# Facile synthesis of Schiff and Mannich bases of isatin derivatives


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**Abstract**

We report herein on the synthesis of some isatin Schiff's bases (1–12), which were prepared from the reaction of isatin and some aromatic amines. These in turn were converted to the corresponding Mannich bases (13-23) by reaction with a number of secondary amines and formaldehyde, taking advantage of the active –NH group in the isatin. The structures of these compounds were elucidated using standard spectroscopic and analytical methods.



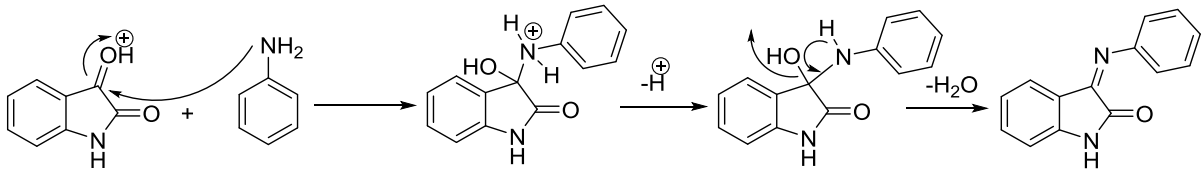
**Keyword:**
Isatin, Isatin Schiff's, Mannich bases


**Introduction:**
Isatin (1H-indoline-2,3-dione) is one of the indole derivatives which was prepared by oxidation of indigo[1]. Isatin Schiff's bases are known to possess a wide range of biological activities such as antimicrobial,[2-8] antifungal,[9] anticancer,[10] anti HIV,[11] and antihelminthic.[12,13] Some were also examined for their anticonvulsant[14] activities. The second type of isatin derivatives is the isatin Schiff's–Mannich bases which combine both the azomethine and methylene amine linkage ($CH_2$-N) in one molecule. This, as well as the wide interest in the biological scope of these compounds, lured us to undertake this research project.

**Results and Discussion**
Reaction of equal molar quantities of isatin and compounds containing $NH_2$ moiety such as 1-phenylhydrazine, Isonicotinohydrazide or 4-pyridinamine gave the required product in moderate to good yield after work up and recrystallization. For further details, see the table below and the experimental section.

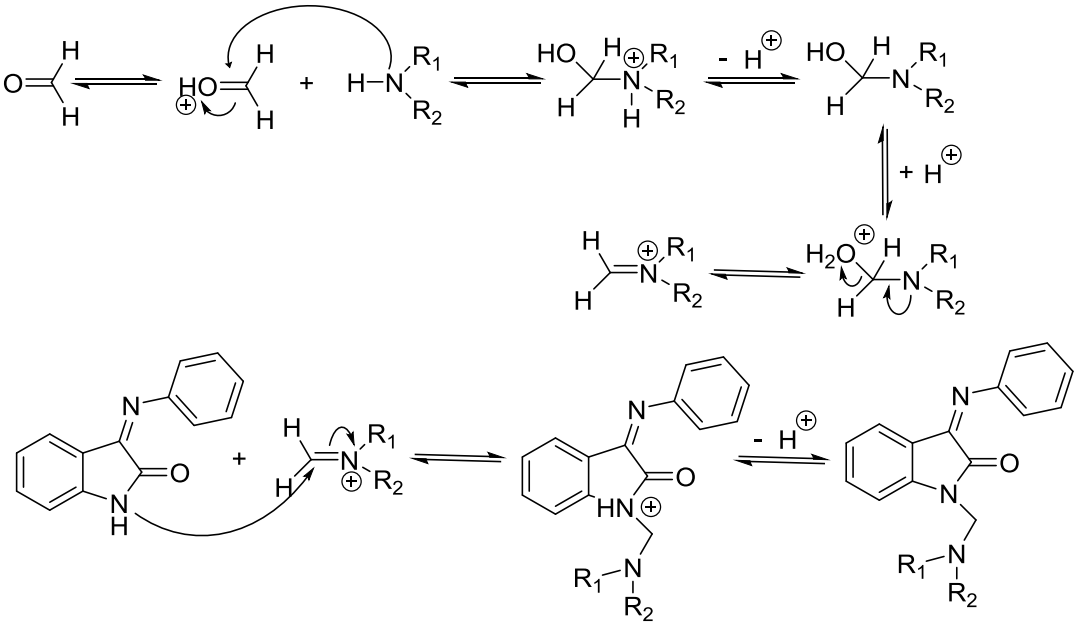
The proposed reaction mechanism, which involved the nucleophilic attack of the amine nitrogen on the carbon atom of the carbonyl followed by water elimination, has been summarised in Scheme (1).

