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Synthesis of some new hydrazide-hydrazones related to isatin and its Mannich and Schiff bases

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Abstract: The hydrazide-hydrazones **6a–d** and **7a**, **b** were obtained by treating isatin (**1**) or its Mannich base **2** with hydrazides incorporating piperidine, morpholine, and piperazine units. The reaction of **1** and **2** with hydrazides related to triazenes having piperidine, morpholine, and 1,2,3,4-tetrahydroisoquinoline moieties gave **12a–c** and **13a–c**. Treatment of **1** and **2** with iminodiacetohydrazide (**14**) and ethylenediamine tetraacetohydrazide (**18**) afforded **15–17** and **19a**, **b**, respectively. The Mannich reaction of the Schiff base **20** with formaldehyde and the appropriate hydrazide or bis(hydrazide) gave **21a**, **b** and **22a**, **b**. The hydrazides related to Schiff bases **20** and **26** were used as precursors in synthesis of compounds incorporating two 2-oxoindoline units or formazan moiety.

Keywords: hydrazide-hydrazones; Mannich bases; Schiff bases; triazenes.

1 Introduction

The chemistry and pharmacological activities of hydrazide-hydrazones have been the object of considerable synthetic effort, and a variety of biologically active hydrazide-hydrazones have been described [1–4]. Variously substituted hydrazide-hydrazones have been extensively studied as ligands in a wide range of metal complexes, and are used as starting materials for the synthesis of biologically active compounds as well as for the construction of heterocyclic systems. Depending on the substitution pattern and functionalization, hydrazide-hydrazones have shown to be effective antitubercular [5–7], anticonvulsant [8, 9], and antimicrobial [10, 11] agents. In particular, considerable attention has been devoted to the reaction of isatin with hydrazine derivatives because of the potent anticonvulsant [12–14] and antitubercular activity [15–18] of the products.

In view of this, and in connection with our studies in this area [19, 20], the reaction of isatin (**1**) and 1-(piperidinomethyl)isatin (**2**) with a variety of hydrazides was further investigated as a route to some new hydrazide-hydrazones of pharmaceutical interest.

2 Results and discussion

The interest in the pharmacological activities of compounds having a piperidine, morpholine, or piperazine moiety as a structural unit prompted us to prepare 2-oxo-2-(piperidin-1-yl)acetohydrazide (**4a**), the morpholino analog (**4b**), and the bis(hydrazide) **5b**, as depicted in Scheme 1. The reaction of **1** with **4a** and **4b** gave 2-oxo-*N*′-(2-oxoindolin-3-ylidene)-2-(piperidin-1-yl)acetohydrazide (**6a**) and 2-morpholino-2-oxo-*N*′-(2-oxoindolin-3-ylidene) acetohydrazide (**6b**), respectively.

A similar reaction of the Mannich base **2** with **4a** and **4b** afforded the corresponding hydrazide-hydrazones **6c** and **6d**. In line with this, treatment of **1** and **2** with the bis(hydrazide) **5b** gave 2,2′-(piperazine-1,4-diyl)-bis(2-oxo-*N*′-(2-oxoindolin-3-ylidene)acetohydrazide) (**7a**) and the related bis(Mannich base) **7b**, respectively (Scheme 1).

In connection with this study, we prepared a new series of hydrazides related to triazenes incorporating a piperidine, morpholine, and 1,2,3,4-tetrahydroisoquinoline moiety as a structural unit. This was achieved by a reaction sequence which involved the coupling of ethyl 4-(chlorodiazenyl)benzoate (**8**) with the appropriate *sec*-amine to give the ethyl 4-(amino-diazenyl)benzoates **9a–c**, which were converted into the corresponding hydrazides **11a–c** (Scheme 2).

The coupling of **8** with piperazine afforded diethyl 4,4′-(piperazine-1,4-diyl-bis(diazene-2,1-diyl))dibenzoate (**10**), which is sparingly soluble in most organic solvents. Treatment of **1** with **11a–c** afforded the *N*′-(2-oxoindolin-3-ylidene)-benzohydrazides **12a–c**. The synthesis of the corresponding Mannich bases **13a–c** was achieved by the reaction of **2** with **11a–c**.

Treatment of **1** and **2** with iminodiacetohydrazide (**14**) [21] afforded iminobis(*N*′-(2-oxoindolin-3-ylidene)

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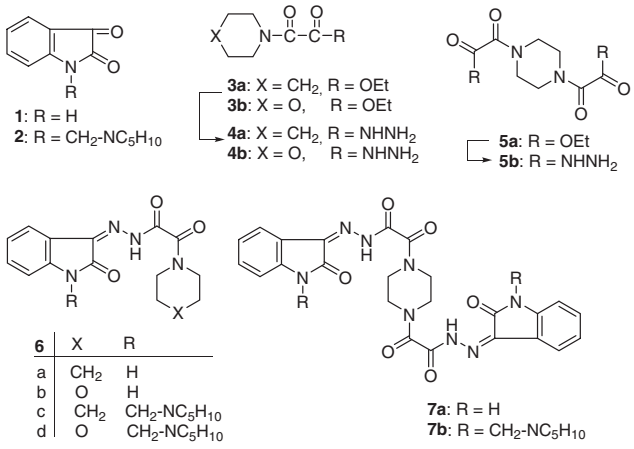
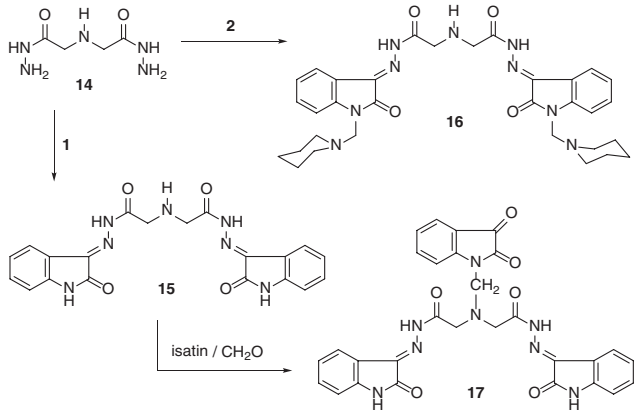
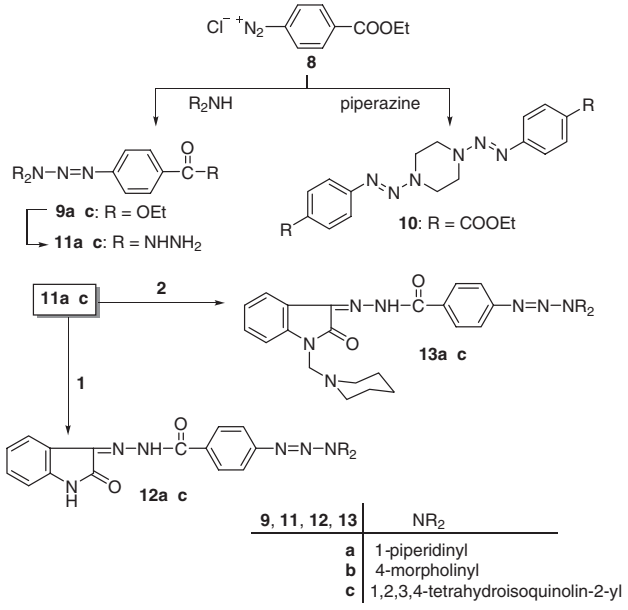


Scheme 1: Synthesis of the hydrazide-hydrazones **6a–d** and **7a, b**.



Scheme 3: Reaction of **1** or its Mannich base **2** with iminodiacetohydrazide **14**.



Scheme 2: Synthesis of the hydrazide-hydrazones **12a–c** and **13a–c**.

