Bioorganic & Medicinal Chemistry 17 (2009) 7795–7801

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis of bis-Schiff bases of isatins and their antiglycation activity

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ARTICLE INFO

Article history:
Received 13 August 2009
Revised 14 September 2009
Accepted 15 September 2009
Available online 19 September 2009

Keywords:
Isatins
Bis-Schiff bases
Antiglycation
AGEPs

ABSTRACT

Bis-Schiff bases **1–27** have been synthesized and their in vitro antiglycation potential has been evaluated. Compounds **21** (IC_{50} = 243.95 ± 4.59 μM), **20** (IC_{50} = 257.61 ± 5.63 μM), and **7** (IC_{50} = 291.14 ± 2.53 μM) showed an excellent antiglycation activity better than the standard (rutin, IC_{50} = 294.46 ± 1.50 μM). This study has identified a series of potential molecules as antiglycation agents. A structure–activity relationship has been studied, and all the compounds were characterized by spectroscopic techniques.

1. Introduction

Schiff bases form an important class of organic compounds with a wide variety of biological properties.[1–5] Development of a new chemotherapeutic Schiff bases is now attracting the attention of medicinal Chemist.[6] Many studies have reported regarding the biological activities of Schiff bases, including their anticancer,[7] antibacterial,[8] antifungal, and herbicidal activities.[9,10] Schiff bases, derived from various heterocycles, were reported to possess cytotoxic,[11] anticonvulsant,[12] antiproliferative,[13] anticancer, and antifungal activities.[14] A number of Schiff bases[15–18] have been tested for antibacterial,[19–22] antifungal,[21–23] anticancer,[24,25] and herbicidal[26] activities.

Isatin and its analogs are versatile substrates, which can be used for the synthesis of numerous heterocyclic compounds. Isatins also have important pharmacological and biological activities.[27]

A variety of biological activities are associated with Schiff bases of isatin including CNS activities as potentiation of pentobarbitone induce nercosis,[28] analgesic,[29] anticonvulsant,[30] antidepressant,[31] antiinflammatory,[32] antimicrobial, and effects on the central nervous system.[33] Isatins are capable of crossing the blood–brain-barrier.[34]

In the present study, in vitro antiglycation activity of a series of bis-Schiff base derivatives **1–27** has been evaluated in continuation of our previous study.[35] Discovery of antiglycation agents is an important approach for the treatment of late diabetic complications. Since currently number of effective antiglycating agents is very small, the need of new antiglycating agents is still unmet.[36]

As the unpleasant incident of type-2 diabetes is increasing, its injurious effects are mostly attributed to the formation of sugar-derived substances called advanced glycation end products (AGEPs)[37] which are important pathogenic mediators of almost all diabetic complications.[38]

Schiff bases are formed initially by reaction between protein and glucose without any enzyme, whereas the rearrangement of Schiff base intermediate to Amadori product takes number of days. Extensive effort has been focused on the discovery of new inhibitors of glycation, because of their therapeutic potential.[39] Certain molecules have been developed that can cleave AGEPs cross-links and perhaps open the possibility of reversing the steady process of diabetic complications.[40] It has been found that aged garlic extract (AGE) inhibit the formation of AGEPs in vitro and prevents the formation of glycation-derived free radicals. *S*-Allylcysteine is a very important component of aged garlic extract that acts as a potent antioxidant and thus inhibit the AGEPs formation.[41,42]

Aminoguanidine, an inhibitor of AGEPs formation was found to prevent retinopathy in diabetic animals and protect them from developments of diabetic vascular complications. However, aminoguanidine has encountered some toxicity problems in phase III clinical trials.[43] Efforts have now been made to develop new and safe synthetic antiglycation agents.[44] It has been demonstrated that polyamines, spermine and spermidine have potent antiglycation effects, comparable to those of aminoguanidine and carnosine.[45]

2. Chemistry

Bis-Schiff bases **1–27** were synthesized from commercially available isatins by refluxing with hydrazine hydrate and then

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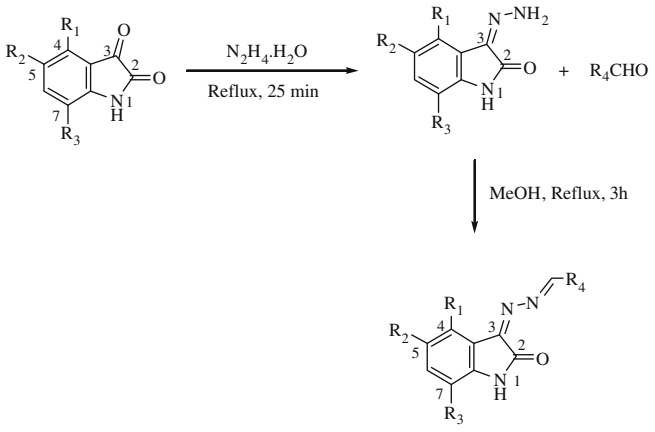
doi:10.1016/j.bmc.2009.09.028

condensing with different aromatic aldehydes in methanol in very high yields (Scheme 1). In a typical reaction isatin (1 g) were dissolved in hydrazine hydrate (10 ml) and refluxed for 25 min to afford hydrazone. Then condensation of these hydrazones with different substituted aromatic aldehydes in equimolar amount in methanol under reflux for 3 h, the progress of reaction was monitored by TLC. After cooling and filtration the crystalline powder of bis-Schiff bases was collected, then washed with methanol and dried to afford compounds **1–27** in high yields. Recrystallization from methanol afforded pure crystals. The structures of synthesized compounds **1–27** were determined by employing different spectroscopic techniques including ^{1}H NMR, EI, IR, and UV spectroscopy.

