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Ring Rearrangements and Reactivity of 3-((4-oxo-4*H*-chromen-3-yl)methylene)-4-phenyl-1*H*-[1,5]benzodiazepin-2(3*H*)-one Towards Some Nucleophiles

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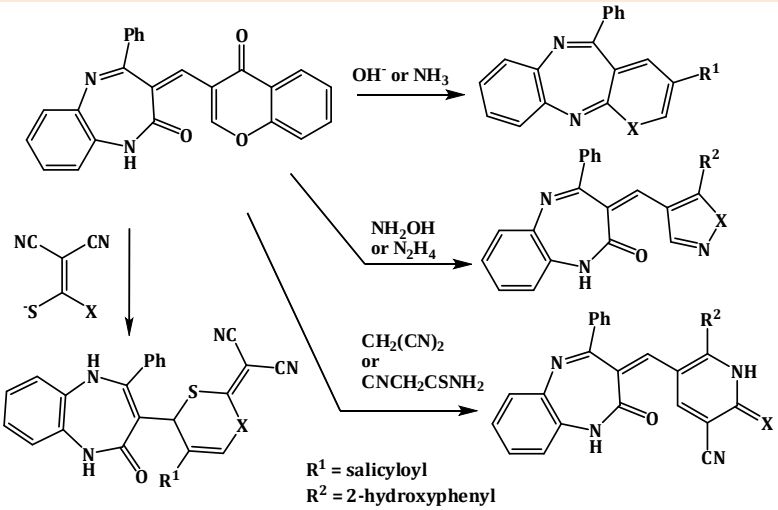
Graphical Abstract



Keywords:
[1,5]Benzodiazepin-2(3H)-one
3-Formylchromone
Nucleophilic reagents
Ring rearrangement
Heterocyclization

Abstract.
Condensation of 4-phenyl-1*H*-[1,5]benzodiazepin-2(3*H*)-one (**1**) with 3-formylchromone (**2**) afforded a mixture of 3-(chromenylmethylene)-[1,5]benzodiazepinone **3** and 14-chromenylbenzo-diazepino[2,3:6,5]pyrano[2,3-b]benzodiazepine **4**. Ring rearrangements of compound **3** with different nucleophilic reagents, such as; potassium hydroxide and/or ammonium acetate led to rearrangement into pyranobenzodiazepine **5** and pyridobenzodiazepine **6**, respectively. Treatment of compound **3** with hydrazine hydrate, hydroxylamine hydrochloride, malononitrile, cyanothioacetamide, 2-cyano-3,3-disufanylacrylonitrile, and/or 2-cyano-3-phenylamino-3-sufanylacrylonitrile, have been carried out at different conditions, leading to versatile heterocyclic substituted benzodiazepines at position 3, *viz*; pyrazole **8**, isoxazole **9**, pyridines **10** and **11**, 1,3-dithiine **12**, and 1,3-thiazine **13** derivatives.

Introduction

Chromone is a gamma pyrone nucleus which has been reported as very useful synthone. Thus chromones and other related analogues have interesting chemical properties towards reaction with mononucleophiles and binucleophiles in which ring opening-ring closure takes place leading to new heterocyclic derivatives [1-6]. Many reports described the implantation of a 3-chromonylmethylene moiety at different active methylene heterocyclic compounds. Consequently, a reactive annular

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enone system, γ-pyrone ring, is generated which is capable to react efficiently with different nucleophiles leading to ring-opening/ring-closure (RORC) to afford new substituted heterocyclic systems [7-10]. For this purpose 3-formylchromone has been successfully used to prepare a variety of heterocyclic systems. [1,5]Benzodiazepin-2-ones have attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. Thus, many of [1,5]benzodiazepin-2-ones are widely used as anticonvulsant [11], anti-inflammatory [12], antiviral [13], anti-HIV-1 [14], antimicrobial [15] and antitumor [16] agents. In extension to our research project dealing with synthesis of [1,5]benzodiazepine derivatives [17–21], we herein subjected the key starting compound to obtain novel [1,5]benzodiazepin-2(3*H*)-ones bearing five and/or six membered heterocyclic substituents. Using the above synthetic strategy, we described the preparation of the desired derivatives of [1,5]benzodiazepine, starting from 3-((4-oxo-4H-chromen-3-yl)methylene)-4-phenyl-1H-[1,5]benzodiazepin-2(3H)-one (**3**).

