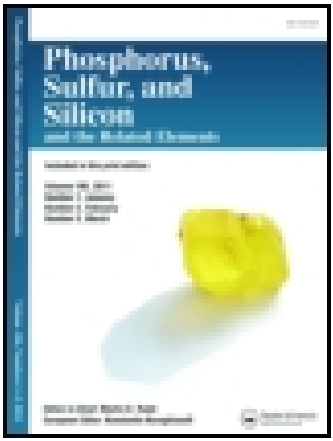

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An Efficient Synthesis of 1,5-Thiadiazepines and 1,5-Benzodiazepines by Microwave-Assisted Heterocyclization

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An Efficient Synthesis of 1,5-Thiadiazepines and 1,5-Benzodiazepines by Microwave-Assisted Heterocyclization

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A novel and efficient method for the synthesis of substituted thiazepines and diazepines has been developed. A simple one-pot reaction of chalcones ***1a–f*** *with 1-amino-2-mercapto-5-phenyl-1,3,4-triazole and o-phenylenediamine in the presence of a catalytic amount of sodium acetate under microwave irradiation gave 2-(3,8-diphenyl-7,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepin-6-yl)phenoles* ***2a–f*** *and 2-(2-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-4-yl)phenoles* ***3a–f****, respectively. The structure of all the synthesized compounds was elucidated on the basis of elemental analysis, IR,* ^{1}H *and* ^{13}C *NMR, and mass spectral data.*

Keywords 1-amino-2-mercapto-5-aryl-1,3,4-triazole; chalcones; heterocycliczation; microwave irradiation; o-phenylenediamine

Received; accepted.

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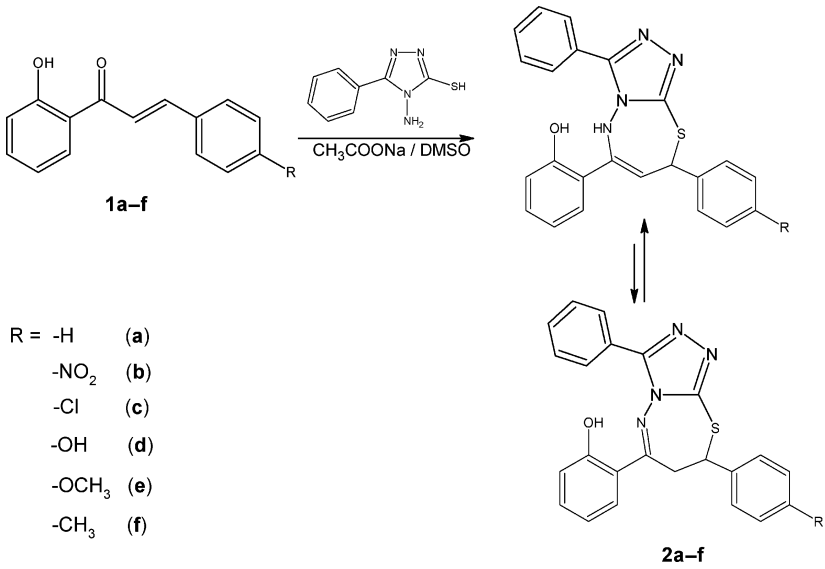
INTRODUCTION

