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ACID AMINE COUPLING OF (1H-INDOLE-6-YL)PPIPERAZIN-1-YL)METHANONE WITH SUBSTITUTED ACIDS USING HATU COUPLING REAGENT AND THEIR ANTIMICROBIAL AND ANTIOXIDANT ACTIVITY

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Keywords:

Piperazine, HATU, Indole, Antimicrobial, Anti oxidant

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ABSTRACT: Acid amine coupling of 1*H*-indol-6-yl(piperazin-1-yl) methanone with different acids has been synthesized in presence of HATU reagent, DIPEA base with DMF solvent at 45 °C 30 mins to yield Indole piperzine derivatives 3a-j. The structures of all the synthesized compounds have been characterised by elemental analysis and spectral studies like 1H-NMR and LCMS. Some selected Indole piperazine derivatives have been tested for antimicrobial activity using by Disc diffusion method and *in vitro* antioxidant activity using DPPH Assay method. Three compounds 3a, 3f and 3h have shown significant antimicrobial and one compound 3b have shown *in vitro* antioxidant activity.

INTRODUCTION: Recent drug discovery studies have focused on the design and synthesis of small molecules that have an indole nucleus as the core structure and that act as tubulin inhibitors [1]. Drugs that bind to tubulin act by interfering with the mitosis of cells during the M-phase, resulting in mitotic arrest and eventually leading to Design, synthesis, and biological evaluation of apoptosis [2]. Due to the introduction of vinca alkaloids such as vincristine and vinblastine for the clinical therapy indole carrying compounds have generated considerable interest [3–8].

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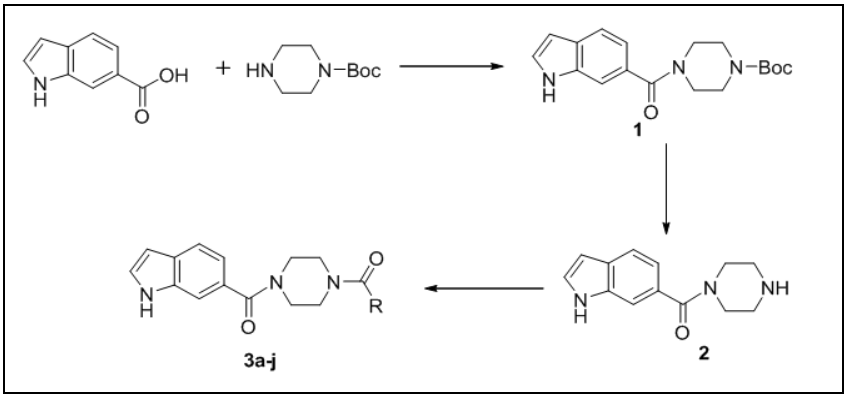
Indole and their derivatives play an important role in biological and medicinal chemistry. They exhibit wide range of pharmacological activities like anti-microbial, antidepressive, anti-inflammatory, anti-fungicidial, antipyretic, antitubercular and antioxidant activities [9-12]. The antioxidant profile of Indole piperazine derivatives [13-15] was compared to well known antioxidants Trolox and Resveratrol. All the compounds and antioxidant standards were investigated in concentration range from 10^{-8} to 10^{-4} mol × L^{-1} (H_2O). In the last ten years a new generation of cardio selective (β1-selective adrenoreceptor) blockers, such as metoprolol, atenolol or acebutolol, as well as nonselective β-blockers with α-adrenoreceptor blocking activity (*e.g.* carvedilol, bucindolol) were introduced to therapy. In the case of carvedilol, beside its β-blocking and antihypertensive function, antioxidant activity *in vitro* and *in vivo* has been shown [16-17].

