dihydro-1H-1,5-benzodiazepines on solventless inorganic solid support and their antibacterial activities

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Síntesis asistida por microondas de 2,4-diaril-2,3-dihidro-1H-1,5-benzodiazepinas sobre un soporte inorgánico sólido sin disolvente, y sus actividades antibacterianas

Síntesi assistida per microones de 2,4-diaril-2,3-dihidro-1H-1,5-benzodiazepines sobre un suport inorgànic sòlid sense dissolvent, i les seves activitats antibacterianes

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RESUMEN

Se utiliza la reactividad química de los sistemas carbonílicos α,β-insaturados de calconas substituidas sintetizadas para la síntesis de benzodiazepinas diversamente substituidas por reacción con *o*-fenilendiamina (OPDA). En el presente trabajo, se realiza esta reacción usando tanto el método convencional como la técnica de síntesis orgánica asistida por microondas (MAOS) en presencia de alúmina básica / gel de sílice. Al comparar los resultados de este último método con los obtenidos con el método convencional, se demuestra la versatilidad del proceso asistido por microondas en fase sólida, resultando en un notable aumento de velocidad y una substancial reducción del tiempo de reacción, acompañado de mejores rendimientos. La estructura de los compuestos es apoyada por datos espectroscópicos y analíticos. También se estudia la relación estructura-actividad de los compuestos sintetizados.

Palabras clave: **Irradiación con microondas. Alúmina básica. Gel de sílice. Actividad antibacteriana.**

SUMMARY

The chemical reactivity of α,β-unsaturated carbonyl system of synthesised substituted chalcones have been utilized for the synthesis of variously substituted benzodiazepines by the reaction of *O*-phenylenediamine (OPDA). In the present investigation we have carried out the reaction under both conventional method and microwave assisted organic synthesis (MAOS) technique in presence of basic alumina / silica gel. The results of this procedure when compared to conventional method, demonstrate the versatility of the solid phase microwave assisted process resulting remarkable rate enhancement and dramatic reduction in reaction time, with better yield. The structure of compounds are supported by spectral and analytical data. The structure-activity relationship of synthesized compounds have also been studied.

Key words: **Microwave irradiation. Basic alumina. Silica gel. Antibacterial activity.**

RESUM

S'utilitza la reactivitat química dels sistemes carbonílics α,β-insaturats de calcones substituïdes sintetitzades per a la síntesi de benzodiazepines diversament substituïdes per reacció amb *o*-fenilendiamina (OPDA). En el present treball, es realitza aquesta reacció emprant tant el mètode convencional com la tècnica de síntesi orgànica assistida per microones (MAOS) en presència d'alúmina bàsica / gel de sílice. En comparar els resultats d'aquest darrer mètode amb els obtinguts amb el mètode convencional, es demostra la versatilitat del procés assistit per microones en fase sòlida, resultant en un notable augment de velocitat i una substancial reducció del temps de reacció, acompanyat de millors rendiments. L'estructura dels compostos es recolzada per dades espectroscòpiques i analítiques. També s'estudia la relació estructura-activitat dels compostos sintetitzats.

Mots clau: **Irradiació amb microones. Alúmina bàsica. Gel de sílice. Activitat antibacteriana.**

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INTRODUCTION

Microwave chemistry is not different from traditional chemistry in as much as it embraces the same creativity and innovation that has always been central to classical chemistry. But with an increase in environmental consciousness throughout the world, there is a challenge for chemists to develop new products, processes and services that achieve necessary social, economical and environmental objectives. By using these technologies energy input reduces, improvement of selectivity, shortening of reaction time occurs. Some reactions, which are not possible with single heating, can be possible with above technique. In current aspects development of more sustainable products and energy efficient processes with reducing waste are discussed in emerging green technologies[1-8].Use of energy sources like light, microwave, ultrasound and electricity are more clean, and efficient.

A great deal of synthesis work has been done in the last few years on various diazepines[9]. Some of these undergo fascinating rearrangements, and others possess valuable pharmacological properties. Compounds having a condensed diazepine nucleus especially the benzodiazepine have attracted the attention of several chemists[10-14].

