# Application of Privileged Molecular Framework of 7-Fluoro-1,4-benzodiazepin-2-one-5-methylcarboxylate to the Synthesis of Its 1- and 5-Disubstituted Analogs of Medicinal Interest



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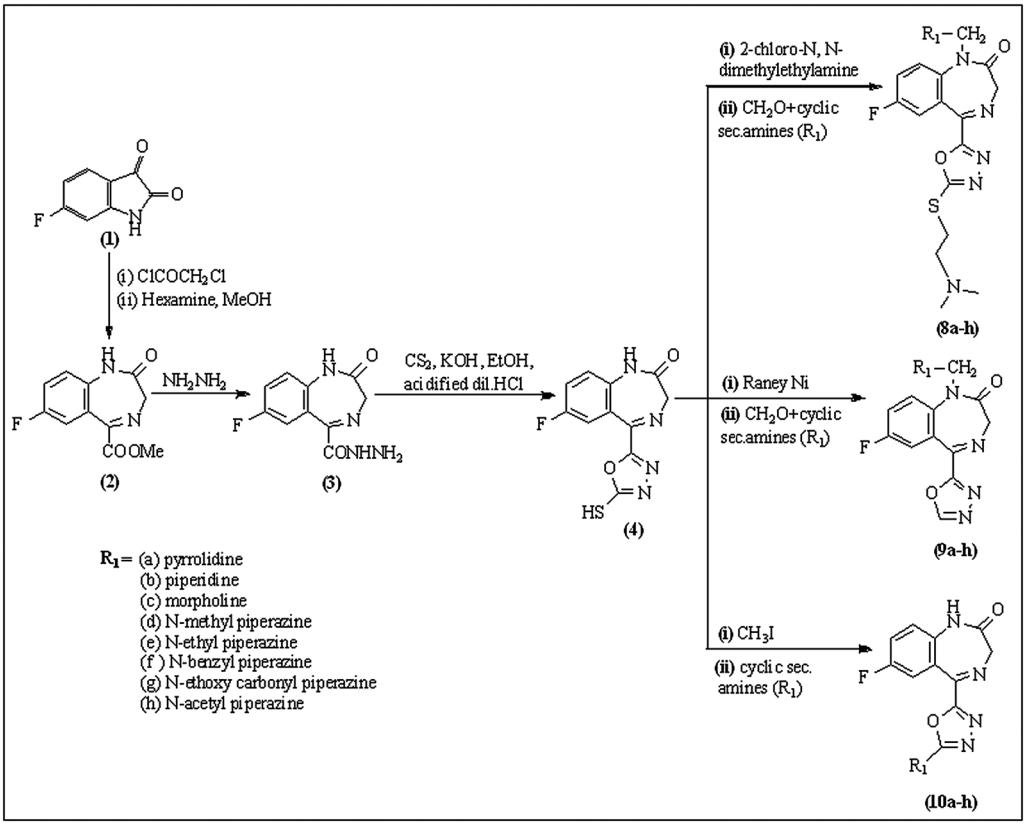


Synthetic potential of the privileged molecular framework of 7-fluoro-1,4-benzodiazepin-2-one containing a methyl carboxylate substituent at its 5-position was exploited to develop efficient protocols to the synthesis of several novel 5-(1′,3′,4′)oxadiazole ring incorporated analogs of medicinal interest, appended with the Mannich's base motifs at the nitrogen atom in its seven-membered ring.

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## INTRODUCTION

Ever since Waldmann *et al.* [1,2] have carried out a quantitative analysis of physiologically active natural products and showed that the ones with two or three rings were most often found in active natural products, the interest on the various facets of the chemistry of small molecules has expanded exponentially thereafter. This led the exploration of the synthetic processes that lead to the development of small molecules of medicinal interest, by telescoping the multicomponent operations to a single step. Recently, the privileged molecular frameworks of bicyclic and tricyclic derivatives of benzodiazepines have been actively studied in view of their ability to provide ligands to a number of functionally and structurally discrete biological receptors. This study resulted in the design and development of efficient molecular probes for biological evaluation from this nucleus. It has been observed that incorporation of five-membered heterocyclic rings to the seven-membered azepine core of benzodiazepines exerted a profound influence in conferring novel biological activities in these molecules [3]. The discovery of anticancer activity in many antibiotics containing pyrrolo [2,1-*c*][1,4]-benzodiazepine nucleus and anti-HIV activity in tetrahydroimidazo[4,5,1-jkj][1,4]benzodiazepin-2(1H)one and -thione (TIBO) [4] (A, Fig. 1) containing an imidazole ring, in 1,4-benzodiazepine nucleus, and in FDA approved nevirapine [5] (B, Fig. 1) containing a dipyrido-1,4-diazepine nucleus is among the few examples that illustrate this phenomenon.

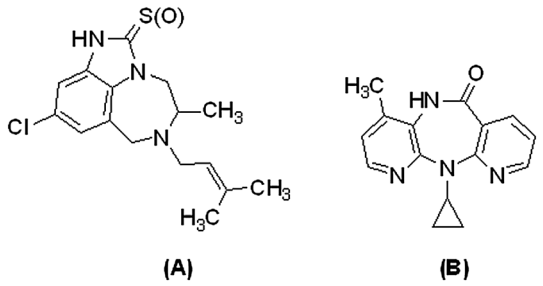



**Figure 1.** Structures of TIBO and nevirapine.

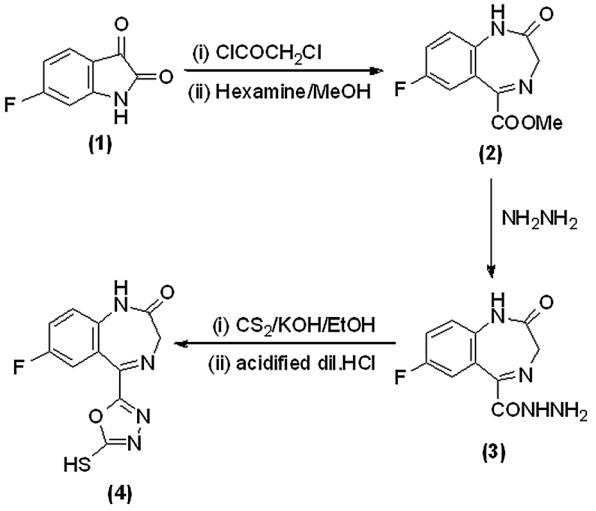
In recent years [6], molecules containing an oxadiazole nucleus have emerged as versatile lead structures in the design and development of potential anti-HIV agents.

