Reactivity Studies on 4-Aminopyrones: Access to Benzimidazole and Benzimidazolone Derivatives

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Reaction of pyrone **1a** or tetronic acid **1b** with *o*-phenylenediamine derivatives gave enaminone compounds **2**. When reacting with different electrophiles, these intermediates allowed versatile access to different heterocyclic structures: when DMA derivatives or triphosgene was used, cyclization occurred through nitrogen, leading to benzimidazoles **3** and benzimidazolones **4**, respectively, while reaction with benzaldehyde yielded benzodiazepines **5**.

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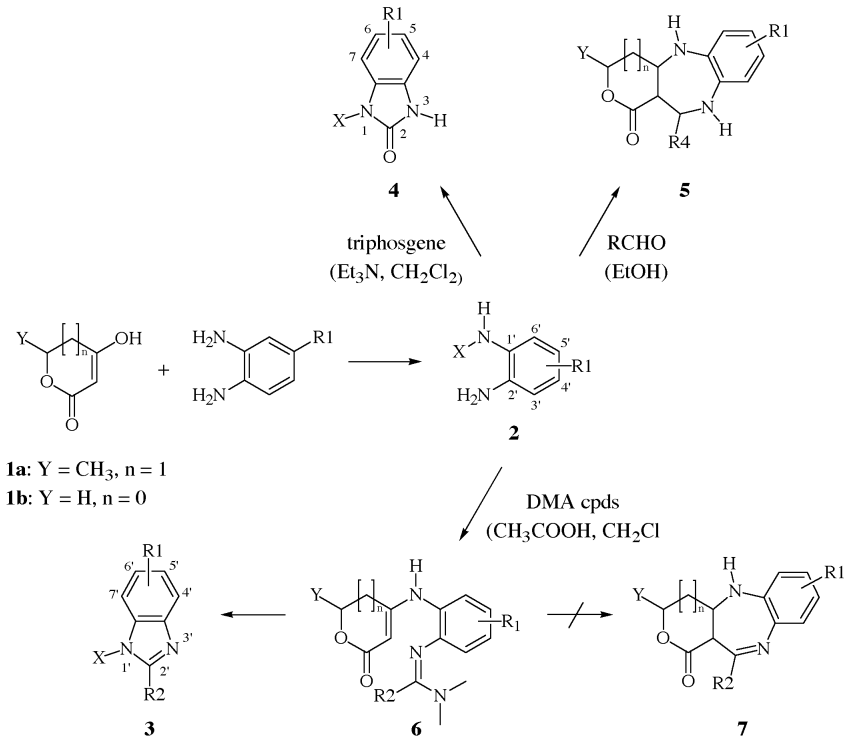
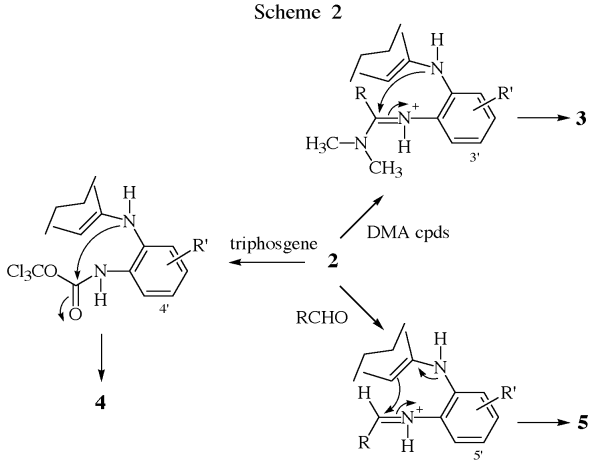
Introduction.

Benzimidazoles have been shown to exhibit a large number of biological activities. Some of them like thiabendazole, mebendazole or albendazole are widely used as antihelmintic drugs [1], due to their ability to bind selectively with high affinity to the β-subunit of helminth microtubule protein [2]. Benzimidazolone derivatives also cover a broad range of biological activities, including opioid receptor antagonistic [3] or antinociceptive [4] effects, and potassium channel activation [5]. In previous studies, 5,6-dihydro-4-hydroxy-6-methyl-2-pyrone or dehydroacetic acid were used as starting materials to prepare a variety of pyrano-benzodiazepine derivatives [6,7]. Here the study is extended to the synthesis of a series of benzimidazoles (**3**) and benzimidazolones (**4**) using as starting compounds pyrone **1a** or tetronic acid (**1b**). Since pyrones and tetronic acid derivatives, such as ascorbic acid or penicillic acid, are widespread in nature and possess a

Scheme 1



Scheme 2



Intramolecular cyclization reactions of intermediate compounds to gain access to benzimidazole, benzimidazolone and diazepine derivatives.

large number of interesting biological activities [8,-11], it was hypothesized that it might be advantageous to combine the two structural moieties in the hope of arriving at biologically relevant compounds.