3. Bioactivity

It is reported that a Schiff base adduct between aminoguanidine and pyridoxal is responsible for inhibiting advanced glycation end product (AGEPs) formation. Moreover, it has been found that the inhibitory potential of adduct against advanced protein glycation was similar/or more than that of aminoguanidine when assessed by fluorometry and ELISA.[46] By taking into account, we have prepared bis-Schiff bases **1–27** of isatin to evaluate their antiglycation potential. Recently we have reported unsymmetrically disubstituted urea derivatives as a new class of potent antiglycating agents.[47] Herein, we are reporting bis-Schiff bases **1–27** which were evaluated for their in vitro antiglycation activity[35] as a new class of antiglycating agents.[47,48] Compounds **1–27** exhibited a varying degree of antiglycation activity IC_{50} values ranging between 243.95 and 634.05 μM, and compared with standard rutin (IC_{50} = 294.46 ± 1.50 μM) (Table 1). Compounds **21** (IC_{50} = 243.95 ± 4.59 μM), **20** (IC_{50} = 257.61 ± 5.63 μM), and **7** (IC_{50} = 291.14 ± 2.53 μM) showed an excellent antiglycation activity better than the standard (rutin, IC_{50} = 294.46 ± 1.50 μM). Compounds **5** (IC_{50} = 311.81 ± 12.62 μM), **2** (IC_{50} = 313.22 ± 5.92 μM), **14** (IC_{50} = 358.58 ± 8.98 μM), **11** (IC_{50} = 361.98 ± 5.56 μM), **18** (IC_{50} = 365.55 ± 1.03 μM), **9** (IC_{50} = 380.30 ± 10.64 μM), **13** (IC_{50} = 405.51 ± 2.69 μM), **19** (IC_{50} = 415.92 ± 8.39 μM), **3** (IC_{50} = 416.0 ± 15.82 μM), **1** (IC_{50} = 444.11 ± 7.29 μM), **6** (IC_{50} = 458.38 ± 7.55 μM), and **27** (IC_{50} = 469.24 ± 0.00 μM) exhibited a moderate antiglycation potential. Nevertheless, both compounds **16** and **22** were found to possess an antiglycation activity with the IC_{50} value of 634.05 ± 3.39 μM, thus considered to be least active among the series. Additionally compounds **4**, **8**, **10**, **12**, **15**, **17**, and **23–26** showed less than 50% inhibition, therefore they were not further evaluated for their IC_{50} values.

Compounds **20** and **21** are the most active analogs of the series with IC_{50} values of 257.61 ± 5.63 μM and 243.95 ± 4.59 μM, having



Scheme 1. Synthesis of bis-Schiff bases from isatin.

Table 1
In vitro antiglycation activity of compounds **1–27**

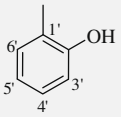
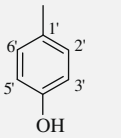
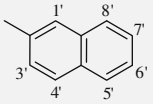
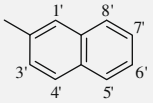
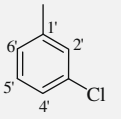
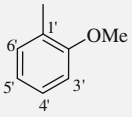
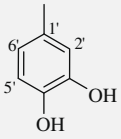
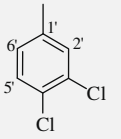
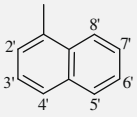
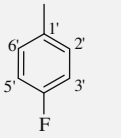
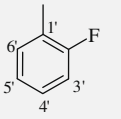
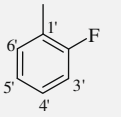
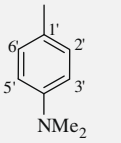
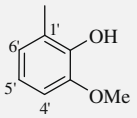
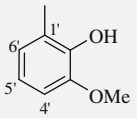
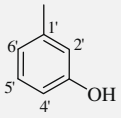
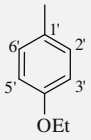
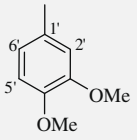
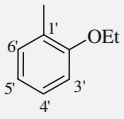
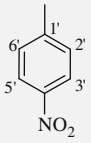
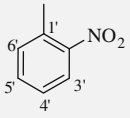
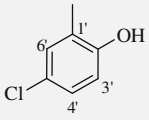
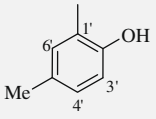
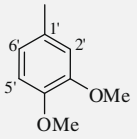
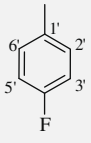
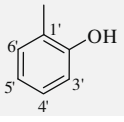
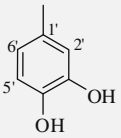
Compounds	R_1	R_2	R_3	R_4	IC_{50} ± SEM[a] (μM)
1	H	H	H		444.11 ± 7.29
2	H	H	H		313.22 ± 5.92
3	Cl	H	Cl		416.00 ± 15.82
4	H	H	H		NA[b]
5	H	H	H		311.81 ± 12.62
6	H	H	H		458.38 ± 7.55
7	H	H	H		291.14 ± 2.53
8	H	H	H		NA[b]
9	H	H	H		380.30 ± 10.64
10	H	H	H		NA[b]
11	H	H	H		361.98 ± 5.56
12	Cl	H	Cl		NA[b]
13	H	H	H		405.51 ± 2.69