The attachments of Mannich's base fragments in chemotherapeutically useful materials have often been found to induce novel bioactivity. Their role, as intermediates in drug synthesis and in imparting such activities as analgesic, antispasmodic, anesthetic, antimalarial, and others, has been well documented in the literature [7–15] and reviewed recently [16].

In recent years, active research has been pursued on halogen-containing heterocycles, particularly fluorine-containing heterocycles. The incorporation of fluorine has been reported [17,18] to increase the lipid solubility thereby enhancing the rate of absorption and transport of drug *in vivo*. Although fluorine has a greater size than hydrogen, several studies have demonstrated [19] that fluorine is a reasonable hydrogen mimic that exerts only a minor steric demand at receptor sites. This observation stimulated us to synthesize the 1,4-benzodiazepine analogs containing a fluorine atom in its core nucleus (Scheme 1).

Encouraged by the impressive bioactive profiles of the privileged template of 1,4-benzodiazepines, oxadiazole nucleus, and the Mannich's base fragments, it was considered of interest to explore the possibility of incorporating these moieties together, in the same molecule, on this premise that their presence in tandem in the same molecular framework was in all probability expected to contribute significantly to provide an additive effect on the overall bioefficacy in the resulting materials. In exercise of this premise, in this communication, we report the preliminary results of our study focused in the direction of incorporating the Mannich's base fragments and oxadiazole ring on 1- and 5-positions of 1,4-benzodiazepine nucleus substituted with a fluorine atom in the arene ring of its molecule.

**Scheme 1**




## RESULTS AND DISCUSSION

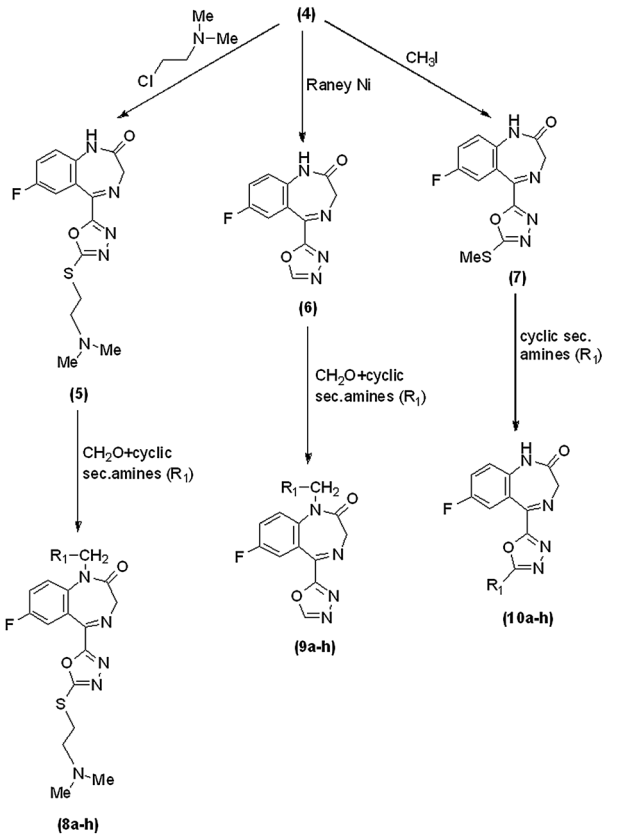
For our synthetic plan (Scheme 1) to succeed to give the 5-oxadiazolyl substituted analog of 7-fluoro-1,4-benzodiazepine (**4**), we required a good synthesis of 5-carbomethoxy substituted derivative of 7-fluoro-1,4-benzodiazepine (**2**). Consideration of factors on reactivity of starting material and simplicity in operational procedure led us to favor the use of 5-fluoroisatin (**1**) for its synthesis. Ogata and Motsumoto [20] in 1976 developed a highly innovative technique for the synthesis of 1,4-benzodiazepine nucleus and its 7-chloro analog from the corresponding 1-chloroacetylisatin through its treatment with methanolic solution of hexamine. An attractive feature of this process was that it provided a very convenient one-pot synthetic entry to the 1,4-benzodiazepine nucleus substituted with a carbomethoxy group at 5-position. We applied this methodology on 5-fluoro-1-chloroacetylisatin to obtain 7-fluoro-5-carbomethoxy substituted analog of 1,4-benzodiazepin-2-one (**2**) in good yield. The ester function of **2** reacted smoothly with hydrazine hydrate [21,22] to form the acid hydrazide (**3**) in excellent yield. Reaction of **3** with $CS_2 + KOH$ followed by treatment with acid [23,24] formed the 1′,3′,4′-oxadiazole derivative **4**. Mass spectrum of **4** exhibited $M^+$ peak at *m/z* 278.26 (86%) and a base peak at *m/z* 245.19 (100%) (because of the loss of SH group) that was consistent to its structure.

In view of obvious reasons (as apparent from Scheme 2), the depicted strategies were allowed to operate in three parts. In the first part, reaction of **4** with 2-chloro-*N*,*N*-dimethylethanamine [25,26] was carried out to append an aminoalkyl chain on the SH group of **4** to give compound **5**, which, on treatment with cyclic secondary amines in presence of formaldehyde, formed the Mannich's bases (**8a–h**). Structural assignments to these compounds were based on elemental analysis, IR, $^1$H-NMR, and mass spectral data.

Subsequent desulphurization of **4** with Raney Ni [27] led to the formation of **6** whose reaction with different cyclic secondary amines and formaldehyde [25,26] produced another series of Mannich's base derivatives (**9a–h**). The structures of these compounds were established on the basis of their spectral data.

A further study involved the conversion of **4** to **7** through the reaction of the former with $CH_3I$ [28]. The resulting lactim thioether function of **7** underwent facile

**Scheme 2**




$R_1$= (a) pyrrolidine, (b) piperidine, (c) morpholine, (d) N-methyl piperazine, (e) N-ethyl piperazine, (f) N-benzyl piperazine, (g) N-ethoxy carbonyl piperazine, (h) N-acetyl piperazine

nucleophilic displacements with a wide variety of cyclic secondary amines [29] to give compounds **10a–h**. Compounds **10a–h** were characterized on the basis of their-spectral data. Physical data of the compounds **8a–10h** have been summarized in Table 1.

