



Synthesis and biological activity of functionalized phosphorus derivatives of isatin imines

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ABSTRACT

Isatin-3-imine derivatives (**1a-d**) have been synthesized. These compounds were then converted into phosphorylated products **2a**, **2c** with triethylphosphite and **3a-d** with triphenylphosphine. The structures of the new compounds were confirmed by elemental analyses, IR, UV/VIS, ^1H NMR, ^{13}C NMR and MS studies. The structure of compound **1a** was also confirmed by single crystal X-ray diffraction studies. Compounds **1b-d** and **3c-d** exhibited potent antibacterial activity against *Bacillus subtilis* and *Escherichia Coli*. Compound **3a** was found to exhibit antifungal activity against the tested organisms.

1. Introduction

The chemistry of isatin and its derivatives is particularly interesting because of their potential applications in medicinal chemistry. The synthetic versatility of isatin has led to the extensive use in organic synthesis. 3-Imino-2-amino-isatins were obtained by a one-pot reaction of an excess of aniline (or its derivatives) with 1,2-bis(dimethylamino)-1,2-dichloroethane followed by hydrolysis to yield the corresponding isatin derivatives [1]. The construction of spiroindole via imino Diels-Alder reaction of in-situ generated isatin imine with dihydropyran [2].

Isatins are known to exhibit variety of biological and pharmaceutical properties [3-5]. Schiff and Mannich bases of isatin derivatives are also reported to show a variety of biological activities [6-11]. Some isatin Schiff bases derivatives have been synthesized and realized as anti-HTV activity [12]. Some organometallic Schiff bases containing Ni(II), Co(II) and Cu(II), were found to be killing agents for *Biomphalaria Alexandrina* snails without affecting the surrounding environment [13]. Other synthesized Schiff bases from the reaction of isatin with primary aromatic amines were randomly screened for their in vitro anti-leishmanial potential [14]. 1-(Substituted phenylaminomethyl)-3-(coumarin-3-yl-carbohydrazine) isatins were synthesized and exhibited potential anti-covulsants [15]. The isatin core structure was found to be a novel chemical scaffold in *trans*-thyretin fibrillogenesis inhibitor design [16].

Organophosphorus derivatives containing isatin-3-hydrazones were detected as chemotherapeutants against fungal pathogens of sugarcane [17]. Isatin derivatives bearing 1,2,4-triazole ring were also synthesized [18], where N-bridged heterocyclic derivatives derived from 1,2,4-triazoles showed varied biological activities such as: antimicrobial [19], anticonvulsant [20], anticancer [21], analgesic [22], anti-HIV

[23], and anti-inflammatory [24]. These biological and the other data prompted us to synthesize new isatin derivatives with potential of interesting biological activities.

2. Experimental

2.1. Instrumentation

Melting points were determined with Gallen Kamp melting point apparatus and were uncorrected.

Elemental analyses were performed by the Microanalytical Center, Cairo University, Giza.

FT-IR spectra were recorded on Mattson 1000 spectrophotometer, Microanalytical Center, Cairo University, Giza.

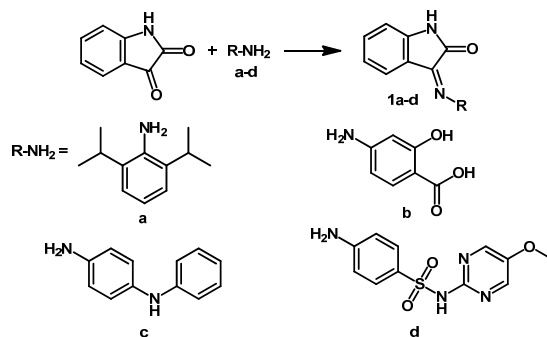
UV/Vis spectra were recorded using Shimadzu UV 1601 Spectrophotometer.

Mass spectra were measured on GCMS-QP 1000 EX Gas Chromatography-Mass spectrometer, Cairo University, Giza and on Gas chromatography-Mass spectrometer in National Research Center, Egypt.

