NH), 1712, 1647 (C=O), 1327, 1147 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.88$ (3H, t, $J = 7.32$ Hz, spd 8-$CH_2CH_2\mathbf{CH_3}$), 1.01–1.10 (2H, m, spd $C_{7/9}$-Hax), 1.14 (3H, t, $J = 5.37$ Hz, spd 8-$\mathbf{CH_2}CH_2CH_3$, spd C_8-Hax), 1.31 (2H, q, $J = 7.32$ Hz, spd 8-$CH_2\mathbf{CH_2}CH_3$), 1.67 (6H, d, $J = 10.25$ Hz, spd $C_{6/10}$-H, spd $C_{7/9}$-Heq), 3.57 (2H, s, spd C_2-H), 7.17 (2H, s, SO_2NH_2), 7.38 (1H, t, $J = 7.32$ Hz, 3-phenyl C_4-H), 7.47 (2H, t, $J = 7.32$ Hz, 3-phenyl $C_{3/5}$-H), 7.54 (2H, d, $J = 6.83$ Hz, 3-phenyl $C_{2/6}$-H), 7.62 (1H, d, $J = 8.79$ Hz, indole C_7-H), 7.73 (1H, dd, $J = 8.54$, 0.97 Hz, indole C_6-H), 8.03 (1H, d, $J = 0.98$ Hz, indole C_4-H), 10.13 (1H, s, CONH), 12.34 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 14.81$ (spd 8-$CH_2CH_2\mathbf{CH_3}$), 20.22 (spd 8-$CH_2\mathbf{CH_2}CH_3$), 28.55 (spd C_2), 29.98 (spd C_7/C_9), 35.46 (spd C_8), 37.08 (spd C_6/C_{10}), 39.89 (spd 8-$\mathbf{CH_2}CH_2CH_3$), 73.00 (spd C_5), 113.47 (indole C_7), 119.37 (indole C_4), 120.21 (indole C_3),

122.03 (indole C_6), 126.25 (indole C_{3a}), 127.76 (3-phenyl C_4), 128.97 (indole C_2), 129.11 (3-phenyl C_3/C_5), 130.87 (3-phenyl C_2/C_6), 133.58 (indole C_5), 137.10 (3-phenyl C_1), 137.51 (indole C_{7a}), 162.30 (CONH), 168.01 (spd C_3) ppm; ESI–MS: *m/z* (%) = 527.2 ($[M+H]^+$, 100).

3-Phenyl-5-sulfamoyl-*N*-(8-*tert*-butyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (12, $C_{27}H_{32}N_4O_4S_2$) White powder (62%); m.p.: 329–330 °C; IR (KBr): $\overline{\nu}$ = 3313, 3219 (NH), 1710, 1641 (C=O), 1330, 1147 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.85–0.89 (10H, m, spd C_8-Hax, 8-C(CH_3)$_3$), 1.13–1.16 (2H, m, spd $C_{7/9}$-Hax), 1.67 (6H, br s, spd $C_{6/10}$-H, $C_{7/9}$-Heq), 3.57 (2H, s, spd C_2-H), 7.18 (2H, s, SO_2NH_2), 7.39 (1H, t, *J* = 7.32 Hz, 3-phenyl C_4-H), 7.48 (2H, t, *J* = 7.81 Hz, 3-phenyl $C_{3/5}$-H), 7.54 (2H, dd, *J* = 7.56, 1.46 Hz, 3-phenyl $C_{2/6}$-H), 7.62 (1H, d, *J* = 8.79 Hz, indole C_7-H), 7.72 (1H, dd, *J* = 8.55, 1.46 Hz, indole C_6-H), 8.02 (1H, s, indole C_4-H), 10.15 (1H, s, CONH), 12.34 (1H, s, indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.61 (spd C_7,C_9), 27.31 (3 CH_3), 27.79 (spd C_2), 31.89 (*tert*-butyl C), 36.60 (spd C_6,C_{10}), 45.45 (spd C_8), 72.07 (spd C_5), 112.70 (indole C_7), 118.62 (indole C_4), 119.46 (indole C_3), 121.32 (indole C_6), 125.51 (indole C_{3a}), 127.09 (3-phenyl C_4), 128.36 (indole C_2), 128.44 (3-phenyl C_3,C_5), 130.13 (3-phenyl C_2,C_6), 132.81 (indole C_5), 136.41 (3-phenyl C_1), 136.69 (indole C_{7a}), 161.53 (CONH), 167.33 (spd C_3) ppm; ESI–MS: *m/z* (%) = 539.3 ($[M\text{-}H]^-$, 100).