Chalcones are Michael acceptors. Chalcones having an enone system have been used recently in the synthesis of various diazepines derivatives of diverse biological activities. Several derivatives of diazepines and related compounds are marketed as drugs e.g. diazepam, propizepine, pirenzepine, haloperidol, clobazam and quazepam etc. The diazepine-based drugs have been found to exhibit tranquilising, antipsychotic, antiulcer and CNS relaxant properties. Diazepines, which are a seven membered heterocyclic compounds, having two nitrogen atoms at various positions in the ring, with a maximum degree of unsaturation (*i.e.* a total of three double bonds) are classified on the basis of the positions of nitrogen atoms. Numbering is done in such a way that the least possible number is given to the second nitrogen atom. Fusion of aromatic system to diazepine system results in benzodiazepines, dibenzodiazepines and pyridobenzodiazepines, etc.

MATERIAL AND METHODS

General Procedures. Melting points are uncorrected and were recorded using open-end capillaries. Thin layer chromatography of synthesised compounds was performed on silicagel-G plates using benzene-ethylacetate (9:1) solvent system and iodine as visualising agent. The IR spectra of synthesised compound were recorded on DIGILAB FTS-14 or Perkin- Elmer 157P spectrophotometer in KBr (ν_{max} in cm^{-1}). ^1H NMR was recorded on $CDCl_3$ on a varian CFT-20 or Brucker DRX-300 (300 MHz) spectrometer using TMS as internal standard (chemical shifts in δ, ppm). FAB MS was recorded on Jeol SX-102 spectrometer. All compounds gave satisfactory elemental analysis and spectral data. All the reactions were carried out in a domestic microwave oven (Kenstar, output energy 1200W, frequency 2450 MHz, model No. MO9706}.

RESULTS AND DISCUSSION

The basic skeleton of chalcones which posses α, β-unsaturated carbonyl group is useful as the starting material for the synthesis of various heterocyclic compounds15 and the presence of enone functionality in chalcone moiety makes it as an important pharmacophoric element in medicinal chemistry[16]. In view of this, we herein report a facile, rapid one-pot condensation of substituted chalcone with o-phenylenediamine (OPDA) to afford substituted 1,5-benzodiazepines (**3a-f**) . Further, we have studied the effect of solvent, role of different solid supports under microwave for synthesis of substituted 1,5 benzodiazepines.

The formation of title compounds involve heterocyclisation of substituted chalcones and o-phenylenediamine via conjugated Michael addition of nucleophilic $-NH_2$ group of the o-phenylenediamine with ,-carbon atom of the 2-propenones followed by subsequent condensation of ortho $-NH_2$ group of the benzene ring with C=O group of the 2-propenones under microwave irradiation condition resulted the heterocyclic title compounds (**3a-f**) through the intermediate (2) formation of Michael adduct in a single step (Scheme 1).

The synthesis of 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepine (**3a-f**) have been carried out under conventional thermal and microwave irradiated solvent and solid phase conditions. The solid phase (Al_2O_3 or SiO_2) microwave irradiated synthesis for 1,5-benzodiazepines (3a-f) is characterized by operational simplicity, shorter reaction time, high yields & employing a reusable catalyst.

The structures of the synthesized compounds were established on the basis of their analytical and spectroscopic data. The IR spectra of condensed products displayed disappearance of bands at 1640-1660 cm^{-1} due to C=O of 2-propenones and appearance of a band at 1580-1620 cm^{-1} due to overlap of the νC=C & νC=N and single broad absorption at 3320-3400 cm^{-1} due to –NH. & Devoid of two peaks due to ν asym. & ν sym. stretching of NH_2 in the region 3460-3300 cm^{-1}. Thus the IR spectra of the products (**3a-f**) indicated the absence of Michael adduct intermediate (2).

The ^1H NMR spectra of the products are characteristic of ABX pattern showing three distinct double doublets in the range of δ 2.9-5.2 showed distinctive signals of prochiral methylene protons H_A & H_B at C-3 and the methine proton HX of C-4. A broad one-proton absorption in the region above δ 4 due to NH to support the formation of 2,3-dihydro derivatives in preference to 2,5-dihydro tautomer. Further support for structure assigned to (**3a-f**) was obtained by mass spectral data. The molecular ion peak corresponding to molecular weight of synthesized compounds was observed along with other fragmentation pattern.

