Research Article

Synthesis of Novel Indole-Curcumin Hybrids as Potential Antimicrobial Agents

Yogesh Kumar Lawaniya* and Pradeep Kumar Goyal*

Bhupal Noble's Institute of Pharmaceutical Sciences, Bhupal Nobles' University, Udaipur -313001, India

Abstract

A series of novel indole-curcumine hybrids was synthesized *via* natural product inspired molecular hybridization method. Each single hybrid was observed for their antimicrobial activity. Most of the examined derivatives display significant *in vitro* antimicrobial activity against *K. Pneumoniae* than the control. Our results show that novel indole-curcumin hybrids indicate a novel structural lead for antimicrobial Chemotherapy.

Keywords: *indole*, curcumine, *K. Pneumoniae*, antimicrobial activity and molecular hybridization approach.

***Correspondence**

Author: Yogesh kumar Lawaniya, Pradeep Kumar Goyal

Email: yogeshlawaniya1984@gmail.com, goel.pradeep@rediffmail.com

Introduction

Antimicrobial resistance is frequently used as a meaning for drug resistance, which happens when microorganisms for example fungi, viruses, bacteria, and parasites withstand a drug that was projected to treat the infection. Microbial diseases are anticipated to reason for 0.7 million deaths yearly and growing on day by day. Warfare antimicrobial resistance has developed into a foremost confront for global health. The increase in resistance of microorganisms against antimicrobial chemotherapy threatens the flourishing cure of increasing bacterial and fungal infections and affects people health all over the world [1-6].

As per WHO information on worldwide antimicrobial resistance, it is anticipated that >10 million people will go through from the multi-drug resistance infections with an increased number of human mortality rates. Additional, it is expected to increase in antimicrobial drug resistance.

Based on these information assessments, it is necessary to reinforce this research field to build up new, comparatively effective antimicrobial and antifungal drugs [7]. Typical drug treatments like naftifine, Amphotericin B, terbinafine, fluconazole, miconazole, target the plasma membrane; hinder protein biosynthesis while flucytosine, norfloxacin, trimethoprim block DNA replication. caspofungin, ampicillin and clarithromycin, linezolid bind to ribosomes [8-14].

Even though a quantity of antimicrobial agents being documented, novel compounds are essential to assemble growing demands for managing infections in the multifaceted patient population.

Recently, the molecular hybridization approach has been become known as a powerful strategy for tackling the problems associated with the standard drugs. In this context, some hybrid molecules (like CZ74) of indole with other heterocycles have been synthesized, which showed potent antimicrobial activity [15-16].

On the other hand, in past decades multicomponent reactions have been proven as a powerful tool for the manufacture of biologically active compounds in a few steps, and generally from readily available starting materials. In the course of these MCRs, the isocyanide based multicomponent reaction (IMCR) mainly helpful for the synthesis of biologically active molecules due to its convergent character, atom economy, operational simplicity, high variability and provide the opportunity of advance transformations [17-18].

The indole group is a necessary fraction of a quantity of compounds with significant biological activity. Indole derivatives are recognized to exert antitubercular, anticancer, antiviral and antioxidant activities. On the other hand, curcumin has been used widely in Ayurveda (Indian system of Medicine) for centuries as a anti-inflammatory agent, pain relieving to relieve pain and inflammation in the muscles and skin. It has also established to have anti-cancer properties. Curcumin holds a high place in Ayurvedic medicine as a "cleanser of the body," and today, science is finding a increasing list of diseased conditions that can be healed by the active ingredients of turmeric. Because of the comprehensive antimicrobial activity of curcumin and safety property yet at high doses (12 g/day) evaluated by clinical trials in human, it was used as a structural model to design the novel antimicrobial agents with modified and increased antimicrobial activities from side to side the synthesis of various derivatives related to curcumin.

In the continuation of our ongoing programme to develop new hybrid molecules, and inspired by the biological importance of curcumin and indole based natural product, Herein, we wish to describe the synthesis and antidyslipidemic evaluation of novel curcumin-indole based hybrids (**Figure 1**) [19-20].

