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SYNTHESIS OF NOVEL 3-METHYL-6, 7-DIARYL-5,6,7,8-TETRAHYDRO-4*H*-ISOXAZOLO[4,5-*d*][1,3]DIAZEPINES

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ABSTRACT

The synthesis of novel 3-methyl-6,7-diaryl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3]diazepine (**6a-j**) is described. A three component reaction of 3,5-dimethyl-4-nitroisoxazole **1**, aromatic aldehyde **2** and substituted anilines **3** in ethanol using ceric ammonium nitrate (CAN) as Lewis acid catalyst yielded *N*-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)aniline (**4a-j)** by Mannich type reaction *via* a variety of aldimines generated *in situ* by reaction of aromatic aldehydes with aromatic amines. Compound **4** on reduction with $SnCl_2$ in ethanol afforded 3-methyl-5-(2-phenyl-2-(phenylamino)ethyl)isoxazol-4-amines (**5a-j**). Cyclocondensation of **5** with formaline furnished novel 3-methyl-6,7-diaryl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3]diazepine (**6a-j**)**.**

Keywords: Ceric ammonium nitrate, Lewis acid catalyst, 3,5-dimethyl-4-nitroisoxazole, cyclocondensation, isoxazolo[4,5-*d*][1,3]diazepines

INTRODUCTION

The prevalence of diazepines[1] in natural product and pharmacological active compounds has resulted in a number of synthetic approaches to these heterocycles[2]. The discovery of diazepam followed by many other psychotropic agents sharing 1,4-benzodiazepines skeleton has also promoted the studies of the isomeric 1,5- and 1,3-benzodiazepines ring system[3]. Among the pharmacological functions, the much less broadly studied 1,3-diazepine derivatives have been of interest due to their inhibitory effects on HIV-1 protease, adenosine deaminase, and guanase, as well as their NK1 receptor binding properties[4,5] (Fig. 1).

Isoxazole derivatives are reported with diverse structural features and versatile biological properties such as antitumor,[6] CNS–active,[7] analgesic,[8] antimicrobial,[9] muscle relaxant,[10] for the treatment of hyper cholsteremia and hyperlipidemia,[11] as organic electrolytes for non-aqueous batteries[12] in photographic emulsions[13] as synthetic intermediates[14]and as chemotherapeutic agents.[15]

Inspired with the biological profile of 1,3-diazepines and isoxazoles, and their increasing importance in pharmaceutical and biological fields, and in connection with our research on the design and synthesis of biological active and pharmacologically important new isoxazolyl heterocycles[16] it was thought worthwhile to synthesize the title compounds **6a-j** with a view to obtain certain new chemical entities with active pharmacophore in a single molecular frame work in order to prepare molecule having with potentially enhanced biological activities.

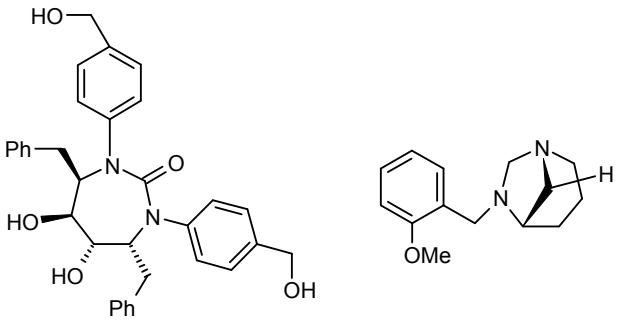
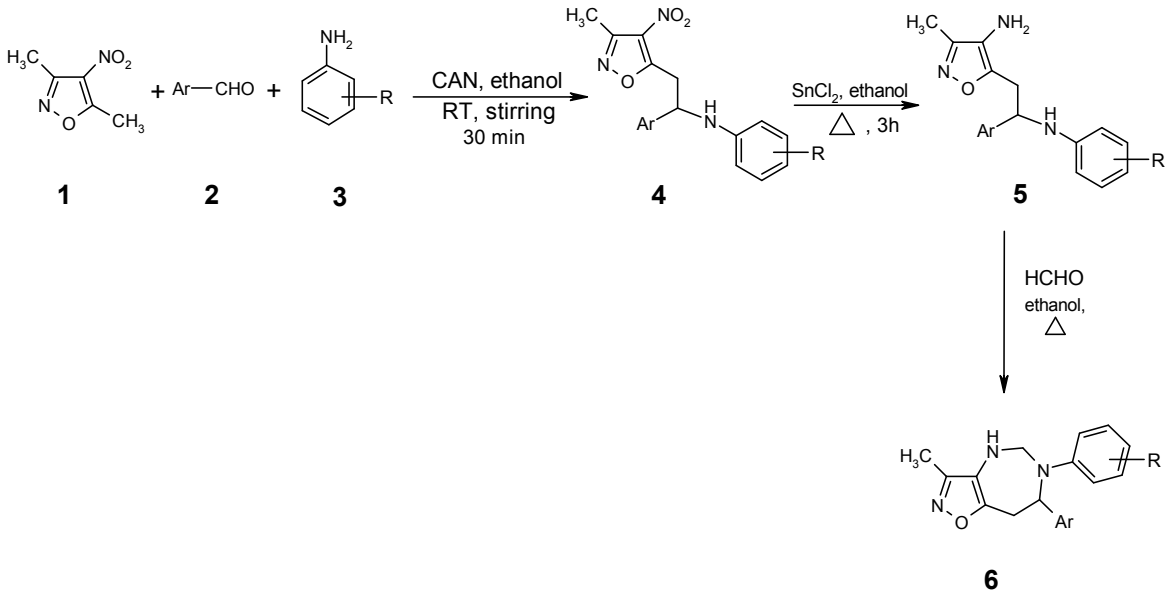


