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Solvent-free, environmentally benign synthesis of some imines and antioxidant activity

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ABSTRACT

Environmentally benign, economically cheap and solvent-free synthesis of series of imines by the condensation of substituted hydroxy naphthyl ketone with iodo anilines under grinding approach is described. Imines were further tested for antioxidant activity; most of them show moderate activity.

Keywords: Solvent-free synthesis, imines, substituted ketone, substituted anilines, grinding technique.

INTRODUCTION

In recent year, use of hazardous and toxic solvents in chemical laboratories, chemical industry has been considered a very serious problem for the health, safety of workers and environmental pollution. For these purposes emerging area of green chemistry play an important role into development of synthetic strategic [1, 2]. Grinding technique reaction under solvent-free conditions is one of green synthetic route has gain popularity towards designing structure of new molecules [3-6]. Grinding technique has been increasingly used in organic synthesis compared to traditional methods [7-9], because these reactions not only of interest from economical point of view, but also in many cases they offer considerable advantages in terms of yield, selectivity, and simplicity of reaction procedure with high atom efficiency. Many of well known reactions have reported under solvent free environments using grinding technique [10-17].

Schiff bases (imines) are well known for their wide applications and are useful intermediates in organic synthesis [18]. These compounds have intrinsic biological activities including anticancer [19], antitumor [20], antitubercular [21], antibacterial [22], antioxidant [23] and anticonvulsant [24] activities. Moreover Schiff bases also exhibits Fluorescent [25], photoluminescence [26], aggregation [27] properties. In view of these observations, we plan to synthesize some novel imines by condensation reaction of substituted hydroxyketone with substituted anilines in presence of glacial acetic acid under grinding technique (Scheme **1**).

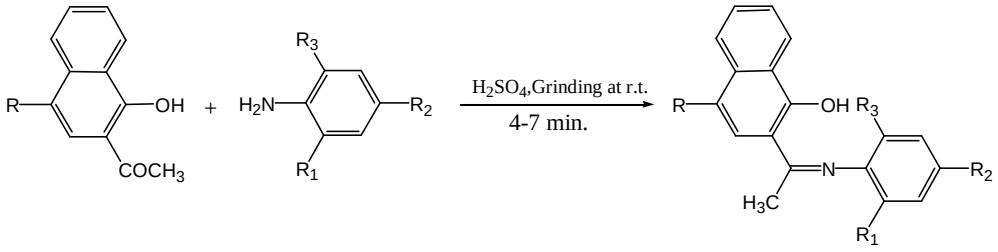
EXPERIMENTAL SECTION

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. ^{1}H NMR spectra were recorded on a Gemini 300-MHZ instrument in DMSO as solvent and TMS as an internal standard. The mass spectra were recorded on EISHIMADZU-GC-MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. The reactions were carried out

in open glass mortar and pestle. Purification of the compound indicated using TLC (ethyl acetate / hexane as mobile phase).

General procedure for synthesis of imines

A mixture of hydroxy ketone **1** (0.01 mol) and substituted anilines **2** (0.01 mol) were grind with a pestle in an open mortar at room temperature for 2-3 minutes. To this reaction mixture sulphuric acid (0.002 mmol) were added and grinding continued for 4-5 minutes. On completion of reaction as monitored by TLC, the light greenish-colored solid was separated out. The obtained solid was diluted with cold water and isolated by simple Buchner filtration and recrystallized from ethanol to give pure product of imines **3a-x**.



1 **2** **3a-x**

Scheme 1: Synthesis of imines under solvent-freee conditions using grinding technique 3a-x

2-[1-(4-Chloro-2-iodo-phenylimino)-ethyl]-4-iodo-naphthalen-1-ol (**3a**): Light Yellow Crystal, Yield 75%, m.p. 145-147 ^{o}C; FT-IR (KBr, ν, cm^{-1}): 1435, 1528 (C=C), 1582 (C=N), 3240 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.32 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.27-6.95 (m, 8H, ArH). (EI, *m/z* (%): 547 (M^+, 42 %). Anal. calcd. For $C_{18}H_{12}I_2ClNO$: C, 39.48; X (I, Cl) 52.83; H, 2.19; N, 2.55%. Found: C, 39.57; X (I, Cl) 52.98; H, 2.28; N, 2.62%.

