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Research Article

Synthesis and Biological Evaluation of Chalconyl Incorporated Schiff's Bases of Sulphonamides

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ABSTRACT
A series of of Chalconyl Incorporated Schiff's Bases of Sulphonamides was synthesized by reacting substituted chalcone derivatives with Sulphacetamide sodium in methanol. All the title compounds synthesized (**2a-2d**) were tested for antibacterial and antifungal activity using *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenus* and *C. albicans*, *A. niger* and *A. clavatus* respectively as microbial strains and Sulphacetamide sodium as standard. The compound **2d** showed significant antibacterial activity and **2a** showed moderate antifungal activity as compared with Sulphacetamide Sodium.

Keywords: Chalcones, Schiff's bases, Antimicrobial activity, Sulphacetamide Sodium.

INTRODUCTION

The infectious diseases are the second major cause of death worldwide and third leading cause of death in economically advanced countries[1]. Bacterial strains are getting resistant towards antibiotics in clinical use[2]. To overcome these problems, the development of new and safe antimicrobial agents with better effectiveness is required day by day. Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as Antimicrobial, Antimalarial, Anticancer, Antioxidant, Anti-inflammatory, Antituberculer, Antiprotozoal, Antifilarial, Antibacterial, Antifungal, Analgesic, Hypoglycemic, Antileishmanial, Cytotoxic activity, Mosquito larvicidal activity, Anticonvulsant, Mammalian Alpha Amylase Inhibitory activity, COX inhibitory activity, MAOs inhibitory activity[3-18]. Sulphacetamide is well known synthetic sulfonamide antibiotic.

In the present work, we planned to incorporate the substituted chalcones to sulfonamide to develop nove antimicrobial lead-candidates.

MATERIAL AND METHODS

Chemistry

Melting points of the synthesized compounds were determined in open capillary tubes and are uncorrected. Elemental analysis (C, H and N) was undertaken with a Perkin-Elmer model 240C analyzer. IR absorption spectra were recorded on Bruker alpha, KBr diffuse reflectance. ^{1}H NMR spectra were recorded on the Bruker DPX-400 instrument at 400 MHz. The ^{1}H chemical shifts are reported as parts per million (ppm) downfield from TMS (Me_4Si). The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer. The homogeneity of the compounds was monitored by ascending thin-layer chromatography (TLC) on silica gel G (Merck)-coated aluminum plates, visualized by iodine vapor.

3-(2-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (1a)

2-chloro benzaldehyde 5.6 gm (0.012 mol) was added to a mixture of *o*-hydroxy acetophenone 4.5 ml (0.01 mol) in 25 ml of ethanol in a 200 ml beaker. The content of the beaker were mixed well and to that 50 ml of 10% potassium hydroxide solution was added and stirred vigorously at 25˚C until the mixture was so thick that stirring was no longer effective (25 min). After the completion of the stirring, the reaction mixture was kept in a refrigerator overnight. The reaction mixture was then diluted with ice cold water, acidified with 10% aqueous hydrochloric acid to precipitate the chalcone. The product was filtered with suction on a Buchner funnel, washed with cold water until the washings were neutral to litmus and then washed with of ice-cold rectified spirit. The dried product was recrystallized from chloroform and dried at room temperature. The completion of reaction was monitored by running TLC[19].

Yield: 45%, M.P: 78-80˚C, Anal Calcd: $C_{15}H_{11}O_2Cl$ (258.70) C, 69.64; H, 4.29 found: C, 69.58; H, 4.36.

1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (1b)

Yield: 44 %. M.P: 53-55˚C. Anal. Calcd. for $C_{15}H_{12}O_2$ (224.25): C, 80.34; H, 5.39 found: C, 80.28; H, 5.44.

