



Research Article

Synthesis of some new Schiff bases of Pharmaceutical Interest

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Submitted: 17 August 2017

Approved: 25 September 2017

Published: 26 September 2017

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Keywords: Schiff base; Diphenylamine derivative; Antibacterial activity; Amines

Abstract

A series of Schiff bases of diphenylamine derivatives have been synthesized and evaluated *in vitro* for their antibacterial activity against pathogenic both Gram-positive bacteria *B. subtilis* and Gram-negative bacteria *E. coli* using ciprofloxacin as standard drug at conc. of 50 µg/ml and 100 µg/ml. The structures of these compounds were established on the basis of IR and ¹H-NMR spectral analysis. The compound (3d) displayed potent antibacterial activity against *Bacillus subtilis* (17 and 15mm) and *Escherichia coli* (19 and 17mm) by disc diffusion method.

Introduction

The major classes of almost all antibiotics are encountering resistance in clinical applications [1,2]. Searching for novel antimicrobial agents is in demand in the global market to counter life-threatening infections. In order to overcome this rapid development of drug resistance, new scaffolds need to be developed, preferably consisting of chemical characteristics that clearly differ from those of existing agents. The compounds with the structure of -C=N- (azomethine group) are known as Schiff base, which are usually synthesized from the condensation of primary amines and active carbonyl groups. Schiff base have been of great interest in medicinal chemistry for their role as potent antimicrobial, antitubercular, anticancer, antiviral, antimalarial, antibacterial and antifungal agents [3-10]. Therefore, Schiff bases are important compounds due to their wide range of biological activities and their industrial applications. They also serve as a back bone for the synthesis of various heterocyclic compounds [11]. In view of the wide interest in the biological activities and profile of Schiff bases, we described herein the synthesis, characterization and antibacterial activity of some new Schiff bases of diphenylamine derivatives.

Materials and Methods

All reagents were purchased from CDH of commercial quality and were used without further purification. Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The IR spectra of synthesized compounds were recorded in potassium bromide discs on Shimadzu FTIR Spectrophotometer 8300. The ¹H NMR spectra of the synthesized compounds were recorded in DMSO using AV-300 BROKE JEOL Spectrophotometer and tetramethylsilane (TMS) as an internal standard. The signals are expressed in δ ppm. The reactions progress was monitored by thin-layer chromatography (TLC) using silica gel G and spots were visualized in an iodine chamber.

Chemistry

Synthesis of 2-Chloro-N, N-diphenylacetamide (1)

Diphenylamine (6.76gm, 0.004mol) was dissolved in toluene (200ml) in a 250ml round bottom flask and chloroacetylchloride (3.18ml, 0.004mol) was added. The

reaction mixture was refluxed for 4hr. A total of 400ml of the water was then added to the reaction mixture and kept overnight for the precipitation of the product, which was filtered, washed with water, dried and recrystallized from ethanol to afford the colorless compound [12].

Synthesis of 2-(4-Formylphenoxy)-N, N-diphenylacetamide (2)

2-Chloro-N, N-diphenylacetamide (0.982gm, 0.004mole) was dissolved in acetonitrile (100ml) in a 250 ml round bottom flask and para hydroxy benzaldehyde (0.488gm, 0.004mol) was added. Anhydrous potassium carbonate (1.008gm 0.008mol) and catalytic amount of potassium iodide was added. The above reaction mixture was allowed to reflux with continuous stirring on magnetic stirrer for 16 hours. After completion of reaction, the reaction mixture was filtered and solvent was removed by vacuum distillation. The obtained product was recrystallized from ethanol and dried.

Yield: 65.45%; mp: 105°C; IR (cm⁻¹): 3057 (C-H Str. Ar), 2919 (C-H Str. Ali), 1593 (C=O Str.) 1315 (C-N Str.), 1250 (C-O-C Str.); ¹H NMR (DMSO-d₆): 4.66 (s, 2H, COCH₂), 6.92-7.82 (14H, Ar), 9.87 (s, 1H, CHO).

General Procedure for the Synthesis of various Schiff bases (3a-e)

2-(4-Formylphenoxy)-N, N diphenylacetamide (0.001mole) and appropriate aniline (0.001mol) was dissolved in an ethanol (100ml) in a 250ml of round bottom flask. The reaction mixture was allowed to reflux for 12h in the presence of glacial acetic acid (2-3 drops). The reaction mixture was cooled and kept overnight for precipitation. The precipitated product was filtered, recrystallized from ethanol and dried.

