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Research Article

LIBR CATALYZED SYNTHESIS OF DIAZEPINE DERIVATIVES VIA MICROWAVE IRRADIATIONS

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Abstract

o-phenylenediamine undergo condensation with ethylacetocaetate in the presence of 10 mol % LiBr under solvent free conditions and microwave exposure to afford a new method of synthesis of benzodiazepine derivatives.In comparison to conventional synthesis involving tedious workup, excessive use of solvent and extra labour for separation and purification of compounds, the present method indicates operational simplicity, shorter reaction time and higher yields which can prove this procedure as a useful alternative for the synthesis of heterocycles. Some of the synthesized compounds were tested for their biological activity.

Keywords: *o*-Phenylenediamine, Diazepines, LiBr, Solvent free condition, Microwave exposure.

Introduction

Compounds containing the benzodiazepine skeleton have attracted the particular attention of medicinal chemist (Hagsan 2000) because this ring system lies at the heart of a wide array of constitutionally diverse models exhibiting profound chemotherapeutic properties (Kumar, 2007). These compounds are widely used as anticonvulsant (sarro et al., 1999 and Fukinaga, 1998) antianxiety (Nannapaneni et al. 2010), analgesic (Kavali et al., 2000), sedative (Wiard et al., 2007), anti-depressive (Singh et al., 2010) hypnotic agents (Sneyd et al., 2010), anti oxidant (Honnaiah et al., 2010) as well as anti- inflammatory agents (Fruscella et al., 2001). Other than their biological importance, benzodiazepine derivatives are also commercially used as light sensitive compound (Rodriguez et al., 2004). Moreover, benzodiazepine derivatives are valuable synthons for the preparation of other fused ring compounds (Masevicius et al., 2007 and Lakatosh et al., 2006).

Research in this area is very active and is directed towards the synthesis of compounds with enhanced pharmacological activity. Generally, these compounds are synthesized by the condensation of *o*-phenylenediamine with α, β-unsaturated carbonyl compounds (Claramunt et al, 2006) β-haloketones or ketones (Kumar et al., 2010). A variety of catalysts, such as BF_3-etherate, $InCl_3$ (Yadav et al., 2005), $NaBH_4$, polyphosphoric acid, SiO_2, MgO,/$POCl_3$, $Yb(OTf)_3$ (Curini et al., 2001), $Sc(OTf)_3$ (Surya et al., 2005), Al_2O_3/P_2O_5 and AcOH have been utilized for the condensation reaction. However, all of these methods have problems such as drastic reaction conditions and several side reactions. Compared to other conventional Lewis acid LiBr (Mojtahedi et al., 2007, **Sun et al., 2010** and Chakraborti et al., 2004) is a flexible, mild, recyclable, efficient and inexpensive reagent, which can potentially replace solvents and conventional corrosive acids in

many of their applications (**Shrivastava et al., 2008, and Naik et al., 2004)**. LiBr catalyzed solvent free reactions are growing interest because of their ease of execution and work – up, mild reaction conditions, high rate of reactions, high yields, lack of solvents and low cost in comparison with other catalysts. As our efforts to explore the utility of LiBr catalyzed reactions we report here a new method for the synthesis of benzodiazepine derivatives with ethylacetoacetate.

It was found that LiBr under solvent free conditions was capable of producing high yield of benzodiazepine derivatives by the condensation of *o*-phenylenediamine with ethylacetoacetate under microwave exposure. Microwave Assisted Organic Synthesis strategies offer feasible solutions as their benefits are manifold: it frequently leads to dramatically reduction in reaction time, higher yields, cleaner reaction profiles and above all, eco-friendlines (Ma et al., 2010 and Epane et al., 2010). We are interested in the synthesis of pyrazole, pyrimidine and oxoazole derivatives containing benzodiazepine moiety due to the importance of this class of compound in the medicinal chemistry (Dumoulin et al., 2010 and Rao et al., 2010). Thus the coupling of this MW enhanced synthesis with solvent free conditions and LiBr is expected to afford an environmentally benign synthesis of some biological active compounds.

Materials and Methods

All reactions were carried out in a domestic oven (Kenstar, Model No. OM-26 EGO). Melting points are uncorrected and determined in open capillaries. Reactions were monitored by thin layer chromatography using silica gel- G as adsorbent using ethyl acetate: n-hexane (7: 3) as eluent and products were detected by iodine vapours. IR spectra (KBr pellets) were recorded on Perkin- Elmer 1800 (FTIR) spectrometer. ^{1}H NMR spectra (DMSO-d_6) were taken on Bruker DRX spectrometer (300 MHz FT NMR) using TMS as internal standard and chemical shift were expressed in δ. Mass spectra were taken on Jeol SX- 102 / PA-600 (EI) spectrometer and elemental analysis was carried out on C, H, N analyzer (Elemental Vario Alba 1180). The results were found to be in good agreement with the calculated values (± 0.2%). The starting compounds were prepared according to reported method.

Microwave induced synthesis of 4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (1):

o- Phenylenediamine (0.01 mol) and ethyl acetoacetate (0.01 mol) and LiBr (10 mol %) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 60% power for 3-3.00 min. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and then stirred foe 5 min. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compound **(1)**.

IR (KBr cm^{-1}) : 3027 (C-H str., Ar-H), 2412 (CH_2 str.), 2911 (CH_3 str.), 1680 (C=O cyclic amide str.), 3295 (NH str.), 1625 (C=N str.) and 1597 (C=C str.).

^{1}H NMR: δ ppm: 4.26 (2H, s, CH_2), 2.63 (3H, s, CH_3), 5.41 (1H, s, NH), and 7.25 – 8.50 (4H, m, Ar-H).