**Scheme (1):** The proposed reaction mechanism for the formation of Isatin Schiff's bases



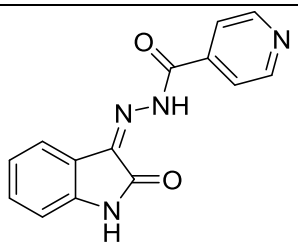
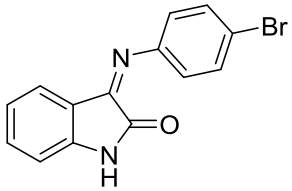
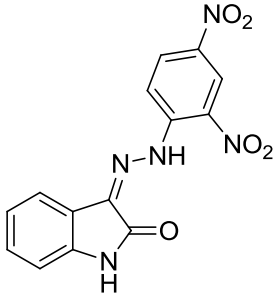
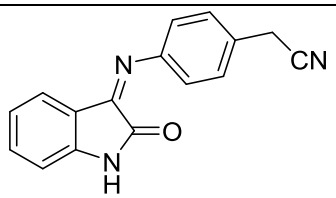

The proposed mechanism for the formation of Mannich bases has been illustrated in Scheme (2) below. This involved the nucleophilic attack of the amine nitrogen on the carbon atom of the formyl carbonyl followed by elimination of water. This in turn was reacted with Isatin Schiff's bases as illustrated in Scheme (2) to give the desired product.

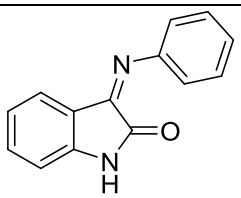
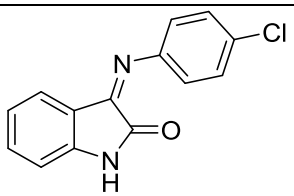
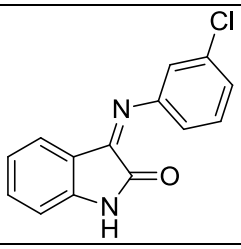
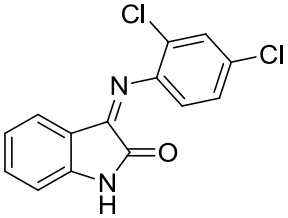
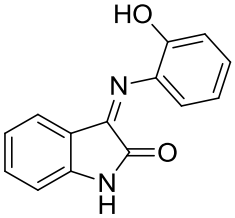
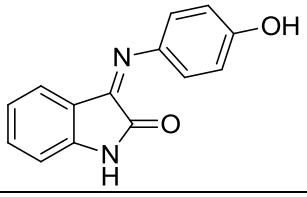
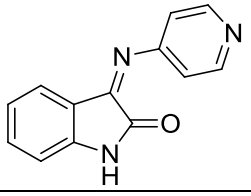
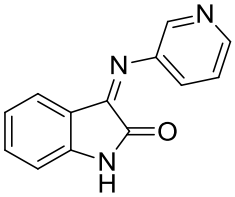
**Scheme (2):** The proposed mechanism for the formation of Mannich bases

