Synthesis of Furo[2,3-*d*]pyridazin-4(5*H*)-one and Its *N(5)*-Substituted Derivatives

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We report the efficient preparation of furo[2,3-*d*]pyridazin-4(5*H*)-one and its *N*-substituted derivatives starting from methyl 2-methylfuran-3-carboxylate. The Me group was converted to the aldehyde group, which was then condensed with hydrazine derivatives. Then, the ester functionalities were hydrolyzed to the corresponding acids, followed by treatment with $SOCl_2$ to give *N*-substituted furopyridazinone derivatives.

Introduction. – Pyridazinone derivatives are an important class of compounds, and they have attracted the attention of chemists in recent decades due to their diverse pharmacological activities [1]. Pyridazinone derivatives show anti-inflammatory, antimicrobial, antitubercular, and antifungal activities, and some of them are used as anti-inflammatory drugs. Recently, pyridazinones have also been reported as anti-convulsant agents [2]. Phthalazinones, with a pyridazinone ring fused to a benzene ring, are also particularly well-known for their biological activities (for selected recent literature, see [3]). They are considered as potential anticancer agents, and they are used in the treatment of autoimmune and inflammatory diseases [4]. Selected examples of phthalazinone-based drugs, *i.e.*, azelastine (**1**; histamine antagonist), poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor **2**, and acetohydroxyacid synthase (AHAS) inhibitor **3**, are shown in *Fig. 1* [5].

Since a thiophene ring is considered a bioisostere of a benzene ring, the replacement of the benzene moiety in phthalazinones with a thiophene ring results in the

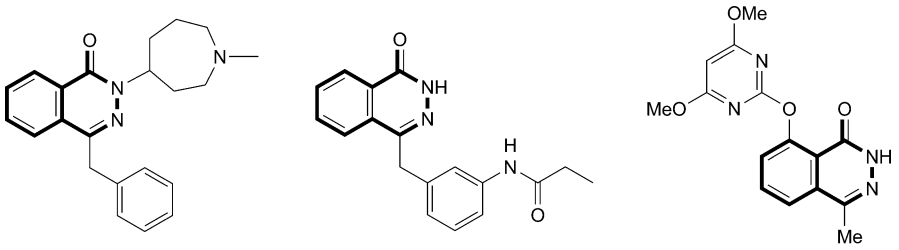


Fig. 1. *Structures of some drugs with a phthalazinone core*

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formation of thienopyridazinones [6]. There are only a few examples with a thienopyridazinone scaffold in the literature [7]. Recently, it has been shown that thienopyridazinone derivatives play an important role in both thromboxane A_2 synthetase inhibition and bronchodilation [8][9].

Derivatives of furo[2,3-*d*]pyridazin-4(5*H*)-one (**4**) are not well-known. *Yamaguchi et al.* synthesized the furo-pyridazinone derivative **5** (*Fig. 2*), which exhibited a weak bronchodilatory activity [8]. A fluorinated derivative **6** was recently synthesized by *Sandford* and co-workers [9]. Therefore, an efficient synthetic methodology for the preparation of furo-pyridazinone derivatives substituted at N(5) would be of interest. Recently, we reported a facile synthesis of aminophthalazinone and aminofuropyridazinone derivatives **7** [10]. Herein, we report a new method for the synthesis of *N(5)*-substituted furopyridazinones.

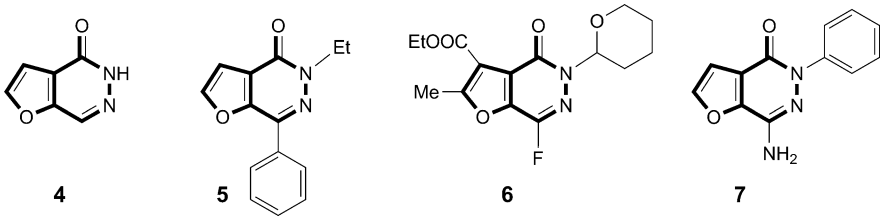


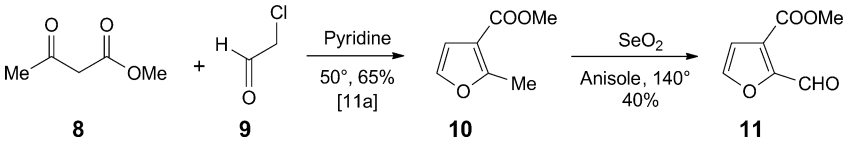
Fig. 2. *Structures of some furopyridazinones*

