

Design, synthesis, and antimicrobial activity of novel 5-substituted indole-2-carboxamide derivatives

Yogesh D. Mane¹ · Yuvaraj P. Sarnikar² ·
Santosh M. Surwase¹ · Dhanraj O. Biradar³ ·
Pratapsinha B. Gorepatil¹ · Vishnu S. Shinde¹ ·
Bhimrao C. Khade⁴

Received: 24 June 2016 / Accepted: 9 August 2016
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Abstract A series of novel, bioactive 5-substituted indole-2-carboxamide derivatives (**10a–t** and **14a–k**) are synthesized by the coupling of 5-substituted indole-2-carboxylic acids with various amines in the presence of EDC HCl/HOBt in DMF/CH₂Cl₂ as a solvent. In vitro, antibacterial activity of titled compounds against pathogenic bacteria *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi* and antifungal activity against pathogenic fungi *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Candida parapsilosis* is evaluated using gentamicin/ciprofloxacin and fluconazole/oxiconazole as standard drugs, respectively. The majority of the synthesized compounds exhibited good antibacterial activity, but surprisingly none showed antifungal activity. Compounds **10c**, **10d**, **10i**, **10j**, **10l–n**, **14g**, **14h**, **14i**, **14j**, and **14k** exhibited high inhibitory antibacterial activity with MIC values in the range of 0.12–6.25 µg/mL. Interestingly, compounds **14i**, **14j**, and **14k** exhibited excellent antibacterial activity against *K. pneumoniae* and *E. coli* compare to synthesized compound. All the experimental results promote us to consider this series as a starting point for the development of novel and more potent antibacterial agents in the future.

Electronic supplementary material The online version of this article (doi:10.1007/s11164-016-2696-3) contains supplementary material, which is available to authorized users.

✉ Yogesh D. Mane
maneyd@gmail.com

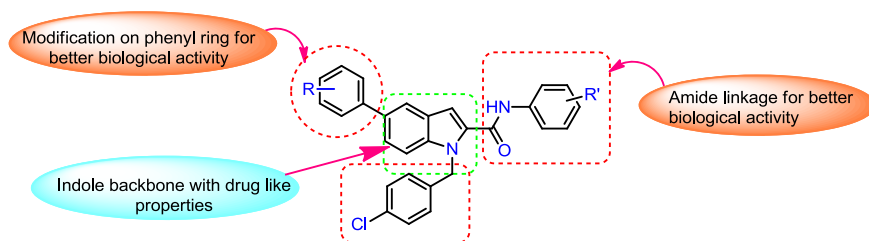
¹ Shri Chhatrapati Shivaji College, Omerga, M.S. 413606, India

² Dayanand Science College, Latur, M.S. 413512, India

³ Indian Institute of Chemical Technology, Hyderabad, T.S. 500007, India

⁴ Dnyanopasak College, Parbhani, M.S. 431401, India

Graphical Abstract



Keywords Indole-2-carboxamide · Antibacterial · Antifungal · SAR study

Introduction

For the normal growth of animals and microbes, the interactions between them are intimate and vital, yet they also have darker side, since microbes trigger a broad range of human diseases. History observes continual battle between human beings and disease-causing microbes. In the field of medicine, invention of and advancements in antibiotics are among the most astonishing achievements of the last century. However, these advances in medical care are threatened by a natural phenomenon known as antimicrobial resistance [1–4]. Antimicrobial resistance is the result of inadequate, empirical, self-medicated, improper, and overuse of antibiotics, a gift of the medical field, for the treatment of diseases. Antibiotic resistance is not new; it is ancient [5].

Infection-causing Gram-negative bacteria, about 50 % of the multidrug-resistant bacteria [6], including *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [7], have become a serious threat in hospitals and community clinics [8]. Increasing multidrug-resistant (MDR) infections caused by Gram-negative bacteria are more difficult to treat, since they increase mortality, morbidity [9, 10], and health care cost. In spite of a large number of antibiotics and chemotherapeutics available for medical use, the emergence of multidrug bacterial resistance to current antibiotics have created an urgent need for either in the development of novel antibiotics or modification of existing antibiotics to fight against MDR infections, which threaten the progress of about 60 years in medicine [11–13]. The majority of antimicrobial agents act on a small group of well-validated targets, which suggests the most effective way to kill cell. In view of the above, the design and synthesis of newer, efficient, and broad-spectrum antimicrobials with fewer side effects will always remain an area of immense significance.

Merck scientists reported that L-161, 240 (aryl oxazoline hydroxamic acid derivative [14]) are potent inhibitors of LpxC [15–19] from *E. coli* [20]. We

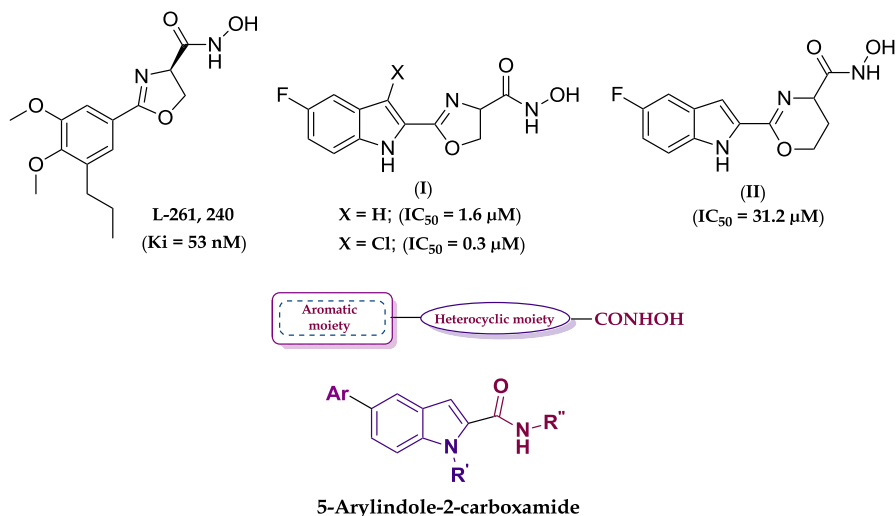


Fig. 1 Previously reported potential inhibitors of LpxC from *E. coli*, their general structural motif, and newly designed molecule

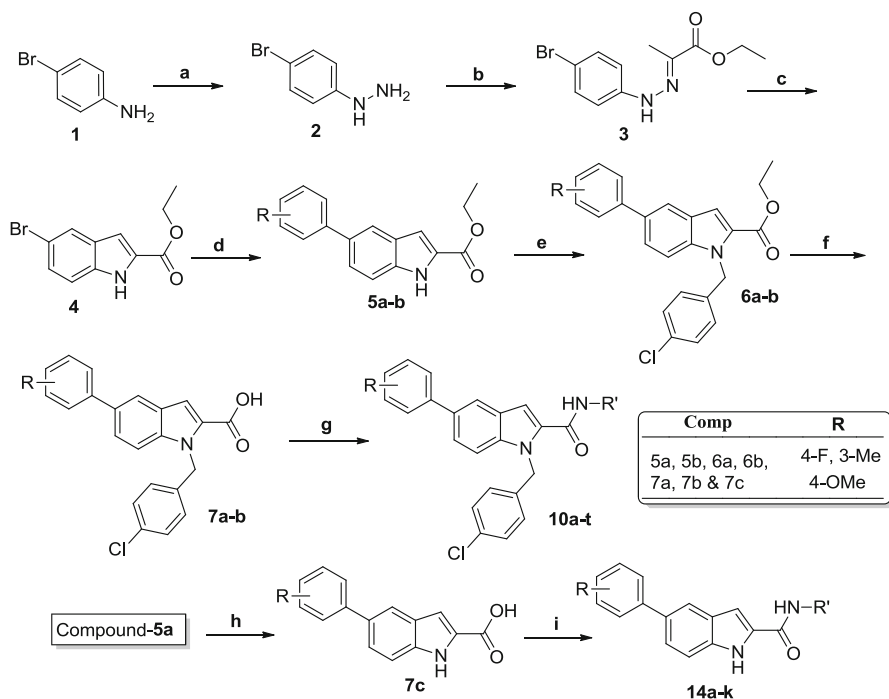
designed and synthesized novel compounds of general motif, shown in Fig. 1, by changing the Zn-binding hydroxamic acid functionality of L-161, 240 to amide functionality, the oxazoline moiety to indole moiety (Fig. 1). We focused on the role of hydrophobic substituent of the aryl group, indole ring, and aliphatic or aromatic amines of amide functionality on antimicrobial activity. Indoles are omnipresent in natural products, as well as in several synthetic bioactive compounds [21–40]. Indole moiety is the most privileged structural motif in the process of discovery of new drugs [41–46]. The inbuilt ability of indole derivatives such as mimicking the structure of proteins and binding reversibly to enzymes [47] creates huge opportunities to discover novel bioactive molecules with different mechanisms of action. U.S. retail reports that many indole-containing drugs are among the best selling drugs [48]. Moreover, 1H-indole-2-carboxamide templates are present in natural products [49], as well as in several synthetic bioactive compounds. This scaffold shows broad-spectrum biological activity [50–52]. Hence, among the pharmacophores responsible for antimicrobial activity, the indole derivatives seem to be a viable lead structure for a more efficacious and systematic antimicrobial drug. However, to the best of our knowledge, the antibacterial and antifungal activity of these bioactive pharmacophores has not been reported to date.

Inspired by these encouraging facts and as a part of our ongoing interest toward the design and synthesis of novel bioactive heterocycles harboring indole nucleus as antimicrobial agents, we have synthesized a series of novel 5-arylindole-2-carboxamide derivatives (**10a–t** and **14a–k**) and screened them for antimicrobial activity.