Conventional synthesis 4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (1): To a solution of *o*-phenylenediamine (0.01mol) in ethanol (30 ml) a few drops of piperidine and ethylacetoacetate (0.01 mol) were added. The mixture was heated under reflux for 3-4 h and then acetic acid (1ml) was added. Refluxing was continued for another 3-4 h. About half of the solvent was evaporated and the oily residue was allowed to stand at room temperature overnight. A solid was separated out, which is crystallized from ethanol to yield compound **(1)**.

Microwave induced synthesis of 4-methyl-3-(phenylmethylidene)-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (2a):

Compound **(1)** (0.01 mol) and substituted aromatic aldehydes (0.01 mol) and LiBr (10 mol %) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 60% power for 5 min. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 ml of water was then added to reaction mixture and then stirred foe 5 min. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compound **(2a).**

IR (KBr cm^{-1}) : 3034 (C-H str., Ar-H), 1665 (C=O cyclic amide str.), 2914 (CH_3 str.), 3287 (NH str.), 1632 (C=N str.) and 1598 (C=C str.), 3070 (C-H str., Ar-CH Str).
^{1}H NMR: δ ppm: 2.61 (3H, s, CH_3), 5.45 (1H, s, NH), and 7.20 – 8.34 (9H, m, Ar-H), 4.68 (1H, s, Ar-CH). Compounds **(2b-e)** were prepared similarly by this method

3-[(4-chlorophenyl)methylidene]-4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (2b):

IR (KBr cm^{-1}) : 3036 (C-H str., Ar-H), 1669 (C=O cyclic amide str.), 3280 (NH str.), 2915 (CH_3 str.), 1622 (C=N str.) and 1597 (C=C str.), 834 (Ar-Cl str.), 3075 (C-H str., Ar-CH Str).
^{1}H NMR: δ ppm: 2.64 (3H, s, CH_3), 5.64 (1H, s, NH), and 7.23 – 8.43 (8H, m, Ar-H), 4.64 (1H, s, Ar-CH).

3-[(4-methoxyphenyl)methylidene]-4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (2c):

IR (KBr cm^{-1}) : 3034 (C-H str., Ar-H), 1662 (C=O cyclic amide str.), 2910 (CH_3 str.), 3284 (NH str.), 1628 (C=N str.) and 1592 (C=C str.), 1109 (C-O-CH_3), 3071 (C-H str., Ar-CH Str).
^{1}H NMR: δ ppm: 2.65 (3H, s, CH_3), 5.50 (1H, s, NH), and 7.32– 8.36 (8H, m, Ar-H), 4. 46 (1H, s, Ar-CH), 3.33 (3H, s, -OCH_3).

4-methyl-3-[(4-nitrophenyl)methylidene]-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (2d):

IR (KBr cm^{-1}) : 3038 (C-H str., Ar-H), 1668 (C=O cyclic amide str.), 2913 (CH_3 str.), 3281 (NH str.), 1625 (C=N str.) and 1579 (C=C str.), 1550, 1410 (Ar-NO_2 str.), 3073 (C-H str., Ar-CH Str).
^{1}H NMR: δ ppm: 2.69 (3H, s, CH_3), 5.52 (1H, s, NH), and 7.45– 8.59 (8H, m, Ar-H), 4.78 (1H, s, Ar-CH).

3-[(4-hydroxyphenyl)methylidene]-4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (2e):

IR (KBr cm^{-1}) : 3035 (C-H str., Ar-H), 16630 (C=O cyclic amide str.), 2905 (CH_3 str.), 3291 (NH str.), 1627 (C=N str.) and 1575 (C=C str.), 3582 (O-H str.), 3072 (C-H str., Ar-CH Str).
^{1}H NMR: δ ppm: 2.63 (3H, s, CH_3), 5.48 (1H, s, NH), and 7.34– 8.46 (8H, m, Ar-H),3.63 (1H, s, OH), 4.71 (1H, s, Ar-CH).

Conventional synthesis of 4-methyl-3-(phenylmethylidene)-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (2a):

To a mixture of compound (**1)** (0.01 mol) and substituted aromatic aldehydes (0.01 mol) in absolute ethanol, a solution of sodium acetate (0.012 mol) in acetic acid (5 mL) was added. The reaction mixture was refluxed on a heating mantle for 12 h. The reaction mixture was concentrated, kept overnight and poured into ice water. The resulting solid was filtered, washed with water and recrystallized from ethanol to yield compound **(2a).** Compounds **(2b-e)** were prepared similarly by this method.

Microwave induced synthesis of 4-methyl-3-phenyl-3a,10-dihydro-3*H*-isoxazolo[3,4-*b*][1,5] benzodiazepine (3a):

Compound **(2a)** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) and LiBr (10 mol %) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 60% power for 8 min. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and then stirred foe 5 min. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compound **(3a)**.

IR (KBr cm^{-1}) : 3045 (C-H str., Ar-H), 3285 (NH str.), 2915 (CH_3 str.), 1250 (C-N str.) 1630 (C=N str.), 1601 (C=C str.), 2801, 2911 (-CH str.), 1091 (C-O str.) and 943 (N-O str.).
^{1}H NMR: δ ppm: 2.58 (3H, s, CH_3), 5.01 (1H, s, NH), and 7.02 – 8.14 (9H, m, Ar-H), 5.25 (1H, d, CH-) and 4.14 (1H, d, Ar-CH isoxazoline ring). Compounds **(3b-e)** were prepared similarly by this method.

