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Synthesis characterization and anti-bacterial activity of novel chalcone derivatives of indole

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ABSTRACT

*Biologically active novel chalcone derivatives of1-(4-(((1H-indol-3-yl)methylene)amino)phenyl)-3-aryl prop-2-en-1-one (**6a-o**) have been synthesised by Claisen-Schmidt condensation reaction.A simple condensation reaction of Schiff's Base i.e., (E)-1-(4-(((1H-indol-3-yl)methylene)amino)phenyl)ethanone**(4)**witharyl aldehydes **(5a-o)**under basic conditions have been carried out. The synthesized chalcone derivatives have been analyzed by IR,[1]H-NMR, Mass, andelemental analysis. All the newly synthesized chalcone derivatives were screened for anti-bacterial activity against gram positive bacteria (S.aureus, B. subtilis) and gram negative bacteria (E. coli, K. pneumonia). It was found that some of thesechalcone derivatives showing the moderate activity.*

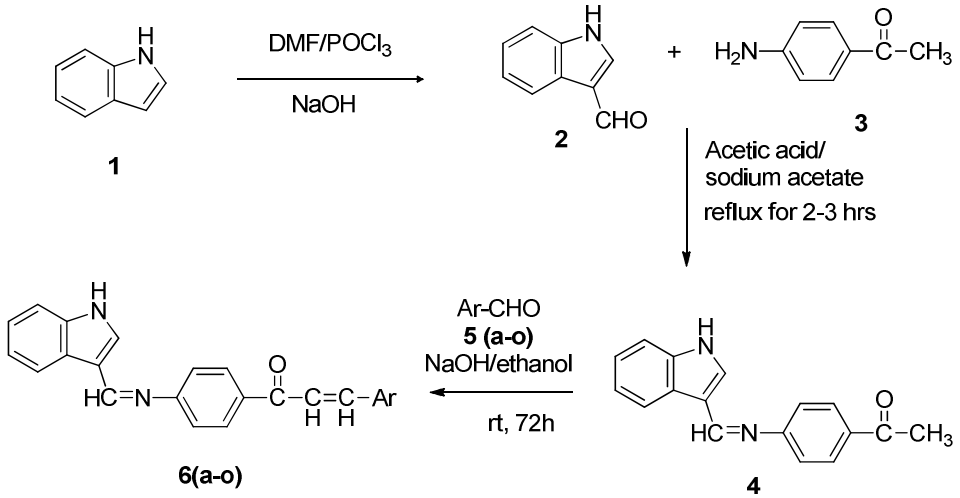
Key words: Schiff's Base, Indole-3-carbaldehyde, 4-aminophenyl ethanone, chalcones, Anti-bacterial activity.

INTRODUCTION

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones with heterocyclic compounds. Compounds havingchalcone backbone have been found to possess various biological activities [1] such as antimicrobial [2], anti-inflammatory [3], antioxidant, anticancer [4], analgesic [5], platelet antiaggregation [6], antiulcerative [7], antimalarial [8], antiviral [9], antileishmanial [10], antitubercular [11],antihyperglycemic [12] activities.

Chemistry:
In the present study the chalcones are linked with indoles to be better pharmacophore for anti-microbial activity. 1*H*-indole-3-Carbaldehyde **2** on reaction with 1-(4-aminophenyl) ethanone**3** in Acetic acid/sodium acetate yielded 1-(4-(((1*H*-indol-3-yl)methylene)amino)phenyl) ethanone**4**. This on further reaction with aryl aldehydes **5(a-o)** produced 1-(4-(((1*H*-indol-3-yl)methylene)amino) phenyl)-3-ary prop-2-en-1-one**6(a-o)**. The synthetic pathway for the preparation of chalcone linked indoles is shown in Scheme-I.