Antibacterial activity:

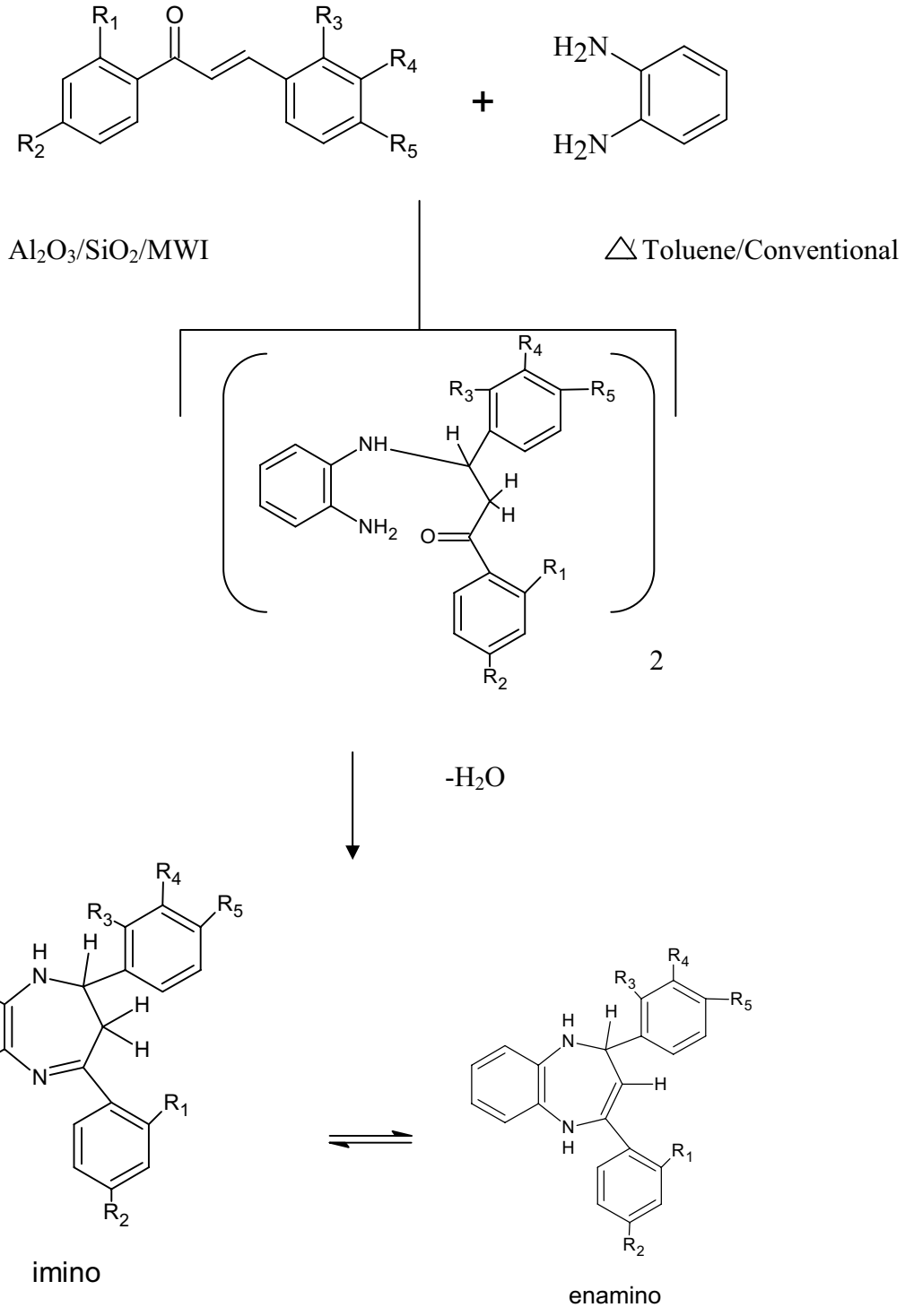
In the determination of antibacterial activity «Peptone» nutrient broth was used. The media was prepared for gram-negative organisms (*Protius mirabilis*, *Pseudomonas aeruginosa*) by adding 2% mecconkey agar to the nutrient broth and for gram positive bacteria (*Staphylococcus aureus*, *Streptococcus fecalis*), it was prepared by adding 10% blood agar and 2% nutrient agar to the nutrient broth. Paper disc diffusion plate method was followed.

