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RESEARCH ARTICLE

SYNTHESIS AND ANTIMICROBIAL EVALUATIONOF BENZ [B]-1,4-THIAZEPINE, BENZ[B]-1,4-DIAZEPINE,AND QUINOXALINE DERIVATIVES VIA GREEN MECHANOCHEMICAL AND CONVENTIONAL TECHNIQUES

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ABSTRACT

Mechano heterocyclic chemistry (MHC) is a recent and quickly growing technique in synthesis of heterocycles. Benzo[b]1,4-thiazepines,benzo[b]1,4-diazepines\were prepared via new mechano-chemical (grinding)technique of α,β-epoxyketoneswith o-aminothiophenol, and o-phenylenediamine, respectively. The same compounds were synthesized under conventional thermal method. However, quinoxalines were obtained from α,β-epoxyketones and o-phenylenediamine, mainly under conventional method. We introduced the yield economy [YE] as a metric to assess the conversion efficiency of grinding and conventional synthetic reactions. Notably, the mechano-chemical reaction provides a green facile access of thiazepines, diazepines,andquinoxalines in excellent yields, as well as providing higher yield economy [YE] compared with conventional thermal methods. The antimicrobial activity of some of the synthesized heterocycles was tested.

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INTRODUCTION

Considerable interest has been focused on the synthesis 1,4-Benzothiazepines, 1,4-benzodiazepines,and quinoxalines. They are a very important class of bioactive compounds, widely used as anticonvulsant, antianginal, antihistamines, edrenolytics, neuroleptics, anti HIV and antiparkinsonism activities (Levai ,1986; Bariwal *et al*.,2008; Chate *et al*., 2011; Wander *et al*., 1996; Wander, 1968; Maffrand *et al*., 1976). Moreover, they are exhibit strong antibacterial activity (Benzeid *et al*, 2008; Douglas *et al*.,1996). Benzodiazepines are used as sedatives, hypnotics and anxiolytics. They become the drugs of choice for the treatment of anxiety, sleep disorders, status epilepticus, and muscle relaxants (Maffrand *et al*., 1976; Fielding and Lal, 1979; Haefely *et al*.,1983; Bartsch and Erker 1988; Pevarello *et al*., 1993).

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In addition to this, 2,4-disubstituted-3H-1,4-benzodizepinesare very useful synthons for the rapid construction of polyheterocyclic systems due to the presence of two possible dipolarophile sites (Barltrop *et al*., 1959). Among several published methods in literature, the synthesis of 2,4-disubstituted-3H-benzo[*b*][1,4]diazepine via the reaction ofynones with *o*-phenylenediamines has been reported (Ried and Koenig ,1972;Palimkar S.S. ,2007; Andreichikov *et al*., 1978). There are several methods for synthesis of Benzo[b]thiazepines among them from the reaction ofynones, and chalcones witho-phenylenediamines (Khairy *et al.*, 2013; Wang *et al*., 2009). As we deal with synthesis of heterocyclic systems (Hemdan and Abd El-Mawgoude, 2015;Hemdan and Abd El-Mawgoude, 2015; Hemdan *et al*.2010; Hemdan, 2010) we will introduce the recent mechanosynthetic tool as a simple, efficient, economic and clean strategy for green synthesis of heterocyclic systems. With increasing the interest in green chemistry concept, such volatile organic solvents are being replaced by alternative non-toxic, non-flammable, ionic liquids, and water or alternatively the reactions are carried out

under solvent free conditions. Mechanoheterocyclic chemistry (MHC) (Katritzky, 2015; Zangade *et al*., 2013; Nikpassand *et al*. 2014) drives the attention of heterocyclic chemists, who have used this technique to achieve the green synthesis of several heterocyclic systems, including pyrazolines (Zangade *et al.*,2013), aurones (Kumar, 2014), bis (indol-3-yl) methanes (Talukdar and Thakur, 2013), 1,3,4-oxadiazoles (Kumar and Makrandi, 2011), pyrimidones (Khaskel *et al*., 2014), coumarins (Nikpass and 2014; ElfiSusanti *et al*., 2014), flavones (ElfiSusanti *et al*., 2014), benzodiazepines (Sharma, 2013),1,6-naphthyridin (Abdel Hamid, 2015) and 1,3,4-thiadiazoles (Abdel-Aziem, 2015).

In view of the advantages associated with solvent-free grinding reactions such as easy handling, simple equipment, less environmentally hazardous reactions, time and energy efficiency, we thought to explore the usage of this strategy to synthesize 1,4-benzothiazepines,1,4-benzodiazepines,and quinoxalines from α,β-epoxy ketones and compare the results with the conventional technique.

MATERIALS AND METHODS

MATERIALS

All chemicals and the reagents used in the study were of synthetic grade purity.Benzaldehyde (Germed, Germany), 2-acetyl naphthalene, o-phenylenediamine, o-aminothiophenol (Merck-Germany),Acetophenone (Laboratory Rasayan, s.d. fine-chem), Hydrogen peroxide, ethanol, methanol and petroleumether (Adwic: EL Nasr Pharmaceutical Comp, Egypt).Solvents was purified by distillation. Melting pointswere determined on an electrothermal melting point apparatus using capillary tubes and uncorrected. The elemental analyses were done on a Perkin-Elmer 2400 CHN Elemental analyzer. The IR spectra were recorded on FTIR Mattson (infinity series) Spectrophotometer as KBr discs. The ^{1}H-NMR and ^{13}C-NMR spectra were measured On Varian Gemini 300MHz spectrometer, with chemical shift (δ) expressed in ppm downfield from TMS as an internal standard, in $CDCl_3$ or DMSO-d_6. Mass spectra were determined on Shimadzu GC-MSQP 1000 EX instrument operating at 70 eV. TLC was performed onpre - coated sheets of silica gel F_{254} (Merck) to monitor the progress of the reaction as well as to check the purity of the products. The spotswere visualized by using UV irradiation (254 nm).

