Synthesis of a New Series of *N*-Mannich Bases and Polyhydroxy Mannich Bases of Pharmaceutical Interest Related to Isatin and Its Schiff Bases

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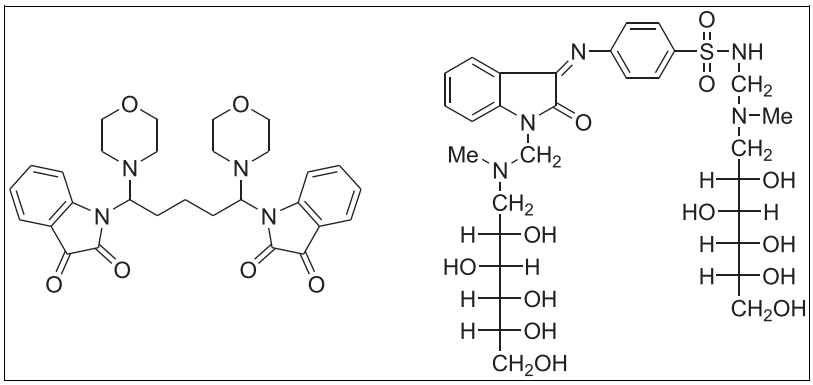

The reaction of isatin **1** with benzaldehyde and a *sec*-amine or the appropriate aldimine afforded the *N*-Mannich bases **2**–**3** and the bis-base **4**. Treatment of **1** with glutaric dialdehyde and morpholine gave the bis-base **5**. Mannich reaction of the Schiff bases **6a**–**f** derived from **1**, led to the new Mannich bases and bis-bases **7**–**9**. The use of *N*-methyl-*D*-glucamine as the amine component in the Mannich reaction with **6b**–**f** led to the polyhydroxy Mannich bases **11**–**13**.

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INTRODUCTION

The *N*-Mannich bases derived from *NH*-heterocycles and their derivatives have received significant attention due to their wide range of biological and pharmacological activities [1–8]. In particular, much interest has centered around *N*-Mannich bases of isatin, and related compounds, which possess a broad spectrum of action including antibacterial [9–12], anticonvulsant [13–15], anti-HIV [9,16,17], antifungal [3–5], cytotoxic, and anticancer [18,19] activities.

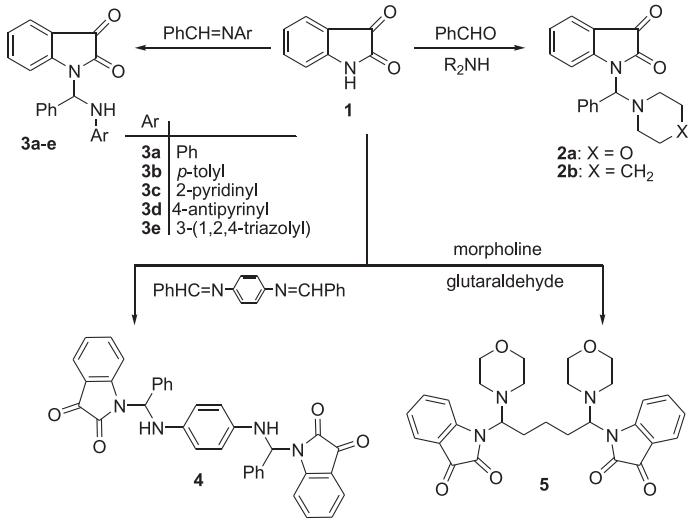
In connection with our studies in the area of Mannich bases [20–30], the present work is concerned with attempts to extend the scope of Mannich reaction with isatin and its Schiff bases, to include the synthesis of a new series of their *N*-Mannich bases and bis(*N*-Mannich bases), of potential pharmaceutical applications.

RESULTS AND DISCUSSION

The conventional route to *N*-Mannich bases of isatin (indolin-2,3-dione) **1** and related compounds, involves its reaction with formaldehyde and the appropriate amine [31]. This reaction is restricted to the use of formaldehyde as the key component. In the present work, the synthesis of *N*-Mannich bases of the type **2**, based on the reaction of **1** with aromatic aldehyde and *sec*-amines, has been achieved by treating **1** with benzaldehyde and morpholine or piperidine to afford 1-(morpholin-4-ylbenzyl)indolin-2,3-dione (**2a**) and the 1-(piperidin-1-ylbenzyl) analog (**2b**), respectively (Scheme 1). The analytical and spectral data of **2a** and **2b** are consistent with their structures. The ^{1}H NMR spectrum of **2a** revealed the presence of a singlet for (Ph─C*H*) at δ = 5.86 and two multiplets at 3.52 (CH_2─O─CH_2) and 2.66 ppm (CH_2─N─CH_2). The mass spectra of **2a** and **2b** indicated the molecular ion peaks at *m/z* 322 and 320, respectively, and exhibited a number of identical peaks at *m/z* = 236 (M^+–the amine component), 147 (isatin ion), 119 (isatin – CO) and 91.