Results and Discussion.

Our general synthetic approach to the title benzimidazoles (**3**) and benzimidazolones (**4**) is depicted in Scheme 1. Reaction of commercially available 5,6-dihydro-4-hydroxy-6-methyl-2-pyrone (**1a**) or tetronic acid (**1b**) with *o*-phenylenediamine derivatives in ethanol gave enaminone compounds **2** (Table I). Starting from these intermediates, we considered possible routes to gain access to new benzimidazoles **3** and benzimidazolones **4**, and also to new benzodiazepines **5** fused to dihydropyrone or tetronic acid moieties. For this purpose, the following electrophiles were investigated: *i)* bis(trichloromethyl)-carbonate (triphosgene), *ii)* with 1,1-dimethoxy-*N*,*N*-dimethylalkylamine derivatives (*N*,*N*-dialkylacetamide dimethylacetal or DMA compounds), and *iii)* aldehydes. Putative intermediates are depicted in Scheme 2.

Table I

Enaminone Compounds **2**

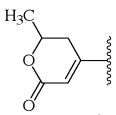
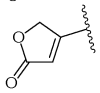
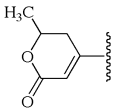
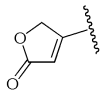
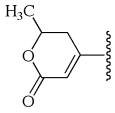
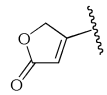
Compound	X	R_1
2a		H
2b		4'-CH_3
2c		5'-Cl
2d		5'-NO_2
2e		H
2f		4'-CH_3
2g		5'-Cl
2h		5'-NO_2

Table II

Benzimidazole (**3**) and Benzimidazolone (**4**) Compounds

Compound	X	R_1	R_2
3a		H	H
3b		5'-CH_3	H
3c		6'-Cl	H
3d		H	CH_3
3e		5'-CH_3	CH_3
3f		6'-Cl	CH_3
3g		5'-CH_3	H
3h		6'-Cl	H
3i		H	CH_3
4a		H	-
4b		5-CH_3	-
4c		6-Cl	-
4d		6-NO_2	-
4e		5-CH_3	-
4f		6-NO_2	-

First, reaction with triphosgene allows access to benzimidazolones **4** (Table II) bearing as X group either a pyrone or a tetronic acid moiety (Scheme 1). As shown in Scheme 2, this reaction results from the harder nucleophile nitrogen attack on the hard electrophilic center, the carbonyl group in the intermediate **4'**. Conversely, the reaction of compounds **2** with an aldehyde leads first to iminium salt **5'** (Scheme 2), since the reaction is carried out in acidic conditions. Cyclization in the latter occurs in that case through the soft nucleophile, the double bond

Table III

Benzodiazepine Compounds (**5**)

Compound	Y (n)	R_1	R_4
5a	CH_3	H	CH_3
5b	(n = 1)	H	C_6H_5
5c	H	H	C_6H_5
5d	(n = 0)	H	3-methylphenyl

reacting with the polarizable soft electrophilic carbon, thus leading to benzodiazepines **5** (Table III). Intramolecular cyclization reaction of **2** to benzodiazepines **5** bears similarities to previous studies in our group [6]. When reacting with DMA derivatives, diamino-compounds **2** also first lead to iminium intermediate **3'**, which ultimately cyclized to benzimidazoles **3** (Table II). It should be noted that in neutral conditions, unstable intermediate **6** (R_1 = CH_3 and R_2 = H, n=1) was isolated and characterized. This slowly evolved in solution for several days to finally give **3b**. For these intermediates **3'**, as for

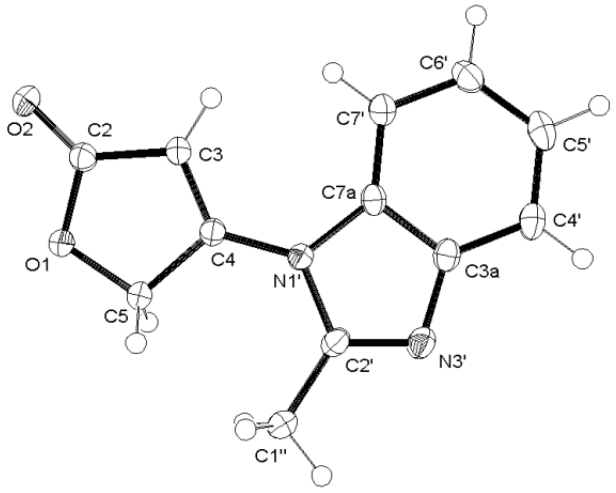


Figure 1. X-Ray crystallography of 4-(2-methyl-1*H*-benzo[*d*]imidazol-1-yl)-2,5-dihydro-2-furanone (**3i**).