1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (1c)

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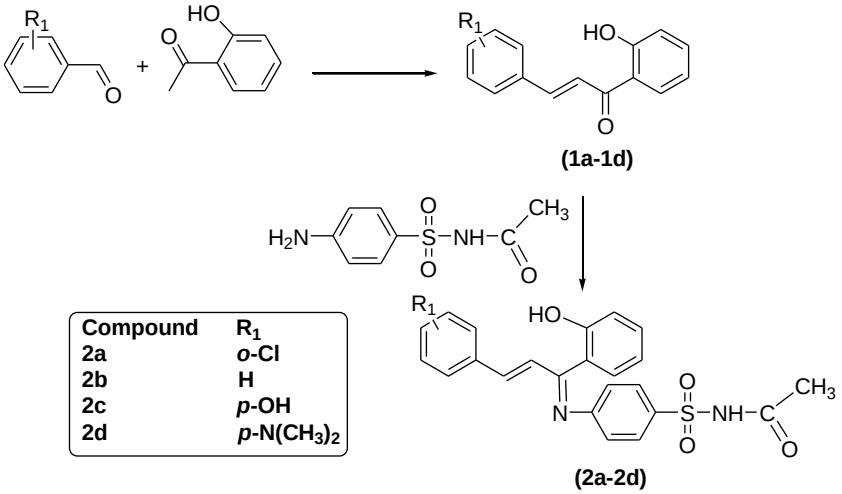

Scheme 1: Synthesis of Chalconyl incorporated Schiff's bases of Sulphonamide.

Table 1: Antimicrobial Activity profile of Chalconyl Incorporated Schiff's Bases of Sulphonamides.

Compound	Minimal Inhibition Concentration (µg/ml)						
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
	MTCC 442	MTCC 441	MTCC 96	MTCC 443	MTCC 227	MTCC 282	MTCC 1323
2a	200	200	100	125	500	1000	1000
2b	125	125	250	125	1000	1000	>1000
2c	200	100	250	200	>1000	1000	1000
2d	100	62.5	200	100	>1000	>1000	>1000
Sulphacetamide sodium	62.5	100	50	100	250	250	250

Yield: 51%. M.P: 138-140°C. Anal. Calcd. for $C_{15}H_{12}O_3$ (240.25): C, 74.99; H, 5.03 found: C, 75.09; H, 4.94.

3-(4-(dimethylamino)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (1d)

Yield: 50%. M.p. 128-130°C. Anal. Calcd. for $C_{17}H_{17}NO_2$ (267.32): C, 76.38; H, 6.41; found: C, 76.24; H, 6.47.

***N*-(4-(1-(2-chlorophenyl)-3-(2-hydroxyphenyl)allylidene)amino)phenylsulfonyl)acetamide (2a)**

0.07 gm of 3-(2-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one with 0.05 gm of Sulfacetamide sodium was mixed in 50 ml of methanol. The mixture was refluxed for 5-6 hours, then was cooled and poured in ice and stirred vigorously. 2-3 drops of conc. HCl was added to acidify the mixture and precipitate the Schiff's base formed and stirred vigorously. The precipitate formed was filtered with suction on a Buchner funnel and washed with water until the washings were neutral to litmus. The dried product was recrystallized using alcohol dried and at room temperature. The completion of reaction was monitored by running TLC.

Yield: 75 %. M.P: 100-102 %. IR (υ_{max}, cm^{-1}): 3406 (-NH), 1601 (C=N), 1359 (SO_2), 1679 (C=O). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.05 (s, 1H, NH), 7.95-7.02 (m, 12H, Ar-H), 5.90-5.9 (d, 1H, CH), 2.50 (s, 3H, $-CH_3$). LC-MS m/z (M^+): 454. Anal Calcd: $C_{23}H_{19}N_2O_4S$ (454) C, 60.72; H, 4.21; N, 6.16; found: C, 60.39; H, 3.81; N, 6.65.

***N*-(4-(3-(2-hydroxyphenyl)-1-phenylallylidene)amino)phenylsulfonyl)acetamide (2b)**

Yield: 80 %. M.P: 58-60˚C. IR (υ_{max}, cm^{-1}): 3554 (-NH), 1370 (SO_2), 1603 (C=N), 1682 (C=O). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.24 (s, 1H, OH), 7.95 (s, 1H, NH), 7.81-7.35 (m,13H, Ar-H), 2.50 (s, 3H, $-CH_3$). LC-MS m/z (M^+): 420.1. Anal Calcd: $C_{23}H_{20}N_2O_4S$ (420) C, 65.70; H, 4.79; N, 6.66; found: C, 65.26; H, 4.35; N, 6.20.