The scope of the above synthesis was developed by treating **1** with aldimines derived from benzaldehyde and primary aromatic or heterocyclic amines to afford 1-(arylaminobenzyl)indoline-2,3-diones (**3a**–**3e**). The reaction allows considerable variation in the aldehyde and amine components of the aminobenzyl moiety of the products. The structure of **3a**–**3e** was confirmed on the basis of analytical and spectral data. The IR spectra of these compounds showed strong absorption bands around 3425 (NH), 1725 (CO), and 1332–1325 cm^{-1} (C─N stretch of *sec*-aryl amine). Their ^{1}H NMR spectra revealed the presence of (Ph─C*H*) proton as a singlet at δ = 6.14–5.75 and a broad singlet due to (N*H*) at 4.19–

Scheme 1. Synthesis of *N*-Mannich bases and bis(*N*-Mannich bases) of isatin.



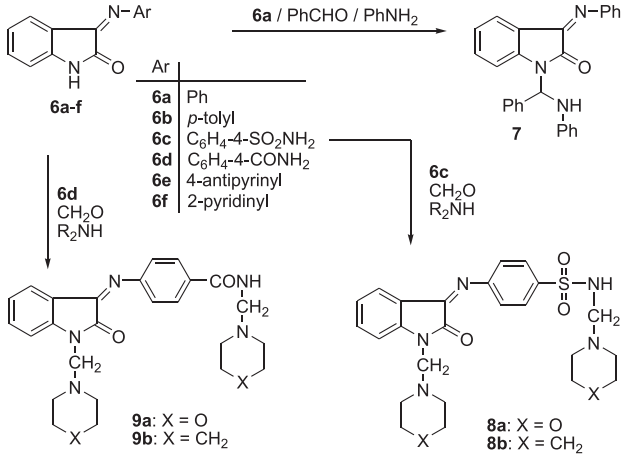
3.44 ppm, and their mass spectra contain peaks of the respective molecular ions, it underwent fragmentation pattern that supported their structures.

The reaction of **1** with N^1,N^4-dibenzylidene-*p*-phenylenediamine proceeded equally well, providing *N*, *N*′-bis(indolin-2,3-dione-1-ylbenzyl)-*p*-phenylenediamine (**4**). In the course of this study, the synthesis of the bis(*N*-Mannich base) **5** has been achieved by treating **1** with glutaric dialdehyde and morpholine. Compounds **4** and **5** were characterized by analytical and spectral data. The mass spectra revealed intense molecular ion peaks at *m/z* = 578 and 532 for **4** and **5**, respectively.

On the other hand, considerable attention has been devoted to isatin Schiff bases and their *N*-Mannich bases as biologically active compounds [3,10,11]. Accordingly, we prepared the isatin Schiff bases **6a** [32], **6b** [10], **6c** [11], and **6f** [16] from **1** and the appropriate aryl or heteroaryl amine. Whereas, the Schiff bases **6d** and **6e** were prepared for the first time in this work. Application of Mannich reaction to compounds **6a**–**f** has been of considerable importance in the synthesis of certain *N*-Mannich bases and bis-bases, which possess considerable synthetic and pharmaceutical interest (Scheme 2). Therefore, treatment of **6a** with benzaldehyde and aniline afforded **7**. The Mannich reaction with the Schiff bases **6c** and **6d**, is of particular interest, because the sulfonamide and the benzamide moieties of these compounds allows the construction of the new hybridized bis(*N*-Mannich bases) of the type **8** and **9**.

Therefore, the synthesis of 4-[1-(morpholinomethyl)-2-oxoindolin-3-ylideneamino]-*N*-(morpholinomethyl)-benzenesulfonamide (**8a**) and the bis(piperidin-1-ylmethyl) analog (**8b**) has been achieved by treating **6c** with formaldehyde and morpholine or piperidine. A similar reaction takes place with **6d**, yielding the bis(*N*-Mannich

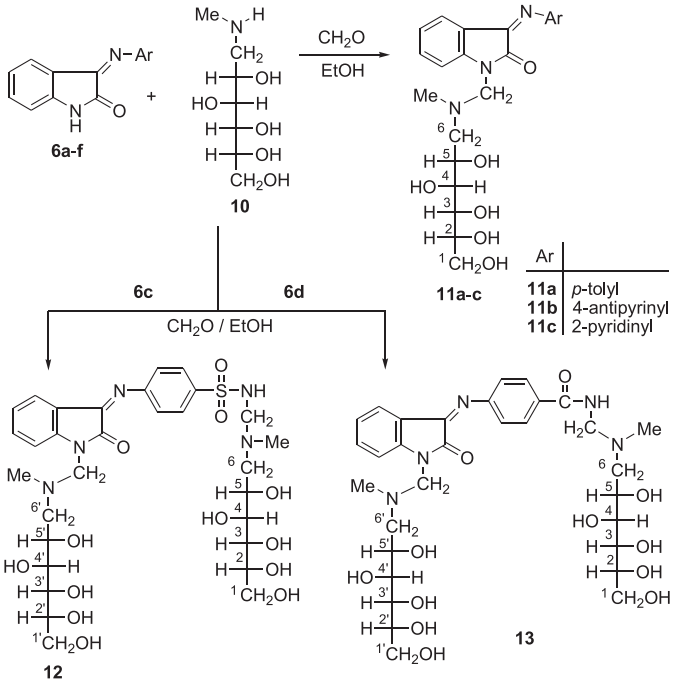
Scheme 2. Mannich reaction with isatin Schiff bases **6a**, **6c**, and **6d**.



