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SYNTHESIS OF PYRAZOLO[3,4-b]- AND PYRIDO[2,3-b]-1,5-BENZODIAZEPINES

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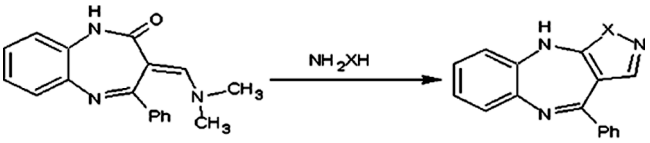
GRAPHICAL ABSTRACT



Abstract *3-Dimethylaminomethyleno-4-phenyl-1H-1,5-benzodiazepin-2-one (**1**) was synthesized and reacted with hydrazines, active nitriles, and amino-heterocyclic compounds to give fused heterocyclic compounds* **2–14**.

Keywords Pyrazolo(3,4-b)- and pyrido(2,3-b)-4-phenyl-1H-1,5-benzodiazepines

INTRODUCTION

The pharmacological activities[1–5] of pyrazolo- and pyridobenzodiazepines prompted us to contine our previous work on the synthesis of fused and spiro-1,5 benzodiazepines.[1,6–9] Enaminones have been utilized extensively as building blocks in organic synthesis of polyfunctionally substituted heterocycles.[10–15] We report here the utility of 3-dimethylaminomethyleno-4-phenyl-1H-1,5-benzodiazepin-2-one (**1**) for the syntheses of pyrazole, isoxazole, and pyridine derivatives, hoping to get compounds with better biological activity for medicinal applications.

RESULTS AND DISCUSSION

3-Dimethylaminomethyleno-4-phenyl-1H-1,5-benzodiazepin-2(3H)-one (**1**) was synthesized from the reaction of 1,3-dihydro-4-phenyl-1,5-benzodiazepin-2-one[1] with dimethylformamidedimethylacetals (DMF-DMA) in refluxing *p*-xylene [Eq. (1)]. ^{1}H NMR spectrum showed new signals at δ 8.00 as a singlet corresponding to the =CH group and at δ 2.36 as a singlet corresponding to the $N(CH_3)_2$ group. Its

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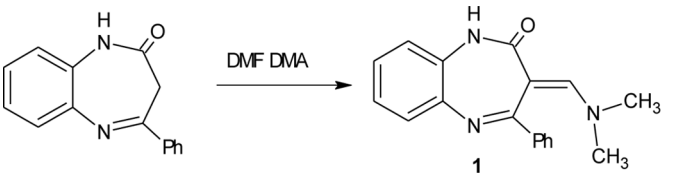
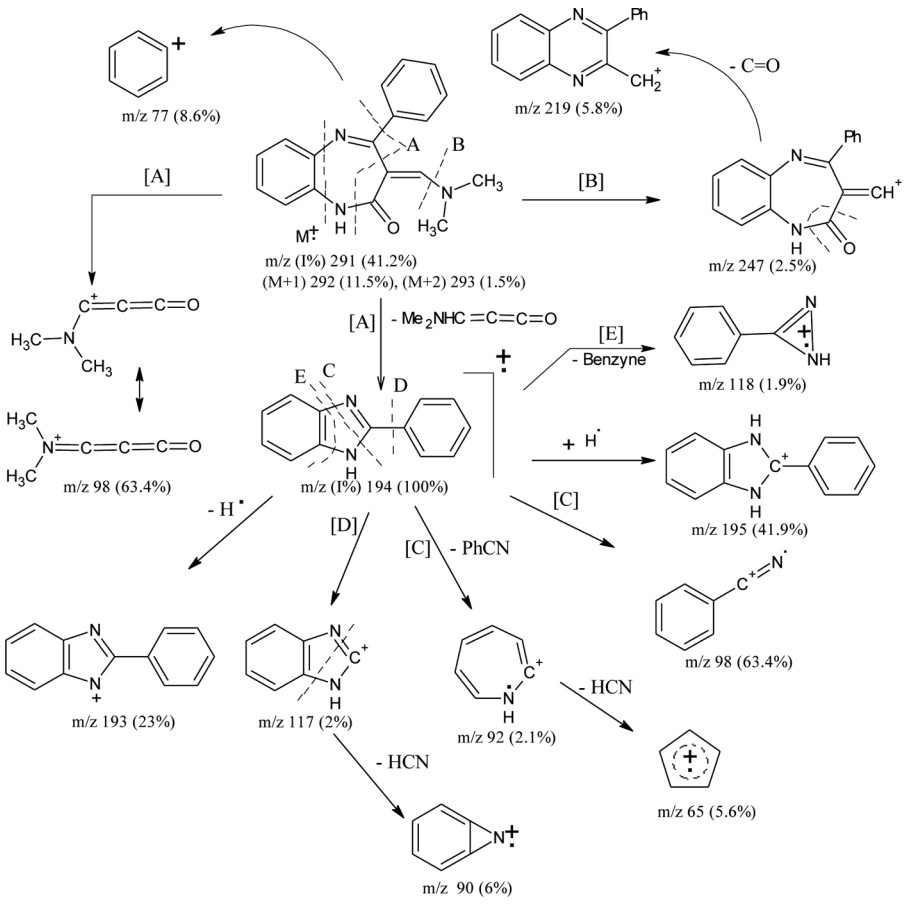
mass spectrum showed m/z (relative abundance) of 291 [(M^+), 41.2%], 392 [($M+1^+$), 11.5%], and 393 [($M+2^+$), 1.5%] (Scheme 1).