3-(4-chlorophenyl)-4-methyl-3a,10-dihydro-3*H*-isoxazolo[3,4-*b*][1,5]benzodiazepine (3b)

IR (KBr cm^{-1}) : 3084 (C-H str., Ar-H), 3280 (NH str.), 2921 (CH_3 str.), 1253 (C-N str.) 1635 (C=N str.), 1512 (C=C str.), 2842, 2925 (-CH str.), 750 (C-Cl str.), 1083 (C-O str.) and 936 (N-O str.).
^{1}H NMR: δ ppm: 2.58 (3H, s, CH_3), 5.21 (1H, s, NH), and 7.15 – 7.72 (9H, m, Ar-H), 5.20 (1H, d, CH-) and 4.78 (1H, d, Ar-CH isoxazoline ring).

3-(4-methoxyphenyl)-4-methyl-3a,10-dihydro-3*H*-isoxazolo[3,4-*b*][1,5]benzodiazepine(3c):

IR (KBr cm^{-1}) : 3080 (C-H str., Ar-H), 3282 (NH str.), 2925 (CH_3 str.), 1241 (C-N str.) 1628 (C=N str.), 1517 (C=C str.), 2849, 2918 (-CH str.), 1119 (C-O-CH_3), 1080 (C-O str.) and 930 (N-O str.).
^{1}H NMR: δ ppm: 2.52 (3H, s, CH_3), 5.23 (1H, s, NH), 7.61 – 7.03 (9H, m, Ar-H), 3.82 (3H, s, -OCH_3), 5.28 (1H, d, CH-) and 4.81 (1H, d, Ar-CH isoxazoline ring).

4-methyl-3-(4-nitrophenyl)-3a,10-dihydro-3*H*-isoxazolo[3,4-*b*][1,5]benzodiazepine (3d)

IR (KBr cm^{-1}) : 3095 (C-H str., Ar-H), 3289 (NH str.), 2931 (CH_3 str.), 1243 (C-N str.), 1625 (C=N str.), 1509 (C=C str.), 2836, 2912 (-CH str.), 1558, 1415 (Ar-NO_2 str.) and 1093 (C-O str.), 940 (N-O str.).
^{1}H NMR: δ ppm: 2.62 (3H, s, CH_3), 5.41 (1H, s, NH), 7.13 – 7.96 (9H, m, Ar-H), 5.30 (1H, d, CH-) and 4.83 (1H, d, Ar-CH isoxazoline ring).

4-(4-methyl-3a,10-dihydro-3*H*-isoxazolo[3,4-*b*][1,5]benzodiazepin-3-yl)phenol (3e):

IR (KBr cm^{-1}) : 3087 (C-H str., Ar-**H), 3282 (NH str.), 2921 (CH3 str.), 1284 (C-N str.), 1657** (C=N str.), 1556 (C=C str.), 2836, 2922 (-CH str.), 3585 (O-H str.), 1039 (C-O str.) and 956 (N-O str.).
^{1}H NMR: δ ppm: 2.78 (3H, s, CH_3), 5.55 (1H, s, NH), 7.25 – 8.04 (9H, m, Ar-H), 3.72 (1H, s, OH), 5.42 (1H, d, CH-) and 4.86 (1H, d, Ar-CH isoxazoline ring).

Conventional synthesis of 4-methyl-3-phenyl-3a,10-dihydro-3*H*-isoxazolo[3,4-*b*][1,5]benzodiazepine (3a):

A mixture of compound **(2a)** (0.01mol), hydroxylamine hydrochloride (0.01mol) in absolute ethanol, solution of sodium acetate (0.012 mol) in acetic acid (5 ml) was added. Then the mixture was refluxed for 9h. The reaction mixture was cooled to room temperature. The resulting solid was filtered, washed with water and recrystallized from acetic acid to yield compound **(3a)**. Compounds **(3b-e)** were prepared similarly by this method.

Microwave induced synthesis of 5-methyl-4-phenyl-3,11-dihydro-2*H*-pyrimido[4,5-*b*][1,5]benzodiazepin-2-one (4a):

Compound **(2a)** (0.01 mol) and urea (0.01 mol) and LiBr (10 mol %) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 60% power for 7 min. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and then stirred foe 5 min. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compound **(4a)**.

IR (KBr cm^{-1}) : 3028 (C-H str., Ar-H), 3327 (NH_a str.), 3271 (NH_b str.),2924 (CH_3 str.), 1267 (C-N str.), 1628 (C=N str.), 1514 (C=C str.) and 1710, 1685 (C=O str.).
^{1}H NMR: δ ppm: 2.58 (3H, s, CH_3), 6.92 (1H, s, NH_a), 5.30 (1H, s, NH_b) and 7.51 – 7.01 (9H, m, Ar-H). Compounds **(4b-e)** were prepared similarly by this method.

4-(4-chlorophenyl)-5-methyl-3,11-dihydro-2*H*-pyrimido[4,5-*b*][1,5]benzodiazepin-2-one (4b):

IR (KBr cm^{-1}) **:** 3021 (C-H str., Ar-H), 3331 (NH_a str.), 3280 (NH_b str.), 2945 (CH_3 str.), 1237 (C-N str.) 1620 (C=N str.), 1507 (C=C str.), 730 (C-Cl str.) and 1711, 1687 (C=O str.).
^{1}H NMR: δ ppm: 2.85 (3H, s, CH_3), 6.97 (1H, s, NH_a), 5.34 (1H, s, NH_b) and 7.69 – 7.11 (8H, m, Ar-H).

