Khalid Mohammed Khan et al. / Journal of Pharmacy Research 2011,4(10),3402-3404

Research Article
ISSN: 0974-6943

Available online through
www.jpronline.info

Bis-Schiff Bases of Isatins: A New Class of Antioxidant

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Received on: 19-06-2011; Revised on: 08-07-2011; Accepted on:01-10-2011

ABSTRACT

Twenty seven (27) derivatives of *bis*-Schiff bases of isatins **1-27** were screened for their antioxidant potential. Out of twenty seven (27), four compounds exhibited a varying degree of superoxide anion radical scavenging activity with IC_{50} values ranging between 156.34 - 273.15 μM. Compounds **7** (IC_{50} = 156.34 ± 0.22 μM**)**, **9** (IC_{50} = 273.15 ± 1.60 μM), **13** (IC_{50} = 224.12 ± 0.80 μM), and **16** (IC_{50} = 225.03 ± 0.73 μM) showed a good superoxide anion radical scavenging activity, when compared to standard *n*-propyl gallate (IC_{50} = 104.04 ± 1.70 μM). However, compounds **3** and **7** exhibited DPPH radical scavenging activity with IC_{50} values 436.90 ± 0.59, 46.63 ± 0.26 μM, respectively.

Key words: Isatins, *bis*-Schiff bases, DPPH radical scavengers, super oxide anion scavengers

INTRODUCTION

Bis-Schiff bases derivatives possess a variety of pharmacological activities, such as anticancer[1], antifungal, herbicidal[2,3] and antibacterial activities[4], while Schiff bases of various heterocycles were reported to possess cytotoxic[5], antiproliferative[6], anticonvulsant [7], anticancer activities[8]. Many of the biological activities of isatins Schiff base include anticonvulsant, analgesic, anti-inflammatory, antidepressant, pro-apoptotic, cytotoxicity, antioxidant, and antimicrobial activities [9]. Antioxidants prevent injury to blood vessel membranes and thus help to optimize blood flow to the heart and brain. They provide defense against DNA mutations, and help to lower the risk of cancers, as well as cardiovascular diseases, and dementia, including Alzheimer's disease [10-13]

MATERIALS AND METHODS:

Chemicals and equipments:

Isatin, Hydrazine Hydrate, Substituted benzaldehyde, Ethanol, Acetic acid, Hot plate, Heating mantle.

METHODS:

Synthesis of *bis*-Schiff bases of isatins:

The preparation of hydrazones was carried out by refluxing a mixture of isatin (1 g) and hydrazine hydrate (10 mL). Then these isatin hydrazones (1 mmol) and different substituted aromatic aldehydes (1 mmol) in methanol were refluxed for 3 h. The progress of reaction was monitored by TLC. After completion of the reaction (TLC analysis), cooled reaction mixture was filtered and crystalline *bis*-Schiff bases were collected, washed with methanol, and dried to afford pure compounds. In some cases, precipitates were obtained which on crystallization from methanol afforded pure crystals. The structures of all the compounds **1-27** were determined by ^{1}H NMR and EI MS techniques. All compounds gave satisfactory elemental analysis [14].

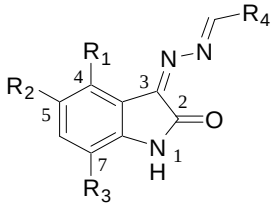

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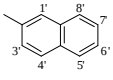
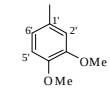
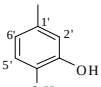
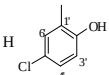
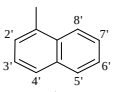
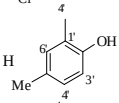
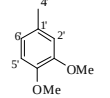
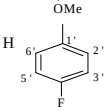
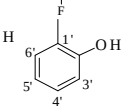
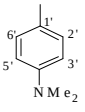
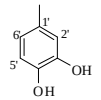
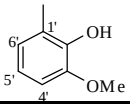
Table-1: Structures of *bis*-Schiff bases of isatins 1-27