(1)

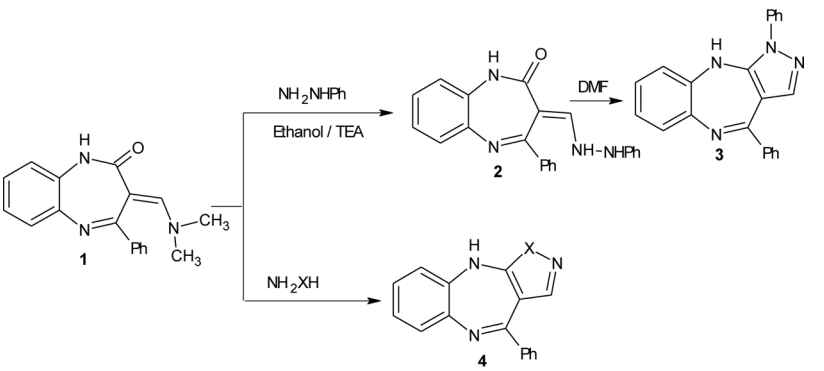
The reaction of enaminone **1** with phenylhydrazine in ethanol in the presence of a catalytic amount of triethylamine afforded 3-(2-phenylhydrazinomethyleno)-4-phenyl-1H-1,5-benzodiazepin-2-one (**2**), which underwent intramolecular cyclization in refluxing dimethylformamide (DMF) to give 1,4-diphenylpyrazolo[3,4-b]-1,5-benzodiazepine (**3**). Treatment of enaminone **1** with hydrazine or hydroxylamine afforded pyrazolo[3,4-b]- and isoxazolo[5,4-b]-1,5-benzodiazepines $\mathbf{4_{a,b}}$, respectively



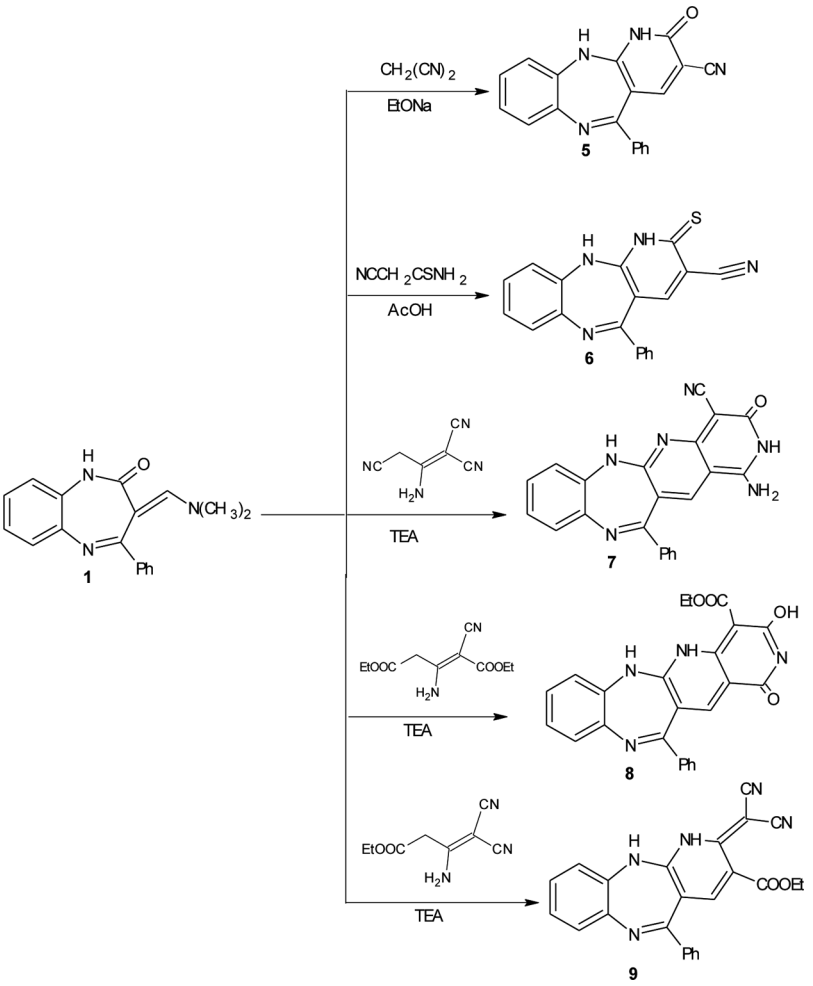
Scheme 1. Mass spectrum fragmentation of enaminone **1**.