SCHEME-I: Synthesis of Chalcone Derivatives of Indole



***Ar**=6a) 3-hydroxyphenyl, 6b) 3-methoxyphenyl, 6c) 3,4-dihydroxyphenyl, 6d) 3-OH-4-OCH_3phenyl,6e) 4-methylphenyl, 6f) 2-Chlorophenyl, 6g) p-isopropylphenyl, 6h) Propionaldehyde, 6i) 2-furaldehyde, 6j) 2,6-dichlorophenyl, 6k) 2,4- dichlorophenyl, 6l) isobutyraldehyde, 6m) butyraldehyde, 6n) 2,4- dimethoxyphenyl, 6o) 3-Bromophenyl,*

RESULTS AND DISCUSSION

All the compounds **6(a-o)** were solid in state, stable to moisture and temperature. The structures were established by IR, ^{1}H-NMR and Mass spectrometry.

IR, ^{1}H-NMR,Mass spectral and Elemental analysis data of 6(a-o):

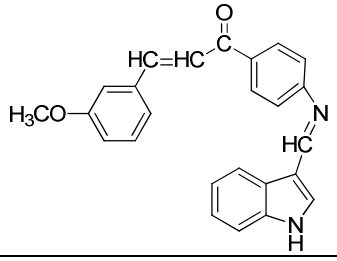
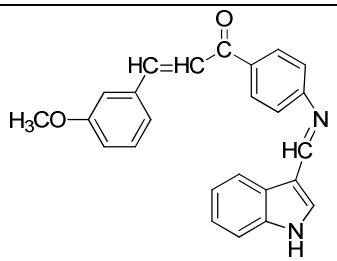
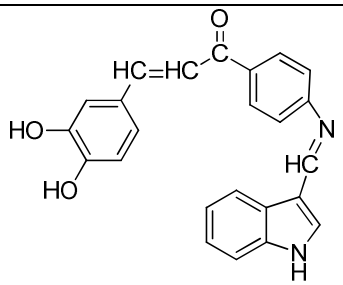
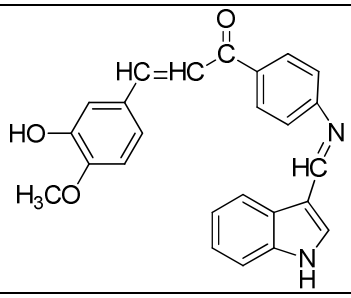
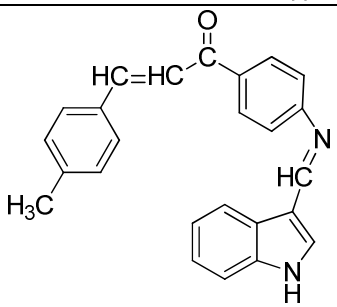
(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one(6a):
IR (KBr, cm^{-1}): 3028 (Ar-CH Str), 2971 (Aliphatic C-H Str), 1740 (C=O), 1593 (C=N Str), 1522 (Ar-C=C Str); ^{1}H-NMR (300MHz, DMSO)δ: 2.30-2.50 (s, 3H), 7.10-7.16 (m, 3H),7.26-7.28 (m, 4H), 7.34-7.38 (m, 3H),7.40-7.46 (m, 4H), 9.90 (s, 1H),10.1-10 (s, 1H); MS (*m/z*): 367 $(M+H)^+$. Elemental Analysis:Calcd. for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.65; H, 4.97; N, 7.64.