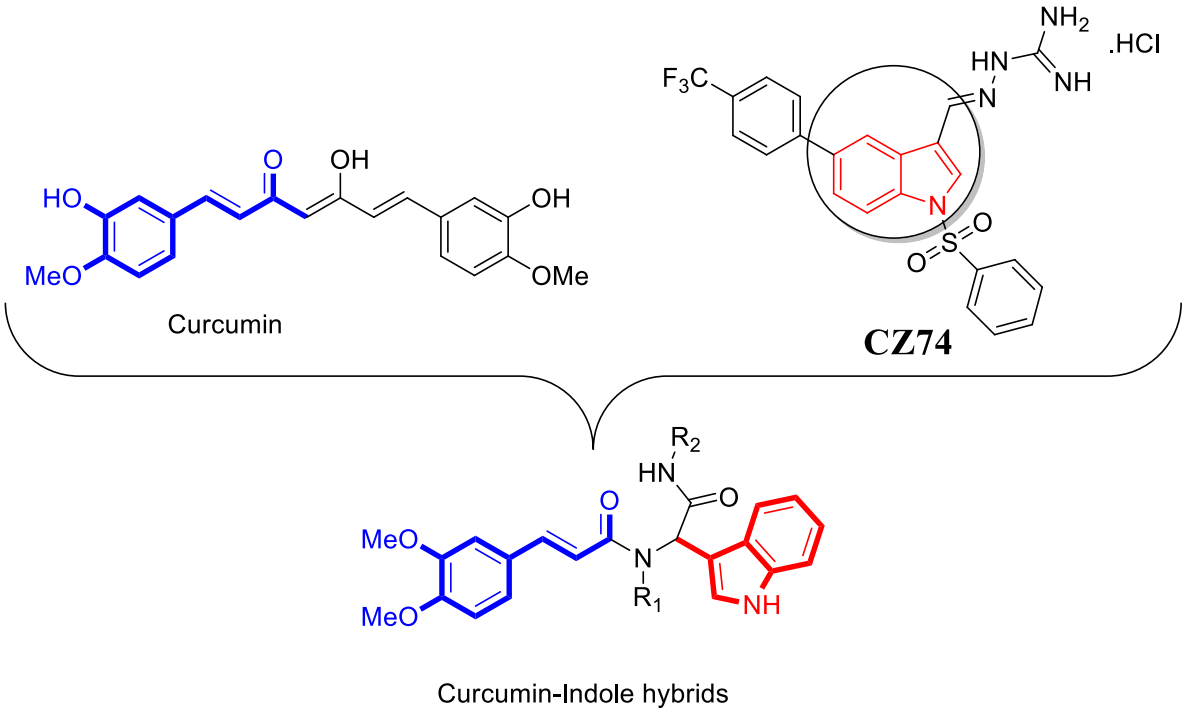


Figure 1 A multicomponent reaction approach to the synthesis of antimicrobial agent

Results and Discussion

The synthesis of Ugi-MCR products **5a-o** (**Table 1**) were accomplished by the condensation of acids **1**, aldehydes **2**, amines **3** and isocyanides **4** in methanol at room temperature. This approach provides the indole-curcumine hybrids in excellent yield (72-93%). All compounds were characterized using ^{1}H NMR, ^{13}C NMR, mass spectrometry and IR spectroscopy (See supporting information). The purity of these compounds was ascertained by TLC and spectral analysis.

