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Research Article

SYNTHESIS OF SCHIFF BASES OF SOME NOVEL N-NITROSOISATIN DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS

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ABSTRACT

In the present study, a novel series of Schiff bases of N-nitrosoisatin were synthesised and characterised by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral and elemental analysis. The compounds were screened for antibacterial *(Escherichia coli* (ATCC 25922), *Salmonella typhi* (ATCC 9076), *Bacillus subtillis* (ATCC11778), and *Stapthylococcus aureus* (ATCC 9144)) and antifungal (*Aspergillus niger* (ATCC 9029)) activities. The minimum inhibitory concentrations of the compounds were also ascertained by agar streak dilution method, N-nitroso-5-bromo-3-(4-bromophenylimino)-indolin-2-one (3j) was found to be the most potent antimicrobial activity with MIC of 18, 19, 17, 20 and 24µg/ml against *E.coli, S.typhi, B.subtillis, S.aureus and A. niger,* respectively. All the other compounds exhibited moderate to good activity against the bacterial and fungal organisms tested.

Keywords: Isatin, Schiff base, Antimicrobial

INTRODUCTION

Isatin, chemically known as 1H-indole-2, 3-dione, has become a popular topic due to its various uses. The chemistry of isatin and its derivatives is particularly interesting because of their potential application in medicinal chemistry [1]. Several of its derivatives were reported to exhibit a wide range of promising pharmacodynamic profile like anticonvulsant [2-3], anti-HIV [4], cytotoxic [5],tuberculostatic [6], antimicrobial [7], Schiff bases derived from various heterocycles have been reported to possess cytotoxic [8], anticonvulsant [9], anti-proliferative [10], antimicrobial [11], anticancer [12], and antifungal activities [13]. In the view of these facts prompted us to synthesize some novel N-nitrosoisatin derivatives. All the synthesized compounds were characterised by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral and elemental analysis and were screened for their in vitro anti-bacterial and anti-fungal activities. The minimum inhibitory concentrations of the compounds were also ascertained by agar streak dilution method.

MATERIALS AND METHODS

Materials

All the chemicals used in the study are either analytical or pharmaceutical grade.

Methods

Chemistry

Melting points were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on the ABB Bomem FT-IR spectrometer MB 104.^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker spectrometer. Mass spectra were recorded on JEOL GC mate. Elemental analysis was performed on Perkin-Elemer 2400 C, H, N analyzer and values were within the acceptable limits (±0.4%) of calculated values. The purity of the synthesized compounds was checked by TLC using E-Merk TLC aluminium sheets sikica gel 60 F254 (0.2 mm) using chloroform / methanol (9:1) as eluent and visualised in an iodine chmber. All the chemicals used were of analytical grade.

Synthesis of N-nitrosoisatin.1

To a solution of 0.1 mol of isatin[14] or 5-bromoisatin in chloroform (200 ml) were added concentrated hydrochloric acid (30 ml) and water (30 ml), and while stirring, solid $NaNO_2$ (1.65 g, 0.024mol) was added in portions during 30 min. The stirring was continued for 4 h. The organic layer was washed with water and saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of the chloroform, the residue was re-crystallized from ethanol.

General procedure for synthesis of the final compounds 3a-p

Equimolar quantity (0.01mol) of N-Nitrosoisatin and the aromatic primary amine **2** were dissolved in 10 ml of warm ethanol and refluxed for 3h and then checked for completion of reaction by TLC. After standing for approximately 24h at room temperature, the products were separated by filtration, vacuum dried and re-crystallized from warm ethanol.

N-nitroso-3-(4-chlorophenylimino)-indolin-2-one 3a

Yield 96.4%; M.P. 254-256^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3178(Ar-CH), 1592(C=C), 1331(C-N), 1461(N-NO), 1738 (C=O), 1611 (C=N), 751(C-Cl); ^{1}H-NMR δ(ppm): 6.58 -7.74 (m, 8H,Ar-H); ^{13}C-NMR δ(ppm):119.2, 122.7, 123.4, 123.7, 124.5,129.6, 130.2, 131.0, 132.3, 133.8, 138.7, 151.3, 161.5, 163.3; MASS *m/z*: 285(M$^+$) (5%),286 (M+1) (5%); Anal. Calcd. For $C_{14}H_8ClN_3O_2$: C, 58.86; H, 2.82; Cl, 12.41;N, 14.71; O, 11.20. Found: C, 58.82; H, 2.77; Cl, 12.38; N, 14.68; O, 11.17.