Results and discussion

Chemistry

The target compounds (**10a–t**) and (**14a–k**) were synthesized following procedures outlined in the scheme (Scheme 1). In the first step, an ice-cold aqueous solution of NaNO_2 was added to an ice-cold solution of 4-bromoaniline (**1**) in 12 M HCl, and the resulting solution was stirred at 0 °C for 15 min. To the stirred solution, an ice-cold solution of SnCl_2 in 12 M HCl was added drop-wise, and the resulting solution was stirred at 0 °C for 4 h to afford 4-bromophenylhydrazine (**2**). Indole-2-carboxylic ester (**4**) was obtained by condensation of **2** with ethyl pyruvate followed by cyclization using polyphosphoric acid. Suzuki coupling of **4** with corresponding phenyl boronic acids in presence of $\text{Pd}(\text{dppf})_2\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ at 90 °C under inert atmosphere gave ester **5a/5b**. Ester **5a/5b** underwent *N*-benzylolation with 4-chlorobenzylchloride in DMF in presence of Cs_2CO_3 to give ester **6a/6b** which was hydrolyzed with LiOH in THF, H_2O and EtOH system to furnish corresponding carboxylic acid **7a/7b**. Hydrolysis of **5a** with LiOH in THF, H_2O and EtOH system



Scheme 1 Synthesis of 5-substituted indole-2-carboxamide derivatives. Reagents and conditions: *a* (i) NaNO_2 , HCl, 0 °C, 15 min; (ii) SnCl_2 , HCl, 0 °C, 4 h; *b* ethyl pyruvate, EtOH, argon, reflux 5.5 h; *c* PPA, 120 °C, 20–30 min; *d* 4-Flouro-3-methylphenylboronic acid or 4-methoxyphenylboronic acid, $\text{Pd}(\text{dppf})_2\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$, KOAc, 1,4-dioxane, H_2O , 80–90 °C, 3 h; *e* 4-chlorobenzyl chloride, Cs_2CO_3 , DMF, 60 °C, 6 h; *f* LiOH, THF, H_2O , EtOH, Stirr, rt, 3–4 h; *h* LiOH, THF, H_2O , EtOH, Stirr, rt, 3–4 h; *g*, *i* amine, EDC-HCl, HOBt, DIPEA, DMF, 0 °C to rt, 20–30 h

gave carboxylic acid (**7c**). To the stirred solution of carboxylic acid (**7a/7b/7c**), EDC.HCl, HOBT, and DIPEA/TEA in DMF, an appropriate amine was added and the resulting solution was stirred for 20–30 h at room temperature to afford the target carboxamide (**10a–t** and **14a–k**) in good to excellent yields.

Biological activity

In the endeavor to identify the antimicrobial activity of 5-arylindole-2-carboxamides, we synthesized a series of 31 compounds (**10a–t** and **14a–k**) and screened them against pathogenic Gram-negative bacteria *Klebsiella pneumoniae*, *E. coli*, *P. aeruginosa*, and *Salmonella typhi* and pathogenic fungi *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Candida parapsilosis* by using the broth microdilution technique described by the Clinical and Laboratory Standards Institute (CLSI), 2012 (Formerly NCCLS) [49] and the results are depicted in Table 1. Many of the synthesized carboxamides exhibited excellent antibacterial activity that was manifold better than the activity of standard drugs, gentamicin and ciprofloxacin.

The compounds **10c**, **10d**, **10j**, **10n**, **14i**, **14j**, and **14k** showed high antibacterial activity against *K. pneumoniae* with respective MIC value of 1.56, 1.25, 1.56, 1.56, 0.39, 0.39, and 0.12 µg/mL. However, **14i**, **14j**, and **14k** exhibited excellent antibacterial activity against *K. pneumoniae*, *E. coli* and moderate activity against *P. aeruginosa* when compared to both standards. Compounds **10d**, **10j**, **10l–n**, **14i**, **14j**, and **14k** have exhibited promising antibacterial activity against *E. coli* in the range of 0.56–3.25 µg/mL. Compound **14h** was found to be as potent as ciprofloxacin against *S. typhi*. Interestingly, **14k** inhibited *K. pneumoniae*, *E. coli*, and *P. aeruginosa* more efficiently than gentamicin and ciprofloxacin. All the tested compounds were inactive (MIC > 50 µg/mL) (Table 1) against tested fungi when compared to standards, fluconazole and oxiconazole, except **14a**, which exhibited moderate activity only against *C. neoformans* and *A. fumigatus* (MIC ~ 25–50 µg/mL).

Structure–activity relationship study

We explored diversity in the designed molecule (5-arylindole-2-carboxamide) by varying the aryl group and especially amines in the amide functionality. Replacement of *para*-OMe substituent of the phenyl ring by hydrophobic *para*-F and *meta*-Me groups increased antibacterial activity by 2–4 and twofold against *K. pneumoniae* and *E. coli*, respectively, and moderately with *P. aeruginosa*. In many cases, deprotection of indole N–H increased antibacterial activity to an acceptable extent against *K. pneumoniae*, *E. coli*, and *P. aeruginosa* indicating the importance of free indole N–H (Fig. 2). Substitution of aromatic amines by few specific alicyclic amines improved the antibacterial activity by 2–10-fold (Table 1). Change in either the aryl group or amines of amide functionality did not change the antifungal activity of titled compounds.

Table 1 In vitro antimicrobial activity of compounds (**10a–t**) and (**14a–k**) against pathogenic Gram-negative bacteria and fungi

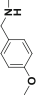
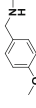
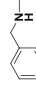
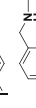
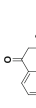
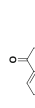
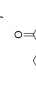
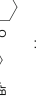
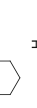
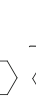
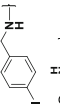
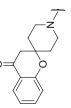
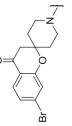
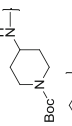
Compound	R	R'	R''	MIC (µg/mL)				MIC (µg/mL)			
				<i>Klebsiella pneumoniae</i>	<i>Escherichia coli</i>	<i>P. aeruginosa</i>	<i>Salmonella typhi</i>	<i>C. albicans</i>	<i>C. neoformans</i>	<i>A. fumigatus</i>	<i>C. parapsilosis</i>
10a	4-OMe		4-chlorobenzyl	12.5	6.05	12.15	25.05	>50	>50	>50	>50
10b	4-F, 3-Me		4-chlorobenzyl	6.25	6.25	50.15	12.5	>50	>50	>50	>50
10c	4-OMe		4-chlorobenzyl	1.56	12.5	12.5	>50	>50	>50	>50	>50
10d	4-F, 3-Me		4-chlorobenzyl	1.25	3.125	>50	12.5	>50	>50	>50	>50
10e	4-OMe		4-chlorobenzyl	6.25	6.25	>50	12.5	>50	>50	>50	>50
10f	4-F, 3-Me		4-chlorobenzyl	12.05	>50	>50	>50	>50	>50	>50	>50
10g	4-OMe		4-chlorobenzyl	6.25	25.05	>50	>50	>50	>50	>50	>50
10h	4-F, 3-Me		4-chlorobenzyl	3.125	>50	12.5	>50	>50	>50	>50	>50
10i	4-OMe		4-chlorobenzyl	6.25	12.5	12.5	>50	>50	>50	>50	>50
10j	4-F, 3-Me		4-chlorobenzyl	1.56	1.125	6.25	>50	>50	>50	>50	>50
10k	4-OMe		4-chlorobenzyl	6.5	6.125	25.5	>50	>50	>50	>50	>50

Table 1 continued

Compound	R	R'	R''	MIC (µg/mL)				MIC (µg/mL)			
				<i>Klebsiella pneumoniae</i>	<i>Escherichia coli</i>	<i>P. aeruginosa</i>	<i>Salmonella typhi</i>	<i>C. albicans</i>	<i>C. neoformans</i>	<i>A. fumigatus</i>	<i>C. parapsilosis</i>
10l	4-F, 3-Me		4-chlorobenzyl	3.56	3.125	25.5	>50	>50	>50	>50	>50
10m	4-OMe		4-chlorobenzyl	6.05	3.125	12.5	>50	>50	>50	>50	>50
10n	4-F, 3-Me		4-chlorobenzyl	1.56	3.125	12.5	>50	>50	>50	>50	>50
10o	4-OMe		4-chlorobenzyl	>50	>50	>50	>50	>50	>50	>50	>50
10p	4-F, 3-Me		4-chlorobenzyl	>50	>50	>50	>50	>50	>50	>50	>50
10q	4-OMe		4-chlorobenzyl	>50	>50	>50	>50	>50	>50	50	>50
10r	4-F, 3-Me		4-chlorobenzyl	>50	>50	>50	>50	>50	>50	50	>50
10s	4-OMe		4-chlorobenzyl	5.25	6.12	25.5	12.75	>50	>50	>50	>50
10t	4-F, 3-Me		4-chlorobenzyl	6.25	6.05	25.5	12.5	>50	>50	>50	>50
14a	4-F, 3-Me		H	12.05	6.25	12.5	50	>50	25	25	>50
14b	4-F, 3-Me		H	3.56	6.125	25	50	>50	>50	>50	>50

Table 1 continued

Compound	R	R'	R''	MIC (µg/mL)			MIC (µg/mL)			
				<i>Klebsiella pneumoniae</i>	<i>Escherichia coli</i>	<i>P. aeruginosa</i>	<i>Salmonella typhi</i>	<i>C. albicans</i>	<i>C. neoformans</i>	<i>A. fumigatus</i>
14c	4-F, 3-Me		H	12.5	25	25.5	6.25	>50	>50	>50
14d	4-F, 3-Me		H	>50	>50	>50	>50	>50	>50	>50
14e	4-F, 3-Me		H	50	25	>50	50	>50	>50	>50
14f	4-F, 3-Me		H	25	25	25.5	50	>50	>50	>50
14g	4-F, 3-Me		H	3.56	6.125	25.5	6.25	>50	>50	>50
14h	4-F, 3-Me		H	1.56	12.5	12.5	3.02	>50	>50	>50
14i	4-F, 3-Me		H	0.39	1.56	3.56	12.5	>50	>50	>50
14j	4-F, 3-Me		H	0.39	3.56	6.25	12.05	>50	>50	>50
14k	4-F, 3-Me		H	0.12	0.56	1.025	12.5	>50	>50	>50
Gentamicin (Fluconazole)	-	-	-	0.25	1.25	3.025	1.65	(0.5)	(1.0)	(2.0)
Ciprofloxacin (Oxiconazole)	-	-	-	0.50	1.05	1.25	3.01	(0.03)	(1.4)	(2.0)