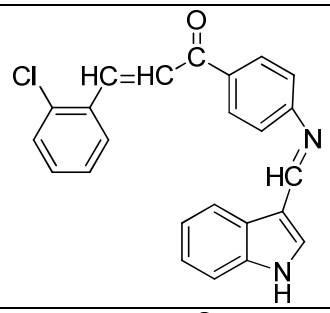
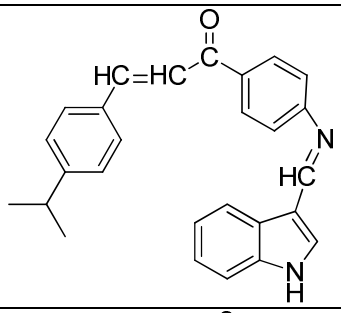
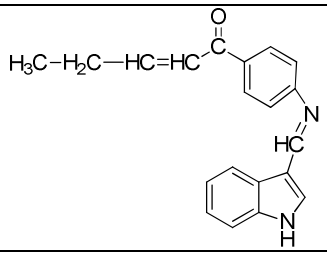
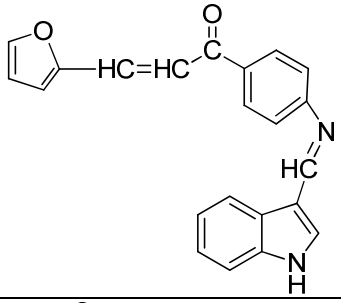
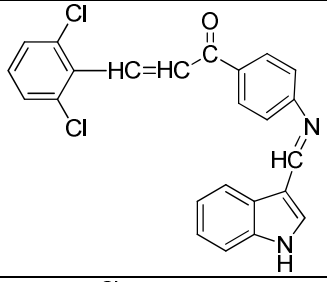
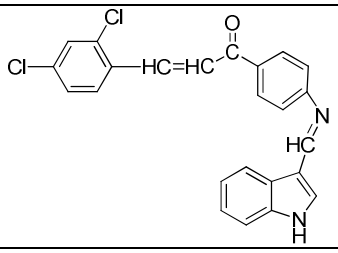
(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(3-methoxyphenyl)prop-2-en-1-one(6b):
IR (KBr, cm^{-1}): 3023 (Ar-CH Str), 2970 (Aliphatic C-H Str), 1741 (C=O), 1592 (C=N Str); ^{1}H-NMR (300 MHz, DMSO)δ:2.10-2.30 (s, 3H), 3.35-3.50 (s, 3H, -OCH_3), 6.0(m, 1H), 6.35-6.42(m, 2H), 7.10-7.16 (m, 1H),7.26-7.35 (m, 3H),8.54-8.76 (m, 4H), 8.80-8.91 (d,2H), 10 (s, 1H); MS (*m/z*): 381 $(M+H)^+$. Elemental Analysis:Calcd. for $C_{25}H_{20}N_2O_2$: C, 78.93; H, 5.30; N, 7.36. Found: C, 78.95; H, 5.28; N, 7.34.

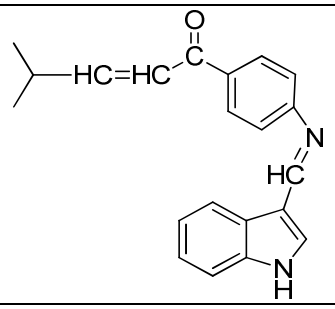
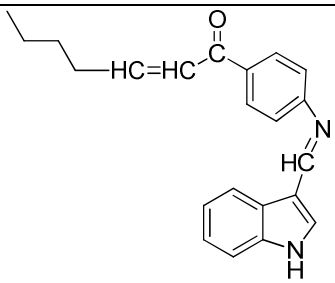
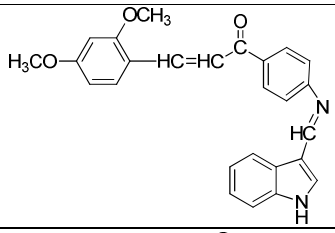
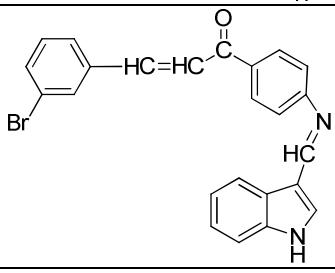
(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(3,4-dihydroxyphenyl)prop-2-en-1-one 6c): IR (KBr, cm^{-1}): 2909 (Ar-CH Str), 2837 (Aliphatic C-H Str), 1720 (C=O), 1592 (C=N Str), 1524 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ:2.10-2.30 (s, 3H), 6.0-6.12(m, 2H),6.85-6.91 (m, 2H),7.15-7.26(m, 4H),8.45-8.54 (m, 3H),8.80-8.91 (m,1H),9.45-9.87 (s, 2H),10.31-10.35 (s, 1H);MS (*m/z*): 383 $(M+H)^+$.Elemental Analysis:Calcd. for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33. Found: C, 75.32; H, 4.76 N, 7.35.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(3-hydroxy-4-methoxyphenyl)prop-2-en-1-one (6d): IR (KBr, cm^{-1}): 2909 (Ar-CH Str), 1720 (C=O), 1592 (C=N Str), 1524 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ:2.85-2.90 (s, 2H), 6.85-6.91 (m, 2H),6.63-7.25 (m, 4H),7.45-7.84 (m, 7H),7.90-8.35 (m,4H),9.98-10.1 (s, 1H); MS (*m/z*): 397 $(M+H)^+$. ElementaiAnalysis:Calcd. for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07. Found: C, 75.77; H, 5.10; N, 7.04.