All the synthesized compounds (**3a-f**) were screened for antibacterial activity at maximum concentration of 200 μg/ml in DMF & compared with standard drugs Amicacin, Amoxyclav, Tobramycin and Amoxicillin. The zones of inhibition measured in millimeter .

All the compounds (**3a-f**) exhibited moderate to good antibacterial activity. The compound **3b**, **3c**, **3d** has shown excellent activity against both gram positive and gram negative bacteria. The compounds having hydroxy and methoxy substituents at specific positions on aromatic ring was found to be more active. Results are summarized in Table 1.

General procedure for synthesis of 2,4-diaryl-2, 3-dihydro-1H-1, 5-benzodiazepines (3a-f): The synthesis of substituted chalcones was performed by the most convenient method which involves the Claisen-Schmidt condensation of equimolar quantities of a substituted acetophenone with substituted benzaldehyde in presence of base.

Method A: Conventional heating: A mixture of substitu-



(3a-f)

Scheme 1.

TABLE I

Antibacterial activity of compounds (3a-f) (zone of inhibition in mm).

Compound No. & Standard Drug	Gram Positive		Gram Negative	
	S. aureus	S. fecalis	Protius mirabilis	Psedumonas aeruginosa
3a-8	15	26	28	16
3b-9	26	23	21	23
3c-10	24	23	21	24
3d-11	23	26	21	23
3e-12	15	24	23	20
3f-13	24	10	19	26
Amicacin	31	34	–	–
Amoxyclav	29	33	–	–
Tobramycin	–	–	28	26
Amoxicillin	–	–	29	26

TABLE II

Reaction time & Yield of synthesized 2,4-diaryl-2, 3-dihydro-1H-1, 5-benzodiazepines (3a-f): -

Compound No.	R_1	R_2	R_3	R_4	R_5	Reaction time				Yield (%)		
						Method A A(hr.)/b	Method-B A(min.)/b	Method-C A(min.)/b	Method-D A(min.)/b	Solid phase toluene	Solid phase Al_2O_3	Solid phase SiO_2
3a	H	H	OH	H	H	7/58	13/72	8/82	6/87	72	82	87
3b	H	OCH_3	OH	H	H	9/45	17/60	9/69	7/75	60	69	75
3c	OH	H	OH	H	H	11/51	15/61	9/73	8/80	61	73	80
3d	H	OH	H	OCH_3	OH	11/43	16/58	9/64	9/71	58	64	71
3e	H	OCH_3	H	OCH_3	OH	9/38	15/43	8/50	10/58	43	50	58
3f	OH	H	H	OCH_3	OH	10/40	14/46	7/54	7/62	46	54	62

a = Time and b =Yield.

ted chalcone (0.1 mole) and O-phenylenediamine (0.1 mole) was refluxed in dry toluene (55 ml) for 7-11 hrs. The progress of the reaction was monitored by tlc. Removal of the solvent under reduced pressure gave a solid which on crystallization with a mixture of acetone and petroleum ether (40-60°C) (2:1,v/v) afforded analytical samples of (**3a-f**).

Method B: Microwave irradiated solution phase: A mixture of substituted chalcone (0.1 mole) and O-phenylenediamine (0.1 mole) in toluene (10-15 ml) was irradiated in a Pyrex conical flask (100 ml) inside the microwave oven (35% power) for 12-19 min, with intermittent 1 min interval after 3-4 minutes. The progress of reaction was monitored by tlc. The reaction mixture was further worked up as mentioned in method A.

