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Synthesis of new methylenedioxybenzylpiperazine analogues of flavones as potent antibacterial agents

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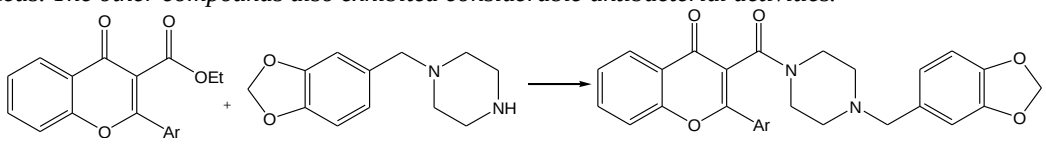
Abstract:
*A series of new 3-[4-(1,3-benzodioxol-5-ylmethyl)piperazino]carbonyl-2-aryl-4H-4-chromenone **10(a-j)** were synthesized and evaluated for their antibacterial activity against Gram-positive bacteria viz. B. subtilis, B. sphaericus, and S. aureus, Gram-negative bacteria viz. P. aeruginosa, K. aerogenes and C. violaceum. Antibacterial evaluation indicates, these compounds were active only towards Gram-positive bacteria. Compounds, which contain 4-fluorophenyl (**10g**) and 2,5-difluorophenyl (**10h**) moiety on flavones ring, displayed higher antibacterial activity than the standard drug towards Gram-positive bacteria. Compounds, containing 4-methylphenyl (**10c**) and 4-methoxyphenyl (**10e**) were equally active against B. subtilis, and B. sphaericus. The other compounds also exhibited considerable antibacterial activities.*



***Keywords**: Flavones, piperazines, Benzodioxole, Antibacterial Activity.*

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I. INTRODUCTION

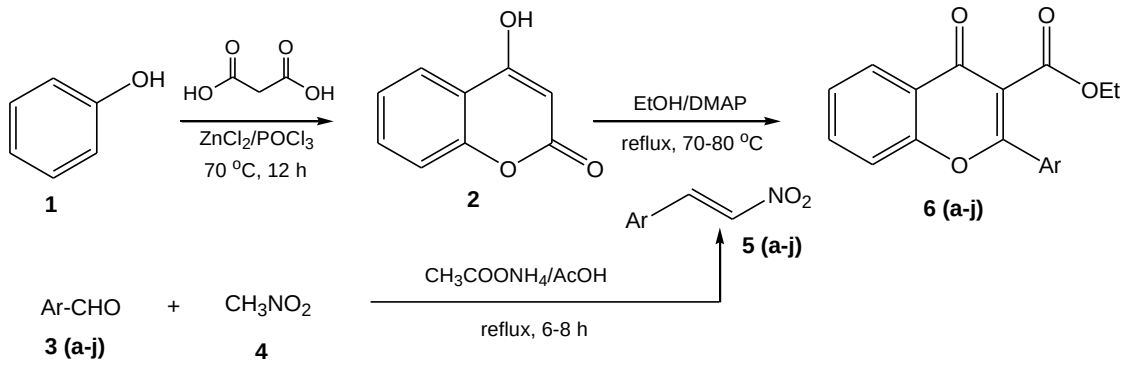
Flavones are a class of heterocyclic compounds with a benzo-γ-pyrone moiety and occupy a special place in pharmaceutical field owing to their significant biological activities such as antioxidant [1], anxiolytic [2], anticancer [3], analgesic [4], antimicrobial [5] and antitumor activity [6]. The derivatives of flavones such as Baicalein, 3,7-dihdroxyflavone and chrysin showed their antitumor activities by acting as inducer of apoptosis in human tumor cell lines through caspases-dependent pathways [7].

Further, the nitrogen containing heterocyclic compounds are much important and possess a broad spectrum of biological activities therefore used in various fields of pharmacy [8]. Among these, the compounds containing piperazine ring are significant [9] and can be found in various well known drugs [10] which showed considerable physiological effect such as antituberculosis [11], anthelmenitics [12], antianginals [13], anticancer [14], analgesic [15], antidepressant [16], antipsychotic [17], antidiabetic [18], antihistamines [19], hypolipidemic [20]. The modification of substitution pattern on the piperazine moiety facilitates a significance difference in the biological and pharmacological effect of the resultant molecules, which encouraged the synthesis of a large number of novel chemotherapeutic agents [21].

