Heterocyclic Letters
Vol. 15| No.4|731-744|August-October|2025
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS, ANTIMICROBIAL AND ANTIOXIDANT SCREENING OF SOME NOVEL INDOLE-GUANIDINE SCAFFOLD HYBIDIZATION MOIETY

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ABSTRACT

Claisen-Schmidt condensation of synthon 5-substituted 2-phenyl-1*H*-indole-3-carbaldehydes (**1a-c**) with acetophenone gave precursor 1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-ones (**2a-c**). These chalcones on cyclization with 1-(4-cyanophenyl) guanidine yielded the target molecules 4-(4-(2-phenyl-1*H*-indol-3-yl) pyrimidin-2-ylamino) benzonitriles (**3a-c**) in good yield. The structures of these previously unknown compounds were confirmed by their spectral studies and elemental analysis. Compounds **(3a-c)** have been screened for their antimicrobial and antioxidant activities. Compound **3b** and **3c** were found to be active against ***S. Aureus, P. Aerujinosa*** and ***E. Coli***. Whereas, compounds **3a** and **3b** showed good activity against C**.** ***Glabreta***. Compound **3b** exhibited promising antibacterial and antifungal activity. Compound **3b** displayed good radical scavenging, ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) and Metal chelating ability which is comparable with standards. Rest of the compounds exhibited moderate activity.

KEY WORDS: Indole analogues, pyrimidine, Benzonitrile, Guanidine, antimicrobial, antioxidant

INTRODUCTION:

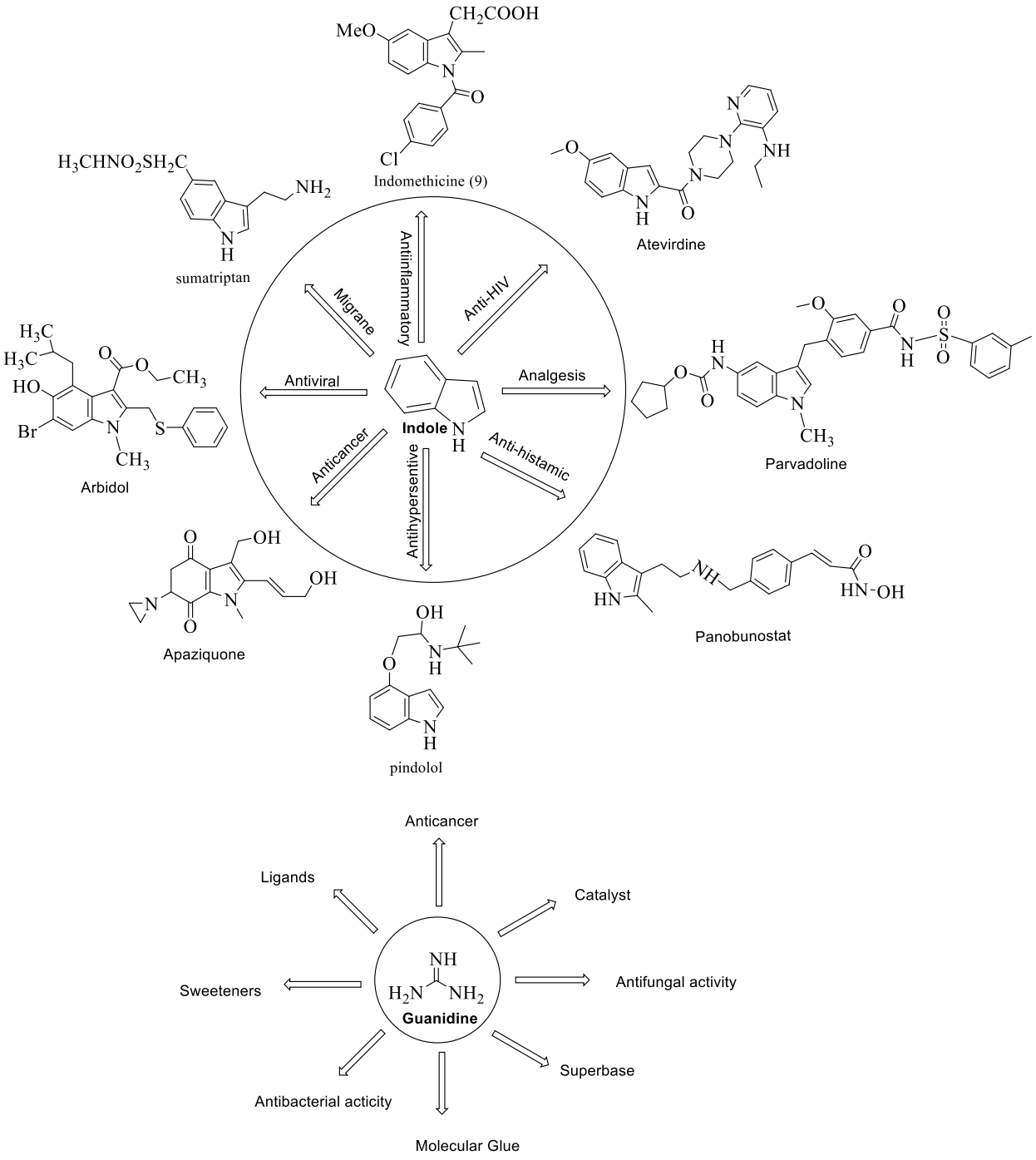
Commonly diseases caused by micro-organisms, are leading to the health hazardous to humans, despite vigorous research in drug chemistry. Antimicrobial resistance refers to micro-organism that has developed the ability to inactivate, exclude or block the inhibitory or lethal mechanism of the antimicrobial agents [i]. In addition, antioxidant compounds in food play vital role as health-protein factor. Scientific evidence advices that antioxidant reduces the risk for chronic diseases including cancer and heart diseases [ii]. The key to substance-oriented drugs design strategy is to select molecular fragment to develop pharmacologically attractive molecules.