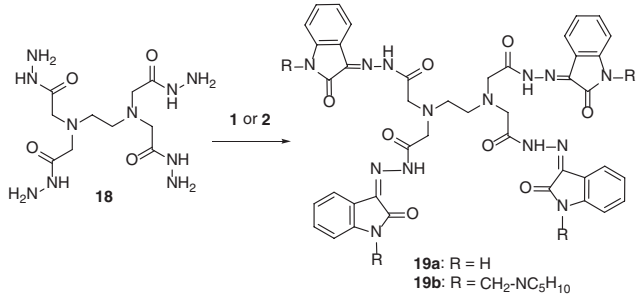
acetohydrazide) (**15**) and the corresponding bis(Mannich base) (**16**), respectively (Scheme 3).

The Mannich reaction of the *sec*-amine moiety of compound **15** with isatin has been of considerable synthetic interest, because it provides access to bis(hydrazide-hydrazones) of isatin, incorporating isatin *N*-Mannich base as a structural unit. Thus, **15** was treated with formalin and isatin to afford **17**. The mass spectra of compounds **15**, **16,** and **17** revealed molecular ion peaks at $m/z = 419$ (36%), 612 (12%, $[M–1]^+$), and 578 (51%), respectively, and fragmentation patterns which support their structures. The major fragmentation peaks can be accounted for cleavage in the hydrazide-hydrazone side chain.

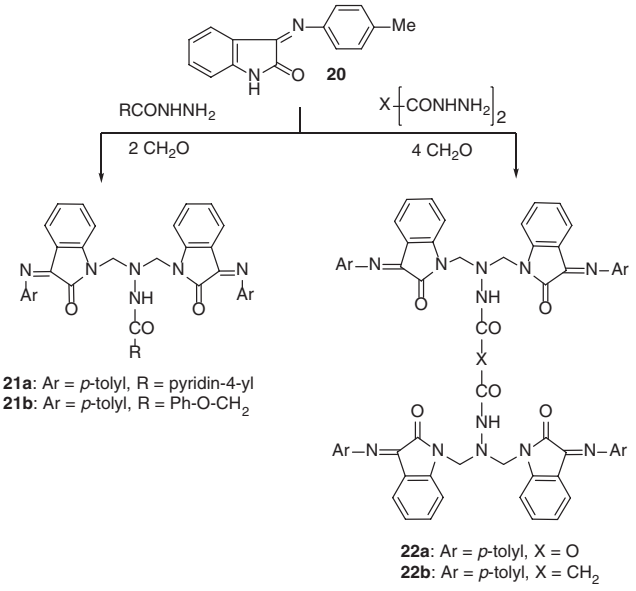
In an extension of this study, the reaction of ethylenediamine tetraacetohydrazide (EDTA)-tetrahydrazide (**18**) [22] with isatin constitutes an interesting approach toward the synthesis of the corresponding tetra(hydrazide-hydrazones). This has been realized by treating isatin with **18** in a molar ratio of 4 to 1 to give the tetra(acetohydrazide) **19a.** The analogous reaction of the Mannich base **2** with **18** afforded the tetrakis(Mannich base) **19b** (Scheme 4).

Although the synthetic utility of various amines in the Mannich reaction with isatin and its Schiff bases is well established, the use of hydrazides as the amine components in such reactions has not been reported. One of the specific objectives of this study was to investigate the possibility of using hydrazides as the amine components in the Mannich reaction with the Schiff bases of isatin. Therefore, the Schiff base **20** [13] was treated with isonicotinic hydrazide and formaldehyde to give the isonicotinohydrazide **21a** (Scheme 5).

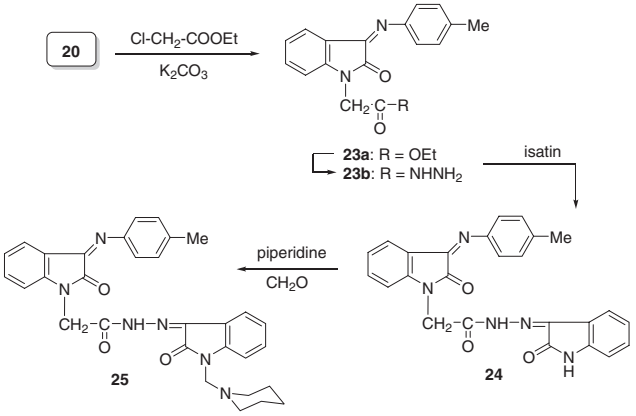
A similar reaction takes place with phenoxyacetohydrazide yielding **21b**. The synthetic potential of Mannich reactions with bis(hydrazides) was established



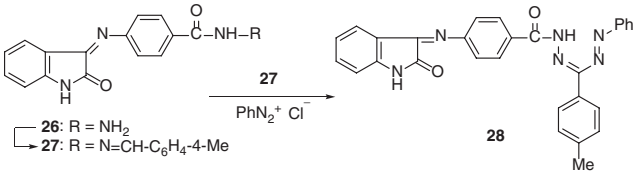
Scheme 4: Reaction of **1** or its Mannich base **2** with EDTA-tetrahydrazide.



Scheme 5: Mannich reaction of **20** with hydrazides and dihydrazides.



Scheme 6: Synthesis of the hydrazide **23b** and the hydrazide-hydrazones **24** and **25**.



Scheme 7: Reaction of the hydrazide-hydrazone **27** with benzenediazonium chloride.

by its application to the synthesis of the Mannich bases **22a** and **22b**. This has been realized by treating **20** with formaldehyde and oxalohydrazide to afford the oxalohydrazide **22a**. The similar reaction with malonohydrazide afforded **22b**.

A variety of isatin Schiff bases with various substitution patterns have been synthesized and studied with interest centered on their potential pharmaceutical activities [12, 23–27]. In view of this, 2-(2-oxo-3-(*p*-tolylimino) indolin-1-yl)acetohydrazide (**23b**) was synthesized starting from the Schiff base **20**. Treatment of isatin with **23b** afforded the hydrazide-hydrazone **24**, incorporating two 2-oxoindoline moieties, and this was subjected to the Mannich reaction with piperidine and formaldehyde to give the Mannich base **25** (Scheme 6).

The mass spectrum of compound **24** indicated the molecular ion peak at $m/z = 437$ (65%, $[M]^+$), whereas the Mannich base **25** is unstable to electron impact. The molecular ion peak $[M]^+$ was absent, and only fragment peaks were detected.

In the course of our study, the hydrazide-hydrazone **27** has been used as a precursor for the synthesis of isatin Schiff bases incorporating a formazan moiety as a structural unit. This has been achieved by coupling benzenediazonium chloride with **27** to afford the formazan **28** (Scheme 7). The formation of **28** is of interest because formazans have been extensively studied as ligands in a wide range of metal complexes [28–30] and a variety of biologically active formazans have been described [31–33].

3 Experimental section

All melting points (uncorrected) were determined on a Gallenkamp electric melting point apparatus (Sanyo Gallenkamp, Southborough, UK). Elemental microanalyses were carried out on a Carlo Erba 1108 Elemental Analyzer (Heraeus, Hanau, Germany) at the Microanalytical Unit, Faculty of Science, Cairo University. Infrared spectra were measured on a Mattson 5000 FTIR spectrometer (Mattson Instruments, Inc., Madison, WI, USA). ^{1}H and ^{13}C NMR data were obtained in [D_6]DMSO solution on a Varian XL 300 MHz instrument (Varian, Inc., CA, USA) using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm (δ) downfield from internal TMS. Mass spectra were recorded on a GC-MS QP-1000 EX Shimadzu instrument (Shimadzu, Tokyo, Japan). The course of the reaction and the purity of the synthesized compounds were monitored by TLC using EM science silica gel coated plates, 0.25 nm, 60 GF 254 (Merck, Darmstadt, Germany) with visualization by irradiation with an ultraviolet lamp. Compounds **7b**, **12c**, **13a–c**, **19a**, **19b**, **21a**, **21b**, **22a**, **22b**, **24,** and **25** are of limited solubility in common ^{1}H NMR solvents. Compounds **2** [34], **5a** [35], **14** [21], **18** [22], **20** [13], and **26** [36] were prepared as previously described.