## CONCLUSION

In view of the positive impact that the presence of an oxadiazole nucleus and the Mannich's base motifs produced on the bioefficacy of the biologically active materials, we developed an expedient protocol to the synthesis of 5-oxadiazolyl -substituted-7-fluoro -1,4-benzodiazepine-2-one and their Mannich's base derivatives to study their biological activity, which is in progress.

## EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. Progress of the reaction was monitored by TLC on silica gel "G" coated plates using benzene/methanol (9:1). IR spectra on KBr were recorded on FTIR-8400S, CE (Shimadzu, Nakagyo-ku-Kyoto, Japan). Mass spectra were taken on 3000 LC/MS System (McKinley Scientific, Sparta, NJ). $^1$H-NMR spectra were recorded on model AC-300F (Bruker, Billerica, MA) using $CDCl_3$ /DMSO-$d_6$ as solvent. Chemical shifts are expressed in δ parts per million relative to the signal for TMS as internal standard.

**Preparation of methyl-7-fluoro-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepin-5-carboxylate (2).** 5-Fluoroisatin (**1**, 3.40 g, 0.02 mol) was vigorously refluxed with chloroacetyl chloride (4.48 g, 0.04 mol) for 5 h, and the mixture was cooled for 2 h in an ice bath. The precipitated product was filtered, washed with 30 mL portion of ether, then air-dried, and recrystallized from ethyl acetate to give 5-fluoro *N*-chloroacetyl isatin. 5-Fluoro *N*-chloroacetyl isatin (2.95 g, 0.012 mol) and hexamethylenetetramine (hexamine) (2.8 g, 0.02 mol) in 50 mL dry methanol were refluxed for 10–11 h. Progress of the reaction was monitored through TLC. After completion of the reaction, the solvent was removed under reduced pressure, and the solid was chromatographed over alumina (neutral) in $C_6H_6$/MeOH (9.5:0.5) as the eluant. The product obtained was recrystallized from benzene to give **2**, 2.50 g, yield (85%), mp, 230–232°C. IR (KBr) cm$^{-1}$: 3400 (NH), 1660, 1700 (C═O), 2970, 1430 (—$CH_2$ next to C═O), 1050 (CF), 1630 (C═N), 2970 (C—H), 1590 (C═C); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 7.84 (1H, d, $J$ = 8.5 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.18 (2H, s, $CH_2$ of benzodiazepine ), 3.68 (3H, s, methyl), 8.00 (1H, s, NH); MS: *m*/*z* (%) 236.20 ($M^+$ 75%), 205.17 (100%), 177.16 (35%); Analytical data: Calcd/found for $C_{11}H_9FN_2O_3$, C: 55.93/55.65, H: 3.84/3.82, N: 11.86/11.80.

**Preparation of 7-fluoro-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepin-5-carbohydrazide (3).** To a solution of **2** (2.15 g, 0.013 mol) in ethanol (30 mL), hydrazine hydrate (1.7 mL, 0.053 mol) was added. The mixture was refluxed for 12 h and cooled, and the obtained product was recrystallized from ethanol to give **3**, 2.00 g, yield (85%), mp, 210–212°C. IR (KBr) cm$^{-1}$: 3410 (NH), 1644, 1670 (C═O), 3315, 3123 (NH, $NH_2$), 1610 (C═N), 2980 (C—H), 2965, 1425 (—$CH_2$ next to C═O), 1580 (C═C), 1055 (C—F); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 7.84 (1H, d, $J$ = 8.5 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.18 (2H, s, $CH_2$ of benzodiazepine ), 2.00 (2H, s, $NH_2$), 8.00 (1H, s, NH of $CONHNH_2$), 8.05 (1H, s, NH); MS: *m*/*z* (%) 236.20 ($M^+$ 72%), 177.25 (25%), 149.1 (100%); Analytical data: Calcd/found for $C_{10}H_9FN_4O_2$, C: 50.85/50.60, H: 3.84/3.82, N: 23.72/23.60.

**Preparation of 7-fluoro-5-(5′-mercapto-1′,3′,4′-oxadiazol-2′-yl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (4).** To a solution of carbohydrazide (**3**, 0.472 g, 0.002 mol) in dry ethanol (20 mL), carbon disulfide (0.76 g, 0.01 mol) and potassium hydroxide (0.112 g, 0.002 mol) were added at 0°C. The resulting solution was refluxed for 40 h with the addition of 0.5 mL of $CS_2$ in four installments after each 10 h. After the completion of the reaction, the solvent was evaporated, and the product was dissolved in water and then brought to neutral point by addition of dil. HCl. The solid obtained was filtered and recrystallized with methanol to give **4**, 0.400 g, yield (72%), mp, 115–117°C. IR (KBr) cm$^{-1}$: 3400 (NH), 1627, 1415 (C═N), 1660 (C═O), 3010 (C—H), 1600 (C═C), 1370, 1245 (C═S), 1168 (C—O—C), 2970, 1420 (—$CH_2$ next to C═O), 1056 (C—F); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 7.84 (1H, d, $J$ = 8.5 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine ), 8.00 (1H, s, NH), 13.05 (1H, s, aromatic C—SH); MS: *m*/*z* (%) 278.26 ($M^+$ 86%), 245.19 (100%), 180.09 (37%); Analytical data: Calcd/found for $C_{11}H_7FN_4O_2S$, C: 47.48/47.24, H: 2.54/2.52, N: 20.13/20.03, S: 11.52/11.46.

**Table 1**

Physical data of compounds **8a–10h**.