Results and Discussion. – For the construction of the furo-pyridazinone skeleton, first we synthesized methyl 2-methylfuran-3-carboxylate (**10**) [11] starting from 2-chloroacetaldehyde (**9**) and methyl 3-oxobutanoate (**8**) by applying the procedure for the synthesis of various substituted furan derivatives [12]. Then, the Me group in **10** was oxidized to aldehyde **11** [13] by treatment with SeO_2 at 140° in anisole for 18 h. The desired aldehyde **11** was formed in 40% yield (*Scheme 1*). All efforts to increase the yield failed.

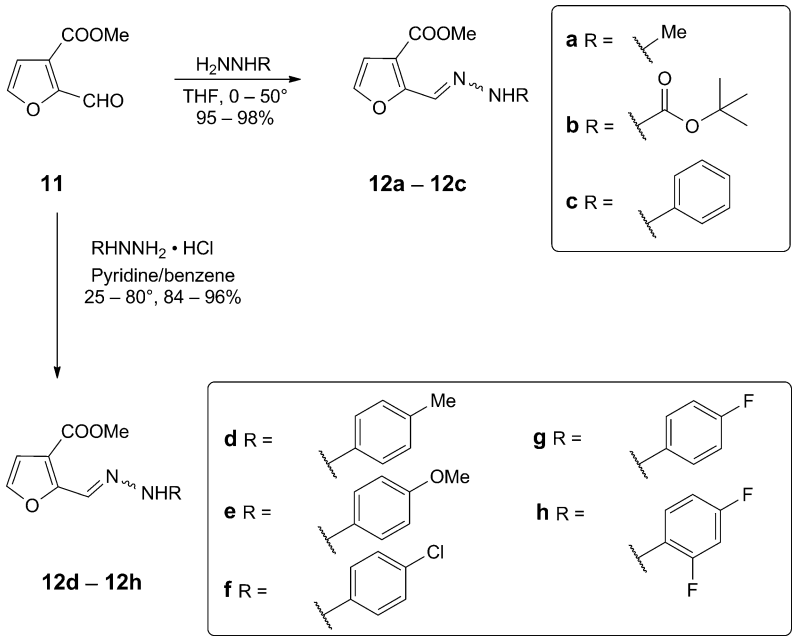
With aldehyde **11** in hand, we turned our attention to the synthesis of **12**, which was achieved by the reaction of substituted hydrazine derivatives with **11** at different temperatures (*Scheme 2*).

The reactions of **11** with $MeNHNH_2$, $PhNHNH_2$ and (*tert*-butoxy)carbonyl hydrazide ($BocNHNH_2$) in THF furnished the hydrazones **12a**–**12c**, respectively. Since most substituted phenylhydrazine derivatives are available as their HCl salt, the condensation with aldehyde **11** did not occur in THF [14]. Therefore, the reaction was carried out in the presence of pyridine in benzene, and the corresponding hydrazones **12d**–**12h** were obtained in high yields (*Scheme 2*). According to the ^{1}H-NMR spectra,

Scheme 1. *Synthesis of Methyl 2-Formylfuran-3-carboxylate* (**11**)



Scheme 2. *Synthesis of Hydrazones* **12** *Derived from* **11**



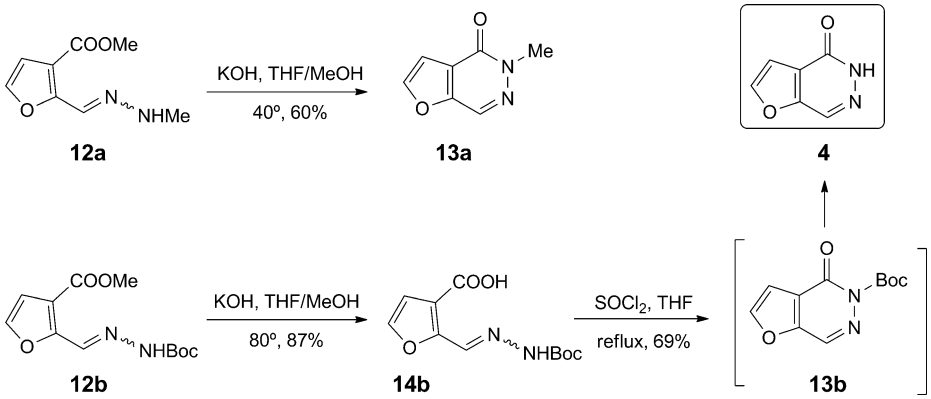
(*E*)- and (*Z*)-isomers were formed in a ratio of 5:1. Fortunately, this was not a problem, since both isomers smoothly underwent cyclization.