N-nitroso-3-(4-bromophenylimino)-indolin-2-one 3b

Yield 92.6%; M.P. 220-222^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3268(Ar-CH), 1592(C=C),

1334(C-N), 1460(N-NO), 1739 (C=O), 1610 (C=N), 582(C-Br); ^{1}H-NMR δ(ppm): 6.42 -7.71 (m, 8H, Ar-H); ^{13}C-NMR δ(ppm):119.8, 121.4, 121.6, 123.7, 124.1, 124.5,129.6, 131.2, 133.0, 133.3, 138.8, 152.8, 161.7, 163.9; MASS *m/z*: 330 (M$^+$) (1.1%),332 (M+1) (5%); Anal. Calcd. For $C_{14}H_8BrN_3O_2$: C, 50.93; H, 2.44; Br, 24.20; N, 12.73; O, 9.69. Found: C, 50.90; H, 2.41; Br, 24.18; N, 12.72; O, 9.68.

N-nitroso-3-(4-fluorophenylimino)-indolin-2-one 3c

Yield 89.2%; M.P. 156-158^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 2987(Ar-CH), 1497(C=C), 1385(C-N), 1463(N-NO), 1728 (C=O), 1615 (C=N), 1288(C-F); ^{1}H-NMR δ(ppm): 6.41 -7.61 (m, 8H, Ar-H); ^{13}C-NMR δ(ppm):116.4, 116.5, 118.7, 121.6, 123.7, 123.9, 124.5,129.6, 131.2, 138.8, 149.0, 161.3, 161.9, 163.9; MASS *m/z*: 270 (M$^+$) (3%); Anal. Calcd. For $C_{14}H_8FN_3O_2$: C, 62.46; H, 3.00; F, 7.06; N, 15.61; O, 11.89. Found: C, 62.42; H, 2.98; F, 7.02; N, 15.58; O, 11.88.

N-nitroso-3-(3-chloro-4-fluorophenylimino)-indolin-2-one 3d

Yield 66.6%; M.P. 210-212^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3196(Ar-CH), 1590(C=C), 1334(C-N), 1463(N-NO), 1726 (C=O), 1611 (C=N), 758(C-Cl), 1204(C-F) ; ^{1}H-NMR δ(ppm): 6.76 -8.21 (m, 7H, Ar-H); ^{13}C-NMR δ(ppm):117.8, 118.4, 121.4, 122.2, 122.3, 124.1, 124.5,129.6, 131.2, 138.5 150.8, 161.2, 161.7, 163.4; MASS *m/z*: 303 (M$^+$) (10%),304 (M+1) (7%); Anal. Calcd. For $C_{14}H_7ClFN_3O_2$: C, 55.37; H, 2.32; Cl, 11.67; F, 6.26; N, 13.84; O, 10.54. Found: C, 55.34; H, 2.30; Br, 11.66; N, 13.84; O, 10.53.

N-nitroso-3-(4-methylphenylimino)-indolin-2-one 3e

yield 37.7%; M.P. 216-218^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3257(Ar-CH), 1592(C=C), 1333(C-N), 1463(N-NO), 1742(C=O), 1611(C=N), 2910(C-CH_3); ^{1}H-NMR δ(ppm): 6.58 -8.04 (m, 8H, Ar-H), 2.2(s.3H, CH_3); ^{13}C-NMR δ(ppm):24.3, 117.6, 121.9, 122.2, 122.3, 124.1, 129.6, 130.2, 130.4, 131.3, 136.8, 138.6, 150.4, 161.0, 163.4; MASS *m/z*: 265(M^+) (15%); Anal. Calcd. For $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84; O, 12.06. Found: C, 67.90; H, 4.17; N, 15.82; O, 12.04.