Compounds	R_1	R_2	R_3	R_4	Compounds	R_1	R_2	R_3	R_4
1	H	H	H		**15**	Cl	H	Cl	
2	H	H	H		**16**	H	H	H	
3	Cl	H	Cl		**17**	H	H	H	
4	H	H	H		**18**	Cl	H	Cl	
5	H	H	H		**19**	H	H	H	
6	H	H	H		**20**	H	H	H	
7	H	H	H		**21**	H	H	H	
8	H	H	H		**22**	H	H	H	
9	H	H	H		**23**	H	H	H	
10	H	H	H		**24**	H	Cl	H	
11	H	H	H		**25**	H	Cl	H	
12	Cl	H	Cl		**26**	H	Cl	H	
13	H	H	H		**27**	H	Cl	H	
14	H	H	H		-	-	-	-	-

2-Hydroxybenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(1)**[13]
Yield: 83%; Anal. Calcd for $C_{15}H_{11}N_3O_2$ (265.09): C, 67.92; H, 4.18; N, 15.84; O, 12.06; Found: C, 67.91; H, 4.19; N, 15.84.

4-Hydroxybenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(2)**[13]
Yield: 87%; Anal. Calcd for $C_{15}H_{11}N_3O_2$ (265.09): C, 67.92; H, 4.18; N, 15.84; O, 12.06; Found: C, 67.90; H, 4.19; N, 15.85.

*2-Naphthaldehyde-N-(4,7-dichloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone (***3)** [13]
Yield: 98%; Anal. Calcd for $C_{19}H_{11}Cl_2N_3O$ (367.03): C, 61.98; H, 3.01; Cl, 19.26; N, 11.41; O, 4.35; Found: C, 61.96; H, 3.02; N, 11.42.

2-Naphthaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(4)** [13]
Yield: 86%; Anal. Calcd for $C_{19}H_{13}N_3O$ (299.11): C, 76.24; H, 4.38; N, 14.04; O, 5.35; Found: C, 76.24; H, 4.39; N, 14.03.

3-Chlorobenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(5)**[13]
Yield: 86 %; Anal. Calcd for $C_{15}H_{10}ClN_3O$ (283.05): C, 63.50; H, 3.55; Cl, 12.50; N, 14.81; O, 5.64; Found: C, 63.48; H, 3.56; N, 14.82.

2-Methoxybenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(6)**[13]
Yield: 82%; Anal. Calcd for $C_{16}H_{13}N_3O_2$ (279.10): C, 68.81; H, 4.69; N, 15.05; O, 11.46; Found: C, 68.82; H, 4.69; N, 15.04.

3,4-Dihydroxybenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(7)**[13]
Yield: 86%; Anal. Calcd for $C_{15}H_{11}N_3O_3$ (281.08): C, 64.05; H, 3.94; N, 14.94; O, 17.07; Found: C, 64.04; H, 3.95; N, 14.93.

3,4-Dichlorobenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(8)**[13]
Yield: 89 %; Anal. Calcd for $C_{15}H_9Cl_2N_3O$ (317.01): C, 56.63; H, 2.85; Cl, 22.29; N, 13.21; O, 5.03; Found: C, 56.65; H, 2.84; N, 13.20.

1-Naphthaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(9)** [13]
Yield: 84%; Anal. Calcd for $C_{19}H_{13}N_3O$ (299.11): C, 76.24; H, 4.38; N, 14.04; O, 5.35; Found: C, 76.25; H, 4.39; N, 14.05.

4-Fluorobenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(10)**[13]
Yield: 88%; Anal. Calcd for $C_{15}H_{10}FN_3O$ (267.08): C, 67.41; H, 3.77; F, 7.11; N, 15.72; O, 5.99; Found: C, 67.42; H, 3.77; N, 15.74.

2-Fluorobenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(11)** [13]
Yield: 78%; Anal. Calcd for $C_{15}H_{10}FN_3O$ (267.08): C, 67.41; H, 3.77; F, 7.11; N, 15.72; O, 5.99; Found: C, 67.43; H, 3.75; N, 15.74.