bases) **9a** and **9b**. The analytical, IR, ^{1}H NMR, and mass spectral data are consistent with the structures proposed for compounds **8a**–**b** and **9a**–**b**. The IR spectrum of **8a** exhibited a strong broad band at 3445 (NH), 1722 (CO), and two bands at 1329 and 1143 cm^{-1} (sulfonamide). Its ^{1}H NMR spectrum displays two multiplets at δ = 2.61 (2 × CH_2─N─CH_2) and 3.58 (2 × CH_2─O─CH_2), two singlets at 4.18 (N─CH_2─N) and 4.39 (SO_2NH─CH_2─N), and a abroad singlet at 3.0 ppm (SO_2NH).

One main goal of the present work is to study the reactivity of *N*-methyl-*D*-glucamine **10** as the amine component in the Mannich reaction with isatin Schiff bases **6**, as a possible route to *N*-polyhydroxy Mannich bases. This has been realized by treating **6b**, **6e**, and **6f** with **10** and formaldehyde to afford the target compounds; 1-[methyl-(2,3,4,5,6-pentahydroxyhexyl) aminomethyl]-3-(arylimino)indolin-2-ones (**11a**–**c**), respectively (Scheme 3). No report seems to have

Scheme 3. Mannich reaction of isatin Schiff bases with *N*-methyl-*D*-glucamine.



appeared in the literature on using *N*-methyl-*D*-glucamine **10** as the amine component in the Mannich reaction with isatin and related compounds.

It is interesting in this connection that treatment of the Schiff bases **6c** and **6d** with **10** and formaldehyde led to the formation of the hybridized bis(*N*-polyhydroxy Mannich bases) **12** and **13**, respectively, via a double *N*-Mannich reaction. The formation of compounds **12** and **13** is in harmony with the formation of **8a**–**b** and **9a**–**b** from **6c** and **6d**. The mass spectra of **12** and **13** revealed intense molecular ion peaks at *m/z* = 714 (M^+–1) and 679, respectively, and the IR and ^{1}H NMR spectral data supported their structures. The *N*-polyhydroxy Mannich bases **11a**–**c**, **12**, and **13** have structural features related to glycosides. In addition, introduction of the polyhydroxy function would increase the hydrophilic character of the compound and hence the bioavailability of the molecule.

CONCLUSION

In conclusion, a new series *N*-Mannich bases and bis(*N*-Mannich bases) of isatin (**1**) was synthesized by treating **1** with benzaldehyde or glutaric dialdehyde and the appropriate amine, or with the appropriate aldimine. Mannich reaction of Schiff bases derived from **1** and 4-aminobenzamide or sulfanilamide afforded new hybridized bis(*N*-Mannich bases). The use of *N*-methyl-*D*-glucamine as the amine component in the Mannich reaction with isatin Schiff bases led to the formation of new *N*-polyhydroxy Mannich bases and hybridized bis(*N*-polyhydroxy Mannich bases), which have structural features related to glycosides.

EXPERIMENTAL

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 NMR data were obtained in [D_6]DMSO solution on a Varian XL 300 MHz instrument (Varian, Inc., CA, USA) using tetramethylsilane as internal standard. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane. 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 thin-layer chromatography 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 **6a** [32], **6b** [10], **6c** [11], and **6f** [16] were prepared as previously described.

1-(Aminobenzyl)indolin-2,3-diones (2a–**2b**). A mixture of **1** (1.47 g, 10 mmol), benzaldehyde (1.1 g, 10 mmol),

and morpholine or piperidine (10 mmol) in ethanol (20 mL) was heated on a steam bath for 30 min, and stirred at room temperature for 24 h. The crude product was purified by column chromatography (aluminum oxide; n-hexane-ether, 8:1).

1-(Morpholin-4-ylbenzyl)indolin-2,3-dione (2a). Red needles, yield 1.51 g (47%), mp 197–198°C; ^{1}H NMR ([D$_6$]DMSO): δ = 2.66 [m, 4H, C*H*$_2$─N─C*H*$_2$], 3.52 (m, 4H, C*H*$_2$─O─C*H*$_2$), 5.86 (s, 1H, Ph─C*H*), 7.12–7.86 ppm (m, 9H, aromatic); IR (KBr): ν = 1726, 1613, 1459, 1327, 1201, 1101, 932, 767 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 322 (M$^+$) (28), 245 (12), 236 (16), 159 (10), 147 (37), 119 (78), 92 (100), 91 (29), 76 (21). *Anal*. Calcd for $C_{19}H_{18}N_2O_3$ (322.36): C 70.79, H 5.63, N 8.69. Found: C 70.71, H 5.59, N 8.59.