In the rat brain homogenates, carvedilol protected α-tocopherol against depletion induced by ferrous ions [18]. Additionally, carvedilol decreased oxidative stress in patients with heart failure and hypertension. Antioxidant capacities of clinically used antiarrhythmic agents *e.g.* mexiletine, amiodarone, propranolol and carvedilol, have been established [19-24]. Thus, based on these observations in the literature, the present study was initiated with aim of identifying the structural requirements of piperazines in terms of antimicrobial and antioxidant activity.

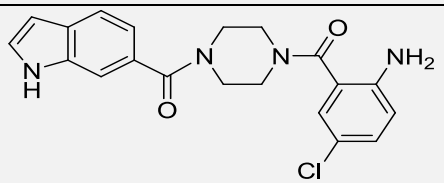
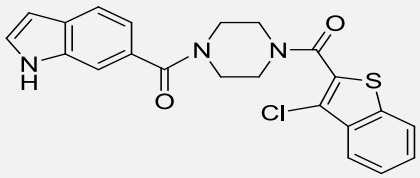
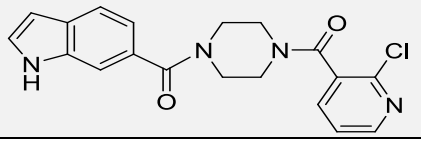
RESULTS AND DISCUSSION:

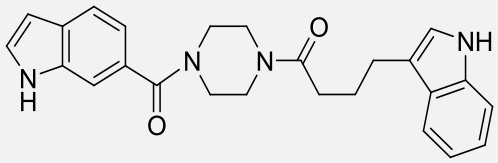
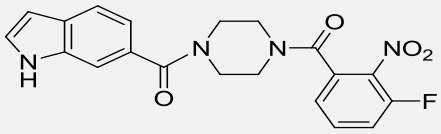
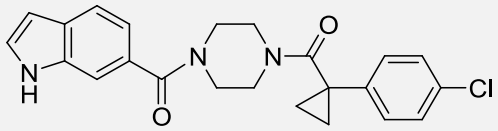
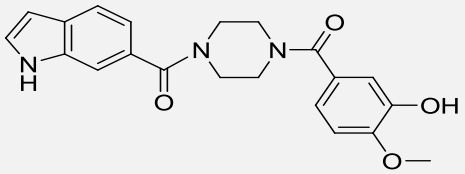
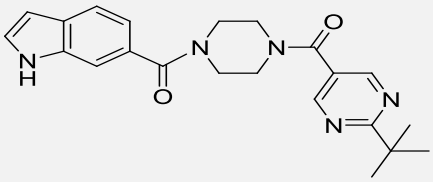
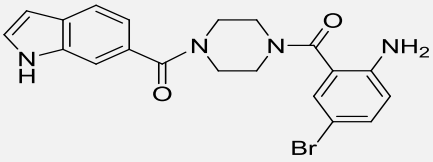
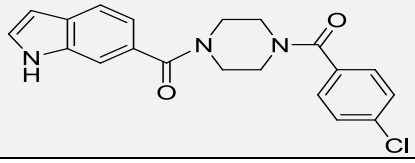
Chemistry: According to our aim, we planned to synthesize Indole piperazines with substituted heterocyclic and aromatic acids using acid amine coupling method with HATU as a coupling reagent. 1*H*-indol-6-yl(piperazin-1-yl)methanone (1.0 eq) was dissolved in dry DMF solvent. The solution was stirred for 10 min at ambient temperature. Then aromatic / heterocyclic acid (1.0 eq) was added followed by HATU (1.2 eq) and diisopropylethylamine (2 eq). The reaction mass was heated to 45-50 °C for 3-4 hr, the completion of reaction was monitored by TLC. After completion, the reaction mass was diluted with ethyl acetate, the organic layer was washed with water, 1N hydrochloric acid and 10% sodium bicarbonate solution, brine solution and dried over anhydrous sodium sulphate. The organic layer was concentrated under vacuum and the crude was purified by column chromatography using 60-120 mesh silica gel using petether and ethyl acetate. The series of reactions carried out have been depicted in **Scheme 1**.