Table 1 (*continued*)

Compounds	R_1	R_2	R_3	R_4	IC_{50} ± SEM[a] (μM)
14	H	H	H		358.58 ± 8.98
15	Cl	H	Cl		NA[b]
16	H	H	H		634.05 ± 3.39
17	H	H	H		NA[b]
18	Cl	H	Cl		365.55 ± 1.03
19	H	H	H		415.92 ± 8.39
20	H	H	H		257.61 ± 5.63
21	H	H	H		243.95 ± 4.59
22	H	H	H		634.05 ± 3.39
23	H	H	H		NA[b]
24	H	Cl	H		NA[b]
25	H	Cl	H		NA[b]
26	H	Cl	H		NA[b]
27	H	Cl	H		469.24±1.7
Rutin[c]					294.46 ± 1.50

[a] SEM is the standard error of the mean.
[b] NA: not active.
[c] Rutin standard inhibitor for antiglycation activity.

nitro groups at *para*- and *ortho*-position, respectively. It is expected that nitro group has formed a Zwitter complex with carbonyl group of methylglyoxal which resulted in potentially high antiglycation activity. Similarly compound **7**, a dihydroxy analog, was found to be the third most active antiglycating agent with IC_{50} of 291.14 ± 2.53 μM. Activity related to this compound might be due to acetal formation by the reaction of dihydroxy analog **7** and the carbonyl group of methylglyoxal.

Compounds **2** and **1** are hydroxyl analogs of Schiff bases with IC_{50} values of 313.22 ± 5.92 and 444.11 ± 7.29 μM, respectively. *para*-Hydroxyl group in compound **2** is suppose to be involved in hemiacetal formation with methylglyoxal, however, the *ortho* analog, which is relatively hindered, shows a lower IC_{50} value than its *para* analog **2**. On the other hand compound **14** (IC_{50} = 358.58 ± 8.98 μM) has *ortho*-hydroxyl group with a *meta*-methoxy group was found to be more active than compound **1**, this probably might be due to electron donating effect of methoxy group.

Compounds **3**, **9**, **13**, **18**, and **19** is a group of compounds which do not have any functional group, capable of reacting with methylglyoxal, however, they exhibited a measurable amount of antiglycation potential. This may be due to electron-donating groups or electron rich substituents such as naphthyl group.

A remarkable effect on the antiglycation activity due to presence of electron withdrawing groups at isatin was observed. Compounds **12**, **15**, **24**–**27** with electron withdrawing groups at isatin moiety, either showed extremely low antiglycation potential or complete lack of activity. Surprisingly, compound **27** (IC_{50} = 469.24 ± 0.00 μM) showed a sharp decline in activity, whereas its closely related compound **7** showed an excellent activity (IC_{50} = 291.14 ± 2.53 μM). This variation in activity may be due to the presence of a chloro group at position 5 of isatin. Similarly, effect of chloro groups at positions 4 and 7 can be seen in the compounds **11** and **12**.

4. General experimental

Melting points were determined on a Büchi 434 melting point apparatus and were uncorrected. NMR experiments were performed on Avance Bruker AM 300 MHz CHN analysis was performed on a Carlo Erba Strumentazion-Mod-1106, Italy. Ultraviolet (UV) spectra were recorded on Perkin–Elmer Lambda-5 UV/vis spectrometer in MeOH. Infrared (IR) spectra were recorded on JASCO IR-A-302 spectrometer as KBr (disk). Electron impact mass spectra (EI MS) were recorded on a Finnigan MAT-311A, Germany. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm.

4.1. Assay for antiglycation

4.1.1. Chemicals

Bovine serum albumin (BSA) was purchased from the Research Organics (Cleveland, USA), while other chemicals {glucose

anhydrous, trichloroacetic acid (TCA) sodium azide (NaN_3), dimethyl sulfoxide (DMSO), sodium dihydrogen phosphate (NaH_2PO_4), sodium chloride (NaCl), disodium hydrogen phosphate (Na_2HPO_4), potassium chloride (KCl), potassium dihydrogen phosphate (KH_2PO_4), and sodium hydroxide (NaOH) were purchased from Sigma–Aldrich. Sodium phosphate buffer (pH 7.4), was prepared by mixing Na_2HPO_4 and NaH_2PO_4 (67 mM) containing sodium azide (3 mM). Phosphate buffer saline (PBS) was prepared by mixing NaCl (137 mM), Na_2HPO_4 (8.1 mM), KCl (2.68 mM), and KH_2PO_4 (1.47 mM) and pH 10 was adjusted with NaOH (0.25 mM). BSA (10 mg/ml) and glucoses anhydrous (50 mg/ml) solutions were prepared in sodium phosphate buffer. Test samples were prepared in DMSO (1 mM/ml).