4-(4-methoxyphenyl)-5-methyl-3,11-dihydro-2*H*-pyrimido[4,5-*b*][1,5]benzodiazepin-2-one(4c):

IR (KBr cm^{-1}) **:** 3025 (C-H str., Ar-H), 3324 (NH_a str.), 3279 (NH_b str.),2951(CH_3 str.), 1248 (C-N str.) 1630 (C=N str.), 1503 (C=C str.), 1079 (C-O-CH_3 str.) and 1705, 1681 (C=O str.).
^{1}H NMR: δ ppm: 2.78 (3H, s, CH_3), 6.85 (1H, s, NH_a), 5.41 (1H, s, NH_b), 3.78 (3H, s, -OCH_3) and 7.61 – 7.07 (8H, m, Ar-H).

5-methyl-4-(4-nitrophenyl)-3,11-dihydro-2*H*-pyrimido[4,5-*b*][1,5]benzodiazepin-2-one(4d):

IR (KBr cm^{-1}) **:** 3028 (C-H str., Ar-H), 3341 (NH_a str.), 3277 (NH_b str.),2921(CH_3 str.), 1254 (C-N str.) 1636 (C=N str.), 1506 (C=C str.), 1561, 1426 (Ar-NO_2 str.), and 1706, 1686 (C=O str.).
^{1}H NMR: δ ppm: 2.62 (3H, s, CH_3), 6.92 (1H, s, NH_a), 5.48 (1H, s, NH_b) and 7.01 – 7.43 (8H, m, Ar-H).

4-(4-hydroxyphenyl)-5-methyl-3,11-dihydro-2*H*-pyrimido[4,5-*b*][1,5]benzodiazepin-2-one(4e):

IR (KBr cm^{-1}) **:** 3015 (C-H str., Ar-H), 3327 (NH_a str.), 3275 (NH_b str.),2911 (CH_3 str.), 1234 (C-N str.) 1620 (C=N str.), 1507 (C=C str.), 3572 (O-H str.) and 1710, 1687 (C=O str.).
^{1}H NMR: δ ppm: 2.86 (3H, s, CH_3), 6.87 (1H, s, NH_a), 5.42(1H, s, NH_b), 3.54 (1H, s, OH) and 7.09 – 7.68 (8H, m, Ar-H).

Conventional synthesis of 5-methyl-4-phenyl-3,11-dihydro-2*H*-pyrimido[4,5- *b*][1,5]benzodiazepin-2-one (4a):

A mixture of compound **(2a)** (0.01mol), urea (0.01mol) in absolute ethanol, few drops of Conc. HCl were added and subjected to reflux for 8h. The reaction mixture was cooled to room temperature. The resulting solid was filtered, washed with water and recrystallized from acetic acid to yield compound **(4a).** Compounds **(4b-e)** were prepared similarly by this method.

Microwave induced synthesis of 4-methyl-3-phenyl-2,3,3a,10-tetrahydropyrazolo[3,4-*b*][1,5] benzodiazepine (5a):

Compound **(2a)** (0.01 mol) and hydrazine hydrate (0.01 mol) and LiBr (10 mol %) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 60% power for 5.50 min. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and then stirred foe 5 min. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compound **(5a)**.

IR (KBr cm^{-1}) : 3074 (C-H str., Ar-H), 3412 (NH_a str.), 3276 (NH_b str.), 2901 (CH_3 str.), 1264 (C-N str.) 1628 (C=N str.) and 1502 (C=C str.), 2852, 2959 (-CH str.), 1045 (N-N str.).

^{1}H NMR: δ ppm: 2.89 (3H, s, CH_3), 7.65 (1H, s, NH_a), 5.34 (1H, s, NH_b), 7.69 - 7.01 (9H, m, Ar-H), 3.31 (1H, d, CH-) and 4.93 (1H, d, Ar-CH pyrazoline ring).

Compounds **(5b-e)** were prepared similarly by this method.

3-(4-chlorophenyl)-4-methyl-2,3,3a,10-tetrahydropyrazolo[3,4-*b*][1,5]benzodiazepine (5b):

IR (KBr cm^{-1}) : 3083 (C-H str., Ar-H), 3415 (NH_a str.), 3280 (NH_b str.), 2912 (CH_3 str.), 1261 (C-N str.) 1627 (C=N str.) and 1510 (C=C str.), 2843, 2965 (-CH str.), 732 (C-Cl str.), 1083 (N-N str.).
^{1}H NMR: δ ppm: 2.65 (3H, s, CH_3), 7.78 (1H, s, NH_a), 5.39 (1H, s, NH_b), 7.73 – 7.01 (8H, m, Ar-H), 5.32 (1H, d, CH-) and 4.98 (1H, d, Ar-CH pyrazoline ring).

3-(4-methoxyphenyl)-4-methyl-2,3,3a,10-tetrahydropyrazolo[3,4-*b*][1,5]benzodiazepine (5c):

IR (KBr cm^{-1}) : 3080 (C-H str., Ar-H), 3409 (NH_a str.), 3277 (NH_b str.), 2932 (CH_3 str.), 1212 (C-N str.) 1620 (C=N str.) and 1511 (C=C str.), 2847, 2954 (-CH str.), 1126 (C-O-CH_3), 1080 (N-N str.).
^{1}H NMR: δ ppm: 2.87 (3H, s, CH_3), 7.66 (1H, s, NH_a), 5.36 (1H, s, NH_b), 7.03 – 7.73 (8H, m, Ar-H), 3.81 (3H, s, -OCH_3), 5.29 (1H, d, CH-) and 5.01 (1H, d, Ar-CH pyrazoline ring).