The Indole moiety is an important pharmaceutical scaffold with a wide range of pharmaceutical field, including anticancer, anti-histaminic, antimicrobial activities, plant growth regulator, anti-HIV, anti-convulsant, anti-inflammatory activities [iii-ix]. Guanidine an important pharmacodynamics group that exist in the structures of various novel drugs and has important biological activities, such as anticancer, anti-inflammatory, inhibitor of Na/H+ exchangers and

epithelial sodium channel blockers, antidiabetic, antiviral and antifungal activities[xviii]. Indole and guanidine are well known molecular fragments that provide a variety of biological activities, among which anticancer activity has been widely, studied [xix].

The pyrimidine is the parent nucleus of a large group of heterocyclic compounds, which have attracted the attention for a long time. Pyrimidine ring system has wide occurrence in natural products [xx] like nucleic acids, nucleotides, cytosine, uracil, thiamine and vitamin B_1. It is also found in many synthetic compounds such as barbiturates and the anti-HIV drug zidovudine [xxi]. It has been reported in the literature that the molecule containing nitrile function are associated with wide applications in perfumes, pharmaceuticals, pesticides, dyes, functional materials, and organic conductors [xxii-xxvi]. So, prompted us to construct several analogues of indole containing these heterocycles so as to get biologically more potent molecule.

Fig 1: Motivation for synthesis of Biological active Molecules



EXPERIMENTAL SECTION:

All the reagents were acquired commercially and used by further purification. Melting points were determined by an open capillary method and are uncorrected. Purity of the compounds was checked by TLC using silica gel-G coated aluminum plates (Merck) and spots

were visualized by exposing the dry plates in iodine vapors. The IR (KBr) spectra were recorded with a Perkin-Elmer Spectrum on FT-IR spectrometer. The ^{1}H NMR (DMSO) spectra recorded with Marcy Plus (Varian 500 MHz) and the chemical shifts were expressed in ppm (δ scale) and ^{13}C NMR (500 MHz, DMSO) spectra recorded with on Bruker NMR. Mass spectra were recorded with a ILS-CHU-C-41-VBV4 MS mass spectrometer. Elemental analysis was carried out using Flash EA 1112 series elemental analyzer.