1-(Piperidin-1-ylbenzyl)indolin-2,3-dione (2b). Dark red needles, yield 1.21 g (38%), mp 209–210°C; ^{1}H NMR ([D$_6$]DMSO): δ = 1.39 [m, 6H, C*H*$_2$(C*H*$_2$)$_2$], 2.61 [m, 4H, C*H*$_2$─N─C*H*$_2$], 5.88 (s, 1H, Ph─C*H*), 7.01–7.77 ppm (m, 9H, aromatic); IR (KBr): ν = 1720, 1698, 1612, 1486, 1311, 1209, 1057, 962, 732 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 320 (M$^+$) (18), 236 (12), 147 (26), 119 (81), 92 (84), 91 (23), 76 (12), 52(100). *Anal*. Calcd for $C_{20}H_{20}N_2O_2$ (320.15): C 74.98, H 6.29, N 8.74. Found: C 74.90, H 6.22, N 8.69.

1-(Arylaminobenzyl)indolin-2,3-diones (3a–3c). A solution of **1** (1.47 g, 10 mmol) and the appropriate aldimine (10 mmol) in ethanol (25 mL) was heated on a steam bath for 30 min, and the reaction mixture was stirred at room temperature for 24 h. The products obtained on cooling were filtered and crystallized from ethanol.

1-(Phenylaminobenzyl)indolin-2,3-dione (3a). Yellow crystals, yield 2.09 g (64%), mp 179°C; ^{1}H NMR ([D$_6$] DMSO): δ = 4.15 (br s, 1H, N*H*), 5.85 (s, 1H, Ph-C*H*), 6.92–7.57 ppm (m, 14H, aromatic); IR (KBr): ν = 3368, 1730, 1654, 1611, 1459, 1332, 1280, 1202, 953 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 328 (M$^+$) (62), 251 (M$^+$−Ph) (40), 236 (M$^+$−PhNH) (10), 222 (35), 194 (81.44), 167 (15), 146 (4), 77(100), 51 (77). *Anal*. Calcd for $C_{21}H_{16}N_2O_2$ (328.36): C 76.81, H 4.91, N 8.53. Found: C 76.79, H 4.88, N 8.48.

1-(*p*-Tolylaminobenzyl)indolin-2,3-dione (3b). Pale orange crystals, yield 1.98 g (58%), mp 180°C; ^{1}H NMR ([D$_6$]DMSO): δ = 2.28 (s, 3H, C*H*$_3$), 3.77 (br s, 1H, N*H*), 5.95 (s, 1H, Ph─C*H*), 6.87–7.64 ppm (m, 13H, aromatic); IR (KBr): ν = 3346, 1725, 1618, 1476, 1331, 1266, 1183, 965, 754 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 342 (M$^+$) (57), 327 (M$^+$−Me) (27), 250 (30), 236 (48), 208 (100), 145 (14), 91 (74), 78 (55), 65 (93). *Anal*. Calcd for $C_{22}H_{18}N_2O_2$ (342.39): C 77.17, H 5.30, N 8.18. Found: C 77.02, H 5.27, N 8.10.

1-(Pyridin-2-ylaminobenzyl)indolin-2,3-dione (3c). Reddish brown crystals, yield 0.82 g (25%), mp 196–197°C; ^{1}H NMR ([D$_6$]DMSO): δ = 4.19 (br s, 1H, N*H*), 6.14 (s, 1H, Ph-C*H*), 6.81–7.84 ppm (m, 13H, aromatic); IR (KBr): ν = 3426, 1724, 1644, 1605, 1463, 1374, 1336, 1140, 944, 739 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 329 (M$^+$) (17), 252 (M$^+$−Ph) (15), 147 (33), 119 (100), 92 (81), 91 (22), 77 (4), 52 (59). *Anal*. Calcd for $C_{20}H_{15}N_3O_2$ (329.35): C 72.94, H 4.59, N 12.76. Found: C 72.89, H 4.51, N 12.70.

1-(Antipyrin-4-ylaminobenzyl)indolin-2,3-dione (3d). Orange crystals, yield 1.18 g (27%), mp 158–160°C; ^{1}H NMR ([D$_6$]DMSO): δ = 3.44 (br s, 1H, N*H*), 2.23 (s, 3H, C─C*H*$_3$), 2.91 (s, 3H, N─C*H*$_3$), 5.75 (s, 1H, Ph─C*H*), 6.91–7.94 ppm (m, 14H, aromatic); IR (KBr): ν = 3386, 1727, 1613, 1399, 1327, 1284, 1196, 1090, 768 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 438 (M$^+$) (34), 439 (M$^+$ + 1) (92), 408 (28), 361 (M$^+$−Me) (37), 331 (31), 303 (28), 254 (42), 251 (37), 178 (63), 147 (57), 119 (85), 108 (54), 92 (94), 77 (60), 52 (100). *Anal*. Calcd for $C_{26}H_{22}N_4O_3$ (438.48): C 71.22, H 5.06, N 12.78. Found: C 71.19, H 4.98, N 12.71.

1-(1,2,4-Triazol-3-ylaminobenzyl)indolin-2,3-dione (3e). Pale orange needles, yield 0.51 g (16%), mp 210°C; ^{1}H NMR ([D$_6$]DMSO): δ = 3.60 (br s, 1H, N*H*), 5.88 (s, 1H, Ph─C*H*), 9.77 (br s, 1H, N*H* of triazole moiety), 7.01–7.86 ppm (m, 10H, aromatic); IR (KBr): ν = 3442, 3395, 1700, 1710, 1612, 1332, 1151, 921, 827, 732 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 319 (M$^+$) (76), 320 (M$^+$ + 1) (28), 292 (81), 278 (31), 251 (M$^+$−triazole ion, (44), 242 (M$^+$–Ph) (100), 236 (46), 173 (33), 144 (48), 117 (26), 91 (39), 85 (33), 77 (22), 51 (65). *Anal*. Calcd for $C_{17}H_{13}N_5O_2$ (319.32): C 63.94, H 4.10, N 21.93. Found: C 63.89, H 4.12, N 21.90.