4-methyl-3-(4-nitrophenyl)-2,3,3a,10-tetrahydropyrazolo[3,4-*b*][1,5]benzodiazepine (5d):

IR (KBr cm^{-1}) : 3081 (C-H str., Ar-H), 3411 (NH_a str.), 3285 (NH_b str.), 2921 (CH_3 str.), 1213 (C-N str.), 1626 (C=N str.) and 1510 (C=C str.), 2821, 2901 (-CH str.), 1561, 1412 (Ar-NO_2 str.), 1093 (N-N str.).
^{1}H NMR: δ ppm: 2.62 (3H, s, CH_3), 7.85 (1H, s, NH_a), 5.41 (1H, s, NH_b), 7.13 – 7.96 (8H, m, Ar-H), 5.30 (1H, d, CH-) and 4.83 (1H, d, Ar-CH pyrazoline ring).

4-(4-methyl-2,3,3a,10-tetrahydropyrazolo[3,4-*b*][1,5]benzodiazepin-3-yl)phenol (5e):

IR (KBr cm^{-1}) : 3085 (C-H str., Ar-H), 3415 (NH_a str.), 3287 (NH_b str.), 2921 (CH_3 str.), 1275 (C-N str.), 1632 (C=N str.), 1616 (C=C str.), 2836, 2922 (-CH str.), 3585 (O-H str.), 1039 (N-N str.).
^{1}H NMR: δ ppm: 2.78 (3H, s, CH_3), 7.88 (1H, s, NH_a), 5.39 (1H, s, NH_b), 7.25 – 8.04 (8H, m, Ar-H), 3.72 (1H, s, OH), 5.42 (1H, d, CH-) and 4.86 (1H, d, Ar-CH pyrazoline ring).

Conventional synthesis of 4-methyl-3-phenyl-2,3,3a,10-tetrahydropyrazolo[3,4-*b*][1,5]benzodiazepine (5a):

A solution of compound **(2a-d)** (0.01 mol) in absolute alcohol was treated with hydrazine hydrate (0.01 mol) in the presence of glacial acetic acid was refluxed for 8h. The reaction mixture was cooled to room temperature. The resulting solid was filtered, washed with water and recrystallized from acetic acid to yield compound **(5a).**

Compounds **(5b-e)** were prepared similarly by this method.

Microwave induced synthesis of 5-methyl-6-phenyl-4,12-dihydro[1,4]diazepino[5,6-b][1,4]benzodiazepine (6a):

Compound **(2a)** (0.01 mol) and o-phenylene diamine (0.01 mol) and LiBr (10 mol %) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 60% power for 3-4 min. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and then stirred foe 5 min. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compound **(6a)**.

IR (KBr cm^{-1}) : 3062 (C-H str., Ar-H), 3416 (NH_a str.), 3274 (NH_b str.), 2900 (CH_3 str.), 1246 (C-N str.), 1619 (C=N str.) and 1500 (C=C str.).

^{1}H NMR: δ ppm: 2.51 (3H, s, CH_3), 7.85 (1H, s, NH_a), 5.41 (1H, s, NH_b str.), and 7.01 - 7.67 (13H, m, Ar-H). Compounds **(6b-e)** were prepared similarly by this method.

6-(4-chlorophenyl)-5-methyl-4,12-dihydro[1,4]diazepino[5,6-b][1,4]benzodiazepine (6b):

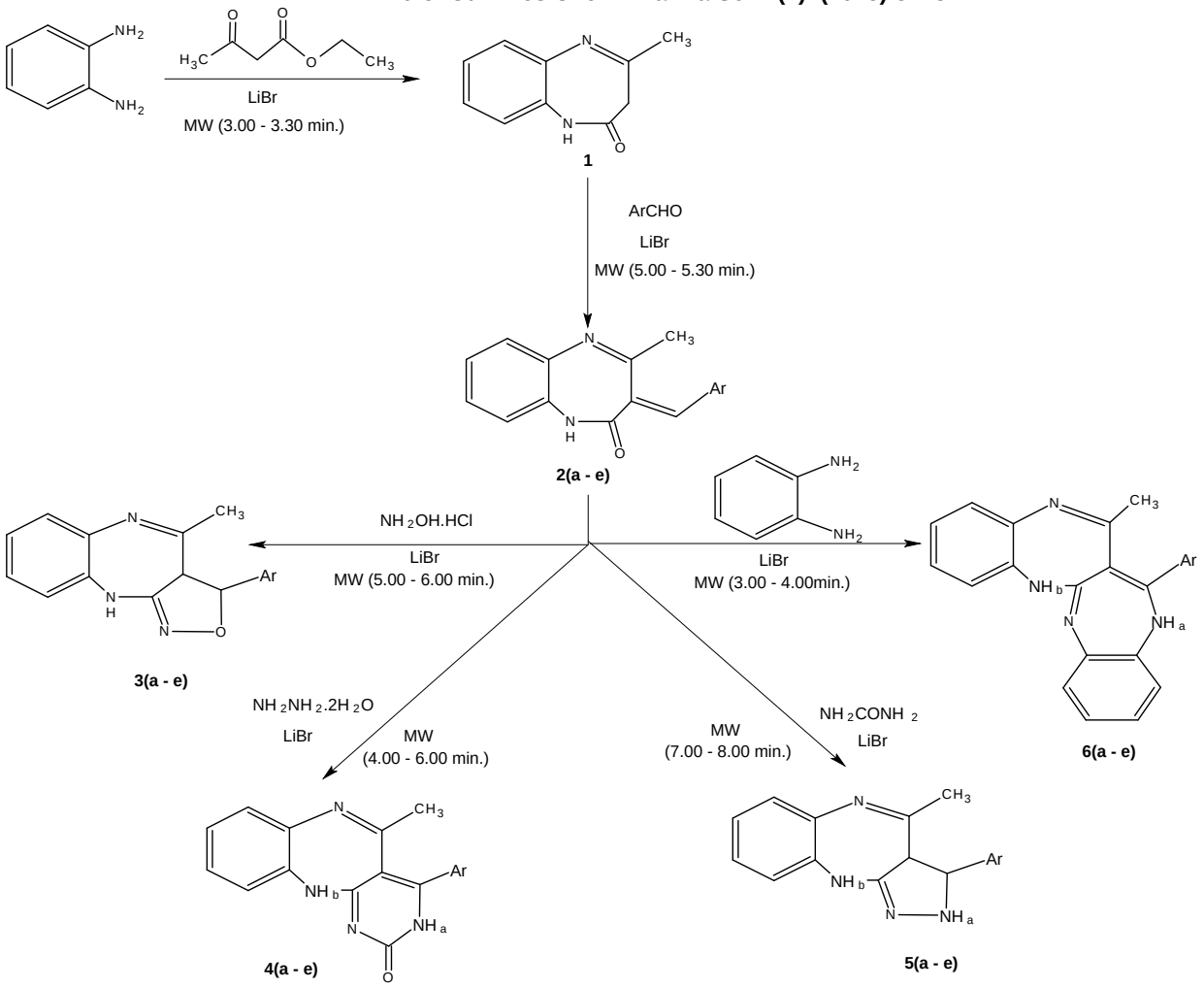
IR (KBr cm^{-1}) : 3081 (C-H str., Ar-H), 3421 (NH_a str.), 3280 (NH_b str.), 2911 (CH_3 str.), 1216 (C-N str.), 1625 (C=N str.), 1515 (C=C str.) and 723 (C-Cl str.).
^{1}H NMR: δ ppm: 2.56 (3H, s, CH_3), 7.91 (1H, s, NH_a), 5.43 (NH_b str.), and 7.05 – 7.37 (12H, m, Ar-H).