The synthesis of compounds belonging to the thiazepine and diazepine series constitute an important area of research due to their interesting diverse biological activities, such as antibacterial,[1] antifeedent,[2] analgesic,[3] anticoagulant,[4] antihypertensive,[5] and antidepresent[6] properties. In addition, 1,5-benzothiazepines and benzodiazepines are used as starting materials for the preparation of fused ring compounds, such as triazolo- and oxadiazolo-benzodiazepines.[7] Despite their importance from a pharmacological and synthetic point of view, few methods for the preparation of benzodiazepines and benzothiazepines are reported in the literature.[8–10] Recently, Dandia et al. reported a solvent-free synthesis of 1,5-benzothiazepines in the presence of a solid support under microwave irradiation.[11] The most straightforward protocol for the synthesis of 1,5- benzothiazepines **2a–f** and benzodiazepines **3a–f** involves the one-pot condensation of chalcones **1a–f** with 1-amino-2-mercapto-5-aryl-1,3,4-triazoles and *o*-phenylenediamine in ethanol under strongly acidic conditions.[12–13] However, the combination of solvents, a strong acid, and long reaction time makes this method environmentally hazardous. Thus, a simple, general, and efficient procedure for the synthesis of this important heterocyclic system is required. Recently, Microwave-Induced Organic Reaction Enhancement (MORE) chemistry is gaining popularity as an unconventional technique for rapid organic synthesis.[14–15] Many researchers have described accelerated organic reactions, and a number of papers appeared proving the synthetic utility of MORE chemistry in routine organic synthesis.[16–17]

In continuation of our work on the synthesis of novel heterocyclic compounds[18–21] under the framework of "green chemistry," we report herein the synthesis of 1,5-benzodiazepines and benzothiazepines by the reaction of chalcones with *o*-phenylenediamine and 1-amino-2-mercapto-5-phenyl-1,3,4-triazole in the presence of sodium acetate in DMSO as an environmentally benign synthesis of the title compounds. A further advantage of this method is the synthesis on a preparative scale in one step.

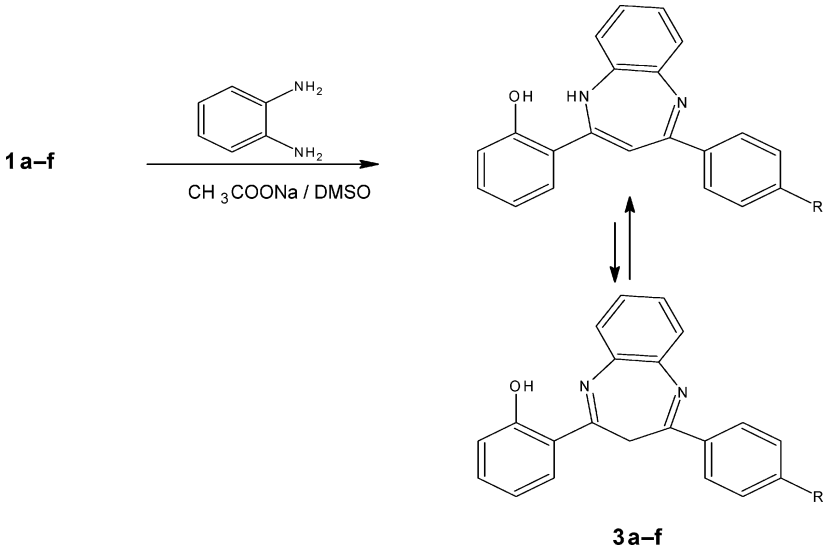
The starting compounds **1a–f** required for the study were prepared by the reaction of 2-hydroxyacetophenone with various benzaldehydes according to the reported method.[22] Chalcones **1a–f**, when reacted with 1-amino-2-mercapto-5-phenyl-1,3,4-triazole in the presence of sodium acetate in DMSO, underwent heterocyclization to give the corresponding 1,5-thiadiazepines **2a–f** (Scheme 1) in good yields.

Similarly, the synthesis of 1,5-diazepines **3a–f** (Scheme 2) was accomplished by employing the reaction of chalcones with *o*-phenylenediamine followed by heterocyclization under microwave