After synthesis of various hydrazone derivatives **12a**–**12h**, we focused on the ring-closure reaction. When methylhydrazone **12a** was reacted with 2M KOH in THF/MeOH at 40°, it underwent a smooth cyclization to give the desired furo-pyridazinone **13a** instead of the hydrolysis product, the carboxylic acid (*Scheme 3*). On the other hand, treatment of the hydrazone **12b** with 2M KOH in THF/MeOH resulted in the formation of the carboxylic acid **14b**. We assume that the initially formed anion of the hydrazone moiety can be stabilized by the neighboring C=O group so that the decreased nucleophilicity of the N-atom hinders the intramolecular cyclization, and hydrolysis of the ester functionality takes place. Treatment of **14b** with $SOCl_2$ at reflux temperature of THF furnished the parent cyclization product **4**, which was synthesized previously in a multistep process starting from 2,3-dibromofuran [15]. The protecting group in **13b**, (*tert*-butoxy)carbonyl (Boc), was hydrolyzed during the course of the reaction.

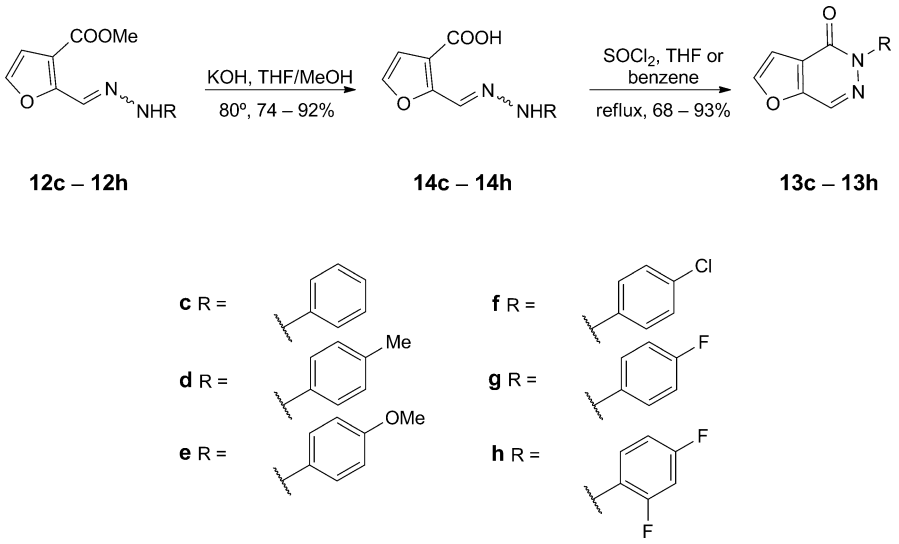
Finally, for the synthesis of *N*-phenyl substituted furo-pyridazinone derivatives **13c**–**13h**, the esters **12c**–**12h** were hydrolyzed to yield the corresponding carboxylic acids **14c**–**14h**, which were then treated with $SOCl_2$ in THF or benzene to give the target furo-pyridazinone derivatives **13c**–**13h** in high yields (*Scheme 4*).

The presented results establish that cyclization of hydrazine derivatives is a valuable method for the synthesis of fused heterocyclic compounds. We developed a synthetic method for the construction of new *N(5)*-substituted furo-pyridazinone derivatives starting from furancarbaldehyde **11**, which can be easily prepared. Ap-

Scheme 3. *Synthesis of Furo[2,3-*d*]pyridazin-4(5*H*)-ones* **4** *and* **13a**



Scheme 4. *Synthesis of Some Furo[2,3-*d*]pyridazin-4(5*H*)-one Derivatives* **13c** – **13h**



plication of this methodology to other heterocycles opens up a new way to prepare new pyridazinone-fused heterocycles.