iminium **5'**, a cyclization through the double bond would be expected; actually the reaction leads exclusively to benzimidazoles **3**, corresponding therefore to a nitrogen reaction. Differences between carbon electrophile centers in intermediates **3'** and **5'** may come from the strong electron donating properties of the dimethylamino group, reducing the electrophilic character at carbon and also the steric hindrance due to this group. To prove a possible selectivity relying on a solvent effect, the reactions with DMA derivatives were carried out in ethanol and dichloromethane. However, a similar cyclization was observed in both cases without detectable formation of benzodiazepine compounds **7**, showing that a solvation through hydrogen bonds of the nitrogen atom did not promote a reaction of the double bond. All benzimidazole (**3**) and benzimidazolone (**4**) compounds were fully characterized by NMR, elemental analysis and mass spectrometry, and X-ray crystallography for compound **3i** (Figure 1).

Conclusion.

In summary, it was demonstrated that a new series of heterocycles related to benzimidazoles and benzimidazolones can be efficiently prepared from tetronic acid or pyrone **1a**. Interestingly, the same intermediates **2**, resulting from a one step reaction between a pyrone or tetronic acid and *o*-phenylenediamine derivatives, allow access to three different structures depending on the electrophile used in the second step. All steps involved in their synthesis are highly efficient in giving the desired compounds in high yields and in mild conditions, thus rendering this approach adaptable to a high-throughput combinatorial synthesis of a variety of heterocycle compounds.

EXPERIMENTAL

General.

Melting points were determined on a Kofler melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Brucker AC 200 at 200 MHz (^{1}H) or AC 250 at 250 MHz (^{1}H) or 60 MHz (^{13}C). IR Spectra on a Perkin-Elmer 1600 FTIR spectrophotometer. Silica gel 60 (70 -230 mesh, Merck) was used for column chromatography and silica plates (60F254, Merck) were used for thin layer chromatography. All chemicals were obtained from Aldrich, and used without further purification. Elemental analyses were performed by the Ecole Nationale Supérieure de Chimie de Toulouse, France.

General Procedure for the Synthesis of Enaminone Compounds **2**.

To an ethanolic solution (20 ml) of **1a** or **1b** (0.01 mol) was added 4-substituted-1,2-phenylenediamine compounds (0.01 mole), and the mixture was heated to reflux under magnetic stirring for 30 minutes (3 hours for 4-nitro-1,2-phenylenediamine). After cooling, the precipitate was collected by filtration. Recrystallization from ethanol gave compounds **2a-h**, which were characterized by ^{1}H, ^{13}C NMR and IR spectroscopies.

4-(2-Aminoanilino)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**2a**).

Compound **2a** was obtained in 75% yield, mp 202-204 °C; ir: 1655 (C=O), 3320 (NH), 3360-3440 (NH_2) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.33 (d, J = 6 Hz, 3H, CH_3), 2.49-2.54 (m, 2H, CH_2), 4.31 (s, 1H, C_3-H), 4.38-4.49 (m, 1H, C_6-H), 4.91 (s, 2H, NH_2), 6.53-7.04 (m, 4H, Ar), 8.17 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.4 ($C_{(6)}H_3$), 33.5 (C_5), 70.9 (C_6), 82.0 (C_3), 115.3, 115.9 (Ar-C), 122.1 (C-NH_2), 127.1-127.4 (Ar-C), 143.8 (Ar-C-N), 159.0 (C_4), 167.6 (C_2).

4-(2-Amino-4-methylanilino)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**2b**).

Compound **2b** was obtained in 70% yield, mp 135-137 °C; ir: 1660 (C=O), 3300 (NH), 3340-3400 (NH_2) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.32 (d, J = 6 Hz, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.47-2.52 (m, 2H, CH_2), 4.26 (s, 1H, C_3-H), 4.40-4.44 (m, 1H, C_6-H), 4.89 (s, 2H, NH_2), 6.37-6.82 (m, 3H, Ar), 8.21 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.4 ($C_{(6)}H_3$), 20.8 (Ar-CH_3), 33.56 (C_5), 70.9 (C_6), 81.9 (C_3), 115.5, 116.8 (Ar-C), 119.7 (C-NH_2), 127.1, 136.5 (Ar-C), 143.5 (Ar-C-N), 159.3 (C_4), 167.3 (C_2).

4-(2-Amino-5-chloroanilino)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**2c**).