4-Bromo-2-[1-(4-chloro-2-iodo-phenylimino)-ethyl]-naphthalen-1-ol (**3b**): Light Yellow Crystal, Yield 78%, m.p. 142-144 ^{o}C; FT-IR (KBr, ν, cm^{-1}): 1432, 1525 (C=C), 1580 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.23-6.89 (m, 8H, ArH). (EI, *m/z* (%): 500 (M^+, 35 %). Anal. calcd. For $C_{18}H_{12}IBrClNO$: C, 43.20; X (I, Br, Cl) 48.40; H, 2.40; N, 2.80%. Found: C, 43.28; X (I, Br, Cl) 48.59; H, 2.52; N, 2.93%.

4-Chloro-2-[1-(4-chloro-2-iodo-phenylimino)-ethyl]-naphthalen-1-ol (**3c**): Light Yellow Crystal, Yield 74%, m.p. 155-157 ^{o}C; FT-IR (KBr, ν, cm^{-1}): 1434, 1528 (C=C), 1582 (C=N), 3234 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.34 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.25-6.89 (m, 8H, ArH). (EI, *m/z* (%): 456 (M^+, 42 %). Anal. calcd. For $C_{18}H_{12}Cl_2INO$: C, 47.36; X (I, Cl) 43.20; H, 2.63; N, 3.07%. Found: C, 47.46; X (I, Cl) 43.34; H, 2.75; N, 3.18%.

4-Iodo-2-[1-(4-iodo-2-nitro-phenylimino)-ethyl]-naphthalen-1-ol (**3d**): Light Yellow Crystal, Yield 81%, m.p. 138-140 ^{o}C; FT-IR (KBr, ν, cm^{-1}): 1436, 1530 (C=C), 1583 (C=N), 3232 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.33 (s, 3H, CH_3), 5.24 (s, 1H, OH), 6.29-6.94 (m, 8H, ArH). (EI, *m/z* (%): 558 (M^+, 48 %). Anal. calcd. For $C_{18}H_{12}O_3N_2I_2$: C, 38.70; X (I) 45.51; H, 2.15; N, 4.83%. Found: C, 38.85; X (I) 45.64; H, 2.27; N, 4.96%.

4-Bromo-2-[1-(4-iodo-2-nitro-phenylimino)-ethyl]-naphthalen-1-ol (**3e**): Light Yellow Crystal, Yield 77%, m.p. 133-135 ^{o}C; FT-IR (KBr, ν, cm^{-1}): 1434, 1535 (C=C), 1580 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.28-6.95 (m, 8H, ArH). (EI, *m/z* (%): 511 (M^+, 53 %). Anal. calcd. For $C_{18}H_{12}O_3N_2IBr$: C, 42.27; X (I, Br) 46.50; H, 2.34; N, 2.73%. Found: C, 42.38; X (I, Br) 46.64; H, 2.47; N, 2.88%.

4-Chloro-2-[1-(4-iodo-2-nitro-phenylimino)-ethyl]-naphthalen-1-ol (**3f**): Light Yellow Crystal, Yield 83%, m.p. 147-150 ^{o}C; FT-IR (KBr, ν, cm^{-1}): 1435, 1536 (C=C), 1583 (C=N), 3236 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.25 (s, 1H, OH), 6.27-6.94 (m, 8H, ArH). (EI, *m/z* (%): 466 (M^+, 53 %). Anal. calcd. For $C_{18}H_{12}O_3N_2ICl$: C, 46.35; X (I, Cl) 34.76; H, 2.57; N, 3.00%. Found: C, 46.47; X (I, Cl) 34.88; H, 2.69; N, 3.12%.