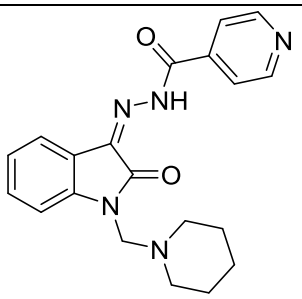
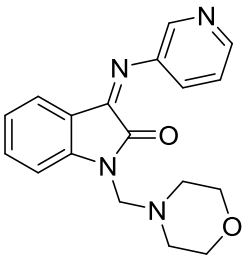
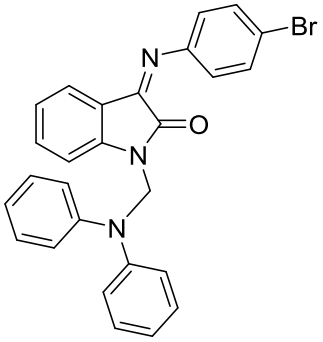
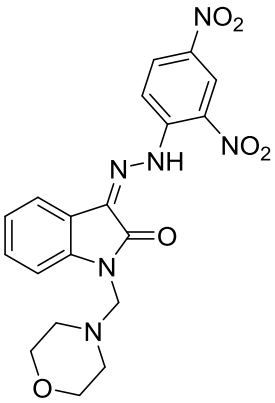
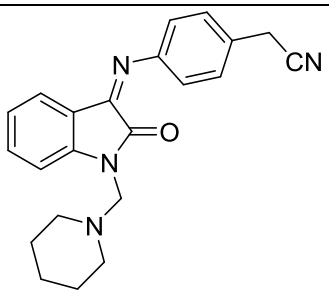


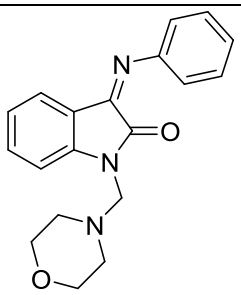
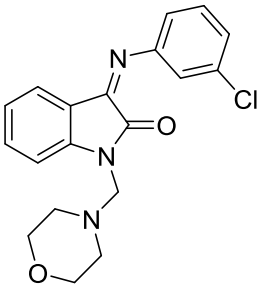
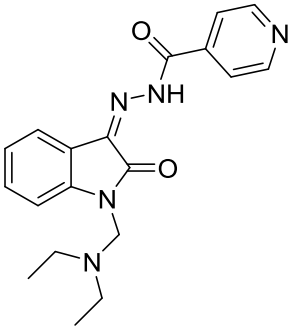
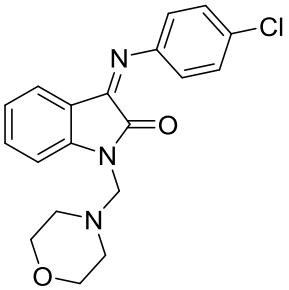
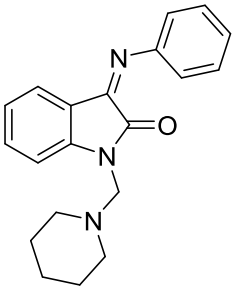
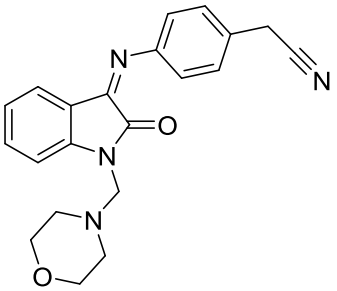
The products from these reactions were confirmed by IR spectroscopy as well as $^{1}H$ NMR and $^{13}C$ NMR in addition to the elemental analyses[15-17].

**Table:** This illustrates the structure, formula, and melting point of the synthesised compounds.

| Compound No | Structure | Formula | MP°C (lit. MP°C) |
|---|---|---|---|
| 1 |  | $C_{14}H_{10}N_4O_2$ | 281-283 (220[18], 299-301[19]) |
| 2 |  | $C_{14}H_9BrN_2O$ | 256-258 (242[20]) |
| 3 |  | $C_{14}H_9N_5O_5$ | 165-167 (>290[21]) |
| 4 |  | $C_{16}H_{11}N_3O$ | 225-227 |

| | | | |
|---|---|---|---|
| 5 |  | $C_{14}H_{10}N_2O$ | 218-220 (232-234[22]) |
| 6 |  | $C_{14}H_9ClN_2O$ | 255-256 (236[23]) |
| 7 |  | $C_{14}H_9ClN_2O$ | 222-225 (N[24]) |
| 8 |  | $C_{14}H_8Cl_2N_2O$ | 172-174 |
| 9 |  | $C_{14}H_{10}N_2O_2$ | 318-320 (194[25]) |
| 10 |  | $C_{14}H_{10}N_2O_2$ | 227-229 (N[26]) |
| 11 |  | $C_{13}H_9N_3O$ | 192-194 (N[27]) |
| 12 |  | $C_{13}H_9N_3O$ | 188-190 (227-228[28]) |