Compound **2c** was obtained in 66% yield, mp 158-160 °C; ir: 1670 (C=O), 3320 (NH), 3320-3390 (NH_2) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.32 (d, J = 6Hz, 3H, CH_3), 2.41-2.53 (m, 2H, CH_2), 4.26 (s, 1H, C_3-H), 4.38-4.47 (m, 1H, C_6-H), 5.28 (s, 2H, NH_2), 6.53-7.05 (m, 3H, Ar), 8.30 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.4 ($C_{(6)}H_3$), 33.5 (C_5), 70.9 (C_6), 82.4 (C_3), 114.2, 115.2 (Ar-C), 121.0 (C-NH_2), 127.0, 136.5 (Ar-C), 145.4 (Ar-C-N), 158.9 (C_4), 167.2 (C_2).

4-(2-Amino-5-nitroanilino)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**2d**).

Compound **2d** was obtained in 60% yield, mp 198-200 °C; ir: 1660 (C=O), 3340 (NH), 3340-3380 (NH_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.25 (d, J = 6 Hz, 3H, CH_3), 2.44-2.60 (m, 2H, CH_2), 4.26 (s, 1H, C_3-H), 4.43-4.52 (m, 1H, C_6-H), 6.60 (s, 2H, NH_2), 6.80-7.97 (m, 3H, Ar), 8.44 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.8 ($C_{(6)}H_3$), 34.0 (C_5), 71.6 (C_6), 83.8 (C_3), 121.4 (C-NH_2), 124.5, 124.6, 125.0 (Ar-C), 135.9 (Ar-C), 151.5 (Ar-C-N), 159.3 (C_4), 167.5 (C_2).

4-(2-Aminoanilino)-2,5-dihydro-2-furanone (**2e**).

Compound **2e** was obtained in 70% yield, mp 217-219 °C; ir: 1670 (C=O), 3330 (NH), 3350-3380 (NH_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.26 (s, 1H, C_3-H), 4.81 (s, 2H, CH_2), 5.02 (s, 2H, NH_2), 6.53-7.07 (m, 4H, Ar), 8.70 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 67.3 (C_5), 81.0 (C_3), 115.5, 116.2, 124.0, 126.4 (Ar-C), 142.2 (Ar-C-N), 166.6 (C_4), 174.8 (C_2).

4-(2-Amino-4-methylanilino)-2,5-dihydro-2-furanone (**2f**).

Compound **2f** was obtained in 75% yield, mp 225-227 °C; ir: 1670 (C=O), 3320 (NH), 3340-3360 (NH_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.18 (s, 3H, CH_3), 4.51 (s, 1H, C_3-H), 4.79 (s, 2H, CH_2), 4.93 (s, 2H, NH_2), 6.37-6.93 (m, 3H, Ar), 8.60 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.7 ($C_{(4)}H_3$), 67.3 (C_5), 80.7 (C_3), 115.9, 117.0 (Ar-C), 121.6 (Ar-NH_2), 124.2 (Ar-C), 135.7 (Ar-C_4), 142.1 (Ar-C-N), 166.9 (C_4), 174.8 (C_2).

4-(2-Amino-5-chloroanilino)-2,5-dihydro-2-furanone (**2g**).

Compound **2g** was obtained in 65% yield, mp 233-235 °C; ir: 1680 (C=O), 3310 (NH), 3320-3360 (NH_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.58 (s, 1H, C_3-H), 4.81 (s, 2H, CH_2), 5.26 (s, 2H, NH_2), 6.54-7.06 (m, 3H, Ar), 8.69 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 67.4 (C_5), 81.6 (C_3), 114.4, 115.5 (Ar-C), 121.6 (C-NH_2), 125.6 (Ar-C), 130.4 (Ar-C_4), 143.9 (Ar-C-N), 166.3 (C_4), 174.7 (C_2).

4-(2-Amino-5-nitroanilino)-2,5-dihydro-2-furanone (**2h**).

Compound **2h** was obtained in 60% yield, mp 250-252 °C; ir: 1680 (C=O), 3330 (NH), 3330-3350 (NH_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.64 (s, 1H, C_3-H), 4.88 (s, 2H, CH_2), 6.62 (s, 2H, NH_2), 6.76-7.95 (m, 3H, Ar), 8.96 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 67.4 (C_5), 82.4 (C_3), 113.8, 121.2, 122.5, 123.7 (Ar-C), 135.6 (Ar-C_2), 149.7 (Ar-C-N), 166.5 (C_4), 174.5 (C-NH_2).

General Procedure for the Synthesis of Benzimidazoles **3**.

A solution of **2** (2 mmoles) and *N*,*N*-dimethylformamide dimethyl acetal or *N*,*N*-dimethylacetamide dimethyl acetal (2 mmoles) in dry dichloromethane (60 ml) and glacial acetic acid (100 µl) was heated to reflux under magnetic stirring for six hours. Evaporation of dichloromethane *in vacuo* and recrystallization from ethanol gave compounds **3a-3i**.