2-[1-(2-Chloro-4-iodo-phenylimino)-ethyl]-4-iodo-naphthalen-1-ol (**3g**): Light Yellow Crystal, Yield 80%, m.p. 162-164 ^{o}C; FT-IR (KBr, ν, cm^{-1}): 1437, 1542 (C=C), 1582 (C=N), 3237 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ,

ppm: 1.36 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.29-6.91 (m, 8H, ArH). (EI, *m/z* (%): 547 (M^+, 60 %). Anal. calcd. For $C_{18}H_{12}I_2ClON$: C, 39.48; X (I, Cl) 52.83; H, 2.19; N, 2.55%. Found: C, 39.56; X (I, Cl) 52.97; H, 2.32; N, 2.64%.

4-Bromo-2-[1-(2-chloro-4-iodo-phenylimino)-ethyl]-naphthalen-1-ol (**3h**): Light Yellow Crystal, Yield 75%, m.p. 168-171 ^oC; FT-IR (KBr, ν, cm^{-1}): 1438, 1542 (C=C), 1582 (C=N), 3236 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.30-6.91 (m, 8H, ArH). (EI, *m/z* (%): 500 (M^+, 55 %). Anal. calcd. For $C_{18}H_{12}IBrClNO$: C, 43.20; X (I, Br, Cl) 48.40; H, 2.40; N, 2.80%. Found: C, 43.36; X (I, Br, Cl) 48.54; H, 2.52; N, 2.93%.

4-Chloro-2-[1-(2-chloro-4-iodo-phenylimino)-ethyl]-naphthalen-1-ol (**3i**): Light Yellow Crystal, Yield 85%, m.p. 150-152 ^oC; FT-IR (KBr, ν, cm^{-1}): 1438, 1540 (C=C), 1582 (C=N), 3235 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.30-6.93 (m, 8H, ArH). (EI, *m/z* (%): 456 (M^+, 52 %). Anal. calcd. For $C_{18}H_{12}Cl_2INO$: C, 47.36; X (I, Cl) 43.20; H, 2.63; N, 3.07%. Found: C, 47.51; X (I, Cl) 43.33; H, 2.70; N, 3.18%.

4-Iodo-2-[1-(2-iodo-4-nitro-phenylimino)-ethyl]-naphthalen-1-ol (**3j**): Light Yellow Crystal, Yield 88%, m.p. 162-165 ^oC; FT-IR (KBr, ν, cm^{-1}): 1434, 1535 (C=C), 1582 (C=N), 3235 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.37 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.28-6.95 (m, 8H, ArH). (EI, *m/z* (%): 558 (M^+, 56 %). Anal. calcd. For $C_{18}H_{12}O_3N_2I_2$: C, 38.70; X (I) 46.51; H, 2.15; N, 4.83%. Found: C, 38.82; X (I) 46.68; H, 2.26; N, 4.96%.

4-Bromo-2-[1-(2-iodo-4-nitro-phenylimino)-ethyl]-naphthalen-1-ol (**3k**): Light Yellow Crystal, Yield 78%, m.p. 139-141 ^oC; FT-IR (KBr, ν, cm^{-1}): 1436, 1535 (C=C), 1582 (C=N), 3235 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.28-6.94 (m, 8H, ArH). (EI, *m/z* (%): 511 (M^+, 65 %). Anal. calcd. For $C_{18}H_{12}O_3N_2IBr$: C, 42.27; X (I, Br) 46.50; H, 2.34; N, 2.73%. Found: C, 42.39; X (I, Br) 46.68; H, 2.40; N, 2.82%.

4-Chloro-2-[1-(2-iodo-4-nitro-phenylimino)-ethyl]-naphthalen-1-ol (**3l**): Light Yellow Crystal, Yield 72%, m.p. 170-172 ^oC; FT-IR (KBr, ν, cm^{-1}): 1438, 1535 (C=C), 1583 (C=N), 3237 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.25 (s, 1H, OH), 6.29-6.96 (m, 8H, ArH). (EI, *m/z* (%): 466 (M^+, 53 %). Anal. calcd. For $C_{18}H_{12}O_3N_2ICl$: C, 46.36; X (I, Cl) 34.76; H, 2.57; N, 3.00%. Found: C, 46.45; X (I, Cl) 34.88; H, 2.64; N, 3.10%.