2-(4-(1-(Phenylimino) methyl) phenoxy)-N, N-diphenylacetamide (3a)

Yield: 74.50 %; mp: 180°C; IR (cm⁻¹): 3019(C-H Str.Ar), 2920 (C-H Str.Ali), 1599(C=O Str.) 1403(C-N Str.), 1216(C-O-C Str.); ¹H NMR (DMSO-d₆): 4.68(s, 2H, COCH₂), 6.93-8.40 (19H, Ar), 9.87(s, 1H, CHO).

Synthesis of 2-(4-(1-(4-Bromophenylimino) methyl) phenoxy) - N, N-diphenylacetamide (3b)

Yield: 77.40%; mp: 210°C; IR (cm⁻¹): 3019 (C-H Str.Ar), 2925(C-H Str.Ali), 1575(C=O Str.) 1321(C-N Str.), 1249(C-O-C Str.); ¹H NMR(DMSO-d₆): 4.68 (s, 2H, COCH₂), 6.93-8.40 (18H, Ar), 9.90(s, 1H, CHO).

Synthesis of 2-(4-(1-(2, 3-Dimethylphenylimino) methyl) phenoxy)-N, N-diphenylacetamide (3c)

Yield: 45.60%; mp: 160°C; IR (cm⁻¹): 3056(C-H Str.Ar), 2921(C-H Str.Ali), 1606(C=O Str.) 1406(C-N Str.), 1253(C-O-C Str.); ¹H NMR (DMSO-d₆): 2.11(3H, CH₃), 2.35(3H, CH₃), 4.68(s, 2H, COCH₂), 6.93-8.29(17H, Ar), 9.90(s, 1H, CHO).

Synthesis of 2-(4-(1-(4-chloro-2-nitrophenylimino) methyl) phenoxy)-N, N-diphenylacetamide (3d)

Yield: 75.70%; mp: 160°C; IR (cm⁻¹): 3037(C-H Str.Ar), 2912(C-H Str.Ali), 1604(C=O Str.) 1305 (C-N Str.), 1251(C-O-C Str.); ¹H NMR(DMSO-d₆): 4.69(s, 2H, COCH₂), 6.13-8.14(17H, Ar), 9.90(s, 1H, CHO).

Synthesis of 2-(4-(1-(4-chlorophenylimino) methyl) phenoxy)-N, N-diphenylacetamide (3e)

Yield: 78.90%; mp: 185°C; IR(cm⁻¹): 3037(C-H Str.Ar), 2920(C-H Str.Ali), 1579(C=O Str.) 1325(C-N Str.), 1251(C-O-C Str.); ¹H NMR(DMSO-d₆): 4.68(s, 2H, COCH₂), 6.61-8.36(18H, Ar), 9.90(s, 1H, CHO).