Fig 1. Examples of pharmaceutically relevant 1,3-diazepine derivatives.

RESULTS AND DISCUSSION

The three-component reaction of 3,5-dimethyl-4-nitroisoxazole **1**, aromatic aldehyde **2**, and substituted anilines **3** in ethanol using ceric ammonium nitrate as Lewis acid catalyst yielded *N*-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)aniline **4** by Mannich type reaction *via* a variety of aldimines generated *in situ* by interaction of aromatic aldehydes with aromatic amines. Compounds **4** on reduction with $SnCl_2$-EtOH afforded the corresponding 3-methyl-5-(2-phenyl-2-(phenylamino)ethyl)isoxazol-4-amines **5.** Cyclocondensation of **5** with formalin furnished the novel title compounds *viz.,* 3-methyl-6,7-diphenyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*] [1,3]diazepine **6** in good yields.

The IR spectra of **4** displayed a strong absorption peak at 3250 cm^{-1} due to NH functional group. ^1H NMR spectra of **4** exhibited two doublet of doublets at δ 4.12 and 4.23 due to CH_2 protons and a multiplet at δ 4.16 due to CH proton confirming the formation of **4**. The mass spectrum of **4a** shown a molecular ion peak $[M+H]^+$ at m/z 324, which is in agreement with the proposed structure. Compound **5** in its IR spectrum exhibited strong absorption peaks at 3345, 3338 and 3250 cm^{-1} due to NH_2 and NH functional groups respectively. ^1H NMR spectra of **5** exhibited peaks at δ 8.19 and 8.30 as broad signals, which are D_2O exchangeable, due to NH_2 and NH protons respectively. The mass spectrum of **5a** also agrees with the structure by displaying a molecular ion peak $[M+H]^+$ at m/z 294. The IR spectra of **6** exhibited absorption peak at 3200 cm^{-1} due to NH functional group. ^1H NMR spectra of **6** displayed the newly formed diazepine ring CH_2 protons signal at δ 4.78 confirming cyclocondensation. The mass spectrum of **6a** exhibited the molecular ion $[M+H]^+$ peak at m/z 306.



1 **2** **3** **4** **5** **6**

4, 5, 6

	Ar	R		Ar	R
a	C_6H_5	H	**f**	4-$OCH_3C_6H_4$	H
b	2-$CH_3C_6H_4$	H	**g**	C_6H_5	4-Br
c	2-ClC_6H_4	H	**h**	C_6H_5	4-CH_3
d	2-BrC_6H_4	H	**i**	C_6H_5	4-Cl
e	4-$CH_3C_6H_4$	H	**j**	C_6H_5	4-OCH_3

Scheme I

In conclusion, we reported synthesis of isoxazolo[4,5-*d*][1,3]diazepines with using inexpensive and commercially available material. This synthesis benefits from a simple method of purification compliments the one-pot synthesis, making the technology practically easy to perform and facile.