***N,N′*-Bis(indolin-2,3-dione-1-ylbenzyl)-*p*-phenylenediamine (4)**. A mixture of **1** (1.47 g, 10 mmol) and N^1,N^4-dibenzylidenebenzene-1,4-diamine (2.84 g, 10 mmol) in ethanol (50 mL) was refluxed on a steam bath for 40 min and stirred at room temperature for 48 h. The crude product was filtered and crystallized from ethanol and purified by column chromatography (aluminum oxide; petroleum ether-EtOAc, 7:3), to give **4** as buff crystals. Yield 1.50 g (26%), mp 218–220°C; ^{1}H NMR ([D$_6$] DMSO): δ = 4.23 (br s, 2H, 2 × N*H*), 6.16 (s, 2H, 2 × Ph─C*H*), 6.72–7.76 ppm (m, 22H, aromatic); IR (KBr): ν = 3410, 3392, 1726, 1705, 1611, 1336, 1299, 937, 749 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 578 (M$^+$) (50), 579 (M$^+$ + 1) (60), 432 (12), 342 (25), 329 (48), 261 (60), 223 (52), 147) (51), 119 (35), 92 (34), 77 (22). *Anal*. Calcd for $C_{36}H_{26}N_4O_4$ (578.62): C 74.73, H 4.53, N 9.68. Found: C 74.69, H 4.50, N 9.61.

1,5-Bis(indolin-2,3-dione-1-yl)-1,5-Bis(morpholin-4-yl) pentane (5). To a solution of **1** (2.94 g, 20 mmol) and morpholine (1.8 g, 20 mmol) in ethanol (40 mL), glutaric dialdehyde (25%, 4 mL, 10 mmol) was added, and the mixture was refluxed on a steam bath for 1 h, and stirred at room temperature for 4 days, and concentrated. The gummy material that obtained was treated with ether to

give a pale brown powder, which was crystallized from ethanol, and purified by preparative thin-layer chromatography (petroleum ether-EtOAc, 7:3), to give **5**. Pale brown powder, yield 3.40 g (32%), mp 156°C; ^{1}H NMR ([D$_6$]DMSO): δ = 1.30 [m, 2H, C*H*$_2$(CH$_2$)$_2$], 1.73 (q, 4H, >CH─C*H*$_2$─CH$_2$─C*H*$_2$─CH<), 2.81 [m, 8H, 2 × N(CH$_2$)$_2$], 3.71 [m, 8H, 2 × O (CH$_2$)$_2$], 4.68 (t, 2H, 2 × CH), 6.82–7.55 ppm (m, 8H, aromatic); IR (KBr): v = 1722, 1708, 1618, 1470, 1333, 1298, 1067, 949, 754 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 532 (M$^+$) (35), 531 (M$^+$−1) (20), 484 (21), 328 (23), 223 (20), 149 (26), 104 (28), 100 (41), 98 (18), 92 (21), 89 (21), 52 (100). *Anal*. Calcd for $C_{29}H_{32}N_4O_6$ (532.59): C 65.40, H 6.06, N 10.52. Found: C 65.38, H 6.01, N 10.49.

4-(2-Oxoindolin-3-ylideneamino)benzamide (6d). A mixture of **1** (1.47 g, 10 mmol) and 4-aminobenzamide (1.36 g, 10 mmol) in ethanol (40 mL) and acetic acid (4 mL) was refluxed on a steam bath for 1 h and stirred at room temperature for 12 h. The product obtained was filtered and crystallized from ethanol – acetic acid (2:1) to give orange crystals, 1.78 g (67%). Mp 259–260°C; IR (KBr): v = 3391, 3368, 1725, 1658, 1635, 1585, 1460, 1275, 1114, 722 cm^{-1}. *Anal*. Calcd for $C_{15}H_{11}N_3O_2$ (265.27): C 67.92, H 4.18, N 15.84. Found: C 67.90, H 4.11, N 15.79.

3-(Antipyrin-4-ylimino)indolin-2-one (6e). This compound was prepared from equimolar amounts of **1** and 4-aminoantipyrine (10 mmol), following the same procedure as described earlier. Crystallization of the product from ethanol gave dark yellow crystals. Yield 2.7 g (81%), mp 160–162°C; IR (KBr): v = 3385, 3310, 1720, 1665, 1589, 1412, 1335, 1275, 1122, 772 cm^{-1}. *Anal*. Calcd for $C_{19}H_{16}N_4O_2$ (332.36): C 68.66, H 4.85, N 16.86. Found: C 68.61, H 4.82, N 16.80.