| | | | |
|---|---|---|---|
| 13 |  | $C_{20}H_{21}N_5O_2$ | 204-206 |
| 14 |  | $C_{18}H_{18}N_4O_2$ | 166-168 ($N^{29}$) |
| 15 |  | $C_{27}H_{20}BrN_3O$ | 246-250 ($N^{29}$) |
| 16 |  | $C_{19}H_{18}N_6O_6$ | 173-175 |
| 17 |  | $C_{22}H_{22}N_4O$ | 162-164 |

| | | | |
|---|---|---|---|
| 18 |  | $C_{19}H_{19}N_3O_2$ | 118-120 (208-209[30]; 168-169[31]) |
| 19 |  | $C_{19}H_{18}ClN_3O_2$ | 132-134.(154[31]) |
| 20 |  | $C_{19}H_{21}N_5O_2$ | 164-166 (150[32]) |
| 21 |  | $C_{19}H_{18}ClN_3O_2$ | 178-180 (158-159[32]) |
| 22 |  | $C_{20}H_{21}N_3O$ | 150-152 (160-161[32]) |
| 23 |  | $C_{21}H_{20}N_4O_2$ | 166-168 |

(N): This compound was cited in that reference, but no mp was reported.

**Experimental Part**

**Instruments and chemicals used**

Melting points (uncorrected) were measured using electrothermal melting point apparatus (Metler). Infrared spectra were measured using sp3-100 infrared spectrophotometer (Perkin–Elmer). $^{1}$H NMR and $^{13}$C NMR spectra were measured at the University of Technology, Jordon, using (Bruker Ultra shield 400MHz) instrument using DMSO-$d_6$ as solvent. Microanalysis was performed using CHN analyzer (Eurovector EA 300A Italy). All chemicals used were supplied by BDH and/or Fluka companies.

**General procedure for the synthesis of Schiff's bases (1-12):**

*N*'-[(3*Z*)-2-Oxo-1,2-dihydro-3*H*-indol-3-ylidene]Isonicotinohydrazide **(1)**[18,19]

1*H*-Indole-2,3-dione (isatin) (7.00 mmol) was dissolved in ethanol (20 mL) in a 100 ml round bottomed flask fitted with a condenser. Isonicotinohydrazide (isoniazid) (7.00 mmol) dissolved in ethanol (15 mL) was added to the mixture, followed by 3-4 drops of glacial acetic acid. The reaction mixture was heated under reflux for 3h (the progress of the reaction was monitored by TLC). The precipitate formed was filtered, recrystallized from ethanol and dried to give the required product as light orange in 91% yield. Microanalysis: Calculated: C, 63.02; H, 3.60, N, 21.03 Found: C, 63.15; H, 3.79; N, 21.14.

$^{1}$H NMR (DMSO-$d_6$): 14.00(1H, s), 11.44(1H, s), 8.87(2H), 7.79(2H), 7.62-7.42(2H), 7.11-6.97(2H).

$^{13}$C NMR (DMSO-$d_6$): 151.3, 121.6, 163.4, 134.7, 168.5, 119.0-143.3

IR (cm$^{-1}$): 1620 (C=N isomethine); 1545-1468 (C=C Aromatic); 3234 (N-H isatin); 3165 (N-H isoniazid); 3060 (C-H Ar); 1721 (C=O amide isatin), 1594 (C=N pyridine); 877-660 (HC= Ar bending).

The following compounds were prepared by similar methods:

**(3*Z*)-3-[(4-Bromophenyl)imino]-1,3-dihydro-2*H*-indol-2-one (2)**[20]

Yellow solid, 61% yield

IR (cm$^{-1}$): 1652 (C=N isomethine); 1615-1463 (C=C Aromatic); 3271 (N-H isatin); 1743 (C=O amide isatin); 833-583 (HC= Ar bending); 749 (C-Br); 3193 (NH isatin); 3037 (C-H Ar).