SCHEME 1

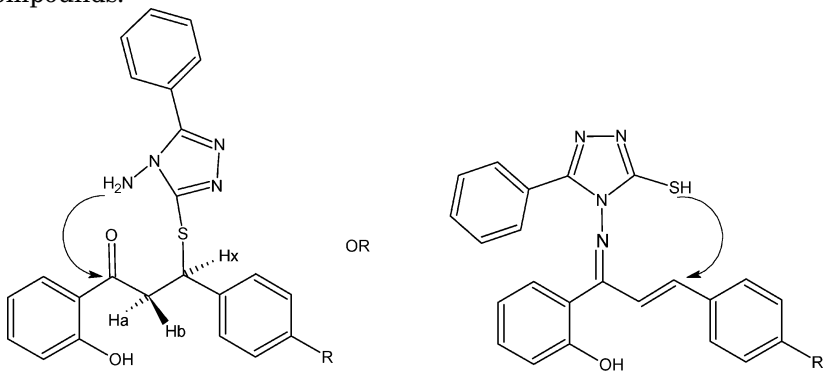
irradiation in excellent yields of 78–95%. This new approach firmly confirms the great utility of microwave stimulation in heterocyclization reactions for the synthesis of complex condensed heterocyclic systems.



SCHEME 2

RESULTS AND DISCUSSION

The formation of the products probably involves the intermediates **4** or **5**, (Scheme 3) which could produce **2a–f** and **3a–f**. The formation of the condensed heterocyclic compounds by the dehydration of **4** could be favorable in a nonaqueous medium. A dipolar transition state is involved in the formation of intermediates **4** and **5** by the 1,2- and 1,4-addition[23] to the carbonyl group and to the β-carbon atom of the α, β-unsaturated carbonyl system, followed by cyclization to give title compounds.



4 **5**

SCHEME 3

Many of the conventional methods for heterocyclization with chalcones need strong basic conditions and give enamines, which tautomerize to diazepines. In this case, cyclization occurred under a microwave irradiation condition even in the presence of the weak base sodium acetate. Microwave-assisted synthesis yielded the tautomerized ring system as indicated by ^{1}H NMR studies. Structures of synthesized compounds were assigned on the basis of their IR, ^{1}H NMR, and mass spectral data. The IR spectrum of **1a** showed an absorption band at 1640 cm^{-1} corresponding to the carbonyl group. 1-amino-2-mercapto-5-phenyl-1,3,4-triazole displayed peaks at 3410–2580 cm^{-1} corresponding to —NH and —SH, which were found to be absent in the IR spectrum of **2a**. Also, **2a** showed the absence of a band at 1650–1653 cm^{-1} corresponding to a carbonyl group, thus further confirming the ring closure.

The ^{1}H NMR spectrum of **2a** recorded in DMSO as a solvent showed signals only in the aromatic region corresponding to 16 protons, of which 14 were attributed to aromatic protons ($\delta = 6.86$–8.18), one to —NH ($\delta = 8.09$), and another to —CH = ($\delta = 7.83$) of the azepine ring. The >CH—S proton was found to resonate at $\delta = 3.40$ ppm. The structure assigned was further confirmed by mass spectral studies. It gave the

molecular ion peak at m/z 398 (M^+), 305, 298, 279, 253 (100%), 224, 197, 165, 121, 105, 89, and 77, and compound **3a** gave m/z 312 (M^+), 235, 209 (100%), 182, 133, 119, 91, and 65.

To conclude, the present investigation describes a two-step synthesis of the heterocycles **2** and **3**. The microwave-assisted route, besides being advantageous because of the simple reaction conditions and the easy work-up procedures, has resulted in improved yields compared to conventional methods.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. Melting points were determined on a Koflar hot-stage apparatus and are uncorrected. IR spectra were recorded with a FT Bruker spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were recorded with a Varian VXR-300 (300 MHz) spectrometer in DMSO-d_6 solutions. Chemical shifts are given in ppm downfield from TMS. Microanalyses were obtained with a fisions EA 1108 instrument. Silica gel (Merck; 60–120 mesh) and DC-Alufolien 60 F254 were normally used for column and thin layer chromatography, respectively. Microwave-assisted procedures were carried out in a domestic Whirlpool microwave oven operating at 1000 W.