GENERAL PROCEDURE FOR THE SYNTHESIS OF DIFFERENTLY SUBSTITUTED CHALCONES (2a-c).

The equimolar mixture of substituted aromatic aldehydes (10 mmol) and substituted aromatic ketones (10 mmol) was dissolved in a minimum amount of ethanol (50 ml) to this mixture NaOH (20%, 10ml)was added slowly and the reaction mixture was stirred at room temperature for 10 hrs using magnetic stirrer. The completion of the reaction was monitored by TLC. Then the reaction mixture was poured slowly into ice-cold water with constant stirring, the product was precipitated out, was filtered, washed with water and dried. The crude product was purified from ethyl alcohol to yield pure chalcones (**2a-c**).

GENERAL PROCEDURE FOR THE SYNTHESIS OF 4-((4-(2-PHENYL-1*H*-INDOLE-3-YL) PYRIMIDIN-2-YL) AMINO) BENZONITRILES (3a-c):

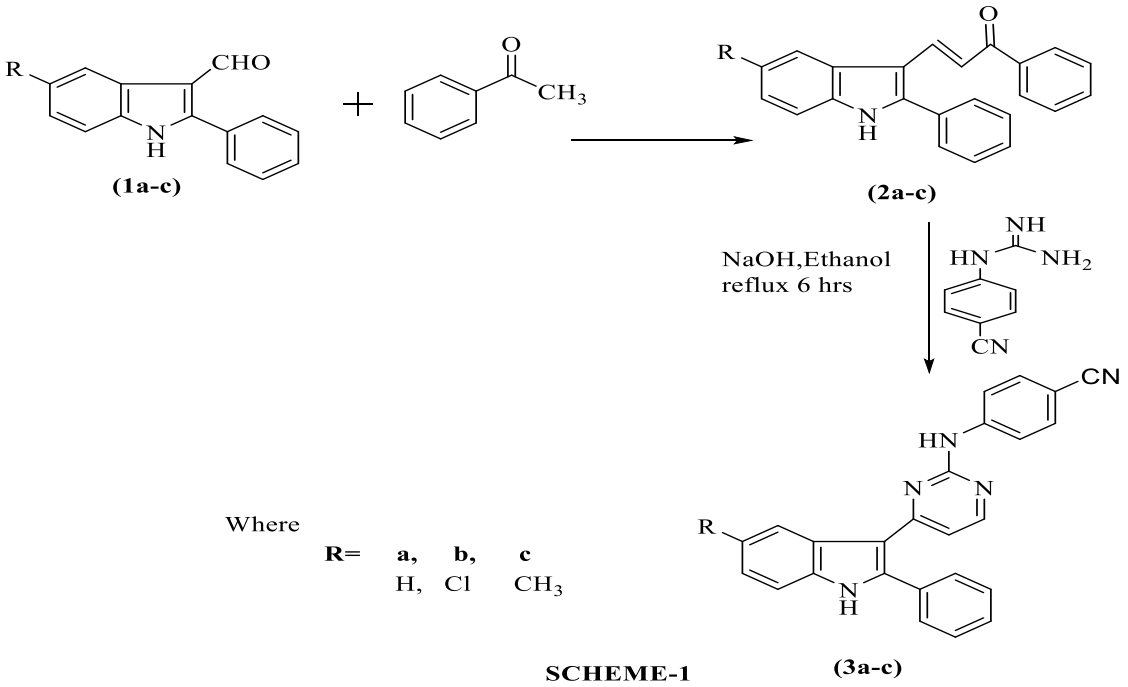
A mixture of chalcone (3 mmol), 1-(4-cyanophenyl) guanidine (3.6 mmol) and sodium hydroxide (4.5 mmol) were refluxed in ethanol at 75-80 ^{0}C for 6 hrs, the completion of the reaction was monitored by TLC. Then, the reaction mixture was cooled and poured slowly into ice-cold water with stirring .The precipitate obtained was filtered, washed with water and dried. The crude product was recrystallized from ethyl alcohol to afford pure 4-((4-(2-phenyl-1*H*-indole-3-yl) pyrimidin-2-yl) amino) benzonitriles (**3a-c**).