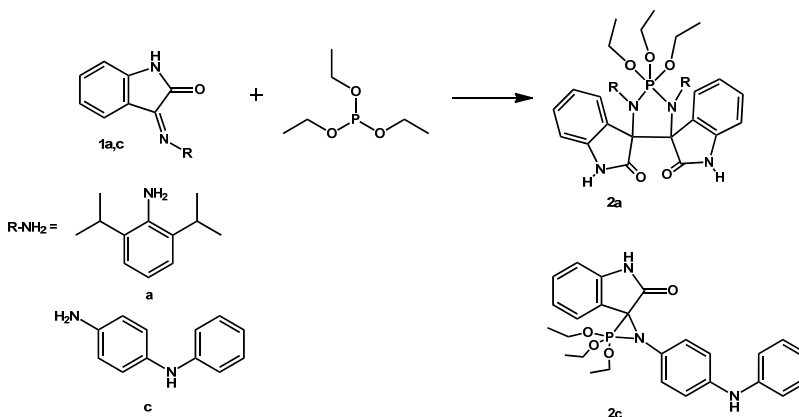
^1H NMR spectra were recorded on Gemini 200, spectrometer in DMSO- d_6 solution with TMS as internal standard in Cairo University, Giza.

X-ray single crystal diffraction studies were performed in National Research Center, Egypt. A suitable crystal (size $0.50 \times 0.50 \times 0.10$ mm) was selected from batch of crystals of compound **1a** obtained by crystallization from alcohol. All diagrams and calculations were performed using maxus (Bruker Nonius, Delft & MacScience, Japan), using graphite monochromated MoK_α radiation ($\lambda=0.71073$ Å).

Biological activity was performed in Micro Analytical Center, Cairo University, Giza, Egypt.



Scheme 1



Scheme 2

2.2. Synthesis

2.2.1. Compounds 1a-d

A mixture of (0.001 mol, 0.146 g) of isatin and amine derivatives namely 2,6-diisopropylaniline, 4-aminosalicylic acid, 4-aminodiphenylamine and 4-amino-*N*-[5-methoxy-2-pyrimidinyl] benzene sulphonamide in ethyl alcohol (20 mL) was refluxed for 3h. The reaction mixture was cooled and the resulting precipitate was filtered, dried and crystallized from the proper solvent (Scheme 1).

(*Z*)-3-((2, 6-diisopropylphenyl)imino)indolin-2-one (**1a**): Orange crystals from ethanol in 86% yield. M.p.: 264-265 °C. IR (KBr, ν_{\max} , cm^{-1}): 3163 (N-H), 2962-2866 (C-H aliph.), 1733 (C=O), 1662 (C=N). UV/Vis (λ_{\max} (nm), ϵ (L/mol.cm)): 459, 11.29×10^3 . ^1H NMR (DMSO- d_6 , δ , ppm): 8.2 (s, 1H, NH), 7.8-6.9 (m, 7H, Arom.), 3.1 (m, 2H, 2(CH)), 1.3 (d, 12H, 4(CH₃)). Anal. calcd. for C₂₀H₂₂N₂O: C, 78.43; H, 7.18; N, 9.15. Found: C, 78.22; H, 7.15; N, 9.00%.

(*Z*)-2-hydroxy-4-((2-oxoindolin-3-ylidene)amino)benzoic acid (**1b**): Brown crystals from ethanol in 85% yield. M.p.: >340 °C. IR (KBr, ν_{\max} , cm^{-1}): 3163 (N-H), 2962-2866 (C-H aliph.), 1733 (C=O), 1683 (C=N). UV/Vis (λ_{\max} (nm), ϵ (L/mol.cm)): 260, 7.2×10^3 ; 298, 9.6×10^3 ; 314, 10.5×10^3 ; 415, 1.8×10^3 . ^1H NMR (DMSO- d_6 , δ , ppm): 11.2 (s, 1H, COOH), 8.3 (s, 1H, NH), 8.0-6.9 (m, 7H, Arom.), 4.9 (s, 1H, OH). Anal. calcd. for C₁₅H₁₀N₂O₄: C, 63.82; H, 3.54; N, 9.92. Found: C, 63.74; H, 3.71; N, 10.24%.