3.1 Synthesis of the hydrazides 4a, b, and 5b

A solution of **3a** (1.85 g, 10 mmol) or **3b** (1.87 g, 10 mmol) or **5a** (1.43 g, 5 mmol) and hydrazine hydrate (80%, 1.9 mL, 30 mmol) in ethanol (30 mL) was refluxed for 1 h. The product obtained was filtered and crystallized from ethanol to give **4a**, **b** and from ethanol–water (2:1) to give **5b**.

3.1.1 2-Oxo-2-(piperidin-1-yl)acetohydrazide (4a)

M.p. 242°C. Yield 82% (white powder). – IR (KBr): ν = 3293–3210 (NH–NH_2), 1696 (CO), 1619 (CO), 1541, 1210 cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 1.65–1.68 (m, 6H, 3-H_2, 4-H_2, 5-H_2 of piperidine), 3.32 (m, 4H, 2-H_2, 6-H_2 of piperidine), 4.55 (s, 2H, NH_2), 9.72 ppm (s, 1H, N*H*). – MS (EI, 70 eV): *m/z* (%) = 173 (1) $[M+2]^+$, 172 (7) $[M+1]^+$, 171 (100) $[M]^+$, 153 (22), 127 (24), 100 (15), 84 (3), 82 (19), 72 (13), 56 (19). – $C_7H_{13}N_3O_2$ (171.20): calcd. C 49.11, H 7.65, N 24.54; found C 49.09, H 7.60, N 24.43.

3.1.2 2-Morpholino-2-oxoacetohydrazide (4b)

M.p. 214°C. Yield 80% (white powder). – IR (KBr): ν = 3286–3217 (NH–NH_2), 1681 (CO), 1649 (CO), 1587, 1215 cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 3.44 (m, 4H, CH_2–N–CH_2 of morpholine), 3.65 (m, 4H, CH_2–O–CH_2 of morpholine), 4.59 (s, 2H, NH_2), 10.11 ppm (s, 1H, N*H*). – MS (EI, 70 eV): *m/z* (%) = 174 (2) $[M+1]^+$, 173 (18) $[M]^+$, 155 (3), 114 (7), 112 (100), 100 (23), 85 (46), 68 (14), 57 (34). – $C_6H_{11}N_3O_3$ (173.17): calcd. C 41.61, H 6.40, N 24.27; found C 41.59, H 6.44, N 24.20.

3.1.3 2,2′-(Piperazine-1,4-diyl)bis(2-oxoacetohydrazide) (5b)

M.p. 220°C. Yield 80% (white powder). – IR (KBr): ν = 3291–3244 (NH–NH_2), 1678 (CO), 1640 (CO), 1467, 1163 cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 3.49 [t, 8H, N(CH_2CH_2)$_2$N], 4.49 [s, 4H, 2×(NH_2)], 8.59 ppm [s, 2H, 2×(N*H*)]. – MS (EI, 70 eV): *m/z* (%) = 258 (12) $[M]^+$, 240 (2), 197 (2), 155 (8), 133 (32), 127 (69), 126 (99), 73 (33), 57 (28). – $C_8H_{14}N_6O_4$ (258.23): calcd. C 37.21, H 5.46, N 32.54; found C 37.19, H 5.40, N 32.48.

3.2 Synthesis of the hydrazide-hydrazones 6a–d

A mixture of **1** (1.47 g, 10 mmol) or the Mannich base **2** [34] (2.44 g, 10 mmol) and the appropriate hydrazide (10 mmol) in ethanol (70 mL) and acetic acid (0.3 mL) was refluxed for 45 min. The product obtained on cooling was filtered and crystallized from chloroform to give **6a–d**.

3.2.1 2-Oxo-*N*′-(2-oxoindolin-3-ylidene)-2-(piperidin-1-yl)acetohydrazide (6a)

M.p. >300°C. Yield 61% (orange crystals). – IR (KBr): ν = 3329 (NH), 3212 (NH), 1725 (CO), 1690 (CO), 1608, 1510, 1211 cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 1.70–1.74 (m, 6H, 3-H_2, 4-H_2, 5-H_2 of piperidine), 331 (m, 4H, 2-H_2, 6-H_2 of piperidine), 9.17 [s, 1H, (=N–N*H*–)], 6.95–7.77 (m, 4.H, aromatic), 10.31 ppm (s, 1H, N*H* of oxoindoline).– ^{13}C NMR ([D_6]DMSO): δ = 23.96 (C-3, C-4, C-5 of piperidine), 45.33 (C-2, C-6 of piperidine), 139.23 (C-3 of oxoindoline moiety), 120.57, 120.71, 121.21, 122.77, 132.23, 142.36 (all Ar *C*), 161.29 (N*C*=O) 162.44 (HN*C*=O), 167.17 ppm (*C*=O of oxoindoline moiety). – MS (EI, 70 eV): *m/z* (%) = 301 (11) $[M+1]^+$, 300 (51) $[M]^+$, 298 (78), 261 (35), 217 (22), 204 (15), 193 (41), 168 (46), 147 (58), 116 (62), 99 (66), 80 (100). – $C_{15}H_{16}N_4O_3$ (300.31): calcd. C 59.99, H 5.37, N 18.66; found C 59.90, H 5.32, N 18.61.

3.2.2 2-Morpholino-2-oxo-*N*′-(2-oxoindolin-3-ylidene) acetohydrazide (6b)

M.p. > 300°C. Yield 57% (orange crystals). – IR (KBr): ν = 3358 (NH), 3242 (NH), 1676 (CO), 1644 (CO), 1610, 1513, 1142 cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 3.34 (m, 4H, CH_2–N–CH_2 of morpholine), 3.61 (m, 4H, CH_2–O–CH_2 of morpholine), 9.22 [s, 1H, (=N–N*H*–)], 6.91–7.76 (m, 4H, aromatic), 10.36 ppm (s, 1H, N*H* of oxoindoline). – ^{13}C NMR ([D_6] DMSO): δ = 44.65 (C-3, C-5 of morpholine), 64.76 (C-2, C-6 of morpholine), 139.45 (C-3 of oxoindoline moiety), 120.53, 120.73, 121.20, 122.74, 132.23, 142.39 (all Ar *C*), 161.27 (N*C*=O) 162.42 (HN*C*=O), 167.58 ppm (*C*=O of oxoindoline moiety). – MS (EI, 70 eV): *m/z* (%) = 302 (10) $[M]^+$, 280 (96), 274 (46), 250 (61), 237 (100), 212 (88), 171 (71), 148 (13), 106 (96), 97 (35), 85 (31). – $C_{14}H_{14}N_4O_4$ (302.29): calcd. C 55.63, H 4.67, N 18.53; found C 55.61, H 4.62, N 18.49.