All the synthesized compounds have been purified by column chromatography. The structures have been confirmed by elemental analysis and spectroscopic techniques like IR, ^{1}H-NMR, LC-MS. Some of the selected compounds have been tested for *in vitro* antioxidant and antimicrobial activity.



SCHEME 1: SYNTHESIS OF INDOLE PIPERAZINE METHANONE DERIVATIVES 3A-J

Compound	Structure	Yield
3a		80%
3b		85%
3c		84%

3d		83%
3e		81%
3f		80%
3g		81%
3h		80%
3i		79%
3j		80%

Pharmacology:

Antimicrobial Activity of Test Drugs by Disc Diffusion Method:

Preparation and Standardization of Stock Cultures: Cultures on receipt were sub cultured in NA plates and further stored in slants as stock cultures. For the experiments, stock culture was prepared by inoculating each culture from slants to flask in sterile NB and incubated at 37 °C for 24hr. The stock culture was adjusted to 0.5 McFarland standard turbidity and used for assay.

Preparation of Discs: The test drug stock solution was prepared by dissolving 10mg of drug in DMSO with sonication and solubilised part was separated by centrifugation. Sufficient amount of stock solution was loaded on to the sterile discs to prepare 700 and 400µg/ml. The discs were allowed to dry under asceptic conditions.

Preparation and Standardization of Stock cultures: Cultures on receipt were sub cultured in NA plates and further stored in slants as stock cultures. For the experiments, stock culture was prepared by inoculating each culture from slants to flask in sterile NB and incubated at 37 °C for 24hr. The stock culture was adjusted to 0.5 McFarland standard turbidity and used for assay.

Experiment: Sterile NA plates were prepared and 0.1ml of the inoculum from standardized culture of test organism was spread uniformly. The prepared discs of the test substance and standard antibiotic were placed on to the plates carefully. The plates were placed at 4 °C for 1 hr to allow the diffusion of test solution into the medium and plates were incubated at a temperature optimal for the test organism and for a period of time sufficient for the growth of at least 10 to 15 generations (usually 24 hours at 37 °C) for bacteria and (usually 48 hrs at

room temperature) for fungi. The zone of inhibition of microbial growth around the disc was measured in mm.

RESULTS: Compounds 3a, 3f, 3h showed moderate inhibitory activity against *E. coli* at 700µg/ml conc. The results are tabulated in **Table 1**.

TABLE 1: ANTIMICROBIAL ACTIVITY OF TEST DRUGS BY DISC DIFFUSION METHOD

Disc diffusion susceptibility in mm Microorganism - *E. coli*			
Test sample	**Concentrations**		**Std**
Compound	**700 µg/disc**	**400 µg/ disc**	**250µg/ disc**
3a	12.6	10.6	27.3
3f	10.6	9.6	25.3
3h	11.3	9.6	24.6

***In vitro* Antioxidant Activities:**

DPPH Assay: The DPPH free radical is reduced to a corresponding hydrazine when it reacts with hydrogen donors. The DPPH radical is purple in colour and upon reaction with hydrogen donor changes to yellow colour. It is a discoloration assay, which is evaluated by the addition of the antioxidant to a DPPH solution in ethanol or methanol and the decrease in absorbance was measured at 490nm.

Reagents:

2-Diphenly 1-picryl Hydrazyl Solution (DPPH, 100 µM): 22 mg of DPPH was accurately weighed and dissolved in 100ml of methanol. From this stock solution, 18ml was taken and diluted to 100ml using methanol to obtain 100µM DPPH solution.

Preparation of Test Solutions: 21mg each of the extracts was dissolved in distilled DMSO separately to obtain solutions of 21mg/ml concentrations. Each of these solutions was serially diluted separately to obtain lower concentrations.

Preparation of Standard Solutions: 10mg each of rutin were weighed separately and dissolved in 0.95ml of Dimethyl sulfoxide (DMSO) to get 10.5mg/ml concentrations. These solutions were serially diluted with DMSO to get lower concentrations.