6-(4-methoxyphenyl)-5-methyl-4,12-dihydro[1,4]diazepino[5,6-b][1,4]benzodiazepine (6c):

IR (KBr cm^{-1}) : 3078 (C-H str., Ar-H), 3409 (NH_a str.), 3278 (NH_b str.), 2923 (CH_3 str.), 1221 (C-N str.), 1624 (C=N str.), 1521 (C=C str.) and 1126 (C-O-CH_3).
^{1}H NMR: δ ppm: 2.62 (3H, s, CH_3), 7.88 (1H, s, NH_a), 5.41 (1H, s, NH_b str.), 7.12 – 7.86 (12H, m, Ar-H) and 3.81 (3H, s, -OCH_3).

5-methyl-6-(4-nitrophenyl)- 4,12-dihydro[1,4] diazepino[5,6-b][1,4]benzodiazepine (6d):

IR (KBr cm^{-1}) : 3082 (C-H str., Ar-H), 3410 (NH_a str.), 3278 (NH_b str.), 2925 (CH_3 str.), 1216 (C-N str.), 1628 (C=N str.), 1516 (C=C str.) and 1565, 1413 (Ar-NO_2 str.).



Scheme- 1

^{1}H NMR: δ ppm: 2.65 (3H, s, CH_3), 7.96 (1H, s, NH_a), 5.48 (1H, s, NH_b str.), 7.13 – 7.96 (12H, m, Ar-H).

5-methyl-4,12-dihydro[1,4]diazepino[5,6-b][1,4] benzodiazepin-3-yl)phenol (6e):

IR (KBr cm^{-1}) : 3085 (C-H str., Ar-H), 3415 (NH_a str.), 3281 (NH_b str.), 2921 (CH_3 str.), 1275 (C-N str.), 1632 (C=N str.), 1519 (C=C str.) and 3582 (O-H str.).
^{1}H NMR: δ ppm: 2.78 (3H, s, CH_3), 7.87 (1H, s, NH_a), 5.53 (1H, s, NH_b str.), 7.25 – 8.04 (12H, m, Ar-H), and 3.72 (1H, s, OH).

Conventional synthesis of 5-methyl-6-phenyl-4,12-dihydro[1,4]diazepino[5,6-b][1,4]benzodiazepine (6a):

A mixture of compound **(2)** (0.01 mol) and *o*-phenylenediamine (0.01) in ethanol were treated with anhydrous sodium acetate (1.25 g) and refluxed for 3 h. The reaction mixture was cooled to room temperature. The resulting solid was filtered, washed with water and recrystallized from ethanol to yield compound **(6a)**. Compounds **(6b-e)** were prepared similarly by this method.

Results and Discussion

4-methyl-1,3-dihydro- 2*H*-1,5 - benzodiazepin- 2- one **(1)** was synthesized by LiBr catalyzed condensation of *o*- phenylenediamine with ethylacetoacetate under solvent free condition and microwave exposure. The structure of **(1)** was confirmed by the IR bands at 1680 cm^{-1} due to cyclic amide group, 3295 cm^{-1} due to NH, 1625 cm^{-1} due to C=N stretching and 2412 due to CH_2 stretching. It is supported by the presence of a singlet of 1 NH protons in the region of 5.41 ppm in ^{1}H NMR spectrum. The compound **(1)** possesses an active methylene group, which undergoes condensation with various aromatic aldehydes (benzaldehyde/ chloro / methoxy / nitro/ hydroxy/ benzaldehydes) in the presence of LiBr to give 4-methyl-3-(4-substituted phenylmethylidene)-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one **(2a-e)**. The IR spectra of compound **(2a)** shows the presence of α, β-unsaturated moiety by the appearance of carbonyl stretch at 1665cm^{-1} due to conjugation rather then at 1680cm^{-1} (C=O of benzodiazepinone nucleus). Other prominent band of arylidine proton (=CH-Ar) of chalcone moiety also appeared at 3070 cm^{-1}. ^{1}H NMR spectrum of compound **(2a)** was characterized by the lack of the singlet of two protons of benzodiazepinone nucleus at 4.26 ppm and appearance of a new singlet at 4.68 ppm due to arylidine proton (=CH-Ar) of chalcone moiety.