Conclusions. – We have developed an efficient method for the synthesis of furopyridazinone **6** and its *N(5)*-subistituted derivatives. The Me group of **10** was oxidized to 2-formylfuran by treatment with SeO_2, and then the aldehyde was coupled with hydrazine derivatives. As the intramolecular cyclization of acyl chlorides is a valuable method for the synthesis of heterocyclic compounds, the ester group was converted to the acyl chloride, followed by spontaneous intramolecular cyclization.

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Experimental Part

General. TLC: *Merck*, 0.2-mm silica-gel *60 F_{254}* anal. aluminum plates. Column chromatography (CC): silica gel (SiO_2, 60 mesh; *Merck*). M.p.: *Thomas-Hoover* cap. melting-point apparatus. IR Spectra: *Perkin Elmer 980* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker* instrument, at 400 and 100.6 MHz, resp.; apparent splitting is given in all cases. High-resolution (HR) MS: *Agilent Technologies 6224 TOF* LC/MS instrument. Elemental analyses: *Leco-932* model CHNS analyzer.

Methyl 2-Methylfuran-3-carboxylate (**10**) [11a]. *2-Chloroacetaldehyde* (**9**; 45%, 46.5 ml, 322.9 mmol) was added dropwise to a stirred soln. of *methyl 3-oxobutanoate* (**8**; 30.0 g, 258.4 mmol) in pyridine (100 ml) at r.t., and the resulting mixture was stirred at 50° for 16 h. The reaction was monitored with TLC. After the completion of the reaction, the mixture was extracted with H_2O (200 ml) and AcOEt (3×200 ml). The combined org. extracts were washed with 2M HCl (250 ml), 5% $NaHCO_3$ (250 ml), 10% NaOH (250 ml), and brine (250 ml), dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by CC (SiO_2; hexane/AcOEt 4:1): **10** (23.5 g, 65%). Colorless oil. IR (ATR): 2954, 1819, 1720, 1668, 1438, 1383, 1302, 1120, 1044. ^{1}H-NMR ($CDCl_3$): 7.20 (*d*, $J = 2.0$, =CH); 6.60 (*d*, $J = 2.0$, =CH); 3.79 (*s*, MeO); 2.54 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 164.4; 159.3; 140.3; 113.2; 110.6; 51.2; 13.6. Anal. calc. for $C_7H_8O_3$ (140.14): C 59.99, H 5.75; found: C, 59.76; H, 5.64.

Methyl 2-Formylfuran-3-carboxylate (**11**) [13]. SeO_2 (1.58 g, 14.24 mmol) was added to a stirred soln. of **10** (1.0 g, 7.14 mmol) in anisole (20 ml), and the resulting mixture was heated at reflux temp. for 18 h. After the completion of the reaction, the mixture was filtered and washed with H_2O (50 ml) and AcOEt (3×70 ml). Then, the combined org. extract was dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by CC (SiO_2; hexane/AcOEt 5:1): **11** (0.44 g, 40%). Yellow solid. M.p. 77–78°. IR (ATR): 3153, 3130, 3014, 2960, 2882, 2846, 1715, 1671, 1575, 1480, 1435, 1403, 1365, 1303, 1264, 1211, 1180. ^{1}H-NMR ($CDCl_3$): 10.23 (*d*, $J = 0.7$, CHO); 7.64 (*dd*, $J = 1.8$, 0.7, =CH); 6.89 (*d*, $J = 1.8$, =CH); 3.95 (*s*, MeO). ^{13}C-NMR ($CDCl_3$): 178.8; 162.0; 152.4; 146.6; 126.2; 112.9; 52.5. Anal. calc. for $C_7H_6O_4$ (154.12): C 54.55, H 3.92; found: C 54.33; H 3.91.

General Procedure for the Synthesis of Hydrazone Derivatives **12** [14]. Hydrazine derivative (6.5 mmol) was added dropwise to a stirred soln. of aldehyde **11** (1.0 g, 6.49 mmol) mmol) in THF (10 ml), and the resulting soln. was stirred at r.t. for 3 h. The reaction was monitored with TLC. After the completion of the reaction, the solvent was removed and H_2O (30 ml) was added, and the resulting mixture was extracted with AcOEt (3×30 ml), dried ($MgSO_4$), and evaporated to give the corresponding hydrazone derivative.