| Entry no. | R | mp (°C) | Yield (%) | | Molecular formula (MW) |
|---|---|---|---|---|---|
| | | | Conventional method | Microwave method | |
| **8a** | Pyrrolidinyl | 101–103 | 75 | 79 | $C_{20}H_{25}FN_6O_2S$ (432.51) |
| **8b** | Piperidinyl | 107–109 | 82 | 85 | $C_{21}H_{27}FN_6O_2S$ (446.54) |
| **8c** | Morpholinyl | 112–114 | 85 | 87 | $C_{20}H_{25}FN_6O_3S$ (448.51) |
| **8d** | *N*-Methyl piperazinyl | 122–124 | 73 | 77 | $C_{21}H_{28}FN_7O_2S$ (461.56) |
| **8e** | *N*-Ethyl piperazinyl | 130–132 | 75 | 78 | $C_{22}H_{30}FN_7O_2S$ (475.58) |
| **8f** | *N*-Benzyl piperazinyl | 147–149 | 86 | 89 | $C_{27}H_{32}FN_7O_2S$ (537.65) |
| **8g** | *N*-Ethoxy carbonyl piperazinyl | 156–158 | 92 | 96 | $C_{23}H_{30}FN_7O_4S$ (519.59) |
| **8h** | *N*-Acetyl piperazinyl | 177–179 | 79 | 85 | $C_{22}H_{28}FN_7O_4S$ (505.57) |
| **9a** | Pyrrolidinyl | 105–107 | 71 | 76 | $C_{16}H_{16}FN_5O_2$ (329.33) |
| **9b** | Piperidinyl | 115–117 | 82 | 85 | $C_{17}H_{18}FN_5O_2$ (343.36) |
| **9c** | Morpholinyl | 138–140 | 85 | 90 | $C_{16}H_{16}FN_5O_3$ (345.33) |
| **9d** | *N*-Methyl piperazinyl | 152–154 | 77 | 83 | $C_{17}H_{19}FN_6O_2$ (358.37) |
| **9e** | *N*-Ethyl piperazinyl | 165–167 | 74 | 80 | $C_{18}H_{21}FN_6O_2$ (372.4) |
| **9f** | *N*-Benzyl piperazinyl | 144–146 | 80 | 86 | $C_{23}H_{23}FN_6O_2$ (434.47) |
| **9g** | *N*-Ethoxy carbonyl piperazinyl | 171–173 | 92 | 97 | $C_{19}H_{21}FN_6O_4$ (416.41) |
| **9h** | *N*-Acetyl piperazinyl | 190–192 | 79 | 82 | $C_{18}H_{19}FN_6O_3$ (386.38) |
| **10a** | Pyrrolidinyl | 128–130 | 75 | 90 | $C_{15}H_{14}FN_5O_2$ (315.3) |
| **10b** | Piperidinyl | 133–135 | 70 | 78 | $C_{16}H_{16}FN_5O_2$ (329.33) |
| **10c** | Morpholinyl | 159–161 | 80 | 86 | $C_{15}H_{14}FN_5O_3$ (331.3) |
| **10d** | *N*-Methyl piperazinyl | 178–180 | 75 | 79 | $C_{16}H_{17}FN_6O_2$ (344.34) |
| **10e** | *N*-Ethyl piperazinyl | 188–190 | 85 | 98 | $C_{17}H_{19}FN_6O_2$ (358.37) |
| **10f** | *N*-Benzyl piperazinyl | 190–192 | 81 | 94 | $C_{22}H_{21}FN_6O_2$ (420.44) |
| **10g** | *N*-Ethoxy carbonyl piperazinyl | 198–200 | 77 | 84 | $C_{18}H_{19}FN_6O_4$ (402.38) |
| **10h** | *N*-Acetyl piperazinyl | 215–217 | 79 | 87 | $C_{17}H_{17}FN_6O_3$ (372.35) |

**Preparation of (*E*)-5-(5-(2-(dimethylamino)ethylthio)-1,3,4-oxadiazol-2-yl)-7-fluoro-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one (5).** Potassium hydroxide (1.12 g, 0.02 mol) was added to a solution of **4** (2.95 g, 0.012 mol) in ethanol (25 mL), and the mixture was heated under reflux for 30 min. 2-Chloro-*N*,*N*-dimethylethanamine (1.07 g, 0.01 mol) was added, and the reaction mixture was heated under reflux for 10 h. The solvent was distilled under *vacuo*. The obtained residue was washed with water and recrystallized from methanol to give **5**, 2.50 g, yield (70%), mp, 95–97°C. IR (KBr) $cm^{-1}$: 3058 (NH), 1612, 1415 (C═N), 1670 (C═O), 3010 (C—H), 1560 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1056 (C—F), 2915, 2850 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 7.84 (1H, d, $J$ = 8.5 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 2.26 [6H, s, —$N(CH_3)_2$], 3.41 (2H, t, $J$ = 6.2 Hz, $NCH_2$), 2.65 (2H, t, $J$ = 5.4 Hz, $SCH_2$), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH); MS: *m*/*z* (%) 349.38 ($M^+$ 80%), 245.19 (100%), 175.68 (46%); Analytical data: Calcd/found for $C_{15}H_{16}FN_5O_2S$, C: 51.55/51.29, H: 4.62/4.60, N: 20.04/19.95, S: 9.18/9.13.

**Preparation of (*E*)-7-fluoro-5-(1,3,4-oxadiazol-2-yl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one (6).** Raney Ni (5 g) was added to a solution of **4** (2.95 g, 0.012 mol) in ethanol (100 mL), and the mixture was heated at 60–70°C for 6 h. After the completion of reaction (monitored by TLC), Raney Ni was filtered off, and the solvent was evaporated off. The product obtained was recrystallized from ethanol to give **6**, 2.40 g, yield (95%), mp, 125–127°C. IR (KBr) $cm^{-1}$: 3060 (NH), 1610, 1412 (C═N), 1670 (C═O), 3015 (C—H), 1565 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1060 (C—F); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 7.84 (1H, d, $J$ = 8.5 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.18 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH), 5.95 (1H, s, methine of oxadiazole ring); MS: *m*/*z* (%) 246.20 ($M^+$ 87%), 176.15 (100%), 148.14 (29%); Analytical data: Calcd/found for $C_{11}H_7FN_4O_2$, C: 53.66/53.49, H: 2.87/2.85, N: 22.76/22.66.

**Preparation of (*E*)-7-fluoro-5-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one (7).** A mixture of **4** (2.95 g, 0.01 mol), methyl iodide (0.08 mol) in ethyl acetate (60 mL) was stirred at room temperature with the addition of extra amount of methyl iodide (about 1 mL) in four installments in 25 h. The precipitate formed was isolated by filteration to give **7**, 2.30 g, yield (75%), mp, 145–147°C. IR (KBr) $cm^{-1}$: 3050 (NH), 1610, 1415 (C═N), 1675 (C═O), 3010 (C—H), 1575 (C═C), 1256 (C—O—C), 2975, 1420 (—$CH_2$ next to C═O), 1060 (C—F), 1475 (C—H str. $CH_3$); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 7.84 (1H, d, $J$ = 8.5 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH), 2.53 (3H, s, $CH_3$); MS: *m*/*z* (%) 292.29 ($M^+$ 85%), 245.20 (100%), 175.14 (23%); Analytical data: Calcd/found for $C_{12}H_9FN_4O_2S$, C: 49.31/49.20, H: 3.10/3.008, N: 19.17/19.11, S: 10.97/10.90.