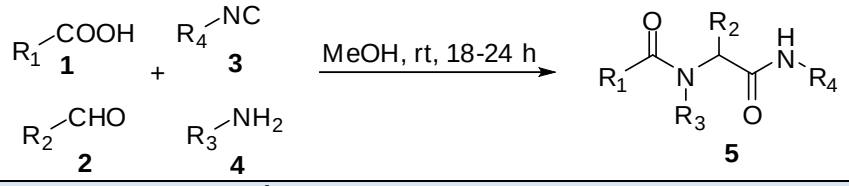
Antimicrobial activities of curcumin-indole based hybrids derivatives

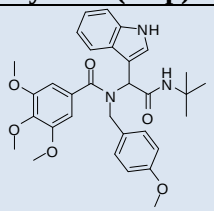
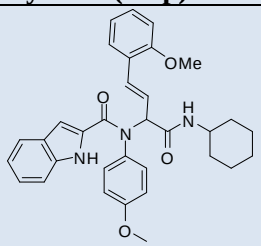
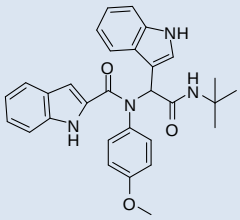
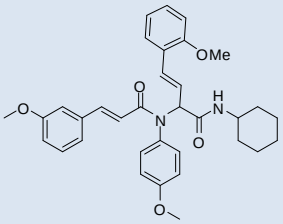
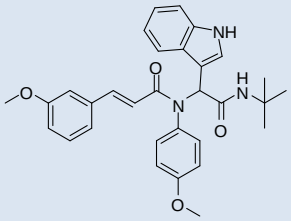
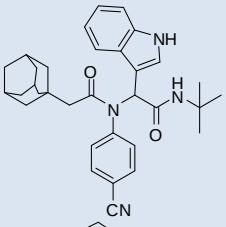
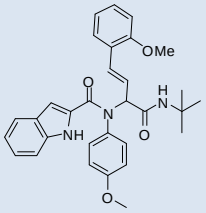
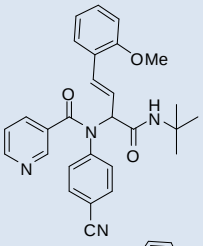
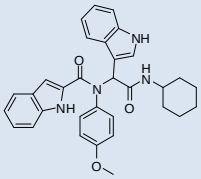
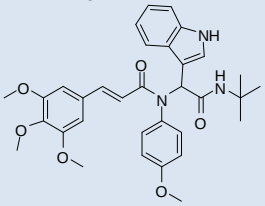
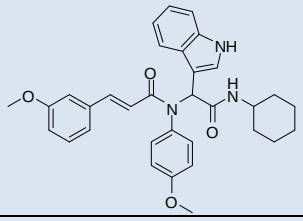
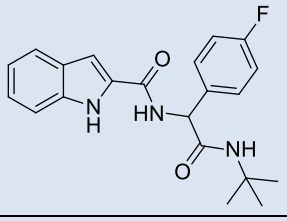
Antimicrobial activity of the compounds examined against E. coli (ATCC 9637), Pseudomonas aeruginosa (ATCC BAA-427), Staphyloccus aerus (ATCC 25923), Klebsiella pneumoniae (ATCC 27736), Cryptococcus neoformans, Candida albicans, Sporothrix schenckii, Trichophyton mentagrophytes, Aspergillus fumigates, Candida parapsilosis (ATCC-22019) bacteria by standard micro broth dilution as per NCCLS protocol with a view to develop therapeutic agents having broad spectrum of antibacterial activity using Gentamicin, as standard antibacterial agent.

Antibacterial activity assay

The bacterial strains were grown on Sabroaud dextrose agar and nutrient agar media respectively. After the incubation fungal and bacterial growth were suspended in normal saline and maintained at 1.0–5.0×10^{3} cfu/mL. The activity of compounds was determined by the NCCLS method for fungus using RPMI-1640 media buffered with MOPS (3-[*N*-morpholino]propanesulfonic acid) (Sigma-Aldrich Company) and Mueller Hinton broth for bacteria. The 96-well tissue culture plates were used for twofold serial dilution. The proper growth control, drug control and the blank were adjusted onto the plate. Compounds were dissolved in DMSO at a concentration of 1 mg/mL and 20 µL of this was added to 96-well tissue culture plate having 180 µL RPMI-1640 so the maximum concentration of the compound became 50 µg/mL. From here the solution was serially diluted resulting into the half of the concentration of test compounds and then inoculum was added and kept for incubation. Micro-titer plates were incubated at 35°C in a moist, dark chamber and MICs were recorded spectrophotometrically.