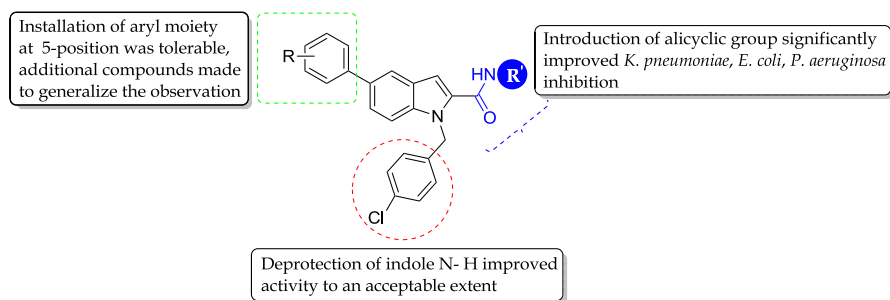


Fig. 2 SAR of 5-substitutedindole-2-carboxamides

Conclusion

We have designed, synthesized, and screened a series of novel 5-arylindole-2-carboxamides (**10a–t** and **14a–k**) for in vitro antibacterial and antifungal activity. All the synthesized compounds show moderate to excellent antibacterial activity compared to standard drugs. However, none of the titled compounds show antifungal activity except **14a**, indicating potency of 5-arylindole-2-carboxamides towards bacterial strains than fungi. Compounds **14i**, **14j**, and **14k** show excellent antibacterial activity against *K. pneumoniae* and *E. coli* than standard drugs and are promising to act as potential antibacterial agent. Compound **14k** have been found to be most efficient than both standards against *K. pneumoniae*, *E. coli*, and *P. aeruginosa*. Our findings underscore the promising potential of the 5-arylindole-2-carboxamides as an important lead structural scaffold in the design and synthesis of new antibacterial agents.

Experimental

All the solvents and reagents were purchased from commercial suppliers, Spectrochem Pvt. Ltd., Sigma Aldrich, and Rankem India Ltd., and were used without further purification. The progress of each reaction was monitored by ascending TLC using TLC aluminum sheets, pre-coated silica gel F254 (Merck, Germany), and by locating the spots using ultraviolet (UV) light as the visualizing agent or iodine vapors. Melting points were taken in an open capillary method and are uncorrected. All compounds were purified by recrystallization/slica gel (100–200 mesh) gravity column with suitable organic solvents. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^1H NMR, ^{13}C NMR was determined in CDCl_3 , and DMSO- d_6 solution on a Bruker Ac 200 MHz or Bruker Ac 400 MHz spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent 6520 (QTOF) ESI-HRMS instrument and elemental analyses (C, H, N) performed at the PerkinElmer 2400 CHN analyzer.

Synthesis of 4-bromophenylhydrazine (2)

To an ice-cold aqueous solution of 12 M HCl (30 mL), 4-bromoaniline **1** (8.00 g, 46.51 mmol) and, dropwise, an ice-cold solution of NaNO₂ (3.20 g, 46.37 mmol) in H₂O (10 mL) was added. The reaction was stirred for 15 min at 0 °C. To the resulting mixture, an ice-cold solution of SnCl₂ (26.44 g, 139.89 mmol) in 12 M HCl (70 mL) was added dropwise. The reaction mixture was stirred for 4 h at 0 °C. The precipitate was filtered, washed with 1 M HCl, and poured into water where the pH value was adjusted to 10 by adding 1 M NaOH. The crude product was extracted with Et₂O, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give an orange solid **2**.

Synthesis of ethyl pyruvate 4-bromophenylhydrazone (3)

A mixture of 4-bromophenylhydrazine **2** (5.0 g, 26.73 mmol), ethyl pyruvate (3.72 g, 32.07 mmol) in EtOH (30 mL) was refluxed under argon for 5 h. The cooled reaction mixture was then filtered, and the precipitate was washed with water. The crude product was triturated with cyclohexane and filtered to give a yellow solid **3**.

Synthesis of ethyl 5-bromo-1H-indole-2-carboxylate (4)

A mixture of ethyl pyruvate 4-bromophenylhydrazone **3** (5.0 g, 17.54 mmol) and polyphosphoric acid (44 g) was heated to 120 °C for 0.5 h. The reaction mixture was then cooled, poured into ice-cold water, and neutralized with saturated aqueous sodium bicarbonate. The crude product was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a pale yellow solid **4**.

Synthesis of ethyl 5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylate (5a) and Ethyl 5-(4-methoxyphenyl)-1H-indole-2-carboxylate (5b)

Potassium acetate (0.914 g, 13.98 mmol) in water (3 mL) was added to a solution of **4** (1.5 g, 05.59 mmol) and 4-fluoro-3-methylphenylboronic acid (06.71 mmol)/4-methoxyphenylboronic acid (06.71 mmol) in 1,4-dioxane (25 mL). The reaction mixture was degassed using argon and Pd(dppf)₂Cl₂ (0.228 g, 0.279 mmol) was added. The reaction mixture was stirred for 16 h at 120 °C. After completion of the reaction, monitored by TLC, the mixture was cooled to room temperature and the solvent was removed under reduced pressure. Water (10 mL) was added to the residue and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (1 × 10 mL), dried over anhydrous Na₂SO₄ and solvent was evaporated in vacuum. The product was purified by silica gel chromatography using Hexane: EtOAc (5:95) to afford 0.463 g (28 %) of compound **5a**/0.469 g (30 %) of compound **5b** as light yellow solids.

Synthesis of ethyl 1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylate (6a) and ethyl 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carboxylate (6b)

4-Chloro benzyl chloride (0.25 mL, 01.55 mmol) was added to a suspension of cesium carbonate (0.546 g, 01.55 mmol) and ethyl 5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylate **5a** (1.55 mmol)/ethyl 5-(4-methoxyphenyl)-1H-indole-2-carboxylate **5b** (1.55 mmol) in DMF (20 mL). The reaction mixture was stirred at 60 °C for 6 h (monitored by TLC). The reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with saturated aqueous NaHCO₃ (1 × 20 mL), water (1 × 10 mL), brine (1 × 10 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuum. The product was isolated by silica gel chromatography using Hexane: EtOAc (90:10) to afford 0.438 g (88 %) of compound **6a**/0.436 g (88 %) of compound **6b** as white solids.

Synthesis of 1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylic acid (7a), 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carboxylic acid (7b) and 5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylic acid (7c)

Ethyl 1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylate **6a** (1.24 mmol)/ethyl 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carboxylate **6b** (1.24 mmol)/ethyl 5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylate **5a** (1.24 mmol) was dissolved in THF (15 mL) and to that lithium hydroxide (0.044 g, 1.86 mmol) dissolved in 4 mL of water, was added dropwise. The reaction mixture was stirred at room temperature for 16 h. The pH of the reaction mixture was lowered to 2–3 with 1 M HCl. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and then concentrated in vacuum. The product was isolated by silica gel chromatography using hexane:EtOAc (50:50) to obtain 0.343 g (94 %) of compound **7a**, 0.340 g (94 %) of compound **7b**, and 0.255 g (94 %) of compound **7c** as white solids.

General procedure for 1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxamide, 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carboxamide (10a–t) and 5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxamide (14a–k) Compound **7a** (0.253 mmol)/compound **7b** (0.253 mmol)/compound **7c** (0.371 mmol) was dissolved in DMF/CH₂Cl₂ (15 mL) and cooled to 0 °C to rt. To that EDC.HCl (0.42 mmol), HOBt (0.42 mmol) and DIPEA/TEA (0.50 mmol) were added. The reaction mixture was stirred for 0.5 h and then appropriate Amine (0.352 mmol) was added and it was stirred for 20–30 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with dichloromethane (20 mL) and washed with saturated aq. NH₄Cl solution (1 × 20 mL), water (1 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuum. The product was

isolated by flash chromatography on silica gel using hexane:EtOAc (95:5) to afford desired targets (**10a–t**) and (**14a–k**) (70–94 %) as white to off-white solids. In the case of DMF, after completion of the reaction, the reaction mixture was poured into water and the obtained solids were filtered and washed thoroughly with water to afford the desired products.

Spectral data

4-Bromophenylhydrazine (2) Yield 82 %, Mp. 224 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 7.24 (d, 2H, J = 8.8 Hz, Ar), 6.92 (s, 1H, NH), 6.73 (d, 2H, J = 8.8 Hz, Ar–H) and 4.42 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 113.4, 117.2, 133.6, and 134.3; HRMS (M+H) Calcd = 185.9793, Found 187.0104.

Ethyl pyruvate 4-bromophenylhydrazone (3) Yield 76 %, Mp. 90–92 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 9.96 (s, 1H, NH), 7.46 (d, 2H, J = 8.8 Hz, Ar–H), 7.22 (d, 2H, J = 8.8 Hz, Ar–H), 4.21 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 2.1 (s, 3H, $-\text{CH}_3$), and 1.29 (t, 3H, J = 7.2 Hz, $-\text{CH}_2-\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 12.4, 14.7, 60.8, 112.6, 116.1, 132.2, 133.3, 144.2, and 165.3; HRMS (M+H) Calcd = 284.0160, Found 285.1304.

Ethyl 5-bromo-1H-indole-2-carboxylate (4) Yield 82 %, Mp. 165 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 12.08 (s, 1H, NH), 7.84 (d, 1H, J = 0.8 Hz, Ar–H), 7.40 (dd, 1H, J = 8.8 and 0.8 Hz, Ar–H), 7.39 (dd, 1H, J = 8.8 and 1.2 Hz, Ar–H), 7.10 (d, 1H, J = 1.2 Hz, Ar–H), 4.32 (q, 2H, J = 7.2 Hz, $-\text{OCH}_2\text{CH}_3$), and 1.32 (t, 3H, J = 7.2 Hz, $-\text{CH}_2-\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 13.8, 61.2, 109.1, 113.8, 114.1, 121.8, 124.9, 126.1, 133.4, 135.6, and 162.3; HRMS (M+H) Calcd = 266.9895, Found 268.0017.