(3a): M.P.:**288-289** °C, IR (KBr) (In cm^{-1}): **3214** (indole-NH), **3155** (pyrimidine-NH), **2210** (CN), **1550** (C=N), ^{1}H NMR (δ ppm): **11.20** (s, 1H, indole NH), **8.20** (s, 1H, pyrimidine-NH), **6.50-7.90** (m, 15H, Ar-H), ^{13}C NMR (500 MHz, DMSO): δ = 169.8, 165.4, 161.5, 158.8, 133.9, 134.9, 132.7, 132.1, 129.9, 128.8, 128.4, 128.3, 128.2, 128.1, 127.8, 126.7, 123.3, 122.1, 119.8, 114.1, 113.8, 113.1, 112.1; MS (EI): *m/z* Mass (m/z) **209** (M+).Yield (%)**75**. Calcd. % $C_{25}H_{17}N_5$: C, 77.50; H, 4.42; N, 18.08 Found: C, 77.52; H, 4.43; N, 18.05.

(3b): M.P.: **285-286** °C, IR (KBr) (In cm^{-1}) **3262** (indole-NH), **3192** (pyrimidine-NH), **2209** (CN), **1550** (C=N), ^{1}H NMR (δ ppm): **11.50** (s, 1H, indole NH), **8.1** (s, 1H, pyrimidine-NH), **7.00-8.00** (m, 14H, Ar-H),^{13}C NMR (500 MHz, DMSO): δ = 169.8, 165.4, 161.5, 158.8, 138.3, 134.1, 133.3, 133.1, 132.8, 132.7, 132.6, 129.3, 129.1, 128.7, 128.3, 128.1, 127.5, 127.3, 127.1, 126.9, 121.6, 119.0, 113.3, 113.1, 112.6, 112.3; Mass (m/z): **267**(M+), **269**(M+2).Yield (%) **63**.

Calcd. % $C_{25}H_{16}N_5Cl$: C, 71.17; H, 3.82; N, 16.60 Found: C, 71.18; H, 3.81; N, 16.62.

(3c): M.P.:**240-241** °C, IR (KBr) (In cm^{-1}): **3210** (indole-NH), **3185** (pyrimidine-NH), **2200** (CN), **1547** (C=N), ^{1}H NMR (δ ppm):**11.52** (s, 1H, indole NH), **8.15** (s, 1H, pyrimidine-NH), **6.90-7.99** (m,14H, Ar-H), **2.1** (s, 3H, CH_3),^{13}C NMR (500 MHz, DMSO): δ = 169.7, 165.3, 161.4, 158.7, 138.1, 134.2, 133.2, 133.4, 132.6, 132.5, 132.4, 129.3, 129.1, 128.7, 128.5, 128.2, 127.4, 127.1, 126.5, 121.5, 119.1, 113.5, 113.3, 113.1, 112.6, 112.3, 24.5; Mass (m/z): **291**(M+). Yield (%) **67**. Calcd. % $C_{26}H_{19}N_5$: C, 77.79; H, 4.77; N, 17.44 Found: C, 77.80; H, 4.78; N, 17.43.



SCHEME-1

ANTIMICROBIAL ACTIVITY

Compounds (**3a-c**) were evaluated for their antibacterial activity against *Staphylococcus Aureus* (ATCC-29513), *Pseudomonas Aeruginosa* (MTCC-1688) and *Escherichia Coli* (MTCC-723) and antifungal screening against, *Candida Glabreta* (MTCC-3814), *Candida Haemulonii* (MTCC-1688), *Candida Topicallis* (MTCC-1406) by cup-plate method at concentration 1000, 750 and 500µg/ml following reported procedure [xxvii]. The zone of inhibition (in mm) were differentiated with the standards streptomycin and flucanazole for antibacterial and antifungal activity, correspondingly. The results are reported in **Table-1** and **2**.