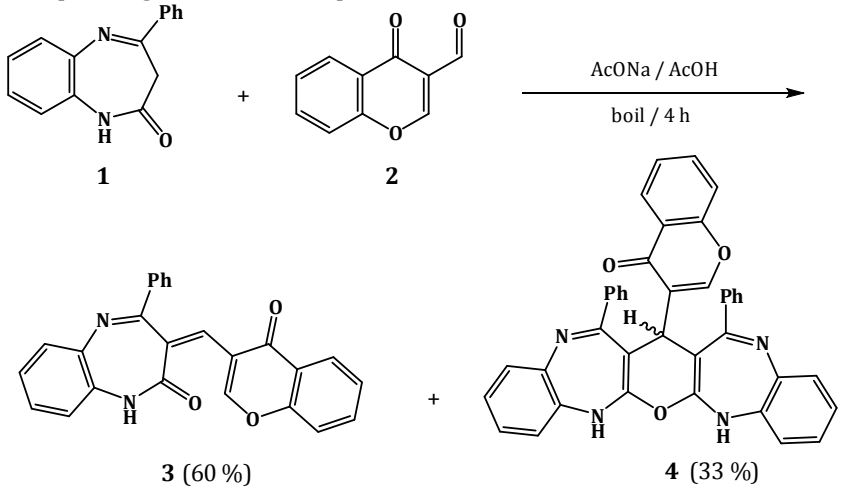
Results and Discussion

3-((4-Oxo-4H-chromen-3-yl)methylene)-4-phenyl-1*H*-[1,5]benzodiazepin-2(3H)-one (**3**) was prepared by condensation of equimolar amounts of 4-phenyl-1*H*-[1,5]benzodiazepin-2(3*H*)-one (**1**) [22] and 3-formylchromone (**2**) [23], in presence of freshly fused sodium acetate, in 60 % yield. Interestingly, 14-chromenyl [1,5]benzodiazepino[2,3:6,5]pyrano[2,3-b][1,5]benzodiazepine **4** was separated as by-product, in 33 % yield (Scheme 1). It was found that yield of both compounds **3** and **4** is dependent on molar ratio of reactants. Notably, starting with excess molar amount of aldehyde **2**, double ratio, gave compound **3** in 90 % yield, while on using half ratio of aldehyde **2** a 2:1 molar ratio led to compound **3** in only 20 % yield (Table 1). Obviously, condensation of diazepinone **1** with aldehyde **2,** leading to methylene derivative **3,** is subsequently underwent nucleophilic addition of another diazepinone molecule. Earlier, similar cyclization type was reported by Haas *et al.* [24], in which the adduct intermediate underwent an intramolecular cyclization *via in situ* elimination of a water molecule, accomplishing formation of a trinuclear ring system.

Table 1. Yields obtained from reaction between diazepinone **1** and aldehyde **2**.

Reactants (*Molar ratios*) $M_{diazepinone}$/ $M_{aldehyde}$	**Yield (%)**	
	Compound **3**	Compound **4**
1/2	90	05
1/1	60	33
2/1	20	60

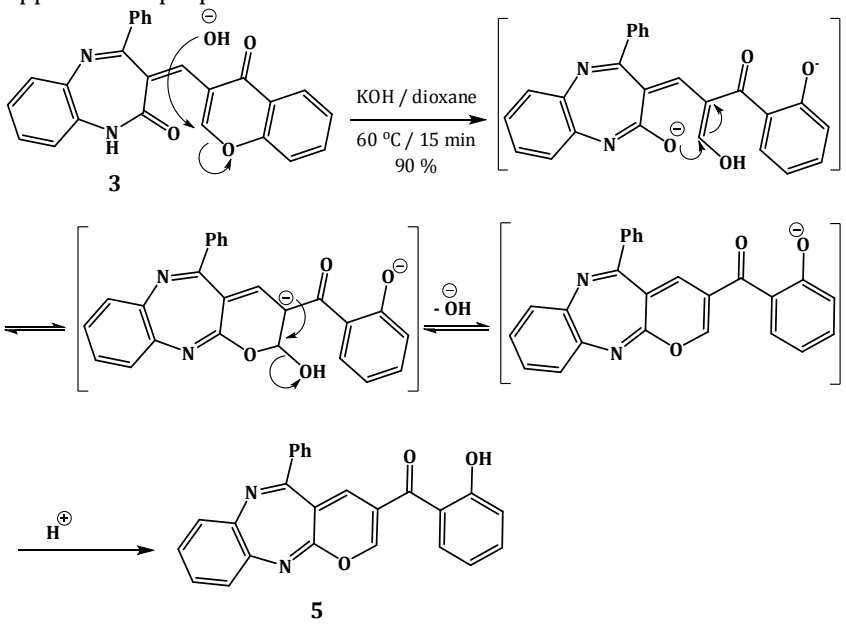
The structure of both compounds **3** and **4** was established on basis of their spectral and analytical data. ^{1}H NMR spectrum of compound **3** showed two singlet signals at δ 7.03 and 8.59, corresponding to methylene and α-chromone protons, respectively. ^{13}C NMR spectrum of which revealed two distinctive chemical shifts at δ 193.10 and 193.50, belong to carbonyl groups, which their stretching vibrations appeared at ν 1686 and 1645 cm^{-1}. On the other hand, IR spectrum of compound **4** exhibited only one carbonyl absorption band, at ν 1684, characteristic for C=O stretching vibration of γ-pyrone. ^{1}H NMR spectrum of this compound indicated the presence of chemical shift signal at δ 5.19 due to methine proton at position 14, beside as singlet peak at δ 8.61 pointing to α-chromone proton.



Scheme 1. Reaction of 4-phenyl-1H-[1,5]benzodiazepin-2(3H)-one (**1**) with 3-formylchromone (**2**).