3-Phenyl-5-sulfamoyl-*N*-(7,7,9-trimethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (13, $C_{26}H_{30}N_4O_4S_2$) White powder (19%); m.p.: 300–302 °C; IR (KBr): $\overline{\nu}$ = 3286, 3230 (NH), 1710, 1647 (C=O), 1327, 1147 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.73 (1H, t, *J* = 12.69 Hz, spd C_8-Hax), 0.87 (6H, s, spd $C_{7,9}$-CH_3), 1.02 (3H, s, spd C_7-CH_3), 1.29 (1H, d, *J* = 12.44 Hz, spd C_8-Heq), 1.53 (4H, br s, spd $C_{6/10}$-H), 1.77 (1H, br s, spd C_9-H), 3.48, 3.59 (2H, 2d, *J* = 15.62, 16.11 Hz, spd C_2-H), 7.16 (2H, s, SO_2NH_2), 7.39 (1H, t, *J* = 7.32 Hz, 3-phenyl C_4-H), 7.47 (2H, t, *J* = 7.32 Hz, 3-phenyl $C_{3/5}$-H), 7.51 (2H, d, *J* = 7.33 Hz, 3-phenyl $C_{2/6}$-H), 7.61 (1H, d, *J* = 8.79 Hz, indole C_7-H), 7.71 (1H, dd, *J* = 8.54, 1.47 Hz, indole C_6-H), 7.99 (1H, s, indole C_4-H), 10.10 (1H, s, CONH), 12.34 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.45 (spd 9-CH_3), 26.19 (spd C_9), 27.88 (spd 7-CH_3 ax), 28.72 (spd C_2), 32.47 (spd C_7), 34.32 (spd 7-CH_3 eq), 47.01 (spd C_8), 47.06 (spd C_6/$_{10}$), 72.08 (spd C_5), 113.45 (indole C_7), 119.98 (indole C_4), 120.21 (indole C_3), 122.12 (indole C_6), 126.34 (indole C_{3a}), 127.98 (3-phenyl C_4), 128.94 (indole C_2), 129.27 (3-phenyl C_3/C_5), 130.89 (3-phenyl C2/C6), 133.57 (indole C_5), 137.14 (3-phenyl C_1), 137.45 (indole C_{7a}), 162.30 (CONH), 168.01 (spd C_3) ppm; ESI–MS: *m/z* (%) = 527.4 ($[M+H]^+$, 100).