Table-1: Physical-Chemical data of 1-(4-(((1*H*-indol-3-yl)methylene)amino)phenyl)-3-argioprop-2-en-1-ones6(a-o)

S.No.	Compound	Molecular formula/MW	Reaction time	Mp(°C)	Yield(%)
6a		$C_{24}H_{18}N_2O_2$ (*m/z*)366	24h	208-210°C	90%
6b		$C_{25}H_{20}N_2O_2$ (*m/z*)380	24h	230°C	85%
6c.		$C_{24}H_{18}N_2O_3$ (*m/z*)382	36h	215-220°C	85%
6d.		$C_{25}H_{20}N_2O_3$ (*m/z*)396	24h	250°C	88%
6e.		$C_{25}H_{20}N_2O$ (*m/z*)364	12h	260°C	85%

6f.		$C_{24}H_{17}N_2OCl$ (*m/z*)383	36h	270°C	90%
6g.		$C_{27}H_{24}N_2O$ (*m/z*)392	20h	280-290°C	86%
6h.		$C_{20}H_{18}N_2O$ (*m/z*)302	15h	250°C	89%
6i.		$C_{22}H_{16}N_2O_2$ (*m/z*)340	20h	240-250°C	91%
6j.		$C_{24}H_{16}N_2OCl_2$ (*m/z*) 419	72h	280-290°C	88%
6k.		$C_{24}H_{16}N_2OCl_2$ (*m/z*) 419	72h	260°C	85%

6l.		$C_{21}H_{20}N_2O$ (*m/z*) 316	18h	220°C	89%
6m.		$C_{21}H_{20}N_2O$ (*m/z*) 316	**16h**	**210-220°C**	86%
6n.		$C_{26}H_{22}N_2O_3$ (*m/z*) 409	24h	290-300°C	92%
6o.		$C_{24}H_{17}N_2BrO$ (*m/z*) 429	36h	288-290°C	87%