3.2.3 2-Oxo-*N*′-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)-2-(piperidin-1-yl)acetohydrazide (6c)

M.p. > 300°C. Yield 44% (yellow crystals). – IR (KBr): ν = 3250 (NH), 1686 (CO), 1671 (CO), 1618, 1546, 1182, 1110 cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 1.68–1.72 [m, 12H, 2×(3-H_2, 4-H_2, 5-H_2 of piperidine)], 2.43 (m, 4H, 2-H_2, 6-H_2 of piperidine), 3.34 (m, 4H, 2-H_2, 6-H_2 of piperidine), 4.12 (s. 2H, N–CH_2–N of side chain), 6.88–7.73 (m, 4H, aromatic),

9.10 ppm (s, 1H, N*H*). – MS (EI, 70 eV): *m/z* (%) = 398 (15) $[M+1]^+$, 397 (61) $[M]^+$, 396 (35) $[M-1]^+$, 395 (100), 369 (91), 322 (37), 289 (70), 277 (48), 182 (60), 142 (19), 112 (74), 97 (53). – $C_{21}H_{27}N_5O_3$ (397.47): calcd. C 63.46, H 6.85, N 17.62; found C 63.40, H 6.82, N 17.59.

3.2.4 2-Morpholino-2-oxo-*N*′-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide (6d)

M.p. > 300°C. Yield 51% (yellow crystals). – IR (KBr): ν = 3421 (NH), 1681 (CO), 1668 (CO), 1614, 1522, 1127, 1102 cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 1.57–1.66 (m, 6H, 3-H_2, 4-H_2, 5-H_2 of piperidine), 2.41 (m, 4H, 2-H_2, 6-H_2 of piperidine), 3.28 (m, 4H, CH_2–N–CH_2 of morpholine), 3.66 (m, 4H, CH_2–O–CH_2 of morpholine), 4.10 (s, 2H, N–CH_2–N of side chain), 6.81–7.25 (m, 4H, aromatic), 9.13 ppm (s, 1H, N*H*). – MS (EI, 70 eV): *m/z* (%) = 400 (16) $[M+1]^+$, 399 (56) $[M]^+$, 383 (60), 323 (47), 260 (55), 235 (37), 222 (93), 149 (50), 134 (100). – $C_{20}H_{25}N_5O_4$ (399.44): calcd. C 60.14, H 6.31, N 17.53; found 60.03, H 6.29, N 17.50.

3.3 2,2′-(Piperazine-1,4-diyl)bis(2-oxo-*N*′-(2-oxoindolin-3-ylidene)acetohydrazide) (7a)

A mixture of **1** (0.88 g, 6 mmol) and **5b** (0.77 g, 3 mmol) in ethanol (50 mL) and acetic acid (0.3 mL) was refluxed for 1 h. The product obtained on cooling was filtered and washed with boiling ethanol (3 × 15 mL) to give **7a**. M.p. > 300°C. Yield 45% (yellow powder). – IR (KBr): ν = 3318 (NH), 3210 (NH), 1710 (CO), 1691 (CO), 1618, 1513, 1156 cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 3.36 [br. s, 8H, N(CH_2CH_2)$_2$N], 9.06 [br. s, 2H, 2 × (=N–N*H*–)], 6.91–7.56 (m, 8H, aromatic), 11.28 ppm [s, 2H, 2 × (N*H*) of oxoindoline]. – ^{13}C NMR ([D_6]DMSO): δ = 45.33 (4 × CH_2 of piperazine), 139.29 (C-3 of oxoindoline moiety), 120.73, 120.82, 121.24, 122.69, 132.29, 142.90 (all Ar *C*), 161.27 (N*C*=O) 162.35 (HN*C*=O), 166.35 ppm (*C*=O of oxoindoline moiety). – MS (EI, 70 eV): *m/z* (%) = 517 (34) $[M+1]^+$, 516 (29) $[M]^+$, 167 (27), 149 (54), 148 (27), 98 (29), 93 (28). – $C_{24}H_{20}N_8O_6$ (516.47): calcd. C 55.81, H 3.90, N 21.70; found C 55.79, H 3.92, N 21.68.

3.4 2,2′-(Piperazine-1,4-diyl)bis(2-oxo-*N*′-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide) (7b)

This compound was obtained from **2** (1.46 g, 6 mmol) and **5b** (0.77 g, 3 mmol), following the procedure described for the synthesis of **7a**. The product was washed with boiling ethanol (3 × 15 mL) to give **7b**. M.p. 252°C. Yield 48% (yellow powder). – IR (KBr): ν = 3418 (NH), 3310 (NH), 1698 (CO), 1684 (CO), 1641, 1466, 1173 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 710 (33) $[M]^+$, 636 (20), 567 (30), 444 (30), 306 (31), 203 (22), 188 (31), 160 (37), 145 (47), 113 (73), 97 (22), 84 (39). – $C_{36}H_{42}N_{10}O_6$ (710.33): calcd. C 60.83, H 5.96, N 19.71; found C 60.79, H 5.90, N 19.68.

3.5 Synthesis of the triazenes 9a–c

Diazotized ethyl 4-aminobenzoate (28 mmol) was added dropwise with stirring to a cold solution at 0–5°C, of the appropriate amine (31 mmol) during 10 min. Then saturated K_2CO_3 solution was added until pH of 8 was reached and the solution was stirred for 30 min at 0–5°C, a pale-yellow suspension resulted. The product was filtered, washed with water (3 × 20 mL) and air dried. The crude product was crystallized from ethyl acetate to give **9a–c**.

3.5.1 Ethyl 4-(piperidin-1-yldiazenyl)benzoate (9a)

M.p. 67°C. Yield 68% (pale-yellow crystals). – IR (KBr): ν = 1712, 1599, 1272, 1098, 773 cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 1.36 (t, 3H, CH_3), 1.63–1.72 (m, 6H, 3-H_2, 4-H_2, 5-H_2 of piperidine), 3.38 (m, 4H, 2-H_2, 6-H_2 of piperidine), 4.36 (q, 2H, CH_2CH$_3$), 7.46 (d, 2H, aromatic), 8.01 ppm (d, 2H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 262 (9) $[M+1]^+$, 261 (59) $[M]^+$, 230 (4), 202 (67), 143 (65), 130 (15), 118 (8), 77 (100). – $C_{14}H_{19}N_3O_2$ (261.32): calcd. C 64.35, H 7.33, N 16.08; found C 64.29, H 7.30, N 16.14.

3.5.2 Ethyl 4-(morpholinodiazenyl)benzoate (9b)

M.p. 70°C. Yield 76% (pale-yellow crystals). – IR (KBr): ν = 1718, 1591, 1266, 1110, 777 cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 1.33 (t, 3H, CH_3), 3.04 (m, 4H, CH_2–N–CH_2 of morpholine), 3.48 (m, 4H, CH_2–O–CH_2 of morpholine), 4.30 (q, 2H, CH_2CH$_3$), 7.48 (d, 2H, aromatic), 8.11 ppm (d, 2H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 264 (7) $[M+1]^+$, 263 (43) $[M]^+$, 217 (94), 193 (7), 148 (6), 119 (4), 99 (100), 90 (13), 57 (46). – $C_{13}H_{17}N_3O_3$ (263.29): calcd. C 59.30, H 6.51, N 15.96; found C 59.27, H 6.49, N 15.83.

3.5.3 Ethyl 4-((3,4-dihydroisoquinolin-2(1*H*)-yl)diazenyl) benzoate (9c)

M.p. 85°C. Yield 60% (yellow crystals). – IR (KBr): ν = 1707, 1598, 1271, 1105, 752 cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 1.41

(t, 3H, CH_3), 3.09 (t, 2H, 4-H_2 of tetrahydroisoquinoline), 4.15 (t, 2H, 3-H_2 of tetrahydroisoquinoline), 4.37 (q, 2H, CH_2CH$_3$), 5.01 (s, 2H, 1-H_2 of tetrahydroisoquinoline), 6.89–8.06 ppm (m, 8H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 311 (1) $[M+2]^+$, 310 (9) $[M+1]^+$, 309 (50) $[M]^+$, 264 (18), 263 (100), 218 (14), 191 (47), 190 (52), 128 (4), 96 (7). – $C_{18}H_{19}N_3O_2$ (309.36): calcd. C 69.88, H 6.19, N 13.58; found C 69.81, H 6.11, N 13.50.