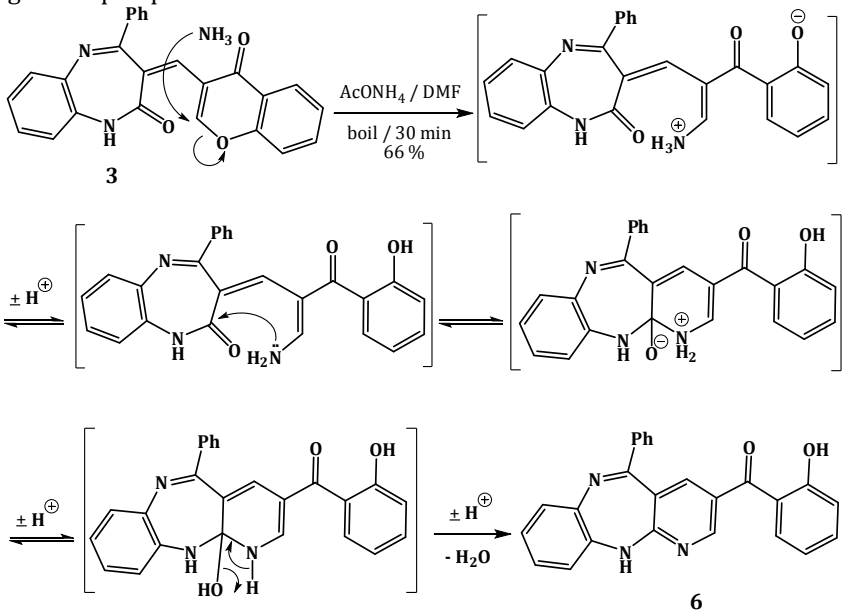
Treatment of compound **3** with aqueous potassium hydroxide underwent nucleophilic ring rearrangement, furnishing pyrano[b]benzodiazepine **5**, in 90 % yield. As depicted in Scheme 2, chromone nucleus is attacked by hydroxide ion at the α-carbon leading to ring-opening. Subsequently, diazepinolate ion underwent an intramolecular aldol addition followed by

elimination of a hydroxide ion. This cascade base catalyzed RORC led to a rearrangement to annulated pyrano[b]diazepine system [25]. Elemental microanalysis for C, H, and N elements (within ± 0.32 %) showed no difference in these elements ratios than the starting material, i.e. both may possess the same formula. Ferric chloride color test indicated the presence of a phenolic OH function, it gives deep violet coloration. IR spectrum of compound **5** showed disappearance of both chromone and diazepinone carbonyl stretching bands and instead a stretching vibrational band was observed at ν 1635 cm^{-1} due to benzoyl C=O. ^{1}H NMR spectrum of the product revealed the presence of two singlet signals at δ 7.74 and 7.79, belong to α- and γ-pyran protons besides a wide range multiplet peaks, at δ 7.09–7.63, due to chemical shift of thirteen aromatic protons. ^{13}C NMR spectrum of compound **5** supported the proposed structure.



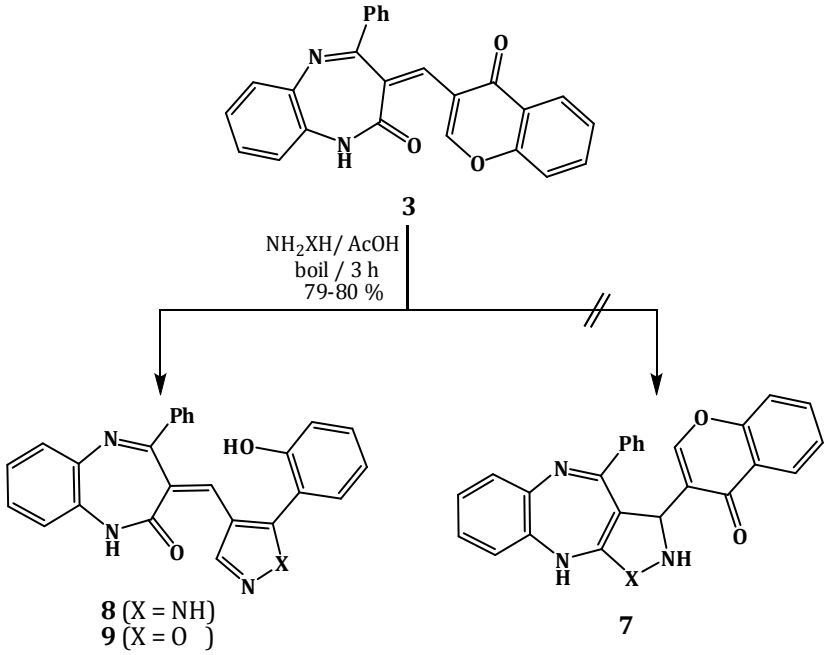
Scheme 2. Rearrangement of compound **3** into pyranobenzodiazepine **5**.

Ammonialysis of compound **2** using ammonium acetate, in boiling dimethylformamide, led to another RORC reaction in which pyrido[3,2-b]benzodiazepine derivative **6** was afforded in 66 % yield (Scheme 3). Herein ammonium acetate liberated ammonia which nucleophilically attacked the α-carbon of chromone ring causing ring-opening [8]. Subsequently, amine intermediate that obtained underwent an intramolecular nucleophilic addition-elimination (condensation reaction) at position 2 of diazepinone. The product gave a violet color with ferric chloride color reaction, showing the presence of a phenolic OH function. IR spectrum represented a stretching vibration at ν 1655 cm^{-1} due to benzoyl C=O. Mass spectrum exhibited an (M+H) ion peak at m/z 392 (7.6 %) beside a base peak at m/z 77 (100 %) characteristic for phenylium ion. ^{1}H NMR spectrum of the product revealed the presence of two singlet signals, at δ 8.05 and 8.25, attributed to α- and γ-pyridine protons besides a wide range multiplet peaks at δ 6.80–7.73 due to chemical shift of thirteen aromatic protons.