(Scheme 2). Infrared (IR) spectra of compounds **3** and $\mathbf{4_{a,b}}$ showed the disappearance of the absorption band corresponding to the C=O group. ^{1}H NMR showed the disappearance of the -N(CH3)$_2$ signal.

Treatment of compound **1** with malononitrile in the presence of sodium ethoxide or cyanothioacetamide in acetic acid gave 3-cyano-5-phenyl-2,11-dihydro-1H-pyrido[2,3-b]-1,5-benzodiazepin-2-one (**5**) or 3-cyano-5-phenyl-2,11-dihydro-1H-pyrido[2,3-b]-1,5-benzodiazepin-2-thione (**6**), respectively (Scheme 3). Their IR spectra showed the new absorption bands corresponding to NH (3310, 3300), CN (2194, 2224), C=O (1688), and C=S (1124), respectively. Mass spectrum of compound **5** showed m/z (relative abundance) M^+, 312 (79%). Treatment of compound **1** with 2-amino-1,1,3-tricyanopropene in the presence of a catalytic amount of triethylamine gave 10-amino-8-oxo-12-phenyl-8,9-dihydro-5H-[1,6]naphthyridino[2,3-b]-1,5-benzodiazepine-7-carbonitrile (**7**) (Scheme 3). Its IR spectrum showed new absorption bands corresponding to NH (3395), NH_2 (3257, 3200), CN (2184), and C=O (1670), respectively. $^{-1}$H NMR spectrum showed deuterium exchangeable proton at $\delta = 10.10$, 7.7, and 5.00–4.64, which are attributed to 2 NH and NH_2 groups. Its MS spectrum showed the fragment ion at m/z 376 due to $(M^+ - 1)$. In analogy, enaminone **1** was reacted with 1,3-diethyl-2-amino-1-cyano-1-propendioate in the presence of triethylamine as a catalyst to give ethyl 8,10-dioxo-12-phenyl-7,8,9,10-tetrahydro-5H-[1,6] naphthyridino[2,3-b]-1,5-benzodiazepine-7-carboxylate (**8**) (Scheme 3). Its IR spectrum showed new absorption bands corresponding to OH (3421), 2NH (3309, 3244), $C{=}O_{ester}$ (1722), and $C{=}O_{amide}$ (1688), respectively. Its ^{1}H NMR spectrum showed deuterium exchangeable protons at $\delta = 10.05$, 6.00, and 2.10, which are attributed to 2 NH and OH groups. Also, enaminone **1** was reacted with 3-ethyl-2-amino-1,1-dicyanopropenoate in the presence of triethylamine as a catalyst to afford pyrido[2,3-b]-1,5-benzodiazepine derivative **9** (Scheme 3). IR spectrum showed new absorption bands corresponding to 2NH (3451, 3244), CN (2222), and CO_{ester} (1714), respectively. ^{1}H NMR spectrum showed the following signals corresponding to $NH_{benzodiazepine}$ at δ 12.00 ppm, =CH at δ 8.20 ppm, $NH_{pyridine}$ at δ 6.20 ppm, aromatic protons at δ 7.00–7.85 ppm, CH_2 at δ 4.10–3.80 ppm, and CH_3 group at δ 1.20–0.90 ppm, respectively, along with a deuterium exchangeable proton at $\delta = 12.00$ ppm and 6.20 ppm, which are attributed to 2 NH groups. The formation