Ethyl 5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylate (5a) Yield 28 %, Mp. 262 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 11.98 (s, 1H, NH), 7.95 (s, 1H, Ar–H), 7.60 (d, 1H, J = 8.0 Hz, Ar–H), 7.53 (d, 1H, J = 8.0 Hz, Ar–H), 7.43 (t, 2H, Ar–H), 7.33 (t, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 4.36 (q, 2H, J = 8 Hz, $-\text{OCH}_2\text{CH}_3$), 2.27 (s, 3H, $-\text{CH}_3$), and 1.36 (t, 3H, J = 8 Hz, $-\text{CH}_2\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 13.7, 14.4, 60.8, 108.1, 113.2, 113.3, 120.1, 122.6, 124.1, 127.9, 129.8, 132.3, 137.3, 141.3, 141.4, 143.2, 160.3, 162.7, and 163.2 (J = 248 Hz); HRMS (M+H) Calcd = 297.1960, Found 298.1994.

Ethyl 5-(4-methoxyphenyl)-1H-indole-2-carboxylate (5b) Yield 30 %, Mp. 230 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 11.84 (s, 1H, NH), 7.86 (d, 1H, J = 7.9 Hz, Ar–H), 7.78 (s, 1H, Ar–H), 7.62 (d, 2H, J = 8.2 Hz, Ar–H), 7.46 (d, 1H, J = 7.9 Hz, Ar–H), 7.32 (s, 1H, Ar–H), 7.20 (d, 2H, J = 8.2 Hz, Ar–H), 4.14 (q, 2H, J = 7.1 Hz, $-\text{OCH}_2\text{CH}_3$), 3.68 (s, 3H, $-\text{OCH}_3$), and 1.18 (t, 3H, J = 7.1 Hz, $-\text{CH}_2\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 14.2, 56.2, 60.2, 107.9, 133.7, 113.6, 115.2, 118.0, 124.6, 129.3, 130.1, 132.9, 133.8, 142.6, 158.8, and 161.2; HRMS (M+H) Calcd = 295.1208, Found 296.1326.

Ethyl 1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylate (6a)
Yield 88 %, Mp. 281 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 8.02 (s, 1H, Ar-H), 7.54 (s, 2H, Ar-H), 7.39 (m, 3H, Ar-H), 7.32 (d, 3H, Ar-H), 7.09 (d, 2H, Ar-H), 5.84 (s, 2H, $-\text{CH}_2$), 4.19 (q, 2H, $J = 7.2$ Hz, $-\text{OCH}_2\text{CH}_3$), 2.27 (s, 3H, $-\text{CH}_3$), and 1.25 (t, 3H, $J = 7.2$ Hz, $-\text{CH}_2\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 14.1, 14.7, 49.6, 60.7, 111.6, 112.4, 113.6, 120.9, 123.1, 124.9, 126.8, 128.4, 129.0, 129.3, 132.0, 132.3, 132.6, 138.0, 139.1, 160.3, 162.7, and 163.2 ($J = 250$ Hz); HRMS (M+H) Calcd = 421.1245, Found 422.1364.

Ethyl 1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carboxylate (6b)
Yield 88 %, Mp. 258 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 8.01 (s, 1H, Ar-H), 7.79 (d, 1H, $J = 8.1$ Hz, Ar-H), 7.72 (d, 1H, $J = 8.1$ Hz, Ar-H), 7.64 (d, 2H, $J = 8.0$ Hz, Ar-H), 7.40 (d, 2H, $J = 7.9$ Hz, Ar-H), 7.23 (s, 1H, Ar-H), 7.16 (d, 2H, $J = 7.9$ Hz, Ar-H), 7.06 (d, 2H, $J = 8.0$ Hz, Ar-H), 5.79 (s, 2H, $-\text{CH}_2$), 4.28 (q, 2H, $J = 7.1$ Hz, $-\text{OCH}_2\text{CH}_3$), 3.72 (s, 3H, $-\text{OCH}_3$), and 1.27 (t, 3H, $J = 7.1$ Hz, $-\text{CH}_2\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 14.3, 49.9, 56.2, 60.8, 110.5, 111.3, 115.1, 116.6, 119.2, 128.3, 128.7, 129.8, 130.9, 131.4, 132.8, 134.7, 137.4, 142.3, 159.5, and 160.3; HRMS (M+H) Calcd = 419.1288, Found 420.1405.

1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylic acid (7a)
Yield 94 %, Mp. 294 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 12.01 (s, 1H, $-\text{COOH}$), 8.0 (s, 1H, Ar-H), 7.60 (s, 2H, Ar-H), 7.41 (m, 3H, Ar-H), 7.31 (d, 3H, Ar-H), 7.01 (d, 2H, Ar-H), 5.87 (s, 2H, $-\text{CH}_2$), and 2.24 (s, 3H, $-\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 13.9, 46.6, 111.2, 111.8, 112.9, 113.1, 120.3, 122.4, 122.6, 124.4, 126.2, 128.2, 128.6, 128.9, 131.7, 132.0, 132.1, 137.7, 138.6, 140.7, 160.0, 162.4, and 162.9 ($J = 248$ Hz); HRMS (M+H) Calcd = 393.0932, Found 394.1472.

1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carboxylic acid (7b) Yield 94 %, Mp. 248 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 8.0 (s, 1H, Ar-H), 7.6 (m, 3H, Ar-H), 7.4 (m, 3H, Ar-H), 7.3 (d, 1H, Ar-H), 7.2 (d, 1H, Ar-H), 7.1 (m, 2H, Ar-H), 6.9 (d, 1H, Ar-H), 5.9 (s, 2H, $-\text{CH}_2$), and 3.6 (s, 3H, $-\text{OCH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 46.4, 55.0, 110.4, 111.4, 112.2, 112.8, 113.8, 119.1, 120.7, 126.2, 128.2, 129.9, 131.5, 132.9, 137.6, 139.0, 141.0, 142.3, and 159.6; HRMS (M+H) Calcd = 391.0975, Found 392.1047.

5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxylic acid (7c) Yield 94 %, Mp. 220 °C, ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 13.04 (s, 1H, $-\text{COOH}$), 11.87 (s, 1H, NH), 7.95 (s, 1H, Ar-H), 7.58 (d, 1H, $J = 8.0$ Hz, Ar-H), 7.51 (d, 1H, $J = 8.0$ Hz, Ar-H), 7.44 (t, 2H, Ar-H), 7.34 (t, 1H, Ar-H), 7.16 (s, 1H, Ar-H), and 2.27 (s, 3H, $-\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} 14.3, 108.2, 113.2, 113.4, 120.2, 122.7, 124.1, 127.9, 129.8, 132.4, 137.4, 141.5, 141.6, 160.4, 162.8, and 163.2 ($J = 250$ Hz); HRMS (M+H) Calcd = 269.0852, Found 270.1074.

1-(4-chlorobenzyl)-N-(4-methoxybenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carboxamide (10a) Yield: 72 %; mp 282 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 8.7 (t, $J = 6.0$ Hz, 1H, NH), 7.6 (m, 2H, ArH), 7.4 (m, 4H, ArH), 7.1 (m, 4H, ArH), 6.9

(m, 3H, ArH), 6.7 (d, 2H, ArH), 6.5 (s, 1H, ArH), 5.2 (s, 2H, CH₂Ar), 4.2 (d, $J = 6.0$ Hz, 2H, CH₂), 3.6 (s, 6H, OCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 42.9, 48.7, 54.8, 110.4, 113.7, 114.2, 114.9, 115.4, 118.5, 127.6, 129.2, 130.7, 131.3, 132.7, 134.4, 141.2, 142.5, 157.3, 158.9, 162.0; MS (ESI) $m/e = 510$ (M⁺), 512 (M+2)⁺; Anal. Calcd. for C₃₁H₂₇ClN₂O₃: C, 72.86 %, H, 5.33 %, N, 5.48 %, Found: C, 72.82 %, H, 5.28 %, N, 5.40 %.

1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-N-(4-methoxybenzyl)-1H-indole-2-carboxamide (10b) Yield: 76 %; mp 297 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 8.6 (t, $J = 6.0$ Hz, 1H, NH), 7.9 (s, 1H, ArH), 7.7 (d, 1H, ArH), 7.6 (d, 1H, ArH), 7.5 (m, 2H, ArH), 7.4 (m, 3H, ArH), 7.2 (d, 2H, ArH), 7.1 (d, 2H, ArH), 6.8 (d, 2H, ArH), 6.7 (s, 1H, ArH), 5.5 (s, 2H, CH₂Ar), 4.2 (d, $J = 6.0$ Hz, 2H, CH₂), 3.7 (s, 3H, OCH₃), 2.3 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 14.0, 43.2, 46.6, 55.2, 141.8, 113.9, 114.8, 115.4, 116.3, 119.6, 124.1, 128.1, 128.6, 130.1, 130.3, 131.3, 132.2, 132.4, 135.2, 137.1, 141.9, 143.4, 157.6, 160.4, 162.2; MS (ESI) $m/e = 512$ (M⁺), 514 (M+2)⁺; Anal. Calcd. for C₃₁H₂₆ClFN₂O₂: C, 72.58 %, H, 5.11 %, N, 5.46 %; Found: C, 72.49 %, H, 5.14 %, N, 5.39 %.

1-(4-chlorobenzyl)-N-(4-iodobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carboxamide (10c) Yield: 78 %; mp > 300 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 8.7 (t, $J = 6.0$ Hz, 1H, NH), 7.8 (m, 2H, ArH), 7.6 (m, 4H, ArH), 7.4 (m, 4H, ArH), 7.2 (m, 3H, ArH), 7.0 (d, 2H, ArH), 6.7 (s, 1H, ArH), 5.7 (s, 2H, CH₂Ar), 4.2 (d, $J = 6.0$ Hz, 2H, CH₂), 3.8 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 43.4, 49.0, 55.2, 91.8, 110.7, 113.4, 114.8, 115.9, 119.1, 127.9, 128.2, 129.7, 130.8, 131.9, 132.8, 135.0, 136.2, 136.7, 141.2, 141.9, 143.1, 159.3, 161.2; MS (ESI) $m/e = 606$ (M⁺), 608 (M+2)⁺; Anal. Calcd. for C₃₀H₂₄ClIN₂O₂: C, 59.37 %, H, 3.99 %, N, 4.62 %; Found: C, 59.31 %, H, 3.90 %, N, 4.56 %.