4-(1*H*-Benzo[*d*]imidazol-1-yl)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**3a**).

Compound **3a** was obtained in 80% yield, mp 172-174 °C; ir: CO 1640 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.49 (d, J = 6 Hz, 3H, CH_3), 2.86-3.02 (m, 2H, CH_2), 4.62-4.80 (m, 1H, C_6-H), 6.24 (s, 1H, C_3-H), 7.18-7.76 (m, 4H, Ar), 8.05 (s, 1H, C_2-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.1 (CH_3), 32.4 (C_5), 72.7 (C_6), 103.9 (C_3), 113.3, 120.3, 123.7, 124.4 (Ar-C), 131.4 (C_{3a}), 144.4 (C_{7a}), 150.1 (C_4), 164.8 (C_2). ms: (70 eV, electron impact) m/z 228 (molecular ion).

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.44; H, 5.42; N, 12.28.

4-(5-Methyl-1*H*-benzo[*d*]imidazol-1-yl)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**3b**).

Compound **3b** was obtained in 65% yield, mp 201-204 °C; ir: CO 1645 cm^{-1}; ^1H nmr): δ 1.52 (d, J = 6 Hz, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.95-2.98 (m, 2H, CH_2), 4.75-4.79 (m, 1H, C_6-H), 6.24 (s, 1H, C_3-H), 7.17-7.58 (m, 3H, Ar); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.1 ($C_{(6)}H_3$), 20.8 ($C_{(5)}H_3$), 32.3 (C_5), 72.7 (C_6), 103.4 (C_3), 112.9, 120.2, 125.4 (Ar-C), 129.4 (C $_{3a}$), 133.2 (C_5), 142.5 (C_2), 144.8 (C_{7a}), 150.1 (C_4), 164.9 (C_2). ms: (70 eV, electron impact) m/z 242 (molecular ion).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56; O, 13.21. Found: C, 69.43; H, 5.83; N, 11.37.

4-(6-Chloro-1*H*-benzo[*d*]imidazol-1-yl)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**3c**).

Compound **3c** was obtained in 70% yield, mp 209-210 °C; ir: CO 1668 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.44 (d, J = 6 Hz, 3H, CH_3), 2.40-2.50 (m, 2H, CH_2), 4.72-4.81 (m, 1H, C_6-H), 6.36 (s, 1H, C_3-H), 7.39-8.08 (m, 3H, Ar), 8.80 (s, 1H, C_2-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.0 ($C_{(6)}$H3), 32.4 (C_5), 72.8 (C_6), 104.7 (C_3), 114.6, 119.8, 124.4 (Ar-C), 128.0 (C_{3a}), 130.2 (C_6), 145.3 (C_{7a}), 149.7 (C_4), 164.7 (C_2). ms: (70 eV, electron impact) m/z 262 (molecular ion).

Anal. Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.19; Cl, 13.50; N, 10.66. Found: C, 59.16; H, 4.19; Cl, 13.54; N,10.65.

4-(2-Methyl-1*H*-benzo[d]imidazol-1-yl)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**3d**).

Compound **3d** was obtained in 60% yield, mp 172-174 °C; ir: CO 1640 cm^{-1} ; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.5 (d, J = 6 Hz, 3H, CH_3), 2.6 (s, 3H, CH_3), 2.6-2.9 (m, 2H, CH_2), 4.7-4.8 (m, 1H, C_6-H), 6.0 (s, 1H, C_3-H), 7.2-7.3 (m, 4H, Ar), 7.7 (s, 1H, C_2-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 15.9 ($C_{(2)}H_3$), 20.9 ($C_{(6)}H_3$), 35.1 (C_5), 74.2 (C_6), 101.1 (C_3), 110.9, 115.5, 120.1, 123.9 (Ar-C), 134.2 (C_{3a}), 143.3 (C_{7a}), 150.48 (C_4), 164.55 (C_2). ms: (70 eV, electron impact) m/z 242 (molecular ion).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56; O, 13.21. Found: C, 69.43; H, 5.83; N, 11.37.

4-(2,5-Dimethyl- 1*H*-benzo[*d*]imidazol-1-yl)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**3e**).

Compound **3e** was obtained in 62% yield, mp 178-180 °C; ir: CO 1650 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.56 (d, J = 6 Hz, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.81-2.85 (m, 2H, CH_2), 4.89-4.96 (m, 1H, C_6-H), 6.10 (s, 1H, C_3-H), 7.11-7.22 (m, 3H, Ar), 7.47 (s, 1H, C_2-H); ms: (70 eV, electron impact) m/z 256 (molecular ion).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.30; H, 6.24; N, 10.92.