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(p-tolyl)prop-2-en-1-one(6e):
IR (KBr, cm^{-1}): 3031 (Ar-CH Str), 2910 (Aliphatic C-H Str), 1739 (C=O), 1563 (C=N Str); ^{1}H-NMR (300 MHz, DMSO) δ:2.85-2.90 (s, 2H), 3.25-3.61 (s, 3H),5.88-6.90 (m, 3H),7.10-8.65 (m, 10H),8.90-9.35 (m,1H),10.08-10.54 (s, 1H);MS (*m/z*): 365 $(M+H)^+$. Elemental Analysis:Calcd. for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.41; H, 5.55; N, 7.71.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(2-chlorophenyl)prop-2-en-1-one (6f):
IR (KBr, cm^{-1}): 3025 (Ar-CH Str), 2971 (Aliphatic C-H Str), 1741 (C=O), 1591 (C=N Str), 1524 (Ar-C=C Str); ^{1}H-NMR(300 MHz, DMSO) δ: 2.0-2.10 (s, 1H), 2.45-2.60(m, 3H), 7.40-7.57 (m, 10H),7.65-8.0(m,3H);MS (*m/z*): 384 $(M+H)^+$.Elemental Analysis:Calcd. for $C_{24}H_{17}ClN_2O$: C, 74.90; H, 4.45; N, 7.28. Found: C, 74.92; H, 4.43; N, 7.30.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(4-isopropylphenyl)prop-2-en-1-one(6g): IR (KBr, cm^{-1}): 3058 (Ar-CH Str), 2985 (Aliphatic C-H Str), 1740 (C=O), 1590 (C=N Str), 1481 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ: 1.90-2.0(s, 1H), 2.24-2.41(s, 3H),2.90-3.82 (m, 10H),4.25-4.43 (s, 1H),6.0-6.90(m, 2H),7.10-7.81(m, 5H),7.93-8.40 (m, 2H),8.45-8.84 (d,*J*=8.6Hz, 2H),8.88-9.25 (m,1H),10.0-10.30 (s, 1H);MS (*m/z*): 393 $(M+H)^+$. Elemental Analysis:Calcd. for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14. Found: C, 82.65; H, 6.18; N, 7.10.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)pent-2-en-1-one (6h):
IR (KBr, cm^{-1}): 3023 (Ar-CH Str), 2970 (Aliphatic C-H Str), 1741 (C=O), 1592 (C=N Str), 1482 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ: 1.92-2.0(s, 1H), 2.24-2.41(s, 3H),2.90-3.82 (m, 10H),4.25-4.43 (s, 1H),6.0-6.90(m, 2H),7.10-7.81(m, 5H),7.93-8.40 (m, 2H),8.45-8.84 (d,*J*=8.6Hz, 2H),8.90-9.25 (m,1H),10.0-10.30 (s, 1H);MS *(m/z)*: 303 $(M+H)^+$. Elemental Analysis:Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.46; H, 5.98; N, 7.24.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(furan-2-yl)prop-2-en-1-one(6i):
IR (KBr, cm^{-1}): 3026 (Ar-CH Str), 2996 (Aliphatic C-H Str), 1740 (C=O), 1580 (C=N Str), 1481 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ: 2.35-2.50 (s, 3H), 6.90-7.05 (m, 9H),7.10-7.50 (m,3H),9.95-10.0 (s, 1H); MS *(m/z)*: 341 $(M+H)^+$. Elemental Analysis:Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.65; H, 4.76; N, 8.20.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(3-bromophenyl)prop-2-en-1-one(6j):
IR (KBr, cm^{-1}): 3029 (Ar-CH Str), 2970 (Aliphatic C-H Str), 1740 (C=O), 1636 (C=N Str), 1591 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO)δ: 3.25-3.86 (m, 3H), 6.75-8.40 (m, 13H),10.0 (s, 1H);MS (*m/z*): 430 $(M+H)^+$.Elemental Analysis:Calcd. for$C_{24}H_{16}N_2OCl_2$: C, 68.75; H, 3.85; N, 6.68. Found: C, 68.78; H, 3.82; N, 6.70.