Method C: Microwave irradiated solid phase (basic alumina): A mixture of substituted chalcone (0.01 mol) and O-phenylenediamine (0.01 mol) & toluene (5 ml) was adsorbed on basic alumina (5 gm) in a Pyrex conical flask and was irradiated at 50% power for the time mentioned in table 2. The completion of reaction was monitored by tlc. The reaction mixture was cooled at room temperature, the reaction mass extracted with acetone (2 x 20 ml.) & filtered. The filterate was then concentrated and crystallized with petroleum ether (40-60°C), to give analytical sample of compound.

Method D: Microwave irradiated solid phase (Silica gel): In this procedure basic alumina was replaced by silica gel with catalytic amount of molecular sieves and rest of experimental details are same as mentioned in method C. In this procedure the purification of compounds was easier which resulted in better yields comparison to above methods B and C.

(3a) 4-Phenyl-2-(2-hydroxy phenyl)-2,3-dihydro-1H,1,5-benzodiazepine: Yellow crystals, m.p. 205ºC. Anal. Calcd for $C_{21}H_{18}N_2O$ (314): C 80.23, H 5.77. Found: 80.21, H 5.70 **NMR (CDCl$_3$, δppm)**: 4.04 [s, Ar-C-NH], 5.12 [dd, 1H, Ar-C-Hx], 3.05 [dd, 1H, H_α methylene], 2.94 [dd, 1H, H_β methylene], 6.71-7.47 [m, broad & unresolved, Ar-H], 13.11 [s, 1H, OH] **IR (ν/cm^{-1})**: 3753, 3327(–NH str.), 3058, 2812, 2363, 1922, 1870, 1753, 1593 ($\nu_{C=C}$ & $\nu_{C=N}$ str.), 1536, 1491, 1453, 1391, 1320, 1261, 1160, 1132, 1036, 1006, 964, 914, 839, 797, 726 **FABMS (m/z)**: 314 $[M]^{+\cdot}$, 313 $[M-H]^+$, 297 $[M-OH]^+$, 294 $[M-OH_4]^{+\cdot}$, 285 $[M-HCO]^+$, 288 $[M-C_2H_2]^{+\cdot}$, 259 $[M-C_3H_3O]^+$, 223 $[M-C_6H_5N]^{+\cdot}$, 209 $[M-C_6H_5N_2]^+$, 221 $[M-C_6H_5O]^+$, 220 $[M-C_6H_6O]^{+\cdot}$, 116 $[M-C_{12}H_{10}N_2O]^{+\cdot}$, 115 $[M-C_{12}H_{11}N_2O]^{+\cdot}$, 113 $[M-C_{12}H_{13}N_2O]^{+\cdot}$

(3b) 4-(4'–Methoxy phenyl)-2-(2-hydroxy phenyl)-2,3-dihydro-1H, 1, 5-benzodiazepine: light brown. m.p. 124ºC Anal. Calcd for $C_{22}H_{20}N_2O_2$ (344): C 76.72, H 5.85. Found: 76.67, H 5.88 **NMR (CDCl$_3$, δppm)**: 4.03 [s, Ar-C-NH], 5.14 [dd, 1H, Ar-C-Hx], 3.05 [dd, 1H, H_α methylene], 2.94 [dd, 1H, H_β methylene], 6.77-7.54 [m, broad & unresolved, Ar-H], 13.20 [s, 1H, OH], 3.81 [s, 3H, OCH_3] **IR (ν/cm^{-1})**: 3341(–NH str.), 3082, 2099, 2982, 2920, 2844, 1584 ($\nu_{C=C}$ & $\nu_{C=N}$ str.), 1561, 1507, 1484, 1446, 1374, 1358, 1310, 1271, 1228, 1180, 1159, 1140, 1088, 1027, 953, 920, 898, 874, 841, 789, 760, 758, 691, 640 **FABMS (m/z)**: 344 $[M]^{+\cdot}$, 343 $[M-H]^+$, 327 $[M-OH]^+$, 313 $[M-OCH_3]^+$, 312 $[M-CH_4O]^{+\cdot}$, 297 $[M-CH_3O_2]^+$, 284 $[M-C_2H_4O_2]^{+\cdot}$, 295 $[M-CH_5O_2]^+$, 258 $[M-C_4H_6O_2]^{+\cdot}$, 206 $[M-C_7H_8O_2N]^+$, 204 $[M-C_7H_{10}O_2N]^{+\cdot}$, 179 $[M-C_8H_9O_2N_2]^+$, 153 $[M-C_{10}H_{11}O_2N_2]^+$, 112 $[M-C_{13}H_{16}N_2O_2]^{+\cdot}$, 76 $[M-C_{16}H_{16}N_2O_2]^{+\cdot}$.

