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Original Research Article

COUMARIN DERIVATIVES AS POTENTIAL THERAPEUTIC AGENTS: SYNTHESIS, CHARACTERIZATION, COMPUTATIONAL STUDIES AND BIOLOGICAL EVALUATION

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Abstract: The present study is to chemical synthesis, characterization and pharmacological evaluation of new phenoxy benzoyl methane Schiff base (SB1-SB5) as an antifungal agents. Among these the SB2 formulation is more potent against Candida Albicans when compared to the standard drug that is Clotrimazole and Terbinafine. Computational studies was also performed here by the Chem 3D Ultra version 11.0, 8.0, Schrodinger suite software programs. The results were showed the good drug like properties. The result revealed that Schiff base work as an antifungal agent as compared to the Clotrimazole and Terbinafine against to the Candida Albicans.

Keywords: Candida Albicans, Computational studies, Clotrimazole and Schiff base.

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INTRODUCTION

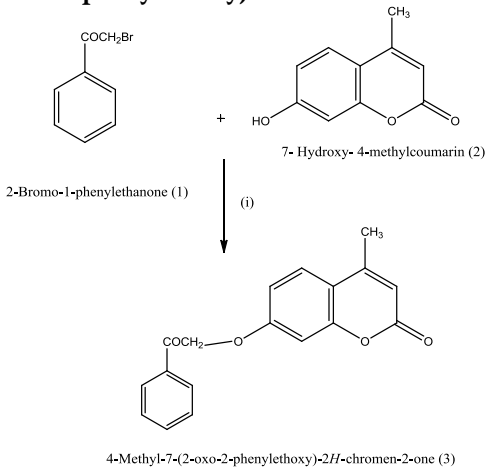
Schiff bases are the vital intermediates also as a common ligands in the organic compound synthesis and have been showed a broad ranges of biological activities, such as antimicarobial, antiviral, antioxidant, antineoplastic, and anthelmintic.in this compound imine are present which is shown an essential biological activities. Clotrimaozole and terbinafine are antifungal drug which contain nitrogen hetero atom into their structure. The sufficientconfirmationrecounted in the literature on the biological potential of Schiff bases containing C=N in their structure 1-5 led us to the synthesis, physico-chemical characterization and antifungal evaluation of new Schiff bases containing nitrogen hetro atom. The pharmacokinetic and pharmacodynamic behavior of molecules inside the human body is influenced by their molecular properties, molecular size, flexibility and the presence of different pharmacophore features. The in vivo experimental determination of pharmacokinetic parameters of newly synthesized compounds is uneconomical and time consuming. From this point of view, molecular properties can predict by the online software11. The molecular properties of the new compounds could help to eliminate the molecules likely to fail in the early stage of drug discovery. In view of these observations, we herein report the synthesis of new Schiff bases and evaluation as antifungal agents.

MATERIALS AND METHODS

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 Schimadzu FTIR Spectrophotometer 8300. The 1H-NMR spectra of the synthesized compounds were recorded in CDCl3 as solvent using AV-300 BROKE JEOL Spectrophotometer and tetramethylsilane (TMS) as an internal standard. All reagents were of commercial quality and were used without further purification. The reactions progress was monitored by thin-layer chromatography (TLC) using silica gel G and spots were visualized with iodine.

Synthesis and Characterization of Schiff bases:
Synthesis of Schiff bases

Step I. Synthesis of 4-methyl-7-(2-oxo-2-phenylethoxy)-2H-chromen-2-one



Scheme. Reagents and conditions :(i) Anhydrous acetonitrile, Anhydrous K_2CO_3, Reflux.