This test was used to evaluate the ability of the candidate compounds to inhibit the methyl glyoxal mediated development of fluorescence of BSA. Activity was performed by using the reported method[48,49] with the following modifications:

Triplicate samples of BSA 100 mg/ml, 14 mM MGO, 0.1 M phosphate buffer (pH 7.4) containing NaN_3 (30 mM) was incubated under aseptic conditions at 37 °C for 9 days in the presence or absence of various concentrations of the test compounds. After 9 days of incubation, each sample was examined for the development of specific fluorescence (excitation, 330 nm; emission, 440 nm) on a microtitre plate spectrophotometer (Spectra Max, Molecular Devices, USA). Rutin was used as a positive control (IC_{50} = 294 μM ± 1.50 SEM).

The percent inhibition of AGE formation in the test sample versus control was calculated for each compound by using the following formula:

$$\% \text{ inhibition} = (1 - \text{fluorescence of test sample/fluorescence of the control group}) \times 100$$

5. General procedure for the synthesis of compounds 1–27

The preparation of hydrazone's was carried out by refluxing a mixture of isatin (1 g) and hydrazine hydrate (10 ml). Then this hydrazone (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 cooling and filtration the crystalline powder of Schiff bases were collected, then washed with methanol and dried to afford compounds **1–27** in high yields. Recrystallization from methanol afforded pure crystals.

5.1. 2-Hydroxybenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (1)

Yield: 0.22 g, 83%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.8 (s, 1H, N–H), 11.27 (s, 1H, O–H), 8.91 (s, 1H, –N=CH), 7.71 (d, 1H, $J_{4,5}$ = 7.8 Hz, H-4), 7.52 (d, 1H, $J_{6',5'}$ = 8.0 Hz, H-6′), 7.41 (t, 2H $J_{6,5,7/5',6',4'}$ = 7.9 Hz, H-6/H-5′), 7.08 (t, 1H, $J_{4',3',5'}$ = 8.0 Hz, H-4′), 7.00 (d, 1H, $J_{3',4'}$ = 8.0 Hz, H-3′), 6.88 (t, 1H, $J_{5,4,6}$ = 7.8 Hz, H-5), 6.85 (d, 1H, $J_{7,6}$ = 7.8 Hz, H-7),; EI MS: *m/z* (rel. abund.%), 265 (M^+, 37.3), 237 (100), 146 (9.5), 118 (65), 91 (18.4), 63 (28.1).

5.2. 4-Hydroxybenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (2)

Yield: 0.23 g, 87%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.99 (s, 1H, N–H), 10.79 (s, 1H, O–H), 8.59 (s, 1H, C=H), 8.02 (d, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 7.84 (d, 2H, $J_{2',3'/6',5'}$ = 8.6 Hz, H-2′/H-6′), 7.50 (d, 1H, $J_{7,6}$ = 7.5 Hz, H-7), 7.00 (d, 2H, $J_{3',2'/5',6'}$ = 8.6 Hz, H-3′/H-5′), 6.9 (m, 2H, H-5/H-6); EI MS: *m/z* (rel. abund.%), 265 (M^+, 4), 237 (100), 210 (8.9), 133 (11), 118 (30), 65.1 (10).

5.3. 2-Naphthaldehyde-*N*-(4,7-dichloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (3)

Yield: 0.33 g, 98%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.87 (s, 1H, –N=CH), 8.1 (s, 1H, C=H), 8.0 (s, 1H, H-1′), 7.90 (m, 4H, H-5′–8′), 7.65 (m, 2H, H-3′,4′), 7.21 (d 1H, $J_{5,6}$ = 8.6 Hz, H-5), 7.00 (d, 1H, $J_{6,5}$ = 8.6 Hz, H-6); EI MS: *m/z* (rel. abund.%), 367 (M^+, 12), 339 (70), 229 (100), 172 (44), 138 (40), 127 (57), 75 (13).

5.4. 2-Naphthaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (4)

Yield: 0.26 g, 86%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.23 (s, 1H, N–H), 8.74 (s, 1H, –N=CH), 8.41 (s, 1H, H-1′), 8.00 (m, 4H, H-5′–8′), 7.8 (d 1H, $J_{4,5}$ = 7.6 Hz, H-5) 7.62 (m, 2H, H-3′,4′), 7.40 (t, 1H, $J_{6,7,5}$ = 7.6 Hz, H-6), 7.04 (t, 1H, $J_{5,4,6}$ = 7.6 Hz, H-5), 6.92 (d, 1H, $J_{7,6}$ = 7.6 Hz, H-7); EI MS: *m/z* (rel. abund.%), 299 (M^+, 8), 271 (100), 243 (18), 153 (11), 127 (42), 77 (6).

5.5. 3-Chlorobenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (5)

Yield: 0.24 g, 86%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.1 (s, 1H, N–H), 8.71 (s, 1H, –N=CH), 7.97 (br s, 1H, H-6′), 7.93 (d, 1H, $J_{4',3'}$ = 8.1 Hz, H-4′), 7.80 (d, 1H, $J_{7,6}$ = 7.5 Hz, H-7), 7.64 (m, 2H, H-4/H-6), 7.40 (t, 1H, $J_{3',2',4'}$ = 8.1 Hz, H-3′), 7.03 (t, 1H, $J_{5,4,6}$ = 7.5 Hz, H-5), 6.90 (d, 1H, $J_{2',3'}$ = 8.1 Hz, H-2′); EI MS: *m/z* (rel. abund.%), 284 (M^+, 6), 225(29), 179 (65), 151 (25), 78 (97), 63 (100).