EXPERIMENTAL SECTION

Melting points are determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra was recorded in KBr on Perkin Elmer spectrum BX series FT-IR spectrometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer using tetramethyl silane as internal standard and mass spectra on a Jeol JMC-300 spectrometer. C, H and N analyses were carried out on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

General procedure for the synthesis of *N*-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)anilines (4a-j)

A mixture of 3,5-dimethyl-4-nitroisoxazole (**1)** (1 mmol), aromatic aldehyde (**2)** (1 mmol), substituted anilines (**3)** (1 mmol), and ceric ammonium nitrate (10 mol%) in ethanol (10 mL) were stirred at ambient temperature for 30 min. After completion of the reaction (monitored by

TLC), the reaction mixture was poured on to crushed ice and the resulted precipitate was filtered and washed with cold alcohol and recrystallized from benzene.

***N*-(2-(3-Methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)aniline (4a)**

Yield 70%, yellow orange solid. mp 152-154^{0}C. IR (KBr) cm^{-1}: 3250, 1546, 1345.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 4.12 (dd, 1H, CH), 4.23 (dd, 1H, CH), 4.61 (m, 1H, Ar-CH), 7.10–7.68 (m, 10H, Ar-H), 8.00 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 324 $(M+H)^+$. Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found. C, 66.81; H, 5.97; N, 13.05%.

***N*-(2-(3-Methyl-4-nitroisoxazol-5-yl)-1-*o*-tolylethyl)aniline (4b)**

Yield 77%, yellow orange solid. mp 148-150^{0}C. IR (KBr) cm^{-1}: 3256, 1535, 1336.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.32 (s, 3H, isoxazole-CH_3), 2.61 (s, 3H, Ar-CH_3), 4.10 (dd, 1H, CH), 4.24 (dd, 1H, CH), 4.79 (m, 1H, Ar-CH), 6.89–7.61 (m, 9H, Ar-H), 8.16 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 338 $(M+H)^+$. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found. C, 67.57; H, 5.69; N, 12.51%.

***N*-(1-(2-Chlorophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)aniline (4c)**

Yield 77%, yellow orange solid. mp 139-141^{0}C. IR (KBr) cm^{-1}: 3256, 1535, 1336.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.32 (s, 3H, isoxazole-CH_3), 4.10 (dd, 1H, CH), 4.24 (dd, 1H, CH), 4.79 (m, 1H, Ar-CH), 6.89–7.61 (m, 9H, Ar-H), 8.10 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 358 $(M+H)^+$. Anal. Calcd for $C_{18}H_{16}ClN_3O_3$: C, 60.42; H, 4.51; N, 11.74. Found. C, 60.46; H, 4.54; N, 11.78%.

***N*-(1-(2-Bromophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)aniline (4d)**

Yield 78%, yellow orange solid. mp 151-153^{0}C. IR (KBr) cm^{-1}: 3247, 1545, 1331.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.21 (s, 3H, isoxazole-CH_3), 4.10 (dd, 1H, CH), 4.22 (dd, 1H, CH), 4.79 (m, 1H, Ar-CH), 6.95–7.77 (m, 9H, Ar-H), 8.21 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 402 $(M+H)^+$. Anal. Calcd for $C_{18}H_{16}BrN_3O_3$: C, 53.75; H, 4.01; N, 10.45. Found. C, 53.72; H, 4.06; N, 10.49%.

***N*-(2-(3-Methyl-4-nitroisoxazol-5-yl)-1-*p*-tolylethyl)aniline (4e)**

Yield 70%, yellow orange solid. mp 142-144^{0}C. IR (KBr) cm^{-1}: 3240, 1535, 1328.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.21 (s, 3H, isoxazole-CH_3), 2.61 (s, 3H, Ar-CH_3), 4.10 (dd, 1H, CH), 4.23 (dd, 1H, CH), 4.87 (m, 1H, Ar-CH), 7.03–7.75 (m, 9H, Ar-H), 8.10 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 338 $(M+H)^+$. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found. C, 67.59; H, 5.62; N, 12.50%.

***N*-(1-(4-Methoxyphenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)aniline (4f)**

Yield 76%, yellow orange solid. mp 159-161^{0}C. IR (KBr) cm^{-1}: 3240, 1541, 1365.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.21 (s, 3H, isoxazole-CH_3), 3.68 (s, 3H, OCH_3), 4.10 (dd, 1H, CH), 4.21 (dd, 1H, CH), 4.89 (m, 1H, Ar-CH), 7.10–7.81 (m, 9H, Ar-H), 8.11 (brs, 1H, NH, D_2O exchangeable; MS: *m/z* 354 $(M+H)^+$. Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found. C, 64.60; H, 5.39; N, 11.94%.