**(3*Z*)-1*H*-Indole-2,3-dione 3-[(2,4-dinitrophenyl)hydrazone] (3)**[21]

Light brown solid, 68% yield

IR (cm$^{-1}$): 1685 (C=N isomethine); 1619-1458 (C=C Aromatic); 3193 (NH isatin); 3037 (C-H Ar), 1737 (C=O amide isatin); 1336 (sy $NO_2$); 1458 (asy $NO_2$); 846-630 (HC=CH Ar bending).

**(4-{[(3*Z*)-2-Oxo-1,2-dihydro-3*H*-indol-3-ylidene]amino}phenyl)acetonitrile (4)**

Yellow solid, 87% yield

Microanalysis: Calculated: C, 73.40; H, 5.03; N, 16.14 Found: C, 73.55; H, 4.24; N, 16.08.

$^{1}$H NMR (DMSO-$d_6$): 4.10(2H), 6.72-7.46(8H), 11.00(1H).

$^{13}$C NMR (DMSO-$d_6$): 118.0, 118.4-150.2, 155.9, 122.2-143, 22.4.

IR (cm$^{-1}$): 1660 (C=N isomethine), 1502-1463 (C=C Aromatic), 3205 (NH isatin); 2724 (sy $CH_2$); 288 (asy $CH_2$); 2244 (CN nitrile); 1746 (C=O amide isatin); 837-663 (HC=CH Ar bending); 3168 (NH isatin).

**(3*Z*)-3-(Phenylimino)-1,3-dihydro-2*H*-indol-2-one (5)**[22]

Yellow solid, 72% yield

$^{1}$H NMR (DMSO-$d_6$): 7.60-6.73 (9H), 11.00 (1H).

IR (cm$^{-1}$): 1655 1611-1459 (C=C Aromatic), 3168 (NH isatin), 1741 (C=O amide isatin), 992-690 (HC=CH Ar bending).

**(3*Z*)-3-[(4-Chlorophenyl)imino]-1,3-dihydro-2*H*-indol-2-one (6)**[23]

Light orange solid, 80% yield
IR ($cm^{-1}$): 1652 (C=N isomethine), 1614-1463 (C=C Aromatic), 3266 (NH isatin), 1742 (C=O amide isatin), 945-748 (HC=CH Ar bending), 1080 (C-Cl).

**(3*Z*)-3-[(3-Chlorophenyl)imino]-1,3-dihydro-2*H*-indol-2-one (7)[24]**
Yellow solid, 60% yield
IR ($cm^{-1}$): 1658 (C=N isomethine), 1587-1462 (C=C Aromatic), 3206 (NH isatin), 1747 (C=O amide isatin), 799-651 (HC=CH Ar bending), 1080 (C-Cl).

**(3*Z*)-3-[(2,4-Dichlorophenyl)imino]-1,3-dihydro-2*H*-indol-2-one (8)**
Brown solid, 69%
IR ($cm^{-1}$): 1667 (C=N isomethine), 1556-1413 (C=C Aromatic), 3188 (NH isatin), 1717 (C=O amide isatin), 1084 (C-Cl).

**(3*Z*)-3-[(2-Hydroxyphenyl)imino]-1,3-dihydro-2*H*-indol-2-one (9)[25]**
Dark brown solid, 60% yield
IR ($cm^{-1}$): 1672 (C=N isomethine), 1507-1452 (C=C Aromatic), 3148 (NH isatin), 3251 (OH phenol), 1724 (C=O amide isatin), 887-665 (HC=CH Ar bending).

**(3*Z*)-3-[(4-Hydroxyphenyl)imino]-1,3-dihydro-2*H*-indol-2-one (10)[26]**
Reddish-brown solid, 76% yield
IR ($cm^{-1}$): 1617 (C=N isomethine), 1470 (C=C Aromatic), 3108 (NH isatin), 3368 (OH phenol), 1688 (C=O amide isatin), 837-749 (HC=CH Ar bending).

**(3*Z*)-3-(4-Pyridinylimino)-1,3-dihydro-2*H*-indol-2-one (11)[27]**
Dark red solid, 57% yield
IR ($cm^{-1}$): 1682 (C=N isomethine), 1402 (C=C Aromatic), 3194 (NH isatin), 3060 (C-H Ar), 1618 (C=N pyridine), 1740 (C=O amide isatin), 884-736 (HC=CH Ar bending).