Procedure: The assay was carried out in a 96 well microtitre plate. To 200µl of DPPH solution, 10µl of each of the test sample or the standard solution was added separately in wells of the microtitre plate. The final concentration of the test and standard solutions used were 1000, 500, 250, 125, 62.5, 31.25 and 15.625, 7.812µg/ml. The plates were incubated at 37 °C for 30 min and the absorbance of each solution was measured at 490 nm, using a microplate reader.

TABLE 2: RESULT

Samples	DPPH
3b	>1000
Standard	Rutin
	3.91 ± 0.10

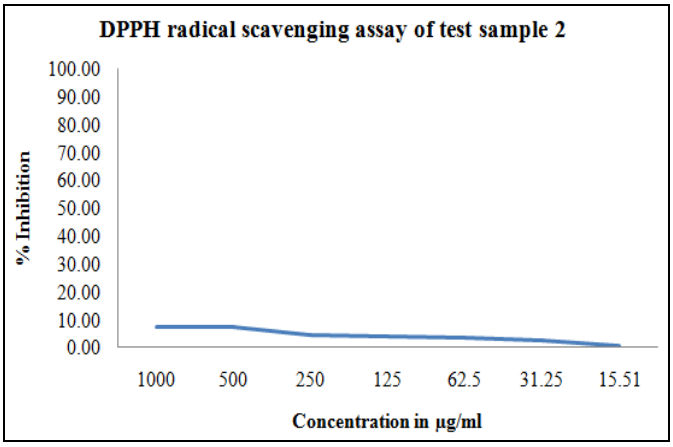


FIG. 1: GRAPHICAL REPRESENTATION

TABLE 3: RAW DATA

DPPH												
	Sample 2							% inhibition				
Conc.	**1**	**2**	**3**	**blk**	**1-blk**	**2-blk**	**3-blk**	**1**	**2**	**3**	**avg**	**std**
1000	0.647	0.647	0.645	0.055	0.592	0.592	0.59	7.06	7.21	7.52	7.27	0.23
500	0.642	0.642	0.648	0.053	0.589	0.589	0.595	7.54	7.68	6.74	7.32	0.51
250	0.659	0.66	0.66	0.052	0.607	0.608	0.608	4.71	4.70	4.70	4.70	0.00
125	0.664	0.659	0.664	0.051	0.613	0.608	0.613	3.77	4.70	3.92	4.13	0.50
62.5	0.667	0.664	0.664	0.051	0.616	0.613	0.613	3.30	3.92	3.92	3.71	0.36
31.25	0.672	0.671	0.67	0.051	0.621	0.62	0.619	2.51	2.82	2.98	2.77	0.24
15.51	0.686	0.681	0.684	0.05	0.636	0.631	0.634	0.16	1.10	0.63	0.63	0.47
control	0.686	0.687	0.687	0.049	0.637	0.638	0.638	0.00	0.00	0.00	0.00	0.00
						IC_{50} Value		>1000	>1000	>1000		

Experimental Section: All the IR spectra were recorded on Bruker alpha FTIR spectrophotometer, ^{1}H NMR spectra were measured on Bruker AV 400Mhz using $CDCl_3$ and DMSO as solvent. Chemical shifts are expressed in δ ppm. All the reactions were followed and checked by TLC (silica coated on alumina) using ethyl acetate-pet ether (1:1) and further purification was done by column chromatography using 60-120 mesh silica gel.