3.6 Diethyl 4,4′-(piperazine-1,4-diylbis (diazene-2,1-diyl))dibenzoate (10)

This compound was obtained from **8** (28 mmol) and piperazine (1.20 g, 14 mmol), following the procedure described above for the synthesis of **9a–c**. The product was washed with boiling ethanol (3×15 mL) to give **10**. M.p. 181°C. Yield 72% (pale-yellow powder). – IR (KBr): ν = 1700, 1602, 1278, 1138, 693 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 1.43 (t, 6H, 2×CH_3), 4.09 ([br. s, 8H, N(CH_2CH_2)$_2$N], 4.39 (q, 4H, 2×CH_2CH$_3$), 7.49–8.06 ppm (m, 8H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 439 (4) $[M+1]^+$, 438 (6) $[M]^+$, 397 (4), 394 (27), 366 (12), 349 (63), 338 (12), 294 (8), 176 (13), 166 (14), 147 (20), 109 (100), 93 (68). – $C_{22}H_{26}N_6O_4$ (438.48): calcd. C 60.26, H 5.98, N 19.17; found C 60.21, H 5.92, N 19.10.

3.7 Synthesis of 4-(substituted-diazenyl) benzohydrazides 11a–c

A solution of **9a**, **9b,** or **9c** (2 mmol) and hydrazine hydrate (80%, 0.5 mL, 8 mmol) in ethanol (20 mL) was refluxed on a steam bath for 3 h. The reaction mixture was cooled to give a solid product which was filtered and crystallized from ethyl acetate to give compounds **11a–c**.

3.7.1 4-(Piperidin-1-yldiazenyl)benzohydrazide) (11a)

M.p. 140°C. Yield 60% (white powder). – IR (KBr): ν = 3318, 3266 (NH–NH$_2$), 1662 (CO), 1607, 1427, 1104, 670 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 1.66–1.71 (m, 6H, 3-H_2, 4-H_2, 5-H_2 of piperidine), 3.82 (m, 4H, 2-H_2, 6-H_2 of piperidine), 4.54 (s, 2H, NH_2), 7.44 (d, 2H, aromatic), 7.90 (d, 2H, aromatic), 9.77 ppm (s, 1H, N*H*). – ^{13}C NMR ([D$_6$]DMSO): δ = 23.55 (C-3, C-4, C-5 of piperidine), 43 (C-2, C-6 of piperidine), 119.66, 127.88, 129.76, 152.40 (all aromatic *C*), 165.67 ppm (*C*=O). – MS (EI, 70 eV): *m/z* (%) = 248 (7) $[M+1]^+$, 247 (49) $[M]^+$, 215 (3), 201 (100), 163 (24), 144 (4), 133 (15), 105 (9), 89 (16), 63 (15). – $C_{12}H_{17}N_5O$ (247.30): calcd. C 58.28, H 6.93, N 28.32; found C 58.21, H 6.89, N 28.30.

3.7.2 4-(Morpholinodiazenyl)benzohydrazide (11b)

M.p. 169°C. Yield 68% (white powder). – IR (KBr): ν = 3310–3214 ((NH–NH$_2$), 1649 (CO), 1621, 1447, 1124, 677 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 2.49 (m, 4H, CH_2–N–CH_2 of morpholine), 3.77 (m, 4H, CH_2–O–CH_2 of morpholine), 4.45 (s, 2H, NH_2), 7.39 (d, 2H, aromatic), 7.82 (d, 2H, aromatic), 9.69 ppm (s, 1H, N*H*). – MS (EI, 70 eV): *m/z* (%) = 250 (5) $[M+1]^+$, 249 (36) $[M]^+$, 231 (16), 218 (100), 201 (7), 184 (5), 172 (27), 155 (8), 142 (11), 129 (6), 76 (6). – $C_{11}H_{15}N_5O_2$ (249.27): calcd. C 53.00, H 6.07, N 28.10; found C 52.96, H 6.01, N 28.02.

3.7.3 4-((3,4-Dihydroisoquinolin-2(1*H*)-yl)diazenyl) benzohydrazide (11c)

M.p. 178°C. Yield 66% (white powder). – IR (KBr): ν = 3318–3219 ((NH–NH$_2$), 1651 (CO), 1619, 1453, 1120, 676 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.12 (t, 2H, 4-H_2 of tetrahydroisoquinoline), 4.19 (t, 2H, 3-H_2 of tetrahydroisoquinoline), 4.51 (s, 2H, NH_2), 5.08 (s, 2H, 1-H_2 of tetrahydroisoquinoline), 6.92–8.01 (m, 8H, aromatic), 9.83 ppm (s, 1H, N*H*). – MS (EI, 70 eV): *m/z* (%) = 295 (2) $[M]^+$, 263 (2), 249 (7), 222 (20) 194 (10) 180 (100), 176 (14), 164 (8), 150 (8), 106 (16), 91 (8). – $C_{16}H_{17}N_5O$ (295.34): calcd. C 65.07, H 5.80, N 23.71; found C 65.01, H 5.83, N 23.69.

3.8 Synthesis of the hydrazide-hydrazones 12a–c

A solution of **1** (0.44 g, 3 mmol) and **11a** (0.74 g, 3 mmol) or **11b** (0.75 g, 3 mmol), or **11c** (0.88 g, 3 mmol) in ethanol (30 mL) and acetic acid (0.3 mL) was refluxed for 30 min. The precipitated product was filtered and washed with boiling ethanol (3×15 mL) to give **12a–c**.

3.8.1 *N*′-(2-Oxoindolin-3-ylidene)-4-(piperidin-1-yldiazenyl)benzohydrazide (12a)

M.p. 260°C. Yield 72% (yellow powder). – IR (KBr): ν = 3437 (NH), 3212 (NH), 1714 (CO), 1676 (CO), 1609, 1519, 1262, 751 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 1.67–1.71 (m, 6H, 3-H_2, 4-H_2, 5-H_2 of piperidine), 3.84 (m, 4H, 2-H_2, 6-H_2 of piperidine), 6.90–7.99 (m, 8H, aromatic), 10.79 (s, 1H, N*H* of oxoindoline), 11.34 ppm (s, 1H, CON*H*). – MS (EI, 70 eV): *m/z* (%) = 377 (2) $[M+1]^+$, 376 (8) $[M]^+$, 292 (18), 264 (28), 236 (22) 217 (15), 216 (100), 160 (21), 145 (18), 132 (10), 121 (16), 105

(31), 104 (45), 85 (19), 84 (55). – $C_{20}H_{20}N_6O_2$ (376.41): calcd. C 63.82, H 5.36, N 22.33; found C 63.80, H 5.32, N 22.30.

3.8.2 4-(Morpholinodiazenyl)-*N*′-(2-oxoindolin-3-ylidene)benzohydrazide (12b)

M.p. 248°C. Yield 53% (yellow powder). – IR (KBr): $\nu = 3430$ (NH), 3222 (NH), 1717 (CO), 1667 (CO), 1613, 1532, 747 cm^{-1}. – ^1H NMR ([D_6]DMSO): $\delta = 3.69$ (m, 4H, CH_2–N–CH_2 of morpholine), 3.91 (m, 4H, CH_2–O–CH_2 of morpholine), 6.90–8,02 (m, 8H, aromatic), 10.79 (s, 1H, N*H* of oxoindoline), 11.35 ppm (s, 1H, CON*H*). – MS (EI, 70 eV): *m/z* (%) = 379 (2) $[M+1]^+$, 378 (5) $[M]^+$, 293 (4), 264 (18), 237 (11), 236 (20), 218 (100), 200 (52), 160 (32), 157 (12), 133 (18), 121 (31), 105 (61), 86 (29). – $C_{19}H_{18}N_6O_3$ (378.38): calcd. C 60.31, H 4.79, N 22.21; found C 60.29, H 4.73, N 22.20.