The investigation of antibacterial screening revealed that compound **3b** showed good activity against *S. Aureus, P. Aerujinosa* and *E. Coli.* Compound **3a** showed good activity against fungi, *C. Glabreta* and *C. Topicallis*. All other compounds showed moderate activity.

Table 1: *In vitro* antibacterial activities of compounds 3a-c

Comp No	Antibacterial activity (zone of inhibition in mm)*								
	S. Aureus			*P. Aeruginosa*			*E. Coli*		
	1000	750	500	1000	750	500	1000	750	500
3a	14	13	12	10	05	05	14	13	11
3b	13	12	12	11	04	05	08	08	05
3c	05	05	04	02	02	04	09	06	06
Std	15	14	13	16	15	14	16	14	13

Zone of inhibition in millimeter,
Std= Streptomycin,
*Concentration in micro gm/ml

Table 2: *In vitro* antifungal activity of compounds 3a-c

Comp No	Antifungal activity (zone of inhibition in mm)*								
	C. Glabreta			*C. Haemulonii*			*C. Topicallis*		
	1000	750	500	1000	750	500	1000	750	500
3a	14	12	12	10	10	08	13	12	12
3b	03	05	03	10	10	05	06	06	08
3c	13	13	11	08	08	02	02	02	03
Std	15	14	13	15	15	14	14	14	13

Zone of inhibition measured in millimeter,
Std= Flucanazole,
*Concentration in micro gm/ml

ANTIOXIDANT ACTIVITIES

I) 1, 1-DIPHENYL-2-PICRYL HYDRAZYL (DPPH) RADICAL SCAVENGING ACTIVITY (RSA)

Free radicals are atomic or molecular species with unpaired electron that are highly reactive. They take part in chemical reactions, make a difference in many chemical processes. The RSA of synthesized compounds (**3a-c**) was carried out using Hatano's method [xxviii] and the outcome are differentiated with the standards 2-tert-butyl-4-methoxy phenol (butylated hydroxyl anisole, BHA), 2-(1, 1-dimethylethyl)-1, 4-benzenediol (tertiary butylated hydroquinone, TBHQ) and Ascorbic acid (AA).

The analysis of results (Figs. 2) indicated that, compounds **3b** and **3c** displayed good radical scavenging activity at conc. of 50 µg/ml, compound **3a** displayed good radical scavenging ability at conc. of 75 µg/ml. whereas compounds **3a** and **3c** displayed good radical scavenging activity at conc. 100 µg/ml.