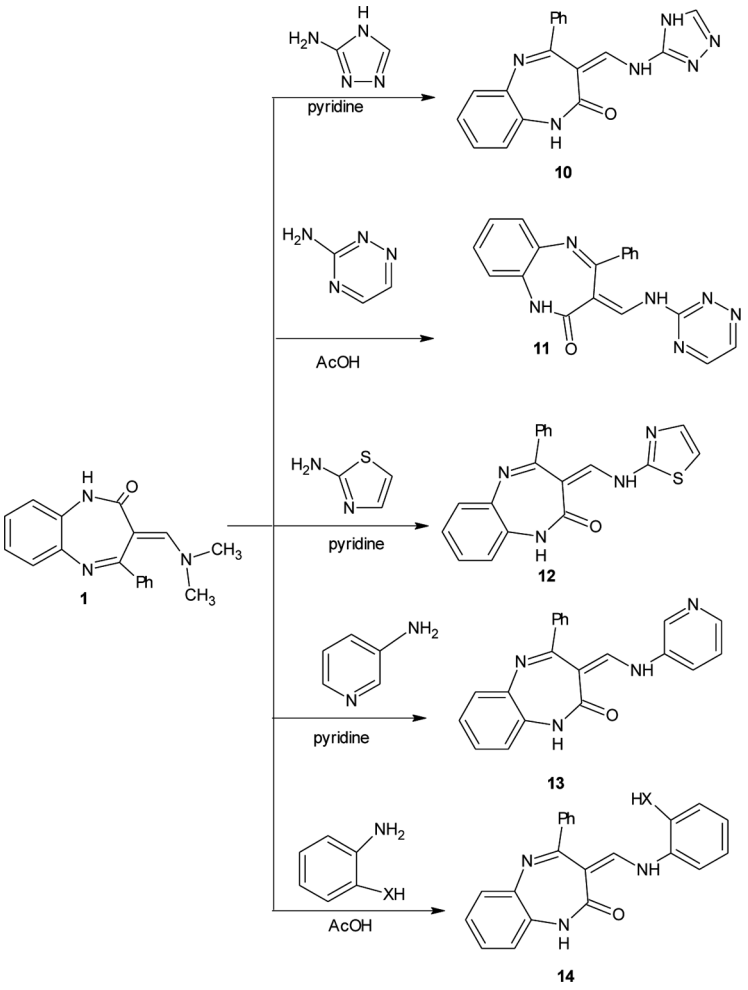
Scheme 2. Reaction of enaminone **1** with hydrazines.



Scheme 3. Reaction of enaminone **1** with active nitriles.

reaction of compounds **7** and **8** was assumed to proceed via nucleophilic attack of the active methylene to the olefinic bond of compound **1** with elimination of dimethylamine, followed by condensation of the amino group with the C=O group, hydrolysation of one of the cyano groups into $CONH_2$, and subsequent addition to the cyano group or the ester group with elimination of the ethanol molecule.

The reaction of compound **1** with 3-amino-1,2,4-triazole, 3-aminotriazene, 2-aminothiazole, 3-aminopyridine, *o*-aminothiophenol, or *o*-phenelenediamine in refluxing pyridine afforded 3-[(1H-1,2,4-triazol-5-yl)aminomethylene]- **10**, 3-[(triazine-3-yl)aminomethylene]- **11**, 3-[(1,3-thiazol-2-yl)aminomethylene]- **12**, 3-[(pyridine-3-yl) aminomethylene]- **13**, 3-[(2-mercaptophenyl)aminomethylene]- $\mathbf{14_a}$, 3-[(2-aminophenyl) aminomethylene]- $\mathbf{14_b}$, and 5-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-ones, respectively (Scheme 4). MS spectrum of compound **10** showed the fragment ion at m/z at 331 (4.5%) due to $(M^+ + 1)$. An attempt was made to cyclize compounds



Scheme 4. Reaction of enaminone **1** with amino-heterocyclic compounds.

10–14$_{a,b}$ in boiling glacial acetic acid[16] but it was unsuccessful. So, we studied these reactions through the minimized energy structure of compounds **10–14$_{a,b}$** by MM2 and AM1, and we noticed that the NH or SH group is out of plan with the carbonyl group of benzodiazepinone (Fig. 1).