4-(2-Methyl-6-chloro-1*H*-benzo[*d*]imidazol-1-yl)-6-methyl-5,6-dihydro-2*H*-2-pyranone (**3f**).

Compound **3f** was obtained in 65% yield, mp 215-217 °C; ir: CO 1680cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.58 (d, J = 6 Hz, 3H, CH_3), 2.64 (s, 3H, CH_3), 2.79-2.90 (m, 2H, CH_2), 4.68-4.82 (m, 1H, C_6-H), 6.15 (s, 1H, C_3-H), 7.24 (s, 4H, Ar), 7.67 (s, 1H, C_2-H); ms: (70 eV, electron impact) m/z 276 (molecular ion).

Anal. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; Cl, 12.81; N, 10.12. Found: C, 60.73; H, 4.69; Cl, 12.82; N, 10.11.

4-(5-Methyl-1*H*-benzo[*d*]imidazol-1-yl)-2,5-dihydro-2-furanone (**3g**).

Compound **3g** was obtained in 65% yield, mp 248-250 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.43 (s, 3H, CH_3), 5.55 (s, 2H, CH_2), 6.59 (s, 1H, C_3-H), 7.22-7.84 (m, 3H, Ar), 8.59 (s, 1H, C_2-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.8 ($C_{(5)}H_3$), 68.3 (C_5), 97.5 (C_3), 112.6, 119.9, 125.8 (Ar-C), 129.2 (C_{3a}), 133.8 (Ar-C_5), 144.2 (C_{7a}), 156.8 (C_4), 172.6 (C_2). ms: (70 eV, electron impact) m/z 214 (molecular ion).

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.42; H, 5.07; N, 12.84.

4-(6-Chloro-1*H*-benzo[*d*]imidazol-1-yl)-2,5-dihydro-2-furanone (**3h**).

Compound **3h** was obtained in 60% yield, mp 224-226 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.56 (s, 2H, CH_2), 6.67 (s, 1H, C_3-H), 7.42-8.02 (m, 3H, Ar), 8.71 (s, 1H, C_2-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 68.4 (C_5), 98.8 (C_3), 114.3, 119.9, 124.9 (Ar-C), 128.7 (C_{3a}), 130.1 (Ar-C_6), 143.7 (C_2), 144.9 (C_{7a}), 156.6 (C_4), 172.4 (C_2=O). ms: (70 eV, electron impact) m/z 234 (molecular ion).

Anal. Calcd for $C_{11}H_7ClN_2O_2$: C, 56.00; H, 3.01; N, 11.94. Found : C,56.09; H, 2.93; N, 11.93.

4-(2-Methyl-1*H*-benzo[*d*]imidazol-1-yl)-2,5-dihydro-2-furanone (**3i**).

Compound **3i** was obtained in 65% yield, mp 172-174 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.72 (s, 3H, CH_3), 5.61 (s, 2H, CH_2), 6.53 (s, 1H, C_3-H), 7.30-7.81 (m, 4H, Ar); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 16.5 ($C_{(2)}H_3$), 69.5 (C_5), 103.6 (C_3), 112.5, 119.1, 123.7, 123.8 (Ar-C), 133.5 (C_{3a}), 142.6 (C_{7a}), 152.0 (C_2), 156.2 (C_4), 172.3 (C_2=O). ms: (70 eV, electron impact) m/z 241 (molecular ion).

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found : C, 67.29; H, 4.61; N, 12.94.

All Compounds **4** were Obtained following a Similar Procedure used for Compound **4a**.

1-(2-Methyl-6-oxo-3,6-dihydro-2*H*-4-pyranyl)-2,3dihydro-1*H*-benzo[*d*]imidazol-2-one (**4a**).

To a magnetically stirred and cooled (0 °C) solution of **2a** (2.18 g, 0.01 mole) and triethylamine (2.8 ml, 0.02 mole) in dichloromethane (20 ml) was added drop by drop bis(trichloromethyl)carbonate (triphosgene) (1 g, 3.33 mmole). After being gradually warmed to room temperature, the mixture was stirred for two hours. The solvent was evaporated to dryness, and the residue was treated with water and extracted with dichloromethane. The organic layer was dried over sodium sulphate and evaporated to dryness to give a yellow solid which was recrystallized from ethanol to give 1.58 g (yield: 65 %) of **4a** as yellow needles. mp 123-125 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.41 (d, J = 6 Hz, 3H, CH_3), 2.95-3.04 (m, 2H, CH_2), 4.65-4.74 (m, 1H, C_6-H), 6.23 (s, 1H, C_3-H), 7.02-7.50 (s, 4H , Ar), 11.34 (broad s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.1 ($C_{(2)}H_3$), 32.3 (C_3), 73.2 (C_2), 107.1 (C_5), 109.5, 111.2, 121.2, 123.1 (Ar-C), 127.3 (C_{7a}), 128.9 (C_{3a}), 150.5 (C_4), 152.1 (C_2), 164.9 (C_6). ms: (70 eV, electron impact) m/z 244 (molecular ion).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found : C, 63.89; H, 5.01; N,11.42.