1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-N-(4-iodobenzyl)-1H-indole-2-carboxamide (10d) Yield: 74 %; mp 291 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 8.8 (t, $J = 6.0$ Hz, 1H, NH), 8.1 (s, 1H, ArH), 7.8 (d, 1H, ArH), 7.7 (d, 1H, ArH), 7.6 (m, 2H, ArH), 7.5 (m, 3H, ArH), 7.4 (d, 2H, ArH), 7.2 (d, 2H, ArH), 7.0 (d, 2H, ArH), 6.8 (s, 1H, ArH), 5.7 (s, 2H, CH₂Ar), 4.1 (d, $J = 6.0$ Hz, 2H, CH₂), 2.2 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 14.4, 43.2, 49.1, 92.5, 110.9, 114.7, 115.2, 116.2, 118.8, 123.7, 127.8, 128.3, 128.8, 130.6, 131.7, 132.0, 134.8, 135.9, 136.6, 137.1, 141.2, 141.9, 143.2, 160.3, 159.9; MS (ESI) $m/e = 608$ (M⁺), 610 (M+2)⁺; Anal. Calcd. for C₃₀H₂₃ClFIN₂O: C, 59.18 %, H, 3.81 %, N, 4.60 % Found: C, 59.14 %, H, 3.78 %, N, 4.54 %.

1'-(1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carbonyl)spiro[chroman-2,4'-piperidin]-4-one (10e) Yield: 70 %; mp 295 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 7.7 (m, 2H, ArH), 7.5 (m, 5H, ArH), 7.2 (m, 5H, ArH), 7.0 (m, 3H, ArH), 6.6 (s, 1H, ArH), 5.4 (s, 2H, CH₂Ar), 4.2 (b, 2H, CH₂), 3.6 (s, 3H, OCH₃), 2.6 (s, 2H, CH₂), 1.6 (b, 4H, CH₂), 1.1 (b, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 34.1, 38.4, 44.2, 49.1, 55.1, 68.2, 112.5, 114.6, 115.0, 116.4, 119.0, 120.1, 121.2, 127.3, 128.4, 129.7, 131.0, 131.8, 133.0, 133.4, 135.1, 141.3, 142.0, 143.2, 159.3, 160.3, 165.1, 190.6; HRMS, m/z , Calcd. = 590.1972, Found

591.2050 (M+H)⁺; Anal. Calcd. for C₃₆H₃₁ClN₂O₄: C, 73.15 %, H, 5.29 %, N, 4.74 % Found: C, 73.09 %, H, 5.23 %, N, 4.70 %.

1'-(1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carbonyl)spiro[chroman-2,4'-piperidin]-4-one (10f) Yield: 73 %; mp 297 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 8.2 (dd, 2H, CH₂), 8.1 (d, 1H, CH₂), 7.7 (d, 1H, CH₂), 7.6 (dd, 2H, CH₂), 7.4 (s, 1H, CH₂), 7.3 (d, *J* = 7.8 Hz, 2H, CH₂), 7.2 (d, *J* = 7.8 Hz, 2H, CH₂), 7.1 (d, 2H, CH₂), 6.9 (dd, 2H, CH₂), 5.7 (s, 2H, CH₂Ar), 3.4 (m, 2H, CH₂), 3.3 (m, 2H, CH₂), 2.7 (s, 2H, CH₂), 2.2 (s, 3H, CH₃), 1.9 (m, 2H, CH₂), 1.7 (m, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 14.6, 34.1, 38.6, 44.2, 49.2, 68.8, 111.4, 114.0, 115.1, 115.7, 116.5, 119.5, 120.4, 121.4, 124.2, 128.0, 128.9, 132.2, 132.6, 133.3, 135.2, 137.3, 141.5, 142.2, 143.4, 161.2, 165.1, 190.4; HRMS, *m/z*, Calcd. = 592.1929, Found 593.2013 (M+H)⁺; Anal. Calcd. for C₃₆H₃₀ClFN₂O₃: C, 72.90 %, H, 5.10 %, N, 4.72 % Found: C, 72.86 %, H, 5.04 %, N, 4.68 %.

7-bromo-1'-(1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carbonyl)spiro[chroman-2,4'-piperidin]-4-one (10g) Yield: 71 %; mp > 300 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 8.2 (dd, 2H, ArH), 8.1 (d, 1H, ArH), 7.7 (d, 1H, ArH), 7.6 (d, *J* = 8.2 Hz, 2H, ArH), 7.4 (s, 2H, ArH), 7.3 (d, *J* = 7.8 Hz, 2H, ArH), 7.2 (d, *J* = 7.8 Hz, 2H, ArH), 7.1 (d, 1H, ArH), 6.9 (d, *J* = 8.2 Hz, 2H, ArH), 5.8 (s, 2H, CH₂Ar), 3.8 (s, 3H, OCH₃), 3.3 (m, 2H, CH₂), 3.2 (m, 2H, CH₂), 2.7 (s, 2H, CH₂), 1.8 (m, 2H, CH₂), 1.6 (m, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 34.2, 38.7, 44.6, 49.4, 55.9, 68.6, 111.4, 114.6, 115.3, 116.5, 117.4, 119.5, 120.3, 123.3, 126.7, 128.5, 130.3, 131.1, 132.4, 133.5, 135.1, 141.6, 142.4, 143.3, 159.2, 159.6, 165.1, 190.4; MS (ESI) *m/e* = 668 (M⁺), 670 (M+2)⁺, 672 (M+4)⁺; Anal. Calcd. for C₃₆H₃₀BrClN₂O₄: C, 64.54 %, H, 4.51 %, N, 4.18 % Found: C, 64.49 %, H, 4.47 %, N, 4.14 %.

7-bromo-1'-(1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carbonyl)spiro[chroman-2,4'-piperidin]-4-one (10 h) Yield: 75 %; mp > 300 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 8.1 (dd, 2H, ArH), 8.0 (d, 1H, ArH), 7.8 (d, 2H, ArH), 7.7 (d, *J* = 8.2 Hz, 2H, ArH), 7.3 (s, 2H, ArH), 7.2 (d, 3H, ArH), 6.9 (d, *J* = 8.2 Hz, 2H, ArH), 5.7 (s, 2H, CH₂Ar), 3.4 (m, 2H, CH₂), 3.3 (m, 2H, CH₂), 2.6 (s, 2H, CH₂), 2.2 (s, 3H, CH₃), 1.9 (m, 2H, CH₂), 1.7 (m, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 14.6, 34.1, 38.7, 44.3, 49.7, 68.6, 111.6, 115.6, 116.4, 117.3, 119.5, 120.6, 123.3, 124.7, 127.1, 128.1, 128.8, 131.5, 132.1, 135.5, 137.3, 141.7, 142.3, 143.5, 159.1, 160.3, 165.1, 190.5; MS (ESI) *m/e* = 670 (M⁺), 672 (M+2)⁺, 674 (M+4)⁺; Anal. Calcd. for C₃₆H₂₉BrClFN₂O₃: C, 64.34 %, H, 4.35 %, N, 4.17 % Found: C, 64.28 %, H, 4.31 %, N, 4.13 %.

1-(4-chlorobenzyl)-N-cyclohexyl-5-(4-methoxyphenyl)-1H-indole-2-carboxamide (10i) Yield: 94 %, MP. 279 °C, ¹H NMR (200 MHz, DMSO-*d*₆): δ_H 7.90 (s, 1H, ArH), 7.82 (d, 1H, *J* = 7.9 Hz, ArH), 7.76 (d, *J* = 8.0 Hz, 1H, NH), 7.60 (d, 1H, *J* = 7.9 Hz, ArH), 7.52 (d, 2H, *J* = 8.2 Hz, ArH), 7.43 (d, 2H, *J* = 8.4 Hz, ArH), 7.34 (s, 1H, ArH), 7.26 (d, 2H, *J* = 8.4 Hz, ArH), 7.14 (d, 2H, *J* = 8.2 Hz, ArH), 5.82 (s, 2H, CH₂), 3.92 (m, 1H, CHN-), 3.78 (s, 3H, OCH₃), 2.1 (d, 2H, CH₂), 1.79 (t, 2H, CH₂-), 1.68 (m, 2H, CH₂-), 1.36 (m, 2H, CH₂-), 1.24 (m, 2H, CH₂); ¹³C

NMR (50 MHz, DMSO- d_6): δ_C 24.8, 25.7, 32.3, 49.4, 50.8, 55.4, 111.2, 114.2, 115.0, 116.2, 118.9, 128.6, 129.8, 130.7, 131.8, 132.6, 134.7, 141.2, 142.0, 143.3, 159.2, and 160.2; HRMS, m/z , Calcd = 472.1918, Found 473.2109 ($M+H$)⁺; Anal. Calcd for C₂₉H₂₉ClN₂O₂: C, 73.64 %, H, 6.18 %, N, 5.92 %; Found: C, 73.59 %, H, 6.14 %, N, 5.89 %.

1-(4-chlorobenzyl)-N-cyclohexyl-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxamide (10j) Yield: 92 %; mp 276 °C; ¹H NMR (400 MHz, DMSO- d_6): δ_H 7.82 (s, 1H, ArH), 7.50 (d, J = 8.0 Hz, 1H, NH), 7.38 (d, 1H, ArH), 7.28 (m, 6H, ArH), 7.09 (d, 2H, ArH), 6.93 (s, 1H, ArH), 5.80 (s, 2H, -CH₂Ar), 3.94 (m, 1H, -CHN), 2.33 (s, 3H, CH₃), 2.0 (d, 2H, CH₂), 1.78 (t, 2H, CH₂), 1.61 (m, 2H, CH₂), 1.29 (m, 2H, CH₂), 1.24 (m, 2H, CH₂); ¹³C NMR (100 MHz, DMSO- d_6): δ_C 14.2, 24.9, 25.5, 33.2, 47.5, 48.5, 104.5, 110.9, 113.7, 119.9, 122.5, 123.9, 126.8, 128.0, 128.7, 131.7, 132.9, 136.8, 138.1, 161.4; HRMS ($M+H$) Calcd. = 474.1874, Found 475.1947; Anal. Calcd. for C₂₉H₂₈ClFN₂O: C, 73.33 %, H, 5.94 %, N, 5.90 % Found: C, 73.28 %, H, 5.89 %, N, 5.84 %.