5.6. 2-Methoxybenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (6)

Yield: 0.23 g, 82%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.05 (s, 1H, N–H), 8.81 (s, 1H, –N=CH), 8.10 (dd, 1H, $J_{4,6}$ = 1.51 Hz, $J_{4,5}$ = 7.7 Hz, H-4), 7.97 (d, 1H, $J_{6',5'}$ = 7.2 Hz, H-6′), 7.58 (td, 1H, $J_{4',2',6'}$ = 1.6 Hz, $J_{4',5',3}$ = 7.2 Hz, H-4′), 7.39 (td, 1H, $J_{6,7,5}$ = 7.7 Hz, $J_{6,4}$ = 1.1 Hz, H-6), 7.20 (d, 1H, $J_{3',4'}$ = 7.2 Hz, H-3′), 7.14 (t, 1H, $J_{5,6,4,}$ = 7.5 Hz, H-5), 7.03 (t, 1H, $J_{5',6',4',}$ = 7.2 Hz, H-5′), 6.90 (d, 1H, $J_{7,6}$ = 7.2 Hz, H-7); EI MS: *m/z* (rel. abund.%), 279 (M^+, 3), 251 (100), 208 (20.1), 118 (32), 91 (25), 77 (19).

5.7. 3,4-Dihydroxybenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (7)

Yield: 0.24 g, 86%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.5 (s, 1H, N–H), 8.51 (s, 1H, –N=CH) 8.09 (d, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 7.4 (s, 1H, H-2′), 7.38 (t, $J_{6,7,5}$ = 7.5 Hz, 1H, H-6), 6.94 (t, 1H, $J_{5,6,4,}$ = 7.5 Hz, H-5), 6.9 (d, 1H $J_{7,6}$ = 7.5 Hz, H-4), 6.88 (d, 1H, $J_{6,'5'}$ = 8.1 Hz, H-6′), 6.86 (d, 1H, $J_{5',6'}$ = 8.1 Hz, H-5′); EI MS: *m/z* (rel. abund.%), 281 (M^+, 3), 253 (100), 226 (11), 118 (24).

5.8. 3,4-Dichlorobenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (8)

Yield: 0.28 g, 89%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.89 (s, 1H, N–H), 8.56 (s, 1H, –N=CH), 8.16 (s, 1H, H-2), 7.98 (dd, 1H, $J_{7,5}$ = 1.5 Hz, $J_{7,6}$ = 8.3 Hz, H-7), 7.84(d, 1H, $J_{4,5}$ = 8.3 Hz, H-4), 7.77(d, 1H, $J_{5',6'}$ = 7.7 Hz, H-5′) 7.40 (t, 1H, $J_{6,7,5}$ = 8.3 Hz, H-6), 7.02 (t, 1H, $J_{5,6,4}$ = 8.3 Hz, H-5), 6.9 (d, 1H, $J_{6',5}$ = 7.7 Hz, H-6′); EI MS: *m/z* (rel. abund.%), 319 (M^+, 4), 289 (100), 145 (24), 118 (74), 91 (17), 91 (17).

5.9. 1-Naphthaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (9)

Yield: 0.25 g, 84%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.90 (s, 1H, N–H), 9.26 (s, 1H, –N=CH), 8.27 (d, 1H, $J_{8',7'}$ = 6.87 Hz, H-8′),

8.18 (d, 1H, $J_{4,5}$ = 8.1 Hz, H-4), 8.07 (d, 1H, $J_{5',6'}$ = 7.6 Hz, H-5′), 7.94 (d, 1H, $J_{4',3'}$ = 7.6 Hz, H-4′), 7.67 (m, 4H, H-), 7.39 (dt, 1H, $J_{5,7}$ = 0.90, $J_{5,4,6}$ = 8.1 Hz H-5), 6.99 (t, 1H, $J_{6,7,5}$ = 8.1 Hz, H-6), 6.92 (d, 1H, $J_{7,6}$ = 8.1 Hz, Ar-H); EI MS: *m/z* (rel. abund.%), 299 (M^+, 3.0), 271 (100), 244 (27), 154 (15), 127 (67), 77 (11).

5.10. 4-Fluorobenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (10)

Yield: 0.24 g, 88%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.65 (s, 1H, N–H), 8.63 (s, 1H, –N=CH), 8.06 (dd, 2H, $J_{3',5'/5',3'}$ = 5.7, $J_{3',2'/5',6'}$ = 8.7 Hz, H-3/5), 7.9 (d, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 7.40 (m, 3H, H-4′/5′/5), 7.03 (t, 1H, $J_{6,5,7}$ = 7.50 Hz, H-6), 6.90 (d, 1H, $J_{7,6}$ = 7.5 Hz, H-7); EI MS: *m/z* (rel. abund.%), 267 (M^+, 7), 239 (100), 212 (9), 118(76), 95 (71).