4-Bromo-*N*-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)aniline (4g)

Yield 71%, yellow orange solid. mp 143-145^{0}C. IR (KBr) cm^{-1}: 3241, 1535, 1330.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.22 (s, 3H, isoxazole-CH_3), 4.13 (dd, 1H, CH), 4.21 (dd, 1H, CH), 4.70 (m, 1H, Ar-CH), 6.90–7.87 (m, 9H, Ar-H), 8.11 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 402 $(M+H)^+$. Anal. Calcd for $C_{18}H_{16}BrN_3O_3$: C, 53.75; H, 4.01; N, 10.45. Found. C, 53.77; H, 4.05; N, 10.41%.

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4-Methyl-*N*-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)aniline (4h)

Yield 71%, yellow orange solid. mp 135-137^{0}C. IR (KBr) cm^{-1}: 3235, 1530, 1322.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.26 (s, 3H, isoxazole-CH_3), 2.64 (s, 3H, Ar-CH_3), 4.12 (dd, 1H, CH), 4.20 (dd, 1H, CH), 4.79 (m, 1H, Ar-CH), 7.00–7.71 (m, 9H, Ar-H), 8.17 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 338 $(M+H)^+$. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found. C, 67.68; H, 5.65; N, 12.43%.

4- Chloro-*N*-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)aniline (4i)

Yield 72%, yellow orange solid. mp 130-132^{0}C. IR (KBr) cm^{-1}: 3250, 1528, 1330.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.30 (s, 3H, isoxazole-CH_3), 4.11 (dd, 1H, CH), 4.25 (dd, 1H, CH), 4.78 (m, 1H, Ar-CH), 6.80–7.66 (m, 9H, Ar-H), 8.13 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 358 $(M+H)^+$. Anal. Calcd for $C_{18}H_{16}ClN_3O_3$: C, 60.42; H, 4.51; N, 11.74. Found. C, 60.39; H, 4.47; N, 11.69%.

4-methoxy-N-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)aniline (4j)

Yield 75%, yellow orange solid. mp 125-127^{0}C. IR (KBr) cm^{-1}: 3215, 1535, 1340.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.29 (s, 3H, isoxazole-CH_3), 3.62 (s, 3H, OCH_3), 4.10 (dd, 1H, CH), 4.28 (dd, 1H, CH), 4.80 (m, 1H, Ar-CH), 6.90–7.81 (m, 9H, Ar-H), 8.01 (brs, 1H, NH, D_2O exchangeable); MS: *m/z* 354 $(M+H)^+$. Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found. C, 64.60; H, 5.40; N, 11.93%.

General procedure for the synthesis of 3-methyl-5-(2-phenyl-2-(phenylamino)ethyl) isoxazol-4-amine (5a-j)

Compound **4** (1 mmol) and $SnCl_2.2H_2O$ (1 mmol) were dissolved in 20 mL of ethanol and refluxed for 3 h. After completion of the reaction (monitored by TLC) solvent was removed in vacuum. The solid mass was decomposed with cold water and the reaction solution was carefully adjusted to pH 8 with 10% $NaHCO_3$ solution and then extracted with ethyl acetate (2 X 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under vacuum and purified by recrystallization from benzene to give pure product **5**.

3-Methyl-5-(2-phenyl-2-(phenylamino)ethyl) isoxazol-4-amine (5a)

Yield 60%, yellow orange solid. mp 172-174^{0}C. IR (KBr) cm^{-1}: 3345, 3338, 3250.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 4.12 (dd, 1H, CH), 4.23 (dd, 1H, CH), 4.61 (m, 1H, Ar-CH), 7.10–7.68 (m, 10H, Ar-H), 8.00 (brs, 1H, NH, D_2O exchangeable), 8.34 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 294 $(M+H)^+$. Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found. C, 73.64; H, 6.56; N, 14.37%.