Antibacterial activity

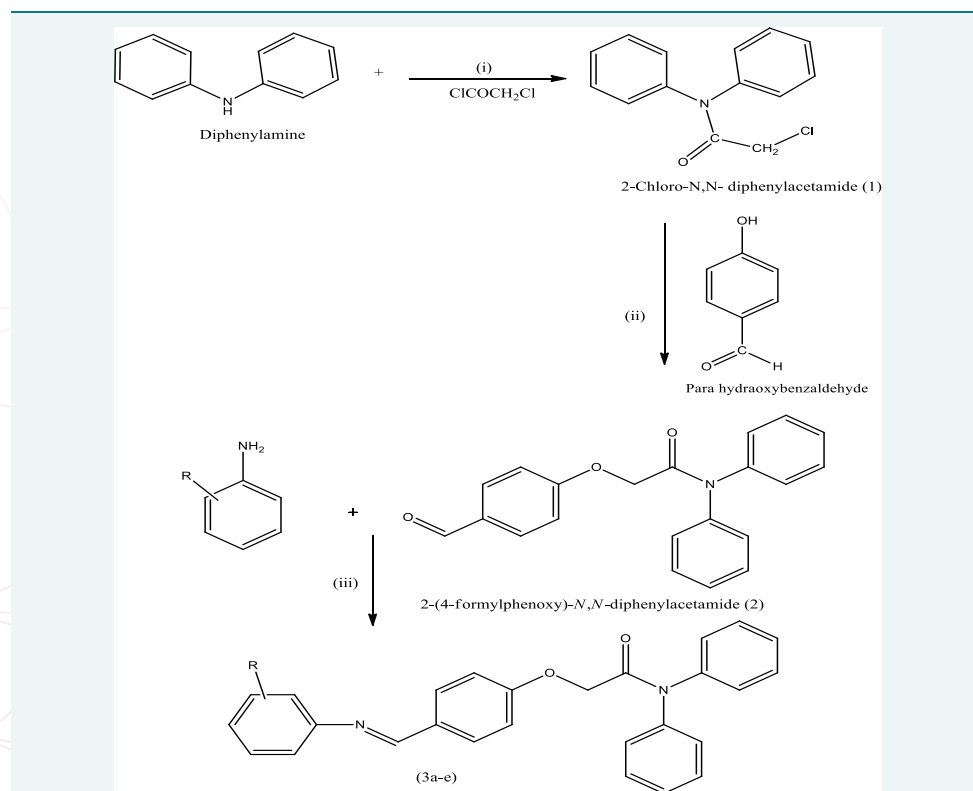
The antimicrobial activity of the compounds against human pathogenic Gram positive and Gram-negative bacteria was measured by measuring the zone of inhibition in disc diffusion method [13]. The synthesized compounds at 50 and 100 μ g/ml solutions in dimethylsulphoxide (DMSO) were evaluated *in vitro* for antibacterial activity against *B. subtilis* and *E. coli* [Table 1]. The measured zones of inhibition for the compounds ranged from 9-17 mm against *B. subtilis* and 8-19mm against *E. coli*. Based on zones of inhibition results, most of the compounds showed better activity against Gram negative bacteria than the activities against Gram positive bacteria. The potency has increased with group of 2-NO₂ and 4-Cl at substituted aromatic ring (3d analogs) against Gram negative as compared to Gram positive bacteria. Ciprofloxacin was used as a standard antibacterial agent. Dimethylsulphoxide was used as a control and did not show any inhibition zones. Sterile *Petri dishes* of 90 mm diameter were used for antibacterial study.

Results and Discussions

Five Schiff bases were synthesized as outlined in Scheme 1 and evaluated for antibacterial activity. The results of antibacterial activity are shown in table 1.

Table 1: Antibacterial activity of target compounds (3a-e) against the microbes.

Compounds	Zone of inhibition in mm			
	<i>B. subtilis</i>		<i>E. coli</i>	
	50 μ g	100 μ g	50 μ g	100 μ g
Control	-	-	-	-
Ciprofloxacin	22	25	22	25
3a	10	13	11	16
3b	12	11	14	15
3c	16	14	13	16
3d	15	17	17	19
3e	09	12	08	11



Scheme 1: Synthesis of target compounds. Reagents and condition: (i) Toluene, Reflux 4hr (ii) Acetonitrile, Anhy. K_2CO_3 , KI, Reflux (iii) Ethanol, Glacial acetic acid, Reflux.

The title compounds (3a-e) were obtained by the reaction of diphenylamine with chloroacetylchloride in toluene afforded 2-chloro-N,N-diphenylacetamide (1) which react with 4-hydroxybenzaldehyde in presence of potassium carbonate in acetonitrile afforded 2-(4-formylphenoxy)-N, N-diphenylacetamide (2), which on further reaction with various aniline in presence of glacial acetic acid in ethanol gave Schiff bases (3a-e). The structures of these compounds were established on the basis of M.P, TLC, IR and ¹H-NMR spectral analysis. The title compounds were screened for their antibacterial activity and showed variable inhibition activities against the tested bacterial strains. Among the compounds tested, 2-(4-(1-(4-chloro-2-nitrophenylimino) methylphenoxy)-N, N-diphenyl acetamide (3d) showed maximum zone of inhibition 19mm against E.coli and 17mm against B. subtilis at 100µg/ml. The activity was due substitution of aromatic ring by 4-chloro and 2-nitro group that indicates evidence of selectivity of the ligand to the tested strain.

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