(*Z*)-3-((4-(phenylamino)phenyl)imino)indolin-2-one (**1c**): Black crystals from ethanol in 93% yield. M.p.: 213-214 °C. IR (KBr, ν_{\max} , cm^{-1}): 3163 (N-H), 2962-2866 (C-H aliph.), 1733 (C=O), 1663 (C=N). UV/Vis (λ_{\max} (nm), ϵ (L/mol.cm)): 487, 17.15×10^3 , 325, 20.07×10^3 . ^1H NMR (DMSO- d_6 , δ , ppm): 8.2 (s,

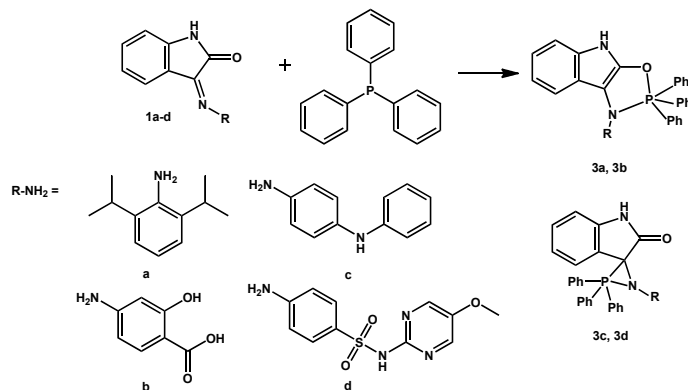
1H, NH-CO), 7.8-6.6 (m, 13H, Arom.), 3.8 (s, 1H, NH). Anal. calcd. for C₂₀H₁₅N₃O: C, 76.67; H, 4.79; N, 13.41. Found: C, 76.62; H, 4.79; N, 13.20%.

(*Z*)-*N*-(5-methoxypyrimidin-2-yl)-4-((2-oxoindolin-3-ylidene)amino)benzenesulfonamide (**1d**): Orange crystals from ethanol in 64% yield. M.p.: 188-189 °C. IR (KBr, ν_{\max} , cm^{-1}): 3163 (N-H), 2962-2866 (C-H aliph.), 1733 (C=O), 1647 (C=N). UV/Vis (λ_{\max} (nm), ϵ (L/mol.cm)): 407, 2.7×10^3 . ^1H NMR (DMSO- d_6 , δ , ppm): 8.2 (s, 1H, NH), 8.0-7.2 (m, 10H, Arom.), 3.9 (s, 1H, SO₂NH), 3.6 (s, 3H, OCH₃). Anal. calcd. For C₁₉H₁₅N₅O₄S: C, 55.74; H, 3.66; N, 17.11. Found: C, 55.69; H, 3.54; N, 17.23%.

2.2.2. Compounds 2a, c

A mixture of (0.001 mol, 0.166 g) triethylphosphite and 3-((2, 6-diisopropylphenyl)imino)indolin-2-one (**1a**) or 3-((4-(phenylamino)phenyl)imino)indolin-2-one (**1c**) in 10 mL THF was stirred for 3 hours at room temperature, then left to stand overnight. The resulting precipitate was filtered and crystallized from petroleum ether (40-60 °C). It gave one spot on (TLC) (Scheme 2).

Compound 2a: Black crystals from THF in 89.47% yield. M.p.: 270-271 °C. IR (KBr, ν_{\max} , cm^{-1}): 1758, 1734 (C=O), 1032 (P-O). ^1H NMR (DMSO, δ , ppm): 8.00 (s, 2H, 2NHCO), 7.6-6.5 (m, 14H, Arom.), 3.6 (q, 6H, 3CH₂), 3.2 (m, 4H, 4CH for isopropyl), 1.3 (d, 24H, 8 CH₃), 1.0 (t, 9H, 3 (OCH₂CH₃)). ^{13}C NMR (DMSO, δ , ppm): 163 (C=O), 155.9-111.5 (aromatic carbons), 40.33-22.81 (aliphatic carbons). Anal. calcd. for C₄₆H₅₉N₄O₅P: C, 70.95; H, 7.58; N, 7.19. Found: C, 70.51; H, 7.56; N, 7.12%.