The Synthesis of 1,5-Thiazepines 2a–f: General Procedure

Equimolar quantities of 1-amino-2-mercapto-5-phenyl-1,3,4-triazole (0.96 g, 5 mmol) and chalcone (1.12 g, 5 mmol) in 15 mL of DMSO containing a catalytic amount of sodium acetate were filled in a conical flask capped with a glass funnel, placed in a microwave oven, and irradiated for 6–8 min at 500 W with short interruptions of 30 sec to 1 min to avoid an excessive evaporation of the solvent. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to r.t., diluted with water (2×50 mL), and extracted with $CHCl_3$(2×25 mL). The solvent was evaporated, and the residue recrystallized from ethanol to afford analytically pure samples of **2a–f**.

2-(3,8-Diphenyl-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepin-6-yl)phenol (2a)

Solid; (83%), m.p. 180–183°C, MS: (M^+) 398; IR (KBr, ν, cm^{-1}): 1320 (C—N), 1595 (C=C), 1689 (C=N); ^1H NMR (δ, DMSO-d_6): 3.41 (d, 1H, —CH—S), 6.85–8.21 (m, 14H, Ar—H), 7.84 (s, 1H, —CH=), 8.05 (s, 1H, —NH), 10.29 (s, 1H, —OH); ^{13}C NMR (δ, DMSO-d_6): 145.1 (C—OH),

112.1, 113.2, 114.4, 115.3, 116.4, 126.1, 126.3, 127.2, 127.4, 128.3, 128.5, 130.1, 131.3, 132.2, 132.1, 133.2, 133.5, 134.1, 134.8 (aromatic carbons), 164.1 (C_4,—C=N), 166.3 (C_{10},—C=N), 167.4 (C_7,—C=N); anal. calcd. for $C_{23}N_4OH_{18}S$ (398.48): C, 69.32; H, 4.55; N, 14.06. Found: C, 69.10; H, 4.50; N, 13.95.

2-[8-(4-Nitrophenyl)-3-phenyl-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepin-6-yl)phenol (2b)

Solid; (92%), m.p. 192–195°C, MS: (M^+) 443; IR (KBr, ν, cm^{-1}): 1325 (C—N), 1350 (N=O), 1625 (C=C), 1689 (C=N); ^{1}H NMR (δ, DMSO-d_6): 3.40 (d, 1H, —CH—S), 6.84–8.20 (m, 13H, Ar—H), 7.81 (s, 1H, —CH=), 8.15 (s, 1H, —NH), 10.28 (s, 1H, —OH); ^{13}C NMR (δ, DMSO-d_6): 121.2 (C—NO_2), 145.13 (C—OH), 112.2, 113.2, 114.4, 115.3, 116.4, 126.2, 126.2, 127.4, 128.3, 128.4, 130.1, 131.3, 132.2, 132.2, 133.1, 133.4, 134.2, 134.8 (aromatic carbons), 164.2 (C_4,—C=N), 166.2 (C_{10},—C=N), 167.4 (C_7,—C=N); anal. calcd. for $C_{23}N_5O_3H_{17}S$ (443.48): C, 62.29; H, 3.86; N, 15.79. Found: C, 61.85; H, 3.90; N, 15.65.

2-[8-(4-Chlorophenyl)-3-phenyl-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepin-6-yl)phenol (2c)

Solid; (87%), m.p. 187–190°C, MS: (M^+) 432; IR (KBr, ν, cm^{-1}): 1315 (C—N), 1615 (C=C), 1679 (C=N); ^{1}H NMR (δ, DMSO-d_6): 3.42 (d, 1H, —CH—S), 6.86–8.19 (m, 13H, Ar—H), 7.83 (s, 1H, —CH=), 8.09 (s, 1H, —NH), 10.30 (s, 1H, —OH); ^{13}C NMR (δ, DMSO-d_6): 134.6 (C—Cl), 145.7 (C—OH), 112.2, 113.2, 114.3, 115.3, 116.4, 126.2, 126.3, 127.2, 128.2, 128.5, 130.1, 131.4, 132.2, 132.1, 133.1, 133.4, 134.2, 134.8 (aromatic carbons), 164.1 (C_4,—C=N), 166.3 (C_{10},—C=N), 167.4 (C_7,—C=N); anal. calcd. for $C_{23}N_4OH_{17}SCl$ (432.93): C, 63.81; H, 3.96; N, 12.94. Found: C, 63.45; H, 3.60; N, 11.95.