3.8.3 4-((3,4-Dihydroisoquinolin-2(1*H*)-yl)diazenyl)-*N*′-(2-oxoindolin-3-ylidene)-benzohydrazide (12c)

M.p. 206°C. Yield 83% (yellow powder). – IR (KBr): $\nu = 3443$ (NH), 3237 (NH), 1710 (CO), 1661 (CO), 1609, 1535, 750 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 426 (8) $[M+2]^+$, 425 (5) $[M+1]^+$, 224 (11) $[M]^+$, 397 (9), 353 (10), 340 (11), 291 (10), 264 (8) 160 (11), 145 (10), 132 (19), 111 (20), 97 (31), 76 (18). – $C_{24}H_{20}N_6O_2$ (424.45): calcd. C 67.91, H 4.75, N 19.80; found C 67.89, H 4.73, N 19.82.

3.9 Synthesis of the hydrazide-hydrazones 13a–c

These compounds were obtained from the Mannich base **2** (0.73 g, 3 mmol) and **11a** (0.74 g, 3 mmol) or **11b** (0.75 g, 3 mmol) or **11c** (0.88 g, 3 mmol) in the manner described for the synthesis of **12a–c**. The product was filtered and washed with boiling ethanol (3 × 15 mL) to give **13a–c**.

3.9.1 *N*′-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)-4-(piperidin-1-yldiazenyl)benzohydrazide (13a)

M.p. 251°C. Yield 58% (yellow powder). – IR (KBr): $\nu = 3446$ (NH), 1701 (CO), 1668 (CO), 1611 (C=N), 1531, 1105, 748 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 474 (11) $[M+1]^+$, 473 (30) $[M]^+$, 455 (29), 389 (34), 363 (21), 347 (26), 295 (29), 222 (28), 192 (28), 188 (21), 175 (28), 131(28), 121 (31), 98 (31), 84 (33), 80 (100). – $C_{26}H_{31}N_7O_2$ (473.57): calcd. C 65.94, H 6.60, N 20.70; found C 65.90, H 6.62, N 20.69.

3.9.2 4-(Morpholinodiazenyl)-*N*′-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)benzohydrazide (13b)

M.p. 246°C. Yield 51% (yellow powder). – IR (KBr): $\nu = 3449$ (NH), 17I5 (CO), 1667 (CO), 1614 (C=N), 1528, 1109, 678 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 476 (4) $[M+1]^+$, 475 (6), $[M]^+$, 445 (6), 388 (4), 327 (7), 295 (6), 175 (51), 168 (8) 148 (12), 147 (100), 119 (11), 104 (14), 87 (17), 86 (7), 77 (21), 76 (33). – $C_{25}H_{29}N_7O_3$ (475.54): calcd. C 63.14, H 6.15, N 20.62; found C 63.07, H 6.10, N 20.59.

3.9.3 4-((3,4-Dihydroisoquinolin-2(1*H*)-yl)diazenyl)-*N*′-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene) benzohydrazide (13c)

M.p. 155°C. Yield 65% (yellow powder). – IR (KBr): $\nu = 3445$ (NH), 1723 (CO), 1655 (CO), 1608 (C=N), 1521, 1114, 749 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 521 (92) $[M]^+$, 520 (92) $[M–1]^+$, 491 (53), 447 (65), 390 (53), 361 (80), 347 (65), 320 (72), 292 (62) 244 (84), 202 (59), 163 (86), 104 (100), 98 (11), 83 (5). – $C_{30}H_{31}N_7O_2$ (521.25): calcd. C 69.08, H 5.99, N 18.80; found C 69.00, H 5.92, N 18.79.

3.10 Synthesis of the bis(hydrazide-hydrazones) 15 and 16

A solution of **1** (1.17 g, 8 mmol) or the Mannich base **2** (1.95 g, 8 mmol) and iminodiacetohydrazide **14** (0.65 g, 4 mmol) in ethanol (50 mL) and acetic acid (0.3 mL) was refluxed for 40 min. The precipitated product was filtered and washed with boiling ethanol (3 × 15 mL) to give **15** and **16**.

3.10.1 Iminobis[*N*′-(2-oxoindolin-3-ylidene) acetohydrazide] (15)

M.p. 202°C. Yield 47% (pale-yellow powder). – IR (KBr): $\nu = 3365$ (NH), 3244 (NH), 1683 (CO), 1664 (CO), 1621 (C=N), 1610, 1466, 1136, 791 cm^{-1}. – ^1H NMR ([D_6]DMSO): $\delta = 3.47$ [s, 4H, 2 × (CO–CH_2–)], 6.88–7.52 (m, 8H, aromatic), 7.57 (s, 1H, CH_2–N*H*–CH_2), 10.75 [s, 2H, 2 × (NH of oxoindoline)], 11.12 ppm [s, 2H, 2 × (CO–N*H*)]. – ^{13}C NMR ([D_6]DMSO): $\delta = 54.67$ (CH_2–NH), 138.54 (C-3 of oxoindoline moiety), 120.51, 120.77, 121.28, 122.66, 132.21, 142.37 (all Ar *C*), 163.21 (HN–*C*=O), 167.71 ppm (*C*=O of oxoindoline moiety). – MS (EI, 70 eV): *m/z* (%) = 421 (21) $[M+2]^+$, 420 (23) $[M+1]^+$, 419 (36) $[M]^+$, 392 (31), 368 (23), 309 (27), 295 (25), 278 (31), 274 (23), 230 (27), 217 (36), 201 (23), 188 (23), 147 (41), 146 (23), 131 (29), 118 (22), 82 (29.7), 69 (100). – $C_{20}H_{17}N_7O_4$ (419.39): calcd. C 57.28, H 4.09, N 23.38; found C 57.21, H 4.00, N 23.30.

3.10.2 Iminobis[*N′*-(2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylidene)acetohydrazide] (16)

M.p. 207°C. Yield 45% (dark-yellow powder). – IR (KBr): ν = 3403 (NH), 1718 (CO), 1669 (CO), 1617 (C=N), 1609, 1470, 1346, 754 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 1.35–1.47 [m, 12H, 2×(3-*H*$_2$, 4-*H*$_2$, 5-*H*$_2$ of piperidine)], 2.44 (m, 4H, 2-*H*$_2$, 6-*H*$_2$ of piperidine), 2.51 (m, 4H, 2-*H*$_2$, 6-*H*$_2$ of piperidine), 3.49 [s, 4H, 2×(CO–C*H*$_2$–)], 4.17 (s, 2H, N–C*H*$_2$–N of side chain), 6.81–7.51 (m, 8H, aromatic), 7.59 (s, 1H, CH$_2$–N*H*–CH$_2$), 10.98 ppm [s, 2H, 2×(CO–N*H*)]. – ^{13}C NMR ([D$_6$] DMSO): δ = 24.33 (C-3, C-4, C-5 of piperidine), 47.87 (C-2, C-6 of piperidine), 54.57 (*C*H$_2$–NH), 67.45 (N–*C*H$_2$–N of side chain), 138.77 (C-3 of oxoindoline moiety), 120.46, 120.68, 121.22, 122.59, 132.26, 142.47 (all Ar *C*), 163.44 (HN–*C*=O), 168.11 ppm (*C*=O of oxoindoline moiety). – MS (EI, 70 eV): *m/z* (%) = 612 (12) [M–1]$^+$, 556 (12), 503 (11), 478 (12), 247 (11), 242 (12), 221 (13), 167 (13), 155 (14), 149 (23), 145 (63), 144 (15), 130 (13), 118 (21), 98 (57), 84 (100), 77 (18). – C$_{32}$H$_{39}$N$_9$O$_4$ (613.71): calcd. C 62.63, H 6.41, N 20.54; found C 62.60, H 6.43, N 20.51.