Methyl 2-[(Methylhydrazono)methyl]furan-3-carboxylate (**12a**). Yellow oil. (0.70 g, 96%). IR (ATR): 3394, 3210, 2951, 1701, 1589, 1437, 1319, 1290, 1196, 1167, 1058, 1031. ^{1}H-NMR ($CDCl_3$): 7.83 (*s*, N=CH); 7.23 (*d*, $J = 2.0$, =CH); 6.61 (*d*, $J = 2.0$, =CH); 6.22 (br. *s*, NH); 3.76 (*s*, MeO); 2.94 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 163.8; 155.4; 141.3; 122.4; 113.1; 111.0; 51.3; 33.7. Anal. calc. for $C_8H_{10}N_2O_3$ (182.18): C 52.74, H 5.53; N 15.38; found: C 52.49, H 5.47, N 15.20.

tert-*Butyl 2-{[3-(Methoxycarbonyl)furan-2-yl]methylidene}hydrazinecarboxylate* (**12b**). (*tert*-Butoxy)carbonyl hydrazide (0.26 g, 1.95 mmol) and **11** (0.3 g, 1.95 mmol) in THF (10 ml) was reacted at 50° for 3 h as described above to give **12b** (0.51 g, 98%). Yellow solid. M.p. 122–123°. IR (ATR): 3201, 2977, 1701, 1536, 1498, 1367, 1276, 1248, 1154, 1038. ^{1}H-NMR ($CDCl_3$): 8.44 (br. *s*, NH); 8.28 (br. *s*, N=CH); 7.43 (*d*, $J = 1.9$, =CH); 6.73 (*d*, $J = 1.9$, =CH); 3.85 (*s*, MeO); 1.53 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 163.3; 152.6; 152.3; 143.3; 132.4, 117.7, 111.4; 81.7; 51.8; 28.1. HR-MS: 291.0961 ($[M + Na]^+$, $C_{12}H_{16}N_2NaO_5^+$; calc. 291.0959).

Methyl 2-[(Phenylhydrazono)methyl]-3-furoate (**12c**). $PhNHNH_2$ (0.64 ml, 6.49 mmol) and **11** (1.0 g, 6.49 mmol) in THF (20 ml) were reacted at r.t. for 2 h as described above to afford **12c** (1.5 g, 95%). Yellow solid. M.p. 133–134°. IR (ATR): 3275, 3127, 3068, 3022, 2951, 1687, 1587, 1494, 1306, 1254,

1206, 1170, 1058. ^{1}H-NMR ($CDCl_3$): 8.24 (*s*, N=CH); 8.04 (br. *s*, NH); 7.40 (*d*, *J* = 2.0, =CH); 7.29 (br. *dd*, *J* = 8.4, 7.4, =CH); 7.13 (br. *dd*, *J* = 8.4, 1.0, =CH); 6.92 (*tt*, *J* = 7.4, 1.0, =CH); 6.73 (*d*, *J* = 2.0, =CH); 3.87 (*s*, MeO). ^{13}C-NMR ($CDCl_3$): 163.7; 154.0; 143.5; 142.4; 129.3; 126.4; 121.0; 115.1; 113.2; 111.4; 51.7. Anal. calc. for $C_{13}H_{12}N_2O_3$ (244.25): C 63.93, H 4.95, N 11.47; found: C 63.81, H 4.94, N 11.29.