Owing to immense biological activities exhibited by piperazine, flavone and their derivatives, it was considered to synthesize the heterocyclic compounds containing piperazine and flavone moieties in one molecule for enhancing biological activity. In the present study, the synthesis and antibacterial screening of new series of 3-[4-(1,3-benzodioxol-5-ylmethyl)piperazino]carbonyl-2-aryl-4*H*-4-chromenone **10(a-j)** with a view to explore their potential biological activity. The antibacterial activities of the compounds have also been evaluated.

II. RESULTS AND DISCUSSION

The compound **2** was prepared according to the procedure reported in the literature [22], by cyclo-condensation of phenol **1** with malonic acid in the presence of phosphorous oxychloride and anhydrous zinc chloride under reflux on a water bath at 70 ^{o}C for 12 h, gave the 4-hydroxy-2*H*-2-chromenone **2** as light yellow powder. The compound **5** also prepared by the literature procedure [23], by condensation of correspoinding aromatic aldehyde **3** with nitromethane **4** in the presence of ammonium acetate in acetic acid at reflux temperature for 6-8 h, resulted the corresponding nitrostyrene **5(a-j)**. Further, compound **2** was reacted with corresponding compound **5** in the presence of dimethylaminopyridine (DMAP) [24] in ethyl alcohol at reflux temperature to afford the ethyl 4-oxo-2-aryl-4*H*-3-chromenecarboxylate **6(a-j)** (**Scheme 1**).

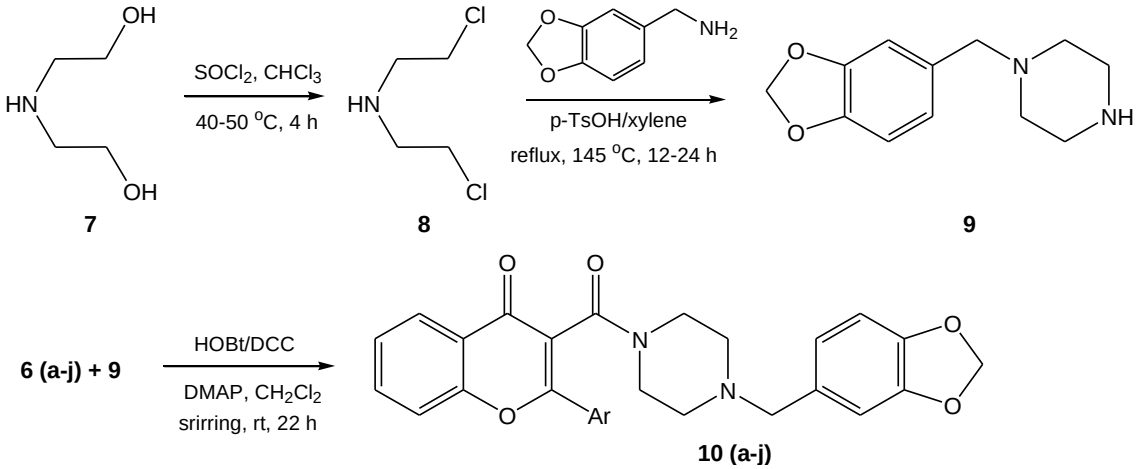


6: Ar = a) phenyl; b) 4-chlorophenyl; c) 4-methylphenyl; d) 4-nitrophenyl; e) 4-methoxyphenyl; f) 4-dimethylaminophenyl; g) 4-fluorophenyl; h) 2,5-difluorophenyl; i) 2-furyl; j) 2-thienyl

Scheme 1

The chlorination of diethanolamine **7** by thionyl chloride at 40-50 0C in chloroform for 4 h, led to the formation of *N*,*N*-di(2-chloroethyl)amine **8**, which on cyclo-condensation with 1,3-benzodioxol-5-ylmethanamine in the presence of *p*-TsOH in xylene at reflux temperature for 12-24 h, to afford 1-(1,3-benzodioxol-5-ylmethyl)piperazine **9** (**Scheme 2**). The IR spectrum of compound **9** showed absorption bands at 3437 (N-H), 3062 (Ar-H) and 925 cm^{-1} for dioxole (O-C-O). Its proton NMR spectra showed the signals corresponding to the aromatic protons at δ 6.90-7.10 ppm as multiplet for three protons. The proton corresponding to the -NH group of piperazine ring appeared at δ 6.10 as a broad singlet, the protons of piperazine ring appeared at δ 2.90-2.95 and δ 3.10-3.15 ppm as multiplets, the other methylene protons appear as singlets at δ 4.03 and δ 6.10 ppm. Its ^{13}C NMR spectra. the signals at δ 48.1 and 57.4 ppm was assigned to piperazinyl carbons, the carbons of methylene group appered at 58.9 and 102.4 ppm.