**Preparation of (*E*)-5-(5-(2-(dimethylamino)ethylthio)-1,3,4-oxadiazol-2-yl)-7-fluoro-1-((pyrrolidin-1-yl)methyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one (8a)**

***Conventional method.*** A mixture of **5** (1.75 g, 0.005 mol), pyrrolidine (0.35 g, 0.005 mol), and 37% formaldehyde solution (0.75 mL) in ethanol (15 mL) was stirred at room temperature for 5 h and allowed to stand overnight. The precipitated product was filtered, washed with water, and recrystallized from ethanol to give **8a**, 1.20 g, yield (75%), mp, 101–103°C. Other products **8** (**b–h**) were prepared using the same procedure.

***Microwave-assisted method.*** Equimolar quantities of **5** (1.75 g, 0.005 mol), pyrrolidine (0.35 g, 0.005 mol), and 37% formaldehyde (2.5 mL) were taken in ethanol (50 mL) and placed in 100 mL flask fitted with a funnel and a loose top. The reaction mixture was subjected to microwave irradiation at 360 W microwave power for 5 min and then at 720 W for 4 min at short interval of 1 min to avoid the excessive evaporation of solvent. The completion of the reaction was checked by TLC. The solution obtained after the reaction had completed was kept at 0°C for 1 h, and the resulting solid obtained was filtered and recrystallized from ethanol to give compound **8a**, 1.50 g, yield (79%), mp, 101–103°C. Other products **8** (**b–h**) were prepared using the same procedure.

**8a**. IR (KBr) $cm^{-1}$: 1625, 1415 (C═N), 1670 (C═O), 3010 (C—H), 1570 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2912, 2865 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.68[4H, m, $(CH_2)_2$ of pyrrolidine], 2.51 [4H, m, $(CH_2)_2$ of pyrrolidine], 2.26 [6H, s, —$N(CH_3)_2$], 2.65 (2H, t, $J$ = 5.4 Hz, $SCH_2$ ), 3.41 (2H, t, $J$ = 6.2 Hz, $NCH_2$), 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine); MS: *m/z* (%) 432.51 ($M^+$ 90%), 328.32 (100%), 258.27 (68%); Analytical data: Calcd/found for $C_{20}H_{25}FN_6O_2S$, C: 55.54/55.39, H: 5.83/5.80, N: 19.43/19.35, S: 7.41/7.37.

**8b**. IR (KBr) $cm^{-1}$: 1627, 1415 (C═N), 1670 (C═O), 3010 (C—H), 1575 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2920 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.59 (2H, m, $CH_2$ of piperidine), 1.53 [4H, m, $(CH_2)_2$ of piperidine], 2.45 [4H, m, $(CH_2)_2$ of piperidine], 2.26 [6H, s, —$N(CH_3)_2$], 2.65 (2H, t, $J$ = 5.4 Hz, $SCH_2$), 3.41 (2H, t, $J$ = 6.2 Hz, $NCH_2$), 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine); MS: *m/z* (%) 446.54 ($M^+$ 76%), 342.35 (100%), 272.30 (50%); Analytical data: Calcd/found for $C_{21}H_{27}FN_6O_2S$, C: 56.48/56.30, H: 6.09/6.07, N: 18.82/18.77, S: 7.18/7.13.

**8c**. IR (KBr) $cm^{-1}$: 1615, 1412 (C═N), 1665 (C═O), 3015 (C—H), 1565 (C═C), 1256 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2917 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.50 [4H, t, $J$ = 5.0 Hz, $(CH_2)_2$ of tetrahydro1,4-oxazine], 3.65 [4H, t, $J$ = 6.0 Hz, $(CH_2)_2$ of tetrahydro1,4-oxazine], 2.26 [6H, s, —$N(CH_3)_2$], 2.65 (2H, t, $J$ = 5.4 Hz, $SCH_2$ ), 3.41 (2H, t, $J$ = 6.2 Hz, $NCH_2$), 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.17 (2H, s, $CH_2$ of benzodiazepine); MS: *m/z* (%) 448.51 ($M^+$ 74%), 344.32 (100%), 274.27 (43%); Analytical data: Calcd/found for $C_{20}H_{25}FN_6O_3S$, C: 53.56/53.45, H: 5.62/5.60, N: 18.74/18.64, S: 7.15/7.10.

**8d**. IR (KBr) $cm^{-1}$: 1605, 1445 (C═N), 1675 (C═O), 3015 (C—H), 1570 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1068 (C—F), 2907, 2850 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.35 [8H, t, $J$ = 5.0 Hz, $(CH_2)_4$ of *N*-methylenepiperazine], 2.26 (3H, s, $CH_3$ ), 2.26 [6H, s, —$N(CH_3)_2$], 2.65 (2H, t, $J$ = 5.4 Hz, $SCH_2$), 3.41 (2H, t, $J$ = 6.2 Hz, $NCH_2$), 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine); MS: *m/z* (%) 461.56 ($M^+$ 68%), 357.37 (100%), 342.35 (25%); Analytical data: Calcd/found for $C_{21}H_{28}FN_7O_2S$, C: 54.65/54.52, H: 6.11/6.09, N: 21.24/21.13, S: 6.95/6.90.

**8e**. IR (KBr) $cm^{-1}$: 1610, 1445 (C═N), 1665 (C═O), 3010 (C—H), 1585 (C═C), 1243 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2906, 2847 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.02 (3H, t, $CH_3$ ), 2.38 (2H, q, $CH_2$ ), 2.35[8H, t, $J$ = 5.0 Hz, $(CH_2)_4$ of *N*-ethylpiperazine], 2.26 [6H, s, —$N(CH_3)_2$ ], 2.65 (2H, t, $J$ = 5.4 Hz, $SCH_2$), 3.41 (2H, t, $J$ = 6.2 Hz, $NCH_2$), 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine); MS: *m/z* (%) 475.58 ($M^+$ 65%), 371.39 (100%), 342.37 (34%); Analytical data: Calcd/found for $C_{22}H_{30}FN_7O_2S$, C: 55.56/55.42, H: 6.36/6.34, N: 20.62/20.53, S: 6.74/6.69.

