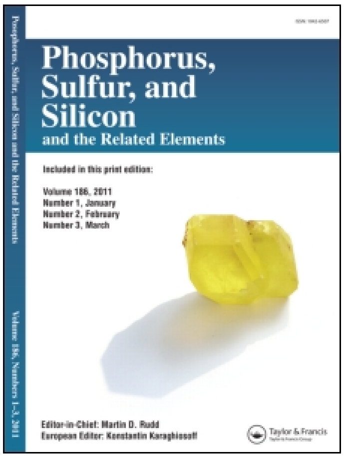

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An Efficient Synthesis of 1,5-Thiadiazepines and 1,5-Benzodiazepines by Microwave-Assisted Heterocyclization

Gundibasappa K. Nagaraja[a]; Vijayavittala P. Vaidya[b]; Koodamara Sheshappa Rai[a]; Kittappa M. Mahadevan[b]
[a] Department of PG Studies and Research in Polymer Science, University of Mysore, Sir M. V. PG Centre, Thubinakere, Mandya, Karnataka, India [b] Department of PG Studies and Research in Chemistry, Kuvempu University, Shankaraghatta, Shimoga, Karnataka, India

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

Gundibasappa K. Nagaraja
Department of PG Studies and Research in Polymer Science, University of Mysore, Sir M. V. PG Centre, Thubinakere, Mandya, Karnataka, India

Vijayavittala P. Vaidya
Department of PG Studies and Research in Chemistry, Kuvempu University, Shankaraghatta, Shimoga, Karnataka, India

Koodamara Sheshappa Rai
Department of PG Studies and Research in Polymer Science, University of Mysore, Sir M. V. PG Centre, Thubinakere, Mandya, Karnataka, India

Kittappa M. Mahadevan
Department of PG Studies and Research in Chemistry, Kuvempu University, Shankaraghatta, Shimoga, Karnataka, India

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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Address correspondence to Kittappa M. Mahadevan, Kuvempu University, Department of PG Studies and Research in Chemistry, Shankaraghatta, Shimoga, Karnataka, 577 451 India. E-mail: mady_kmm@yahoo.co.uk

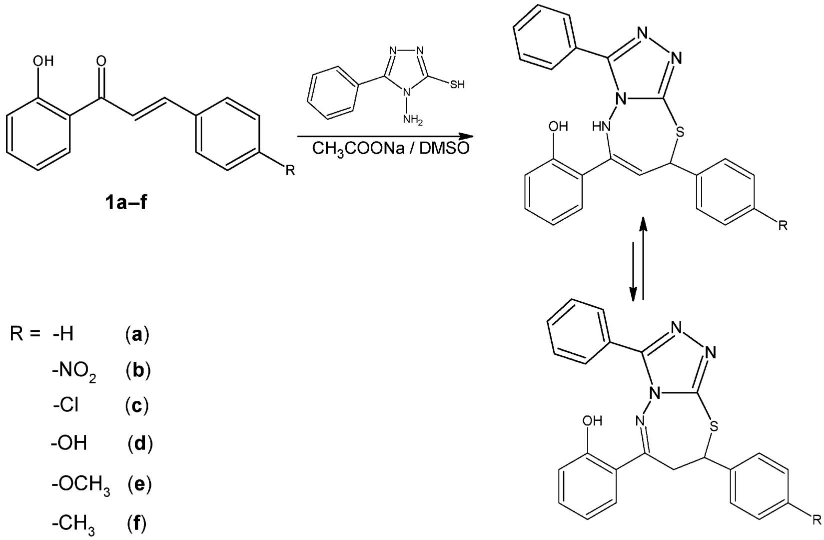
INTRODUCTION

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.

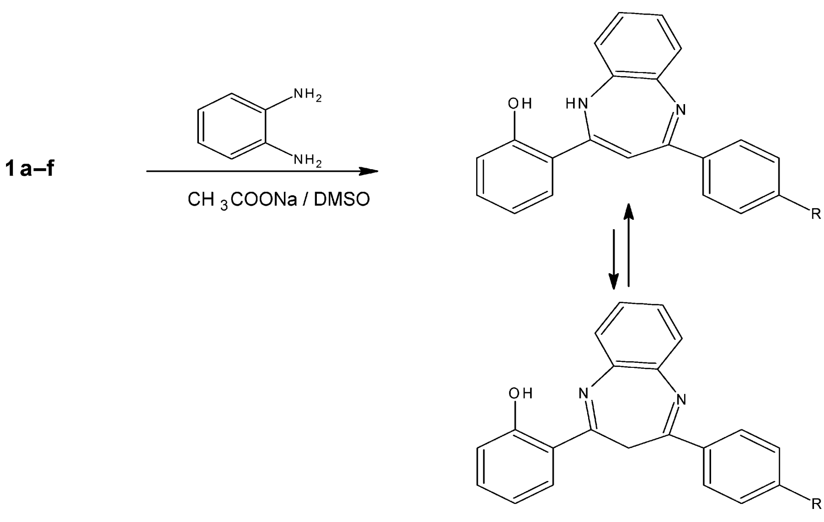
Similarly, the synthesis of 1,5-diazepines **3a–f** (Scheme 2) was accomplished by employing the reaction of chalcones with *o*-phenylenediamine followed by heterocyclization under microwave



2a–f

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.

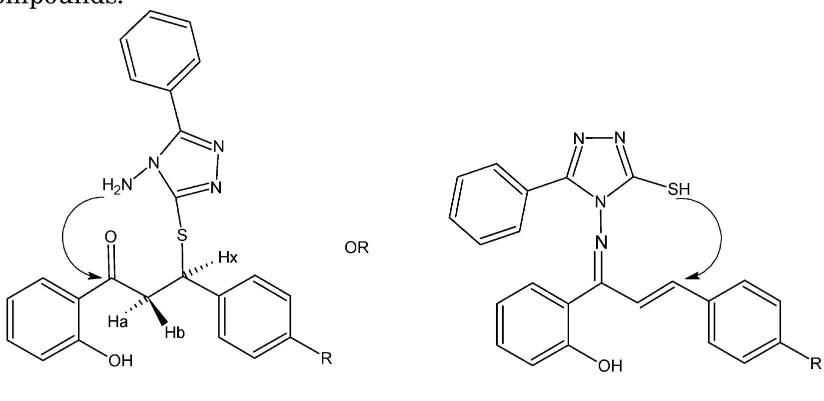


3 a–f

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 (δ = 6.86–8.18), one to —NH (δ = 8.09), and another to —CH = (δ = 7.83) of the azepine ring. The >CH—S proton was found to resonate at δ = 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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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