2-[1-(2,6-Dichloro-4-iodo-phenylimino)-ethyl]-4-iodo-naphthalen-1-ol (**3m**): Light Yellow Crystal, Yield 88%, m.p. 128-131 ^oC; FT-IR (KBr, ν, cm^{-1}): 1442, 1540 (C=C), 1581 (C=N), 3235 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.31-6.96 (m, 7H, ArH). (EI, *m/z* (%): 582 (M^+, 85 %). Anal. calcd. For $C_{18}H_{11}I_2Cl_2NO$: C, 37.11; X (I, Cl) 55.67; H, 1.89; N, 2.40%. Found: C, 37.23; X (I, Cl) 55.80; H, 1.96; N, 2.52%.

4-Bromo-2-[1-(2,6-dichloro-4-iodo-phenylimino)-ethyl]-naphthalen-1-ol (**3n**): Light Yellow Crystal, Yield 84%, m.p. 140-142 ^oC; FT-IR (KBr, ν, cm^{-1}): 1444, 1540 (C=C), 1582 (C=N), 3235 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.33-6.99 (m, 7H, ArH). (EI, *m/z* (%): 535 (M^+, 80 %). Anal. calcd. For $C_{18}H_{11}Cl_2IBrNO$: C, 40.37; X (I, Br, Cl) 42.23; H, 2.05; N, 2.61%. Found: C, 40.46; X (I, Br, Cl) 42.36; H,2.12; N, 2.73%.

4-Chloro-2-[1-(2,6-dichloro-4-iodo-phenylimino)-ethyl]-naphthalen-1-ol (**3o**): Light Yellow Crystal, Yield 82%, m.p. 148-150 ^oC; FT-IR (KBr, ν, cm^{-1}): 1440, 1543 (C=C), 1580 (C=N), 3235 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.31-6.97 (m, 7H, ArH). (EI, *m/z* (%): 490 (M^+, 76 %). Anal. calcd. For $C_{18}H_{11}Cl_3INO$: C, 44.08; X (I, Cl) 40.20; H, 2.24; N, 2.85%. Found: C, 44.15; X (I, Cl) 40.31; H, 2.32; N, 2.95%.

2-[1-(4-Bromo-2,6-dichloro-phenylimino)-ethyl]-4-iodo-naphthalen-1-ol (**3p**): Light Yellow Crystal, Yield 86%, m.p. 144-146 ^oC; FT-IR (KBr, ν, cm^{-1}): 1444, 1545 (C=C), 1584 (C=N), 3232 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.33-6.99 (m, 7H, ArH). (EI, *m/z* (%): 535 (M^+, 87 %). Anal. calcd. For $C_{18}H_{11}Cl_2IBrNO$: C, 43.37; X (I, Br, Cl) 51.77; H, 2.05; N, 2.61%. Found: C, 43.46; X (I, Br) 51.86; H, 2.18; N, 2.80%.

4-Bromo-2-[1-(4-bromo-2,6-dichloro-phenylimino)-ethyl]-naphthalen-1-ol (**3q**): Light Yellow Crystal, Yield 80%, m.p. 150-152 ^oC; FT-IR (KBr, ν, cm^{-1}): 1442, 1546 (C=C), 1582 (C=N), 3234 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.31-6.98 (m, 7H, ArH). (EI, *m/z* (%): 488 (M^+, 81 %). Anal. calcd.

For $C_{18}H_{11}Cl_2Br_2NO$: C, 44.26; X (Cl, Br) 47.13; H, 2.25; N, 2.86%. Found: C, 44.38; X (Cl, Br) 47.22; H, 2.34; N, 2.98%.