**(3*Z*)-3-(3-Pyridinylimino)-1,3-dihydro-2*H*-indol-2-one (12)[28]**
Dark brown, 48% yield
IR ($cm^{-1}$): 1681 (C=N isomethine), 14-90-1403 (C=C Aromatic), 3194 (NH isatin), 3060 (C-H Ar), 1490 (C=N pyridine), 1740 (C=O amide isatin), 884-736 (HC=CH Ar bending).

**General procedure for the synthesis of Schiff's bases and Mannich bases of isatin derivatives (13-23):**

***N*'-[(3*Z*)-2-Oxo-1-(1-piperidinylmethyl)-1,2-dihydro-3*H*-indol-3-ylidene]isonicotinohydrazide (13)**
*N*'-[(3*Z*)-2-Oxo-1,2-dihydro-3*H*-indol-3-ylidene]Isonicotinohydrazide **(1)** (10.00 mmol) was dissolved in methanol (25 ml) and then (15.00 mmol) of formaldehyde (37%) was added to the mixture. The reaction mixture was cooled to $0^{o}$C and then piperidine (10.00 mmol) was added with stirring. The stirring was continued for 3h and then it was left at room temperature for 24h. The precipitate was collected and recrystallized from methanol and the required product was obtained as orange solid, 72% yield
IR ($cm^{-1}$): 3034-2863 (C-H aliphatic), 1346 (C-N aliphatic), 1675 (C=N isomethine), 1545-1409 (C=C Aromatic), 3233 (NH isatin), 3034 (CH Ar), 1721 (C=O amide isatin), 1620 (C=N), 877-715 (HC= Ar bending).

The following compounds were prepared similarly:
**(3*Z*)-1-(4-Morpholinylmethyl)-3-(3-pyridinylimino)-1,3-dihydro-2*H*-indol-2-one (14)[29]**
Light orange solid, 79% yield

IR ($cm^{-1}$): 2950-2856 (C-H aliphatic), 1335 (C-N aliphatic), 1611 (C=N isomethine), 1467-1348 (C=C Aromatic), 3039 (CH Ar), 1736 (C=O amide isatin), 1151 (C-O morpholine), 855-710 (HC= Ar bending).

**(3*Z*)-3-[(4-Bromophenyl)imino]-1-[(diphenylamino)methyl]-1,3-dihydro-2*H*-indol-2-one (15)**[29]
Dark yellow solid, 71% yield
IR ($cm^{-1}$): 2877 (C-H aliphatic), 1335 (C-N aliphatic), 1652 (C=N isomethine), 1614-1464 (C=C Aromatic), 1741 (C=O amide isatin), 883-748 (HC= Ar bending), 582 (C-Br).

**(3*Z*)-1-(4-Morpholinylmethyl)-1*H*-indole-2,3-dione 3-[(2,4-dinitrophenyl)hydrazone] (16)**
Dark yellow, 82% yield
IR ($cm^{-1}$): 2855-2949 (C-H aliphatic), 1336 (C-N aliphatic), 1268 (C=N isomethine), 1428 (C=C Aromatic), 3109 (C-H Ar), C=O 1736 (amide isatin), 1460 ($NO_2$ asy), 1151 (C-O morpholine), 848-710 (HC= Ar bending)

**(4-{[(3*Z*)-2-Oxo-1-(1-piperidinylmethyl)-1,2-dihydro-3*H*-indol-3-ylidene]amino}phenyl)acetonitrile (17)**
Orange solid, 86% yield
$^1$H NMR (DMSO-$d_6$): 7.75-6.72 (8H), 5.21(2H), 4.49(2H), 3.41(4H), 1.54(6H).
IR ($cm^{-1}$): 2935-2804 (C-H aliphatic), 1344 (C-N aliphatic), 1659 (C=N isomethine), 1501-1465 (C=C Aromatic), 2246 (CN nitrile), 1731 (C=O amide isatin), 847-696 (HC= Ar bending).