Tert-butyl 4-(1H-indole-6-carbonyl) piperazine-1-carboxylate (1): Indole-6-carbaxlic acid (10g, 0.062090 mol, 1.0 eq) was dissolved in dry tetrahydrofuran (150 cm^3). The solution was stirred for 10 min at ambient temperature. HATU (30.10g, 0.093135 mol, 1.5 eq) was charged followed by *N*, *N*-diisopropylethylamine (16.04 g, mol, 2.0 eq). The reaction mixture was stirred for 20 min at ambient temperature, and then it was cooled to 0°C. Boc-piperazine (11.56 g, mol, 1.0 eq) was added portion-wise to the mixture and stirring was continued for 3-4 hr at ambient temperature. The completion of the reaction was monitored by TLC. The reaction mass was diluted with ethyl acetate (250 cm^3) and washed with sodium bicarbonate solution (10%, 50 cm^3) and 1.5N HCl solution (50) followed by water (50 cm^3) and brine (50 cm^3). It was finally dried over sodium sulphate (10.0 g) and concentrated under reduced pressure. The crude mass was purified by column chromatography using silica gel and 20% ethyl acetate in hexane to get 9.0gm of tert-butyl 4-(1H-indole-6-carbonyl) piperazine-1-carboxylate.

LC-MS (ESI, Positive): m/z: $[M+H]^+$: 230.3; ^{1}H NMR: (400 MHz, DMSO-d_6): δ 11.29 (1H, s), 7.59-7.56 (1H, d, j=9.2 Hz), 7.47-7.45 (2H, m), 7.06-7.02 (1H, m), 6.47 (1H, s), 3.49-3.34 (8H, m), 1.41 (9H, s); Elemental analysis: Calculated (%) for $C_{18}H_{23}N_3O_3$: C 65.63, H 7.04, N 12.76; Found: C 65.55, H 7.05, N 12.75.

(1H-indol-6-yl) (piperazin-1-yl) methanone (2): Compound 1 (8 g, 0.02428 mol, 1.0 eq) was dissolved in dry methylene dichloride (80 cm^3) and the mixture was cooled to o to 5 °C. Trifluoroacetic acid (8.3 g, 0.07284 mol, 3.0 eq) was added slowly to the cooled mixture and stirred for 2-3 hr at ambient temperature. The completion of the reaction was confirmed by checking the TLC. The reaction mixture was concentrated under reduced pressure and the crude was dissolved in methylene dichloride (100mL). The organic layer was washed with brine (50 cm^3) and dried over sodium sulphate (10 g). The organic layer was concentrated under reduced vaccum. The obtained crude was purified by column chromatography using silica gel and methanol (3%) in methylene dichloride to get 5 g of purified (1H-indol-6-yl) (piperazin-1-yl) methanone LC-MS (ESI, Positive): m/z: $[M+H]^+$: 230.3; ^{1}H NMR: (400 MHz, DMSO-d_6): δ 11.31 (1H, s), 7.58-7.56 (1H, d, j=8.0 Hz), 7.46-7.45 (2H, m), 7.04-7.01 (1H, m), 6.47 (1H, s), 3.52 (4H, bs), 2.82 (4H, bs); Elemental analysis: Calculated for $C_{13}H_{15}N_3O$: C 68.10, H 6.59 N, 18.33; Found: C, 68.08 H 6.57, N 18.35.

General Procedure for 3a-J: Compound 2 (0.5 g, 0.00218 mol 1.0 eq) was dissolved in dry DMF (10 cm^3). The solution was stirred for 10 min at ambient temperature. Acid (1.0 eq) was added, followed by HATU (1.2 eq) and Diisopropyl ethylamine (2 eq).The reaction mass was heated to 45-50 °C for 1-2 hr, the completion of reaction was monitored by TLC. After completion of the reaction, the reaction mass was diluted with ethyl acetate the organic layer was washed with water followed by 10% sodium bicarbonate solution, brine solution dried over anhydrous sodium sulphate. The organic layer was concentrated under vacuum and the crude was purified by column chromatography.