2-[1-(4-Bromo-2,6-dichloro-phenylimino)-ethyl]-4-chloro-naphthalen-1-ol (**3r**): Light Yellow Crystal, Yield 89%, m.p. 182-184 ^oC; FT-IR (KBr, ν, cm^{-1}): 1442, 1544 (C=C), 1584 (C=N), 3236 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.34 (s, 3H, CH_3), 5.25 (s, 1H, OH), 6.28-6.94 (m, 7H, ArH). (EI, *m/z* (%): 443 (M^+, 74 %). Anal. calcd. For $C_{18}H_{11}Cl_3BrNO$: C, 48.36; X (Cl, Br) 42.09; H, 2.43; N, 3.16%. Found: C, 48.45; X (Cl, Br) 42.18; H, 2.51; N, 3.23%.

2-[1-(2,6-Dichloro-phenylimino)-ethyl]-4-iodo-naphthalen-1-ol (**3s**): Light Yellow Crystal, Yield 81%, m.p. 176-178 ^oC; FT-IR (KBr, ν, cm^{-1}): 1442, 1544 (C=C), 1583 (C=N), 3234 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.28-6.92 (m, 8H, ArH). (EI, *m/z* (%): 456 (M^+, 78 %). Anal. calcd. For $C_{18}H_{12}Cl_2INO$: C, 47.36; X (I, Cl) 43.42; H, 2.63; N, 3.07%. Found: C, 47.45; X (I, Cl) 43.55; H, 2.70; N, 3.14%.

4-Bromo-2-[1-(2,6-dichloro-phenylimino)-ethyl]-naphthalen-1-ol (**3t**):): Light Yellow Crystal, Yield 87%, m.p. 168-170 ^oC; FT-IR (KBr, ν, cm^{-1}): 1443, 1543 (C=C), 1585 (C=N), 3235 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.28-6.94 (m, 8H, ArH). (EI, *m/z* (%): 409 (M^+, 92 %). Anal. calcd. For $C_{18}H_{12}Cl_2BrNO$: C, 52.81; X (Br, Cl) 36.91; H, 2.93; N, 3.42%. Found: C, 52.81; X (Br, Cl) 37.03; H, 3.02; N, 3.50%.

4-Chloro-2-[1-(2,6-dichloro-phenylimino)-ethyl]-naphthalen-1-ol (**3u**): Light Yellow Crystal, Yield 77%, m.p. 186-188 ^oC; FT-IR (KBr, ν, cm^{-1}): 1446, 1547 (C=C), 1583 (C=N), 3233 (OH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.27-6.94 (m, 8H, ArH). (EI, *m/z* (%): 364 (M^+, 96 %). Anal. calcd. For $C_{18}H_{12}Cl_3NO$: C, 59.34; X (Cl) 29.25; H, 3.29; N, 3.84%. Found: C, 59.41; X (Cl) 29.30; H, 3.38; N, 3.92%.

4-[1-(4-Bromo-1-hydroxy-naphthalen-2-yl)-ethylideneamino]-3,5-diiodo-benzoic acid (**3v**): Light Yellow Crystal, Yield 72%, m.p. 159-161 ^oC; FT-IR (KBr, ν, cm^{-1}): 1254 (C-O), 1445, 1551 (C=C), 1584 (C=N). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.29 (s, 1H, OH), 6.32-7.05 (m, 7H, ArH). (EI, *m/z* (%): 636 (M^+, 54 %). Anal. calcd. For $C_{19}H_{12}O_3I_2BrN$: C, 35.84; X (I, Br) 52.51; H, 1.88; N, 2.20%. Found: C, 35.92; X (I, Br) 52.60; H, 1.95; N, 2.27%.

4-[1-(1-Hydroxy-4-iodo-naphthalen-2-yl)-ethylideneamino]-3,5-diiodo-benzoic acid (**3w**): Light Yellow Crystal, Yield 78%, m.p. 152-154 ^oC; FT-IR (KBr, ν, cm^{-1}): 1257 (C-O), 1448, 1554 (C=C), 1584 (C=N). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.32-7.07 (m, 7H, ArH). (EI, *m/z* (%): 683 (M^+, 59 %). Anal. calcd. For $C_{19}H_{12}O_3I_3N$: C, 33.38; X (I) 55.78; H, 1.75; N, 2.04%. Found: C, 33.46; X (I) 55.86; H, 1.82; N, 2.12%.