EXPERIMENTAL

All melting points are uncorrected and were recorded on a Melt-Temp II melting-point apparatus. Infrared (IR) spectra were measured as KBr pellets on a Nicolet 710 Fourier transform (FT)–IR spectrometer. ^{1}H NMR spectra were recorded in deuterated chloroform or dimethylsulfoxide (DMS) at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane (TMS) as an internal reference. The D_2O experiment was carried out to check acidic protons. Mass

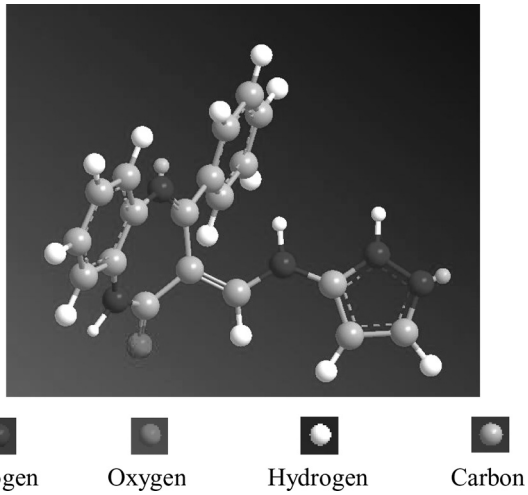


Figure 1. Minimized energy structure of **14** by MM2 and AM1. Software used to minimize energy structures is Chemoffice Ultra 2008, v. 11 (Chem3D Pro 11.0).

spectrometry was performed on a Shimadzu GCMS-QP 1000 mass spectrometer at 70 eV. The elemental analyses were carried on a Perkin-Elimer 2400 analyzer.

3-Dimethylaminomethylene-4-phenyl-1H-1,5-benzodiazepin-2-one (1)

Dimethylformamide dimethylacetal (10 mmol) was added to 4-phenyl-2(H)-1,5-benzodiazepin-2-one[1] (10 mmol), in *p*-xylene (20 ml), and the reaction mixture was refluxed for 3 h, then left to cool. The solid product so formed was filtered, dried, and crystallized from *p*-xylene. Yield 60%; mp 217–219 °C. Found: C, 74.20; H, 5.88; N, 14.42. $C_{18}H_{17}N_3O$ (291.34) requires: C, 74.77; H, 5.45; N, 14.76. IR (KBr): $\nu = 3245$ (NH) cm^{-1}, 1704 (C=O) cm^{-1}, 1605 (C=N) cm^{-1}; ^1H NMR (DMSO): 10.2 (s, 1H, NH), 8.00 (s, 1H, =CH), 7.97–6.90 (m, 9H, arom.), 2.63 [s, 6H, $N(CH_3)_2$] ppm; MS (m/e): 65 (5.6%), 51 (3.5%), 77 (8.6%), 90 (6%), 92 (2.1%), 98 (63.4%), 117 (2%), 118 (1.9%), 193 (23%), 194 (100%), 195 (41.9%), 219 (5.8%), 247 (2.5%), 291 [(M^+), 41.2%], 392 [($M + 1^+$), 11.5%], 393 [($M + 2^+$), 1.5%].

3-(2-Phenylhydrazinomethylene)-4-phenyl-1H-1,5-benzodiazepin-2-one (2)

Phenylhydrazine (10 mmol) and a few drops of triethylamine were added to a suspension of compound **1** (10 mmol) in ethanol (30 ml). The reaction mixture was refluxed for 3 h, then left to cool. The solid product so formed was filtered, dried, and crystallized from dioxane. Yield 66%; mp 237–239 °C. Found: C, 74.20; H, 5.44; N, 15.62. $C_{22}H_{18}N_4O$ requires: C, 74.56; H, 5.12; N, 15.81. IR (KBr): $\nu = 3390$, 3300, 3225 (NH) cm^{-1}, 1690 (C=O) cm^{-1}, 1605 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 10.5$ (s, 1H, NH), 8.00 (s, 1H, =CH), 7.97–6.90 (m, 15H, arom. +NH), 6.4 (br, 1H, NH) ppm.