5-Methyl-1-(2-methyl-6-oxo-3,6-dihydro-2*H*-4-pyranyl)-2,3dihydro-1*H*-benzo[*d*]imidazo-2-one (**4b**).

Compound **4b** was obtained in 60% yield, mp 142-144 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.41 (d, J = 6 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.87-2.93 (m, 2H, CH_2), 4.63-4.74 (m, 1H, C_6-H), 6.20 (s, 1H, C_3-H), 6.88-7.26 (s, 3H, Ar), 11.25 (broad s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.2 ($C_{(2)}H_3$), 20.8 ($C_{(5)}H_3$), 32.3 (C_3), 73.1 (C_2), 106.1 (C_5), 109.9, 111.2, 121.7 (Ar-C), 125.1 (C_5), 129.0 (C_{7a}), 132.5 (C_{3a}), 150.7 (C_4), 152.3 (C_2), 165.0 (C_6). ms: (70 eV, electron impact) m/z 258 (molecular ion).

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found : C, 65.09; H, 5.39; N, 10.97.

6-Chloro-1-(2-methyl-6-oxo-3,6-dihydro-2*H*-4-pyranyl)-2,3dihydro-1*H*-benzo[*d*]imidazo-2-one (**4c**).

Compound **4c** was obtained in 66% yield, mp 188-190 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.41 (d, J = 6 Hz, 3H, CH_3), 2.66-3.06 (m, 2H, CH_2), 4.63-4.88 (m, 1H, C_6-H), 6.21 (s, 1H, C_3-H), 7.08-7.39 (s, 3H, Ar), 11.57 (broad s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.1 ($C_{(2)}H_3$), 32.2 (C_3), 73.2 (C_2), 107.6 (C_5), 109.3, 112.5, 120.8 (Ar-C), 126.3 (C_{7a}), 127.1 (C_{3a}), 130.2 (C_6), 150.1 (C_4), 152.0 (C_2), 164.7 (C_6). ms: (70 eV, electron impact) m/z 278 (molecular ion).

Anal. Calcd for $C_{13}H_{11}ClN_2O_3 \cdot H_2O$: C, 52.62; H, 4.42; N, 9.44. Found : C, 52.60; H, 4.05; N, 9.42.

6-Nitro-1-(2-methyl-6-oxo-3,6-dihydro-2*H*-4-pyranyl)-2,3-dihydro-1*H*-benzo[*d*]imidazo-2-one (**4d**).

Compound **4d** was obtained in 55% yield, mp 190-192 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.43(d, J = 6 Hz, 3H, CH_3), 2.77-3.04 (m, 2H, CH_2), 4.72-4.78 (m, 1H, C_6-H), 6.31 (s, 1H, C_3-H), 7.22-8.10 (s, 3H, Ar), 11.57 (broad s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.1 ($C_{(2)}H_3$), 32.0 (C_3), 73.3 (C_2), 106.4 (C_5), 109.2, 109.6, 119.7 (Ar-C), 127.5 (C_{7a}), 134.9 (C_{3a}), 141.6 (C_6), 149.6 (C_4), 152.4 (C_2), 164.6 (C_6). ms: (70 eV, electron impact) m/z 289 (molecular ion).

Anal. Calcd for $C_{13}H_{11}N_3O_5$.HCl: C, 47.94; H, 3.71; N, 12.90. Found: C, 47.56; H, 3.73; N, 12.69.

1-(5-Oxo-2,5-dihydro-3-furanyl)-5-methyl-2,3dihydro-1*H*-benzo[*d*]imidazol-2-one (**4e**).

Compound **4e** was obtained in 68% yield, mp 218-220 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.34 (s, 3H, CH_3), 5.48 (s, 2H, CH_2), 6.29 (s, 1H, C_4-H), 6.91-7.49 (m, 3H, Ar), 11.41 (broad s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.8

($C_{(5)}H_3$), 69.4 (C_2), 95.8 (C_4), 110.1, 111.9, 122.2 (Ar-C), 124.5 (C_{7a}), 129.7 (C_{3a}), 133.8 (Ar-C_5), 152.0 (C_2=O), 157.2 (C_3), 172.9 (C_5=O). ms: (70 eV, electron impact) m/z 230 (molecular ion).

Anal. Calcd for $C_{12}H_{10}N_2O_3.H_2O$: C, 58.06; H, 4.87; N, 11.29. Found : C, 57.87; H, 4.77; N, 11.01.