3-Methyl-5-(2-(phenylamino)-2-*o*-tolylethyl)isoxazol-4-amine (5b)

Yield 68%, yellow orange solid. mp 178-180^{0}C. IR (KBr) cm^{-1}: 3336, 3327, 3256.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.28 (s, 3H, isoxazole-CH_3), 2.60 (s, 3H, Ar-CH_3), 4.11 (dd, 1H, CH), 4.24 (dd, 1H, CH), 4.74 (m, 1H, Ar-CH), 6.99–7.67 (m, 9H, Ar-H), 8.10 (brs, 1H, NH, D_2O exchangeable), 8.24 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 308 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found. C, 74.20; H, 6.83 N, 13.69%

5-(2-(2-Chlorophenyl)-2-(phenylamino)ethyl)-3-methylisoxazol-4-amine (5c)

Yield 65%, yellow orange solid. mp 169-171^{0}C. IR (KBr) cm^{-1}: 3336, 3327, 3256.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.20 (s, 3H, isoxazole-CH_3), 4.12 (dd, 1H, CH), 4.20 (dd, 1H, CH), 4.73 (m, 1H, Ar-CH), 7.00–7.71 (m, 9H, Ar-H), 8.15 (brs, 1H, NH, D_2O exchangeable), 8.30 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 328 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82. Found. C, 65.98; H, 5.51; N, 12.85%.

5-(2-(2-Bromophenyl)-2-(phenylamino)ethyl)-3-methylisoxazol-4-amine (5d)

Yield 67%, yellow orange solid. mp 190-192^{0}C. IR (KBr) cm^{-1}: 3331, 3327, 3247.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.27 (s, 3H, isoxazole-CH_3), 4.11 (dd, 1H, CH), 4.28 (dd, 1H, CH), 4.89 (m, 1H, Ar-CH), 6.90–7.81 (m, 9H, Ar-H), 8.19 (brs, 1H, NH, D_2O exchangeable), 8.30 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 372 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}BrN_3O$: C, 58.08; H, 4.87; N, 11.29. Found. C, 58.13; H, 4.81; N, 11.31%.

3-Methyl-5-(2-(phenylamino)-2-*p*-tolylethyl)isoxazol-4-amine (5e)

Yield 66%, yellow orange solid. mp 186-188^{0}C. IR (KBr) cm^{-1}: 3325, 3318, 3240.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.21 (s, 3H, isoxazole-CH_3), 2.61 (s, 3H, Ar-CH_3), 4.11 (dd, 1H, CH), 4.20 (dd, 1H, CH), 4.87 (m, 1H, Ar-CH), 7.03–7.75 (m, 9H, Ar-H), 8.10 (brs, 1H, NH, D_2O exchangeable), 8.37 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 308 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found. C, 74.20; H, 6.83 N, 13.69%

5-(2-(4-Methoxyphenyl)-2-(phenylamino)ethyl)-3-methylisoxazol-4-amine (5f)

Yield 64%, yellow orange solid. mp 195-197^{0}C. IR (KBr) cm^{-1}: 3330, 3320, 3237.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H, isoxazole-CH_3), 3.60 (s, 3H, OCH_3), 4.09 (dd, 1H, CH), 4.20 (dd, 1H, CH), 4.77 (m, 1H, Ar-CH), 7.00–7.88 (m, 9H, Ar-H), 8.10 (brs, 1H, NH, D_2O exchangeable), 8.31 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 324 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found. C, 70.51; H, 6.59; N, 13.02%.

5-(2-(4-Bromophenylamino)-2-phenylethyl)-3-methylisoxazol-4-amine (5g)

Yield 61%, yellow orange solid. mp 201-203^{0}C. IR (KBr) cm^{-1}: 3331, 3320, 3249.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.32 (s, 3H, isoxazole-CH_3), 4.18 (dd, 1H, CH), 4.27 (dd, 1H, CH), 4.70 (m, 1H, Ar-H), 6.93–7.75 (m, 9H, Ar-CH), 8.20 (brs, 1H, NH, D_2O exchangeable), 8.38 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 372 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}BrN_3O$: C, 58.08; H, 4.87; N, 11.29. Found. C, 58.03; H, 4.90; N, 11.23%.