METHODS

Herein, we wish to report for the solvent free mechanochemical green synthesis of 3,4-disubstituted benzo[b][1,4]thiadiazepines2a-fvia grinding together α,β-epoxy ketones 1a-f and o-aminothiophenol in the presence of a catalytic amount of silica gel at room temperature in a porcelain mortar under solvent-free conditions.The reaction takes place in a short time (4-6 min.) and high yields (68-90%). However, refluxing a solution of α,β-Epoxy ketones 1a-f with o-aminothiophenol in absolute ethanol afforded the same compounds 2a-f in a longer reaction time (90-120 min.), and moderate to high yields (50% -92%).(scheme-1). Similarly grinding a mixture of equivalent amounts of α,β-epoxy-ketones 1a,d,ewith o-phenylenediamine in a porcelain mortar with a pestle for few minutes afforded benzo[b][1,4]diazepine derivative 3a, and 2,3-dihydro-1H-benzo[b][1,4]diazepin-3-ol derivatives 4a,b, respectively with yields (80%-87%), after short reaction time. However, treatments of α, β-epoxy ketones 1a-e with o-phenylenediamine in absolute ethanol under refluxingconditions afforded quinazoline derivatives 3a-e in good yields. On the other hand refluxing of epoxy ketone derivatives 1d, ewith o-phenylene -diamine in dry benzene gave 1[H] benzo[b] [1, 4 diazepin-3-ol derivatives 4a, b. The reaction probably goes via the following mechanism(scheme 2).

Formation of compounds 2-4 Under Grinding Technique: General procedure

A mixture of equivalent amounts of α, β-epoxy ketones **1** (3mmol) with o-aminothiophenol (3mmol) or o-phenylenediamine (3mmol), was grinded together in a porcelain mortar with a pestle for few minutes (Table 1). A catalytic amount of silica gel was used (in case of o-phenylenediamine) in the presence of a few drops of water. Upon completion of grinding as monitored by TLC, the reaction mixture turned colored solid mass, washed with cold water, and recrystallized from a suitable solvent to give the corresponding product(Table 1).

Formation of Compounds 2-4 under Conventional Thermal Conditions

General procedure: A Solution of α, β- epoxy ketones 1a-f (3mmol) in absolute ethanol (30 ml) or dry benzene was refluxed with o-aminothiophenol (3 mmol) for 1.5 - 2 hrs. (monitored by TLC), then the reaction mixtures were vacuum-distilled to *ca* half volume. The solid products that were obtained after cooling, filtered off and recrystallized from the suitable solvents to give compounds 2a-f. Similar procedure was carried out with epoxides 1a-e (3mmol) and o-phenylenediamine (3mmol) in absolute ethanol (30 ml) to give compounds 3a-e or with epoxides 1d, 1e in dry benzene (30 ml) to give compounds 4a,b.Refluxing 4a,b in absolute ethanol(2hrs) afforded the corresponding 3d,e (Table 1).

Characterization

3,4-diphenylbenzo[b][1,4]thiazepine (2a): Pale green crystals (light petroleum ether 40/60 ^{o}C), m.p 220-222 °C; IR (KBr) *v*: 3058 (C–H_{arom}), 1597, 1567 (C=N), 691, 755 δ_{5H}; ^{1}H-NMR (DMSO-d_6) *δ*: 4.34 (s, 1H, CH=), 6.87 (d, 2H, *J* = 7.2 Hz), 7.16 (t, 2H, *J* = 7.2 Hz), 7.30 (t, 2H, *J* = 7.6 Hz), 7.39 (t, 2H, *J* = 7.2 Hz), 7.44 (t, 2H, *J* = 6.8 Hz), 7.63 (t, 4H, *J* = 7.2 Hz);^{13}C-NMR(DMSO-d_6) *δ*: 120.40, 127.32, 127.41, 127.97, 128.06, 128.31, 128.72, 131,14, 137.83, 142.92, 155.95; MS(EI) (70 eV) *m/z* (%):211 (18), 209 (13), 197 (19), 180 (24), 165 (31), 145 (33), 120 (87), 107 (30), 88 (32), 76 (100),44.92(16.56)44(2) ; *Anal*.Calcd for $C_{21}H_{15}NS$ (313.42): C, 80.48; H, 4.82; N, 4.47. Found C, 80.23; H, 4.67; N, 4.11 %.

3-(4-methoxyphenyl)-4-phenylbenzo[b][1,4]thiazepine (2b): Yellow crystals (light petroleum ether 60/80 °C), m.p 90-92 °C; IR (KBr) *v*: 3054 (C–H_{arom}), 2952, 2918, 2848 (C–H_{alkyl}), 1571 (C=N), 692, 757 δ_{5H}; ^{1}H-NMR (DMSO-d_6) *δ*: 3.85 (s, 3H, OCH_3), 4.36 (s, 1H, CH=), 6.89 -8.12 (m, 13H);MS (EI) (70 eV) *m/z* (%): 343 (M+·, 1.5), 313 (1.5), 269 (3), 241 (100), 226 (55), 211 (90), 198 (46), 135 (55), 105 (93), 77 (73), 69 ((54),44(9.08);*Anal.*Calcd for $C_{22}H_{17}NOS$ (343.44): C, 76.94; H, 4.99; N, 4.08. Found C, 76.82 ; H, 4.68; N, 3.88 %.

3-(4-chlorophenyl)-4-phenylbenzo[b][1,4]thiazepine (2c): Yellow crystals (EtOH), m.p 216-218 °C; IR (KBr) *v*: 3059 (C–H_{arom}), 1597, 1567 (C=N), 691, 755 δ_{5H}; ^{1}H-NMR (DMSO-d_6) *δ*: 4.33 (s, 1H, CH=), 6.87 (d, 2H, *J* = 7.6 Hz), 7.16 (t, 2H, *J* = 8.4 Hz), 7.30 (t, 2H, *J* = 7.6 Hz), 7.37 (t, 2H, *J* = 6.8 Hz), 7.45 (t, 2H, *J* = 6.8 Hz), 7.61 (t, 3H, *J* = 7.6 Hz);^{13}C-NMR(DMSO-d_6) *δ*: 120.40, 127.32, 127.41, 127.96, 128.06, 128.31, 128.72, 131,14, 137.83, 142.92, 155.95;MS (EI) (70 eV) *m/z* (%): 348 ($M^{+\cdot}$+ 1, 2.4), 299 (3), 288 (5), 243 (32), 222 (13), 159 (100), 141 (25), 102 (28), 89 (90), 44(17.54) ; *Anal.*Calcd for $C_{21}H_{14}ClNS$ (347.86): C, 72.51; H, 4.06; N, 4.03. Found C, 72.72 ; H, 3.77; N, 3.92%.