3-Phenyl-5-sulfamoyl-*N*-(3-oxo-8-phenyl-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (14, $C_{29}H_{28}N_4O_4S_2$) White powder (62%); m.p.: 378–379 °C; IR (KBr): $\overline{\nu}$ = 3292, 3223 (NH), 1712, 1647 (C=O), 1323, 1147 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.61–1.66 (3H, m, spd $C_{7/9}$-Hax, C_8-Hax), 1.81 (6H, d, *J* = 10.73 Hz, spd $C_{6/10}$-H, $C_{7/9}$-Heq), 3.63 (2H, s, spd C_2-H), 7.18–7.21 (3H, m, SO_2NH_2, 8-phenyl C_4-H), 7.24 (2H, d, *J* = 6.83 Hz, spd 8-phenyl $C_{3/5}$-H), 7.30 (2H, t, *J* = 7.32 Hz, spd 8-phenyl $C_{2/6}$-H), 7.44 (1H, t, *J* = 7.32 Hz, 3-phenyl C_4-H), 7.53 (2H, t, *J* = 7.32 Hz, 3-phenyl $C_{3/5}$-H), 7.59 (2H, d, *J* = 7.56 Hz, 3-phenyl $C_{2/6}$-H), 7.64 (1H, d, *J* = 8.79 Hz, indole C_7-H), 7.74 (1H, dd, *J* = 8.06, 1.46 Hz, indole C_6-H), 8.04 (1H, s, indole C_4-H), 10.20 (1H, s, CONH), 12.37 (1H, s, indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.87 (spd C_7,C_9), 30.41 (spd C_2), 36.62 (spd C_6,C_{10}), 41.43 (spd C_8), 71.61 (spd C_5), 112.74 (indole C_7), 118.69 (indole C_4), 119.61 (indole C_3), 121.40 (indole C_6), 125.54 (indole C_{3a}), 126.17 (3-phenyl C_4), 126.56 (phenyl C_4), 127.20 (phenyl C_2,C_6), 128.29 (indole C_2), 128.37, 128.43 (3-phenyl C_3,C_5), 128.52 (phenyl C_3,C_5), 130.22 (3-phenyl C_2,C_6), 132.82 (indole C_5), 136.46 (3-phenyl C_1), 136.75 (indole C_{7a}), 145.78 (phenyl C_1), 161.60 (CONH), 167.38 (spd C_3) ppm; ESI–MS: *m/z* (%) = 561.4 ($[M+H]^+$, 100).

3-Phenyl-5-sulfamoyl-*N*-(2-methyl-3-oxo-1-thia-4-azaspiro[4.4]non-4-yl)-1*H*-indole-2-carboxamide (15, $C_{23}H_{24}N_4O_4S_2$) White powder (31%); m.p.: 285 °C; IR (KBr): $\overline{\nu}$ = 3292, 3223 (NH), 1712, 1647 (C=O), 1323, 1147 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.43 (3H, d, *J* = 6.83 Hz, C_2-CH_3), 1.59–1.70 (6H, m, spn $C_{7/8}$-H, $C_{6/9}$-Hax), 1.91–2.05 (2H, m, spn $C_{6/9}$-Heq), 3.94 (1H, q, *J* = 6.83 Hz, spn C_2-H), 7.18 (2H, s, SO_2NH_2), 7.40 (1H, tt, *J* = 7.32, 1.46 Hz, 3-phenyl C_4-H), 7.49 (2H, td, *J* = 7.32, 1.95 Hz, 3-phenyl $C_{3/5}$-H), 7.53 (2H, dd, *J* = 8.29, 1.95 Hz, 3-phenyl $C_{2/6}$-H), 7.64 (1H, d, *J* = 9.27 Hz, indole C_7-H), 7.74 (1H, dd, *J* = 8.79, 1.46 Hz, indole C_6-H), 8.04 (1H, d, *J* = 0.98 Hz, indole C_4-H), 10.18 (1H, s, CONH), 12.35 (1H, s, indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.35 (2-CH_3), 21.96, 22.05 (spn C_7/C_8), 37.54 (spn C_2), 37.76, 37.89 (spn C_6/C_{10}), 74.52 (spn C_5), 112.81 (indole C_7), 118.74 (indole C_4), 119.70 (indole C_3), 121.48 (indole C_6), 125.53 (indole C_{3a}), 127.23 (3-phenyl C_4), 128.08 (indole C_2), 128.41 (3-phenyl C_3,C_5), 130.12 (3-phenyl C_2,C_6), 132.66 (indole C_5), 136.49 (3-phenyl C_1), 136.80 (indole C_{7a}), 161.53 (CONH), 170.17 (spn C_3) ppm.