Procedure

Equimolar amounts of 2-bromo-1-phenylethanone **1** (0.01mol), 7-hydroxy-4-methylcoumarin **2** (0.01 mol) and

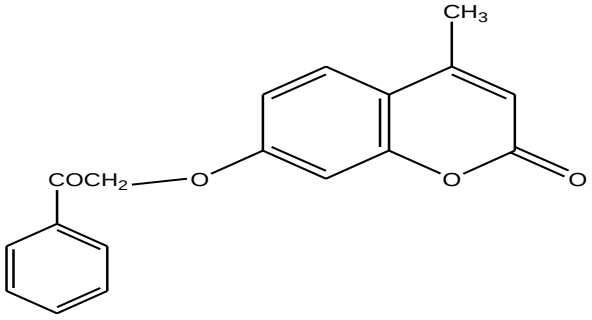
Anhydrous K_2CO_3 (0.02 mol) in dry acetonitrile was refluxed for about 8 h. The mixture was filtered and solvent was removed under reduced pressure. The resulting solid was washed with aqueous sodium hydroxide solution (20%) and with excess of water. The crude product was purified by recrystallization from ethanol to afford compound **3**.

The physical parameters were of 4-Methyl-7-(2-oxo-2-phenylethoxy)-2H-chromen-2-one **(3)** the following:

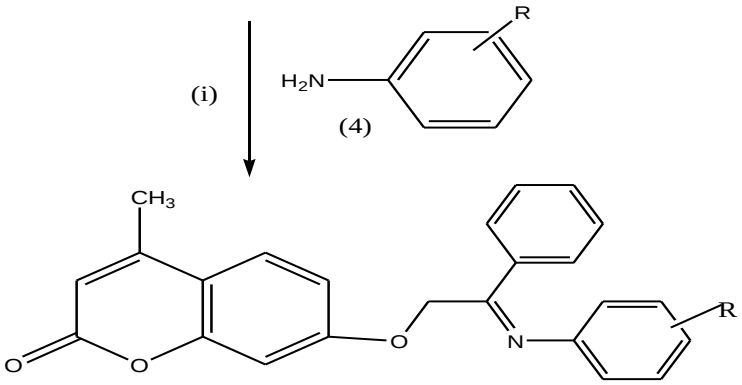
Percentage yield : 55.00%
Melting range : 138-140°C
R_f value : 0.86
Mobile phase : n-Hexane: Ethyl acetate (1:2)
Molecular formula : $C_{18}H_{14}O_4$

IR (KBr) ν (cm^{-1}): 3032 (CH, Ar Str.), 2932 (CH, Ali Str.), 1085 (C-O-C, Str.), 1690 (C=O Str). ^{1}H NMR ($CDCl_3$, δ ppm): 6.70-8.01 (9H, Ar.), 5.28 (2H, s, OCH_2), 2.81(3H, s, CH_3).

Step II. Synthesis of target compounds (Schiff bases)



4-methyl-7-(2-oxo-2-phenylethoxy)-2*H*-chromen-2-one (3)



7-(2-((substituted phenyl) imino)-2-phenylethoxy)-4-methyl-2H-chromen-2one

Scheme. Synthesis of the target compounds. Reagents and conditions :(i) Methanol, Glacial Acetic acid, Reflux.

Table 1- Substituents of compounds

Compound Code	R
SB-1	H
SB-2	4-CH_3
SB-3	4-Cl
SB-4	4-Br
SB-5	3,4-Cl

General procedure of synthesis for Schiff base:

A mixture of compound **3** (0.01 mol), substituted aniline **4** (0.01mol) and 1 ml of glacial acetic acid in methanol was refluxed on water bath for12 h. The mixture was allowed to cool, and then the separated solid waswashed with waterfiltered and recrystallized from methanol to afford the **SB-1 to SB-5**. The physical parameters were of the target compounds were following:

7-(2-((phenyl) imino)-2-phenylethoxy)-4-methyl-2H-chromen-2-one (SB-1)

Percentage yield : 52.00%
Melting range : 168-170 °C
R_f value : 0.30
Mobile phase : n-Hexane: Ethyl acetate (3:1)
Molecular formula : $C_{24}H_{19}NO_3$

IR (KBr) ν (cm^{-1}): 3064 (CH, Ar Str.), 2900 (CH, Ali Str.), 1152 (C-O-C, Str.), 1594 (C=N Str), 1228 (C-N Str.). ^{1}H NMR ($CDCl_3$, δ ppm): 6.51-8.45 (14H, Ar.), 5.41 (2H, s, OCH_2), 2.58 (3H, s, CH_3).