1,4-Diphenylpyrazolo[3,4-b]-1,5-benzodiazepine (3)

A suspension of compound **2** (5 mmol) in DMF (10 ml) was refluxed for 3 h. The reaction was left to cool and poured into crused ice with HCl (5 ml). The separated solid was filtered, dried, and crystallized from ethanol. Yield 45%; mp 205–207 °C. Found: C, 78.19; H, 4.54; N, 16.92. $C_{22}H_{16}N_4$ requires: C, 78.55; H, 4.79; N, 16.66. IR (KBr): $\nu = 3275$ (NH) cm^{-1}, 1605 (C=N) cm^{-1}; ^1H NMR (DMSO): 10.6 (s, 1H, NH), 8.40 (s, 1H, =CH), 7.97–6.90 (m, 14H, arom.) ppm.

4-Phenylpyrazolo[3,4-b]-1,5-benzodiazepine (4_a)

Hydrazine hydrazine (10 mmol) was added to a suspension of compound **1** (10 mmol) in ethanol (30 ml). The reaction mixture was refluxed for 3 h, then left to cool. The solid product so formed was filtered, dried, and crystallized from benzene. Yield 56%; mp 177 °C. Found: C, 73.60; H, 4.74; N, 21.72. $C_{16}H_{12}N_4$ (260.29) requires: C, 73.83; H, 4.65; N, 21.52. IR ($\nu_{max}\backslash cm^{-1}$): 3380, 3265 (2NH), 1640 (C=N); ^1H NMR ($CDCl_3$): 10.5 (s, 1H, NH), 8.30 (s, 1H, =CH), 7.80–6.50 (m, 10H, arom. +NH) ppm.

5-Phenylisoxazolo[5,4-b](1,5)benzodiazepines (4_b)

A mixture of compound **1** (10 mmol) and hydroxylamine hydrochloride (10 mmol) in dry pyridine (20 ml) was refluxed for 4 h. The reaction mixture was left to cool and poured into a mixture of cold water (50 ml) and HCl (5 ml). The solid product was collected by filtration, dried, and crystallized from chloroforme. Yield 76%; mp 226–228 °C; Found: C, 73.70; H, 4.64; N, 16.32. $C_{16}H_{11}N_3O$ (261.27) requires: C, 73.55; H, 4.24; N, 61.08. IR (KBr): $\nu = 3244$ (NH) cm^{-1}, 1615 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): 10.7 (s, 1H, NH), 8.20 (s, 1H, =CH), 7.97–6.90 (m, 9H, arom.) ppm.

3-Cyano-5-phenyl-2,11-dihydro-1H-pyrido[2,3-b]-1,5-benzodiazepin-2-one (5)

Malononitrile (10 mmol) was added to a suspension of compound **1** (10 mmol) in ethanolic sodium ethoxide (Na, 10 mmol in 20 ml ethanol). The mixture was refluxed for 1 h, left to cool, and poured into a mixture of cold water (20 ml) and HCl (2 ml). The precipitate was collected by filtration, dried, and crystallized in ethanol. Yield 96%; mp 240–242 °C. Found: C, 72.61; H, 4.34; N, 17.62. $C_{19}H_{13}N_4O$ (313.33) requires: C, 72.83; H, 4.18; N, 17.88. IR (KBr): $\nu = 3412$ (OH) cm^{-1}, 3300, 3225 (NH) cm^{-1}, 2194 (CN) cm^{-1}, 1654 (C=O) cm^{-1}; ^1H NMR (DMSO): 10.3 (s, 1H, NH), 8.50 (s, 1H, =CH), 7.70–6.50 (m, 9H, arom.), 5.5 (s, 1H, NH); MS (m/e): 312 (79%), 270 (71.8), 195 (28.7), 134 (98.6), 51 (100) ppm.

3-Cyano-5-phenyl-2,11-dihydro-1H-pyrido[2,3-b]-1,5-benzodiazepine-2-thione (6)

Cyanothioacetamide (10 mmol) was added to a suspension of compound **1** (10 mmol) in glacial acetic acid (30 ml). The reaction mixture was refluxed for 3 h, left

to cool, and poured into cold water (20 ml). The solid product was filtered, dried, and crystallized from dioxane. Yield 80%; mp 186–188 °C. Found: C, 69.60; H, 3.44; N, 17.22; S, 9.90. $C_{19}H_{12}N_4S$ (328.39) requires: C, 69.49; H, 3.68; N, 17.09; S, 9.79. IR (KBr): $\nu = 3310$, 3233 (NH) cm^{-1}, 2221 (CN) cm^{-1}, 1144 (C=S) cm^{-1}; ^1H NMR (DMSO): 10.8 (s, 1H, NH), 8.10 (s, 1H, =CH), 7.70–6.50 (m, 9H, arom.), 6.00 (s, 1H, NH).