Table 1 Synthesis of indole-curcumin hybrids[a]



Entry	Hybrids (5a-p)	[b]Yields%	Entry	Hybrids (5a-p)	[b]Yields%
5a		87%	5g		93%
5b		72%	5h		79%
5c		78%	5i		83%
5d		89%	5j		89%
5e		91%	5k		91%
5f		81%	5l		62%

[a]*Reaction conditions:* acids (1 mmol), aldehydes (1.2 mmol), amines (1 mmol), isocyanides (1.2 mmol) MeOH (5 ml), rt, 18-24 h, [b] isolated yields of MCR products

As shown in **Table2**, the synthesized compounds having **curcumin-indole based hybrids** moiety demonstrated tremendous activity against *K. Pneumoniae* as compared to others, even additional inhibitory activity than the mentioned drugs. i.e. compounds **5i** (MIC = 0.35 μg/mL), **5k** (MIC = 0.04 μg/mL), **5l** (MIC = 12.5 μg/mL). Rest of the compounds illustrated poor inhibitory activity next to the tested microbial strains.

Table 2 *In vitro* antimicrobial activity of curcumin-indole based hybrids derivatives (MIC in µg/ml)

Compounds	Antibacterial activity MIC(µg/mL)[a]									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
5a	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
5b	>50	>50	>50	>50	>50	>50	>50	50	>50	>50
5c	>50	>50	3.12	50	>50	>50	25	>50	25	50
5d	>50	>50	50	25	50	50	50	50	50	50
5e	>50	>50	>50	12.5	>50	>50	>50	50	>50	>50
5f	>50	>50	>50	25	50	50	50	50	50	50
5g	>50	>50	>50	50	50	50	>50	>50	>50	50
5h	>50	>50	>50	25	>50	>50	50	>50	>50	>50
5i	>50	>50	>50	0.35	>50	>50	>50	50	>50	>50
5j	>50	>50	>50	25	>50	>50	>50	50	>50	>50
5k	>50	>50	>50	0.04	>50	>50	>50	50	>50	>50
5l	>50	>50	>50	12.5	>50	>50	>50	>50	>50	>50
Gentamicin	0.76	0.78	0.78	0.78	-	-	-	-	-	-

E. coli (ATCC 9637), 2. *Pseudomonas aeruginosa* (ATCC BAA-427), 3. *Staphyloccus aerus* (ATCC 25923), 4. *Klebsiella pneumoniae* (ATCC 27736). 5. *Cryptococcus neoformans*, 6. *Candida albicans*, 7. *Sporothrix schenckii*, *8*. *Trichophyton mentagrophytes*, 9. *Candida parapsilosis* (ATCC-22019), 10. *Aspergillus fumigates*

Conclusions

In conclusion, a novel sequence of indole-curcumine hybrids was synthesized and estimated for their microbial activity. Compounds **5i**, **5k** and **5l** emerged as promising agents and appear to be good candidates for the development of a new type of drug for treating microbial strains.

Experimental: General information

All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 300 MHz spectrometers for ^{1}H NMR and 50 MHz for ^{13}C NMR on Bruker Supercon Magnet Avance DRX-300 spectrometers in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant *J* in Hz.). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad singlet (br s). Mass spectra and HRMS were taken in the ESI positive ion mode. The reaction progress was monitored by thin layer chromatography (TLC) on pre-coated silica gel plates. Column chromatography was performed over Merck silica gel (230-400 flash).

General procedure for the synthesis of Ugi-MCR products 5a-l

To the solution of the amine (1 mmol), acid (1 mmol), and aldehyde (1.2 mmol) in methanol (5 mL) was added isocyanide (1.2 mmol) through a microsyringe at room temperature. After stirring at room temperature for 18-24 h, the solvent was removed to obtained crude products on which purification by flash column chromatography on silica gel (eluent: hexane/ EtOAc) afforded Ugi-IMCR product **(5a-o)** in 72-93% yield.