7-(2-((4-methylphenyl) imino)-2-phenylethoxy)-4-methyl-2H-chromen-2-one (SB-2)

Percentage yield : 54.00%
Melting range : 70-71 °C
R_f value : 0.45
Mobile phase : n-Hexane: Ethyl acetate (3:1)
Molecular formula : $C_{25}H_{21}NO_3$

IR (KBr) ν (cm^{-1}): 3061 (CH, Ar Str.), 2902 (CH, Ali Str.), 1152 (C-O-C, Str.), 1594 (C=N Str), 1228 (C-N Str.). ^{1}H NMR ($CDCl_3$, δ ppm): 6.62-7.98 (13H, Ar.), 5.41 (2H, s, OCH_2), 2.58 (3H, s, CH_3), 2.38 (3H, s, CH_3).

7-(2-((4-chlorophenyl) imino)-2-phenylethoxy)-4-methyl-2H-chromen-2-one (SB-3)

Percentage yield : 60.00%
Melting range : 140-142 oC
Rf value : 0.43
Mobile phase : n-Hexane: Ethyl acetate (3:1)
Molecular formula : C24H18ClNO3

IR (KBr) ν (cm-1): 3061 (CH, Ar Str.), 2900 (CH, Ali Str.), 1163 (C-O-C, Str.), 1615 (C=N Str), 1209 (C-N Str.). 1H NMR (CDCl3, δ ppm): 6.61-8.08 (13H, Ar.), 5.47 (2H, s, OCH2), 2.57 (3H, s, CH3).

7-(2-((4-bromophenyl) imino)-2-phenylethoxy)-4-methyl-2H-chromen-2-one (SB-4)

Percentage yield : 62.00%
Melting range : 150-152 oC
Rf value : 0.35
Mobile phase : n-Hexane: Ethyl acetate (3:1)
Molecular formula : C24H18BrNO3

IR (KBr) ν (cm-1): 3064 (CH, Ar Str.), 2901 (CH, Ali Str.), 1163 (C-O-C, Str.), 1615 (C=N Str), 1209 (C-N Str.). 1H NMR (CDCl3, δ ppm): 6.60-8.00 (13H, Ar.), 5.58 (2H, s, OCH2), 2.58 (3H, s, CH3).

7-(2-((3, 4-dichlorophenyl) imino)-2-phenylethoxy)-4-methyl-2H-chromen-2-one (SB-5)

Percentage yield : 67.00%
Melting range : 68-70 oC
Rf value : 0.43
Mobile phase : n-Hexane: Ethyl acetate (3:1)
Molecular formula : C24H17Cl2NO3

IR (KBr) ν (cm-1): 3064 (CH, Ar Str.), 2900 (CH, Ali Str.), 1162 (C-O-C, Str.), 1594 (C=N Str), 1228 (C-N Str.). 1H NMR (CDCl3, δ ppm): 6.67-8.11 (12H, Ar.), 5.41 (2H, s, OCH2), 2.58 (3H, s, CH3).