Methyl 2-{[(4-Methylphenyl)hydrazono]methyl}furan-3-carboxylate (**12d**). *4-Methylphenylhydrazinium chloride* (0.52 g, 3.24 mmol) in pyridine (0.26 ml, 3.24 mmol) was added to a stirred soln. of aldehyde **11** (0.5 g, 3.24 mmol) in benzene (30 ml), and the mixture was stirred at r.t. for 3 h. The mixture was worked up as described above. The product was purified by CC (SiO_2; hexane/AcOEt 3 : 1) to furnish **12d** (0.75 g, 89.5%). Brown solid. M.p. 155–157°. IR (ATR): 3282, 2988, 2950, 2913, 1685, 1582, 1530, 1508, 1441, 1304, 1250, 1059, 1038. ^{1}H-NMR ($CDCl_3$): 8.21 (*s*, N=CH); 7.96 (br. *s*, NH); 7.40 (*d*, *J* = 1.9, =CH); 7.10 (br. *d*, *A* of *AA′BB′*, *J* = 8.4, =CH); 7.04–7.02 (br. *d*, *B* of *AA′BB′*, *J* = 8.4, =CH); 6.73 (*d*, *J* = 1.9, =CH); 3.86 (*s*, MeO); 2.29 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 163.7; 154.2; 142.2; 141.3; 130.4; 129.8; 125.8; 114.7; 113.2; 111.4; 51.6; 20.6. HR-MS: 259.1088 ($[M+H]^+$, $C_{14}H_{15}N_2O_3^+$; calc. 259.1084).

Methyl 2-{[(4-Methoxyphenyl)hydrazono]methyl}-3-furoate (**12e**). *4-Methoxyphenylhydrazinium chloride* (0.28 g, 1.62 mmol) and pyridine (0.13 ml, 1.62 mmol) were added to a stirred soln. of **11** (0.25 g, 1.62 mmol) in benzene (15 ml), and the mixture was stirred at 50° for 2 h. The product was isolated as described above. The crude product was then purified by CC (SiO_2; hexane/AcOEt 3 : 1) to give **12e** (0.41 g, 92%). Brown solid. M.p. 127–129°. IR (ATR): 3273, 2997, 2951, 2901, 1693, 1584, 1534, 1507, 1439, 1300, 1237, 1134, 1058, 1036. ^{1}H-NMR ($CDCl_3$): 8.20 (*s*, N=CH); 7.94 (br. *s*, NH); 7.39 (*d*, *J* = 1.9, =CH); 7.07 (br. *d*, *A* of *AA′BB′*, *J* = 8.2, =CH); 6.87 (br. *d*, *B* of *AA′BB′*, *J* = 8.4, =CH); 6.72 (*d*, *J* = 1.9, =CH); 3.86 (*s*, MeO); 3.78 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 163.7; 154.2; 142.1; 137.5; 125.5; 118.7; 114.7; 114.5; 112.0; 111.4; 55.6; 51.6. Anal. calc. for $C_{14}H_{14}N_2O_4$ (272.27): C 61.31, H 5.14 N 10.21; found: C 61.32, H 5.14. N, 9.82.

Methyl 2-{[(4-Chlorophenyl)hydrazono]methyl}furan-3-carboxylate (**12f**). *4-Chlorophenylhydrazinium chloride* (0.58 g, 3.24 mmol) in pyridine (0.26 ml, 3.24 mmol) were added to a stirred soln. of **11** (0.5 g, 3.24 mmol) in benzene (30 ml), and the mixture was stirred at 75° for 30 min. The product was isolated as described above: **12f** (0.87 g, 96%). M.p. 152–154°. IR (ATR): 3734, 3690, 3279, 2988, 2952, 2900, 1686, 1581, 1527, 1485, 1442, 1266, 1252, 1058, 1039. ^{1}H-NMR ($CDCl_3$): 8.24 (*s*, N=CH); 7.99 (br. *s*, NH); 7.41 (*d*, *J* = 1.9, =CH); 7.24 (br. *d*, *A* of *AA′BB′*, *J* = 8.3, =CH); 7.06 (br. *d*, *B* of *AA′BB′*, *J* = 8.3, =CH); 6.74 (*d*, *J* = 1.9, =CH); 3.86 (*s*, MeO). ^{13}C-NMR ($CDCl_3$): 163.6; 153.7; 142.6; 142.2; 129.3; 127.0; 125.7; 115.6; 114.3; 111.5; 51.7. Anal. calc. for $C_{13}H_{11}ClN_2O_3$: C 56.03, H 3.98, N 9.53; found: C 56.28, H 3.77, N 9.27.