N-nitroso-3-(4-methoxyphenylimino)-indolin-2-one 3f

Yield 61.3%; M.P. 225-227^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3118(Ar-CH), 1499(C=C), 1332(C-N), 1460(N-NO), 1738 (C=O), 1611 (C=N), 2833(CO-CH_3); ^{1}H-NMR δ(ppm): 6.78 - 8.21 (m, 8H, Ar-H), 3.3 (s, 3H, OCH_3); ^{13}C-NMR δ(ppm): 55.8, 115.4, 115.6, 117.6, 121.7, 123.1, 123.3,124.6, 129.4, 131.2, 138.8, 145.6, 159.3, 161.8, 163.6; MASS *m/z*: 281(M^+) (3%); Anal. Calcd. For $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94; O, 17.07. Found: C, 64.03; H, 3.93; N, 14.92; O, 17.05.

N-nitroso-3-(4-nitrophenylimino)-indolin-2-one 3g

Yield 95.4%; M.P. 88-90^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3370(Ar-CH), 1584(C=C), 1301(C-N), 1471(N-NO), 1734 (C=O), 1621 (C=N), 1367(C-NO_2); ^{1}H-NMR δ(ppm): 6.92 -8.21 (m, 8H, Ar-H);^{13}C-NMR δ(ppm): 117.8, 121.4, 122.6, 122.7, 123.1, 123.3, 124.5, 129.6, 131.2, 138.8, 146.8, 158.8, 161.7, 163.9; MASS *m/z*: 296 (M^+) (7%); Anal. Calcd. For $C_{14}H_8N_4O_4$: C, 56.76; H, 2.72; N, 18.91; O, 21.60. Found: C, 56.74; H, 2.71; N, 18.90; O, 21.58.

N-nitroso-3-(2, 4-dinitrophenylimino)-indolin-2-one 3h

Yield 76.4%; M.P. 120-122^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3335(Ar-CH), 1584(C=C), 1301(C-N), 1464(N-NO), 1732 (C=O), 1624 (C=N), 1388(C-NO_2); ^{1}H-NMR δ(ppm): 7.03 – 8.28 (m, 7H, Ar-H); ^{13}C-NMR δ(ppm):117.8, 120.4, 121.6, 124.1, 124.5, 128.3, 129.6, 131.2, 138.0, 142.3, 147.8, 154.2, 161.0, 163.3; MASS *m/z*: 341 (M^+) (2%); Anal. Calcd. For $C_{14}H_8N_5O_6$: C, 49.28; H, 2.07; N, 20.52; O, 28.13. Found: C, 49.26; H, 2.07; N, 20.50; O, 28.11.

N-nitroso-5-bromo-3-(4-chlorophenylimino)-indolin-2-one 3i

Yield 42.6%; M.P. 278-280^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3057(Ar-CH), 1583(C=C), 1308 (C-N), 1489(N-NO), 1749 (C=O), 1604 (C=N), 642(C-Cl), 604(C-Br); ^{1}H-NMR δ(ppm): 6.53- 7.68 (m,7H, Ar-H); ^{13}C-NMR δ(ppm):118.6, 120.4, 123.6, 123.7, 123.9, 130.2, 130.4, 132.2, 132.4, 134.3, 137.8, 151.2, 161.1, 163.0; MASS *m/z*: 364(M^+) (22%),366 (M+2) (5%); Anal. Calcd. For $C_{14}H_7BrClN_3O_2$: C, 46.12; H, 1.94; N, 11.53; O, 8.78. Found: C, 46.11; H, 1.90; N, 11.50; O, 8.77.

N-nitroso-5-bromo-3-(4-bromophenylimino)-indolin-2-one 3j

Yield 38%; M.P. 278-280^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3252 (Ar-CH), 1568 (C=C), 1298 (C-N), 1457 (N-NO), 1742 (C=O), 1609 (C=N), 568 (C-Br); ^{1}H-NMR δ(ppm): 6.56 - 7.62 (m,7H, Ar-H); ^{13}C-NMR δ(ppm):118.6, 120.4, 121.6, 123.9, 124.5, 124.6, 132.6, 133.2, 133.4, 134.3, 137.6, 152.2, 161.0, 163.6; MASS *m/z*: 409 (M^+) (18%),411 (M+2) (12%); Anal. Calcd. For $C_{14}H_7Br_2N_3O_2$: C, 41.11; H, 1.72; Br, 39.07, N, 10.27; O, 7.82. Found: C, 41.10; H, 1.71; Br, 39.04; N, 10.25; O, 7.81.