4-[1-(4-Chloro-1-hydroxy-naphthalen-2-yl)-ethylideneamino]-3,5-diiodo-benzoic acid (**3x**): FT-IR (KBr, ν, cm^{-1}): Light Yellow Crystal, Yield 84%, m.p. 163-166 ^oC; 1256 (C-O), 1446, 1555 (C=C), 1583 (C=N). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.33-7.06 (m, 7H, ArH). (EI, *m/z* (%): 591 (M^+, 65 %). Anal. calcd. For $C_{19}H_{12}O_3I_2N$: C, 38.57; X (I, Cl) 48.98; H, 2.03; N, 2.36%. Found: C, 38.64; X (I, Cl) 49.10; H, 2.13; N, 2.44%.

RESULTS AND DISCUSSION

The present studies describe reactions were carried out using grindstone technique simply by mixing corresponding substituted hydroxy ketones **1** and substituted anilines **2**. The mixture was grind together in mortar with pestle at room temperature for 2-3 minutes, and then a catalytic amount of sulphuric acid was added to this grinded reaction mixture. The grinding was continued for 4-7 minutes and progress of reaction was monitored on thin layer chromatography (TLC). The completion of reaction was indicated by wetting with the formation of yellow colored reaction mixture. Obtained solid was easily separated by using cold water and simple Buchner filtration; final purification was achieved by crystallization from ethanol to give pure sample of Schiff bases **3a-x** (Scheme **1**). The reasons to use grinding technique [28] in synthesis of titled compounds which make the simple reaction procedure, short reaction time, increase the purity of resulting products and enhance the quantitative yield. Other advantage of method is too consistent with green chemistry approach because it does not require heating or microwave irradiation. It occurs at room temperature and is completely free from organic solvents during both the reaction and

separation of the product; except for recrystallization of product. Therefore method avoids use of organic solvents during the reaction leads to easy isolation of product.
In order to optimize the capability and efficiency of present method, we carried out above reaction by conventional method using ethanol as reaction solvent (Table **1**). We found that solid- state reaction occur more efficiently and more selectively than does the solution reaction. Since molecules in the crystal are arranged tightly and regularly. Thus, in grindstone technique reaction occurs efficiently in terms of clean reaction conditions, operationally simple, short reaction time giving quantitative yields of product and environmentally and eco-friendliness.

Table 1: Comparison of grinding technique reaction with conventional method

Entry	Conventional method			Grinding technique	
	Solvent	Time (min)	Yield (%)	Time (min)	Yield (%)
3a	Ethanol (10 ml)	25	60	5	75
3d	Ethanol (15 ml)	28	65	4	81
3g	Ethanol (10 m)	30	68	7	80

The results of antioxidant activity expressed as IC_{50} value with two different antioxidant agents are shown in Table **2**. The compound **3m** and **3n** tested using DPPH scavenging method, showed IC_{50} value at 70.13, 70.28 µM, when compared with to that of the standard ascorbic acid at 69.08 µM respectively. However the compound **3d** and **3k** did not show significant activity. Further, the antioxidant studies carried out using NO scavenging method, the only compound **3m** and **3w** showed IC_{50} value at 92.04 and 91.25 µM in comparison with standard. The compound **3f** and **3j** did not show antioxidant activity.

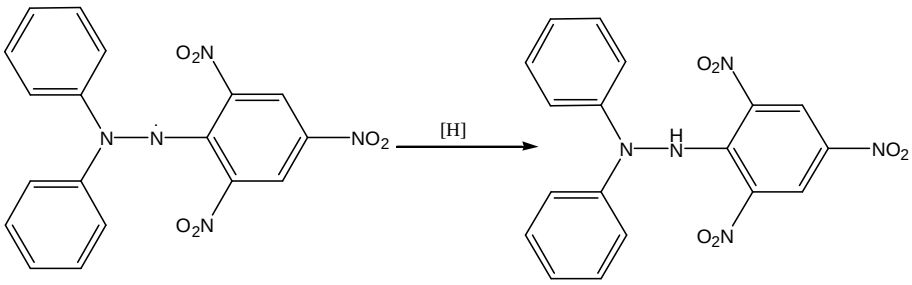
Antioxidant activity
The following antioxidant methods were used to evaluate the antioxidant properties of our test compounds.