Characterization of compounds

N-(2-(tert-butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-3,4,5-trimethoxy-N-(4-methoxybenzyl)benzamide (5a)

Solid, Yield = 87%, mp = 183-185 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3409, 2932, 1632, 1534 1220, 771; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.0 (s, 1H), 7.85-7.51 (m, 2H), 7.35-6.33 (m, 11H), 4.31 (d, *J* = 15.9 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 6H), 3.71-3.66 (m, 1H), 3.59 (s, 3H), 1.26 (s, 9H) ppm.

N-(2-(tert-butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-(4-methoxyphenyl)-1H-indole-2-carboxamide (5b)

Solid, Yield = 72%, mp = 148-150 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3417, 2823, 1630, 1478 1230, 771; 668, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.5 (s, 1H), 10.8 (s, 1H), 7.64 (s, 1H), 7.53 (d, *J* = 6.0 Hz, 1H), 7.43 (d, *J* = 6.0 Hz, 1H), 7.30-7.24 (m, 1H), 7.14-6.97 (m, 7H), 6.91-6.87 (m, 2H), 6.57 (s, 2H), 4.94 (s, 1H), 3.65 (s, 3H), 1.29 (s, 9H) ppm.

(E)-N-(2-(tert-butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-3-(3-methoxyphenyl)-N-(4-methoxyphenyl)acrylamide (5c)

Solid, Yield = 78%, mp = 172-174 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3417, 2928, 2330, 1620, 1440, 1221, 771,^{1}H NMR (300 MHz, DMSO-d_6): δ 10.8 (s, 1H), 7.65-7.49 (m, 4H), 7.27 (br s, 2H), 7.01-6.88 (m, 7H), 6.51 (s, 2H), 6.15 (d, *J* = 14.7 Hz, 1H), 3.71 (s, 3H), 3.63 (s, 3H), 1.28 (s, 9H) ppm.

(E)-N-(1-(tert-butylamino)-4-(2-methoxyphenyl)-1-oxobut-3-en-2-yl)-N-(4-methoxyphenyl)-1H-indole-2-carboxamide (5d)

Solid, Yield = 89%, mp = 180-182 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3419, 2940, 2401, 1606, 1518, 1423, 928, 759, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.5 (s, 1H), 7.70 (s, 1H), 7.41-7.20 (m, 5H), 7.15-7.10 (m, 2H), 7.02-6.84 (m, 6H), 6.02-5.94 (m, 1H), 5.76 (s, 1H), 5.65 (d, *J* = 8.1 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 1.30 (s, 9H) ppm.

N-(2-(cyclohexylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-(4-methoxyphenyl)-1H-indole-2-carboxamide (5e)

Solid, Yield = 91%, mp = 150-152 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3421, 2813, 2457, 1621, 1441, 930, ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.6 (s, 1H), 10.9 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.31-7.24 (m, 2H), 7.14-6.97 (m, 5H), 6.90 (s, 2H), 6.61 (s, 1H), 6.54 (br s, 1H), 4.94 (s, 1H), 3.66 (s, 4H), 1.82-1.53 (m, 5H), 1.31-0.98 (m, 5H) ppm.

(E)-N-(2-(cyclohexylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-3-(3-methoxyphenyl)-N-(4-methoxyphenyl)acrylamide (5f)

Solid, Yield = 81%, mp = 160-162 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3440, 2975, 2401, 1606, 1518, 1423, 928, 759 ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.8 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.53-7.43 (m, 3H), 7.28-7.23 (m, 4H), 7.07-6.87 (m, 7H), 6.53 (s, 1H), 6.14 (d, *J* = 15.6 Hz, 1H), 3.79 (s, 1H), 3.71 (s, 3H), 3.63 (s, 3H), 1.79-1.53 (m, 5H), 1.36-0.97 (m, 5H) ppm.