Compounds **(2a-e)** are convenient starting material for the synthesis of fused benzodiazepine derivatives due to their α, β-unsaturated moiety. Firstly, the absence of carbonyl stretching frequency in the region of 1680 cm^{-1} in the IR spectra confirms the formation of products. Isoxazoline derivatives **(3a-e)** were synthesized by the reaction of compound **(2a-e)** with equimolar ratio of hydroxylamine hydrochloride in the presence of LiBr. The structure of (**3a)** was confirmed by appearance of absorption band at 1091 cm^{-1} due to C-O stretch and at 943 cm^{-1} due to N-O stretch in IR spectrum. It is supported by the presence of two doublets of two methine protons of isoxazolino moiety at about 5.25 and 4.14 ppm in ^{1}H NMR.

Compounds **(2a-e)** treated with urea in the presence of LiBr as a catalyst yielded 5-methyl-4-(4-substituted phenyl)-3,11-dihydro- 2*H*- pyrimido [4,5-*b*] [1,5] benzodiazepine - 2-one **(4a-e).** The IR spectrum of compound **(4a)** shows a new absorption band in the region of 1685 cm^{-1} was assigned to new carbonyl group (=N-C=O) and in the region of 3327cm^{-1} due to NH_a stretch rather than 3070 cm^{-1} (Ar-CH str.) . ^{1}H NMR spectrum of **(4a)** shows the appearance of two singlets due to NH_a and NH_b protons at 6.92 ppm and at 5.30 ppm and disappearance of singlet due to one proton (CH) at 4.80 ppm of Ar-CH moiety which confirms the formation of the product **(4a)**. Pyrazoline derivatives of compounds **(5a-e)** were synthesized by the reaction of compounds **(2a-e)** with equimolar ratio of hydrazine hydrate in the presence of LiBr as a catalyst. The structure of compound **(5a)** was confirmed by the disappearance of carbonyl stretching frequency in the region of 1685 cm^{-1} in IR spectra and appearance of a additional band of NH_a stretch at 3412 cm^{-1}. The signal of methane protons of pyrazoline ring appeared as two doublets centered at 3.31 and 4.93 ppm in its ^{1}H NMR spectra.

5-methyl-6-(4-substituted phenyl)-4,12-dihydro[1,4] diazepino [5,6-b][1,4]benzodiazepine **(6a-e)** were synthesized by the reaction of compounds **(2a-e)** with *o*- phenylenediamine in the presence of LiBr under dry condition and microwave exposure. The formation of compounds **(6a-e)** was confirmed by the disappearance of band 1683 cm^{-1}(cyclic amide stretch) and appearance of an additional band at 3274 due to NH_a stretch in IR spectra. ^{1}H NMR spectrum of compound was characterized by the lack of a singlet of arylidine proton (=CH-Ar) of chalcone moiety and the presence of a singlet of 1 NH_a proton at 7.85 ppm and additional multiptes at 7.01 - 7.67 ppm of 4 aromatic protons (Ar-H).

Antimicrobial activity

Four compounds were screened *in vitro* for their antimicrobial activities against four strains of bacteria (*Escherichia coli, Bacillus subtilis, Klebsiella pneumoniae, Pseudomonas aeuroginosa*) and two strains of fungi (*Aspergillus fumigatus, Candida albicans*) using the disc diffusion method. Commercial antibacterial ciprofloxacin and antifungal fluconazole were also screened under similar conditions for comparison. The results have been tabulated in the form of inhibition zones and activity index in Table 2.

The results revealed that all tested compounds exhibit moderate to strong activity against both fungi and bacteria. Compounds (**5a)** show considerable potency against. Similarly, compounds (**3a), (4a)** and (**6a)** were moderately active against all the six organisms.

Table 1 – Physical data of synthesized compounds
a = Conventional, b = Microwave + Solvent, c = Microwave + LiBr (solvent free) under microwave irradiati**on**