1-(5-Oxo-2,5-dihydro-3-furanyl)-6-nitro-2,3dihydro-1*H*-benzo[*d*]imidazol-2-one (**4f**).

Compound **4f** was obtained in 55% yield, mp > 330 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.54 (s, 2H, CH_2), 6.53 (s, 1H, C_4-H), 7.25-8.23 (m, 3H, Ar), 12.20 (broad s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 69.2 (C_2), 96.4 (C_4), 107.2, 109.6, 120.9 (Ar-C), 126.7 (C_{7a}), 135.6 (C_{3a}), 142.0 (C_6), 152.2 (C_2), 156.5 (C_3), 172.4 (C_5). ms: (70 eV, electron impact) m/z 261 (molecular ion).

Anal. Calcd for $C_{11}H_7N_3O_5$.HCl: C, 47.94; H, 3.71; N, 12.90. Found : C, 47.56; H, 3.73; N, 12.57.

General Procedure for the Synthesis of Diazepine Compounds **5**.

To a solution of enaminone **2** (0.01 mol) in ethanol (20 ml) was added 0.01 mol. of aldehyde (acetaldehyde for **5a**, benzaldehyde for **5b** and **5c** or *m*-tolualdehyde for **5d**), and the mixture was allowed to react under magnetic stirring at room temperature for 6 hours. The white precipitate was then collected by filtration, and recrystallization from methanol gave compounds **5a-d**.

3,11-Dimethyl-1,3,4,5,10,11-hexahydrobenzene[*b*]pyrano-[4,3-*e*][1,4]diazepin-1-one (**5a**).

Compound **5a** was obtained in 80% yield, mp 228-230 °C; ir (KBr): 1640 (C=O), 3250-3350 (NH) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.05 (d, 1H, J = 6 Hz, $C_{(11)}H_3$), 1.35 (d, 1H, J = 6 Hz, $C_{(3)}H_3$), 2.50 (m, 2H, $C_{(4)}H_2$), 4.35 (m, 1H, $C_{(11)}$-H), 4.55 (m, 1H, $C_{(3)}$H), 5.6 (d, 1H, J = 8 Hz, $N_{(10)}$H), 6.70-8.23 (m, 4H, Ar), 8.8 (s, 1H, $N_{(5)}$H).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.85; H, 6.56; N, 11.48. Found: C, 68.72; H, 6.59; N, 11.59.

3-Methyl-11-phenyl-1,3,4,5,10,11-hexahydrobenzene[*b*]pyrano-[4,3-*e*][1,4]diazepin-1-one (**5b**).

Compound **5b** was obtained in 85% yield, mp 244-246 °C; ir (KBr): 1680 (C=O), 3340 (NH) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.34 (d, 1H, J = 6 Hz, $C_{(3)}H_3$), 2.62 (m, 2H, $C_{(4)}H_2$), 4.53 (m, 1H, $C_{(11)}$-H), 4.58 (m, 1H, $C_{(3)}$H), 5.6 (d, 1H, J = 6 Hz, $N_{(10)}$H), 6.84-8.06 (m, 9H, Ar), 8.87 (s, 1H, $N_{(5)}$H).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.51; H, 5.88; N, 9.15. Found: C, 74.36; H, 6.00; N, 9.25.

10-Phenyl-3,4,9,10-tetrahydro-1*H*-benzo[*b*]furo[3,4-*e*]-[1,4]diazepin-1-one (**5c**).

Compound **5c** was obtained in 80% yield, mp 295-297 °C; ir (KBr): 1690 (C=O), 3330 (NH) cm^{-1} ; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 4.89 (s, 2H, CH_2), 5.08 (d, 1H, J = 4.8 Hz, CH), 5.98 (d, 1H, J = 4.8 Hz, $N_{(9)}$H), 6.59-7.23 (m, 9H, Ar), 9.75 (s, 1H, $N_{(4)}$H). ms: (70 eV, electron impact) m/z 278 (molecular ion).

10-(3-Methylphenyl)-3,4,9,10-tetrahydro-1*H*-benzo[*b*]furo-[3,4-*e*][1,4]diazepin-1-one (**5d**).

Compound **5d** was obtained in 85% yield, mp 236-238 °C; ir (KBr): 1670 (C=O), 3320 (NH) cm^{-1} ; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.20 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 5.03 (d, 1H, J = 4.8 Hz, CH), 5.96 (d, 1H, J = 4.8 Hz, $N_{(9)}$H), 6.80-7.09 (m, 8H, Ar), 9.75 (s, 1H, $N_{(4)}$H). ms: (70 eV, electron impact) m/z 229 (molecular ion).

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