Scheme 3

Compound 2c: Deep violet crystals from THF in 77% yield, M.p.: 98-99 °C. IR (KBr, ν_{\max} , cm^{-1}): 1727 (C=O (NH-CO)), 1020 (P-O). The ¹H NMR (DMSO, δ , ppm): 8.1 (s, 1H, NHCO), 7.6-6.2 (m, 13H, Arom.), 4.1 (s, 1H, NH), 1.5 (q, 6H, 3CH₂), 1.1 (t, 9H, 3 CH₃). Anal. calcd. for C₂₆H₃₀N₃O₄P: C, 65.13; H, 6.26; N, 8.76. Found: C, 65.02; H, 6.17; N, 8.54%.

2.2.3. Compounds 3a-d

A mixture of (0.001 mol, 0.262 g) triphenylphosphine and imine derivatives namely (2, 6-diisopropylphenylimino)indolin-2-one (**1a**), 2-hydroxy-4-(2-oxoindolin-3-ylideneamino)benzoic acid (**1b**), 3-(4-(phenylamino)phenylimino)indolin-2-one (**1c**) and N-(5-methoxypyrimidin-2-yl)-4-(2oxoindolin-3-ylideneamino)-benzenesulphonamide (**1d**) in 30 mL THF was stirred for 3 h at room temperature, then left to stand overnight. The resulting precipitate was filtered and crystallized from the proper solvent (Scheme 3).

Compound 3a: Yellow crystals from THF in 92% yield, M.p.: 190-191 °C. IR (KBr, ν_{\max} , cm^{-1}): 1758, 1734 (C=O), 1432 (P-Ph) [25]. UV/Vis (λ_{\max} (nm), ϵ (L/mol.cm)): 403, 4.65x10³; 294, 10.5x10³. ¹H NMR (DMSO, δ , ppm): 11.01 (s, H, NH), 7.62-6.70 (m, 22H, Arom.), 2.67 (m, 2H, 2CH), 1.09 (d, 12H, 4CH₃). ¹³C NMR (DMSO, δ , ppm): 163 (C=O), 155.9-111.5 (Arom.), 40.33-22.82 (Aliphatic). MS (m/z , %): 874 (M⁺, 0.01), 568 (0.05), 306 (3.00), 304 (8.93), 277 (30), 262 (57, 44), 247 (9.09), 132 (53.05), 108 (100), 107 (98), 77 (83), 55 (55). Anal. calcd. for C₃₈H₃₇N₂OP: C, 80.28; H, 6.51; N, 4.92. Found: C, 79.88; H, 6.46; N, 4.86%.

Compound 3b: Pale brown crystals from THF in 85% yield, M.p.: 111-112 °C. IR (KBr, ν_{\max} , cm^{-1}): 1435 (P-Ph) [25]. UV/Vis (λ_{\max} (nm), ϵ (L/mol.cm)): 254, 8.4x10³; 298, 10.06x10³; 315, 10.9x10³. ¹H NMR (DMSO, δ , ppm): 11.2 (s, 1H, COOH), 10 (s, 1H, NH), 7.8-6.2 (m, 22 H, Arom.), 4.9 (s, 1H, OH). Anal. calcd. for C₃₃H₂₅N₂O₄P: C, 72.75; H, 4.58; N, 5.14. Found: C, 72.45; H, 4.56; N, 5.34%.

Compound 3c: Black crystals from THF in 81.48% yield, M.p.: 156-157 °C. IR (KBr, ν_{\max} , cm^{-1}): 1725 (C=O (NH-CO)), 1432 (P-Ph). UV/Vis (λ_{\max} (nm), ϵ (L/mol.cm)): 493, 6.36x10³; 309, 12x10³. ¹H NMR (DMSO, δ , ppm): 8.2 (s, 1H, NHCO), 7.7-6.2 (m, 28H, Arom.) and 4.2 (s, 1H, NH). MS (m/z , %): 512 (3), 360 (96), 283 (C₁₅H₁₄N₃OP⁺, 100), 277 (6), 179 (34), 164 (50), 77 (13), 51(4). Anal. calcd. for C₃₈H₃₀N₃OP: C, 79.30; H, 5.21; N, 7.30. Found: C, 79.20; H, 5.40; N, 7.25%.