The title compounds 3-[4-(1,3-benzodioxol-5-ylmethyl)piperazino]carbonyl-2-aryl-4*H*-4-chromenone **10(a-j)** were synthesized by the reaction of corresponding ethyl 4-oxo-2-aryl-4*H*-3-chromenecarboxylate **6(a-j)** with 1-(1,3-benzodioxol-5-ylmethyl)piperazine **9** in the presence of *N*-hydroxy-benzotriazole (HOBt), 4-dimethylaminopyridine (DMAP) and *N*,*N*-dicyclohexyl-carbodiimide (DCC) in dichloromethane under stirring at room temperature for 22 h to gave final compounds (**Scheme 2**). Structure of compounds **10(a-j)** was established from their IR, MS and NMR spectral analyses. The IR spectrum of **10a** showed absorption bands at 1689 and 1588 cm^{-1} due to C=O and C=C of flavones ring, the bands at 1723 and 1286 cm^{-1} due to C=O and C-N of amide group, the dioxole (O-C-O) band observed at 922 cm^{-1}. Its proton NMR spectra, the signal for methylene protons attached to piperazine ring appeared at δ 4.05 as singlet, and the dioxole ring methylene protons appeared at δ 6.10 as singlet. The piperazine protons signals appeared at δ 2.80-2.85 and 3.60-3.65 ppm as multiplets. The signal for aromatic protons appeared in the region of δ 6.90-6.95, 7.60-7.65 and 7.70-7.80 ppm as multiplets and at δ 8.23 ppm as doublet. Its ^{13}C NMR spectra the signals of flavones carbons appeared at δ 117.8, 124.2, 156.5, 173.1, 175.4 (C=O) ppm, the piperazine ring carbons at δ 49.1 and 57.4 ppm, the amide (C=O) appeared at δ 165.3 and methylene carbon attached to piperazine ring appeared at δ 58.5 ppm.



10: Ar = a) phenyl; b) 4-chlorophenyl; c) 4-methylphenyl; d) 4-nitrophenyl; e) 4-methoxyphenyl; f) 4-dimethylaminophenyl; g) 4-fluorophenyl; h) 2,5-difluorophenyl; i) 2-furyl; j) 2-thienyl

Scheme 2

ANTIBACTERIAL ACTIVITY

The *in vitro* antibacterial activitiy of compounds **10**(**a-j**) was assessed against three representative Gram-positive bacteria *viz. Bacillus subtilis*, *Bacillus sphaericus*, and *Staphylococcus aureus*, three Gram-negative bacteria *viz. Pseudomonas aeruginosa*, *Klebsiella aerogenes* and *Chromobacterium violaceum*, by the broth dilution method recommended by National Committee for Clinical Laboratory Standards [25]. Bacteria were grown overnight in Luria Bertani (LB) broth at 37°C, harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 100 to 0.8 μg/mL. Ten microliters of the broth containing about 10^5 colony-forming units (cfu)/mL of test bacteria wasere added to each well of a 96-well microtiter plate. Culture plates were incubated for 24 h at 37 °C, and the growth was monitored by visually and spectrophotometrically. Streptomycin was also screened under identical conditions for comparison. The minimal inhibitory concentration (MIC, μg/mL) of the compounds **10**(**a-j**) were determined and presented in **Table 1**.

The evaluation of antibacterial activity of compounds **10(a-j)** indicated that, these compounds were active only towards Gram-positive bacteria. Compounds, which contain 4-fluorophenyl (**10g**) and 2,5-difluorophenyl (**10h**) moiety on flavones ring, displayed higher antibacterial activity than the standard drug towards Gram-positive bacteria. Compounds, containing 4-methylphenyl (**10c**) and 4-methoxyphenyl (**10e**) were equally active against *B. subtilis*, and *B. sphaericus* (**Table 1**). The other compounds also exhibited considerable antibacterial activities.