Synthesis of Compounds 7–9

2-Amino-1,1,3-tricyano-1-propene (10 mmol), 1,3-diethyl-2-amino-1-cyano-1-propenate (10 mmol), or 3-ethyl-2-amino-1,1-dicyanopropenate (10 mmol), and a few drops of triethylamine were added to a suspension of compound **1** (10 mmol) in ethanol (30 ml). The mixture was refluxed for 4 h, and the precipitated solid so formed was collected by filteration (product **8**). The mixture was left to cool, and the formed solid was obtained by filtration (products **9** and **10**) and crystallized.

10-Amino-8-oxo-12-phenyl-8,9-dihydro-5H-[1,6]naphthyridino[2,3-b]-1,5-benzodiazepine-7-carbonitrile (7). From ethanol. Yield 80%; mp 260–262 °C; MS: $m/z = 376$ (18.5, M), 356 (51.9), 152 (25.9), 153 (18.5), 106 (74.1), 79 (100), 51 (74.1). Found: C, 69.60; H, 3.94; N, 22.45. $C_{22}H_{14}N_6O$ (378.38) requires: C, 69.83; H, 3.73; N, 22.21. IR(KBr): $\nu = 3440$, 3395, 3257, 3200 (NH, NH_2) cm^{-1}, 2184 (CN) cm^{-1}, and 1670 (C=O) cm^{-1}; ^1H NMR (DMSO): 10.10 (s, 1H, NH), 8.20 (s, 1H, =CH), 7.70–6.50 (m, 10H, arom. $+NH_{pyridine}$), 4.3–4.1 (br, 2H, NH_2) ppm.

8,10-Dioxo-12-phenyl-7,8,9,10-tetrahydro-5H-[1,6]naphthyridino[2,3-b]-1,5-benzodiazepine-7-carboxylate (8). From dioxane. Yield 55%; mp 187–189 °C. Found: C, 67.90; H, 4.55; N, 13.31. $C_{24}H_{18}N_4O_4$ (426.42) requires C, 67.60; H, 4.25; N, 13.14. IR(KBr): $\nu = 3309$, 3244 (OH, NH), 1717 ($C{=}O_{ester}$), and 1688 (C=O) cm^{-1}. ^1H NMR (DMSO): 10.60 (s, 1H, NH), 8.40 (s, 1H, =CH), 7.70–6.50 (m, 9H, arom.), 6.00 (s, 1H, NH), 4.10–3.80 (q, CH_2), 2.4–2.1 (br, 1H, OH), 1.20–0.90 (t, 3H, CH_3) ppm.

5-Phenylpyrido[2,3-b]-1,5-benzodiazepine (9). From ethanol. Yield (60%); mp 166–168 °C. Found: C, 70.45; H, 4.50; N, 17.31. $C_{24}H_{17}N_5O_2$ (407.42) requires C, 70.76; H, 4.21; N, 17.19. IR (KBr): $\nu = 3244$, 3200 (2NH), 2222 (CN), and 1714 ($C{=}O_{ester}$) cm^{-1}; ^1H NMR (DMSO): 10.00 (s, 1H, NH), 8.30 (s, 1H, =CH), 7.80–6.90 (m, 9H, arom.), 6.30–6.50 (br, 1H, NH), 4.3–4.00 (q, 2H, CH_2), 1.40–1.00 (t, 3H, CH_3) ppm.

Synthesis of Compounds 10–14

A solution of compound **1** (10 mmol) and 3-amino-1,2,4-triazole, 3-aminotriazene, 3-aminopyridine, 2-aminothiazole, *o*-aminothiophenol, and *o*-phenelenediamine (10 mmol) in pyridine (15 ml) was refluxed for 6 h. The reaction mixture was concentrated, cooled, and poured into a mixture of cold water (50 ml) and HCl (5 ml). The solid product that was obtained on cooling was filtered and crystallized.