4-(naphthalen-2-yl)3-Phenylbenzo[b][1,4]thiazepine (2d): Green crystals (EtOH), m.p 144-146 °C; IR (KBr) *v*: 3053 (C–H_{arom}), 1595, 1583 (C=N), 719, 750 δ_{5H}; ^{1}H-NMR (DMSO-d_6) *δ*: 3.96 (s, 1H, CH=), 7.13 (t, 2H, *J* = 7.6 Hz), 7.21 (t, 2H, *J* = 7.6 Hz), 7.34 (t, 2H, *J* = 8.0 Hz), 7.37-7.42 (m, 2H), 7.54-7.55 (m, 2H), 7.90-7.97 (m, 2H), 8.22 (d, 2H, *J* = 7.6Hz), 8.53-8.55 (m, 2H);^{13}C-NMR(DMSO-d_6) *δ*: 123.92, 124.65, 126.96, 127.15, 127.25, 127.50, 128.08, 128.23, 128.66, 129.05, 129.41, 133.06, 134.54, 134.59, 143.59 (C=C), 157.34 (C=N);MS(EI) (70 eV) *m/z* (%): 363 ($M^{+\cdot}$, 0.97), 332 (6), 325 (5), 275 (24), 242 (22), 189 (10), 153 (50), 136 (100), 111 (38), 81 (84), 44.97(15) ;*Anal.*Calcd for $C_{25}H_{17}NS$ (363.47): C, 82.61; H, 4.71; N, 3.85. Found C, 82.43; H, 4.57; N, 3.70%.

3-(4-methoxyphenyl)-4-(naphthalen-2-yl) benzo [b] [1,4] thiazepine (2e): Pale Green crystals (EtOH), m.p 150-152 °C; IR (KBr) *v*: 3052 (C–H_{arom}), 2918, 2849 (C–H_{alkyl}), 1595, 1568 (C=N), 833 δ_{2H}; ^{1}H-NMR (DMSO-d_6) *δ*: 3.82 (s, 3H, OCH3), 3.96 (s, 1H, CH=), 7.25 -7.62 (m, 7H), 7.96 -8.05 (m, 4H), 8.31 (d, 2H, *J* = 8.4 Hz), 8.58 -8.67 (m, 2H);^{13}C-NMR(DMSO-d_6) *δ*: 22.54, 123.92, 124.65, 126.96, 127.15, 127.25, 127.50, 128.08, 128.23, 128.66, 129.05, 129.41, 133.06, 134.54, 134.59, 143.74 (C=C), 157.34 (C=N);MS(EI) (70 eV) *m/z* (%): 393 ($M^{+\cdot}$, 0), 304 (2), 299 (3), 284 (3), 236 (14), 210 (6), 197 (16), 183 (38), 136 (100), 109 (24), 95 (36), 44(9);*Anal.*Calcd for $C_{26}H_{19}NOS$ (393.50): C, 79.36; H, 4.87; N, 3.56. Found C, 79.48 ; H, 4.49; N, 3.29%.

3-(4-chlorophenyl)-4-(naphthalen-2-yl) benzo [b] [1,4] thiazepine (2f): Green crystals (EtOH), m.p 150-152 °C; IR (KBr) *v*: 3053 (C–H_{arom}), 1594, 1568 (C=N); ^{1}H-NMR (DMSO-d_6) *δ*: 3.96 (s, 1H, CH=), 7.17 (t, 2H, *J* = 7.2 Hz), 7.27 (t, 2H, *J* = 5.7 Hz), 7.40 (d, 2H, *J* = 8.0 Hz), 7.46 (d, 2H, *J* = 8.0 Hz), 7.56-7.63 (m, 2H), 7.96-8.05 (m, 3H), 8.31 (d, 1H, *J* = 8.8), 8.67 (m, 1H);^{13}C-NMR(DMSO-d_6) *δ*: 110.00, 123.92, 124.65, 126.96, 127.15, 127.25, 127.50, 128.09, 128.22, 128.24, 128.66, 129.05, 129.41, 133.06, 134.54, 134.59, 143.73 (C=C), 157.34 (C=N);MS(EI) (70 eV) *m/z* (%): 397 ($M^{+\cdot}$, 0), 325 (3), 324 (4), 272 (14), 262 (10), 247 (17), 211 (43) 193 (14), 155 (48), 136 (64), 125 (100), 98 (89), 44(18.5) ;*Anal.*Calcd for $C_{25}H_{16}ClNS$ (397.92): C, 75.46; H, 4.05; N, 3.52. Found C, 75.22 ; H, 4.16; N, 3.18 %.

2-benzyl-3-phenylquinoxaline(3a): Yellow crystals (light petroleum ether 60/80 °C), m.p 82-84 °C; IR (KBr) *v*: 3055, 3028 (C–H_{arom}), 1632, 1590 (C=N), 699, 749 δ_{5H}; ^{1}H-NMR ($CDCl_3$) *δ*: 4.42 (s, 2H, CH_2), 6.98 (d, 2H, *J* = 7.8 Hz), 7.17 (t, 3H, *J* = 6.0 Hz), 7.36-7.45 (m, 5H), 7.72 -7.80 (m, 2H), 8.13 (t, 2H, *J* = 7.5 Hz) ;MS (EI) (70 eV) *m/z* (%): 296 ($M^{+\cdot}$, 77), 295 ($M^{+\cdot}$-1, 100), 280 (2), 219 (8), 178 (4), 165 (3), 151 (2), 126 (1), 101 (3), 91(6.45), 88 (2),65(2.53); *Anal.*Calcd for $C_{21}H_{16}N_2$ (296.37): C, 85.11; H, 5.44; N, 9.45. Found C, 84.86; H, 5.18; N, 9.51 %.

2-(4-methoxybenzyl)-3-phenylquinoxaline(3b): Yellow crystals (EtOH), m.p 110-112 °C; IR (KBr) *v*: 3059 (C–H_{arom}), 2992, 2837 (C–H_{alkyl}), 1608, 1508 (C=N), 810 δ_{2H}, 697, 767 δ_{5H}; ^{1}H-NMR (DMSO-d_6) *δ*: 3.65 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2), 6.71 (d, 2H, *J* = 8.7 Hz), 6.82 (d, 2H, *J* = 8.7 Hz), 7.47 – 7.57 (m, 5H), 7.80 – 7.86 (m, 2H), 8.06 – 8.10 (m, 2H); MS(EI) (70 eV) *m/z* (%): 327 ($M^{+\cdot}$+1, 5.4), 315 (6), 293 (7), 275 (5), 232 (22), 212 (10), 165 (14), 177 (13), 122 (21), 121(4.91),120 (15.95),104 (21),90(24.16), 77 (58), 74 (100),65(18.26);*Anal.*Calcd for $C_{22}H_{18}N_2O$ (326.39): C, 80.96; H, 5.56; N, 8.58. Found C, 80.73; H, 5.44; N, 8.36%.