Table 1: Antibacterial Activity of Compounds **10**(**a-j**)

Compound	Minimum inhibitory concentration (MIC μg/mL)					
	B. subtilis	***B. sphaericus***	***S. aureus***	***P. aeruginosa***	***K. aerogenes***	***C. violaceum***
10a	12.5	25.0	25.0	–	12.5	12.5
10b	12.5	12.5	12.5	25.0	–	25.0
10c	6.25	12.5	12.5	50.0	12.5	12.5
10d	25.0	25.0	12.5	25.0	25.0	50.0
10e	6.25	12.5	12.5	12.5	12.5	25.0
10f	25.0	12.5	25.0	12.5	25.0	50.0
10g	6.25	6.25	3.12	6.25	6.25	6.25
10h	6.25	6.25	6.25	12.5	6.25	6.25
10i	25.0	50.0	25.0	–	–	50.0
10j	25.0	25.0	25.0	–	25.0	25.0
Streptomycin	6.25	12.5	6.25	1.56	1.56	3.12

III. MATARIALS AND METHODS

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer.

Synthesis of 4-hydroxy-2*H*-2-chromenone (2): A mixture of phenol **1** (0.01 mol), malonic acid (0.01 mol), $POCl_3$ (40 mL) and anhy. $ZnCl_2$ (30 g) were heated on a water bath at 70 ^{o}C for 12 h. The reaction mass was cooled and poured into ice. The solid separated was digested in 10% Na_2CO_3 and filtered. The filtrate upon acidification gave compound **2** as light yellow powder, mp. 211-213 ^{o}C.

Synthesis of 1-[(*E*)-2-nitro-1-ethenyl]benzene 5(a-j): The corresponding aromatic aldehyde **3** (0.01 mol), nitromethane **4** (0.02 mol) were added to the stirred solution of acetic acid (10 mL) and ammonium acetate (2 g). The resulting solution was refluxed in an oil bath at 110 ^{o}C for 6-8 h. After the clearance of TLC, the total dark solution was distilled under *vacume* completely brown colored syrup obtained, the syrup was poured in crushed ice and product was extracted with ethyl acetate (50 mL × 3), the combined organic layer

dried over Na_2SO_4. The combined organic layers were evaporated under vacuum to afford the impure reaction mixture which was purified by column chromatography (silica gel) to obtain the pure β-nitrostyrene.

General procedure for the synthesis of ethyl 4-oxo-2-aryl-4*H*-3-chromenecarboxylate 6 (a-j): To a stirred solution of compound **2** (0.01 mol) and corresponding compound **5** (0.02 mol) in ethanol (6 mL) was added 4-dimethylaminopyridine (DMAP, 0.04 mol). The reaction mixture was heated at 70-80 ^oC, and the progress of the reaction was monitored by TLC of ethyl acetate and hexane (15:85%). After the formation of the product, the crude reaction mixture was extracted with EtOAc (2x10 mL), the combined organic layers were washed with H_2O (10 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (60-120 mesh) to afford the pure products **6 (a-j)**.

Ethyl 4-oxo-2-phenyl-4*H*-3-chromenecarboxylate (6a)
IR: 3067 (CH-Ar), 2957 (CH-Ali), 1734 (C=O), 1687 (C=O), 1652 (C=C), 1278 (C-O).
PMR: 1.32 (t, 3H, CH_3), 4.56 (q, 2H, CH_2), 7.45-7.55 (m, 6H, ArH), 7.92 (d, J = 7.9 Hz, 2H, ArH), 8.22 (d, J = 8.1 Hz, 1H, ArH).
CMR: 15.6, 62.8, 110.9, 119.0, 123.2, 124.9, 125.7, 127.3, 128.4, 129.1, 132.5, 133.3, 156.6, 166.1, 170.8, 174.4.
MS: 295 (M^+ + 1).