5-(2-(*p*-Toluidino)-2-phenylethyl)-3-methylisoxazol-4-amine (5h)

Yield 66%, yellow orange solid. mp 211-213^{0}C. IR (KBr) cm^{-1}: 3325, 3318, 3240.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.26 (s, 3H, isoxazole-CH_3), 2.63 (s, 3H, Ar-CH_3), 4.11 (dd, 1H, CH), 4.20 (dd, 1H, CH), 4.82 (m, 1H, Ar-CH), 7.00–7.74 (m, 9H, Ar-H), 8.21 (brs, 1H, NH, D_2O exchangeable), 8.44 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 308 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found. C, 74.29; H, 6.82; N, 13.64%

5-(2-(4-Chlorophenylamino)-2-phenylethyl)-3-methylisoxazol-4-amine (5i)

Yield 67%, yellow orange solid. mp 216-218^{0}C. IR (KBr) cm^{-1}: 3336, 3327, 3256.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.26 (s, 3H, isoxazole-CH_3), 4.11 (dd, 1H, CH), 4.27 (dd, 1H, CH), 4.69 (m, 1H, Ar-CH), 7.10–7.89 (m, 9H, Ar-H), 8.00 (brs, 1H, NH, D_2O exchangeable), 8.23 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 328 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82. Found. C, 66.00; H, 5.50; N, 12.88%.

5-(2-(4-Methoxyphenylamino)-2-phenylethyl)-3-methylisoxazol-4-amine (5j)

Yield 70%, yellow orange solid. mp 213-215^{0}C. IR (KBr) cm^{-1}: 3336, 3327, 3256.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.26 (s, 3H, isoxazole-CH_3), 3.68 (s, 3H, OCH_3), 4.08 (dd, 1H, CH), 4.21 (dd, 1H, CH), 4.70 (m, 1H, Ar-CH), 6.99–7.60 (m, 9H, Ar-H), 8.13 (brs, 1H, NH, D_2O exchangeable), 8.32 (brs, 1H, NH_2, D_2O exchangeable); MS: *m/z* 324 $(M+H)^+$. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found. C, 70.49; H, 6.60; N, 13.00%.

General procedure for the synthesis of 3-methyl-6,7-diaryl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3]diazepine (6a-j)

30% Formaldehyde (1 mmol) was slowly added to an ethanolic solution (15 mL) of amines **4** (1 mmol) by stirring. The reaction mixture was refluxed for 6-8 h (monitored with TLC). The gummy product obtained, after the removal of solvent, was triturated with pet ether repeatedly to get the solid compound. The resultant crude product was purified by recrystallization from ethanol.

3-Methyl-6,7-diphenyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3]diazepine (6a)

Yield 69%, yellow orange solid. mp 232-234^{0}C. IR (KBr) cm^{-1}: 3200 .^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.32 (s, 3H, isoxazole-CH_3), 4.21 (dd, 1H, CH), 4.36 (dd, 1H, CH), 4.78 (s, 2H, CH_2), 4.89 (m, 1H, Ar-CH), 6.81–7.86 (m, 10H, Ar-H); MS: *m/z* 306 $(M+H)^+$. Anal. Calcd for C19H19N3O: C, 74.73; H, 6.27; N, 13.76. Found. C, 74.68; H, 6.29; N, 13.71%

3-Methyl-6-phenyl-7-*o*-tolyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3]diazepine (6b)

Yield 64%, yellow orange solid. mp 226-228^{0}C. IR (KBr) cm^{-1}: 3215.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.21 (s, 3H, isoxazole-CH_3), 4.12 (dd, 1H, CH), 4.26 (dd, 1H, CH), 4.86 (s, 2H, CH_2), 5.11 (m, 1H, Ar-CH), 6.90–7.70 (m, 9H, Ar-H), 8.01 (brs, 1H, OH, D_2O exchangeable), ; MS: *m/z* 320 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found. C, 75.17; H, 6.60; N, 13.21%.

7-(2-Chlorophenyl)-3-methyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3] diazepine (6c)

Yield 62%, yellow orange solid. mp 246-248^{0}C. IR (KBr) cm^{-1}: 3218.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.31 (s, 3H, isoxazole-CH_3), 4.10 (dd, 1H, CH), 4.24 (dd, 1H, CH), 4.81 (s, 2H, CH_2), 5.10 (m, 1H, Ar-CH), 6.99–7.71 (m, 9H, Ar-H); MS: *m/z* 340 $(M+H)^+$. Anal. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.15; H, 5.34; N, 12.37. Found. C, 67.19; H, 5.30; N, 12.39%.