2-(4-chlorobenzyl)-3-phenylquinoxaline(3c): Yellow crystals (EtOH), m.p 128-130 °C; IR (KBr) *v*: 3054, 3035 (C–H_{arom}), 1560 (C=N), 698, 764 δ_{5H}; ^{1}H-NMR (DMSO-d_6) *δ*: 4.36 (s, 2H, CH_2), 6.93 (d, 2H, *J* = 8.8 Hz), 7.20 (d, 2H, *J* = 8.8 Hz), 7.47 -7.55 (m, 5H), 7.80 – 7.84 (m, 2H), 8.04 – 8.08 (m, 2H);^{13}C-NMR(DMSO-d_6) *δ*: 41.34, 128.62, 128.73, 128.87, 129.27, 129.38, 130.34, 130.65, 131.05, 131.32, 137.61, 138.85, 140.77, 141.04, 154.45, 155.31; MS(EI) (70 eV) *m/z* (%):330 ($M^{+\cdot}$, 88), 331 ($M^{+\cdot}$+1, 48), 332 ($M^{+\cdot}$+2, 29), 333 ($M^{+\cdot}$+3, 6), 329 ($M^{+\cdot}$-1, 100), 294 (11), 293 (11), 253 (17), 127(11.47),125(31.05),90(6.08)102 (23), 88 (21), 77 (38), 65(2.01); *Anal.*Calcd for $C_{21}H_{15}ClN_2$ (330.81): C, 76.24; H, 4.57; N, 8.47. Found C, 76.35; H, 4.39; N, 8.23 %.

2-benzyl-3-(naphthalen-2-yl)quinoxaline(3d): Colorless crystals (light petroleum 40/60 °C), m.p 140-142 °C; IR (KBr) *v*: 3077, 3055 (C–H_{arom}), 1598 (C=N); ^{1}H-NMR (DMSO-d_6) *δ*: 4.47 (s, 2H, CH_2), 6.94 (d, 2H, *J* = 6.3 Hz), 7.12 – 7.14 (m, 3H), 7.58 – 7.64 (m, 3H), 7.71 (d, 1H, *J* = 9.0 Hz), 7.85 -8.14 (m, 7H); ^{13}C-NMR(DMSO-d_6) *δ*: 41.60, 126.77, 127.79, 128.44, 128.79, 130.12 132.34, 132.68, 135.88, 138.27, 140.30, 140.61, 154.41, 154.76; MS(EI) (70 eV) *m/z* (%):346 (M+·, 100), 322 (3), 269 (17), 255 (8), 228 (17), 165 (14), 153 (30), 127 (27), 91 (19), 77 (7),65(51);*Anal.*Calcd for $C_{25}H_{18}N_2$ (346.42): C, 86.68; H, 5.24; N, 8.09. Found C, 86.59; H, 5.02; N, 7.73 %.

2-(4-methoxybenzyl)-3-(naphthalen-2-yl) quinoxaline (3e): Green crystals (light petroleum 60/80 °C), m.p 68 -70 °C; IR (KBr) *v*: 3051 (C–H_{arom}), 2922, 2852 (C–H_{alkyl}), 1558 (C=N), 814 δ_{2H}; ^{1}H-NMR ($CDCl_3$) *δ*: 3.84 (s, 3H, OCH_3), 4.73 (s, 2H, CH_2), 6.69 (d, 2H, *J* = 8.7 Hz), 6.92 (d, 1H, *J* = 9.0 Hz), 6.96

(d, 2H, *J* = 8.7 Hz), 7.20 – 7.23 (m, 2H), 7.52 – 7.59 (m, 3H), 7.73 -7.78 (m, 2H), 7.92 (d, 1H, *J* = 8.4 Hz), 7.97 (d, 1H, *J* = 8.4 Hz), 8.13 – 8.19 (m, 1H); ^{13}C-NMR($CDCl_3$) *δ*: 46.11, 55.88, 113.87, 114.53, 122.64, 122.75, 126.37, 128.16, 129.41, 129.69, 130.01, 137.89, 140.22, .152.16; MS(EI) (70 eV) *m/z* (%): 376 (M+·, 14), 377 (M+· + 1, 3), 361 (4), 297 (2), 268 (7), 256 (4), 244 (3), 224 (100), 209 (50), 181 (57), 127 (34), 121(38),91(22.85),90 (25.17),77 (42),65(17.38) ;*Anal.*Calcd for $C_{26}H_{20}N_2O$ (376.45): C, 82.95; H, 5.35; N, 7.44. Found C, 82.88; H, 5.16; N, 7.30 %.

4-(naphthalen-2-yl)-2-phenyl-2,3-dihydro-1H-benzo [b] [1,4] diazepin-3-ol(4a): Colorless crystals (light petroleum 60/80 ^{o}C), m.p 84 - 86 °C; IR (KBr) *v*: 3385 (OH), 3286, 3188 (NH), 3055, 3025 (C–H_{arom}), 1631 (C=N), 708, 750 δ_{5H}; ^{1}H-NMR (DMSO-d_6) *δ*: 5.49 (d, 1H, J = 12.6 Hz), 5.53 (d, 1H, J = 11.1 Hz), 6.47 (br.s, 1H, OH excheangeable), 6.63 (br.s, 1H, NH excheangeable), 6.94 – 7.58 (m, 7H), 7.54 -7.72 (m, 3H), 7.88 -7.96 (m, 5H), 8.29 (m, 1H); ^{13}C-NMR(DMSO-d_6) *δ*: 83.14, 89.42, 123.72, 125.75, 127.28, 127.70, 128.40, 128.78, 132.60, 133.39, 138.66, 157.64; MS (EI) (70 eV) *m/z* (%): 363 (M+·-H, 0.1), 346 ($M^{+\cdot}$-H_2O, 100), 332 (14), 267 (25), 255 (11), 228 (21), 192 (7), 165 (16), 153 (45), 127 (45), 91 (55), 77 (22), 65 (20); *Anal.*Calcd for $C_{25}H_{20}N_2O$ (364.44): C, 82.39; H, 5.53; N, 7.69. Found C, 82.46 ; H, 5.31; N, 7.58%.

2-(4-methoxyphenyl)-4-(naphthalen-2-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-3-ol (4b): Yellow crystals (light petroleum 60/80 ^{o}C/benzene mixture), m.p> 300 °C; IR (KBr) *v*: 3420 (OH), 3329, 3180 (NH), 3058 (C–H_{arom}), 2952 (C–H_{alkyl}), 1651 (C=N), , 831 δ_{2H}; ^{1}H-NMR (DMSO-d_6) *δ*: 3.78 (s, 3H, OCH_3), 4.12 (m, 1H), 4.96 (m, 1H), 6.76 (br.s, 1H, OH excheangeable), 6.99 (d, 1H, *J* = 9.0 Hz), 7.40 – 7.45 (m, 3H), 7.72 (d, 2H, *J* = 8.7 Hz), 7.82 -7.90 (m, 3H), 7.99 (d, 2H, *J* = 7.2 Hz), 8.11 (d, 1H, *J* = 7.8 Hz), 8.31 (m, 2H), 8.55 (br.s, 1H, NH exchangeable), 8.80 (m, 1H);MS (EI) (70 eV) *m/z* (%): 377 ($M^{+\cdot}$-OH, 1), 341 (10), 311 (9), 283 (7), 260 (11), 193 (13), 167 (27), 121 (49), 96 (55), 93(26), 77 (6), 41 (100); *Anal.*Calcd for $C_{26}H_{22}N_2O_2$ (394.47): C, 79.16; H, 5.62; N, 7.10. Found C, 78.82; H,5.47, N, 6.79.