3.11 2,2′-[(2,3-Dioxoindolin-1-yl)methyl-imino)bis(*N′*-(2-oxoindolin-3-ylidene) acetohydrazide] (17)

A mixture of **16** (1.25 g, 3 mmol), **1** (0.44 g, 3 mmol), and formalin (36%, 0.25 mL, 3 mmol) in pyridine–ethanol (1:4) (40 mL) was heated under reflux for 1 h. After cooling, the reaction mixture was poured on cold water and the product obtained was filtered and crystallized from chloroform to give compound **17**. M.p. 240°C. Yield 63% (pale-yellow powder). – IR (KBr): ν = 3422 (NH), 1693 (CO), 1655 (CO), 1619 (C=N), 1605, 1466, 1349, 757 cm^{-1}. – ^{1}H NMR ([D$_6$] DMSO): δ = 3.50 [s, 4H, 2×(CO–C*H*$_2$–)], 4.21 (s, 2H, N–C*H*$_2$–N of side chain), 6.86–7.61 (m, 12H, aromatic), 10.71 [s, 2H, 2×(NH of oxoindoline)], 11.10 ppm [s, 2H, 2×(CO–N*H*)]. – MS (EI, 70 eV): *m/z* (%) = 579 (57) [M+1]$^+$, 578 (51) [M]$^+$, 577 (52), 536 (85), 508 (55), 470 (68), 425 (58), 416 (48), 393 (64), 244 (46), 188 (49), 160 (68), 145 (56), 132 (47), 107 (100). – C$_{29}$H$_{22}$N$_8$O$_6$ (578.53): calcd. C 60.21, H 3.83, N 19.37; found C 60.11, H 3.80, N 19.32.

3.12 Synthesis of the tetrakis(hydrazide-hydrazones) 19a, b

A solution of EDTA-tetrahydrazide **18** [22] (1 g, 3 mmol) and **1** (1.76 g, 12 mmol) or the Mannich base **2** (2.93 g, 12 mmol) in aqueous ethanol (60%, 50 mL) and acetic acid (0.3 mL) was heated over a steam bath for 1 h. The product obtained on cooling was filtered and washed by boiling aqueous ethanol (60%, 3×15 mL) to give **19a**, **b**.

3.12.1 2,2′,2″,2‴-(Ethane-1,2-diylbis(azanetriyl)) tetrakis(*N′*-(2-oxoindolin-3-ylidene) acetohydrazide) (19a)

M.p. 215°C. Yield 72% (yellow powder). – IR (KBr): ν = 3357 (NH), 3188 (NH), 1685 (CO), 1658 (CO), 1620 (C=N), 1588, 1464, 1195, 757 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 866 (2) [M+2]$^+$, 865 (2) [M+1]$^+$, 848 (3), 815 (3), 599 (2), 532 (2), 360 (2), 232 (3) 173 (3), 162 (11), 161 (100), 149 (5), 133 (17), 118 (8), 116 (10), 105 (27), 104 (92), 90 (24), 80 (10), 77 (21). – C$_{42}$H$_{36}$N$_{14}$O$_8$ (864.82): calcd. C 58.33, H 4.20, N 22.67; found C 58.31, H 4.21, N 22.62.

3.12.2 2,2′,2″,2‴-(Ethane-1,2-diylbis(azanetriyl)) tetrakis(*N′*-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)-acetohydrazide) (19b)

M.p. 208°C. Yield 40% (yellow powder). – IR (KBr): ν = 3359 (NH), 1688 (CO), 1667 (CO), 1617 (C=N), 1588, 1444, 1163, 759 cm^{-1}. – C$_{66}$H$_{80}$N$_{18}$O$_8$ (1253.46): calcd. C 63.24, H 6.43, N 20.11; found C 63.21, H 6.40, N 20.09.

3.13 Synthesis of the bis(Mannich bases) 21a, b

A solution of **20** (0.94 g, 4 mmol), isonicotinic hydrazide (0.27 g, 2 mmol) or phenoxyacetohydrazide (0.33 g, 2 mmol), and formalin (36%, 0.40 mL, 5 mmol) in ethanol (50 mL) was heated over a steam bath for 1 h. The product obtained on cooling was filtered and washed with boiling ethyl acetate (3×10 mL) to give **21a**, **b**.

3.13.1 *N′*,*N′*-bis((2-oxo-3-(p-tolylimino)indolin-1-yl) methyl)isonicotinohydrazide (21a)

M.p. 287°C. Yield 57% (orange crystals). – IR (KBr): ν = 3331 (NH), 1719 (CO), 1674 (CO), 1618 (C=N), 1596, 1274, 1150, 753 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 632 (2) [M–1]$^+$, 631 (1), 289 (5), 266 (22), 238 (19), 160 (68), 133 (98), 132 (79), 116 (36), 107 (85), 104 (52), 90 (7), 79 (58), 78 (100), 76 (18). – C$_{38}$H$_{31}$N$_7$O$_3$ (633.70): calcd. C 72.02, H 4.93, N 15.47; found C 71.98, H 4.90, N 15.41.

3.13.2 *N′*,*N′*-bis((2-oxo-3-(p-tolylimino)indolin-1-yl) methyl)-2-phenoxyacetohydrazide (21b)

M.p. 180°C. Yield 50% (brown crystals). – IR (KBr): $\nu = 3426$ (NH), 1721 (CO), 1667 (CO), 1610 (C=N), 1526, 1255, 1144, 755 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 663 (4) $[M+1]^+$, 662 (5) $[M]^+$, 609 (4), 568 (5), 552 (6), 468 (6), 394 (6), 247 (4), 234 (18), 191 (25), 147 (33), 119 (100), 107 (12), 97 (11), 80 (10), 77 (3). – $C_{40}H_{34}N_6O_4$ (662.74): calcd. C 72.49, H 5.17, N 12.68; found 72.43, H 5.14, N 12.61.

3.14 Synthesis of the tetrakis(Mannich bases) 22a, b

These compounds were obtained from **20** (2.36 g, 10 mmol), formalin (36%, 0.85 mL, 10 mmol), and oxalohydrazide (0.29 g, 2.5 mmol) or malonohydrazide (0.33 g, 2.5 mmol) in the manner described for the synthesis of **21a**, **b**. The product was filtered and washed with boiling ethyl acetate (3 × 15 mL) to give **22a**, **b**.

3.14.1 *N1′*,*N1′*,*N2′*,*N2′*-tetrakis((2-oxo-3-(p-tolylimino) indolin-1-yl)methyl)oxalohydrazide (22a)

M.p. > 300°C. Yield 40% (dark-red powder). – IR (KBr): $\nu = 3396$ (NH), 1699 (CO), 1665 (CO), 1615 (C=N), 1523, 1347, 1176, 745 cm^{-1}. – $C_{66}H_{54}N_{12}O_6$ (1111.21): calcd. C 71.34, H 4.90, N 15.13; found C 71.30, H 4.89, N 15.11.