1) DPPH• Scavenging Activity
DPPH is a stable free radical that can accept an electron or hydrogen radical to become a stable diamagnetic molecule. Due to its odd electron, the methanol solution of DPPH shows a strong absorption band at 517 nm. DPPH radical reacts with various electron donating molecules (reducing agents or antioxidants). When electrons become paired off, bleaching of the DPPH solution is the result. This results in the formation of the colorless 2,2'-diphenyl-1-picryl hydrazine. Reduction of the DPPH radicals can be estimated quantitatively by measuring the decrease in absorbance at 517 nm.

Procedure: Equal volumes of 100 µM 2,2'-diphenyl-1-picrylhydrazyl (DPPH) in methanol was added to different concentrations of test compounds (0 – 200 µM/ml) in methanol, mixed well and kept in dark for 20 min. The absorbance at 517 nm was measured using the spectrophotometer UV-1650, Shimadzu [29]. Plotting the percentage DPPH• scavenging against concentration gave the standard curve and the percentage scavenging was calculated from the following equation:

$$\% \text{ scavenging} = \frac{\text{Absorbance of blank - Absorbance of test}}{\text{Absorbance of blank}} \times 100$$

IC50 was obtained from a plot between concentration of test compounds and % scavenging. Ascorbic acid was used as standard for comparison.



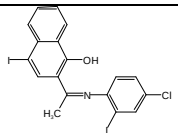
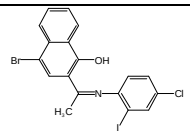
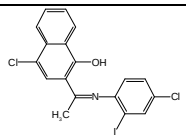
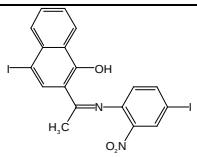
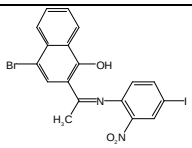
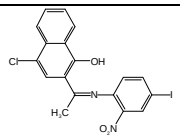
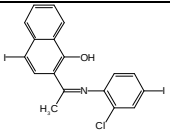
Structural changes occurs of DPPH during oxidation

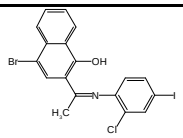
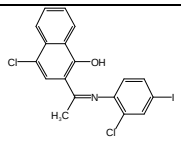
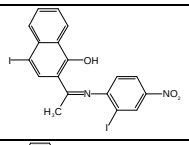
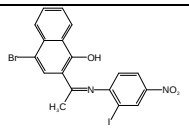
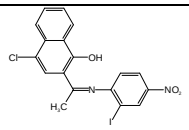
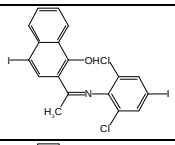
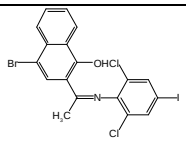
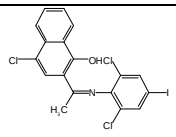
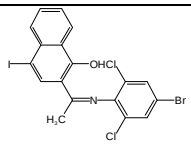
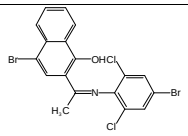
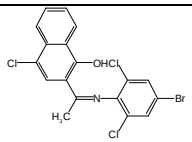
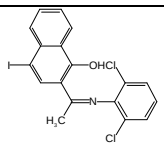
2) Nitric Oxide Scavenging Activity

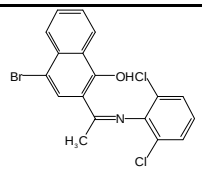
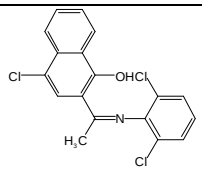
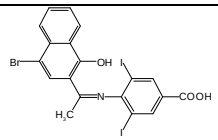
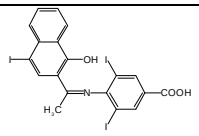
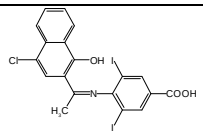
Nitric oxide (NO) will be generated by sodium nitropruside in solution. In the presence of an antioxidant or nitric oxide scavenger the amount of NO generated will be less. The excess NO will be estimated by Griess reagent is the mixture of sulphanilic acid and naphthylethylenediamine dihydrochloride. The nitric oxide will give pink colour complex estimated at 540 nm.