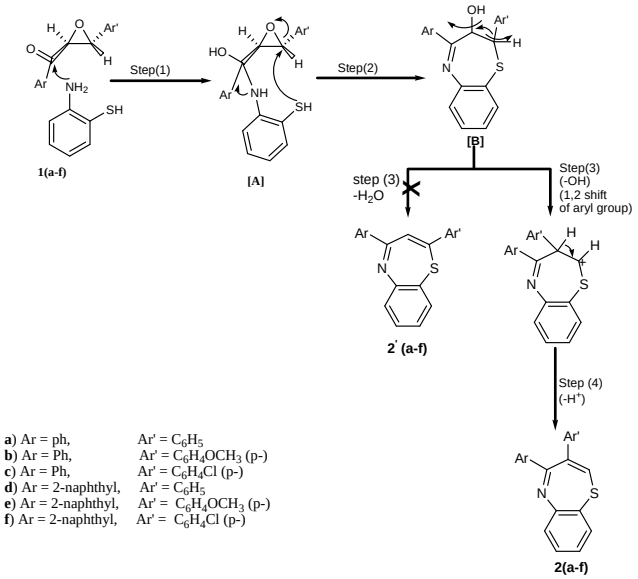
Assessment of the antimicrobial activity using the agar well diffusion technique

The chemically synthesized compounds were screened for their antibacterial and antifungal activities using the agar well diffusion technique (Naz*et al*., 2010)· The microorganisms (reference and clinical isolates) used include *Escherichia coli* (ATCC-25922) and *K. pneumonia*, gram-positive *S. epidermidis* and *S. aureus* (ATCC-25923) and Fungi *C. albicans* (ATCC- 10231) and *A. flavus* For the antibacterial assay, a standard inoculum (10 ^{5} CFU/ml) was distributed on the surface of the agar plates using a sterile glass spreader, whereas for the antifungal assay a loopful of a particular fungal isolate was transferred to 3 ml sterile saline to get a suspension of the corresponding species; 0.1 ml of the spore suspension was distributed on the surface of sterile Sabouraud dextrose agar plates. Six millimeter diameter wells were punched in the agar media and filled with 100 µL of the tested chemical compound (500 µg/ml in DMSO) which is previously sterilized through 0.45 sterile membrane filters. The plates were kept at room temperature for 1-2 hrs.then incubated at 37°C for 24 h for bacteria and at 30°C for 4 days for fungi. Commercial antibiotic discs were used as positive reference standard to determine the sensitivity of the strains(Kandil*et al*., 2011).

Determination of the minimum inhibitory concentration (MIC) of the chemical compounds: Compounds inhibiting the growth of the above microorganisms were tested for their MIC by the broth dilution method strains(Volgas*et al*., 2007).The nutrient broth and the yeast extract broth media containing 1 ml of the serial dilutions of the tested compounds were inoculated with the microbial strains; the bacterial cultures were incubated at 37 ^{o}C for 24 hrs.whereas the fungal ones were incubated at 30 ^{o}C for 48 hrs. The lowest concentration required to arrest the microbial growth was regarded as the MIC of the tested compounds.

RESULTS AND DISCUSSION

In this study we use the solvent free mechanochemical green synthesis to afford 3, 4-disubstituted benzo[b][1,4]thiadiazepines2a-fvia grinding and conventional techniques. The reaction probably takes place according to the following proposedmechanism (scheme 1).



Scheme 1

The above mechanism shows that o-aminothiopehenol reacts with epoxy ketones in a [4+3] hetero annulation reaction and behaves as bis-nucleophilic reagent started attack on the carbonyl carbon of epoxy ketone 1 to give an open chain non isolable intermediate [A] which undergoes cyclization reaction via the nucleophilic attack of the SH group on the β-C atom ofoxirane ring to give cyclic intermediate [B]which either undergoes dehydration to 2,4-diaryl benzo[b] 1,4 thiazepines2*a-for undergoes 1,2-shift of the aryl group from

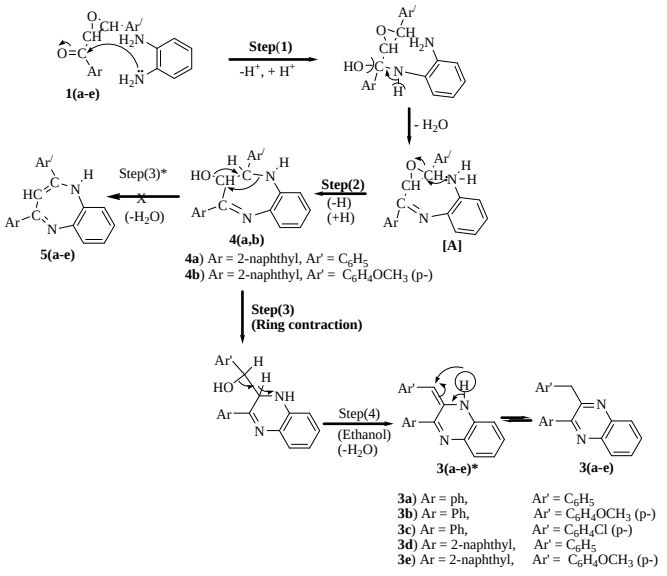
C-2 to C-3 with dehydration to givethe isomeric 3,4-diaryl benzo[b] 1,4 thiazepines2a-f.