**8f**. IR (KBr) $cm^{-1}$: 1609, 1440 (C═N), 1670 (C═O), 3016 (C—H), 1570 (C═C), 1248 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2905. 2851 ($CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.35–2.48 [8H, t, $J$ = 5.0 Hz, $(CH_2)_4$ of piperazine], 2.26 [6H, s, —$N(CH_3)_2$ ], 2.65 (2H, t, $J$ = 5.4 Hz, $SCH_2$), 3.41 (2H, t, $J$ = 6.2 Hz, $NCH_2$), 3.66 (2H, s, —N—$CH_2$—C linkage), 4.45 (2H, s, N—$CH_2$—N linkage), 7.23–7.33 (5H, m, C—H, benzene), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine); MS: *m/z* (%) 537.65 ($M^+$ 77%), 433.46 (100%), 363.41 (15%); Analytical data: Calcd/found for $C_{27}H_{32}FN_7O_2S$, C: 60.32/60.25, H: 6.00/5.98, N: 18.24/18.13, S: 5.96/5.91.

**8g**. IR (KBr) $cm^{-1}$: 1625, 1415 (C═N), 1685, 1650 (C═O), 3010 (C—H), 1570 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2995, 2925, 2855 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.29 (3H, t, $CH_3$), 4.13 (2H, q, $CH_2$), 2.51[4H, t, $J$ = 5.0 Hz, $(CH_2)_2$ of piperazine], 3.20 [4H, t, $J$ = 5.5 Hz, $(CH_2)_2$ of piperazine], 2.26 [6H, s, —$N(CH_3)_2$], 2.65 (2H, t, $J$ = 5.4 Hz, $SCH_2$), 3.41 (2H, t, $J$ = 6.2 Hz, $NCH_2$), 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.18 (2H, s, $CH_2$ of benzodiazepine); MS: *m/z* (%) 519.59 ($M^+$ 87%), 415.40 (100%), 370.34 (48%); Analytical data: Calcd/found for $C_{23}H_{30}FN_7O_4S$, C: 53.17/53.05, H: 5.82/5.80, N: 18.87/18.76, S: 6.17/6.13.

**8h**. IR (KBr) $cm^{-1}$: 1608, 1458 (C═N), 1680, 1665 (C═O), 3015 (C—H), 1578 (C═C), 1243 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2904, 2832 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm:3.68 (3H, s, $CH_3$), 2.51[4H, t, $J$ = 5.0 Hz, $(CH_2)_2$ of piperazine], 3.20 [4H, t, $J$ = 5.5 Hz, $(CH_2)_2$ of piperazine], 2.26 [6H, s, —$N(CH_3)_2$], 2.65 (2H, t, $J$ = 5.4 Hz, $SCH_2$), 3.41 (2H, t, $J$ = 6.2 Hz, $NCH_2$), 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine); MS: *m/z* (%) 505.57 ($M^+$ 90%), 401.19 (100%), 370.35 (54%); Analytical data: Calcd/found for $C_{22}H_{28}FN_7O_4S$, C: 53.97/53.84, H: 5.76/5.74, N: 20.03/19.94, S: 6.55/6.51.

**Preparation of (*E*)-7-fluoro-5-(1,3,4-oxadiazol-2-yl)-1-((pyrrolidin-1-yl)methyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one (9a)**

***Conventional method.*** A mixture of **6** (2.46 g, 0.01 mol), pyrrolidine (0.71 g, 0.01 mol), and 37% formaldehyde solution (1.5 mL) in ethanol (20 mL) was stirred at room temperature for 8 h and allowed to stand overnight. The precipitated product was filtered, washed with water, and recrystallized from ethanol

to give **9a**, 2.00 g, yield (71%), mp, 105–107°C. Other products **9** (**b–h**) were prepared using the same procedure.

***Microwave-assisted method.*** Equimolar quantities of **6** (2.46 g, 0.01 mol), cyclic secondary amine (0.71 g, 0.01 mol), and 37% formaldehyde (5 mL) were taken in ethanol (100 mL) and placed in 250 mL flask fitted with a funnel and a loose top. The reaction mixture was subjected to microwave irradiation at 360 W microwave power for 8 min and then at 720 W for 5 min with short interval of 1 min to avoid the excessive evaporation of solvent. The completion of the reaction was checked by TLC. The solution obtained after the reaction had completed was kept at 0°C for 2 h, and the resulting solid obtained was filtered and recrystallized from ethanol to give compound **9a**, 2.20 g, yield (76%), mp, 105–107°C. Other products **9** (**b–h**) were prepared using the same procedure.

**9a**. IR (KBr) $cm^{-1}$: 1627, 1415 (C═N), 1670 (C═O), 3010 (C—H), 1570 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.68 [4H, m, $(CH_2)_2$ of pyrrolidine], 2.51 [4H, m, $(CH_2)_2$ of pyrrolidine], 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.85 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 6.00 (1H, s, methine of oxadiazole ring); MS: *m/z* (%) 329.33 ($M^+$ 92%), 259.28 (100%), 231.27 (63%); Analytical data: Calcd/found for $C_{16}H_{16}FN_5O_2$, C: 58.35/58.25, H: 4.90/4.88, N: 21.27/21.20.

**9b**. IR (KBr) $cm^{-1}$: 1628, 1412 (C═N), 1675 (C═O), 3016 (C—H), 1578 (C═C), 1255 (C—O—C), 2975, 1426 (—$CH_2$ next to C═O), 1065 (C—F); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.59 (2H, m, $CH_2$ of piperidine), 1.53 [4H, m, $(CH_2)_2$ of piperidine], 2.45 [4H, m, $(CH_2)_2$ of piperidine], 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.85 (1H, s, Ar—CH), 4.18 (2H, s, $CH_2$ of benzodiazepine), 5.95 (1H, s, methine of oxadiazole ring); MS: *m/z* (%) 343.36 ($M^+$ 79%), 273.31 (100%), 245.34 (30%); Analytical data: Calcd/found for $C_{17}H_{18}FN_5O_2$, C: 59.47/59.39, H: 5.28/5.26, N: 20.40/20.31.

**9c**. IR (KBr) $cm^{-1}$: 1615, 1412 (C═N), 1665 (C═O), 3015 (C—H), 1565 (C═C), 1256 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.50[4H, t, $J$ = 5.0 Hz, $(CH_2)_2$ of tetrahydro1,4-oxazine], 3.65 [4H, t, $J$ = 6.0 Hz, $(CH_2)_2$ of tetrahydro1,4-oxazine], 4.45 (2 H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.85 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 5.90 (1H, s, methine of oxadiazole ring); MS: *m/z* (%) 345.33 ($M^+$ 74%), 275.28 (100%), 247.98 (38%); Analytical data: Calcd/found for $C_{16}H_{16}FN_5O_3$, C: 55.65/55.51, H: 4.67/4.65, N: 20.28/20.18.