Scheme 3. Rearrangement of compound **3** into pyridobenzodiazepine **6**.

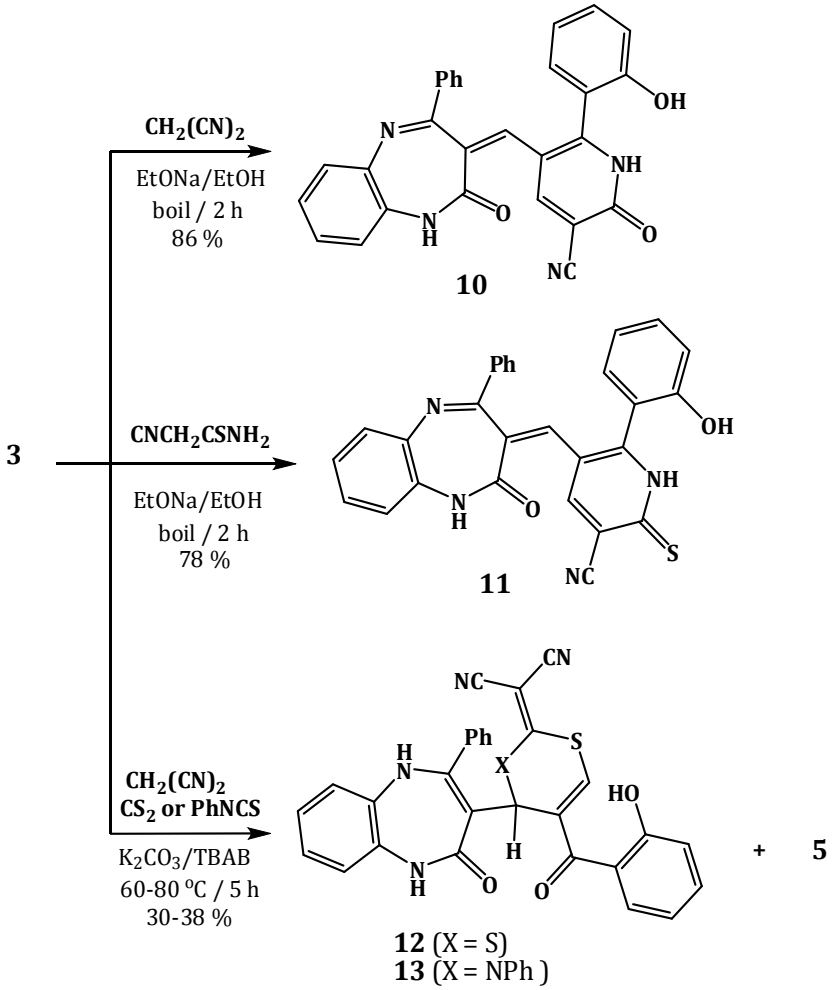
Surprisingly, when compound **1** was reacted with hydrazine hydrate and/or hydroxyl amine hydrochloride, in glacial acetic acid, afforded 3-((pyrazolyl and isoxazolyl)methylene)benzodiazepin-2-one derivatives **8** and **9**, respectively (Scheme 4). According to literature reports in similar cases [3,4,26], pyrazolo[3,4-b]- and/or isoxazolo[4,5-b]benzodiazepines **7**, are probable products for such reaction. In acidic medium addition of binucleophiles may regioselectively be oriented to methylenediazepinone exocyclic enone system rather than attack the chromone nucleus. Elemental microanalyses as well as mass spectra cannot differ between the two possible products. However, the ferric chloride color reaction gives violet coloration with both products **8** and **9**, indicating the presence of phenolic OH function. IR spectra of compounds **8** and **9** fortified this result where broad bands appeared at ν 3377–3337 and 3204–3207 cm^{-1}, due to H-bonded O–H and N–H functions. Moreover, ^1H NMR spectra of both compounds **8** and **9** revealed the existence of a methylenic proton appears as singlet signal at δ 7.03–7.06 besides a broad singlet peak at δ 13.09–13.13, due to a downfield shifted chemical shift of H-bonded O–H.



Scheme 4. Reaction of compound **3** with hydrazine and hydroxylamine.

Reaction of the compound **3** with malononitrile, in presence of sodium ethoxide, gave 3-(pyridin-5-yl)methylenebenzodiazepin-2(3H)-one **10**, in 86 % yield (Scheme 5). Formation of the compound **10** is explicable by the nucleophilic attack, of carbanion *in situ* obtained from malononitrile, at α-carbon of chromone nucleus. Consequent enolized side chain oxygen added at a cyano function leading to an iminopyran intermediate, which in turn underwent Dimroth-type rearrangement into pyridone [27]. IR spectrum of compound **10** showed absorption bands at ν 3450–3209 cm^{-1} due to H-bonded N–H and tautomeric O–H. In addition, the spectrum represented a sharp medium band at ν 2201 cm^{-1} due to C≡N function and two strong absorption bands at ν 1665 and 1624, attributed to C=O of diazepinone and pyridone. ^1H NMR spectrum of compound **10** revealed the existence of chemical shifts appeared as singlets corresponding to methylenic and γ-proton of pyridone at δ 6.80 and 8.74, respectively. ^{13}C NMR spectrum showed the chemical shift corresponding to *sp*-carbon (C≡N) at δ 200 and the two sp2-carbon due to C=O appeared at δ 181.