The structures of **2a-f** were elucidated from;

- M.p. and mixed m.p.and comparison of their IR, spectra with authenticsample excludes the possibility of the isomeric 2, 4- diphenylbenzo[b] 1, 4-thiazepines2*a (Ried and Koenig, 1972).
- Theirmicro analytical and spectral data. Thus their IR spectra showed absorption frequencies correlated with C=N groups. Their ^{1}HNMR revealed their aromatic protons at *δ*: 6.87-8.67 ppm in addition toolefinic protons at *δ*: 3.82-4.33 ppm. Mass spectra showed molecular ions and signals at m/z 44 and/or 45 corresponding to C=S, HC=S, respectively, which excludes location of aryl groupsatposition 2 of thiazepines andhence excludesthe isomeric 2, 4-diaryl-benzo[b] 1,4-thiazepines

2*a-e

Similarly, we use the solvent free mechanochemical green synthesis to synthesize quinoxaline derivative **3a**, and 2, 3-dihydro-1H-benzo[b] [1, 4] diazepin-3-ol derivatives **4a, b**, respectively. However, quinazoline derivatives **3a-e**and 1[H]benzo[b] [1, 4 diazepin-3-ol derivatives **4a, b**were synthesized under conventional methods. The reaction probably goes via the following mechanism (scheme-2)



Scheme 2

The above scheme shows that the reaction probably goes via four step mechanism based on o-phenylenediamine as bis-nucleophilic reagent started attack on the carbonyl carbon of 1a [step-1] to give an open chain non isolable intermediate [A] which undergoes cyclization reaction via nucleophilic attack of the NH2 groupon the β-carbon atom of oxirane ring [step-2] to give an intermediate 4a,b [non isolable in case of refluxing ethanol]which either undergoes dehydration to give 3[H]benzo[b]1,4-diazepines 5a-d or undergoes ring contraction to give intermediate [step-3] followed by dehydration [step-4] to give the quinoxalines3a-e.

The reaction stops at step-2to give [IH] benzo[b] 1, 4 diazepine-3-oles 4a, b. if we start with 1b, d in benzene solution and/ or under grinding conditions.The prove of this mechanism comes from refluxing benzo[b] 1, 3-diazepin-2-ol derivatives 4a, b in ethanol to give quinoxaline derivatives 3d, e. The structure of the synthesized compounds 3-5 was proved from;

1) m.p. and mixed m.p. and comparison of their IR, spectra with authenticsamples excludes the possibility of the isomeric 2,4-diaryl benzo[b]1,4-diazepines 5a,b Sanjay *et al*., (2007).
2) Their spectral properties and micro analytical data correspond very well with their proposed structures (see Experimental). Their IR spectra showed absorption bands of C=N groups for compounds 3 and 4, The ^{1}HNMR spectra of the synthesized compounds showedsignals due to their aromatic protons. Compounds 3a-e revealed singlet signals for the benzyl protons in the range 4.31 -4.73 ppm and coupled signals for methine protons for compounds 4a,b in the range 4.12 -5.54 ppm, beside OH and NH protons that exchangeable with D_2O shake in down field region. The ^{13}CNMR spectra of compounds 3c-e,4a showed carbon chemical shift signals in agreement with their proposed structures. MS (EI) of 4a showed signals corresponding to M^+, and ,M^+- H2O(100%), also 4b showed signals corresponding to M^+, and M^+- OH which indicates the presence of OH group in the diazepines 4a,b. The appearance of ion peaks at m/z 90 due to cyclotropyliumionsindicates the existence of Ar CH2-side chain and excludes the possibility of the expected 3[H] Benzo[b] 1, 4-diazepine structure for 5a-e.

We initially compared our mechanochemical (grinding) approach for the synthesis ofbenzo[b] [1, 4] thiadiazepines2a-f, and1H-benzo[b] [1, 4] diazepine-3-olderivatives4a-bwith a conventional approach in terms of their atom economy. The atom economy (AE) Sheldon, (2000) relates to the efficiency with which the atoms in the starting materials of a reaction are incorporated into the desired product (i.e., how efficiently a particular reaction makes use of the reactant atoms). However, the AE values were the same for the mechanochemical and conventional procedures because we used two alternative reaction conditions to obtain the same target compounds.

We consequently introduced yield economy (YE) as a new metric to assess of the conversion efficiency of these two different approaches. The YE basically measures how much yield (%) of the desired product is obtained over a certain reaction time (i.e., yield (%) / reaction time (min)). A higher YE are therefore indicative of a higher level of conversion, a much more efficient chemical process and more economical reaction. The YE of a reaction can be calculated using the following equation.

YE = Yield (%) / Reaction time (min).

YE were used in this study to provide a decisive assessment of the yields obtained under the mechanochemical and conventional conditions (Table 1). Assessing a chemical reaction based entirely on its percentage yield can be misleading.

Table 1. Physical data of the synthesized compounds 2-4 under thermal and grinding procedures

Conv..	(Thermal)	Method		Grinding	Method			
No	Time(min)	Yield (%)	m.p^{0}C	Time(min)	Yield (%)	m.p^{0}C	AE	YE (Conv./G)
2a	120	92	220-2	4	77	220-2	89.68	0.76/19.25
2b	120	74	67/0	5	68	64-6	90.54	0.61/13.6
2c	120	50	216-8	5	86	214-6	87.02	0.41/17.2
2d	90	86	144-6	6	90	144-5	91.01	0.95/15.0
2e	120	59	150-2	5	77	150-2	91.64	0.49/15.4
2f	105	78	150-2	5	89	150-2	91.73	0.74/17.8
3a	180	73	82-4	12	87	78-0	89.16	0.40/7.25
3b	150	81	110-2	-	-	-	90.05	-
3c	180	73	128-0	-	-	-	90.17	-
3d	120	83	140-2	-	-	-	97.45	-
3e	300	93	68-0	-	-	-	91.26	-
4a	840	67	84-6	10	80	86-7	95.29	0.07/8.0
4b	900	84	300>	10	83	300>	95.63	0.09/7.54

G. = Grinding; Conv. = convetional; (AE) = atom economy,(YE) = yield economy

Table 2. Antimicrobial Activity of chemically synthesized Compounds

Inhibition zone diameter (mm/mg sample)						
No	E.coli	K.pneumoniai	S.epidermidis	S.aureus	C.albicans	A.flavus
2a	35	36	35	33	28	25
2b	34	31	34	35	26	24
2c	36	34	35	34	27	25
2d	30	29	31	31	26	25
2e	34	35	37	36	27	28
2f	33	33	35	35	28	27
3a	34	32	33	32	31	29
3c	35	34	34	36	30	28
3d	31	30	29	30	26	24
4b	36	33	35	34	28	25
S	39	38	37	37	N	N
F	N	N	N	N	32	30

S = Sulfamethoxazol 10µg/ml **(**antibacterial agent**) ; F**= Fluconazol 10µg/ml (antifungal agent).
The concentration of all synthesized compounds were (500µg/mL in DMSO); 0.0 = no inhibition. N= not tested.