1-(Phenylaminobenzyl)-3-(phenylimino)indolin-2-one (7). This compound was prepared from equimolar amounts of **6a**, benzaldehyde, and aniline (5 mmol), following the procedure described above for compounds **3a**–**e**. Crystallization of the product from ethanol gave **7** as yellow crystals. Yield 1.2 g (60%), mp 217°C; ^{1}H NMR ([D$_6$]DMSO): δ = 3.81 (br s, 1H, N*H*), 5.81 (s, 1H, Ph-C*H*), 6.75–7.66 ppm (m, 19H, aromatic); IR (KBr): v = 3328, 1722, 1655, 1611, 1499, 1335, 1262, 1212, 955 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 403 (M$^+$) (48), 326 (M$^+$−Ph) (18), 300 (47), 249 (46), 217 (50), 181 (71), 147 (55), 146 (27), 92 (20), 77 (100). *Anal*. Calcd for $C_{27}H_{21}N_3O$ (403.48): C 80.37, H 5.25, N 10.41. Found: C 80.31, H 5.20, N 10.38.

Synthesis of bis(*N*-Mannich bases) 8a and **8b**. To a solution of **6c** (1.5 g, 5 mmol) and morpholine or piperidine (10 mmol) in acetic acid (20 mL), there was added formalin (37%, 1 mL, 12 mmol), and the mixture was stirred at room temperature for 24 h, then diluted with water (5 mL) and basified to pH8 by ammonia. The product obtained was filtered and crystallized from ethanol.

4-[1-(Morpholin-4-ylmethyl)-2-oxoindolin-3-ylideneamino]-N-(morpholin-4-ylmethyl)benzenesulfonamide (8a). Yellow powder; yield 1.19 g (48%), mp 170°C; ^{1}H NMR ([D$_6$] DMSO): δ = 2.61 (m, 8H, 2 × C*H*$_2$─N─C*H*$_2$), 3.0 (br s, 1H, SO$_2$N*H*), 3.58 (m, 8H, 2 × C*H*$_2$─O─C*H*$_2$), 4.18 (s, 2H, N─C*H*$_2$─N), 4.39 (s, 2H, SO$_2$NH─C*H*$_2$─N), 7.12–7.86 ppm (m, 8H, aromatic); IR (KBr): v = 3445, 1722, 1612, 1459, 1420, 1329, 1251, 1143, 1043, 933, 821, 714 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 499 (M$^+$) (34), 413 (21), 399 (11), 327 (32), 299 (12), 255 (15), 244 (11), 156 (9), 144 (16), 100 (22), 86 (18), 52 (100). *Anal*. Calcd for $C_{24}H_{29}N_5O_5S$ (499.58): C 57.70, H 5.85, N 14.02. Found: C 57.68, H 5.80, N 13.95.

4-[1-(Piperidin-1-ylmethyl)-2-oxoindolin-3-ylideneamino]-N-(piperidin-1-ylmethyl)benzenesulfonamide (8b). Pale orange powder, yield 1.10 g (44%), mp 145°C; ^{1}H NMR ([D$_6$] DMSO): δ = 1.35 [m, 12H, 2 × C*H*$_2$(C*H*$_2$)$_2$], 2.64 [m, 8H, 2 × C*H*$_2$─N─C*H*$_2$], 3.11 (br s, 1H, SO$_2$N*H*), 4.12 (s, 2H, N─C*H*$_2$─N), 4.36 (s, 2H, SO$_2$NH─C*H*$_2$─N), 7.21–7.83 ppm (m, 8H, aromatic); IR (KBr): v = 3440, 1718, 1610, 1453, 1412, 1323, 1244, 1140, 1038, 931, 818, 712 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 495 (M$^+$) (17), 496 (M$^+$ + 1) (3), 399 (5), 327 (22), 253 (6), 299 (17), 246 (7), 148 (12), 146 (24), 133 (44), 100 (100), 76 (14). *Anal*. Calcd for $C_{26}H_{33}N_5O_3S$ (495.64): C 63.01, H 6.71, N 14.13. Found: C 62.95, H 6.66, N 14.01.

Synthesis of bis(*N*-Mannich bases) 9a and **9b**. These compounds were obtained from **6d** (1.3 g, 5 mmol), morpholine or piperidine (10 mmol), and formalin (12 mmol), following the general procedure described earlier for **8a**, **b**. The product obtained was filtered and crystallized from ethanol.

4-[1-(Morpholin-4-ylmethyl)-2-oxoindolin-3-ylideneamino]-N-(morpholin-4-ylmethyl)benzamide (9a). Orange powder, yield 1.08 g (47%), mp 186°C; ^{1}H NMR ([D$_6$]DMSO): δ = 2.67 (m, 8H, 2 × C*H*$_2$─N─C*H*$_2$), 3.70 (m, 8H, 2 × C*H*$_2$─O─C*H*$_2$), 3.91 (s, 2H, N─C*H*$_2$─N), 4.23 (s, 2H, CONH─C*H*$_2$-N), 6.82–7.76 (m, 8H, aromatic), 8.16 ppm (br s, 1H, CON*H*); IR (KBr): v = 3385, 1719, 1685, 1608, 1446, 1333, 1313, 1267, 1150, 1110, 1042, 998, 855, 764 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 463 (M$^+$) (15), 464 (M$^+$ + 1) (6), 348 (11), 320 (7), 246 (5), 132 (12), 100 (100), 90 (9), 56 (10). *Anal*. Calcd for $C_{25}H_{29}N_5O_4$ (463.53): C 64.78, H 6.31, N 15.11. Found: C 64.70, H 6.28, N 15.01.