(3c) 4-(2'–Hydroxy phenyl)-2-(2-hydroxy phenyl)-2,3-dihydro-1H, 1, 5-benzodiazepine: orange, m.p. 55ºC Anal. Calcd for $C_{21}H_{18}N_2O_2$ (330): C 76.34, H 5.49. Found: 76.31, H 5.53 **NMR (CDCl$_3$, δppm)**: 4.03 [s, Ar-C-NH], 5.12 [dd, 1H, Ar-C-Hx], 3.12 [dd, 1H, H_α methylene], 2.94 [dd, 1H, H_β methylene], 6.75-7.57 [m, broad & unresolved, Ar-H], 13.13 [s, 1H, OH], 9.68 [s, 1H, OH] **IR (ν/cm^{-1})**: 3391(–NH str.), 2368, 1849, 1803, 1777, 1595 ($\nu_{C=C}$ & $\nu_{C=N}$ str.), 1462, 1383, 1353, 1271, 1153, 1059, 1030, 749, 673, **FABMS (m/z)**: 331[M+1]$^+$, 330 $[M]^{+\cdot}$, 313 $[M-OH]^+$, 302 $[M-CO]^{+\cdot}$, 273 $[M-C_2HO_2]^+$, 261 $[M-C_4H_5O]^+$, 239 $[M-C_6H_5N]^{+\cdot}$, 225 $[M-C_6H_5N_2]^+$, 223 $[M-C_6H_7N_2]^+$, 211 $[M-C_7H_5NO]^+$, 210 $[M-C_7H_6NO]^{+\cdot}$, 195 $[M-C_8H_9NO]^+$, 194 $[M-C_7H_6NO_2]^{+\cdot}$, 182 $[M-C_{10}H_{12}O]^{+\cdot}$, 148 $[M-C_{13}H_{10}NO]^+$.

(3d) 4-(4'–Hydroxy phenyl)-2-(4-hydroxy-3-methoxy phenyl)-2,3-dihydro-1H, 1, 5-benzodiazepine: orange, m.p. 140ºC Anal. Calcd for $C_{22}H_{20}N_2O_3$ (360): C 73.32, H 5.59. Found: 73.30 H 5.61 **NMR (CDCl$_3$, δppm)**: 4.06 [s, Ar-C-NH], 5.11 [dd, 1H, Ar-C-Hx], 3.14 [dd, 1H, H_α methylene], 2.91 [dd, 1H, H_β methylene], 6.86-7.49 [m, broad & unresolved, Ar-H], 9.81 [s, 1H, OH], 3.85 [s, 3H, OCH_3], 9.44 [s, 1H, OH] **IR (ν/cm^{-1})**: 3320 (–NH str.), 1598 ($\nu_{C=C}$ & $\nu_{C=N}$ str.), 1571, 1488, 1452, 1350, 1283, 1105, 891, 837, 814, 728, 630 **FABMS (m/z)**: 360 $[M]^{+\cdot}$, 359 $[M-H]^+$, 326 $[M-O_2H_2]^{+\cdot}$, 313 $[M-CH_3O_2]^+$, 312 $[M-CH_4O_2]^{+\cdot}$, 300 $[M-C_2H_4O_2]^+$, 296 $[M-CH_4O_3]^+$, 269 $[M-C_3H_7O_3]^+$, 222 $[M-C_7H_8O_2N]^+$, 205 $[M-C_7H_9O_3N]^{+\cdot}$, 195 $[M-C_8H_9O_2N_2]^+$, 152 $[M-C_{10}H_{12}O_3N_2]^{+\cdot}$, 88 $[M-C_{15}H_{16}N_2O_3]^+$, 75 $[M-C_{16}H_{17}N_2O_3]^{+\cdot}$.