Methyl 2-{[(4-Fluorophenyl)hydrazono]methyl}furan-3-carboxylate (**12g**). 4-Fluorophenylhydrazinium chloride (0.53 g, 3.24 mmol) and pyridine (0.26 ml, 3.24 mmol) were added to a stirred sol. of **11** (0.5 g, 3.24 mmol) in benzene (15 ml), and the mixture was stirred at r.t. for 2 h. The product was isolated as described above. **12g** (0.77 g, 90%). White solid. M.p. 135–136°. IR (ATR): 3278, 3138, 3020, 2955, 1686, 1589, 1534, 1505, 1439, 1272, 1257, 1060, 1039. ^{1}H-NMR ($CDCl_3$): 8.24 (*s*, N=CH); 8.06 (br. *s*, NH); 7.41 (*d*, *J* = 1.9, =CH); 7.10–7.06 (*m*, =CH); 7.03–6.97 (*m*, =CH); 6.74 (*d*, *J* = 1.9, =CH); 3.86 (*s*, MeO). ^{13}C-NMR ($CDCl_3$): 163.6; 157.8 (*d*, *J* = 231.4); 153.9; 142.4; 139.9 (*d*, *J* = 1.8); 126.5; 115.9 (*d*, *J* = 22.8); 115.2; 114.2 (*d*, *J* = 7.5); 111.5; 51.7. Anal. calc. for $C_{13}H_{11}FN_2O_3$ (262.24): C 59.54, H 4.23, N 10.68; found: C 59.16, H 3.97, N,10.25.

Methyl 2-{[(2,4-Difluorophenyl)hydrazono]methyl}furan-3-carboxylate (**12h**). *(2,4-Difluorophenyl)hydrazinium chloride* (0.48 g, 2.6 mmol) and pyridine (0.21 ml, 2.6 mmol) were added to a stirred soln. of **11** (0.4 g, 2.6 mmol) in benzene (30 ml), and stirring was continued at 80° for 2 h. The product was purified by CC (SiO_2: hexane/ethyl acetate 4 : 1) to yield **12h** (0.61 g, 84%). Yellow solid. M.p. 127–129°. IR (ATR): 3304, 2930, 2880, 1707, 1625, 1525, 1503, 1432, 1299, 1256, 1198, 1174, 1137, 1058, 1037. ^{1}H-NMR ($CDCl_3$): 8.32 (*s*, N=CH); 8.03 (br. *s*, NH); 7.57–7.51 (*m*, =CH); 7.42 (*d*, *J* = 1.9, =CH); 6.88–6.81 (*m*, =CH); 6.75 (*d*, *J* = 1.9, =CH); 3.87 (*s*, MeO). ^{13}C-NMR ($CDCl_3$): 163.5; 156.6 (*dd*, *J* = 241.6, 10.9); 153.4; 149.3 (*dd*, *J* = 242.8, 11.7); 142.7; 128.7 (*dd*, *J* = 9.2, 3.3); 128.5; 116.0; 115.3 (*dd*, *J* = 8.8, 3.4); 111.6; 111.5 (*dd*, *J* = 22.0, 3.5); 103.7 (*dd*, *J* = 26.7, 22.0); 51.7. Anal. calc. for $C_{13}H_{10}F_2N_2O_3$ (280.23): C 55.72, H 3.60, N 10.00; found: C 56.05, H 3.56, N 9.64.

5-Methylfuro[2,3-d]pyridazin-4(5H)-one (**13a** [7b]). A soln. of KOH (3.57 ml, 7.14 mmol, 2M) in MeOH was added to a stirred soln. of **12a** (0.65 g, 3.57 mmol) in a mixture of THF (20 ml), MeOH

(10 ml), and H_2O (1 ml). The mixture was stirred at 40° for 3 h. The solvent was evaporated to give a crude product, which was then treated with H_2O (30 ml). The mixture was extracted with AcOEt (3 × 50 ml), dried ($MgSO_4$), and concentrated. The product was purified by CC (SiO_2; hexane/AcOEt 2:1): **13a** (0.32 g, 60%). White solid. M.p. 107–108°. IR (ATR): 3118, 3101, 3054, 3039, 1647, 1575, 1502, 1379, 1274, 1142, 1004. ^{1}H-NMR ($CDCl_3$): 8.18 (*d*, *J* = 0.7, N=CH); 7.67 (*d*, *J* = 2.0, =CH), 7.04 (*dd*, *J* = 2.0, 0.7, =CH); 3.85 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 158.9; 153.0; 146.6; 126.0; 122.6; 107.2; 39.6. Anal. calc. for $C_7H_6N_2O_2$ (150.13): C 56.00, H 4.03, N 18.66; found: C 55.98; H 4.04, N 18.49.