5.11. 2-Fluorobenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (11)

Yield: 0.21 g, 78%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.55 (s, 1H, N–H), 8.86 (s, 1H, –N=CH), 8.15 (dt, 1H, $J_{4',6'}$ = 1.7 Hz, $J_{4',5',3'}$ = 7.6 Hz, H-4′), 7.89 (d, 1H, $J_{4,5}$ = 7.2 Hz, H-4), 7.64 (m, 1H, H-6′) 7.42 (m, 3H, H-3′/5′/6), 7.03 (t, 1H, $J_{5,4,6}$ = 7.2 Hz, H-5), 6.89 (d, 1H, $J_{7,6}$ = 7.2 Hz, H-7); EI MS: *m/z* (rel. abund.%), 267 (M^+, 7), 239 (100), 212 (7), 118(92), 75 (44).

5.12. 2-Florobenzaldehyde-*N*-(4,7-dichloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (12)

Yield: 0.28 g, 84%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.97 (s, 1H, N–H), 8.5 (s, 1H, –N=CH), 7.31 (m, 4H, H-6′,5′,4′,3′), 7.25 (d, 1H, $J_{6,5}$ = 8.4 Hz, H-6), 6.99 (d, 1H, $J_{5,6}$ = 8.4 Hz, H-5); EI MS: *m/z* (rel. abund.%), 335 (M^+, 19), 307 (64), 229 (76), 186 (100), 122 (65) 75 (81).

5.13. 4-(Dimethylamino)benzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (13)

Yield: 0.25 g, 86%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.90 (s, 1H, N–H), 8.61 (s, 1H, –N=CH), 8.20 (d, 1H, $J_{4,5}$ = 7.3 Hz, H-4), 7.89 (d, 2H, $J_{2',3'/6',5'}$ = 9 Hz, H-2/6), 7.36 (t, 1H, $J_{6,7,5}$ = 7.3 Hz, H-6), 7.3 (t, 1H, $J_{5,6,4}$ = 7.3 Hz, H-5), 6.88 (d, 2H, $J_{3',2'/5',6'}$ = 9.0 Hz, H-3′/5′), 6.84 (d, 1H, $J_{7,6}$ = 7.3 Hz, H-7), 3.05 (s, 6H, N(Me)$_2$); EI MS: *m/z* (rel. abund.%), 292 (M^+, 55), 264 (100), 147 (58), 118 (35), 77 (45).

5.14. 2-Hydroxy-3-methoxybenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (14)

Yield: 0.21 g, 71%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.98 (s, 1H, N–H), 11 (s, 1H, O–H), 9.00 (s, 1H, –N=CH) 7.6 (br d, 1H, $J_{4,5}$ = 7.7 Hz, H-4), 7.4 (dt, 1H, $J_{6,4}$ = 1.06 Hz, $J_{6,5,7}$ = 7.7 Hz, H-6), 7.20 (dd, $J_{6',4'}$ = 1.15 Hz, $J_{6',5'}$ = 7.8 Hz, 1H, H-6′), 7.1 (dd, 1H, $J_{3',4'}$ = 1.09 Hz, J = 7.8 Hz, H-3′), 7.0 (dt, 1H, $J_{5,7}$ = 1.44 Hz, $J_{5,6,4}$ = 7.7 Hz, H-5), 6.9 (t, 1H, $J_{5',6',4'}$ = 7.8 Hz, H-5′), 7.0 (br d, 1H, $J_{7,6}$ = 7.7 Hz, H-7), 3.82 (s, 3H, OMe); EI MS: *m/z* (rel. abund.%), 295 (M^+, 48), 267 (99), 252 (100), 135 (47), 118 (89).

5.15. 2-Hydroxy,3-methoxybenzaldehyde-*N*-(4,7-dichloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (15)

Yield: 0.28 g, 77%; (^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.79 (s, 1H, N–H), 11.61 (s, 1H, O–H), 8.98 (s, 1H, –N=CH) 7.50 (d, 1H, $J_{6,5}$ = 8.7 Hz, H-6), 7.29 (d, 1H, $J_{6',5'}$ = 7.8 Hz, H-6′), 7.18 (d, 1H, $J_{4',5'}$ = 7.8 Hz, H-4′), 7.12(d, $J_{5,6}$ = 8.7 Hz, H-5), 6.94 (t, 1H, $J_{5',4',6'}$ = 7.8 Hz, H-5′), 3.82 (s, 1H, OMe); EI MS: *m/z* (rel. abund.%), 363 (M^+, 54), 335 (49), 215 (52), 135 (73), 108 (82), 52 (100).

5.16. 3-Hydroxybenzaldehyde *N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (16)

Yield: 0.22 g, 81%; (^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.98 (s, 1H, N–H), 9.8 (s, 1H, O–H), 8.7 (s, 1H, –N=CH), 7.57 (d, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 7.4(d, 1H, $J_{6',5'}$ = 8.2 Hz, H-6′), 7.31 (t, 1H, $J_{5',4',6'}$ = 8.2 Hz, H-5′), 7.11 (d, 1H, $J_{4',5'}$ = 8.2 Hz, H-4′), 7.0 (t, 1H, $J_{6,7,5}$ = 7.5 Hz, H-6), 6.9 (t, 1H, $J_{5,6,4}$ = 7.5 Hz, H-5), 6.80 (s, 1H, H-2′), 6.72 (d, 1H, $J_{7,6}$ = 7.5 Hz, H-7); EI MS: *m/z* (rel. abund.%), 265 (M^+, 40), 234 (86), 144 (59.6), 118 (100).