N-nitroso-5-bromo-3-(4-fluorophenylimino)-indolin-2-one 3k

Yield 40%; M.P. 202 -204^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3236(Ar-CH), 1499(C=C), 1293 (C-N), 1459(N-NO), 1739 (C=O), 1610 (C=N), 1198(C-F), 599(C-Br); ^{1}H-NMR δ(ppm): 6.43- 7.76 (m,7H, Ar-H); ^{13}C-NMR δ(ppm): 116.6, 116.8, 118.4, 120.6, 123.1, 123.5, 123.8, 132.6, 134.4, 137.2, 148.6, 161.0, 161.4, 163.2; MASS *m/z*: 348(M^+) (14%),350 (M+2) (10%); Anal. Calcd. For $C_{14}H_7BrFN_3O_2$: C, 48.30; H, 2.03; Br, 22.95, N, 12.07; O, 9.19. Found: C, 48.28; H, 2.01; Br, 22.93, N, 12.05; O, 9.17.

N-nitroso-5-bromo-3-(3-chloro-4-fluorophenylimino)-indolin-2-one 3l

Yield 42%; M.P.192-194^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3178(Ar-CH), 1491(C=C), 1399 (C-N), 1446(N-NO), 1712 (C=O), 1613 (C=N), 751(C-Cl),1264(C-F), 596(C-Br); ^{1}H-NMR δ(ppm): 6.83- 7.76 (m, 6H, Ar-H); ^{13}C-NMR δ(ppm):117.8, 118.2, 120.6, 122.1, 122.5, 123.3, 124.6, 132.2, 134.5, 137.8, 150.3, 161.0, 161.2, 163.3; MASS *m/z*: 382(M^+) (15%),384 (M+2) (18%); Anal. Calcd. For $C_{14}H_6BrClFN_3O_2$: C, 43.95; H, 1.58; Br, 20.89; Cl, 9.27; F, 4.97; N, 10.98; O, 8.36. Found: C, 43.93; H, 1.56; Br, 20.86; Cl, 9.24; F, 4.93; N, 10.96; O, 8.33.

N-nitroso-5-bromo-3-(4-methylphenylimino)-indolin-2-one 3m

Yield 55.2%; M.P. 252-254^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3256(Ar-CH), 1586(C=C), 1292 (C-N), 1459(N-NO), 1740 (C=O), 1611 (C=N),2831(C-CH_3), 521(C-Br); ^{1}H-NMR δ(ppm): 6.78- 7.82 (m, 7H, Ar-H), 2.3 (s, 3H, CH_3); ^{13}C-NMR δ(ppm): 24.1, 118.8, 120.4, 122.2, 122.6, 123.5, 130.3, 130.6, 132.2, 134.0, 136.3, 137.8, 150.2, 161.0, 163.5; MASS *m/z*: 344(M^+) (5%),346 (M+2) (10%) Anal. Calcd. For $C_{15}H_{10}BrN_3O_2$: C, 52.35; H, 2.93; Br, 23.22; N, 12.21; O, 9.30. Found: C, 52.33; H, 2.91; Br, 23.20; N, 12.20; O, 9.29.

N-nitroso-5-bromo-3-(4-methoxyphenylimino)-indolin-2-one 3n

Yield 69.4%; M.P. 282-284^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3107(Ar-CH), 1503(C=C), 1291 (C-N), 1460(N-NO), 1748 (C=O), 1609 (C=N), 2834(CO-CH_3), 529(C-Br); ^{1}H-NMR δ(ppm): 6.67- 7.96 (m, 7H, Ar-H), 3.5 (s, 3H, OCH_3); ^{13}C-NMR δ(ppm): 55.6, 115.6, 115.8, 118.4, 120.6, 123.1, 123.5, 123.9, 132.2, 134.5, 137.3, 145.8, 159.2, 161.0, 163.3; MASS *m/z*: 360(M^+) (24%),362 (M+2) (20%); Anal. Calcd. For $C_{15}H_{10}BrN_3O_3$: C, 50.02; H, 2.80; N, 11.67; Br, 22.19, O, 13.33. Found: C, 50.00; H, 2.78; N, 11.66; Br, 22.17, O, 13.31.