**(3*Z*)-1-(4-Morpholinylmethyl)-3-(phenylimino)-1,3-dihydro-2*H*-indol-2-one (18)**[30,31]
Yellow solid, 83% yield
$^1$H NMR (DMSO-$d_6$): 7.64-6.36(9H), 4.47(2H), 3.36(4), 2.49(4).
IR ($cm^{-1}$): 2959-2892 (C-H aliphatic), 1340 (C-N aliphatic), 1660 (C=N isomethine), 1468 (C=C Aromatic), 3049 (C-H Ar), 1727 (C=O amide isatin), 1152 (C-O morpholine), 862-750 (HC= Ar bending).

**(3*Z*)-3-[(3-Chlorophenyl)imino]-1-(4-morpholinylmethyl)-1,3-dihydro-2*H*-indol-2-one (19)**[31]
Pale yellow solid, 76%
IR ($cm^{-1}$): 2946-2827 (C-H aliphatic), 1360 (C-N aliphatic), 1661 (C=N isomethine), 1465-1427 (C=C Aromatic), 3068 (C-H Ar), 1731 (C=O amide isatin), 1151 (C-O morpholine), 829-714 (HC= Ar bending), 1082 (C-Cl).

***N*'-{(3*Z*)-1-[(Diethylamino)methyl]-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene}isonicotinohydrazide (20)**[32]
Light orange, 72% yield
IR ($cm^{-1}$): 3032 (C-H aliphatic), 1347 (C-N aliphatic), 1695 (C=N isomethine), 1483-1408 (C=C Aromatic), 3234 (N-H isonazide), 2247 (C-H Ar), 1722 (C=O amide isatin), 1593 (C=N pyridine ring), 841-717 (HC= Ar bending).

**(3*Z*)-3-[(4-Chlorophenyl)imino]-1-(4-morpholinylmethyl)-1,3-dihydro-2*H*-indol-2-one (21)**[32]
Pale yellow, 57% yield
IR ($cm^{-1}$): 1778-1753 (C-H aliphatic), 1356 (C-N aliphatic), 1659 (C=N isomethine), 1469-1399 (C=C Aromatic), 3067 (C-H Ar), 1731 (C=O amide isatin), 837 -712 (HC= Ar bending), 1084 (C-Cl).

**(3*Z*)-3-(Phenylimino)-1-(1-piperidinylmethyl)-1,3-dihydro-2*H*-indol-2-one (22)**[32]
Pale yellow, 150-152
Microanalysis: Calculated for: C, 74.78; H, 6.35; N, 13.14 Found: C, 75.21; H, 6.63; N, 13.16%.
$^1$H NMR (DMSO-$d_6$): 7.75-6.72(9H), 4.45(2H), 3.21(4H), 1.54(6H).

$^{13}$C NMR (DMSO-$d_6$): 163.4, 128.5-115.9, 117.5-148.2, 62.3, 51.3, 26.1
IR ($cm^{-1}$): 2850-2800 (C-H aliphatic), 1437 (C-N aliphatic), 1664 (C=N isomethine), 1468(C=C Aromatic), 3021 (C-H Ar), 1726 (C=O amide isatin), 860-753 (HC= Ar bending).

**(4-{[(3*Z*)-1-(4-Morpholinylmethyl)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]amino}phenyl)acetonitrile (23)**
Yellow solid, 80 yield
Microanalysis: Calculated for: C, 69.51; H, 5.53; N, 15.83 Found: C, 69.98; H, 5.59; N, 15.55%.
$^{1}$H NMR (DMSO-$d_6$): 7.88-7.05 (8H), 5.27(2H), 4.52(2H), 4.02(4H), 3.63(4H).
$^{13}$C NMR (DMSO-$d_6$): 125.3-116.9, 164.8, 118.5-150.1, 69.6, 51.6, 66.6
IR ($cm^{-1}$): 2960-2854 (C-H aliphatic), 1336 (C-N aliphatic), 1658 (C=N isomethine), 1465-1428(C=C Aromatic), 2960 (C-H Ar), 1729 (C=O amide isatin), 1163 (CO-morpholine), 869-756 (HC= Ar bending).

**Conclusion**
Versatile methods were used for the synthesis of a variety of Schiff and Mannich bases of isatin derivatives. Spectroscopic data: Infra Red and 1H NMR and 13C NMR were employed for the assessment of the structures of these compounds. Elemental analysis technique was also used to further establish the identity of the required products.

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