2-Florobenzaldehyde-N-(4,7-dichloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(12)**[13]
Yield: 84%; Anal. Calcd for $C_{15}H_8Cl_2FN_3O$ (335.00): C, 53.60; H, 2.40; Cl, 21.09; F, 5.65; N, 12.50; O, 4.76; Found: C, 53.61; H, 2.40; N, 12.49.

4-(Dimethylamino)benzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(13)** [13]
Yield: 86%; Anal. Calcd for $C_{17}H_{16}N_4O$ (292.13): C, 69.85; H, 5.52; N, 19.17; O, 5.47; Found: C, 69.85; H, 5.53; N, 19.16.

2-Hydroxy-3-methoxybenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(14)** [13]
Yield: 71%; Anal. Calcd for $C_{16}H_{13}N_3O_3$ (295.10): C, 65.08; H, 4.44; N, 14.23; O, 16.25; Found: C, 65.09; H, 4.42; N, 14.24.

2-Hydroxy,3-methoxybenzaldehyde-N-(4,7-dichloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(15)**[13]
Yield: 77%; Anal. Calcd for $C_{16}H_{11}Cl_2N_3O_3$ (363.02): C, 52.77; H, 3.04; Cl, 19.47; N, 11.54; O, 13.18; Found: C, 52.76; H, 3.06; N, 11.53.

3-Hydroxybenzaldehyde N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(16)**[13]
Yield: 81%; Anal. Calcd for $C_{15}H_{11}N_3O_2$ (265.09): C, 67.92; H, 4.18; N, 15.84; O, 12.06; Found: C, 67.92; H, 4.19; N, 15.83.

4-Ethoxybenzaldehyde N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(17)** [13]
Yield: 86%; Anal. Calcd for $C_{17}H_{15}N_3O_2$ (293.12): C, 69.61; H, 5.15; N, 14.33; O, 10.91; Found: C, 69.62; H, 5.13; N, 14.33.

3,4-Dimethoxybenzaldehyde-N-(4,7-dichloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(18)**[13]
Yield: 68%; Anal. Calcd for $C_{17}H_{13}Cl_2N_3O_3$ (377.03): C, 53.99; H, 3.46; Cl, 18.75; N, 11.11; O, 12.69; Found: C, 54.00; H, 3.45; N, 11.11.

2-Ethoxybenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(19)**[13]
Yield: 85%; Anal. Calcd for $C_{17}H_{15}N_3O_2$ (293.12): C, 69.61; H, 5.15; N, 14.33; O, 10.91; Found: C, 69.62; H, 5.12; N, 14.35.

4-Nitrobenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(20)**[13]
Yield: 86%; Anal. Calcd for $C_{15}H_{10}N_4O_3$ (294.08): C, 61.22; H, 3.43; N, 19.04; O, 16.31; Found: C, 61.21; H, 3.43; N, 19.05.

2-Nitrobenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(21)**[13]
Yield: 87%; Anal. Calcd for $C_{15}H_{10}N_4O_3$ (294.08): C, 61.22; H, 3.43; N, 19.04; O, 16.31; Found: C, 61.22; H, 3.41; N, 19.05.

5-Chloro-2-hydroxybenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(22)**[13]
Yield: 90%; Anal. Calcd for $C_{15}H_{10}ClN_3O_2$ (299.05): C, 60.11; H, 3.36; Cl, 11.83; N, 14.02; O, 10.68; Found: C, 60.10; H, 3.38; N, 14.01.

2-Hydroxy-5-methylbenzaldehyde-N-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(23)**[13]
Yield: 87%; Anal. Calcd for $C_{16}H_{13}N_3O_2$ (279.10): C, 68.81; H, 4.69; N, 15.05; O, 11.46; Found: C, 68.80; H, 4.70; N, 15.05.

3,4-Dimethoxybenzaldehyde-N-(5-chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(24)**[13]
Yield: 70%; Anal. Calcd for $C_{17}H_{14}ClN_3O_3$ (343.07): C, 59.40; H, 4.10; Cl, 10.31; N, 12.22; O, 13.96; Found: C, 59.37; H, 4.12; N, 12.21.