Compound 3d: Reddish brown crystals from THF in 50% yield, M.p.: 76-77 °C, IR (KBr, ν_{\max} , cm^{-1}): 1725 (C=O (NH-CO)), 1431 (P-Ph). UV/Vis (λ_{\max} (nm), ϵ (L/mol.cm)): 395, 1.35x10³. ¹H NMR (DMSO, δ , ppm): 11.00 (s, 1H, (N=C-OH)), 8.00-6.57 (m, 25H, Arom.), 4.00 (s, 1H, SO₂NH), 3.77 (s, 3H, CH₃). ¹³C NMR (DMSO, δ , ppm): 153 (C=O), 151 (-S-NH-C), 150 (-N-C), 149

(benzene-C-NH), 144 (pyrimidine-C-O); 138-128 (triphenyl phosphine), 125-112 (indolyl), 109 ((indolyl) C-P), 56 ((aliphatic) C-O). MS (m/z , %): 479 (1.22), 279 (9), 278 (32), 277 (100), 262 (14), 201 (11), 147 (2), 118 (4), 77 (6). Anal. calcd. for C₃₇H₃₀N₅O₄SP: C, 66.16; H, 4.47; N, 10.43. Found: C, 66.54; H, 4.45; N, 10.32%.

2.3. In vitro antimicrobial activity (Disc diffusion method)

A filter paper sterilized disc saturated with measured quantity of the sample is placed on plate containing solid bacterial medium (nutrient agar broth) or fungal medium (Doxs medium) which has been heavily seeded with the spore suspension of the tested organism. After inoculation, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism [26-29].

3. Results and discussion

3.1. Synthesis

Isatin reacted with 2,6-diisopropylaniline, 4-aminosalicylic acid, 4-aminodiphenylamine and 4-amino-N-[5-methoxy-2-pyrimidinyl] benzene sulphonamide in ethyl alcohol under reflux to afford 3-imine derivatives; 3-(2,6-diisopropylphenylimino)indolin-2-one (**1a**), 2-hydroxy-4-(2-oxoindolin-3-ylideneamino)benzoic acid (**1b**), 3-(4-(phenylamino)phenylimino)indolin-2-one (**1c**) and N-(5-methoxypyrimidin-2-yl)-4-(2oxoindolin-3-ylideneamino)-benzenesulphonamide (**1d**). The structures of these compounds were confirmed by elemental analyses, IR, UV/Vis spectra. All characterization data is given in experimental section.

In addition, the structure of the compound **1a** is confirmed by X-ray single crystal diffraction studies. The perspective view of the molecular structure of compound **1a** is shown in Figure 1. X-ray single crystal diffraction data for compound **1a**: C₂₀H₂₂N₂O; tetragonal; 14₁/a; unit cell dimensions $a = 28.8600(9)$ Å, $b = 28.8600(9)$ Å, $c = 8.7587(5)$ Å; $V = 7295.1(5)$ Å³; $Z = 16$; $D_x = 1.116$ Mg m⁻³; 1721 independent reflections; $\theta_{\max} = 19.57^\circ$; 1158 observed reflections. Refinement method was full matrix least squares refinement, $R(\text{all}) = 0.087$, $R(\text{gr}) = 0.063$, $wR(\text{ref}) = 0.128$; $wR(\text{all}) = 0.130$. $wR(\text{gt}) = 0.128$, $\delta(\text{ref}) = 4.068$, $S(\text{all}) = 3.632$, $S(\text{gt}) = 4.067$. Selected geometrical parameters are given in Table 1.

3-(2,6-diisopropylphenylimino)indolin-2-one (**1a**) reacted with triethyl phosphite and triphenylphosphine in tetrahydrofuran to afford two new compounds **2a** and **3a** containing five-membered hetero ring similar to dimeric spiro phospholanes [30-33]. The two suggested structures were inferred from their elemental analyses, IR, UV/Vis, ¹H-NMR,

^{13}C -NMR and MS spectra. The IR spectra for compound (**2a**, **3a**) showed two $\nu_{\text{C=O}}$ at 1758 and 1734 cm^{-1} and $\nu_{\text{P-O-alkyl}}$ at 1032 cm^{-1} for **2a**, while for compound **3a**, it showed $\nu_{\text{P-PH}}$ at 1432 cm^{-1} [25]. Comparing the ^1H -NMR spectra of compounds **2a** and **3a**, the spectrum of **3a** showed fifteen aromatic protons extra than the aromatic protons in **2a** due to triphenylphosphinyl protons, also the spectrum of **2a** showed signals at δ 4 ppm and 1.2 ppm due to aliphatic protons. The ^{13}C NMR spectrum of compound **3a** showed extra carbons between δ 128 and 136 ppm due to phenyl carbons of triphenylphosphinyl.