3-Phenyl-5-sulfamoyl-*N*-(2-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (16, $C_{24}H_{26}N_4O_4S_2$) Yellow powder (31%); m.p.: 272–273 °C; IR (KBr): $\overline{\nu}$ = 3294, 3230 (NH), 1708, 1645 (C=O), 1328, 1145 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.04–1.07 (1H, m, spd C_8-Hax), 1.35 (2H, dd, J = 13.18, 2.93 Hz, spd $C_{7/9}$-Hax), 1.41 (3H, d, J = 6.84 Hz, C_2-CH_3),1.56 (2H, d, J = 12.69 Hz, spd $C_{7/9}$-Heq), 1.69 (5H, d, J = 11.22 Hz, spd $C_{6/10}$-H, C_8-Heq), 3.87 (1H, s, spd C_2-H), 7.18 (2H, s, SO_2NH_2), 7.40 (1H, tt, J = 7.32, 1.46 Hz, 3-phenyl C_4-H), 7.50 (2H, t, J = 7.81 Hz, 3-phenyl $C_{3/5}$-H), 7.55 (2H, dd, J = 8.05, 0.97 Hz, 3-phenyl $C_{2/6}$-H), 7.64 (1H, d, J = 8.78 Hz, indole C_7-H), 7.74 (1H, dd, J = 8.79, 1.95 Hz, indole C_6-H), 8.04 (1H, d, J = 0.98 Hz, indole C_4-H), 10.16 (1H, s, CONH), 12.36 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.36 (2-CH_3), 23.20, 23.59 (spd C_7/C_9), 24.30 (spd C_8), 37.21, 37.26 (spd C_6/C_{10}), 38.13 (spd C_2), 71.30 (spd C_5), 113.23 (indole C_7), 119.19 (indole C_4), 120.05 (indole C_3), 121.88 (indole C_6), 126.01 (indole C_{3a}), 127.64 (3-phenyl C_4), 128.74 (indole C_2), 128.94 (3-phenyl C_3,C_5), 130.65 (3-phenyl C_2,C_6), 133.25 (indole C_5), 136.91 (3-phenyl C_1), 137.24 (indole C_{7a}), 162.04 (CONH), 170.41 (spd C_3) ppm.

3-Phenyl-5-sulfamoyl-*N*-(2,6-dimethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (17, $C_{25}H_{28}N_4O_4S_2$) White powder (41%); m.p.: 268 °C; IR (KBr): $\overline{\nu}$ = 3334, 3250 (NH), 1705, 1647 (C=O), 1323, 1147 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.76–0.95 (3H, m, spd C_6-CH_3), 1.05–1.15 (2H, m, spd), 1.23–1.29 (1H, m, spd), 1.40 (3H, d, J = 6.83 Hz, C_2-CH_3), 1.52–1.60 (3H, m, spd), 1.62–1.85 (3H, m, spd), 3.79, 3.90 (1H, 2d, spd C_2-H), 7.18 (2H, s, SO_2NH_2), 7.41 (1H, tt, J = 7.32, 1.47 Hz, 3-phenyl C_4-H), 7.50 (2H, td, J = 7.32, 1.95 Hz, 3-phenyl $C_{3/5}$-H), 7.55 (2H, dd, J = 7.56, 1.49 Hz, 3-phenyl $C_{2/6}$-H), 7.64 (1H, dd, J = 8.30, 2.44 Hz, indole C_7-H), 7.74 (1H, dd, J = 8.30, 1.47 Hz, indole C_6-H), 8.02 (1H, dd, J = 6.34, 1.46 Hz, indole C_4-H), 10.04 (1H, s, CONH), 12.37 (1H, s, indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.66 (2-CH_3), 23.20 (6-CH_3), 24.40 (spd C_9), 24.46 (spd C_8), 31.32 (spd C_7), 36.27 (spd C_{10}), 36.48 (spd C_6), 37.42 (spd C_2), 75.24 (spd C_5), 112.77 (indole C_7), 118.71 (indole C_4), 119.73 (indole C_3), 121.43 (indole C_6), 125.62 (indole C_{3a}), 127.15 (3-phenyl C_4), 128.31 (indole C_2), 128.36, 128.46 (3-phenyl C_3/C_5), 130.20 (3-phenyl C_2,C_6), 132.87 (indole C_5), 136.44 (3-phenyl C_1), 136.71 (indole C_{7a}), 161.67 (CONH), 169.97 (spd C_3) ppm.