Synthesis of 1-(1,3-Benzodioxol-5-ylmethyl)piperazine (9): To a stirred solution of diethanolamine **7** (0.1 mol) in 15 mL of $CHCl_3$, a mixture of thionylchloride (28 mL) and $CHCl_3$ (15 mL) was slowly added dropwise for 1 h and the reaction was continued for 2 more hours. The excess of solvent was removed under reduced pressure to give compound **8** as pale yellow solid, which was purified by crystallization from ethylacetate. To a solution of compound **8** (0.1 mol) in xylene (25 mL), 1,3-benzodioxol-5-ylmethanamine (0.1 mol) and *p*-toluenesulphonic acid (PTSA) (3%) was added and then heated the mixture to reflux at 140-145 ^oC for 12-24 h. After the completion of the reaction, crystalized the product by cooling to rt and purified by recrystallization to give the compound **9**. IR (KBr) ν_{max}: 3437 (N-H), 3062 (CH-Ar), 2972 (CH-Ali), 1287 (C-N), 925 (O-C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.90-2.95 (m, 4H, piperazine-H), 3.10-3.15 (m, 4H, pipeazine-H), 4.03 (s, 2H, CH_2), 6.12 (s, 1H, NH), 6.10 (s, 2H, CH_2), 6.90-7.10 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 48.1, 57.4, 58.9, 102.4, 109.1, 111.3, 122.7, 133.7, 147.5, 149.5.; MS: *m/z* 221 (M^+ +1).

General procedure for the synthesis of compounds 10 (a-j): A mixture of corresponding compound **6** (0.01 mol), hydroxybenzotriazole (HOBt) (0.01 mol), 4-dimethylaminopyridine (DMAP) (0.01 mol) and *N*,*N*-dicyclohexylcarbodiimide (DCC) (0.011 mol) in 25 mL CH_2Cl_2 was stirred at room temperature for 30 min. To the stirred mixture, a solution of compound **9** (0.01 mol) in 25 mL CH_2Cl_2 was added and continued the stirring for 20 h at rt. Filtered the reaction mixture and the organic layer was washed with $NaHCO_3$ and then with HCl, dried over anhydrous $MgSO_4$. Concentrated the solvent under vacuum and purified by column chromatography using ethyl ace-pertrolium ether (1:5) to obtain pure compounds **10(a-j)**.

3[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-phenyl-4*H*-4-chromenone (10a): IR (KBr) ν_{max}: 3044 (CH-Ar), 2966 (CH-Ali), 1723 (C=O), 1689 (C=O), 1588 (C=C), 1286 (C-N), 922 (O-C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.80-2.85 (m, 4H, piperazine-H), 3.60-3.65 (m, 4H, piperazine-H), 4.05 (s, 2H, CH_2), 6.10 (s, 2H, CH_2), 6.90-6.95 (m, 3H, ArH), 7.60-7.65 (m, 4H, ArH), 7.70-7.80 (m, 4H, ArH), 8.23 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.1, 57.4, 58.5, 101.4, 106.8, 111.3, 112.8, 117.8, 122.3, 124.2, 125.1, 125.8, 126.0, 127.7, 128.6, 132.9, 133.6, 134.2, 146.8, 148.7, 156.5, 165.3, 173.1, 175.4; MS: *m/z* 469 (M^++1).

3-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-(4-chlorophenyl)-4*H*-4-chromenone (10b): IR (KBr) ν_{max}: 3032 (CH-Ar), 2943 (CH-Ali), 1718 (C=O), 1686 (C=O), 1584 (C=C), 1281 (C-N), 924 (O-C-O), 686 (C-Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.80-2.85 (m, 4H, piperazine-H), 3.62-3.66 (m, 4H, piperazine-H), 4.02 (s, 2H, CH_2), 6.07 (s, 2H, CH_2), 6.85-6.90 (m, 3H, ArH), 7.60-7.65 (m, 1H, ArH), 7.75-7.80 (m, 6H, ArH), 8.21 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.2, 57.3, 58.9, 101.1, 106.4, 111.3, 112.8, 116.3, 121.5, 124.2, 125.3, 126.2, 127.3, 128.0, 129.4, 132.9, 133.6, 135.4, 145.7, 148.4, 156.5, 165.3, 173.1, 175.2; MS: *m/z* 502 (M^+).
3-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-(4-methylphenyl)-4*H*-4-chromenone (10c): IR (KBr) ν_{max}: 3035 (CH-Ar), 2978 (CH-Ali), 1718 (C=O), 1686 (C=O), 1582 (C=C), 1282 (C-N), 924 (O-C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.42 (s, 3H, CH_3), 2.75-2.80 (m, 4H, piperazine-H), 3.60-3.65 (m, 4H, piperazine-H), 4.00 (s, 2H, CH_2), 6.11 (s, 2H, CH_2), 6.85-6.90 (m, 3H, ArH), 7.60-7.65 (m, 3H, ArH), 7.75-7.80 (m, 4H, ArH), 8.20 (d, J = 8.3 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.5, 48.2, 57.3, 58.8, 101.2,

105.9, 111.4, 112.7, 116.6, 122.5, 124.4, 124.9, 125.2, 125.9, 126.2, 128.5, 132.7, 133.1, 138.3, 145.8, 147.8, 155.4, 165.5, 173.3, 175.5; MS: *m/z* 482 (M^++1).