4- ((1H-indol-3-yl) methyl) piperazin- 1- yl) (1-(4Chlorophenyl) cyclopropyl) methanone (3a): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 382.1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 1H), 7.59-7.57 (d, *J* = 8.0 Hz, 1H), 7.47-7.45 (m, 2H), 7.1-7.09 (m, 1H),7.06-7.03 (m, 2H) 6.83-6.81 (d, *J*= 8.8 hz, 1H), 5.37 (bs, 2H), 3.59-3.30 (m, 8H); Elemental analysis: Calculated (%) for $C_{20}H_{19}ClN_4O_2$: C 62.74, H 5.00, N 14.63; Found: C 62.72, H 4.98, N 14.61.

(3-chloro-1- benzothiophen-2-yl) [4-(1H-indol-6-ylcarbonyl)piperazin-1-yl] methanone (3b): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 423.08; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 8.13-8.11 (dd, *J* =6.8 Hz, 3.32 Hz 1H), 7.87-7.85 (dd, *J* =6.8 Hz, 3.32 Hz 1H), 7.61-7.55 (m, 3H),7.50 (s, 1H) 7.46-7.45 (d, *J*= 5.2 Hz, 1H), 7.08-7.06 (dd, *J* =8

Hz, 1.2 Hz 1H) 6.47 (s, 1H), 3.71-3.51 (m, 8H); IR (KBr) ν(cm^{-1}): 1718 (C=O), 760 (C-Cl) Elemental analysis: Calculated (%) for $C_{22}H_{18}ClN_3O_2S$: C 62.33, H 4.28, N 9.11 S 7.56; Found: C 62.32, H 4.26, N 9.12 S 7.53.

(2- chloropyridin- 3- yl) [4- (1H- indol- 6-yl carbonyl)piperazin-1-yl]methanone (3c): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 368.1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 8.49-8.47 (m, 1H), 7.94-7.91 (m, 1H), 7.59-7.46 (m, 4H),7.08-7.04 (dd, *J* =10.8 Hz, 2.0 Hz 1H) 6.48-6.47 (d, *J*= 5.6 Hz, 1H), 3.71-3.54 (m, 8H); Elemental analysis: Calculated (%) for $C_{19}H_{17}ClN_4O_2$: C 67.11, H 4.65, N 15.19; Found: C 67.10, H 4.64, N 15.18.

1- (4- (1H-indole-6-carbonyl) piperazin-1-yl)-4-(1H-indol-3-yl)butan-1-one (3d): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 414.21; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (bs, 2H), 7.50-7.46 (m, 3H), 7.33-7.31 (d, *J* =8 Hz, 2H), 7.10-6.93 (m, 5H), 3.50-3.30 (m, 8H) 2.35-2.30 (m, 2H) 2.27-2.23 (m, 2H), 1.90-1.84 (m, *J* =8 Hz, 2H) 6.47 (s, 1H), 3.71-3.51 (m, 8H); IR (KBr) ν(cm^{-1}): 1699 (C=O), 773 (C-Cl); 3338 (N-H); Elemental analysis: Calculated (%) for $C_{25}H_{26}N_4O_2$: C 72.44, H 6.32, N 13.52; Found: C 72.43, H 6.31, N 13.50.

(3- fluoro- 2- nitrophenyl) [4- (1H- indol- 6-yl carbonyl) piperazin-1-yl] methanone (3e): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 396.12; δ 11.29 (s, 1H), 7.83-7.80 (m, 1H), 7.71-7.66 (m, 1H), 7.59-7.57 (m, 1H) 7.49-7.44 (m, 3H), 7.08-7.06 (dd, *J* =8 Hz, 1.2 Hz 1H) 6.47 (s, 1H) 3.67-3.56 (m, 8H); Elemental analysis: Calculated (%) for $C_{20}H_{17}FN_4O_4$: C 60.60, H 4.32, N 14.13; Found: C 30.59, H 4.33, N 14.12.