***N*-(4-(3-(2-hydroxyphenyl)-1-(4-hydroxyphenyl)allylidene)amino)phenylsulfonyl)acetamide (2c)**

Yield: 88.87 %. M.P: 140-142˚C. IR (υ_{max}, cm^{-1}): 3157 (OH), 1368 (SO_2), 1603 (C=N), 1669 (C=O). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.15 (s, 1H, OH), 8.27 (s, 1H, NH), 7.81-6.69 (m, 12H, Ar-H), 6.86-6.78 (m, 1H, CH) 2.50 (s, 3H, $-CH_3$). LC-MS m/z (M^+): 436.1. Anal Calcd: $C_{23}H_{20}N_2O_5S$ (436) C, 63.29; H, 4.62; N, 6.42; found: C, 62.88; H, 4.21; N, 5.98.

***N*-(4-(1-(4-(dimethylamino)phenyl)-3-(2-hydroxyphenyl)allylidene)amino)phenylsulfonyl) acetamide (2d)**

Yield: 75 %. M.P: 130-132˚C. IR (υ_{max}, cm^{-1}): 3228 (OH), 1370 (SO_2), 1603 (C=N), 1669 (C=O). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.41 (s, 1H, OH), 8.24-8.21 (m, 1H, NH), 7.84-7.48 (m, 12H, Ar-H), 3.04 (s, 6H, $N(CH_3)_2$), 2.50 (s, 3H, $-CH_3$). LC-MS m/z (M^+): 463.1. Anal Calcd: $C_{25}H_{25}N_3O_4S$ (436) C, 64.78; H, 5.44; N, 9.06; found: C, 64.33; H, 5.09; N, 9.56.

Antimicrobial activity

All the title compounds synthesized (**2a-2d**) were tested for antibacterial activity by Broth Dilution Method against *E.coli, P.aeruginosa, S.aureus, S.pyogenus, C.albicans,*

A.niger and *A.clavatus* using Sulphacetamide sodium as standard.

The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculum. The test mixture should contain 10^8 organism/ml[20-24].

RESULTS AND DISCUSSION

Chemistry

All title compounds were synthesized as per the scheme developed and confirmed by IR, ^{1}H NMR, LC-MS, TLC and Elemental Analysis.

o-hydroxyacetophenone was reacted with substituted aromatic aldehyde to yield various substituted chalcones **(1a-1d)**. All the substituted chalcones were refluxed with Sulphacetamide sodium which led to the formation of Schiff's bases (**2a-2d**). Structures of the titled compounds were further confirmed by the appearance of C=N bands at 1601-1603 cm^{-1} in IR spectra, in ^{1}H NMR shifts, appearances of a singlet –NH and $–CH_3$ at region δ= 8.27-7.29 and 2.51-2.50 respectively. The remaining protons appeared at the expected chemical shifts.

Antimicrobial Activity

All the title compounds synthesized (2a-2d) were tested for antibacterial activity by Broth Dilution Method method using *E.coli, P.aeruginosa, S.aureus, S.pyogenus* as microbial strains and Sulphacetamide sodium as standard. The compound 2d showed significant antibacterial activity at 62.5µg/ml as compared with Sulphacetamide Sodium.

All the title compounds synthesized (2a-2d) were tested for antifungal activity by Broth Dilution Method method using *C.albicans, A.niger* and *A.clavatus* as microbial strains and Sulphacetamide sodium as standard. The compound 2a showed moderate antifungal activity at 500 µg/ml as compared with Sulphacetamide Sodium.

CONCLUSION

In summary, the present work concludes a simple and novel method for the synthesis of Chalconyl incorporated Schiff's bases without using any costly chemicals and any drastic conditions.

Most of the compounds have displayed considerable antimicrobial activity as indicated in Broth dilution method in comparison with standard drug. Compound **2d** showed significant antibacterial activity and rest showed poor activity against the test. Therefore, the nature of groups in chalcone moiety is very important for antimicrobial activity. Compound **2a** showed moderate antifungal activity while the rest showed its absence. These new findings might be beneficial in future research and development of Schiff's bases containing chalcone nucleus as novel antimicrobial agent.

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