3-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-(4-nitrophenyl)-4*H*-4-chromenone (10d): IR (KBr) ν_{max}: 3063 (CH-Ar), 2954 (CH-Ali), 1721 (C=O), 1683 (C=O), 1586 (C=C), 1571, 1339 (NO_2), 1282 (C-N), 928 (O-C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.76-2.80 (m, 4H, piperazine-H), 3.55-3.60 (m, 4H, piperazine-H), 4.02 (s, 2H, CH_2), 6.12 (s, 2H, CH_2), 6.85-6.90 (m, 3H, ArH), 7.55-7.60 (m, 1H, ArH), 7.70-7.80 (m, 4H, ArH), 8.27 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.6, 56.8, 58.1, 102.3, 106.2, 110.5, 112.2, 116.9, 122.5, 124.8, 125.0, 125.7, 126.3, 129.2, 131.7, 133.6, 134.9, 145.2, 147.5, 149.0, 156.1, 165.0, 173.7, 175.0; MS: *m/z* 513 (M^+).

3-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-(4-methoxyphenyl)-4*H*-4-chromenone (10e): IR (KBr) ν_{max}: 3057 (CH-Ar), 2971 (CH-Ali), 1724 (C=O), 1682 (C=O), 1582 (C=C), 1280 (C-N), 1071 (C-O), 925 (O-C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.75-2.82 (m, 4H, piperazine-H), 3.60-3.63 (m, 4H, piperazine-H), 3.92 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2), 6.15 (s, 2H, CH_2), 6.86-6.90 (m, 3H, ArH), 7.55-7.65 (m, 3H, ArH), 7.72-7.80 (m, 4H, ArH), 8.15 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 48.3, 56.8, 57.2, 58.7, 102.1, 106.8, 111.3, 112.2, 113.9, 116.9, 120.9, 122.0, 124.2, 124.9, 126.5, 130.6, 131.7, 133.6, 138.6, 145.4, 147.6, 156.2, 164.1, 172.9, 175.2; MS: *m/z* 499 (M^+ +1).

3-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-[4-(dimethylamino)phenyl]-4*H*-4-chromenone (10f): IR (KBr) ν_{max}: 3055 (CH-Ar), 2971 (CH-Ali), 1716 (C=O), 1682 (C=O), 1589 (C=C), 1288 (C-N), 923 (O-C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.70-2.75 (m, 4H, piperazine-H), 3.12 (s, 6H, 2N-CH_3), 3.55-3.60 (m, 4H, piperazine-H), 4.03 (s, 2H, CH_2), 6.07 (s, 2H, CH_2), 6.86-6.90 (m, 5H, ArH), 7.50-7.55 (m, 3H, ArH), 7.72-7.80 (m, 2H, ArH), 8.11 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 40.4, 49.3, 57.5, 58.2, 101.5, 106.5, 111.7, 112.3, 112.9, 115.8, 117.8, 122.3, 124.4, 125.1, 126.2, 127.0, 132.9, 133.5, 146.8, 148.2, 153.0, 156.5, 165.5, 172.4, 174.5; MS: *m/z* 511 (M^+).

3-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-(4-fluorophenyl)-4*H*-4-chromenone (10g): IR (KBr) ν_{max}: 3056 (CH-Ar), 2957 (CH-Ali), 1712 (C=O), 1682 (C=O), 1578 (C=C), 1311 (C-F), 1284 (C-N), 927 (O-C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.72-2.77 (m, 4H, piperazine-H), 3.53-3.60 (m, 4H, piperazine-H), 4.01 (s, 2H, CH_2), 6.14 (s, 2H, CH_2), 6.82-6.90 (m, 3H, ArH), 7.50-7.55 (m, 3H, ArH), 7.74-7.80 (m, 4H, ArH), 8.15 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 48.4, 57.7, 58.9, 102.1, 105.2, 111.7, 113.4, 117.2, 118.0, 122.9, 123.3, 124.0, 124.9, 126.2, 130.1, 132.9, 133.2, 145.9, 148.5, 155.2, 161.2, 165.5, 172.4, 174.1; MS: *m/z* 486 (M^+).