(4- (1H-indole-6-carbonyl) piperazin-1-yl) (1-(4-chlorophenyl) cyclopropyl) methanone (3f): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 407.14; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 1H), 7.59-7.50 (m, 3H), 7.48-7.46 (m, 1H),7.45-7.43 (m, 2H) 7.19-7.17 (m, 2H), 7.07-7.05 (m, 1H) 6.47 (s, 1H) 3.59-3.31 (m, 8H) 1.35-1.32 (m, 2H) 1.18-1.15 (m, 2H); IR (KBr) ν(cm^{-1}): 1698 (C=O),779 (C-Cl); Elemental analysis: Calculated (%) for $C_{22}H_{23}ClN_3O_2$: C 67.73, H 5.44, N 10.30; Found: C, 67.71, H 5.42, N 10.31.

(3- hydroxy- 4- methoxyphenyl) [4- (1H- indol-6-ylcarbonyl) piperazin-1-yl] methanone (3g): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 379.15; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 1H), 7.61-7.59 (d, *J*=8.8 Hz, 1H), 7.56-7.50 (m, 4H),7.07-7.04 (dd, *J*=8.8 Hz, 1.6 Hz 1H) 6.86-6.84 (m, 1H), 6.47 (s, 1H) 3.87 (s, 3H) 3.55-3.50 (m, 8H); IR (KBr) ν(cm^{-1}): 1714 (C=O), 779 (C-Cl); Elemental analysis: Calculated (%) for $C_{21}H_{21}N_3O_4$: C 66.48, H 5.58, N 11.08; Found: C 66.46, H 5.57, N 11.10.

(4- (1H-indole- 6-carbonyl) piperazin- 1- yl) (2-tert-butylpyrimidin -5 -yl) methanone (3h): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 391.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 8.92 (s, 2H), 7.59-7.57 (d, 1H),7.50-7.45 (m, 2H) 7.08-7.05 (dd, J=8.0 Hz, 1.2 Hz 1H),6.47 (s, 1H) 3.59-3.31 (m, 8H) 1.35 (s, 9H) Elemental analysis: Calculated (%) for $C_{22}H_{25}N_5O_2$: C 67.50, H 6.44, N 17.89; Found: C 67.51, H 6.45, N 17.87.

(4- (1H-indole- 6- carbonyl) piperazin- 1- yl) (2-amino-5-bromophenyl) methanone (3i): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 426.07; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 7.60-7.58 (d, *J* = 8.0 Hz, 1H), 7.49-7.47 (m, 2H), 7.12-7.10 (m, 1H), 7.08-7.06 (m, 2H) 6.85-6.83 (d, *J*= 8.8 hz, 1H), 5.40 (bs, 2H), 3.60-3.35 (m, 8H); IR (KBr) ν(cm^{-1}): 1710 (C=O); Elemental analysis: Calculated (%) for $C_{20}H_{19}BrN_4O_2$: C 56.22, H 4.48, N 13.11; Found: C 56.20, H 4.50 N 13.13.

(4- chlorophenyl) [4- (1H-indol- 6- ylcarbonyl) piperazin-1-yl] methanone (3j): LC-MS (ESI, Positive): m/z: $[M+H]^+$: 367.11; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 7.59-7.57 (d, *J*=8.0 Hz 1H),7.53-7.41 (m, 4H) 7.36-7.34 (m, 2H), 7.06-7.04 (dd, J=8.8 Hz, 1.6 Hz 1H) 6.47(s, 1H) 3.58-3.50 (m, 8H) IR (KBr) ν(cm^{-1}): 779 (C-Cl) Elemental analysis: Calculated (%) for $C_{20}H_{18}ClN_3O_2$: C 65.31, H 4.93, N 11.42; Found: C 65.32, H 4.95, N 11.41.

CONCLUSION: The research work is focused on the efficient synthesis of Indole piperazine derivatives. In addition, some of the tested compounds have exhibited significant antimicrobial and antioxidant activity. The publication of these facts would be of significant use for the scientific community. Some selected Indole piperazine derivatives have been tested for antimicrobial and

in vitro antioxidant activity. Three compounds 3a, 3f and 3h have shown significant antimicrobial and one compound 3b have shown *in vitro* antioxidant activity.

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