**9d**. IR (KBr) $cm^{-1}$: 1600, 1439 (C═N), 1675 (C═O), 3015 (C—H), 1570 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1068 (C—F), 2906 ($CH_3$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.35 (8H, t, $J$ = 5.0 Hz, $(CH_2)_4$ of *N*-methylenepiperazine ), 2.26 (3H, s, $CH_3$), 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1 H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 5.95 (1H, s, methine of oxadiazole ring); MS: *m/z* (%) 358.37 ($M^+$ 68%), 288.32 (100%), 273.30 (18%); Analytical data: Calcd/found for $C_{17}H_{19}FN_6O_2$, C: 56.98/56.85, H: 5.34/5.32, N: 23.45/23.38.

**9e**. IR (KBr) $cm^{-1}$: 1610, 1440 (C═N), 1695 (C═O), 3010 (C—H), 1586 (C═C), 1246 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2906, 2847 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.02 (3H, t, $CH_3$ ), 2.38 (2H, q, $CH_2$), 2.35[8H, t, $J$ = 5.0 Hz, $(CH_2)_4$ of *N*-ethylpiperazine], 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.85 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 5.95 (1H, s, methine of oxadiazole ring); MS: *m/z* (%) 372.4 ($M^+$ 89%), 302.35 (100%), 273.79 (62%); Analytical data: Calcd/found for $C_{18}H_{21}FN_6O_2$, C: 58.05/57.93, H: 5.68/5.66, N: 22.57/22.44.

**9f**. IR (KBr) $cm^{-1}$: 1609, 1440 (C═N), 1670 (C═O), 3016 (C—H), 1570 (C═C), 1248 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2905. 2851 ($CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.35–2.48 [8H, t, $J$ = 5.0 Hz, $(CH_2)_4$ of piperazine], 3.66 (2H, s, —N—$CH_2$—C linkage), 4.45 (2H, s, N—$CH_2$—N linkage), 7.23–7.33 (5H, m, C—H, benzene), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.86 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 6.05 (1H, s, methine of oxadiazole ring); MS: *m/z* (%) 434.47 ($M^+$ 75%), 343.47 (100%), 273.37 (28%); Analytical data: Calcd/found for $C_{23}H_{23}FN_6O_2$, C: 63.58/63.46, H: 5.34/5.32, N: 19.34/19.26.

**9g**. IR (KBr) $cm^{-1}$: 1625, 1412 (C═N), 1710, 1670 (C═O), 3012 (C—H), 1570 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2995, 2925, 2855 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.29 (3H, t, $CH_3$), 4.13 (2H, q, $CH_2$), 2.51[4 H, t, $J$ = 5.0 Hz, $(CH_2)_2$ of piperazine], 3.20 [4H, t, $J$ = 5.5 Hz, $(CH_2)_2$ of piperazine], 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30 (1H, d, $J$ = 8.6 Hz, Ar—CH), 7.86 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 5.95 (1H, s, methine of oxadiazole ring); MS: *m/z* (%) 416.41 ($M^+$ 87%), 371.35 (100%), 343.39 (43%); Analytical data: Calcd/found for $C_{19}H_{21}FN_6O_4$, C: 54.80/54.68, H: 5.08/5.06, N: 20.18/20.10.

**9h**. IR (KBr) $cm^{-1}$: 1608, 1458 (C═N), 1695, 1650 (C═O), 3015 (C—H), 1578 (C═C), 1243 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2904 ($CH_3$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.35 (3H, s, $CH_3$), 2.51 [4H, t, $J$ = 5.0 Hz, $(CH_2)_2$ of piperazine], 3.45 [4H, t, $J$ = 5.5 Hz, $(CH_2)_2$ of piperazine], 4.45 (2H, s, N—$CH_2$—N linkage), 7.41 (1H, d, $J$ = 8.3 Hz, Ar—CH), 7.30(1H, d, $J$ = 8.6 Hz, Ar—CH), 7.85 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 5.98 (1H, s, methine of oxadiazole ring); MS: *m/z* (%) 386.38 ($M^+$ 90%), 371.30 (100%), 343.78 (66%); Analytical data: Calcd/found for $C_{18}H_{19}FN_6O_3$, C: 55.95/55.84, H: 4.96/4.94, N: 21.75/21.66.

**Preparation of (*E*)-7-fluoro-5-(5-(pyrrolidin-1-yl)-1,3,4-oxadiazol-2-yl)-1*H*-benzo[e][1,4]diazepin-2(3H)-one (10a)**

***Conventional method.*** A mixture of **7** (1.46 g, 0.005 mol), 5.0 mL of pyrrolidine, 1 mL AcOH, and 20 mL of xylene was heated at reflux temperature for 45 h. The reaction mixture was concentrated, and the residue was diluted with $H_2O$ and filtered. The product was stirred with 30 mL of 2*N* AcOH, and the insoluble material was collected. The filtrate was treated with 9 mL of concentrated $NH_4OH$ and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layer was washed with $H_2O$, dried over $MgSO_4$, and concentrated to remove the solvent. The residue was recrystallized from ethyl acetate to give **10a**, 1.00 g, yield (75%), mp, 128–130°C. Other products **10** (**b–h**) were prepared using the same procedure.

***Microwave-assisted method.*** Equimolar quantities of **7** (1.46 g, 0.005 mol) and pyrrolidine (0.35 g, 0.005 mol) were

taken in ethanol (50 mL) and placed in 100 mL flask fitted with a funnel and a loose top. The reaction mixture was subjected to microwave irradiation at 360 W microwave power for 6 min and then at 720 W for 4 min with short interval of 1 min to avoid the excessive evaporation of solvent. The completion of the reaction was checked by TLC. The solution obtained after the reaction had completed was kept at 0°C for 1 h, and the resulting solid obtained was filtered and recrystallized from ethanol to give compounds **10a**, 1.30 g, yield (90%), mp, 128–130°C. Other products **10** (**b–h**) were prepared using the same procedure.

**10a**. IR (KBr) $cm^{-1}$: 1625, 1415 (C═N), 1675 (C═O), 3015 (C—H), 1579 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.92 [4H, m, $(CH_2)_2$ of pyrrolidine], 3.59 [4H, m, $(CH_2)_2$ of pyrrolidine], 7.84 (1H, d, $J$ = 8.4 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH); MS: *m/z* (%) 315.3 ($M^+$ 89%), 245.20 (100%), 175.14 (38%); Analytical data: Calcd/found for $C_{15}H_{14}FN_5O_2$, C: 57.14/57.05, H: 4.48/4.46, N: 22.21/22.14.