2-[8-(4-Hydroxyphenyl)-3-phenyl-7,8-dihydro[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazepin-6-yl)phenol (2d)

Solid; (90%), m.p. 195–197°C, MS: (M^+) 414; IR (KBr, ν, cm^{-1}): 1325 (C—N), 1645 (C=C), 1680 (C=N), 3325 (O—H, H-bonding), 3594 (O—H); ^{1}H NMR (δ, DMSO-d_6): 3.40 (d, 1H, —CH—S), 6.87–8.21 (m, 13H, Ar—H), 7.86 (s, 1H, —CH=), 8.10 (s, 1H, —NH), 9.81 (s, 1H, —OH), 10.29 (s, 1H, —OH); ^{13}C NMR (δ, DMSO-d_6): 145.5 (C—OH), 112.4, 113.2, 114.4, 115.4, 116.4, 126.17, 126.22, 127.2, 128.2, 128.5, 130.2, 131.4, 132.13, 132.15, 133.2, 133.5, 134.1, 134.8 (aromatic carbons), 164.1 (C_4,—C=N), 166.3

($C_{10,}$—C=N), 167.5 ($C_{7,}$—C=N); anal. calcd. for $C_{23}N_4O_2H_{18}S$ (414.98): C, 66.65; H, 4.38; N, 13.52. Found: C, 65.95; H, 4.10; N, 13.50.

2-[8-(4-Methoxyphenyl)-3-phenyl-7,8-dihydro[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazepin-6-yl)phenol (2e)

Solid; (84%), m.p. 183–185°C, MS: (M^+) 428; IR (KBr, ν, cm^{-1}): 1260 (O—C), 1340 (C—N), 1669 (C=N), 1675 (C=C); ^{1}H NMR (δ, DMSO-d_6): 3.42 (d, 1H, —CH—S), 3.82 (s, 3H, OCH_3), 6.83–8.17 (m, 13H, Ar—H), 7.87 (s, 1H, —CH=), 8.03 (s, 1H, —NH), 10.31 (s, 1H, —OH); ^{13}C NMR (δ, DMSO-d_6): 56.2 (OCH_3), 145.6 (C—OH), 159.4 (C—OCH_3), 112.6, 113.2, 114.2, 115.3, 116.4, 126.2, 126.3, 127.2, 128.2, 128.5, 130.1, 131.4, 132.2, 132.1, 133.1, 133.4, 134.2, 134.8 (aromatic carbons), 164.1 (C_4,—C=N), 166.3 ($C_{10,}$—C=N), 167.5 ($C_{7,}$—C=N); anal. calcd. for $C_{24}N_4O_2H_{20}S$ (428.51): C, 67.27; H, 4.70; N, 13.07. Found: C, 67.10; H, 4.97; N, 13.45.

2-[8-(4-Methylphenyl)-3-phenyl-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepin-6-yl]phenol (2f)