Similarly, when compound **3** was subjected to react with cyanothioacetamide, in presence of sodium ethoxide, chromone ring-opening and a consequent pyridine ring-closure took place. This ring transformation led to 3-(2-thioxopyridin-5-yl)methylene) benzodiazepin-2-one **11**, in 78 % yield (Scheme 5). The reaction mechanism may proceed *via* first nucleophilic addition of carbanion of cyanothioacetamide, at the α-carbon of chromone, leading to ring-opening. Thence, nucleophilic addition of NH_2 and elimination of water molecule took place, resulting in pyridinethione ring-closure. The product gave a violet color against ferric chloride color test, indicating the presence of phenolic OH function. Elemental analysis revealed presence of sulfur in the product. IR spectrum showed bands corresponding to O–H, N–H and C≡N groups at ν 3436, 3344–3280 and 2156 cm^{-1}, respectively. ^1H NMR spectrum showed two singlet signals corresponding to methylenic and γ-proton of pyridone at δ 6.90 and 8.14, respectively. Furthermore, inspection of the ^1H NMR spectrum using deuterium oxide showed that there are three deuterium exchangeable protons appeared as broad singlets at δ 8.55, 10.60, and 13.18. The first two are back to the ring N–H of both pyridinethione and diazepinone while the last one is attributed to the phenolic O–H.



Scheme 5. Reaction of compound **3** with some 1,3-binucleophiles.

Ketene S,S- and N,S-acetals had attracted an exceptional concern due to their synthetic role in preparation of a versatile heterocyclic compounds [28-30]. Hence, multi-component reaction (MCR) including compound **3** and a mixture of carbon disulfide and malononitrile or phenyl isothiocyanate and malononitrile was investigated. The reaction was carried out under phase transfer catalysis conditions (PTC), using potassium carbonate as base catalyst and tetrabutylammonium bromide (TBAB) as PTC-agent. Surprisingly, the reaction in both cases afforded a mixture of pyrano[b]benzodiazepine **5** and 2-(4-benzodiazepinyl-1,3-dithiinylidene)malononitrile **12** or 2-(4-benzodiazepinyl-1,3-thiazinylidene)malononitrile **13**, in 30–38 % yields (Scheme 5). Formation of compound **5** as the main product, in 45–55 % yields, can be attributed to effect of base catalyst (K_2CO_3) which is mandatory used during this reaction. It is well known that chromone ring can be easily opened under this conditions which is also enough for annulation of pyrano[b]benzodiazepine ring. Elemental analyses of both products **12** and **13** revealed the presence of sulfur element. Also both of them gave violet coloration against ferric chloride color test. IR spectra of these two compounds exhibited vibrational bands at ν 2205 cm^{-1}, characteristic for C≡N function in addition to strong stretching vibration at ν 1660–1669 and 1645–1635 cm^{-1} due to C=O functions of benzoyl and diazepinone moieties, respectively. ^{1}H NMR spectrum of dithiine derivative **12** demonstrated two chemical shifts due to dithiine ring hydrogens appeared as singlet peaks at δ 3.80 and 6.80 in addition to three deuterium exchangeable protons appeared as broad singlets at δ 8.92, 10.60, and 13.14 due to two N–H of diazepinone and O–H of salicyloyl moiety. Similar evidences were observed in spectra and analysis of compound **13**. Furthermore ^{13}C NMR of compound **13** revealed the presence of two chemical shifts at δ 190 and 188 due to two *sp* carbons of C≡N functions and two signals at δ 183 and 180 due two sp^2 carbons of C=O functions. Elemental microanalyses for C, H, and N-elements (within ± 0.4 %) of both compounds **12** and **13**, are satisfactorily in good accordance with the calculated formula.

Experimental Section

General

All melting points were determined on a Koffler melting points apparatus and are uncorrected. IR spectra were obtained on a Nicolet 710 FT-IR spectrometer. ^{1}H NMR spectra, at 400 MHz, and ^{13}C NMR spectra, at 100 MHz, were recorded on a Bruker Avance III-400 MHz instrument, using DMSO-d_6 as solvent. The mass spectra were scanned on a Varian Mat CH-7

instrument at 70 eV. Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 elemental analyzer. All compounds were checked for their purity on TLC plates. Starting materials; 4-phenyl-1*H*-[1,5]benzodiazepin-2(3*H*)-one (**1**) [22] and 3-formylchromone (**2**) [23] were prepared as described in the literature.

Reaction between 4-Phenyl-1H-[1,5]benzodiazepin-2(3H)-one (1) and 3-Formylchromone (2)

A mixture of benzodiazepinone **1** (2.36 g, 10 mmol), 3-formylchromone **2** (1.74 g, 10 mmol), and freshly fused sodium acetate (3 g, 36 mmol), in glacial acetic acid (50 mL) was heated under reflux 4 h. The reaction mixture was left to cool to room temperature, and then poured onto crushed-ice. The solid so formed was filtered, washed with cold water, and dried. This crude solid material was boiled in absolute ethanol (50 mL) for 15 min. and filtered off insoluble residue. The filtered solid was washed thoroughly several times with hot ethanol (*ca.* 50 mL) and crystallized from glacial acetic acid to give compound **3**. The collected ethanol filtrate was concentrated to about one-fourth of its volume (*ca.* 25 mL) and left to stand at room temperature over-night to give crystalline needle-like deposits which were collected by filtration to afford compound **4**.