5.17. 4-Ethoxybenzaldehyde *N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (17)

Yield: 0.25 g, 86%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.04 (s, 1H, N–H), 8.85 (s, 1H, –N=CH), 8.10 (dd, 1H, $J_{4,7}$ = 1.41 Hz, $J_{4,5,}$ = 7.8 Hz H-4), 8.00 (d, 2H, $J_{6',5'/2',3'}$ = 7.5 Hz, H-6′/2′), 7.55 (td, 1H, $J_{6,4}$ = 1.54 Hz, $J_{6,5,7}$ = 7.8 Hz, H-6) 7.39 (td, 1H, $J_{5,7}$ = 1.40 Hz, $J_{5,6,4}$ = 7.8 Hz H-5), 7.18 (d, 1H, $J_{7,6}$ = 7.8 Hz, H-7), 6.89 (d, 2H, $J_{5',6'/3',2'}$ = 7.5 Hz, H-3/5), 4.15 (q, J = 7.0 Hz, 2H, OCH_2), 1.38 (t, 3H, J = 7 Hz, CH_3); EI MS: *m/z* (rel. abund.%), 293 (M^+, 4.09), 265 (97), 160 (27), 133 (90), 118 (100), 90 (77).

5.18. 3,4-Dimethoxybenzaldehyde-*N*-(4,7-dichloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (18)

Yield: 0.26 g, 68%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.5 (s, 1H, N–H), 8.75 (s, 1H, –N=CH), 7.85 (s, 1H, H-2′), 7.75 (d, 1H, $J_{7,6}$ = 8.4 Hz, H-7), 7.72 (d, 1H, $J_{6',5'}$ = 7.5 Hz, H-6′), 7.25 (d, 1H, $J_{5,6}$ = 8.4 Hz, H-5), 7.10 (s, 1H, H-2′), 6.99 (d, 1H, $J_{5',6'}$ = 7.5 Hz, H-5), 3.8 (s, 3H, OCH_3), 3.7 (s, 3H, OCH_3); EI MS: *m/z* (rel. abund.%), 378 (M^+, 19), 307 (64), 229 (75.89), 186 (100), 122 (65) 75 (81).

5.19. 2-Ethoxybenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (19)

Yield: 0.25 g, 85%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.09 (s, 1H, N–H), 8.85 (s, 1H, –N=CH), 8.10 (dd, 1H, $J_{4,6}$ = 1.42 Hz, $J_{4,5}$ = 7.5 Hz, H-4), 8.00 (d, 1H, $J_{6',5'}$ = 8.2 Hz, H-6′), 7.58 (td, 1H, $J_{4',6'}$ = 1.6 Hz, $J_{4',5',3'}$ = 8.2 Hz, H-4′), 7.39 (t, 1H, $J_{6,7,5}$ = 7.5 Hz, H-6) 7.2 (d, 1H, $J_{3',4'}$ = 8.2 Hz, H-3′), 7.1 (t, 1H, $J_{5,4,6}$ = 7.5 Hz, H-5), 7.0 (t, 1H, $J_{5',4'6'}$ = 8.2 Hz, H-5′), 9.90 (d, 1H, $J_{7,6}$ = 7.5 Hz, H-7), 4.15 (q, 2H, J = 6.9 Hz, OCH_2), 1.38 (t, 3H, J = 6.9 Hz, CH_3); EI MS: *m/z* (rel. abund.%), 293 (M^+, 4), 265 (92), 160 (28), 133 (100), 118 (98), 91 (69).

5.20. 4-Nitrobenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (20)

Yield: 0.25 g, 86%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.92 (s, 1H, N–H), 8.67 (s, 1H, –N=CH), 8.39 (d, 2H, $J_{3',2'/5',6'}$ = 8.7 Hz, H-3′/5′), 8.21 (d, 2H, $J_{2',3'/6',5'}$ = 8.7 Hz, H-2′/6′), 7.74 (d, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 7.4 (t, 1H, $J_{6,7,5}$ = 7.5 Hz, H-6), 7.01 (t, 1H, $J_{5,4,6}$ = 7.5 Hz, H-5), 6.9 (d, 1H, $J_{7,6}$ = 7.5 Hz, H-7); EI MS: *m/z* (rel. abund.%), 294 (M^+, 19), 266 (100), 220 (76), 118 (91), 91 (20).

5.21. 2-Nitrobenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (21)

Yield: 0.26 g, 87%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.92 (s, 1H, N–H), 8.79 (s, 1H, –N=CH) 8.23 (d, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 8.15 (d, 1H, $J_{3',4'}$ = 7.8 Hz, H-4′), 7.93 (t, 1H, $J_{4',5',3'}$ = 7.8 Hz, H-4′), 7.84 (t, 1H, $J_{3',2',4'}$ = 7.8 Hz, H-3′), 7.75 (d, 1H, $J_{6',5'}$ = 7.8 Hz, H-6′); 7.41 (t, 1H, $J_{6,7,5}$ = 7.5 Hz, H-6), 7.00 (t, 1H, $J_{5,4,6}$ = 7.5 Hz, H-5), 6.90 (d, 1H, $J_{7,6}$ = 7.5 Hz, H-7); EI MS: *m/z* (rel. abund.%), 294 (M^+, 6), 264 (5), 159 (76), 131 (100), 103 (67), 91 (38).