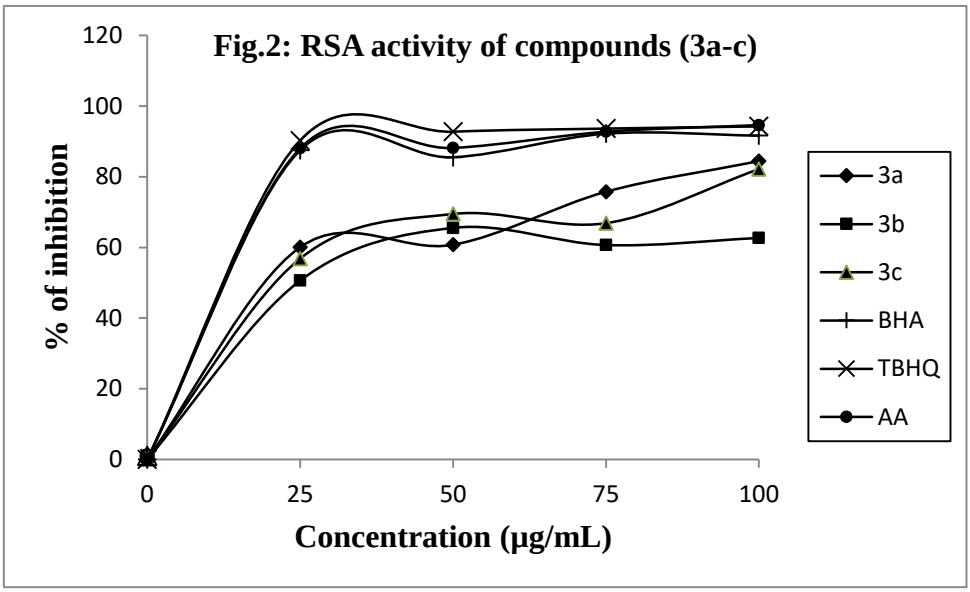
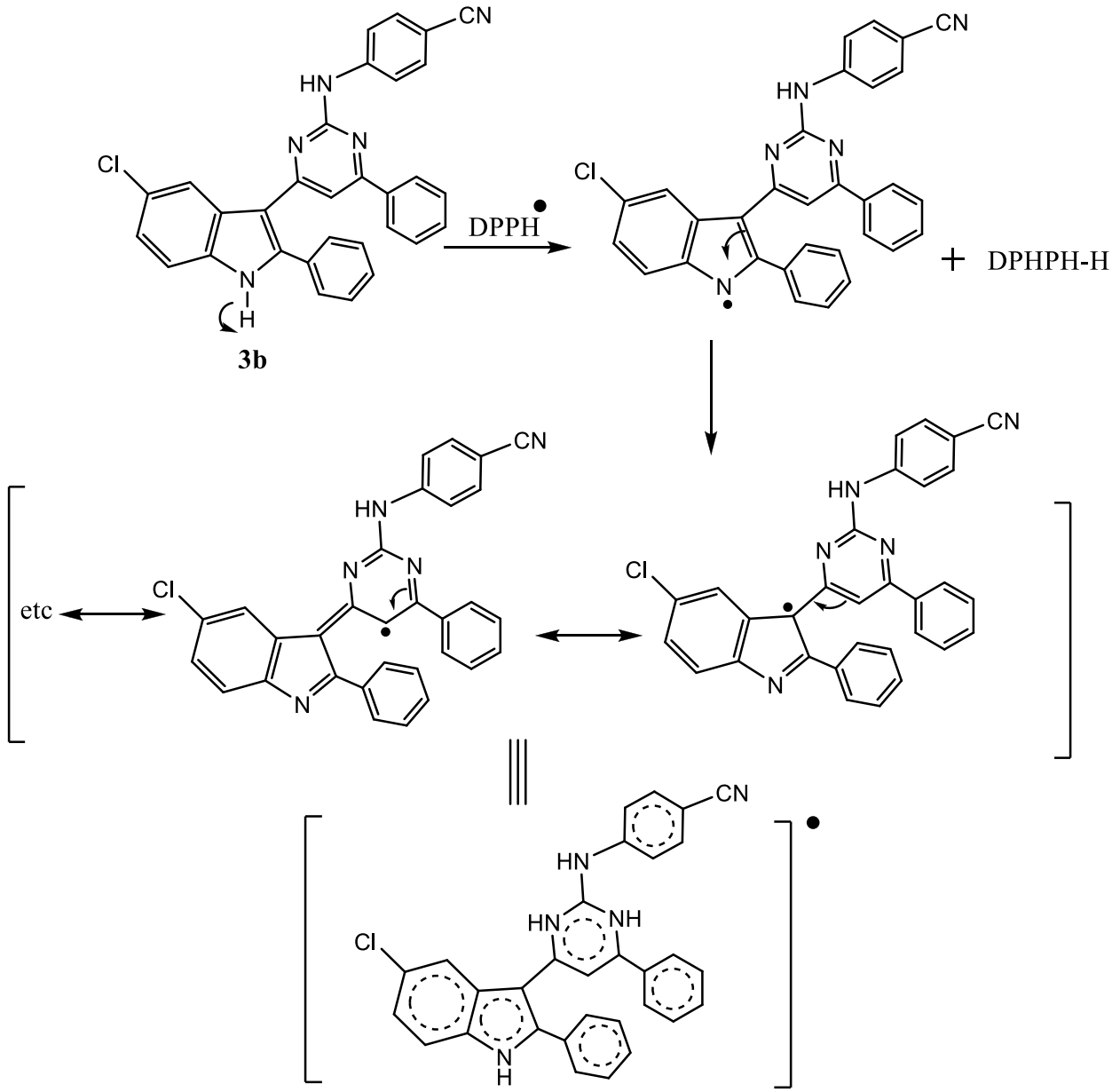