3-((4-Oxo-4H-chromen-3-yl)methylene)-4-phenyl-1H-[1,5]benzodiazepin-2(3H)-one (3). Yield (2.36 g, 60 %), mp 240–242 °C. IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3245 (N–H), 1686 (C=$O_{chromone}$), 1645 (C=$O_{diazepinone}$), 1606, 1592, 1554. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.03 (s, 1H, H_{olefin}), 7.14–7.93 (m, 13H, H_{arom}), 8.59 (s, 1H, α-$H_{chromone}$), 10.46 (bs, 1H, N–H disappeared on addition of D_2O). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 69.47, 105.32, 111.43, 112.11, 113.51, 117.43, 120.04, 122.66, 124.62, 125.56, 127.22, 129.22, 130.39, 131.30, 134.42, 136.19, 137.33, 139.22, 141.54, 143.32, 144.40, 145.19, 157.16, 193.10, 193.50. Analysis calcd. for $C_{25}H_{16}N_2O_3$ (392.41); C, 76.52; H, 4.11; N, 7.14 %**.** Found. C, 76.30; H, 4.00; N, 7.20 %.

13,15-Diphenyl-14-(4-oxo-4H-[1]chromen-3-yl)-5H,7H,14H-[1,5]benzodiazepino[2,3:6,5]pyrano[2,3-b][1,5]benzodiazepine (4). Yield (1.0 g, 33 %), mp 271–272 °C. IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3266 (N–H), 1684 (C=$O_{chromone}$), 1608 (C=N), 1580, 1553, 1495. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.19 (s, 1H, 14-$H_{\gamma\text{-pyran}}$), 6.80–8.08 (m, 22 H, H_{arom}), 8.61 (s, 1H, α-$H_{chromone}$), 13.75 (b, 2H, N-$H_{diazepine}$, disappeared on addition of D_2O). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 90.91, 96.76, 99.32, 100.55, 110.45, 111.09, 113.60, 117.06, 119.09, 120.12, 122.38, 123.03, 124.52, 126.71, 127.11, 130.63, 131.54, 132.55, 133.11, 135.22, 137.44, 140.76, 143.43, 144.88, 146.60, 147.80, 150.12, 152.77, 155.41, 158.44, 159.11, 160.22, 163.07, 165.70, 168.22, 170.00, 174.55, 176.74, 176.44, 186.55. Analysis calcd. for $C_{40}H_{26}N_4O_3$ (610.66); C, 78.67; H, 4.29; N, 9.17 %. Found: C, 78.40; H, 4.20; N; 9.20 %.

3-(2-Hydroxybenzoyl)-5-phenylpyrano[2,3-e][1,5]benzodiazepine (5)

To a solution of compound **3** (1.02 g, 2.6 mmol) in dioxane (25 mL), aqueous potassium hydroxide solution (25 mL, 50 mmol; 2M) was added. The alkaline solution was warmed at 60 °C and stirred for 15 min. The turbid solution was diluted with excess cold water (100 mL) to get a clear yellow solution. Acidification of the solution using dilute hydrochloric acid (0.5 M) till be red to litmus gave a pale yellow fine particles which was digested for 15 min over a boiling water-bath. Filtration, drying and crystallization of the pale yellow precipitate from DMF furnished compound **5**. Yield (0.92 g, 90 %), mp > 300 °C. IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3447(O–H), 1635 (C=O), 1605 (C=N), 1590, 1575, 1552, 1509. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.09–7.63 (m, 13H, H_{arom}), 7.74 (s, 1H, γ-H_{pyran}), 7.79 (s, 1H +α-H_{pyran}), 13.09 (b, 1H, H-bonded O–H, disappeared on addition of D_2O). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 102.85, 105.08, 109.66, 110.90, 112.33, 118.11, 120.32, 122.98, 124.87, 126.44, 128.55, 129.00, 130.43, 133.09, 137.77, 139.08, 140.33, 143.09, 145.66, 148.33, 150.65, 153.00, 154.09, 157.06, 188.00. Analysis calcd. for $C_{25}H_{16}N_2O_3$ (392.41): C, 76.52; H, 4.11; N, 7.14 %. Found: C; 76.20; H, 3.90; N, 7.00 %.

3-(2-Hydroxybenzoyl)-5-phenyl-11H-pyrido[2,3-b][1,5]benzodiazepine (6). A mixture of compound **3** (0.78 g, 2 mmol) and ammonium acetate (0.23 g, 3 mmol), in DMF (10 mL), was heated under reflux for 30 min. The reaction mixture was poured into ice cold water (100 mL) containing HCl (5 mL). The formed precipitate was filtered, dried, and crystallized from dioxane to give pyridobenzodiazepine **6**. Yield (0.52 g, 66 %), mp 285–286 °C. IR (KBr), ν (cm^{-1}): 3442 (O–H), 3280 (N–H), 3075, 1655 (C=O), 1612, 1605, 1585. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.80–7.73 (m, 13H, H_{arom}), 8.05 (s, 1H, γ-$H_{pyridine}$), 8.25 (s, 1H, α-$H_{pyridine}$), 9.92 (s, 1H, N–H disappeared on addition of D_2O), 13.20 (s, 1H, O–H, disappeared on addition of D_2O). MS, *m/z* (*I* %): 392 (7.60, M+1), 363 (5.20), 290 (4.80), 289 (15.20), 288 (4), 275 (3.2), 274 (10), 167 (25.2), 121 (34.2), 77 (100). Analysis calcd. for $C_{25}H_{17}N_3O_2$ (391.42): C, 76.71; H, 4.38; N, 10.74%. Found: C, 76.80; H, 4.50; N, 10.50 %.