7-(2-Bromophenyl)-3-methyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3]diazepine (6d)

Yield 64%, yellow orange solid. mp 239-241^{0}C. IR (KBr) cm^{-1}: 3211.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.29 (s, 3H, isoxazole-CH_3), 4.10 (dd, 1H, CH), 4.21 (dd, 1H, CH), 4.80 (s, 2H, CH_2), 5.13 (m, 1H, Ar-CH), 6.87–7.54 (m, 9H, Ar-H); MS: *m/z* 382 $(M+H)^+$. Anal. Calcd for $C_{19}H_{16}BrN_3O$: C, 59.70; H, 4.22; N, 10.99. Found. C, 59.74; H, 4.18; N, 10.94%.

3-Methyl-6-phenyl-7-*p*-tolyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3]diazepine (6e)

Yield 63%, yellow orange solid. mp 241-243^{0}C. IR (KBr) cm^{-1}: 3226.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.32 (s, 3H, isoxazole-CH_3), 4.10 (dd, 1H, CH), 4.22 (dd, 1H, CH), 4.78 (s, 2H, CH_2), 5.10 (m, 1H, Ar-CH), 7.22–7.87 (m, 9H, Ar-H); MS: *m/z* 320 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found. C, 75.26; H, 6.58; N, 13.20%.

7-(2-Methoxyphenyl)-3-methyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3] diazepine (6f)

Yield 61%, yellow orange solid. mp 235-237^{0}C. IR (KBr) cm^{-1}: 3230.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.34 (s, 3H, isoxazole-CH_3), 3.70 (s, 3H, OCH_3), 4.11 (dd, 1H, CH), 4.21 (dd, 1H, CH), 4.83 (s, 2H, CH_2), 5.13 (m, 1H, Ar-CH), 7.00–7.81 (m, 9H, Ar-H); MS: *m/z* 336 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found. C, 71.68; H, 6.34; N, 12.49%.

6-(4-Bromophenyl)-3-methyl-7-phenyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3]diazepine (6g)

Yield 64%, yellow orange solid. mp 239-241^{0}C. IR (KBr) cm^{-1}: 3210.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.21 (s, 3H, isoxazole-CH_3), 4.13 (dd, 1H, CH), 4.28 (dd, 1H, CH), 4.89 (s, 2H, CH_2), 5.26 (m, 1H, Ar-CH), 7.00–7.86 (m, 9H, Ar-H); MS: *m/z* 382 $(M+H)^+$. Anal. Calcd for $C_{19}H_{16}BrN_3O$: C, 59.70; H, 4.22; N, 10.99. Found. C, 59.67; H, 4.19; N, 10.96%.

3-Methyl-7-phenyl-6-*p*-tolyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3]diazepine (6h)

Yield 63%, yellow orange solid. mp 250-252^{0}C. IR (KBr) cm^{-1}: 3200.^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.32 (s, 3H, isoxazole-CH_3), 4.10 (dd, 1H, CH), 4.22 (dd, 1H, CH), 4.84 (s, 2H, CH_2), 5.10 (m, 1H, Ar-CH), 7.22–7.87 (m, 9H, Ar-H); MS: *m/z* 320 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found. C, 75.17; H, 6.60; N, 13.20%.

6-(4-Chlorophenyl)-3-methyl-7-phenyl-5,6,7,8-tetrahydro-4H-isoxazolo[4,5-d][1,3] diazepine (6i)

Yield 60%, yellow orange solid. mp 256-258^{0}C. IR (KBr) cm^{-1}: .^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.21 (s, 3H, isoxazole-CH_3), 4.16(dd, 1H, CH), 4.20 (dd, 1H, CH), 4.78 (s, 2H,

CH_2), 5.11 (m, 1H, Ar-CH), 6.89–7.78 (m, 9H, Ar-H); MS: *m/z* 340 $(M+H)^+$. Anal. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.15; H, 5.34; N, 12.37. Found. C, 67.11; H, 5.39; N, 12.31%.

6-(4-Methoxyphenyl)-3-methyl-7-phenyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*d*][1,3] diazepine (6j)

Yield 65%, yellow orange solid. mp 253-255^{0}C. IR (KBr) cm^{-1}: .^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.20 (s, 3H, isoxazole-CH_3), 4.13 (dd, 1H, CH), 4.27 (dd, 1H, CH), 4.78 (s, 2H, CH_2), 5.01 (m, 1H, Ar-CH), 7.00–7.70 (m, 9H, Ar-H); MS: *m/z* 336 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found. C, 71.66; H, 6.28; N, 12.47%.

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