3.14.2 *N1′*,*N1′*,*N2′*,*N2′*-tetrakis((2-oxo-3-(p-tolylimino) indolin-1-yl)methyl)malonohydrazide (22b)

M.p. > 300°C. Yield 44% (orange powder). – IR (KBr): $\nu = 3377$ (NH), 1694 (CO), 1660 (CO), 1611 (C=N), 1519, 1467, 1351, 1126, 757 cm^{-1}. – $C_{67}H_{56}N_{12}O_6$ (1125.24): calcd. C 71.52, H 5.02, N 14.94; found C 71.50, H 5.05, N 14.91.

3.15 Synthesis of compounds 23a, b

3.15.1 Ethyl 2-(2-oxo-3-(p-tolylimino)indolin-1-yl)acetate (23a)

A mixture of **20** (1.42 g, 6 mmol), ethyl chloroacetate (0.80 g, 6.6 mmol), and K_2CO_3 (1.20 g) in DMF (20 mL) was heated in an oil bath at 120°C for 1 h. After cooling, the reaction mixture was poured in cold water. The product was filtered and crystallized from ethanol to give **23a**. M.p. 190°C. Yield 40% (red crystals). – IR (KBr): $\nu = 1742$ (ester), 1657 (C=O), 1611 (C=N), 1500, 1462, 1202 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 323 (1) $[M+1]^+$, 322 (5) $[M]^+$, 237 (12), 236 (65), 221 (18), 209 (16), 208 (100), 192 (5), 180 (10), 145 (5), 131 (2), 118 (13), 91 (58), 76 (8). – $C_{19}H_{18}N_2O_3$ (322.36): calcd. C 70.79, H 5.63, N 8.69; found 70.74, H 5.60, N 8.61.

3.15.2 2-[2-Oxo-3-(p-tolylimino)indolin-1-yl] acetohydrazide (23b)

A mixture of **23a** (0.8 g, 2.5 mmol) and hydrazine hydrate (80%, 0.20 mL, 3 mmol) in ethanol (30 mL) was refluxed for 90 min. The product obtained on cooling was filtered and crystallized from ethanol to give **23b**. M.p. 236°C. Yield 60% (pale-brown crystals). – IR (KBr): $\nu = 3557$, 3158 (NH–NH_2), 1682 (CO), 1594, 152, 1200, 746 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 248 (6) $[M-(CONHNH_2+1)]^+$, 247 (8), 234$[M-(CH_2CONHNH_2+1)]^+$ (27), 219 (6), 202 (16), 174 (59), 161 (57), 146 (61), 133 (33), 118 (100), 104 (86), 91 (69), 78 (24), 77 (45), 76 (30), 59 (16). – $C_{17}H_{16}N_4O_2$ (308.33): calcd. C 66.22, H 5.23, N 18.17; found C 66.20, H 5.21, N 18.13.

3.16 2-[2-Oxo-3-(p-tolylimino)indolin-1-yl]-*N′*-(2-oxoindolin-3-ylidene)acetohydrazide (24)

A solution of **1** (0.44 g, 3 mmol) and **23b** (0.92 g, 3 mmol) in aqueous ethanol (50%, 40 mL) and acetic acid (0.2 mL) was refluxed for 40 min. After standing at room temperature for 24 h, the product obtained was filtered and washed with boiling ethanol to give **24**. M.p. 268°C. Yield 45% (orange crystals). – IR (KBr): $\nu = 3438$ (NH), 1692 (CO), 1615, 1552, 1514, 1169, 751 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 438 (50) $[M+1]^+$, 437 (65) $[M]^+$, 424 (58), 418 (50), 402 (62), 366 (57), 332 (68), 309 (50), 250 (54), 235 (47), 205 (68), 160 (2), 152 (100), 145 (45), 131 (57), 97 (29), 92 (62), 76 (33). – $C_{25}H_{19}N_5O_3$ (437.45): calcd. C 68.64, H 4.38, N 16.01; found C 68.60, H 4.34, N 15.92.

3.17 *N′*-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)-2-(2-oxo-3-(p-tolylimino) indolin-1-yl)acetohydrazide (25)

This compound was obtained from **23b** (0.92 g, 3 mmol) and the Mannich base **2** (0.73 g, 3 mmol), following the

procedure described for the synthesis of **24**. The product was filtered and washed with boiling ethanol to give **25**. M.p. > 300°C. Yield 40% (yellow powder). – IR (KBr): ν = 3410 (NH), 1690 (CO), 1609 (C=N), 1467, 1163, 745 cm^{-1}. – $C_{31}H_{30}N_6O_3$ (534.61): calcd. C 69.65, H 5.66, N 15.72; found C 69.61, H 5.63, N 15.70.

3.18 *N*′-(4-methylbenzylidene)-4-(2-oxoindolin-3-ylideneamino)benzohydrazide (27)

A mixture of **26** [36] (1.12 g, 4 mmol) and *p*-tolualdehyde (0.48 g, 4 mmol) in ethanol (30 mL) and acetic acid (0.3 mL) was heated under reflux for 3 h. After standing at room temperature for 24 h, the product obtained was filtered and crystallized from ethanol to give **27**. M.p. 212°C. Yield 65% (yellow powder). – IR (KBr): ν = 3424 (NH), 1690 (CO), 1649 (CO), 1619 (C=N), 1544, 1133 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 2.38 (s, 3H, Ar-C*H*$_3$), 6.88–7.75 (m, 12H, aromatic), 8.43 (s, 1H, Ar-C*H*=N), 9.42 (s, 1H, CO–N*H*), 10.81 ppm (s, 1H, N*H* of oxoindoline). – $C_{23}H_{18}N_4O_2$ (382.40): calcd. C 72.24, H 4.74, N 14.65; found C 72.20, H 4.71, N 14.61.

3.19 1-[4-(2-Oxoindolin-3-ylideneamino) benzoyl]-5-phenyl-3-p-tolylformazan (28)

Benzenediazonium chloride (10 mmol, prepared by diazotization of aniline) (10 mmol) was added dropwise with stirring to a cold solution at 0–5°C, of **27** (2.67 g, 7 mmol) during 5 min. Then saturated K_2CO_3 solution was added until pH of 8 was reached and the solution was stirred for 30 min at 0–5°C, a dark brownish-red suspension resulted. The product was filtered, washed with water (3 × 20 mL) and air dried. The crude product was crystallized from DMF–ethanol (1:1) to give **28**. M.p. 248°C. Yield 55% (brownish-red powder). – IR (KBr): ν = 3422 (NH), 1708 (CO), 1666 (CO), 1617, 1546, 1204, 756 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 2.35 (s, 3H, Ar-C*H*$_3$), 6.91–8.05 (m, 17H, aromatic), 8.58 (s, 1H, N*H* of formazan), 10.85 ppm (s, 1H, N*H* of oxoindoline). – ^{13}C NMR ([D$_6$]DMSO): δ = 21.24 (*C*H$_3$), 116.46, 120.72, 122.47, 126.43, 128.35, 128.75, 128.85, 129.42, 129.75, 130.76, 131.16, 133.53, 141.22, 144.94, 146.45 (all aromatic *C*), 151.48 (N=*C*), 160.66 (*C*=O), 164.54 ppm (*C*=O). – MS (EI, 70 eV): *m/z* (%) = 487 (51) [M+1]$^+$, 486 (63) [M]$^+$, 486 (58), 406 (48), 402 (62), 338 (60), 324 (69), 305 (67), 294 (60), 243 (60), 225 (50), 208 (9), 189 (48), 182 (46), 166 (100), 161 (65), 144 (70), 130 (60), 104 (6), 91 (28), 74 (50). – $C_{29}H_{22}N_6O_2$ (486.52): calcd. C 71.59, H 4.56, N 17.27; found C 71.54, H 4.53, N 17.22.

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