Table 3. Minimum inhibition concentration (MIC) of the chemically synthesized compounds

	MIC values (µg/ml)					
No	E.coli	K.pneumoniai	S.epidermidis	S.aureus	C.albicans	A.flavus
2a	15	10	10	10	10	15
2b	5	15	15	15	15	20
2c	5	5	5	5	10	10
2d	15	15	15	15	20	20
2e	5	10	5	10	15	15
2f	10	10	10	10	10	15
3a	10	15	10	10	15	15
3c	5	10	5	5	5	15
3d	15	15	15	15	20	20
4b	5	10	10	10	15	10
S	5	5	5	5	N	N
F	N	N	N	N	5	5

For example, the yields for compound **2a** under the mechanochemical and conventional conditions were 77% and 92%, respectively. However, the YE values for the mechanochemical and conventional conditions were 19.55 and 0.76, respectively, representing a much bigger difference and highlighting the superiority of the former approach. Similar trends were observed for all of the other compounds in the series. The YE values of **2-4** are listed in Table 1.

General conditions for the mechanochemical procedure:

epoxy ketones (**1a-f**) (3mmol), o-aminothiophenol (3 mmol) / o-phenylenediamine (3mmol), a catalytic amount of silica gel(in case of o-phenylenediamine) and few drops of water in a pestle and mortar at room temperature for 4–12 min.

General conditions for the conventional procedure:

epoxy ketones (**1a-f**) (3mmol), o-aminothiophenol (3 mmol) / o-phenylenediamine (3mmol) were refluxed in absolute ethanol (30 mL) or dry Benzene for 1.5 - 2 h (monitored by TLC).

Screening of the antimicrobial activity of the chemically synthesized compounds

The possible antimicrobial activities of the chemically synthesized compounds 2a-f, 3a, 3c, 3d and 4b were

investigated against six reference microbial isolates including; gram-negative *Escherichia coli* (ATCC-25922) and *Klebsiella pneumonia*, gram-positive *Staphylococcusepidermidis* and *Staphylococcus aureus* (ATCC-25923) and Fungi *Candida albicans* (ATCC- 10231) and *Aspergillusflavus* as shown in the results of Table 2. The tested compounds 2a-f, 3a, 3c, 3d and 4b are exhibited high activity against both *Escherichia coli* (ATCC-25922) and *Klebsiella pneumonia* (as examples of gram –negative), *Staphylococcus aureus* (ATCC-25923), and *Staphylococcusepidermidis*, (as example of gram-positive), *Candida albicans* (ATCC- 10231) (pathogenic yeast) and *Aspergillusflavus (*pathogenic mold). The tested compounds were showed zone of inhibition diameters ranged from 30 to 36 mm against *E. coli*, 29 to 36 mm against *K. pneumonia*, 29 to 37 mm against *S. epidermidis* and 31 to 36 mm against *S. aureus* at 500µg/mL of DMSO. In comparison with Fluconazol, the tested compounds were showed zone of inhibition diameters ranged from 26 to 31 mm and 24 to 29 mm against *C.albicans* and *A. flavus* respectively at 500µg/ml of DMSO. Evident MIC values on the entire set of the tested microbial organism were determined for the chemical agent's 2a-f, 3a, 3c, 3d and 4b and the results are summarized in Table 3. The MIC values are ranged from 5 µg to 15 µg in case of all chemically synthesized compounds against all used microbial. Compounds **2c** and **3c** are the most potent

Conclusion

The synthesis of biologically active benzothiazepine, benzodiazepine and quinoxaline derivatives was done under green solvent free grinding and conventional techniques. The key advantages of grinding strategy over conventional approaches include its simple, solvent-free conditions, as well as its facile work-up, high yield economy and environmental friendliness. It is also successful in achieving three of the green chemistry objectives of a solvent free operation, high atom economy and save energy. Thus, combining the features of both economic and environmental advantages.

REFERENCES

Abdel Aziem, A. 2015. An efficient and simple synthesis of 2,3-dihydro-1,3,4-thiadiazoles, pyrazoles and coumarins containing benzofuran moiety using both conventional and grinding methods. *Int. J Pharm. Sci.,* 7(1) 61-68.

Abdel Hamid, A.M. 2015 Rapid synthesis of 1,6-naphthyridines by grindstone chemistry Env. Chem. Lett., 13,125-129.

Andreichikov Yu, S., Pitirimova, S.G., Tendryakoya, S.P., Saraeya, R.F. and P. Tokmakova T N. 1978. *J. Org. Chim.*, 14. 169, Chem. Abstr. 1978, 89, 59627.

Andreichikov Yu, S., Pitirimova, S.G., Tendryakoya, S.P., Saraeya, R.F. and PTokmakova, T.N. 1978, Zh. Org. Khim.,14,156, *Chem. Abstr.* 1978, 89, 59627.

Bariwal, J.B., Upadhyay, K.D., Manvar, A.T., *et al.* 2008. 1,5-Benzothiazepine a versatile pharmacophore (review), *European Journal of Medicinal Chemistry*, 43, no. 11, 2279– 2290.

Barltrop, J. A., Richards, C. G., Russel, D. M. and Ryback, G. J. 1959. Seven membered heterocyclic compounds. Part I. 1:5-benzodiazepines and derivatives of 3:6-diaza-4:5-benzotropone, *J. Chem. Soc.*, 1132.

Bartsch, H. and Erker, T.1988. Studies on the chemistry of O, N- and S, N- containing Heterocycles. Synthesis of 1,5-benzothiazepines with potential CNS activity, *J. Heterocycl. Chem.* 1, 25, 1151–1154.

Benzeid, H., Chammache, M., Essassi, E M., Imelouane, B., Ohmani, F., Charof, R. and Khedid, K. 2008, Antibacterial Activity of novel Pyrrolobenzodiazepine, *Int J Agric Biol*, 10, NO 1, 77-80.

Chate, A.V., Joshi, R.S., Badadhe, P.V., Dabhade, S.K. and Gill, C.H. 2011. Efficient ultrasound enhance novel series of 2-((E)-2,3-Dihydro-2-(4-(phenylthio)phenyl)-benzo[b][1, 4]thiazepin-4-yl)phenol as an antimicrobial agent, Bulletin of the Korean Chemical Society, 32, no. 11, 3887–3892.

Douglas K H., Michael R B., Steven J B., Ronald B G.and Patel M V.1996, Oxazolidinone Antimicrobials Containing Substituted Diazine Moietifs, US Appl, 5, 547, 950.

Elfi Susanti V H., Matsjeh S., Mustofa, and Wahyuningsih T. D.2014, Improved Synthesis of 2',6'-Dihydroxy-3,4-Dimethoxy chalcone by Grinding Technique to synthesize 5-hydroxy-3',4'-dimethoxy flavone, *Indo. J. Chem.,* 14(2), 174 – 178.

Fielding, S. and Lal, H. Eds.1979. Pre.clinical neuropsy chopharmacological testing procedures for anxiolytic, Anxiolyrics; Futurea: New York.