3-[(1,2,4-Triazol-5-yl)aminomethylene]-4-phenyl-1,3-dihydro-1H-benzodiazepin-2-one (10). From ethanol. Yield (92%); mp 280–282 °C. Found: C, 65.68;

H, 4.60; N, 25.66. $C_{18}H_{14}N_6O$ (330.34) requires C, 65.44; H, 4.27; N, 25.44. IR (ν_{max}\cm^{-1}): 3332, 3225 (NH), 1704 (C=O) cm^{-1}; ^{1}H NMR (DMSO): 10.3 (s, 1H, NH), 9.0 (s, 1H, =$CH_{triazole}$), 8.50 (br, 1H, =CH), 7.70–6.50 (m, 9H, arom.), 6.5–6.3 (br, 1H, NH) ppm.

3-[(Triazine-3-yl)aminomethylene]-5-phenyl-1,3-dihydro-2H-1,5-benzodiazepin-2-one (11). From dioxane. Yield 80%; mp 233–235 °C. Found: C, 66.85; H, 4.40; N, 24.31. $C_{19}H_{14}N_6O$ (342.35) requires: C, 66.66; H, 4.12; N, 24.55. IR (ν_{max}\cm^{-1}): 3300, 3225 (NH), 1706 (C=O) cm^{-1}; ^{1}H NMR (DMSO): 10.1 (s, 1H, NH), 8.50 (s, 1H, =CH), 7.70–6.50 (m, 10H, arom. +NH), 6.6–6.3 (br, 2H, CH=$CH_{triazene}$) ppm.

3-[(Pyridine-3-yl)aminomethylene]-4-phenyl-1,3-dihydro-2H-1,5-benzodiazepin-2-one (12). From ethanol. Yield 94%; mp 300–302 °C. Found: C, 65.50; H, 4.22; N, 16.39; S, 9.39. $C_{19}H_{14}N_4OS$ (346.40) requires: C, 65.88; H, 4.07; N, 16.17; S, 9.26. IR (ν_{max}\cm^{-1}): 3289, 3221 (NH), 1700 (C=O) cm^{-1}. ^{1}H NMR (DMSO): 11.0 (s, 1H, NH), 8.10 (s, 1H, =CH), 7.70–6.50 (m, 10H, arom. + = $CH_{thiazole}$), 6.5 (s, 1H, NH)ppm.

3-[(Pyridine-3-yl)aminomethylene]-4-phenyl-1,3-dihydro-2H-1,5-benzodiazepin-2-one (13). From acetic acid. Yield (70%); mp 200 °C. Found: C, 74.40; H, 4.520; N, 16.66. $C_{21}H_{16}N_4O$ (340.37) requires: C, 74.10; H, 4.74; N, 16.46. IR (ν_{max}\cm^{-1}): 3280, 3229 (NH), 1701 (C=O) cm^{-1}; ^{1}H NMR (DMSO): 11.0 (s, 1H, NH), 9.1 (s, 1H, CH pyridine), 8.7–8.6 (d, 2H, CH pyridine), 8.30 (s, 1H, =CH), 7.90–6.50 (m, 10H, arom. + = $CH_{thiazole}$), 6.5 (s, 1H, NH) ppm.

3-[(2-Mercaptophenyl)aminomethylene]-4-phenyl-1,3-dihydro-2H-1,5-benzo-diazepin-2-one (14_a). From benzene. Yield 45%; mp 160–162 °C. Found: C, 71.35; H, 4.80; N, 11.51; S, 8.90. $C_{22}H_{17}N_3OS$ (371.45) requires: C, 71.14; H, 4.61; N, 11.31; S, 8.63. IR (ν_{max}\cm^{-1}): 3380, 3219 (NH), 1703 (C=O) cm$^{-1,}$ ^{1}H NMR (DMSO): 10.50 (s, 1H, NH), 8.20 (s, 1H, =CH), 7.80–6.50 (m, 10H, arom. +NH), 2.5 (s, 1H, SH) ppm.

3-[(2-Aminophenyl)aminomethylene]-4-phenyl-1,3-dihydro-2H-1,5-benzodiazepin-2-one (14_b). From dioxane. Yield 70%; mp 255–257 °C. Found: C, 74.25; H, 5.33; N, 15.66. $C_{22}H_{18}N_4O$ (354.40) requires: C, 74.56; H, 5.12; N, 15.81. IR (ν_{max}\cm^{-1}): 3322, 3290, 3230, 3143 (NH_2, NH), 1700 (C=O) cm$^{-1,}$ ^{1}H NMR (DMSO): 11.0 (s, 1H, NH), 8.00 (s, 1H, =CH), 7.90–6.50 (m, 10H, arom. +NH), 5.5–5.3 (br, 2H, NH_2) ppm.

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