3-Phenyl-5-sulfamoyl-*N*-(2,7-dimethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (18, $C_{25}H_{28}N_4O_4S_2$) Ivory powder (41%); m.p.: 226–228 °C; IR (KBr): $\overline{\nu}$ = 3489, 3238 (NH), 1708, 1658 (C=O), 1338, 1145 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.76–0.81 (2H, m, spd), 0.87 (3H, d, J = 5.86 Hz, spd 7-CH_3), 1.23 (1H, s, spd), 1.41 (3H, t, J = 6.34 Hz, C_2-CH_3), 1.50–1.57 (1H, m, spd), 1.65–1.75 (3H, m, spd), 3.88 (1H, d, J = 4.88 Hz, spd C_2-H), 7.18 (2H, s, SO_2NH_2), 7.41 (1H, tt, J = 7.32, 1.46 Hz, 3-phenyl C_4-H), 7.50 (2H, t, J = 7.81 Hz, 3-phenyl $C_{3/5}$-H), 7.54 (2H, dd, J = 6.83, 0.98 Hz, 3-phenyl $C_{2/6}$-H), 7.63 (1H, d, J = 8.78 Hz, indole C_7-H), 7.73 (1H, dd, J = 8.54, 1.47 Hz, indole C_6-H), 8.02 (1H, s, indole C_4-H), 10.15 (1H, s, CONH), 12.37 (1H, s, indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.16 (2-CH_3), 21.93 (7-CH_3), 22.26 (spd C_9), 29.40 (spd C_7), 32.49 (spd C_{10}), 36.88 (spd C_8), 37.22 (spd C_2), 44.93 (spd C_6), 70.77 (spd C_5), 112.76 (indole C_7), 118.70 (indole C_4), 119.57 (indole C_3), 121.41 (indole C_6), 125.57 (indole C_{3a}), 127.18 (3-phenyl C_4), 128.31 (indole C_2), 128.54 (3-phenyl C_3,C_5), 130.22 (3-phenyl C_2,C_6), 132.83 (indole C_5), 136.43 (3-phenyl C_1), 136.77 (indole C_{7a}), 161.62 (CONH), 169.89 (spd C_3) ppm.

3-Phenyl-5-sulfamoyl-*N*-(2,8-dimethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (19, $C_{25}H_{28}N_4O_4S_2$) Ivory powder (51%); m.p.: 260–263 °C; IR (KBr): $\overline{\nu}$ = 3325, 3213 (NH), 1710, 1654 (C=O), 1321, 1145 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.89 (3H, d, J = 6.84 Hz, spd 8-CH_3), 1.04–1.20 (2H, m, spd $C_{7/9}$-Hax), 1.28–1.38 (1H, m, spd C_8-Hax), 1.41 (3H, t, J = 6.83 Hz, C_2-CH_3), 1.60–1.90 (6H, m, spd $C_{6/10}$-H, spd $C_{7/9}$-Heq), 3.88 (1H, q, J = 6.83 Hz, spd C_2-H), 7.18 (2H, s, SO_2NH_2), 7.40 (1H, tt, J = 7.32, 1.46 Hz, 3-phenyl C_4-H), 7.49 (2H, t, J = 7.81 Hz, 3-phenyl $C_{3/5}$-H), 7.56 (2H, dd, J = 8.05, 1.46, Hz, 3-phenyl $C_{2/6}$-H), 7.63 (1H, d, J = 8.79 Hz, indole C_7-H), 7.73 (1H, dd, J = 8.78, 1.46 Hz, indole C_6-H), 8.04 (1H, d, J = 1.46 Hz, indole C_4-H), 10.14 (1H, s, CONH), 12.35 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.37 (2-CH_3), 22.37 (8-CH_3), 30.80 (spd C_8), 31.70, 32.12 (spd C_7/C_9), 37.02, 37.21 (spd C_6/C_{10}), 37.87 (spd C_2), 71.16 (spd C_5), 113.22 (indole C_7), 119.20 (indole C_4), 120.05 (indole C_3), 121.90 (indole C_6), 126.00 (indole C_{3a}), 127.63 (3-phenyl C_4), 128.67 (indole C_2), 128.93 (3-phenyl C_3,C_5), 130.47, 130.63 (3-phenyl C_2/C_6), 133.22 (indole C_5), 136.93 (3-phenyl C_1), 137.24 (indole C_{7a}), 162.01 (CONH), 170.47 (spd C_3) ppm.