**10b**. IR (KBr) $cm^{-1}$: 1628, 1412 (C═N), 1675 (C═O), 3016 (C—H), 1578 (C═C), 1255 (C—O—C), 2975, 1426 (—$CH_2$ next to C═O), 1065 (C—F); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.59 [2H, m, $CH_2$ of piperidine], 1.53[4H, m, $(CH_2)_2$ of piperidine], 3.71 [4H, m, $(CH_2)_2$ of piperidine], 7.84 (1H, d, $J$ = 8.4 Hz, Ar—CH), 7.35 (1H, d, $J$ = 8.7 Hz,Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH); MS: *m/z* (%) 329.33 ($M^+$ 76%), 245.69 (100%), 177.65 (19%); Analytical data: Calcd/found for $C_{16}H_{16}FN_5O_2$, C: 58.35/58.21, H: 4.90/4.89, N: 21.27/21.17.

**10c**. IR (KBr) $cm^{-1}$: 1615, 1416 (C═N), 1665 (C═O), 3014 (C—H), 1576 (C═C), 1256 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 3.57 [4H, t, $J$ = 5.6 Hz, $(CH_2)_2$ of tetrahydro1,4-oxazine], 3.65 [4H, t, $J$ = 6.0 Hz, $(CH_2)_2$ of tetrahydro1,4-oxazine], 7.84 (1H, d, *J = 8.4 Hz*, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.76 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH); MS: *m/z* (%) 331.3 ($M^+$ 74%), 258.67 (100%), 180.67 (20%); Analytical data: Calcd/found for $C_{15}H_{14}FN_5O_3$, C: 54.38/54.29, H: 4.26/4.24, N: 21.14/21.07.

**10d**. IR (KBr) $cm^{-1}$: 1600, 1439 (C═N), 1675 (C═O), 3015 (C—H), 1570 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1068 (C—F), 2906 ($CH_3$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.36 [4H, t, $J$ = 5.0 Hz, $(CH_2)_2$ of *N*-methylenepiperazine], 3.15 [4H, t, $J$ = 5.8 Hz, $(CH_2)_2$ of *N*-methylenepiperazine], 2.26 (3H, s, $CH_3$), 7.84 (1H, d, $J$ = 8.4 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH); MS: *m/z* (%) 344.34 ($M^+$ 87%), 329.35 (100%), 257.89 (54%); Analytical data: Calcd/found for $C_{16}H_{17}FN_6O_2$, C: 55.81/55.70, H: 4.98/4.96, N: 24.41/24.33.

**10e**. IR (KBr) $cm^{-1}$: 1612, 1446 (C═N), 1695 (C═O), 3010 (C—H), 1586 (C═C), 1248 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2906, 2847 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.02 (3H, t, $CH_3$), 2.38 (2H, q, $CH_2$), 3.44 [4H, t, $J$ = 5.6 Hz, $(CH_2)_2$ of *N*-ethylpiperazine], 3.15 [4H, t, $J$ = 5.3 Hz, $(CH_2)_2$ of *N*-ethylpiperazine], 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.84 (1H, d, $J$ = 8.4 Hz, Ar—CH), 7.86 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH); MS: *m/z* (%) 358.37 ($M^+$ 68%), 329.45 (100%), 245.90 (25%); Analytical data: Calcd/found for $C_{17}H_{19}FN_6O_2$, C: 56.98/56.85, H: 5.34/5.32, N: 23.45/23.36.

**10f**. IR (KBr) $cm^{-1}$: 1609, 1440 (C═N), 1670 (C═O), 3016 (C—H), 1570 (C═C), 1248 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2851 ($CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.62 [4H, t, $J$ = 5.0 Hz, $(CH_2)_2$ of piperazine], 3.15 [4H, t, $J$ = 5.3 Hz, $(CH_2)_2$ of piperazine], 3.66 (2H, s, —N—$CH_2$—C linkage), 7.23–7.33 (5H, m, C—H, benzene), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.85 (1H, d, $J$ = 8.4 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH); MS: *m/z* (%) 420.44 ($M^+$ 78%), 335.59 (100%), 268.21 (56%); Analytical data: Calcd/found for $C_{22}H_{21}FN_6O_2$, C: 62.85/62.72, H: 5.03/5.01, N: 19.99/19.90.

**10g**. IR (KBr) $cm^{-1}$: 1625, 1412 (C═N), 1710, 1670 (C═O), 3012 (C—H), 1570 (C═C), 1254 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2995, 2925, 2855 ($CH_3$, $CH_2$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 1.29 (3H, t, $CH_3$), 4.13 (2H, q, $CH_2$), 3.33 [4H, t, $J$ = 5.6 Hz, $(CH_2)_2$ of piperazine], 3.31 [4H, t, $J$ = 5.6 Hz, $(CH_2)_2$ of piperazine], 7.86 (1H, d, $J$ = 8.4 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH); MS: *m/z* (%) 402.38 ($M^+$ 87%), 357.35 (100%), 329.56 (38%); Analytical data: Calcd/found for $C_{18}H_{19}FN_6O_4$, C: 54.80/54.68, H: 4.76/4.74, N: 20.89/20.81.

**10h**. IR (KBr) $cm^{-1}$: 1608, 1458 (C═N), 1695, 1650 (C═O), 3015 (C—H), 1578 (C═C), 1243 (C—O—C), 2975, 1425 (—$CH_2$ next to C═O), 1065 (C—F), 2904 ($CH_3$, CH); $^1$H-NMR (300 MHz, $CDCl_3$ + DMSO-$d_6$) δ ppm: 2.35 (3H, s, $CH_3$), 3.31 [4H, t, $J$ = 5.5 Hz, $(CH_2)_2$ of piperazine], 3.57 [4H, t, $J$ = 5.8 Hz, $(CH_2)_2$ of piperazine], 7.85 (1H, d, $J$ = 8.4 Hz, Ar—CH), 7.34 (1H, d, $J$ = 8.7 Hz, Ar—CH), 7.78 (1H, s, Ar—CH), 4.19 (2H, s, $CH_2$ of benzodiazepine), 8.00 (1H, s, NH); MS: *m/z* (%) 372.35 ($M^+$ 92%), 341.32 (100%), 313.67 (58%); Analytical data: Calcd/found for $C_{17}H_{17}FN_6O_3$, C: 54.84/54.71, H: 4.60/4.58, N: 22.57/22.48.

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