(E)-N-(1-(cyclohexylamino)-4-(2-methoxyphenyl)-1-oxobut-3-en-2-yl)-N-(4-methoxyphenyl)-1H-indole-2-carboxamide (5g)

Solid, Yield = 93%, mp = 186-188 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 2926, 2365, 1660, 1440, 1221, 771, ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.38 (s, 1H), 7.42-7.36 (m, 5H), 7.28-7.20 (m, 2H), 7.10-6.88 (m, 6H), 6.38-6.27 (m, 2H), 5.57 (d, *J* = 9.3 Hz, 1H), 5.27 (s, 1H), 3.91 (s, 3H), 3.84 (s, 4H), 1.94-1.59 (m, 5H), 1.32-1.18 (m, 5H) ppm.

(E)-N-cyclohexyl-4-(2-methoxyphenyl)-2-((E)-3-(3-methoxyphenyl)-N-(4-methoxy phenyl)acrylamido)but-3-enamide (5h)

Solid, Yield = 79%, mp = >200 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3418, 2928, 2365, 1650, 1430, 1243, 1030, 769, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.39 (d, *J* = 7.8 Hz, 1H), 7.58-7.14 (m, 6H), 7.04-6.79 (m, 7H), 6.21-6.16 (m, 1H), 6.01-5.93 (m, 1H), 5.59 (d, *J* = 8.1 Hz, 1H), 3.77-3.72 (m, 9H), 3.58 (br s, 1H), 1.73-1.54 (m, 5H), 1.36-1.15 (m, 5H) ppm.

2-(adamantan-1-yl)-N-(2-(tert-butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-(4-cyanophenyl)acetamide (5i)

Solid, Yield = 83%, mp = 198-200 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3417, 2940, 2265, 1650, 1543, 1247, 769, 518, ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.8 (s, 1H), 7.75 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 3H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.06-6.95 (m, 2H), 6.84 (s, 1H), 6.44 (s, 1H), 5.76 (s, 2H), 1.99-1.71 (m, 5H), 1.64-1.50 (m, 13H), 1.28 (s, 9H) ppm.

(E)-N-(1-(tert-butylamino)-4-(2-methoxyphenyl)-1-oxobut-3-en-2-yl)-N-(4-cyano phenyl)nicotinamide (5j)

Solid, Yield = 89%, mp = >200 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3330, 2918, 2340, 1658, 1440, 1249, 767, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.21 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.54-7.46 (m, 3H), 7.28-7.21 (m, 3H), 6.96 (s, 1H), 6.91-6.65 (m, 2H), 6.11-6.03 (m, 1H), 5.97 (s, 1H), 5.21 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 1.34 (s, 9H) ppm.

(E)-N-(2-(tert-butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acrylamide (5k)