N-nitroso-5-bromo-3-(4-nitrophenylimino)-indolin-2-one 3o

Yield 50.6%; M.P. 206-208^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3364(Ar-CH), 1586(C=C), 1291 (C-N), 1458(N-NO), 1748 (C=O), 1607 (C=N), 1339(C-NO_2), 566(C-Br); ^{1}H-NMR δ(ppm): 6.76- 8.21 (m, 7H, Ar-H); ^{13}C-NMR δ(ppm):118.6, 120.4, 122.4, 122.6, 123.5, 123.7, 123.9, 132.3, 134.2, 137.8, 146.3, 161.0, 163.3; MASS *m/z*: 375(M^+) (2%),377 (M+2) (4%); Anal. Calcd. For $C_{14}H_7BrN_4O_4$: C, 44.82; H, 1.88; N, 14.94; O, 17.96. Found: C, 44.80; H, 1.85; N, 14.93; O, 17.94.

N-nitroso-5-bromo-3-(2,4-dinitrophenylimino)-indolin-2-one 3p

Yield 41.6%; M.P.156-158^{0}C; DMF/DMSO; IR (KBR,cm^{-1}): 3336(Ar-CH 507(C=C), 1290 (C-N), 1471(N-NO), 1748 (C=O), 1610 (C=N),1338 (C-NO_2), 565(C-Br); ^{1}H-NMR δ(ppm): 6.74 – 8.81 (m, 7H, Ar-H); ^{13}C-NMR δ(ppm): 118.6, 120.4, 120.6, 123.9, 124.1, 128.5, 132.8, 134.6, 137.2, 142.8, 147.8, 154.2, 161.0, 163.3; MASS *m/z*: 420 (M^+) (2%), 422 (M+2) (5%); Anal. Calcd. For $C_{14}H_6BrN_5O_6$: C, 40.02; H, 1.44; Br, 19.02; N, 16.67; O, 22.85. Found: C, 40.00; H, 1.41; Br, 19.00; N, 16.66; O, 22.83.

Pharmacology

The antibacterial activity of the synthesised compounds was tested against *E.coli, S.typhi, B.subtillis, and S.aureus* using nutrient agar medium). The antifungal activities of the compounds were tested against *A. niger* using Rose Bengal agar medium (Hi-Media Laboratories, India).

Cup plate method[15]

The nutrient agar and Rose Bengal Agar medium was prepared and sterilized by autoclaving at 121°C 15 lbs pressure for 15 minutes then aseptically poured the medium into the sterile petri plates and allowed to solidify the bacterial broth culture and fungal culture was swabbed on each petri plates using sterile buds. Then wells were made by well cutter. The organic solvent extracts of samples were added to each well aseptically. This procedure was repeated for each petri plates then the nutrient agar petri plates were incubated at 37°C for 24 hrs and Rose Bengal Agar Petri plates were incubated at 25°C for 3 -5days. After incubation, the plates were observed for the zone of inhibition (Table-2). Ciprofloxacin and ketoconazole were used as standard for antibacterial and antifungal activity respectively.

Minimum inhibitory concentration[16]

Minimum inhibitory concentration of the synthesized compound was determined by agar streak dilution method. A stock solution of the synthesized compound (100 µg mL^{-1}) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for anti-bacterial activity and sabouraud dextrose agar medium

for anti-fungal activity). A specified quantity of the medium (40-50°C) containing the compound was poured into a petridish to give a depth of 3-4 mm and allowed to solidify. Suspension of the microorganism were prepared to contain approximately 10^5 cfu mL^{-1} and applied to plates with serially diluted compounds in dimethylformamide to be tested and incubated at 37°C for 24 h and 48 h for bacteria and fungi, respectively. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate. The observed MIC is given in (Table-2).