(1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indol-2-yl)(piperidin-1-yl)methanone (10k) Yield: 87 %; mp 283 °C; ¹H NMR (400 MHz, DMSO- d_6): δ_H 8.1 (s, 1H, ArH), 7.6 (m, 3H, ArH), 7.4 (m, 3H, ArH), 7.3 (m, 2H, ArH), 7.2 (m, 2H, ArH), 7.0 (d, 1H, ArH), 5.9 (s, 2H, CH₂Ar), 3.8 (s, 3H, OCH₃), 3.4 (b, 4H, CH₂), 1.4 (b, 6H, CH₂); ¹³C NMR (100 MHz, DMSO- d_6): δ_C 24.4, 25.6, 47.3, 49.2, 55.8, 116.4, 114.5, 115.3, 116.7, 119.2, 128.5, 130.4, 131.2, 132.3, 133.2, 135.1, 141.7, 142.6, 159.4, 165.5; MS (ESI) m/e = 458 ($M+$), 460 ($M+2$)⁺; Anal. Calcd. for C₂₈H₂₇ClN₂O₂: C, 73.27 %, H, 5.93 %, N, 6.10 % Found: C, 73.21 %, H, 5.88 %, N, 6.04 %.

(1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indol-2-yl)(piperidin-1-yl)methanone (10l) Yield: 84 %; mp 279 °C; ¹H NMR (400 MHz, DMSO- d_6): δ_H 7.9 (s, 1H, ArH), 7.6 (d, 1H, ArH), 7.5 (d, 1H, ArH), 7.4 (t, 2H, ArH), 7.3 (m, 3H, ArH), 7.1 (d, 2H, ArH), 6.7 (s, 1H, ArH), 5.6 (s, 2H, CH₂Ar), 3.5 (m, 4H, CH₂), 2.3 (s, 3H, CH₃), 1.5–1.2 (m, 6H, CH₂); ¹³C NMR (100 MHz, DMSO- d_6): δ_C 14.3, 24.4, 46.7, 104.0, 111.5, 113.4, 119.7, 122.7, 127.2, 128.9, 129.3, 131.9, 132.4, 133.3, 137.0, 137.7, 141.5, 160.4, 162.0, 162.8; HRMS, m/z , Calcd. = 460.1718, Found 461.1788 ($M+H$)⁺; Anal. Calcd. For C₂₈H₂₆ClFN₂O: C, 72.95 %, H, 5.69 %, N, 6.08 % Found: C, 72.91 %, H, 5.64 %, N, 6.02 %.

(1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indol-2-yl)(pyrrolidin-1-yl)methanone (10 m) Yield: 90 %; mp 274 °C; ¹H NMR (400 MHz, DMSO- d_6): δ_H 8.1 (d, 2H, ArH), 7.9 (d, 1H, ArH), 7.6 (d, 2H, J = 8.1 Hz, ArH), 7.3 (d, 2H, J = 7.8 Hz, ArH), 7.2 (s, 1H, ArH), 7.1 (d, 2H, J = 7.8 Hz, ArH), 7.0 (d, 2H, J = 8.1 Hz, ArH), 5.7 (s, 2H, CH₂Ar), 3.7 (s, 3H, OCH₃), 3.5 (t, 4H, CH₂), 2.0 (t, 4H, CH₂); ¹³C NMR (100 MHz, DMSO- d_6): δ_C 25.3, 47.3, 49.2, 55.7, 111.4, 114.6, 115.1, 116.6, 119.3, 128.5, 130.5, 131.4, 132.3, 133.4, 135.2, 141.6, 142.3, 143.5, 159.1, 165.3; MS (ESI) m/e = 444 ($M+$), 446 ($M+2$)⁺; Anal. Calcd. for C₂₇H₂₅ClN₂O₂: C, 72.88 %, H, 5.66 %, N, 6.30 % Found: C, 72.83 %, H, 5.63 %, N, 6.26 %.

(1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indol-2-yl)(pyrrolidin-1-yl)methanone (**10n**) Yield: 89 %; mp 268 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 8.2 (d, 2H, ArH), 8.0 (s, 1H, ArH), 7.7 (d, 1H, ArH), 7.4 (d, 2H, $J = 7.6$ Hz, ArH), 7.3 (s, 1H, ArH), 7.20 (d, 2H, ArH), 7.1 (d, 2H, $J = 7.6$ Hz, ArH), 5.8 (s, 2H, CH_2Ar), 3.5 (t, 4H, CH_2), 2.3 (s, 3H, CH_3), 2.0 (t, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 14.7, 25.2, 47.3, 49.3, 116.5, 115.2, 116.6, 119.3, 124.6, 128.4, 128.9, 131.3, 132.3, 132.5, 135.4, 137.3, 141.7, 142.3, 143.5, 160.2, 165.3; MS (ESI) $m/e = 446$ (M^+), 448 ($\text{M}+2$) $^+$; Anal. Calcd. for $\text{C}_{27}\text{H}_{24}\text{ClFN}_2\text{O}$: C, 72.56 %, H, 5.41 %, N, 6.27 % Found: C, 72.52 %, H, 5.38 %, N, 6.23 %.

Tert-butyl-4-(1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-1H-indole-2-carboxamido)piperidine-1-carboxylate (**10o**) Yield: 80 %; mp 293 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 8.3 (d, $J = 8.0$ Hz, 1H, NH), 8.1 (d, 2H, ArH), 8.0 (d, 1H, ArH), 7.6 (d, $J = 8.2$ Hz, 2H, ArH), 7.4 (d, $J = 7.8$ Hz, 2H, ArH), 7.3 (s, 1H, ArH), 7.1 (d, $J = 7.8$ Hz, 2H, ArH), 7.0 (d, $J = 8.2$ Hz, 2H, ArH), 5.8 (s, 2H, CH_2Ar), 3.7 (s, 3H, OCH_3), 3.6 (m, 1H), 3.4 (m, 2H), 3.3 (m, 2H), 1.8 (m, 2H), 1.6 (m, 2H), 1.4 (s, 9H, CH_3); ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 28.3, 26.7, 43.4, 47.8, 49.3, 55.7, 79.6, 111.4, 114.9, 115.3, 116.7, 119.3, 128.6, 130.2, 131.2, 132.0, 133.1, 135.2, 141.7, 142.0, 143.6, 159.4, 159.6, 160.4; MS (ESI) $m/e = 573$ (M^+), 575 ($\text{M}+2$) $^+$; Anal. Calcd. for $\text{C}_{33}\text{H}_{36}\text{ClN}_3\text{O}_4$: C, 69.04 %, H, 6.32 %, N, 7.32 % Found: C, 69.0 %, H, 6.27 %, N, 7.28 %.

Tert-butyl-4-(1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxamido)piperidine-1-carboxylate (**10p**) Yield: 76 %; mp 287 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 8.5 (d, $J = 8.0$ Hz, 1H, NH), 7.9 (s, 1H, ArH), 7.5 (dd, 2H, ArH), 7.4 (dd, 2H, ArH), 7.3 (d, 3H, ArH), 7.2 (s, 1H, ArH), 7.1 (d, 2H, ArH), 5.8 (s, 2H, CH_2Ar), 3.9 (b, 3H), 2.3 (s, 3H, CH_3), 1.8 (s, 2H), 1.4 (s, 13H); ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 14.3, 28.6, 331.7, 46.7, 46.9, 79.1, 106.3, 111.8, 113.3, 113.5, 120.0, 120.8, 126.9, 128.8, 129.0, 132.0, 133.0, 138.0, 138.3, 141.3, 141.4, 154.4, 160.4, 161.4, 162.7; MS (ESI) $m/e = 575$ (M^+), 577 ($\text{M}+2$) $^+$; Anal. Calcd. for $\text{C}_{33}\text{H}_{35}\text{ClFN}_3\text{O}_3$: C, 68.80 %, H, 6.12 %, N, 7.29 % Found: C, 68.74 %, H, 6.08 %, N, 7.26 %.

1-(4-chlorobenzyl)-*N'*-isonicotinoyl-5-(4-methoxyphenyl)-1H-indole-2-carbohydrazide (**10q**) Yield: 83 %; mp 263 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 9.1 (s, 2H, NH), 8.7 (d, $J = 8.2$ Hz, 2H, ArH), 8.2 (d, 2H, ArH), 8.0 (d, 1H, ArH), 7.8 (d, $J = 8.2$ Hz, 2H, ArH), 7.6 (d, $J = 8.0$ Hz, 2H, ArH), 7.4 (d, $J = 7.8$ Hz, 2H, ArH), 7.3 (s, 1H, ArH), 7.1 (d, $J = 7.8$ Hz, 2H, ArH), 7.0 (d, $J = 8.0$ Hz, 2H, ArH), 5.8 (s, 2H, CH_2Ar), 3.6 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 50.2, 55.7, 111.6, 114.6, 115.1, 116.6, 119.2, 121.4, 128.5, 130.0, 131.1, 132.0, 133.1, 135.3, 140.6, 141.6, 142.0, 143.5, 149.6, 159.4, 161.2, 164.6; MS (ESI) $m/e = 510$ (M^+), 512 ($\text{M}+2$) $^+$; Anal. Calcd. for $\text{C}_{29}\text{H}_{23}\text{ClN}_4\text{O}_3$: C, 68.17 %, H, 4.54 %, N, 10.96 % Found: C, 68.12 %, H, 4.49 %, N, 10.90 %.