General Procedure for Preparation of 3-(Diazolylmethyl-ene)benzodiazepinones 8 and 9

A mixture of compound **3** (0.78 g, 2 mmol) and hydrazine hydrate (0.1 mL, 2 mmol) or hydroxylamine hydrochloride (0.14 g, 2 mmol) was heated under reflux, in glacial acetic acid (20 mL), for 3 hrs. Then the reaction mixture was left to cool and the precipitate so formed was filtered, dried, washed with water and crystallized from ethanol.

3-((5-(2-Hydroxyphenyl)-1H-pyrazol-4-yl)methylene)-4-phenyl-1H-[1,5]benzodiazepin-2(3H)-one (8). Yield (0.65 g, 80 %), m.p. >300°C. IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3377, 3207 (O–H, N–H), 1668 (C=O), 1608, 1582. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.03 (s, 1H, H_{olefin}), 7.20–7.86 (m, 12H, H_{arom}), 8.54 (s, 1H, 3-$H_{pyrazole}$), 10.32–10.47 (bs, 2H, N–H, disappeared on addition of D_2O), 13.13 (b, 1H, H-bonded O–H, disappeared on addition of D_2O). MS, *m/z* (*I* %): 406 ($M^{+\cdot}$; not detected), 404 (M-2, 15.30), 401 (15.10), 300 (70.54), 301 (45.02), 302 (25.89), 303 (15.47), 285 (23.99), 274 (34.95), 261 (24.28), 243 (16.59), 233 (33.51),

218 (27.05), 205 (14.37), 171 (56.57), 156 (19.05), 145 (15.01), 131 (25.08), 119 (30.49), 105 (100), 102 (24.79), 92 (30.82), 77 (24.53). Analysis calcd. for $C_{25}H_{18}N_4O_2$ (406.44): C, 73.88; H, 4.46; N, 13.78 %. Found: C, 73.60; H, 4.20; N, 13.50 %.

3-((5-(2-Hydroxyphenyl)isoxazol-4-yl)methylene)-4-phenyl-1H-[1,5]benzodiazepin-2(3H)-one (9). Yield (0.64 g, 79 %), m.p. > 300 °C. IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3337, 3240 (O–H, N–H), 1659 (C=O), 1604, 1590, 1565. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.06 (s, 1H, H_{olfen}), 7.18–8.20 (m, 12H, H_{arom}), 8.70 (s, 1H, 3-$H_{isoxazole}$), 9.99 (s, 1H, N–H, disappeared on addition of D_2O), 13.09 (b, 1H, O–H, disappeared on addition of D_2O). MS, *m*/*z* (*I* %): 407 ($M^{+\cdot}$; 1.7), 318 (11.6), 263 (11.3), 170 (16.1), 105 (100). Analysis calcd. for $C_{25}H_{17}N_3O_3$ (407.42): C, 73.70; H, 4.21; N, 10.31 %. Found. C, 73.50; H; 4.10; N, 10.20 %.

General Procedure for Preparation of 3-(pyridylmethylene)- benzodiazepinones 10 and 11.
A mixture of compound **3** (0.78 g, 2 mmol,) and malononitrile (0.132 g, 2 mmol) or cyanothioacetamide (0.2 g, 2 mmol), in ethanol (25 mL) was treated with sodium ethoxide (sodium metal (0.23 g) was dissolved in absolute ethanol (5 mL); 10 mmol). Then the reaction mixture was heated, at water-bath, under reflux for 1 hr. The mixture was left to cool to room temperature and then poured into ice-cold dilute hydrochloric acid solution (100 mL, 3 %). The resulting solid product was filtered, washed with water and crystallized from ethanol.

3-((3-Cyano-6-(2-hydroxyphenyl)-2-oxo-1,2-dihydropyridin-5-yl)methylene)-4-phenyl-1H-[1,5]benzodiazepin-2(3H)-one (10). Yield (0.79 g, 86 %), mp 279–281 °C. IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3450 (O–H), 3340 (N–H), 3209 (N–H), 2201 (C≡N), 1665 (C=O), 1624 (C=O), 1605, 1590, 1545. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.80 (s, 1H, H_{olefin}), 7.06–7.92 (m, 13H, H_{arom}), 8.55 (m, 1H, 9-$H_{benzodiazepine}$), 8.74 (s, 1H, γ-$H_{pyridone}$), 9.49 (bs, 1H, N–$H_{pyridone}$, disappeared on addition of D_2O), 9.87 (bs, 1H, N–$H_{diazepinone}$, disappeared on addition of D_2O), 13.60 (b, 1H, O–H, disappeared on addition of D_2O). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 200.09(C≡N), 181.15 (C=O), 158.00, 155.84, 152.77, 149.65, 146.88, 145.09, 144.77, 143.89, 142.65, 140.99, 140.55, 139.54, 138.09, 136.88, 131.76, 130.54, 128.44, 126.54, 124.65, 123.12, 118.35, 117.90, 114.81, 112.09, 110.00, 99.32 Analysis calcd. for $C_{28}H_{18}N_4O_3$ (458.47): C; 73.35; H, 3.96; N, 12.22 %. Found. C, 73.54; H, 3.66; N, 12.43 %.