Computational Studies

A set of physicochemical properties was computed for the target compounds as well as two standard drugs Clotrimazole and Terbinafine by using Chem 3D Ultra version 11.0, 8.0, Schrodinger suite software programs. The observations are depicted in given Table. The log P values of test compounds were calculated and also for standard drugs. Steric and molecular surface descriptors computed include Connolly solvent accessible surface area (SAS, A2), Connolly molecular surface area (MSA, A2), Connolly solvent excluded volume (SEV, A3), and Ovality. Global physiochemical properties computed were molecular weight (MW), molar refractivity (MR), molecular topological index (MTI) and Wiener index (WI) for the test compounds

Table- Calculation of physicochemical properties for Series B: Schiff bases (SB-1 to SB-5)

Cpd. Code.	MW[a]	MR[b]	tPSA[c]	SAS[d] (A^2)	MSA[e] (A^2)	SEV[f] (A^3)	MTI[g]	WI[h]	Ov[i]	Log P
SB-1	369.41	110.64	47.89	600.78	319.53	277.42	16633	2183	1.550	4.91
SB-2	443.44	120.54	47.87	636.54	346.65	306.12	18750	2681	1.573	5.74
SB-3	403.86	115.24	47.87	616.36	332.89	292.78	17740	2418	1.561	5.47
SB-4	448.31	118.33	47.89	621.61	337.54	298.96	17740	2418	1.561	5.23
SB-5	438.30	119.85	47.89	630.61	333.18	291.86	18110	2486	1.526	6.03
Clotrimazole	344.82	102.07	15.6	540.05	284.92	270.21	9498	1225	1.409	5.19
Terbinafine	291.43	99.36	3.24	596.56	311.07	265.26	10280	1273	1.558	5.52

aMolecular weight
bMolar refractivity
cTopological polar surface area
dConnolly solvent accessible surface area
eConnolly molecular surface area
fConnolly solvent excluded volume
gMolecular topological index
hWienner index

iOvality
NC: Not calculated

Pharmacological evaluation of Schiff Base:

Antifungal Activity: The antifungal testing was performed using the cup diffusion technique. The synthesized compounds, as 1 mg/ml solutions in dimethylformamide (DMF), were evaluated in vitro for activity against C. albicans by the cup diffusion technique [Kumar et al., 2010]. Compounds showing inhibitory zones of at least 20 mm were considered active and were further evaluated for their minimal inhibitory concentration (MIC) using the two-fold serial dilution method [Sikarwar et al., 2016]. Clotrimazole and Terbinafine were used as standard antifungal agents. Dimethylformamide was used as a control. Sterile nutrient agar was inoculated with the test organisms (each 100 mL of the medium received 1 mL of 24 h broth culture), and then seeded agar was poured into sterile petri dishes. Cups (8 mm in diameter) were cut in the agar, and each cup received 0.1 mL of the test compound solution. The plates were then incubated at 37°C for 24 h. The activity was estimated as zones of inhibition in mm diameter. Clotrimazole and Terbinafine solutions (0.01%) were used as reference standards. DMF did not show any inhibition zones.

Minimum inhibitory concentration (MIC) measurement

Using the two-fold serial dilution method, the test organisms were grown in suitable broth for 48 h for fungi at 37°C. Two-fold serial dilutions of the test compounds solutions were prepared using the suitable broth to obtain concentrations between 1000 and 15.62 µg/ml. The tubes were then inoculated with the test organism (each 5 ml received 0.1 ml of the above inoculum) and were incubated at 37°C for 48 hr. The tubes were then observed for the presence or absence of microbial growth. The lowest concentration showing no growth was taken as the minimum inhibitory concentration. The MIC values of the prepared compounds are listed in given Table.

Table- The Antifungal Activity: Schiff bases (SB-1 to SB-5).

Compound Code	Zone of Inhibition (in mm) Against *C. Albicans*	MIC (µg/ml) Against *C. Albicans*
SB-1	20	31.24
SB-2	25	31.24
SB-3	20	NC
SB-4	24	15.62
SB-5	14	NC
Clotrimazole	26	1.95
Terbinafine	26	2.60

CONCLUSION

The present study is concluded that the synthesis, characterization, computational study and pharmacological evaluation were revealed the result that SB2 formulation of Schiff base has a potent drug action as an antifungal which is against to the Candida Albicans with comparison to Clotrimazole and Terbinafine. As standard drug. As a result, the synthesised chemicals offer a fresh platform for the creation of innovative antifungal drugs.

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