1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-*N'*-isonicotinoyl-1H-indole-2-carbohydrazide (**10r**) Yield: 71 %; mp 289 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 9.0 (s, 2H), 8.8 (d, $J = 8.2$ Hz, 2H, ArH), 8.2 (d, 2H, ArH), 8.0 (d, 1H), 7.7 (d,

$J = 8.2$ Hz, 2H, ArH), 7.6 (d, 1H, ArH), 7.4 (s, 1H, ArH), 7.3 (d, $J = 8.0$ Hz, 2H, ArH), 7.2 (d, 2H, ArH), 7.0 (d, $J = 8.0$ Hz, 2H, ArH), 5.8 (s, 2H, CH₂Ar), 2.3 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 14.6, 50.2, 111.6, 115.1, 115.8, 116.6, 119.2, 121.5, 124.2, 128.0, 128.5, 131.1, 132.0, 132.2, 135.3, 137.1, 140.6, 141.6, 142.0, 143.5, 149.5, 160.2, 161.4, 164.6; MS (ESI) $m/e = 512$ (M⁺), 514 (M+2)⁺; Anal. Calcd. for C₂₉H₂₂ClFN₄O₂: C, 67.90 %, H, 4.32 %, N, 10.92 % Found: C, 67.84 %, H, 4.26 %, N, 10.88 %.

1-(4-chlorobenzyl)-5-(4-methoxyphenyl)-N-(1-(2-methoxyphenyl)propan-2-yl)-N-methyl-1H-indole-2-carboxamide (10s) Yield: 84 %; mp 277 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 8.2 (d, 2H, ArH), 8.0 (d, 1H, ArH), 7.6 (d, 2H, $J = 8.1$ Hz, ArH), 7.4 (d, 2H, $J = 7.8$ Hz, ArH), 7.1 (d, 2H, $J = 7.8$ Hz, ArH), 7.0 (d, 2H, $J = 8.1$ Hz, ArH), 7.3 (s, 1H, ArH), 6.9–7.1 (m, 4H, ArH), 5.8 (s, 2H, CH₂Ar), 4.1 (m, 1H, CH), 3.8 (s, 6H, OCH₃), 3.4 (s, 3H, NCH₃), 2.9 (dd, 1H, CH), 2.6 (dd, 1H, CH), 1.2 (d, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 18.2, 33.2, 49.2, 55.3, 56.1, 60.1, 111.6, 112.3, 114.5, 115.1, 116.7, 119.4, 120.8, 127.2, 127.8, 128.5, 130.2, 130.2, 130.4, 131.4, 131.1, 132.0, 133.0, 135.2, 141.6, 142.2, 143.5, 158.6, 159.3, 161.5; MS (ESI) $m/e = 552$ (M⁺), 554 (M+2)⁺; Anal. Calcd. for C₃₄H₃₃ClN₂O₃: C, 73.83 %, H, 6.01 %, N, 5.06 % Found: C, 73.78 %, H, 5.97 %, N, 5.01 %.

1-(4-chlorobenzyl)-5-(4-fluoro-3-methylphenyl)-N-(1-(2-methoxyphenyl)propan-2-yl)-N-methyl-1H-indole-2-carboxamide (10t) Yield: 79 %; mp 281 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 8.2 (d, 2H, ArH), 7.9 (d, 1H, ArH), 7.7 (d, 1H, ArH), 7.5 (d, 2H, $J = 7.6$ Hz, ArH), 7.4 (s, 1H, ArH), 7.3 (d, 2H, ArH), 7.2 (d, 2H, $J = 7.6$ Hz, ArH), 6.9–7.1 (m, 4H, ArH), 5.8 (s, 2H, CH₂Ar), 4.1 (m, 1H, CH), 3.7 (s, 3H, OCH₃), 3.5 (s, 3H, NCH₃), 2.9 (dd, 1H, CH), 2.6 (dd, 1H, CH), 2.2 (s, 3H, CH₃), 1.1 (d, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 14.7, 18.2, 33.4, 49.3, 56.2, 60.2, 111.6, 112.2, 115.1, 115.7, 116.6, 119.2, 121.0, 124.2, 127.2, 127.5, 128.1, 128.6, 130.4, 131.1, 132.2, 132.5, 135.2, 137.1, 141.7, 142.2, 143.5, 158.5, 160.4, 161.5; MS (ESI) $m/e = 554$ (M⁺), 556 (M+2)⁺; Anal. Calcd. for C₃₄H₃₂ClFN₂O₂: C, 73.57 %, H, 5.81 %, N, 5.05 % Found: C, 73.51 %, H, 5.77 %, N, 5.01 %.

(5-(4-fluoro-3-methylphenyl)-1H-indol-2-yl)(3-phenoxyazetidin-1-yl)methanone (14a) Yield: 74 %; mp 279 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 11.8 (s, 1H, NH), 7.9 (s, 1H, ArH), 7.6 (d, 1H, Ar–H), 7.5 (d, 1H, Ar–H), 7.4 (t, 2H, Ar–H), 7.3 (d, 3H, Ar–H), 7.1 (s, 1H, Ar–H), 7.0 (d, 3H, ArH), 4.4 (m, 1H, CH), 4.3 (d, 2H, CH₂), 4.0 (d, 2H, CH₂), 2.3 (s, 3H, –CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 14.6, 52.5, 70.7, 111.4, 114.3, 114.8, 115.7, 116.6, 119.2, 120.1, 124.2, 128.1, 129.1, 131.6, 132.3, 137.1, 138.6, 143.5, 157.2, 160.2, 172.4; MS (ESI) $m/e = 400$ (M⁺); Anal. Calcd. for C₂₅H₂₁FN₂O₂: C, 74.98 %, H, 5.29 %, N, 7.0 % Found: C, 74.92 %, H, 5.23 %, N, 6.96 %.

5-(4-fluoro-3-methylphenyl)-N-(4-methoxybenzyl)-1H-indole-2-carboxamide (14b) Yield: 89 %; mp 295 °C; ¹H NMR (200 MHz, DMSO-*d*₆): δ_H 11.7 (t, $J = 6.0$ Hz, 1H, NH), 9.0 (t, 1H, NH), 7.9 (s, 1H, Ar–H), 7.4 (m, 4H, Ar–H), 7.3

(m, 4H, Ar-H), 6.9 (d, 2H, Ar-H), 4.5 (d, $J = 6.0$ Hz, 2H, CH₂N), 3.4 (s, 3H, OCH₃), 2.2 (s, 3H, CH₃); ¹³C NMR (50 MHz, DMSO-*d*₆): δ_C 13.8, 41.7, 55.0, 103.0, 112.6, 112.8, 113.0, 113.7, 119.4, 122.2, 122.6, 127.7, 128.6, 130.7, 130.8, 131.5, 131.8, 131.9, 132.5, 136.2, 141.1, 141.3, 158.3, 158.7, 163.5; MS (ESI) $m/e = 388$ (M⁺); Anal. Calcd. for C₂₄H₂₁FN₂O₂: C, 74.21 %, H, 5.45 %, N, 7.21 % Found: C, 74.15 %, H, 5.40 %, N, 7.18 %.

5-(4-fluoro-3-methylphenyl)-N-(4-iodobenzyl)-1H-indole-2-carboxamide (14c)

Yield: 87 %; mp 286 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 11.8 (t, $J = 6.0$ Hz, 1H, NH), 9.1 (t, 1H, NH), 7.9 (s, 1H, Ar-H), 7.6 (m, 4H, Ar-H), 7.3 (m, 4H, Ar-H), 6.8 (d, 2H, Ar-H), 4.4 (d, $J = 6.0$ Hz, 2H, CH₂N), 2.2 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 14.7, 43.5, 92.1, 111.6, 114.7, 115.8, 116.6, 119.2, 124.2, 128.1, 128.6, 131.7, 132.1, 136.7, 137.1, 137.5, 138.4, 138.7, 143.5, 160.1, 161.2; MS (ESI) $m/e = 484$ (M⁺); Anal. Calcd. for C₂₃H₁₈FIN₂O: C, 57.04 %, H, 3.75 %, N, 5.78 % Found: C, 56.98 %, H, 3.71 %, N, 5.74 %.

5-(4-fluoro-3-methylphenyl)-N'-isonicotinoyl-1H-indole-2-carbohydrazide (14d)

Yield: 71 %; mp 270 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 11.9 (s, 1H, NH), 8.8 (d, 2H, $J = 8.2$ Hz, Ar-H), 8.2 (s, 2H, NH), 7.8 (d, 1H, ArH), 7.7 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.6 (d, 1H, Ar-H), 7.5 (d, 2H, Ar-H), 7.4 (s, 1H, ArH), 7.2 (d, 2H, Ar-H), 2.2 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 14.6, 111.6, 114.7, 115.8, 116.6, 119.2, 121.2, 124.2, 128.1, 131.6, 132.2, 137.1, 138.6, 140.6, 143.5, 149.5, 160.2, 161.1, 164.6; MS (ESI) $m/e = 388$ (M⁺); Anal. Calcd. for C₂₂H₁₇FN₄O₂: C, 68.03 %, H, 4.41 %, N, 14.43 % Found: C, 67.97 %, H, 4.37 %, N, 14.38 %.

1'-(5-(4-fluoro-3-methylphenyl)-1H-indole-2-carbonyl)spiro[chroman-2,4'-piperidin]-4-one (14e)

Yield: 73 %; mp 293 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 11.7 (s, 1H, NH), 7.9 (s, 1H, Ar-H), 7.7 (d, 1H, ArH), 7.6 (d, 1H, ArH), 7.4 (m, 5H, Ar-H), 7.2 (m, 2H, Ar-H), 6.9 (s, 1H, Ar-H), 3.4 (s, 4H, CH₂), 2.8 (s, 2H, CH₂), 2.2 (s, 3H, CH₃), 2.1 (m, 2H, CH₂), 1.8 (m, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 14.8, 34.1, 38.7, 44.3, 68.6, 111.6, 114.1, 114.7, 115.7, 116.6, 119.2, 120.1, 121.5, 124.2, 127.6, 131.6, 132.1, 133.5, 137.1, 138.6, 143.1, 160.1, 160.4, 172.1, 190.6; MS (ESI) $m/e = 468$ (M⁺); Anal. Calcd. for C₂₉H₂₅FN₂O₃: C, 74.34 %, H, 5.38 %, N, 5.98 % Found: C, 74.0 %, H, 5.31 %, N, 5.93 %.