3-((3-Cyano-6-(2-hydroxyphenyl)-2-thioxo-1,2-dihydropyridin-5-yl)methylene)-4-phenyl-1H-[1,5]benzodiazepin-2(3H)-one (11). Yield (0.74 g, 78 %), mp 280–282 °C. IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3436 (O–H), 3344, 3280 (N–H), 2156 (C≡N), 1665 (C=O), 1155 (N–C=S). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.90 (s, 1H, H_{olefin}), 7.02–7.79 (m, 13H, H_{arom}), 8.14 (s, 1H, γ-$H_{pyridine}$), 8.55 (s, 1H, N–$H_{pyrdinethione}$, disappeared on addition of D_2O), 10.60 (bs, 1H, N–$H_{diazepinone}$, disappeared on addition of D_2O), 13.18 (b, 1H, O–H, disappeared on addition of D_2O). Analysis calcd. for $C_{28}H_{18}N_4O_2S$ (474.53): C, 70.87; H, 3.82; N, 11.81 %. Found, C, 70.50; H, 3.60; N, 11.70 %.

General Procedure for Preparation of benzodiazepinyldithiin 12 and benzodiazepinylthiazine 13
A mixture of anhydrous potassium carbonate (3 g, 20 mmol), TBAB (0.32 g, 1 mmol), carbon disulfide (0.25 mL, 3 mmol), or phenyl isothiocyanate (0.4 mL, 3 mmol) and malononitrile (0.2 g, 3 mmol), in dry dioxane (30 mL), was stirred, with gradual warming at 30–60 °C, for 4 hr. Afterwards, compound **3** (1.18 g, 3 mmol) was added to the previous reaction mixture and stirred, at 80 °C, till the completion of the reaction (TLC) for *ca.* 3 hr. The reaction mixture was filtered off. The filtrate was evaporated *in vacuum* and the solid residue was washed with water and crystallized from ethanol to give compounds **12** or **13**, respectively. The filtered potassium carbonate was washed with dioxane (25 mL), collected, and dissolved in cold water (50 mL). On acidification of the carbonate solution using hydrochloric acid (15 mL, 2N), pyranobenzodiazepine **5** was precipitated as pale yellow deposits. The product was collected by filtration and crystallized from ethanol.

2-(5-(2-Hydroxybenzoyl)-4-(2-oxo-4-phenyl-2,5-dihydro-1H-[1,5]benzodiazepin-3-yl)-4H-1,3-dithiin-2-ylidene)malononitrile (12). Yield (0.48 g, 30 %), mp 200–202 °C. IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3447 (O–H), 3275, 3174 (N–H), 2204 (C≡N), 1660 (C=O), 1635 (C=O), 1608, 1595, 1540. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.80 (s, 1H, 4-$H_{dithiin}$), 6.80 (s, 1H, 6-$H_{dithiin}$), 6.94–8.14 (m, 13H, H_{arom}), 8.92 (s, 1H, N5–$H_{diazepinone}$, disappeared on addition of D_2O), 10.60 (bs, 1H, N1–$H_{diazepinone}$, disappeared on addition of D_2O), 13.14 (b, 1H, O–H, disappeared on addition of D_2O). Analysis calcd. for $C_{29}H_{18}N_4O_3S_2$ (534.61): C, 65.15; H, 3.39; N, 10.48 %. Found. C; 64.90; H, 3.10; N, 10.20 %.

2-(5-(2-Hydroxybenzoyl)-4-(2-oxo-4-phenyl-2,5-dihydro-1H-[1,5]benzodiazepin-3-yl)-3-phenyl-3,4-dihydro-2H-1,3-thiazin-2-ylidene)malononitrile (13). Yield (0.68 g, 38 %), mp 213–215 °C. IR (KBr), $\tilde{\nu}$ (cm^{-1}): 3400 (O–H), 2205 (C≡N), 1669 (C=O), 1645 (C=O), 1608, 1580. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.70 (s, 1H, 4-$H_{dithiazin}$), 7.00 (s, 1H, 6-$H_{dithiazin}$), 7.14–7.90 (m, 18H, H_{arom}), 8.92 (s, 1H, N5–$H_{diazepinone}$, disappeared on addition of D_2O), 10.56 (bs, 1H, N1–$H_{diazepinone}$, disappeared on addition of D_2O), 13.90 (b, 1H, O–H, disappeared on addition of D_2O). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 58.50, 60.55, 103.71, 105.90, 109.77, 111.88, 113.55, 114.77, 115.99, 117.54, 119.37, 120.43, 122.90, 123.64, 125.88, 127.78, 130.00, 131.70, 133.73, 135.55, 137.66, 139.12, 140.00, 143.99, 145.56, 147.08, 148.86, 150.06, 155.66, 161.13, 166.00, 180.23, 183.54, 188.22, 190.22. Analysis calcd. for $C_{35}H_{23}N_5O_3S$ (593.65): C, 70.81; H, 3.91; N, 11.80 %. Found. C, 70.60; H, 3.60; N, 11.50 %.

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