Haefely, W., Parnham, M.J. Bruinvals, J., Eds, 1983. In Discooeries in Pharmacology; Elsevier: Amsterdam, 1, 239-306.

Hemdan, M.M. 2010. Synthesis and Antimicrobial Activities of Some Heterocyclic Systems from 2-Furoyl Isothiocyanate. Phosphorus, Sulfur Silicon, 185, 620.

Hemdan, M.M. and Abd El-Mawgoude, H.K. 2015. Synthesis and Antimicrobial Evaluation of Thieno[2,3-d]-pyrimidine, Thieno[2′,3′:4,5]pyrimido[1,2-a][1,3,5]triazine, Thieno[2,3-d]-1,3-thiazine and 1,2,4-Triazole Systems, *Chem. Pharm. Bull.* 63, 812–818.

Hemdan, M.M. and Abd El-Mawgoude, H.K. 2015. Uses of 1-(3-Cyano-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)-3-dodecanoylthiourea as a Building Block in the Synthesis of Fused Pyrimidine and Thiazine Systems, *Chem. Pharm. Bull.* 63, 450–456.

Hemdan, M.M., Fahmy, A.F. El-Sayed, A.A. 2010. Synthesis and antimicrobial study of 1,2,4-triazole, quinazoline and benzothiazole derivatives from 1-naphthoylisothiocyanate, *J Chem Res.*, 219,no 4.

Kandil, N., Zaki, H., Mohamed, M., Ismaeel, H. and Ahmed, N. 2012. Synthesis,characterization and in vitro antimicrobial evaluation of new compounds incorporating oxindole nucleus. *J. Enz. Inhib. Med. Chem.* 27, Issue 4.

Katritzky, A.R. 2015., Mechano Heterocyclic Chemistry: Grinding and Ball Mills, Advances Heterocyclic Chemistry, 115, 117.

Khairy A.M. El-Bayouki, 2013. Benzo[1,5]thiazepine: Synthesis, Reactions, Spectroscopy, and Applications, *Organic Chemistry International*, 2013, Article ID 210474, 71,2013

Khaskel, A., Gogoi, P., Barman, P. and Bandyopadhyay, B. 2014. A Highly Efficient and Green Method for Synthesis of 3,4-Dihydropyrimidin-2-(1H)-ones by L-Tyrosine as an Organocatalyst, RSA , 67 (4) 35559-35567.

Kumar, A. and Makrandi, J.K. 2011. An iodine-mediated green synthesis of 1,3,4-oxadiazoles under solvent-free conditions using grinding technique. Green Chem. Lett. and Rev., 4(1), 87-89.

Kumar, S. 2014. An improved one-pot and eco-friendly synthesis of aurones under solvent-free conditions, Green Chem. *Lett. and Rev.*, 7(1) 95-97, 2014.

Levai, A. 1986. Synthesis of benzodiazepines (review), Khlmlya Geterotsiklicheskikh Soedinenli, 2, 1443–1452.

Maffrand, J.P. and Eloy, F. 1976, Nouvelles syntheses de thieno [3,2-c] et thieno[2,3-c]pyridines, *J. Heterocyclic Chem.*,13, 1347.

Micheli, F., Degiorgis, F., Feriani, A., Paio, A., Pozzan, A., Zarantonello, P. and Seneci, P. 2001. A Combinatorial Approach to [1,5] Benzothiazepine Derivatives as Potential Antibacterial Agents, *J. Comb. Chem.*, 3(2), 224–228.

Naz, S., Jabeen, S., Ilyas, S., Farkhanda M. F., Aslam F., Ali A., *Pak. J. Bot.* 2010. Antibacterial activity of Curcuma longa varieties against different strains of bacteria.42 (1). 455-462.

Nikpassand, M., Fekri, L. Z., Changiz, N. and Imani, F. 2014. Synthesis of New 3-Cyanocoumarins with C-6 Azo Function Using Ultra- sound and Grinding Techniques in the Presence of Nano Fe3O4, Lett. *Org. Chem.*, 11, 29-34.

Palimkar, S.S, Lahotiand, R.J. and Srinivasan, K.V. 2007, A Novel one-pot three component synthesis of 2,4-disubstituted[b][1,4] diazepine in water, Green Chem,9,146-152.

Pevarello, P., Amici, R., Colombo, M. and Varasi, M. 1993. Nitrile oxide cycloaddition of non-activated alkynes: a novel approach to the synthesis of neuroactive isoxazoles. *J. Chem. Soc. Perkin Trans.* 1 , 18, 2151–2152.

Ried, W. and Koenig, E. 1972. Reaktionen von acetlenketonen mit nucleophilen Agenzien von Typ des o-phenylene diamines,o-Amino-thiophenols und N1-disubstituierten Hydrazins, *Justus Liebigs Ann. Chem.*, 24, 755.

Sanjay S. Palimkar, Rajgopal J. Lahoti and Kumar V. Srinivasan, 2007. A novel one-pot three-component synthesis of 2,4-disubstituted-3 H-benzo[b][1,4]diazepines in water, Green Chem, 9, 146-152

Sharma, S., Jain, R. and Chawla, C. 2013. Synthesis and Biological Activities of Some Benzodiazepine Derivatives. *J. Chem. Pharma, Res.*, 5(7), 46-55.

Sheldon R. A. 2000. Atom efficiency and catalysis in organic synthesis. Pure Appl. Chem., 72(7), 1233–1246.

Talukdar, D. and Thakur, A. J. 2013. A green synthesis of symmetrical bis (indol-3-yl) methanes using phosphate-impregnated titania catalyst under solvent free grinding conditions. Green Chem. *Lett. and Rev.*, 6 (1)55-61.

Volgas, C., De Souza, S., Samania, E., Jr A .2007. Screening methods to determine antibacterial activity of natural product. *Braz. J. Microb.*, 38 : 369-380.

Wander, A. 1968, Swiss 422, 793; chem. Abstr. 68, 105265.

Wander, A., 1996, Netherlands Appl 293, 201, Chem. Abstr. 64, 8220e.

Wang, L., Zhang, P., Zhang, X., Zhang, Y., Li, Y. and Wang, Y. 2009, Synthesis and biological evaluation of a novel series of 1,5-benzothiazepine derivatives as potential antimicrobial agents, *European Journal of Medicinal European Journal of Medicinal Chemistry*, 44, no.7,2815–2821.

Zangade, S.B., Mokle, S.S., Shinde, A.T. and Vibhute, Y. B. 2013. An atom efficient, green synthesis of 2-pyrazoline derivatives under solvent-free conditions using grinding technique. Green Chem. *Lett. and Rev.*, 6(2), 123-127.

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