Fig.2: RSA activity of compounds (3a-c)
% of inhibition
120
100
80
60
40
20
0
0
25
50
75
100
Concentration (µg/mL)
3a
3b
3c
BHA
TBHQ
AA



SCHEME-2

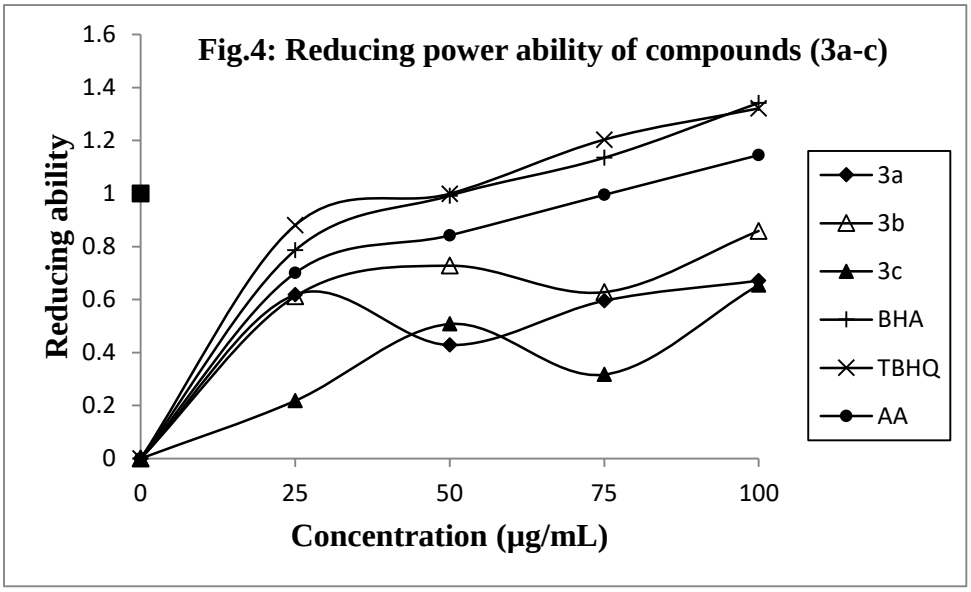
Fig 3: Probable Mechanism for H-donation to DPPH radical and stabilization of free radical formed from Indole systems.

II) FERRIC IONS (Fe^{+3}) REDUCING ANTIOXIDANT POWER (FRAP)

The ferric ion (Fe^{3+}) is the relatively biologically latent form of iron. However, it can be reduced to an active ferrous (Fe^{2+}), depending on condition, particularly pH [xxix] and oxidized back through Fenton type reaction with production of hydroxyl radical or Haber-Weiss reaction with superoxide anions. Reducing power is to measure the reductive ability of an antioxidant and it is evaluated by the transformation of Fe^{3+} to Fe^{2+} by transfer of an electron in the presence of test compounds. Therefore, the Fe^{2+} can be monitored by measuring the formation of Perl's Prussian blue at 700 nm.

The FRAP of synthesized compounds (**3a-c**) was determined at four different concentrations (25, 50, 75 and 100 µg/mL) at pH 6.6 by Oyaizu method [xxx] using BHA, TBHQ and AA as standards. The higher absorbance of the reaction mixture show greater the reducing power of the test compounds. The analysis of results (Figs. 4) suggested that, compounds **3a** exhibited good reducing activity at 25 µg/ml concentration, whereas compound **3b** showed reducing power at 25, 50 and 100 µg/ml concentration.