Compd.	Ar	Mol. Formula	Mol. Weight	M.P.(ºC)	Yield[a] [Time] (hr.)	Yield[b] [Time] (min.)	Yield[c] [Time] (min.)
1	-	$C_{10}H_{10}N_2O$	174	119-120	64 [3]	68 [5]	82 [3]
2a	$-C_6H_5$	$C_{17}H_{14}N_2O$	262	127-128	60 [12]	69 [8.30]	86 [5.30]
2b	$-4ClC_6H_4$	$C_{17}H_{13}Cl\ N_2O$	296	132-133	62 [12]	71 [8]	80 [5]
2c	$-4OCH_3C_6H_4$	$C_{18}H_{16}N_2O_2$	292	126-127	66 [12]	69 [8.30]	81 [5]
2d	$-4NO_2C_6H_4$	$C_{17}H_{13}N_3O_3$	307	138-139	65 [12]	72 [8.30]	80 [5]
2e	$-4OHC_6H_4$	$C_{17}H_{14}N_2O_2$	278	142-145	68 [12]	72 [8]	89 [5]
3a	$-C_6H_5$	$C_{17}H_{15}N_3O$	277	95-96	64 [9]	70 [6]	86 [5]
3b	$-4ClC_6H_4$	$C_{17}H_{14}Cl\ N_3O$	311	101-102	70 [9]	76 [6]	87 [5]
3c	$-4OCH_3C_6H_4$	$C_{18}H_{17}N_3O_2$	307	110-111	68 [9]	72 [6]	86 [5]
3d	$-4NO_2C_6H_4$	$C_{17}H_{14}N_4O_3$	322	108-109	69 [9]	72 [6]	88 [5]
3e	$-4OHC_6H_4$	$C_{17}H_{15}N_3O_2$	293	115-116	68 [9]	70 [6]	80 [5]
4a	$-C_6H_5$	$C_{18}H_{14}N_4O$	302	212-213	68 [8]	70 [7]	86 [4]
4b	$-4ClC_6H_4$	$C_{18}H_{13}Cl\ N_4O$	336	220-221	79 [8]	82 [7]	90 [4.30]
4c	$-4OCH_3C_6H_4$	$C_{19}H_{16}N_4O_2$	332	225-226	68 [8]	72 [7]	89 [5]
4d	$-4NO_2C_6H_4$	$C_{18}H_{13}N_5O_3$	347	223-224	73 [8]	75 [7]	87 [4.30]
4e	$-4OHC_6H_4$	$C_{18}H_{14}N_4O_2$	318	228-229	70 [8]	76 [5.30]	87 [5]
5a	$-C_6H_5$	$C_{17}H_{16}N_4$	276	110-111	68 [8]	72 [9]	89 [7]
5b	$-4ClC_6H_4$	$C_{17}H_{15}ClN_4$	310	115-116	63 [8]	75 [9]	87 [7.30]
5c	$-4OCH_3C_6H_4$	$C_{18}H_{18}N_4O$	306	121-122	70 [8]	76 [9.30]	87 [8]
5d	$-4NO_2C_6H_4$	$C_{17}H_{15}N_5O_2$	321	124-125	68 [8]	72 [9]	89 [7]
5e	$-4OHC_6H_4$	$C_{17}H_{16}N_4O$	292	129-130	73 [8]	75 [9]	87 [7]
6a	$-C_6H_5$	$C_{23}H_{18}N_4$	350	76-77	62 [3]	73 [5]	85 [3.30]
6b	$-4ClC_6H_4$	$C_{23}H_{17}ClN_4$	384	85-86	63 [3]	72 [5]	86 [3]
6c	$-4OCH_3C_6H_4$	$C_{24}H_{20}N_4O$	380	92-93	60 [3]	67 [6]	81 [4]
6d	$-4NO_2C_6H_4$	$C_{23}H_{17}N_5O_2$	395	97-98	68 [3]	72 [5]	86 [3]
6e	$-4OHC_6H_4$	$C_{23}H_{18}N_4O$	366	88-89	69 [3]	72 [5.30]	88 [3]

Table 2 – Analytical data of synthesized compounds

Compd.	Calculated / Found (%)		
1	68.95 / 68.80	5.79 / 5.83	16.08 / 16.01
2a	77.84 / 77.65	5.38 / 5.21	10.68 / 10.51
2b	68.81 / 68.61	4.42 / 4.25	9.44 / 9.21
2c	73.95 / 73.59	5.52 / 5.21	9.58 / 9.82
2d	66.44 / 66.12	4.26 / 4.61	13.67 /13.14
2e	73.37 /73.70	5.07 /5.10	10.07 /10.35
3a	73.63 /73.32	5.45 /5.56	15.15 /15.52
3b	65.49 /65.91	4.53 /4.31	13.48 /13.81
3c	70.34 /70.41	5.58 /5.80	13.67 /13.70
3d	63.35 / 63.51	4.38 / 4.78	17.38 / 17.20
3e	69.61 / 69.17	5.15 / 5.46	4.33 / 4.20
4a	71.51 / 71.12	4.67 / 4.51	18.53 / 18.31
4b	64.19 / 64.03	3.89 / 3.71	16.64 / 16.42
4c	68.66 / 68.52	4.85 / 4.52	16.86 / 16.58
4d	62.24 / 62.41	3.77 / 3.35	20.16 / 20.61
4e	67.91 / 67.25	4.43 / 4.35	17.60 / 17.09
5a	73.89 / 73.61	5.84 / 5.91	20.27 / 20.75
5b	65.70 / 65.65	4.86 / 4.66	18.03 / 18.30
5c	70.57 / 70.72	5.92 / 5.29	18.29 / 18.52
5d	63.54 / 63.45	4.71 / 4.15	21.79 / 21.86
5e	69.85 / 69.62	5.52 / 5.32	19.11 / 19.45
6a	78.83 / 78.45	5.18 / 5.63	15.99 / 15.84
6b	71.78 / 71.81	4.45 / 4.51	14.56 / 14.63
6c	75.77 / 75.82	5.30 / 5.51	14.73 / 14.45
6d	69.86 / 69.62	4.33 / 4.41	17.71 / 17.62
6e	75.39 / 75.26	4.95 / 4.61	15.29 / 15.35

Table - 3 Antimicrobial activities of some synthesized compounds (500 ppm)

Compd.	Antifungal activity (Activity index)		Antibacterial activity (Activity index)			
	A. fumigatus	*C. albicans*	*E.coli*	*B.subtilis*	*P.aeuroginosa*	*K.pneumoniae*
3a	15	18 (0.60)	12 (0.33)	15 (0.47)	11 (0.27)	10 (0.28)
4a	16	17 (0.56)	14 (0.39)	09 (0.28)	10 (0.25)	10 (0.28)
5a	25	28 (0.93)	23 (0.64)	22 (0.68)	21 (0.52)	24 (0.67)
6a	15	11 (0.37)	10 (0.28)	19 (0.69)	15 (0.37)	18 (0.50)
C_1	Nil	30	-	-	-	-
C_2	-	-	36	32	40	36

[a] Activity index = Inhibition area of the sample / inhibition area of the standard.

Standard: C_1 = Fluconazole, C_2 = Ciprofloxacin.

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