Table 1: Physical constants of the synthesized compounds

Code	R	R_1	R_2	R_3	Yield in%
3a	H	H	H	Cl	96.4
3b	H	H	H	Br	92.6
3c	H	H	H	F	89.2
3d	H	H	Cl	F	66.6
3e	H	H	H	CH_3	37.7
3f	H	H	H	OCH_3	61.3
3g	H	H	H	NO_2	95.4
3h	H	NO_2	H	NO_2	76.4
3i	Br	H	H	Cl	42.6
3j	Br	H	H	Br	38.0
3k	Br	H	H	F	40.0
3l	Br	H	Cl	F	42.0
3m	Br	H	H	CH_3	55.2
3n	Br	H	H	OCH_3	69.4
3o	Br	H	H	NO_2	50.6
3p	Br	NO_2	H	NO_2	41.6

Table 2: Antimicrobial activity of the synthesized compounds (3a-p)

Compound	In vitro activity- Zone of inhibition in mm (MIC in µg/ml)				
	E.coli	*S.typhi*	*B.subtillis*	*S.aureus*	*A.niger*
3a	18(23)	18(22)	*16(21)*	18(22)	35(21)
3b	23(21)	19(19)	*18(22)*	19(23)	25(20)
3c	30(24)	24(22)	*22(18)*	27(19)	27(23)
3d	14(42)	12(79)	*14(45)*	13(23)	14(46)
3e	34(20)	2218)	*26(19)*	24(20)	14(33)
3f	17(39)	14(42)	*18(37)*	14(66)	20(38)
3g	28(22)	19(23)	*26(21)*	19(21)	38(16)
3h	28(16)	23(19)	*23(18)*	25(19)	30(19)
3i	18(40)	18(38)	*23(24)*	21(24)	NA(>100)
3j	20(18)	23(21)	*20(17)*	21(19)	16(20)
3k	18(22)	21(23)	*23(23)*	21(19)	16(23)
3l	18(20)	22(21)	*23(19)*	21(20)	17(21)
3m	19(21)	22(24)	*23(21)*	21(21)	16(22)
3n	18(24)	22(42)	*24(66)*	21(71)	NA(>100)
3o	19(17)	22(20)	*24(20)*	21(20)	22(21)
3p	18(23)	21(21)	*24(22)*	21(21)	15(24)
Ciprofloxacin (100µg/disc)	20(0.1)	22(3)	*24(1.2)*	23(1.6)	-
Ketoconazole (100µg/disc)	-	-	-	-	16(6.1)

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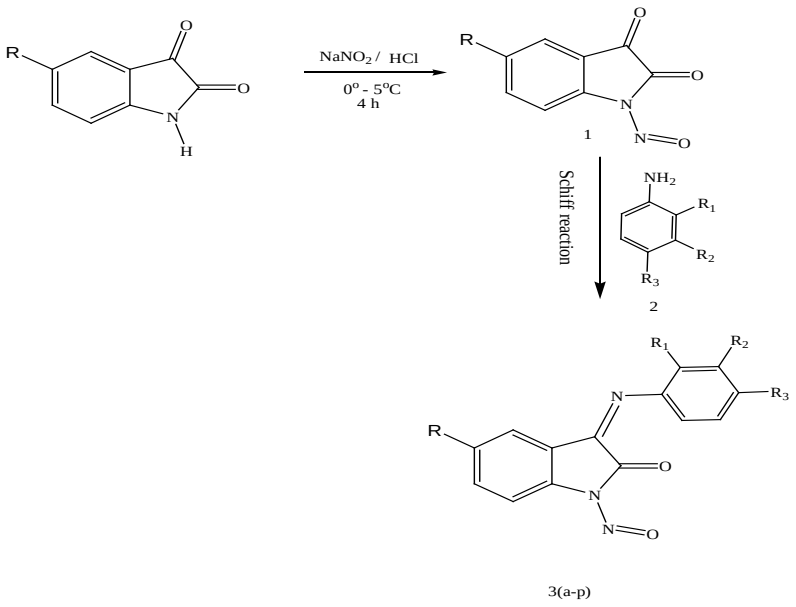

Fig. 1: Synthesis of title compound

CONCLUSION

The results revealed that most of the synthesised compounds exhibited significant antibacterial and antifungal activities.

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