4-[1-(Piperidin-1-ylmethyl)-2-oxoindolin-3-ylideneamino]-N-(piperidin-1-ylmethyl)benzamide (9b). Pale brown powder, yield 0.98 g (43%), mp 182°C; ^{1}H NMR ([D$_6$]DMSO): δ = 1.48 [m, 12H, 2 × C*H*$_2$(C*H*$_2$)$_2$], 2.76 [m, 8H, 2 × C*H*$_2$─N─C*H*$_2$], 4.02 (s, 2H, N─C*H*$_2$─N), 4.30 (s, 2H, CONH─C*H*$_2$─N), 6.71–7.68 (m, 8H, aomatic), 8.25 ppm (br s, 1H, CON*H*); IR (KBr): v = 3414, 1715,

1675, 1609, 1416, 1331, 1316, 1262, 1170, 1112, 1012, 948, 853, 764 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 459 (M^+) (25), 381 (23), 320 (21), 255 (18), 247 (13), 144 (19), 98 (100), 85 (25), 78 (16), 56 (11). *Anal*. Calcd for $C_{27}H_{33}N_5O_2$ (459.58): C 70.56, H 7.24, N 15.24. Found: C 70.50, H 7.21, N 15.19.

1-[Methyl-(2,3,4,5,6-pentahydroxyhexyl)aminomethyl]-3-aryl(heteroaryl)imino]-indolin-2-ones 11a–11c. To a solution of *N*-methyl-*D*-glucamine **10** (1 g, 5 mmol) and **6b**, or **6e**, or **6f** (5 mmol) in ethanol (25 mL), there was added formalin (37%, 0.5 mL, 6 mmol), and the mixture was heated for 30 min, and stirred at room temperature for 24 h. The product obtained was filtered and crystallized from ethanol.

1-[Methyl-(2,3,4,5,6-pentahydroxyhexyl)aminomethyl]-3-(p-tolylimino)indolin-2-one (11a). Pale orange powder, yield 0.98 g (44%), mp 205°C; ^{1}H NMR ([D_6]DMSO): δ = 2.21 (s, 3H, NCH_3), 2.28 (s, 3H, ArCH_3), 2.37 (dd, *J* = 7.8, 15.6 Hz, 1H, H_a-6), 2.66 (dd, *J* = 7.2, 14.4 Hz, 1H, H_b-6), 3.19 (m, 4H, 4 × C*H*─OH), 3.31 (dd, *J* = 7.5, 15.0 Hz, 1H, H_a-1), 3.52 (dd, *J* = 7.2, 14.5 Hz, 1H, H_b-1), 4.18 (s, 2H, N─CH_2─N), 4.56 (br s, 5H, 5 × O*H*), 7.10–7.81 ppm (m, 8H, aromatic); IR (KBr): *v* = 3505, 3192, 1705, 1597, 1321, 1072, 944, 825, 732 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 443 (M^+) (10), 444 (M^+ + 1) (4), 428 (M^+−Me) (8), 236 (50), 208 (100), 180 (23), 91 (70), 77 (6), 65 (24), 52 (12). *Anal*. Calcd for $C_{23}H_{29}N_3O_6$ (443.49): C 62.29, H 6.59, N 9.47. Found: C 62.21, H 6.52, N 9.40.

1-[Methyl-(2,3,4,5,6-pentahydroxyhexyl)aminomethyl]-3-(antipyrin-4-ylimino)-indolin-2-one (11b). Pale orange powder, yield 1.25 g (46%), mp 148°C; ^{1}H NMR ([D_6] DMSO): δ = 2.17 (s, 3H, NCH_3 of glucamine moiety), 2.39 (s, 3H, C─CH_3 of antipyrine moiety), 2.59 (s, 3H, NCH_3 of antipyrine moiety), 2.71 (dd, *J* = 7.5, 15 Hz, 1H, H_a-6), 3.01 (dd, *J* = 7.5, 15 Hz, 1H, H_b-6), 3.51 (m, 4H, 4 × C*H*─OH), 3.72 (dd, *J* = 7.5, 15.0 Hz, 1H, H_a-1), 4.02 (dd, *J* = 8.1, 16.2 Hz, 1H, H_b-1), 4.40 (br s, 5H, 5 × O*H*), 4.79 (s, 2H, N─CH_2─N), 7.11–7.88 ppm (m, 9H, aromatic); IR (KBr): *v* = 3483, 3228, 1709, 1691, 1612, 1421, 1209, 1051, 956, 832 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 539 (M^+) (12), 494 (10), 408 (17), 233 (16), 150 (26), 119 (29), 91 (26), 75 (17), 60 (37), 57 (100). *Anal*. Calcd for $C_{27}H_{33}N_5O_7$ (539.58): C 60.10, H 6.16, N 12.98. Found: C 60.02, H 6.12, N 12.91.