3-Phenyl-5-sulfamoyl-*N*-(8-ethyl-2-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (20, $C_{26}H_{30}N_4O_4S_2$) White powder (43%); m.p.: 221–222 °C; IR (KBr): $\overline{\nu}$ = 3311, 3217 (NH), 1705, 1645 (C=O), 1323, 1143 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.89 (3H, t, J = 7.32 Hz, spd 8-$CH_2\mathbf{CH_3}$), 1.01–1.08 (3H, m, spd C_8-H, $C_{7/9}$-Hax), 1.21 (2H, quint, J = 6.83 Hz, spd 8-$\mathbf{CH_2}CH_3$),

1.41 (3H, t, $J = 6.83$ Hz, C_2-CH_3), 1.62–1.80 (6H, m, spd $C_{7/9}$-Heq, $C_{6/10}$-H), 3.87 (1H, d, $J = 6.34$ Hz, spd C_2-H), 7.18 (2H, s, SO_2NH_2), 7.40 (1H, tt, $J = 7.32$, 1.47 Hz, 3-phenyl C_4-H), 7.49 (2H, td, $J = 7.32$, 1.46 Hz, 3-phenyl $C_{3/5}$-H), 7.55 (2H, dd, $J = 8.05$, 1.46 Hz, 3-phenyl $C_{2/6}$-H), 7.63 (1H, d, $J = 9.27$ Hz, indole C_7-H), 7.74 (1H, dd, $J = 8.54$, 1.95 Hz, indole C_6-H), 8.04 (1H, d, $J = 1.95$ Hz, indole C_4-H), 10.17 (1H, s, CONH), 12.35 (1H, s, indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 11.45$ (8-CH_2**C**H_3), 19.91 (2-CH_3), 28.77 (8-**C**H_2CH_3), 29.20 (spd C_7,C_9), 36.51 (spd C_8), 36.76, 36.95 (spd C_6/C_{10}), 37.35 (spd C_2), 70.96 (spd C_5), 112.74 (indole C_7), 118.71 (indole C_4), 119.57 (indole C_3), 121.41 (indole C_6), 125.54 (indole C_{3a}), 127.16 (3-phenyl C_4), 128.27 (indole C_2), 128.47 (3-phenyl C_3,C_5), 130.03, 130.17 (3-phenyl C_2/C_6), 132.78 (indole C_5), 136.46 (3-phenyl C_1), 136.76 (indole C_{7a}), 161.53 (CONH), 170.00 (spd C_3) ppm.