(3e) 4-(4'-Methoxy phenyl)-2-(4-hydroxy-3-methoxy phenyl)-2,3-dihydro-1H, 1, 5-benzodiazepine: Lemon Yellow, m.p. 160ºC Anal. Calcd for $C_{23}H_{22}N_2O_3$ (374): C 73.78, H 5.92. Found: 73.80 H 5.90 **NMR (CDCl$_3$, δppm)**: 4.07 [s, Ar-C-NH], 5.28 [dd, 1H, Ar-C-Hx], 3.12 [dd, 1H, H_α methylene], 2.91 [dd, 1H, H_β methylene], 6.81-7.48 [m, broad & unresolved, Ar-H], 9.83 [s, 1H, OH], 3.84 [s,s, 2x3H, 2x -OCH_3] **IR (ν/cm^{-1})**: 3338 (–NH str.), 2830, 1598 ($\nu_{C=C}$ & $\nu_{C=N}$ str.), 1560, 1490, 1402, 1348, 1292, 1238, 1182, 1124, 1088, 1028, 998, 950, 884, 818, 784, 748, 698, 650 **FABMS (m/z)**: 374 $[M]^{+\cdot}$, 357 $[M-OH]^{+\cdot}$, 344 $[M-OCH_2]^{+\cdot}$, 343 $[M-OCH_3]^{+\cdot}$, 296 $[M-C_2H_6O_3]^{+\cdot}$, 283 $[M-C_3H_7O_3]^+$, 257 $[M-C_5H_9O_3]^+$, 235 $[M-C_7H_9O_2N]^{+\cdot}$, 190 $[M-C_8H_{12}O_3N_2]^{+\cdot}$, 191 $[M-C_8H_{11}O_3N_2]^+$, 188 $[M-C_8H_{14}O_3N_2]^{+\cdot}$, 75 $[M-C_{17}H_{19}N_2O_3]^{+\cdot}$.

(3f) 4-(2'-Hydroxy phenyl)-2-(4-hydroxy-3-methoxy phenyl)-2,3-dihydro-1H, 1, 5-benzodiazepine: Dark Yellow, m.p. 154ºC Anal. Calcd for $C_{22}H_{20}N_2O_3$ (360): C 73.32, H 5.59. Found: 73.31, H 5.62 **NMR (CDCl$_3$, δppm)**: 4.09 [s, Ar-C-NH], 5.06 [dd, 1H, Ar-C-Hx], 3.12 [dd, 1H, H_α methylene], 2.91 [dd, 1H, H_β methylene], 6.75-7.47 [m, broad & unresolved, Ar-H], 9.64 [s, 1H, OH], 3.82 [s, 3H, OCH_3] **IR (ν/cm^{-1})**: 3402 (–NH str.), 2850, 1595 ($\nu_{C=C}$ & $\nu_{C=N}$ str.), 1575, 1488, 1458, 1353, 1278, 1102, 888, 817, 733, 628 **FABMS (m/z)**: 360 $[M]^{+\cdot}$, 343 $[M-OH]^+$, 326 $[M-O_2H_2]^{+\cdot}$, 313 $[M-CH_3O_2]^+$, 311 $[M-CH_5O_2]^+$, 300 $[M-C_2H_4O_2]^{+\cdot}$, 296 $[M-CH_4O_3]^+$, 257 $[M-C_4H_7O_3]^+$, 237 $[M-C_7H_9ON]^{+\cdot}$, 222 $[M-C_7H_8O_2N]^+$, 195 $[M-C_8H_9O_2N_2]^+$, 152 $[M-C_{10}H_{12}O_3N_2]^{+\cdot}$.

CONCLUSION

In conclusion, the synthesis of 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepine (**3a-f**) have been carried out under conventional (thermal) and microwave irradiated solvent and solid phase conditions. Microwave assisted silica gel supported reaction resulted in improved yields with easier work up of the desired product as compares to other methods .Potential significant antibacterial activity was observed with compound **3b**, **3c**, **3d** both gram positive and gram negative bacteria.

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