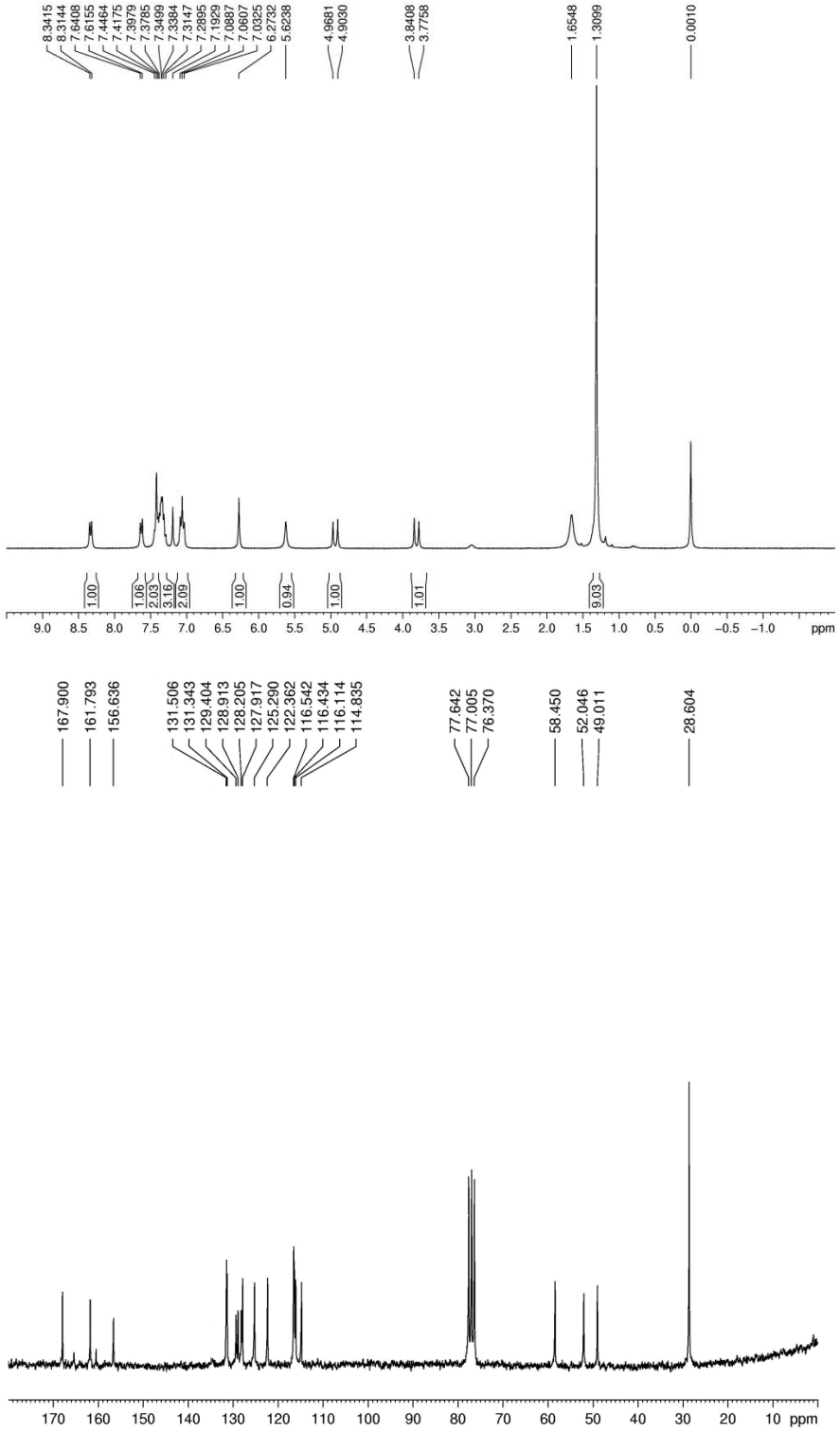
Solid, Yield = 91%, mp = 183-185 ^{0}C, FT-IR (KBr) ν (cm^{-1}): 3429, 3019, 2927, 1664, 1430, 1213, 1078, 757, 669, ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.8 (s, 1H), 7.64 (s, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.07-6.96

(m, 3H), 6.87 (s, 1H), 6.62 (s, 4H), 6.51 (s, 1H), 6.03 (d, *J* = 15.6 Hz, 1H), 3.68 (s, 6H), 3.61 (s, 6H), 1.28 (s, 9H) ppm.

N-(2-(tert-butylamino)-1-(4-fluorophenyl)-2-oxoethyl)-1H-indole-2-carboxamide(5l)

White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.34 (d, 1H, *J* = 8.1 Hz), 7.64(d, 1H, *J* =7.6 Hz), 7.44-7.39(m, 2H), 7.38-7.29 (m, 3H), 7.09 (t, 2H, *J* = 8.4 Hz), 6.27 (s, 1H), 5.62 (s, 1H), 4.97 (d, 1H, *J* = 19.5 Hz), 3.84 (d, 1H, *J* =19.5 Hz), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.9, 161.8, 156.6, 131.5, 131.3, 129.4, 128.9, 128.3, 127.9, 125.3, 122.3, 116.5, 116.4, 116.1, 114.8, 58.4, 52.0, 49.0, 28.6.

N-(2-(tert-butylamino)-1-(4-fluorophenyl)-2-oxoethyl)-1H-indole-2-carboxamide(5l)
^{1}H NMR and ^{13}C NMR



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