3-Phenyl-5-sulfamoyl-*N*-(2-methyl-3-oxo-8-propyl-1-thia-4-azaspiro4.5]dec-4-yl)-1*H*-indole-2-carboxamide (21, $C_{27}H_{32}N_4O_4S_2$) White powder (63%); m.p.: 260–262 °C; IR (KBr): $\overline{\nu} = 3315$ (NH), 1705, 1670 (C=O), 1328, 1141 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.89$ (3H, t, $J = 7.32$ Hz, spd 8-CH_2CH_2**C**$\mathbf{H_3}$), 1.00–1.10 (3H, m, spd $C_{7/9}$-Hax and C_8-Hax), 1.16 (2H, t, $J = 6.35$ Hz, spd 8-**C**$\mathbf{H_2}CH_2CH_3$, spd), 1.32 (2H, quint, $J = 7.32$ Hz, spd 8-CH_2**C**$\mathbf{H_2}CH_3$), 1.41 (3H, t, $J = 6.83$ Hz, C_2-CH_3), 1.60–1.80 (6H, m, spd $C_{6/10}$-H, spd $C_{7/9}$-Heq), 3.87 (1H, d, $J = 6.34$ Hz, spd C_2-H), 7.18 (2H, s, SO_2NH_2), 7.39 (1H, tt, $J = 7.81$, 1.46 Hz, 3-phenyl C_4-H), 7.48 (2H, t, $J = 7.81$ Hz, 3-phenyl $C_{3/5}$-H), 7.55 (2H, dd, $J = 8.30$, 1.47 Hz, 3-phenyl $C_{2/6}$-H), 7.63 (1H, d, $J = 8.79$ Hz, indole C_7-H), 7.73 (1H, dd, $J = 8.78$, 1.96 Hz, indole C_6-H), 8.03 (1H, d, $J = 1.96$ Hz, indole C_4-H), 10.18 (1H, s, CONH), 12.35 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 14.58$ (8-CH_2CH_2**C**H_3), 19.99 (8-CH_2**C**H_2CH_3), 20.37 (2-CH_3), 29.60, 30.03 (spd C_7/C_9), 35.22 (spd C_8), 36.99, 37.22 (spd C_6/C_{10}), 37.85 (spd C_2), 38.78 (8-**C**$H_2CH_2CH_3$), 71.41 (spd C_5), 113.21 (indole C_7), 119.17 (indole C_4), 120.01 (indole C_3), 121.87 (indole C_6), 126.02 (indole C_{3a}), 127.59 (3-phenyl C_4), 128.78 (indole C_2), 128.91 (3-phenyl C_3,C_5), 130.66 (3-phenyl C_2,C_6), 133.28 (indole C_5), 136.92 (3-phenyl C_1), 137.22 (indole C_{7a}), 162.01 (CONH), 170.46 (spd C_3) ppm.

3-Phenyl-5-sulfamoyl-*N*-(8-*tert*-butyl-2-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (22, $C_{28}H_{34}N_4O_4S_2$) White powder (62%); m.p.: 270–272 °C; IR (KBr): $\overline{\nu} = 3315$, 3261 (NH), 1701, 1668 (C=O), 1311, 1147 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.84$–0.91 (10H, m, spd C_8-Hax, 8-C$(CH_3)_3$), 1.10–1.23 (2H, m, spd $C_{7/9}$-Hax), 1.41 (3H, t, $J = 6.83$ Hz, C_2-CH_3), 1.70 (6H, d, $J = 8.78$ Hz, spd $C_{6/10}$-H, $C_{7/9}$-Heq), 3.87 (1H, d, $J = 6.34$ Hz, spd C_2-H), 7.18 (2H, s, SO_2NH_2), 7.40 (1H, tt, $J = 6.83$, 1.46 Hz, 3-phenyl C_4-H), 7.49 (2H, t, $J = 7.56$ Hz, 3-phenyl $C_{3/5}$-H), 7.55 (2H, dd, $J = 7.56$, 1.46 Hz, 3-phenyl $C_{2/6}$-H), 7.63 (1H, d, $J = 8.30$ Hz, indole C_7-H), 7.73 (1H, dd, $J = 8.78$, 1.46 Hz, indole C_6-H), 8.02 (1H, d, $J = 0.98$ Hz, indole C_4-H), 10.20 (1H, s, CONH), 12.36 (1H, s, indole NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.34$ (2-CH_3), 23.96, 24.36 (spd C_7/C_9), 27.77 (3 CH_3), 32.37 (spd C_6,C_{10}), 37.22 (spd C_2), 38.08 (spd C_8), 45.90 (8-*tert*-butyl C), 71.23 (spd C_5), 113.17 (indole C_7), 119.11 (indole C_4), 119.96 (indole C_3), 121.81 (indole C_6), 126.02 (indole C_{3a}), 127.57 (3-phenyl C_4), 128.84 (indole C_2), 128.91 (3-phenyl C_3,C_5), 130.64 (3-phenyl C_2,C_6), 133.29 (indole C_5), 136.88 (3-phenyl C_1), 137.17 (indole C_{7a}), 161.97 (CONH), 170.46 (spd C_3) ppm.