4-Florobenzaldehyde-N-(5-chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(25)**[13]
Yield: 55%; Anal. Calcd for $C_{15}H_9ClFN_3O$ (301.04): C, 59.71; H, 3.01; Cl, 11.75; F, 6.30; N, 13.93; O, 5.30; Found: C, 59.70; H, 3.03; N, 13.96.

2-Hydroxybenzaldehyde-N-(5-chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(26)**[13]
Yield: 83%; Anal. Calcd for $C_{15}H_{10}ClN_3O_2$ (299.05): C, 60.11; H, 3.36; Cl, 11.83; N, 14.02; O, 10.68; Found: C, 60.10; H, 3.38; N, 14.02.

3,4-Dihydroxybenzaldehyde-N-(5-chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazone **(27)** [13]
Yield: 69%; Anal. Calcd for $C_{15}H_{10}ClN_3O_3$ (315.04): C, 57.07; H, 3.19; Cl, 11.23; N, 13.31; O, 15.20; Found: C, 57.08; H, 3.19; N, 13.30.

***In Vitro* Assay for Superoxide Anion Radical Scavenging Activity**

The superoxide producing system was set up by mixing phenazine methosulfate (PMS), NADH, and oxygen (air), and the production of superoxide was estimated by the nitroblue tetrazolium method. Measurement of superoxide radical scavenging activity was carried out by the modified method used by Candan 2003[15]. In aerobic reaction mixtures containing NADH, phenazine methosulphate and nitroblue tetrazolium, PMS was reduced by NADH and then gave raise to O_2^-, which in turn reduced NBT. On the basis of this, PMS has frequently been used to mediate O_2^-.

The reaction mixture comprises 40 μL of 100 µM β-nicotinamide adenine dinucleotide reduced form (NADH), 40 μL of 80 μM nitroblue tetrazolium (NBT), 20 μL of 8 μM phenazine methosulphate (PMS) 10 μM of 1 mM sample, and 90 µM of 0.1 M M phosphate buffer (pH 7.4). The reagents were prepared in buffer and sample in DMSO. The reaction was performed in 96-well microtitre plate at room temperature and absorbance was measured at 560 nm. The formation of superoxide was monitored by measuring the formation of water soluble blue Formazan dye. A lower absorbance of reaction mixture indicated a higher scavenging activity of sample.

Percent Radical Scavenging Activity (% RSA) by samples were determined in comparison with a control.

% RSA= 100 – {(OD test compound / OD control) X 100

DPPH (1, 1-Diphenyl-2-picryl hydrazyl) free radical scavenging activity

The hydrogen donating activity of compounds was measured by 1,1-diphenyl-2-picrylhydrazil (DPPH), using literature protocol of Khan *et. al*. 2003 [16]. Reaction mixture contains 5 µL of test sample (1 mM in DMSO) and 95 µL of DPPH (Sigma, 300 µM) in ethanol. The reaction mixture was taken into a 96-well microtiter plates and incubated at 37 ˚C for 30 min. The absorbance was measured at 515 nm on microtiter plate reader (Spectra Max Molecular Devices, CA, USA). Percent radical scavenging activity was determined by comparing with a DMSO containing control. IC_{50} Values represent the concentration of compounds to scavenge 50% of DPPH radicals. *n*-Propyl gallate was used as a positive control. All the chemicals used were of analytical grade (Sigma, USA).

RESULTS AND DISCUSSION

Superoxide anion and DPPH radical scavenging potential studies

We have previously reported the *bis*-Schiff bases of isatins **1**-**27** as novel antiglycating agents [13]. Oxidative stress seems to be involved in the pathophysiology of diabetes, and cardiovascular complications of metabolic syndrome [15]. Keeping in view the above-mentioned relationship between diabetes and oxidative stress, we decided to re-synthesize the compounds **1**-**27** screened them for their antioxidant potential and the results showed that theses compounds have also antioxidant potential. Compound **7** showed an excellent antiglycation activity in our previous studies also showed reasonable superoxide anion radical and DPPH radical scavenging activities. Therefore, this compound with dual activities can be the more appropriate lead compound for antidiabetic drug development.