Solid; (80%), m.p. 180–184°C, MS: (M^+) 412; IR (KBr, ν, cm^{-1}): 1340 (C—N), 1635 (C=C), 1675 (C=N); ^{1}H NMR (δ, DMSO-d_6): 3.15 (s, 3H, CH_3), 3.41 (d, 1H, —CH—S), 6.86–8.20 (m, 13H, Ar—H), 7.89 (s, 1H, —CH=), 8.05 (s, 1H, —NH), 10.30 (s, 1H, —OH); ^{13}C NMR (δ, DMSO-d_6): 36.2 (CH_3), 136.2 (C—CH_3), 145.3 (C—OH), 112.3, 113.2, 114.5, 115.3, 116.4, 126.15, 126.24, 127.4, 128.3, 128.4, 130.1, 131.3, 132.17, 132.15, 133.1, 133.4, 134.2, 134.8 (aromatic carbons); 164.1 (C_4,—C—N), 166.3 ($C_{10,}$—C=N), 167.4 ($C_{7,}$—C=N); anal. calcd. for $C_{24}N_4OH_{20}S$ (412.51): C, 69.88; H, 4.89; N, 13.58. Found: C, 69.75; H, 4.25; N, 12.90.

The Synthesis of 1,5-Diazepines 3a–f: General Procedure

The same procedure that was previously described was followed with equimolar quantities of *o*-phenylenediamine (0.54 g, 5 mmol) and chalcone (1.12 g, 5 mmol) in 15 mL of DMSO containing a catalytic amount of sodium acetate.

2-(2-Phenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-4-yl)phenol (3a)

Solid; (86%), m.p. 108–110°C, MS: (M^+) 312; IR (KBr, ν, cm^{-1}): 1320 (C—N), 1595 (C=C), 1689 (C=N), 3300 (O—H), 3340 (N—H); ^{1}H NMR (δ, DMSO-d_6): 6.87–8.21 (m, 13H, Ar—H), 7.86 (s, 1H, —CH=), 8.06 (s, 1H, —NH), 10.29 (s, 1H, —OH); ^{13}C NMR (δ, DMSO-d_6): 145.6 (C—OH),

112.4, 113.3, 114.1, 114.4, 115.6, 116.6, 126.2, 126.6, 127.4, 128.3, 128.6, 130.1, 131.2, 132.1, 132.5, 133.5, 133.6, 134.2, 134.6, (aromatic carbons), 165.8 (C=N); anal. calcd. for $C_{21}H_{16}N_2O$ (312.36): C, 80.75; H, 5.16; N, 8.97. Found: C, 80.60; H, 5.05; N, 8.86.

2-[2-(4-Nitrophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-4-yl]phenol (3b)

Solid; (95%), m.p. 123–125°C, MS: (M^+) 357; IR (KBr, ν, cm^{-1}): 1325 (C–N), 1350 (N=O), 1625 (C=C), 1690 (C=N), 3310 (O–H), 3345 (N–H); ^{1}H NMR (δ, DMSO-d_6): 6.86–8.20 (m, 12H, Ar–H), 7.82 (s, 1H, –CH=), 8.07 (s, 1H, –NH), 10.30 (s, 1H, –OH); ^{13}C NMR (δ, DMSO-d_6): 145.3 (C–OH), 121.2 (C–NO_2), 112.4, 113.3, 114.2, 114.3, 115.6, 116.6, 126.2, 126.6, 128.3, 128.6, 130.1, 131.2, 132.1, 132.4, 133.4, 133.7, 134.1, 134.5, (aromatic carbons), 165.7 (C=N); anal. calcd. for $C_{21}H_{15}N_3O_3$ (357.36): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.51; H, 4.25; N, 11.75.

2-[2-(4-Chlorophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-4-yl]phenol (3c)

Solid; (85%), m.p. 117–120°C, MS: (M^+) 346; IR (KBr, ν, cm^{-1}): 1320 (C–N), 1630 (C=C), 1635 (C=N), 3325 (O–H), 3345 (N–H); ^{1}H NMR (δ, DMSO-d_6): 6.83–8.17 (m, 12H, Ar–H), 7.78 (s, 1H, –CH=), 8.09 (s, 1H, –NH), 10.28 (s, 1H, –OH); ^{13}C NMR (δ, DMSO-d_6): 134.6 (C–Cl), 145.4 (C–OH), 112.5, 113.3, 114.1, 114.3, 115.5, 116.6, 126.2, 126.6, 127.4, 128.3, 128.6, 130.1, 131.2, 132.1, 132.5, 133.3, 133.7, 134.2, 134.5, (aromatic carbons), 164.2 (C=N); anal. calcd. for $C_{21}N_2OH_{15}Cl$ (346.81): C, 72.73; H, 4.36; N, 8.08. Found: C, 72.90; H, 4.59; N, 8.05.