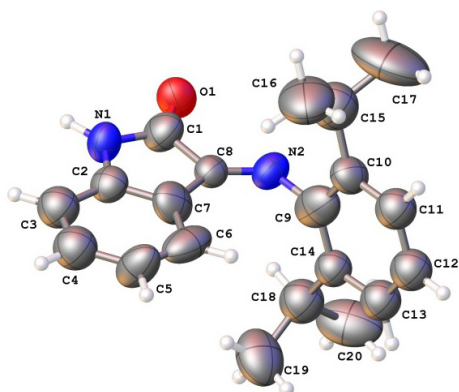


Figure 1. The perspective view of the molecular structure of compound 1a.

Table 1. Selected geometrical parameters (\AA , $^{\circ}$)

Bond distance, \AA	
O1-C1	1.222(2)
N1-C1	1.351(3)
N1-C2	1.411(3)
C2-C7	1.376(3)
C7-C8	1.461(3)
N2-C8	1.269(2)
N2-C9	1.434(3)
Bond angles, $^{\circ}$	
C1-N1-C2	110.1(2)
C8-N2-C9	121.1(2)

Triphenylphosphine reacted with 2-hydroxy-4-(2-oxoindolin-3-ylideneamino) benzoic acid (**1b**) in tetrahydrofuran to form five membered hetero ring of compound **3b**. The IR spectrum showed the absence of one $\nu_{\text{C=O}}$ (NH-CO) and $\nu_{\text{C=N}}$ and the presence of a new absorption band at 1435 cm^{-1} due to $\nu_{\text{P-PH}}$ [25].

The reaction of 3-(4-(phenylamino)phenylimino)indolin-2-one (**1c**) with triethylphosphite and triphenylphosphine yielded compounds **2c** and **3c**, respectively, with three-membered hetero rings.

The reaction of *N*-(5-methoxy-2-yl)-4-(2-oxoindolin-3-ylideneamino)-benzenesulphonamide (**1d**) with triphenylphosphine yielded compound **3d** with three membered hetero ring. IR spectrum showed a new absorption band at 1431 cm^{-1} due to $\nu_{\text{P-PH}}$. The presence of $\nu_{\text{C=O}}$ (NH-CO) at 1727 cm^{-1} confirmed the three membered heterophosphorus form. The UV/Vis spectrum indicated λ_{max} at 395 nm due to $\text{n-}\pi^*$ transition.

3.2. In vitro antimicrobial activity

The synthesized compounds were screened for their antimicrobial activity against *Bacillus subtilis* (G^+) and *Escherichia Coli* (G^-). Control experiment was carried out under similar condition by using tetracycline as standard. The inhibition zone measure in mm showed that compounds **1a**, **2a** and **3a** were inactive towards bacteria. The antifungal activity was tested against the fungal species *Aspergillus flavus* and *Candida albicans* at 100 μg concentration. Amphotericin B was used as

standard under the same condition. The antifungal data revealed that the compounds **1a-d**, **2a**, **3c** and **3d** showed no effect towards fungus, while the compounds **3a** were effective towards the above fungus (Table 2).

Table 2. Antibacterial and antifungal activities of compounds.

Compound No	Inhibition zone diameter (mm/mg sample)			
	<i>Bacillus Subtilis</i>	<i>Escherichia Coli</i>	<i>Aspergillus flavus</i>	<i>Candida albicans</i>
1a	0	0	0	0
1b	14	14	0	0
1c	13	14	0	0
1d	15	13	0	0
2a	0	0	0	0
3a	0	0	13	13
3c	14	14	0	0
3d	16	15	0	0
Tetracycline	32	35	0	0
Amphotericin B	0	0	17	21

Supplementary material

CCDC-766320 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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