(E)-1-(4-((E)-((1H-indol-3-yl)methylene)amino)phenyl)-3-(2,6-dichlorophenyl)prop-2-en-1-one (6k):IR (KBr, cm^{-1}): 3028 (Ar-CH Str), 2971 (Aliphatic C-H Str), 1740 (C=O), 1593 (C=N Str), 1677 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ:2.20-2.62 (s, 3H), 6.0-6.99 (m, 2H),7.0-7.68 (m, 5H),7.69-7.90 (m, 2H), 7.90-8.50 (m, 2H),8.54-9.10 (m, 1H),10.35(s, 1H);MS (*m/z*): 420 $(M+H)^+$. Elemental Analysis:Calcd. for$C_{24}H_{16}N_2OCl_2$: C, 68.75; H, 3.85; N, 6.68. Found: C, 68.78; H, 3.82; N, 6.70.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(2,4-dichlorophenyl)prop-2-en-1-one(6l):IR (KBr, cm^{-1}): 3028 (Ar-CH Str), 2971 (Aliphatic C-H Str), 1740 (C=O), 1592 (C=N Str), 1434 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ:2.0-2.20(m, 1H), 6.5-7.0 (m, 5H),7.0-7.45 (m,4H),7.50-8.15 (m, 2H),8.20-8.36 (m, 3H), 10.40 (s, 1H);MS (*m/z*): 420 $(M+H)^+$. Elemental Analysis:Calcd. for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.75; H, 6.34; N, 8.83.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-4-methylpent-2-en-1-one(6m):
IR (KBr, cm^{-1}): 3031 (Ar-CH Str), 2910 (Aliphatic C-H Str), 1739 (C=O), 1647 (C=N Str), 1563 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ: 1.8-2.1 (m, 3H), 2.15-2.30 (s, 1H),2.35-3.0 (s, 6H,-CH_3), 7.46-8.50 (m, 9H), 10 (s, 1H);MS (*m/z*): 317 $(M+H)^+$.Elemental Analysis:Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.95; H, 6.73; N, 8.44.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)hept-2-en-1-one(6n):
IR (KBr, cm^{-1}): 3031 (Ar-CH Str), 2910 (Aliphatic C-H Str), 1739 (C=O), 1647 (C=N Str), 1563 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ: 1.5-2.1 (m, 3H), 2.15-2.79 (s, 6H),2.8-2.9 (s, 3H,-CH_3), 6.0-8.50 (m, 9H), 10 (s, 1H); MS (*m/z*): 317 $(M+H)^+$. Elemental Analysis:Calcd. for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82. Found: C, 76.05; H, 5.38; N, 6.84.

(*E*)-1-(4-((*E*)-((1*H*-indol-3-yl)methylene)amino)phenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one(6o):IR (KBr, cm^{-1}): 3031 (Ar-CH Str), 2910 (Aliphatic C-H Str), 1739 (C=O), 1593 (C=N Str), 1676 (Ar-C=C Str); ^{1}H-NMR (300 MHz, DMSO) δ:2.0-2.20 (s, 1H), 2.5-2.9 (s, 3H, -OCH_3),2.9-3.70 (s, 3H, -OCH_3), 4.4-4.6 (m, 1H),6.80-6.90(m, 1H), 6.90-8.50 (m, 12H), 10 (s, 1H);MS (*m/z*): 410 $(M+H)^+$. Elemental Analysis:Calcd. for $C_{24}H_{17}N_2OBr$: C, 67.14; H, 3.99; N, 6.53. Found: C, 67.12; H, 3.97; N, 6.48.

Biological activity:
All the newly synthesized compounds **6(a-o)** are evaluated for antibacterial activity by disc diffusion method. The Zone of inhibition of test compounds was compared to that of the standard drugGentamycin. All the compounds **6(a-o)** (Table: **2**) have shown zone of inhibitionagainst Gram-positive bacteria viz., *S. aureus*and *B. subtilis*and Gram-negative bacteria viz., *E. coli*, and *K. pneumonia.*

Table: 2: Antimicrobial activity of chalcones derivatives

Compound	Zone of inhibition (in mm)			
	Gram-positive bacteria		Gramnegativebacteria	
	S. aureus	*B. subtilis*	*E. Coli*	*K. pneumonia*
6a	-	7	6	8
6b	6	6	-	-
6c	7	-	-	5
6d	-	-	7	6
6e	5	-	-	-
6f	-	8	6	-
6g	6	7	-	-
6h	-	8	5	-
6i	5	-	6	5
6j	-	6	-	-
6k	-	-	-	7
6l	7	5	-	-
6m	-	-	6	-
6n	-	-	7	5
6o	6	8	8	7
Gentamycin	15	15	15	15