Out of twenty seven (27), four compounds *i.e.* **7** (IC_{50} = 156.34 ± 0.22 µM), **9** (IC_{50} = 273.15 ± 1.60 µM), **13** (IC_{50} = 224.12 ± 0.80 µM), and **16** (IC_{50} = 225.03 ± 0.73 µM) exhibited a varying degree of superoxide anion radical scavenging activity, while compound **3** (IC_{50} = 436.90 ± 0.59 µM), and **7** (IC_{50} = 46.63 ± 0.26 µM) exhibited a DPPH radical scavenging potential. The most active analog against both superoxide anion, and DPPH radicals was compound **7** with IC_{50} values 156.34 ± 0.22, and 46.63 ± 0.26 µM, respectively. The potent radical scavenging activity of compound **7** may be attributed to the catechol moiety. Compound **7** was reported as a novel antiglycating agent in our previous study with IC_{50} value of 291.14 ± 2.53 µM antiglycation activity [25]. This dual inhibition property makes compound **7** an excellent candidate for further research. However, compound **3** with moderate antiglycation potential (IC_{50} = 416.0 ± 15.82 µM) was found to be a week DPPH radical scavenger (IC_{50} = 436.90 ± 0.59 µM).

Table-2: Results of Superoxide anion and DPPH Radical Scavenging assays of *bis*-Schiff bases of isatins 1-27

Compounds	Superoxide IC_{50} ± SEM[a] (µM)	DPPH IC_{50} ± SEM[a] (µM)
1	NA[b]	NA[b]
2	NA[b]	NA[b]
3	NA[b]	436.90 ± 0.59
4	NA[b]	NA[b]
5	NA[b]	NA[b]
6	NA[b]	NA[b]
7	156.34 ± 0.22	46.63 ± 0.26
8	NA[b]	NA[b]
9	273.15 ± 1.60	NA[b]
10	NA[b]	NA[b]
11	NA[b]	NA[b]
12	NA[b]	NA[b]
13	224.12 ± 0.80	NA[b]
14	NA[b]	NA[b]
15	NA[b]	NA[b]
16	225.03 ± 0.73	NA[b]
17	NA[b]	NA[b]
18	NA[b]	NA[b]
19	NA[b]	NA[b]
20	NA[b]	NA[b]
21	NA[b]	NA[b]
22	NA[b]	NA[b]
23	NA[b]	NA[b]
24	NA[b]	NA[b]
25	NA[b]	NA[b]
26	NA[b]	NA[b]
27	NA[b]	NA[b]
n-Propyl gallate (st)	106.04 ± 1.70	30.13 ± 0.27

SEM[a] is the standard error of the mean, NA[b] Not active, n-propyl gallate (st) standard inhibitor for Superoxide anion and DPPH radical scavenging assay.

Compounds **13**, **16,** and **9** exhibited superoxide anion radical scavenging activity with IC_{50} values of 224.12 ± 0.80, 225.03 ± 0.73 and 273.15 ± 1.60 µM, respectively. These compounds were found to have an antiglycation potential with IC_{50} values of 405.51 ± 2.69, 634.05 ± 3.39, and 380.30 ± 10.64 µM, respectively in our previous study [15].

CONCLUSION:

In conclusion, compound **7** was found to have a dual inhibitory potential, both as antioxidants as well as antiglycating agents. This study provides a basis to study the dual pharmacological potentials against diabetes. In compounds **3**, **9**, **13**, and **16** may also be modified synthetically for approaching a molecule having both, antiglycation and antioxidant properties.

ACKNOWLEDGEMENTS:

This work was supported by the Higher Education Commission (HEC) Pakistan, project No. 20-1394/R&D/09 under National Research Support Program for Universities.

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Source of support: Nil, Conflict of interest: None Declared