5.22. 5-Chloro-2-hydroxybenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (22)

Yield: 0.27 g, 90%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.86 (s, 1H, N–H), 10.99 (s, 1H, O–H), 8.95 (s, 1H, –N=CH) 7.78 (d, 1H, $J_{6',4'}$ = 2.7 Hz, H-6′), 7.63 (d, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 7.46 (m, 2H, H-6/4′), 7.07 (t, 1H, $J_{5,4,6}$ = 7.5 Hz, H-5), 7.03 (d, 1H, $J_{3',4'}$ = 8.7, H-3′), 6.96 (d, 1H, $J_{7,6}$ = 7.5 Hz, H-7); EI MS: *m/z* (rel. abund.%), 279 (M^+, 94), 251 (100), 134 (28), 118 (89), 77 (27).

5.23. 2-Hydroxy-5-methylbenzaldehyde-*N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (23)

Yield: 0.24 g, 87%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.67 (s, 1H, N–H), 10.96 (s, 1H, O–H), 8.95 (s, 1H, –N=CH) 7.62 (d, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 7.43 (m, 2H, H-6/7), 7.3 (dd, $J_{4',6'}$ = 1.8 Hz, $J_{4',3'}$ = 8.4 Hz, 1H, H-4′), 7.06 (t, 1H, $J_{5,4,6}$ = 7.5 Hz, H-5), 6.94 (d, 1H, $J_{3',4'}$ = 8.4 Hz, H-3′), 2.26 (s, 3H, Me); EI MS: *m/z* (rel. abund.%), 299 (M^+, 100), 271 (82), 118 (83), 91 (11).

5.24. 3,4-Dimethoxybenzaldehyde-*N*-(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (24)

Yield: 0.24 g, 70%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.97 (s, 1H, N–H), 8.67 (s, 1H, –N=CH), 8.09 (d, 1H, $J_{4,6}$ = 1.8 Hz, H-4), 7.58 (br s, 1H, H-2′), 7.53 (d, 1H, $J_{7,6}$ = 8.4 Hz, H-7), 7.45 (dd, 1H, $J_{6,4}$ = 1.8 Hz, $J_{6,7}$ = 8.4 Hz, H-6), 7.17 (d, 1H, $J_{6',5'}$ = 8.4 Hz, H-6′), 6.92 (d, 1H, $J_{5',6'}$ = 8.4 Hz, H-5′), 3.87 (s, 6H, OMe); EI MS: *m/z* (rel. abund.%), 343 (M^+, 8), 315 (100), 245 (42), 152 (39), 79 (46.9).

5.25. 4-Florobenzaldehyde-*N*-(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (25)

Yield: 0.17 g, 55%; (^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.9 (s, 1H, N–H), 8.65 (s, 1H, –N=CH), 8.04 (dd, 2H, $J_{3',5'/5',3'}$ = 5.7 Hz, $J_{3',2'/5',6'}$ = 8.7 Hz, H-3/5), 7.84 (d, 1H, $J_{4,6}$ = 2.4 Hz, H-4), 7.5 (d, 2H, $J_{2',3'/6',5'}$ = 8.7 Hz, H-2′/6′), 7.3 (d, 1H $J_{6,7}$ = 8.4 Hz, H-6), 6.93 (d, 1H, $J_{7,6}$ = 8.4 Hz H-7); EI MS: *m/z* (rel. abund.%), 301 (M^+, 4.80), 273 (87), 152 (55), 122 (37), 95 (100).

5.26. 2-Hydroxybenzaldehyde-*N*-(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (26)

Yield: 0.25 g, 83%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 11.80 (s, 1H, N–H), 10.96 (s, 1H, O–H), 9.01 (s, 1H, –N=CH), 7.7 (d, 1H $J_{6,7}$ = 8.4 Hz, H-6), 7.65 (s, 1H, H-4), 7.60 ((d, 1H, $J_{6',5'}$ = 8.1 Hz, H-6′), 7.46 (t, 1H $J_{5',6',4'}$ = 8.1 Hz, H-5′), 7.3 (d, 1H $J_{3',4'}$ = 8.1 Hz, H-3′), 7.00 (m, 2H, H-7/4′), 6.92 (d, 1H, J = 8.4 Hz, Ar-H); EI MS: *m/z* (rel. abund.%), 299 (M^+, 75), 271 (100), 152 (81), 120 (33), 65 (50).

5.27. 3,4-Dihydroxybenzaldehyde-*N*-(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (27)

Yield: 0.22 g, 69%; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 10.9 (s, 1H, N–H), 9.6 (s, 1H, O–H), 8.57 (s, 1H, –N=CH), 7.4 (s, 1H, H-4), 7.38 (d, 1H $J_{6,7}$ = 7.5 Hz, H-6), 7.25 (d, 1H, $J_{6',5'}$ = 7.8 Hz, H-6′), 7.1 (s, 1H, H-2′), 6.9 (d, 1H, $J_{5',6'}$ = 7.8 Hz, H-5′), 6.86 (d, 1H, $J_{7,6}$ = 7.5 Hz, H-7); EI MS: *m/z* (rel. abund.%), 315 (M^+, 5), 287 (100), 180 (32), 152 (85), 109 (36), 63 (40).

Acknowledgements

This work was supported by the Higher Education Commission (HEC) Pakistan, under National Research Support Program for Universities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.09.028.

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