1-[Methyl-(2,3,4,5,6-pentahydroxyhexyl)aminomethyl]-3-(pyridin-2-ylimino)indolin-2-one (11c). Orange powder, yield 0.87 g (40%), mp 142°C; ^{1}H NMR ([D_6]DMSO): δ = 2.20 (s, 3H, NCH_3), 2.43 (dd, *J* = 7.8, 15.6 Hz, 1H, H_a-6), 2.74 (dd, *J* = 7.8, 15.6 Hz, 1H, H_b-6), 3.30 (m, 4H, 4 × C*H*─OH), 3.81 (dd, *J* = 7.8, 15.6 Hz, 1H, H_a-1), 3.87 (dd, *J* = 7.5, 15 Hz, 1H, H_b-1), 4.64 (s, 2H, N─CH_2─N), 4.79 (br s, 5H, 5 × O*H*), 6.89–7.86 ppm (m, 8H, aromatic); IR (KBr): *v* = 3492, 3252, 1710, 1590, 1362, 1062, 954, 835, 697 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 430 (M^+) (21), 429 (M^+−1) (8), 286 (15), 253 (12), 190 (22), 148 (24), 120 (15), 91 (35), 77 (20), 52 (100), 51 (36). *Anal*. Calcd for $C_{21}H_{26}N_4O_6$ (430.45): C 58.59, H 6.09, N 13.02. Found: C 58.51, H 6.01, N 12.90.

Synthesis of bis(*N*-polyhydroxy Mannich bases) 12 and **13**. To a solution of *N*-methyl-*D*-glucamine **10** (2 g, 10 mmol) and **6c** or **6d** (5 mmol) in ethanol (25 mL), there was added formalin (37%, 1 mL, 12 mmol), and the mixture was heated for 30 min, and stirred at room temperature for 48 h. The product obtained was filtered and crystallized from ethanol.

4-[1-(Methyl-2,3,4,5,6-pentahydroxyhexyl)aminomethyl)-2-oxoindolin-3-ylideneamino]-*N*-(methyl-2,3,4,5,6-pentahydroxyhexyl)aminomethyl) benzenesulfonamide (12). Dark yellow powder, yield 1.7 g (47%), mp 234–236°C; ^{1}H NMR ([D_6]DMSO): δ = 1.98 (s, 6H, 2 × NCH_3), 2.21 (s, 1H, N*H*), 2.59 (dd, *J* = 7.2, 14.4 Hz, 2H, 2 × H_a-6), 2.95 (dd, *J* = 7.2, 14.4 Hz, 2H, 2 × H_b-6), 3.01 (m, 8H, 8 × C*H*─OH), 3.51 (dd, *J* = 7.5, 15 Hz, 2H, 2 × H_a-1), 3.74 (dd, *J* = 7.5, 15 Hz, 2H, 2 × H_b-1), 4.17 (s, 2H, N─CH_2─N), 4.39 (s, 2H, SO_2NH─CH_2─N), 4.76 (br s, 10H, 10 × O*H*), 7.12–7.77 ppm (m, 8H, aromatic); IR (KBr): *v* = 3478, 3272, 1711, 1617, 1539, 1322, 1230, 946, 765, 640 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 714 (M^+−1) (52), 712 (16), 627 (30), 540 (22), 458 (44), 299 (13) 235 (51), 151 (12), 91 (31), 83 (100), 52 (25). *Anal*. Calcd for $C_{30}H_{45}N_5O_{13}S$ (715.77): C 50.34, H 6.34, N 9.78. Found: C 50.29, H 6.30, N 9.71.

4-[1-(Methyl-2,3,4,5,6-pentahydroxyhexyl)aminomethyl)-2-oxoindolin-3-ylideneamino]-*N*-(methyl-2,3,4,5,6-pentahydroxyhexyl)aminomethyl) benzamide (13). Yellow powder, yield 1.7 g (50%), mp 280–282°C; ^{1}H NMR ([D_6]DMSO): δ = 1.81 (s, 6H, 2 × NCH_3), 2.16 (s, 1H, N*H*), 2.67 (dd, *J* = 8.1, 16.2 Hz, 2H, 2 × H_a-6), 2.81 (dd, *J* = 7.8, 15.6 Hz, 2H, 2 × H_b-6), 3.05 (m, 8H, 8 × C*H*─OH), 3.41 (dd, *J* = 7.8, 15.6 Hz, 2H, 2 × H_a-1), 3.64 (dd, *J* = 7.2, 14.4 Hz, 2H, 2 × H_b-1), 4.02 (s, 2H, N─CH_2─N), 4.23 (s, 2H, CONH─CH_2─N), 4.65 (br s, 10H, 10 × O*H*), 7.21–7.78 ppm (m, 8H, aromatic); IR (KBr): *v* = 3474, 3252, 1705, 1698, 1617, 1412, 1320, 1251, 949, 745, 684 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 679 (M^+) (52), 675 (33), 665 (18), 650 (41), 532 (45), 426 (16), 159 (40), 109 (35), 83 (73), 81 (100). *Anal*. Calcd for $C_{31}H_{45}N_5O_{12}$ (679.72): C 54.78, H 6.67, N 10.30. Found: C 54.70, H 6.61, N 10.23.

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