Note: Zone of Inhibition given (in mm),

MATERIALS AND METHODS

All the chemicals used were laboratory reagents obtained from SD-fine, Moly chem, reactions are monitored by TLC using pre coated TLC plates (0.25 mm silica gel) were obtained from E.Merck. Melting points were determined on Sheetal precision melting point apparatus and are uncorrected. NMR Spectra were recorded on BRUKER UX-NMR 400 MHz Instrument in DMSO-d_6 solvent using Tetra methyl silane (Me_4Si) as the internal standard. All the Mass spectra were recorded on VG Micro mass 7070H (ESI and EI). IR (KBr, ν, cm^{-1}) spectra were recorded on Shimadzu-435 IR Spectrometer. Gram-positive bacteria viz., *S. aureus*and *B. subtilis*and Gramnegative bacteria viz., *E. coli*, and *K. pneumonia* were used for anti-bacterial activity studies.

General Procedure for the synthesis of Indole-3-carboxaldehyde (2): Phosphorus oxy chloride (2 mL, 0.01 mmol) was added in portions to N, N-dimethyl formamide (5 mL) with stirring at 0^oC. After addition of phosphorus oxy chloride, the mixture was stirred for 60 minutes at the same temperature. And then, a solution of Indole**1** (117 mg 0.01 mmol) in minimum quantity of *N*,*N*-dimethylformamide was added and the resulting mixture was stirred at 0-5ºC for 1 h. The reaction mixture was allowed to stir at 35ºC for 60 minutes and then poured into ice-cold water (90 mL) while a clear red coloured solution was obtained. A 10% sodium hydroxide solution was added, boiled for 1 min and filtered. Upon cooling the filtrate, crystals were formed, which were collected by filtration and subsequently recrystallized from aqueous DMF. Yield: 90%, mp 192-193^oC.

Procedure for the synthesis of *(E)-1-(4-(((1H-indol-3-yl)methylene)amino)phenyl)ethanone* (3): In a 100 mL round bottomed flask Indole-3-carboxaldehyde **2** (0.01mmol, 145 mg) is taken and 1-(4-aminophenyl)ethanone**3**(0.01mmol,135 mg), sodium acetate (0.04mmol, 326 mg) and 10mLglacial acetic acid was added then, refluxed for 2-3 h. Completion of the reaction was monitered by TLC using silica gel-G. After completion of the reaction, the mixture was poured onto crushed ice, acidified if necessary with dilute hydrochloric acid, and the solid that separated was isolated by filtration, dried and purified by column chromatography on silica gel (100-200 mesh, Merck) with a mixture of chloroform and methanol as the mobile phase. The schiff's base is characterized by melting point, ^1H NMR, and Mass spectrometry. mp: 110^oc , yield: 88%**.**

General Procedure for synthesis of Chalcones (6a-o) : Equimolar quantities (0.01 mmol) of (*E*)-1-(4-(((1*H*-indol-3-yl)methylene)amino)phenyl)ethanone**4**and respective aldehydes **5(a-o)** were mixed and dissolved in minimum amount of alcohol. To this, aqueous sodium hydroxide solution (50%, 7.5 mL) was added slowly and mixed occasionally for 72 h, at room temperature. Completion of the reaction was identified by TLC using silica gel-G. After completion of the reaction, the mixture was poured onto crushed ice, acidified if necessary with dilute hydrochloric acid, and the solid that separated was isolated by filtration, dried and purified by column chromatography on silica gel (100- 200 mesh, Merck), with a mixture of chloroform and methanol as the mobile phase.

CONCLUSION

In the present study, newly synthesized biologically active chalcone linked indolederivatives having the expected pharmacophore. Anti-bacterial activity of these compounds was evaluated under standardized conditions using Gentamycin as standard drug. All the newly synthesized compounds **6(a-o)** have shown moderate activity against Gram-positive bacteria viz., *S. aureus*and *B. subtilis*and Gramnegative bacteria viz., *E. coli*, and *K. pneumonia*.by disc diffusion method.

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