3-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-(2,5-difluorophenyl)-4*H*-4-chromenone (10h): IR (KBr) ν_{max}: 3066 (CH-Ar), 2972 (CH-Ali), 1719 (C=O), 1690 (C=O), 1585 (C=C), 1314 (C-F), 1281 (C-N), 923 (O-C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.72-2.75 (m, 4H, piperazine-H), 3.52-3.60 (m, 4H, piperazine-H), 4.01 (s, 2H, CH_2), 6.14 (s, 2H, CH_2), 6.87-6.91 (m, 4H, ArH), 7.56-7.60 (m, 2H, ArH), 7.70-7.75 (m, 3H, ArH), 8.18 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 48.5, 56.1, 58.2, 102.7, 105.6, 112.8, 113.4, 116.0, 116.9, 117.5, 118.2, 120.8, 123.5, 124.1, 125.9, 126.2, 131.9, 133.6, 145.5, 147.4, 149.5, 156.5, 157.8, 165.0, 172.9, 175.8; MS: *m/z* 504 (M^+).

3-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-(2-furyl)-4*H*-4-chromenone (10i): IR (KBr) ν_{max}: 3072 (CH-Ar), 2965 (CH-Ali), 1719 (C=O), 1681 (C=O), 1589 (C=C), 1282 (C-N), 1114 (C-O-C), 921 (O-C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.75-2.80 (m, 4H, piperazine-H), 3.54-3.60 (m, 4H, piperazine-H), 4.00 (s, 2H, CH_2), 6.12-6.16 (m, 4H, CH_2, ArH), 6.85-6.90 (m, 4H, ArH), 7.60-7.65 (m, 1H, ArH), 7.65-7.70 (m, 2H, ArH), 8.11 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.4, 57.5, 58.7, 101.0, 105.2, 109.5, 111.6, 112.2, 117.0, 120.7, 122.5, 124.6, 125.2, 125.9, 132.3, 133.6, 145.0, 146.5, 148.2, 151.2, 156.4, 165.1, 172.4, 175.0; MS: *m/z* 458 (M^+).

3-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]carbonyl-2-(2-thienyl)-4*H*-4-chromenone (10j): IR (KBr) ν_{max}: 3056 (CH-Ar), 2951 (CH-Ali), 1717 (C=O), 1683 (C=O), 1584 (C=C), 1282 (C-N), 925 (O-C-O), 842 (C-S-C) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.75-2.80 (m, 4H, piperazine-H), 3.55-3.60 (m, 4H, piperazine-H), 4.02 (s, 2H, CH_2), 6.29 (m, 5H, CH_2, ArH), 6.91-6.95 (m, 3H, ArH), 7.57-7.62 (m, 1H, ArH), 7.67-7.72 (m, 2H, ArH), 8.21 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 49.3, 57.4, 58.1, 101.1, 106.5, 110.9, 112.2, 117.3, 122.0, 124.5, 125.1, 125.9, 126.3, 132.9, 133.6, 134.1, 135.0, 136.2, 146.8, 147.9, 156.2, 165.3, 172.5, 174.8; MS: *m/z* 474 (M^+).

IV. CONCLUSION

A series of new 3-[4-(1,3-benzodioxol-5-ylmethyl)piperazino]carbonyl-2-aryl-4*H*-4-chromenone **10(a-j)** were synthesized and evaluated for their antibacterial activity against Gram-positive bacteria *viz*. *B. subtilis*, *B. sphaericus*, and *S. aureus*, Gram-negative bacteria *viz*. *P. aeruginosa*, *K. aerogenes* and *C. violaceum*. Antibacterial evaluation indicates, these compounds were active only towards Gram-positive bacteria. Compounds, which contain 4-fluorophenyl (**10g**) and 2,5-difluorophenyl (**10h**) moiety on flavones ring, displayed higher antibacterial activity than the standard drug towards Gram-positive bacteria. Compounds, containing 4-methylphenyl (**10c**) and 4-methoxyphenyl (**10e**) were equally active against *B. subtilis*, and *B. sphaericus*. The other compounds also exhibited considerable antibacterial activities.

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