3-Phenyl-5-sulfamoyl-*N*-(2-methyl-3-oxo-8-phenyl-1-thia-4-azaspiro[4.5]dec-4-yl)-1*H*-indole-2-carboxamide (23, $C_{30}H_{30}N_4O_4S_2$) Ivory powder (62%); m.p.: 315–316 °C; IR (KBr): $\overline{\nu} = 3319$, 3244 (NH), 1716, 1651 (C=O), 1317, 1151 (S=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.44$ (3H, t, $J = 6.83$ Hz, C_2-CH_3), 1.58–1.70 (3H, m, spd $C_{7/9}$-Hax, C_8-Hax), 1.75–2.05 (6H, m, spd $C_{6/10}$-H, $C_{7/9}$-Heq), 3.94 (1H, d, $J = 5.37$ Hz, spd C_2-H), 7.19 (2H, s, SO_2NH_2), 7.21 (1H, dd, $J = 7.32$, 1.46 Hz, 8-phenyl C_4-H), 7.25 (2H, d, $J = 6.83$ Hz, spd 8-phenyl $C_{3/5}$-H), 7.32 (2H, t, $J = 7.81$ Hz, spd 8-phenyl $C_{2/6}$-H), 7.45 (1H, tt, $J = 7.32$, 1.46 Hz, 3-phenyl C_4-H), 7.56 (2H, t, $J = 7.32$ Hz, 3-phenyl $C_{3/5}$-H), 7.60 (2H, dd, $J = 8.30$, 1.47 Hz, 3-phenyl $C_{2/6}$-H), 7.66 (1H, d, $J = 8.78$ Hz, indole C_7-H), 7.75 (1H, dd, $J = 8.79$, 1.46 Hz, indole C_6-H), 8.05 (1H, d, $J = 1.46$ Hz, indole C_4-H), 10.25 (1H, s, CONH), 12.39 (1H, s, indole NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 20.30$ (2-CH_3), 30.75, 31.23 (spd C_7/C_9), 37.26, 37.33 (spd C_6/C_{10}), 38.11 (spd C_2), 41.93 (spd C_8), 70.78 (spd C_5), 113.24 (indole C_7), 119.20 (indole C_4), 120.13 (indole C_3), 121.91 (indole C_6), 126.07 (indole C_{3a}), 126.66 (8-phenyl C_4), 127.05 (3-phenyl C_4), 127.71 (8-phenyl C_2,C_6), 128.78 (indole C_2), 128.93 (indole-3-phenyl C_3,C_5), 129.02 (8-phenyl C_3,C_5), 130.74 (indole-3-phenyl C_2,C_6), 133.31 (indole C_5), 136.95 (3-phenyl C_1), 137.25 (indole C_{7a}), 146.29 (8-phenyl C_1), 162.07 (CONH), 170.52 (spd C_3) ppm.

Antibacterial activity

Antibacterial activity was assayed in vitro against *Staphylococcus aureus* ATCC 33951 (meticillin resistant *Staphylococcus aureus*—MRSA), Staphylococcus aureus ATCC 29213 (meticillin susceptible *Staphylococcus aureus*—MSSA), and *Staphylococcus epidermidis* ATCC 12228. The evaluation was done using the micro broth dilution technique following the Clinical Laboratory Standards Institute (CLSI) recommendations [46]. Mueller–Hinton broth for bacteria was used as the test medium. Serial twofold

dilutions ranging from 5000 to 4.9 μg/cm^3 were prepared in the medium. The inoculum was prepared using a 4–6 h broth culture of each bacteria adjusted to a turbidity equivalent to a 0.5-Mc Farland standard, diluted in broth media to give a final concentration of 5×10^5 cfu/cm^3 for bacteria in the test tray. To avoid evaporation, trays were protected with plastic bags. After incubating the trays at 35 °C for approximately 1–20 h, the antibacterial effects of the solvents were measured against the test strains to determine the MIC of the compounds. The MIC was defined as the minimum concentration of a compound giving a complete growth suppression. The obtained results were compared to the reference drugs.

The newly synthesized molecules have also been tested against Gram (−) bacteria in the test panel, but since there is no activity, it is not included in table.

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