7-bromo-1'-(5-(4-fluoro-3-methylphenyl)-1H-indole-2-carbonyl)spiro[chroman-2,4'-piperidin]-4-one (14f)

Yield: 70 %; mp > 300 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 11.9 (s, 1H, NH), 7.8 (d, 3H, Ar-H), 7.7 (d, 2H, ArH), 7.4 (s, 1H, Ar-H), 7.3 (d, 1H, Ar-H), 7.2 (d, 3H, Ar-H), 3.4 (m, 2H, CH₂), 3.3 (m, 2H, CH₂), 2.7 (s, 2H, CH₂), 2.2 (s, 3H, CH₃), 1.9 (m, 2H, CH₂), 1.7 (m, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ_C 14.7, 34.2, 38.8, 44.5, 68.8, 111.6, 114.7, 115.8, 116.6, 117.4, 119.2, 120.5, 124.3, 126.7, 128.1, 130.4, 131.6, 132.2, 137.1, 138.6, 143.2, 159.2, 160.2, 172.1, 190.8; HRMS (M⁺+Na+2) Calcd. = 546.0954, Found 571.0825; Anal. Calcd. for C₂₉H₂₄BrFN₂O₃: C, 63.63 %, H, 4.42 %, N, 5.12 % Found: C, 62.97 %, H, 4.37 %, N, 5.09 %.

Tert-butyl 4-(5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxamido)piperidine-1-carboxylate (14g) Yield: 78 %; mp 290 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 11.8 (d, J = 8.0 Hz, 1H, NH), 8.2 (d, 1H, NH), 7.8 (d, 2H, ArH), 7.7 (d, 2H, Ar-H), 7.4 (s, 1H, Ar-H), 7.2 (d, 2H, Ar-H), 3.6 (m, 1H, CH), 3.4 (m, 2H, CH₂), 3.3 (m, 2H, CH₂), 2.2 (s, 3H, CH₃), 1.8 (m, 2H, CH₂), 1.6 (m, 2H, CH₂), 1.4 (s, 9H, CH₃); ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 14.8, 28.3, 26.5, 43.4, 47.5, 79.9, 111.6, 114.7, 115.8, 116.6, 119.2, 124.1, 128.1, 131.6, 132.2, 137.1, 138.6, 143.5, 159.4, 160.2, 161.1; HRMS (M+Na) Calcd. = 451.2271, Found 474.2155; Anal. Calcd. for C₂₆H₃₀FN₃O₃: C, 69.16 %, H, 6.70 %, N, 9.31 % Found: C, 69.10 %, H, 6.65 %, N, 9.27 %.

(5-(4-fluoro-3-methylphenyl)-1H-indol-2-yl)(piperidin-1-yl)methanone (14h) Yield: 92 %; mp 260 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 11.0 (s, 1H, NH), 7.9 (s, 1H, NH), 7.7 (d, 1H, ArH), 7.4 (d, 1H, Ar-H), 7.3 (m, 3H, Ar-H), 6.8 (s, 1H, Ar-H), 3.7 (b, 4H, CH₂), 2.2 (s, 3H, CH₃), 1.7 (b, 6H, CH₂); ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 14.6, 24.1, 25.2, 47.1, 111.6, 114.7, 115.7, 116.6, 119.2, 124.3, 128.1, 131.7, 132.3, 137.1, 138.7, 143.6, 160.3, 172.1; MS (ESI) m/e = 336 (M+); Anal. Calcd. for C₂₁H₂₁FN₂O: C, 74.98 %, H, 6.29 %, N, 8.33 % Found: C, 74.92 %, H, 6.24 %, N, 8.28 %.

(5-(4-fluoro-3-methylphenyl)-1H-indol-2-yl)(pyrrolidin-1-yl)methanone (14i) Yield: 90 %; mp 254 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 11.8 (s, 1H, NH), 7.8 (d, 2H, ArH), 7.7 (d, 2H, ArH), 7.4 (s, 1H, Ar-H), 7.2 (d, 2H, Ar-H), 3.5 (t, 4H, CH₂), 2.2 (s, 3H, CH₃), 1.9 (t, 4H, CH₂); ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 14.8, 25.2, 47.3, 111.6, 114.8, 115.6, 116.5, 119.3, 124.1, 128.1, 131.5, 132.1, 137.3, 138.6, 143.7, 160.5, 172.2; HRMS (M+H) Calcd. = 322.1481, Found 323.1548; Anal. Calcd. for C₂₀H₁₉FN₂O: C, 74.51 %, H, 5.94 %, N, 8.69 % Found: C, 74.47 %, H, 5.89 %, N, 8.64 %.

N-cyclohexyl-5-(4-fluoro-3-methylphenyl)-1H-indole-2-carboxamide (14j) Yield: 94 %, MP. 268 °C, ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 10.64 (d, J = 8.0 Hz, 1H, NH), 7.32 (d, 1H, NH), 6.93 (s, 1H, Ar-H), 6.52 (d, 2H, Ar-H), 6.46 (d, 2H, Ar-H), 6.36 (t, 1H, Ar-H), 6.25 (s, 1H, Ar-H), 1.54 (s, 1H, -CH-), 1.29 (s, 3H, -CH₃), 0.84 (d, 4H, -CH₂-), 0.65 (d, 1H, -CH-), 0.36–0.39 (m, 4H, -CH₂-) and 0.17–0.19 (m, 1H, -CH-); ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 13.9, 25.2, 32.6, 48.1, 103.1, 112.8, 113.0, 119.4, 121.9, 122.1, 122.3, 122.5, 127.7, 130.8, 132.0, 132.9, 136.1, 141.3, 160.0, 160.1, 162.4; HRMS (M+H) Calcd. = 350.1794, Found 351.1836; Anal. Calcd for C₂₂H₂₃FN₂O: C, 75.40 %, H, 6.62 %, N, 7.99 %; Found: C, 75.41 %, H, 6.61 %, N, 7.98 %.

5-(4-fluoro-3-methylphenyl)-N-(1-(2-methoxyphenyl)propan-2-yl)-N-methyl-1H-indole-2-carboxamide (14k) Yield: 74 %; mp 281 °C; ^1H NMR (400 MHz, DMSO- d_6): δ_{H} 11.8 (s, 1H, NH), 7.8 (d, 2H, ArH), 7.7 (d, 2H, ArH), 7.4 (s, 1H, Ar-H), 7.2 (d, 3H, Ar-H), 6.8–6.9 (m, 3H, ArH), 4.1 (m, 1H, CHN), 3.7 (s, 3H, OCH₃), 3.4 (s, 3H, CH₃N), 2.9 (d, 1H, CH), 2.6 (d, 1H, CH), 2.2 (s, 3H, CH₃), 1.1 (d, 3H, CH₃); ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 14.7, 18.2, 33.4, 35.6, 56.0, 60.3, 111.6, 112.2, 114.7, 115.8, 116.6, 119.2, 121.0, 124.3, 127.1, 127.5, 128.1, 130.4, 131.6, 132.2,

137.1, 138.6, 143.5, 158.5, 160.2, 161.6; MS (ESI) $m/e = 430$ (M^+); Anal. Calcd. for $C_{27}H_{27}FN_2O_2$: C, 75.33 %, H, 6.32 %, N, 6.51 % Found: C, 75.28 %, H, 6.28 %, N, 6.48 %.

Experimental protocol for biological activity

Antibacterial activity assay [53]

The in vitro antimicrobial susceptibility of prepared compounds (**10a–t** and **14a–k**) (in terms of minimum inhibitory concentration; MIC) against strains of pathogenic Gram-negative bacteria *K. pneumoniae* (ATCC 27736), *E. coli* (ATCC 9637), *P. aeruginosa* (ATCC BAA427), and *S. typhi* were evaluated by the broth microdilution technique described by the Clinical and Laboratory Standards Institute (CLSI), 2012 (formerly NCCLS) [53]. The minimum inhibitory concentration (MIC, $\mu\text{g/mL}$) was defined as the lowest concentration of an antimicrobial agent that will inhibit the visible growth of microbe. Gentamicin and ciprofloxacin were used as standard drugs for comparison of antibacterial activity. Dimethyl sulfoxide (DMSO) was used as a solvent or negative control. To clarify any effect of DMSO on the antifungal activity, separate studies were carried out with solutions alone of DMSO, and these studies showed no activity against any microbial strains. The MIC of tested compounds was determined using the twofold serial dilution technique by assaying at 51.2, 25.6, 12.8, 6.4, 3.2, 1.6, 0.8, 0.4, 0.2, 0.1, and 0.05 $\mu\text{g/mL}$ concentrations along with standards at the same concentrations.

Antifungal activity assay [54, 55]

The in vitro antifungal susceptibility (AFST) of prepared compounds (**10a–t** and **14a–k**) (in terms of minimum inhibitory concentration; MIC) against strains of pathogenic fungi, for example, *C. albicans*, *C. neoformans*, *A. fumigatus* (all strains are patients' isolates), and *C. parapsilosis* (ATCC 22019) were evaluated by the broth microdilution technique described by the Clinical and Laboratory Standards Institute (CLSI), 2012 (formerly NCCLS) [54, 55]. Fluconazole and oxiconazole were used as standard drugs for comparison of antifungal activity. DMSO was used as a solvent or negative control. To clarify any effect of DMSO on the antifungal activity, separate studies were carried out with solutions alone of DMSO and these studies showed no activity against any microbial strains. MIC (the lowest concentration of an antimicrobial agent that will inhibit the visible growth of microbe) of tested compounds was determined using the twofold serial dilution technique by assaying at 64, 32, 16, 8, 4, 2, 1, and 0.5 $\mu\text{g/mL}$ concentrations along with standards at the same concentrations.

Acknowledgments The author, Y. D. Mane, is grateful to the Department of Postgraduate Studies and Research in Chemistry, Dnyanopasak College, Parbhani, and Shri Chhatrapati Shivaji College, Omerga, for providing laboratory facilities, Indian Institute of Chemical Technology, Hyderabad, and National Chemical Laboratory for spectral data, and finally to Smita S. Patil for proofreading.

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