Procedure: To a reaction mixture (6 ml) containing sodium nitroprusside (10 mM, 4 ml), phosphate buffer saline (PBS, 1.0 ml) and 1.0 ml of different concentration of test compounds/standard were incubated at 25ºC for 150 min. After incubation, 0.5 ml of the reaction mixture containing nitrate was removed and 1.0 ml of sulphanilic acid was added, mixed well and allowed to stand for 5 min for completion of diazotization. Then 1.0 ml of naphthylethylenediaminedihydrochloride was added, mixed and allowed to stand for 30 min in dark at room temperature. The absorbance of these solutions was measured at 540 nm against corresponding blank solution without sodium nitroprusside [30]. The % scavenging and IC50 values were determined as explained in DPPH assay. The standard rutin were used for comparison antioxidant activity of synthesized compounds.

Table 2: Antioxidant scavenging of newly synthesized imines 3a-x at different concentration

Structure of Compound	DPPH scavenging (Concentration μM/ml)			NO scavenging		
	50	100	200	50	100	200
3a 	40.0	52.52	78.07	38.0	50.10	97.89
3b 	43.34	54.06	85.27	39.10	47.08	105.64
3c 	38.0	43.23	75.84	28.03	43.97	114.02
3d 	NSA	NSA	NSA	30.96	76.54	146.97
3e 	58.23	42.63	170.12	75.87	65.89	165.24
3f 	48.16	63.72	155.09	NSA	NSA	NSA
3g 	30.79	42.65	91.04	43.14	87.24	107.03

3h		40.28	37.28	96.37	32.58	61.09	102.34
3i		63.04	43.21	123.14	40.67	93.67	144.78
3j		52.84	50.60	183.08	NSA	NSA	NSA
3k		NSA	NSA	NSA	71.90	97.02	152.43
3l		59.05	60.32	170.06	NSA	NSA	NSA
3m		20.93	18.74	70.13	39.05	59.07	92.04
3n		16.48	28.90	70.28	38.81	60.45	96.28
3o		39.67	43.72	83.59	76.06	89.23	116.93
3p		32.87	37.50	73.09	28.78	58.91	94.68
3q		37.39	23.06	78.53	41.02	73.93	99.14
3r		50.09	43.02	86.28	27.03	48.23	107.47
3s		40.57	58.98	137.03	45.02	98.45	183.58

3t		34.83	60.31	92.07	30.24	58.26	132.04
3u		60.23	73.49	150.73	48.34	74.71	125.97
3v		47.39	43.87	112.36	24.05	42.90	93.65
3w		51.08	58.98	126.41	23.78	43.87	91.25
3x		56.09	66.12	137.92	45.89	65.98	102.57
Standard		67.90	68.96	69.08*	89.90	90.87	91.05*

CONCLUSION

In conclusion we reported short library of imines **3a-x** by the condensation of substituted hydroxy ketone with substituted anilines under solvent-free conditions using grinding method. The method is efficient, convenient in terms of simple reaction procedure, short reaction time, increase the purity of resulting products and enhance the quantitative yield. Further preliminary *in vitro a*ntioxidant activity of newly synthesized compounds reveals that **3m**, **3n** and **3w** shows significant activity in comparison with standard antioxidant ascorbic acid and rutin. The remaining compound shows comparative antioxidant activity. Compound **3d** and **3k** were did not shows significant activity (NSA) in comparison with ascorbic acid. Similarly compound 3f, 3j, 3l were also did not possess antioxidant activity in comparison with rutin. Thus present study is useful in the field of medicinal chemistry.

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