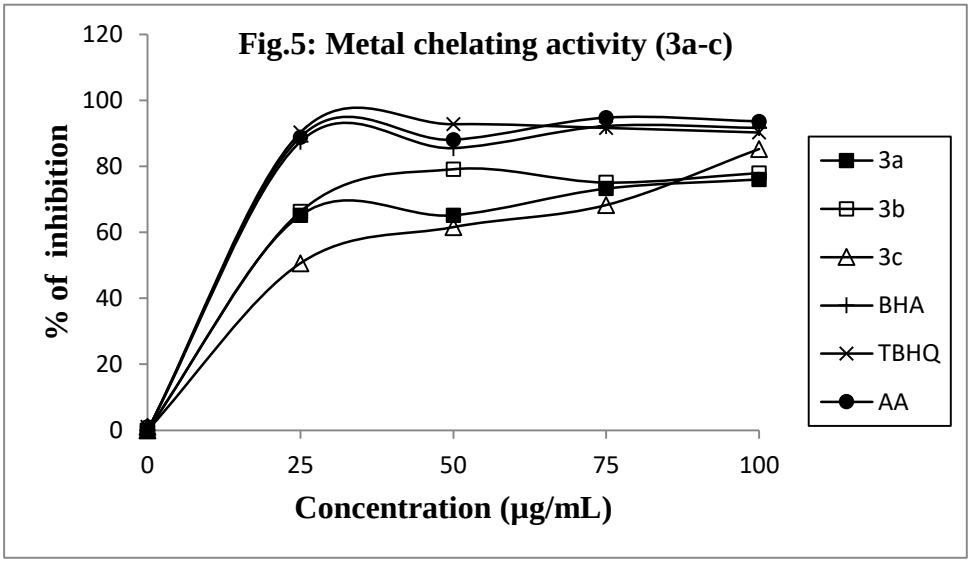
III)



FERROUS IONS (Fe^{+2}) METAL CHELATING ACTIVITY

The chelating effect of ferrous ion (Fe^{2+}) towards the test compounds (**3a-c**) and standards was determined by following Dinis method [xxxi] and the result were compared with standards BHA, TBHQ and AA. Ferrozine can make complex with ferrous ion. In the presence of chelating agents, complex (red colored) formation is interrupted and as a result, the red color of the complex is decreased. Thus, the chelating effect of the coexisting chelator can be determined by measuring the rate of color reduction.

The analysis of results (Figs. 5) indicated that, compounds **3a** showed good metal chelating activity at 25 µg/ml concentration, whereas compound **3b** exhibited promising metal chelating activity at 25, 50 and 75 µg/ml concentrations. Compound **3b** displayed good metal chelating activity at 75 µg/ml concentration. Compound **3c** displayed good metal chelating activity at 100 µg/ml concentration.



RESULT AND DISCUSSION

Starting material was synthesized to design and develop hybrid indole-guanidine to synergize two pharmacologically attractive heterocyclic systems in one molecule. The starting material 5-substituted 2-phenylindol-3-carboxyaldehydes (**1)** were prepared according to the reported procedure [xxxii]. The chalcones (**2**) were synthesized by Claisen-Schmidt condensation between equimolar quantities of acetophenone and indole aldehydes. Further, the chalcones [xxxiii] **(2)** on reaction with 1-(4-cyano phenyl) guanidine was refluxed for 6 hrs in ethanol. The completion of reaction was monitored by TLC and product was isolated4-((4-(2-phenyl-1*H*-indole-3-yl) pyrimidin-2-yl) amino) benzonitriles **(3).**

CONCLUSION

From the results of antimicrobial and antioxidant study revealed that, it could be assumed that, the compounds having chloro and methyl substitution exhibited maximum activity. The electronegative nature of the chloro group may be responsible to inhibit the growth of the microbes.

ACKNOWLEDGEMENTS

The authors are thankful to the Chairman, Department of Chemistry, Gulbarga University, Kalaburagi for providing laboratory facilities and Chairman, Department of Botany, Gulbarga University, Kalaburagi for providing facilities to carry out antimicrobial activity. We are also thankful to Director, SAIF, Punjab University, Chandigarh and Sophisticated Test and Instrumentation Centre (STIC), Cochin University of Science and Technology, Cochin for providing spectral data.

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Received on July 14, 2025.