2-[2-(4-Hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-4-yl]phenol (3d)

Solid; (91%), m.p. 110–115°C, MS: (M^+) 328; IR (KBr, ν, cm^{-1}): 1335 (C-N), 1589 (C=N), 1595 (C=C), 3320 (N–H), 3345 (O–H, H–bonding), 3684 (O–H); ^{1}H NMR (δ, DMSO-d_6): 6.87–8.21 (m, 12H, Ar–H), 7.76 (s, 1H, –CH=), 8.12 (s, 1H, –NH), 9.79 (s, 1H, –OH), 10.30 (s, 1H, –OH), ^{13}C NMR (δ, DMSO-d_6)δ: 145.5 (C=OH), 112.5, 113.4, 114.2, 114.4, 115.5, 116.7, 126.2, 126.6, 127.4, 128.3, 128.6, 130.2, 131.2, 132.2, 132.5, 133.4, 133.7, 134.2, 134.5, (aromatic carbons), 165.1 (C=N); anal. calcd. for $C_{21}N_2O_2H_{16}$(328.36): C, 76.81; H, 4.91; N, 8.53. Found: C, 76.20; H, 5.20; N, 8.45.

2-[2-(4-Methoxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-4-yl]phenol (3e)

Solid; (86%), m.p. 120–122°C, MS: (M^+) 342; IR (KBr, ν, cm^{-1}): 1230 (C—O), 1330 (C—N), 1625 (C=C), 1659 (C=N), 3300 (N—H), 3335 (O—H); ^{1}H NMR (δ, DMSO-d_6): 3.75 (s, 3H, —OCH_3), 6.83–8.17 (m, 12H, Ar—H), 7.81 (s, 1H, —CH=), 8.06 (s, 1H, —NH), 10.28 (s, 1H, —OH); ^{13}C NMR (δ, DMSO-d_6): 56.6 (OCH_3), 145.3 (C—OH), 112.4, 113.3, 114.2, 114.3, 115.6, 116.6, 126.2, 126.6, 128.3, 128.6, 130.1, 131.2, 132.1, 132.4, 133.4, 133.7, 134.1, 134.5, (aromatic carbons), 165.7 (C=N); anal. calcd. for $C_{22}N_2O_2H_{18}$ (342.39): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.59; H, 5.25; N, 8.05.

2-[2-(4-Methylphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepin-4-yl]phenol (3f)

Solid; (78%), m.p. 125–127°C, MS: (M^+) 326; IR (KBr, ν, cm^{-1}): 1320 (C-N), 1620 (C=C), 1689 (C=N), 3310 (O—H), 3350 (N—H); ^{1}H NMR (δ, DMSO-d_6): 3.21 (s, 3H, CH_3), 6.86–8.20 (m, 12H, Ar—H), 7.82 (s, 1H, —CH=), 8.05 (s, 1H, —NH), 10.31 (s, 1H, —OH); ^{13}C NMR (δ, DMSO-d_6) δ: 36.2 (CH_3), 145.6 (C—OH), 112.5, 113.3, 114.1, 114.4, 115.5, 116.7, 126.2, 126.6, 128.3, 128.6, 130.1, 131.2, 132.2, 132.4, 133.4, 133.7, 134.1, 134.5, (aromatic carbons), 166.0 (C=N); anal. calcd. for $C_{22}N_2OH_{18}$ (326.39): C, 80.96; H, 5.56; N, 8.58. Found: C, 79.95; H, 6.05; N, 8.49.

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