*2-{[[(*tert*-Butoxy)carbonyl]hydrazono}methyl)furan-3-carboxylic Acid* (**14b**). A soln. of KOH (1.96 ml, 3.92 mmol, 2M) in MeOH (10 ml) was added to a stirred soln. of **12b** (0.52 g, 1.94 mmol) in THF (10 ml), MeOH (5 ml), and H_2O (0.5 ml). The mixture was stirred at 80° for 3 h (TLC monitoring). After the completion of the reaction, the solvent was removed to give the crude product, which was then treated with H_2O (50 ml). The aq. phase was extracted with AcOEt (2 × 50 ml) and acidified with 1M HCl to pH 2, and then extracted with AcOEt (3 × 50 ml) and H_2O. The combined org. extract was washed with H_2O, dried ($MgSO_4$), and concentrated to give **14b** (0.43 g, 87%). Brown solid. M.p. 164–165°. IR (ATR): 3100, 2978, 2930, 1696, 1669, 1483, 1440, 1391, 1280, 1162, 1050, 1035. ^{1}H-NMR ((D$_6$)DMSO): 13.03 (br. *s*, COOH); 11.19 (*s*, NH); 8.47 (*s*, N=CH); 7.81 (*d*, *J* = 1.9, =CH); 6.78 (*d*, *J* = 1.9, =CH); 1.45 (*s*, Me). ^{13}C-NMR ((D$_6$)DMSO): 163.7; 152.3; 152.2; 144.3; 132.6; 118.6; 112.2; 80.1; 28.1. Anal. calc. for $C_{11}H_{14}N_2O_5$ (254.24): C 51.97, H 5.55, N 11.02; found: C 51.69 H, 5.40, N 10.64.

*Furo[2,3-*d*]pyridazin-4(5*H*)-one* (**4**) [7b]. To a stirred soln. of **14b** (0.27 g, 1.06 mmol) in THF (10 ml) was added $SOCl_2$ dropwise (0.15 ml, 2.12 mmol), and the resulting mixture was stirred at reflux temp. overnight. After the completion of the reaction (TLC monitoring), the solvent was evaporated, and the crude product was purified by CC (SiO_2; AcOEt/hexane 1:1) to give **4** (0.1 g, 69%). White solid. M.p. 203–204°. IR (ATR): 3155, 3128, 3101, 2970, 2922, 1655, 1572, 1501, 1422, 1380, 1183. ^{1}H-NMR ((D$_6$)DMSO): 12.93 (br. *s*, NH); 8.53 (*d*, *J* = 0.7, N=CH); 8.20 (*d*, *J* = 2.0, =CH); 7.13 (*dd*, *J* = 2.0, 0.7, =CH). ^{13}C-NMR ((D$_6$)DMSO): 159.3; 153.0; 147.9; 127.2; 122.1; 106.5. Anal. calc. for $C_6H_4N_2O_2$ (136.11): C 52.95, H 2.96, N 20.58; found: C 52.72, H 3.09, N 20.15.

General Procedure for the Hydrolysis of Hydrazone Derivatives (**12c**–**12h**). A soln. of KOH (0.97–2.7 ml, 2 mol-equiv., 2M) in MeOH was added to a stirred soln. of **12c**–**12h** (0.24–0.76 g) in THF (10–20 ml), MeOH (5–10 ml), and H_2O (0.5–1 ml). The mixture was stirred at appropriate temp. (TLC monitoring). After the completion of the reaction, the solvent was removed to give the crude product, which was then treated with H_2O (50 ml). The aq. phase was extracted with AcOEt (3 × 50 ml), and acidified with 1M HCl to pH 2, and then extracted with AcOEt (3 × 50 ml) and H_2O. The combined org. extract was washed with H_2O, dried ($MgSO_4$), and concentrated to give the acid **14c**–**14h**.

2-[(Phenylhydrazono)methyl]furan-3-carboxylic Acid (**14c**). Compound **12c** (0.66 g, 2.70 mmol) was hydrolyzed at r.t. for 3 h as described above: **14c** (0.57 g, 92%). Brown solid. M.p. 196–197°. IR (ATR): 3301, 3124, 2997, 2874, 2676, 2573, 1670, 1583, 1498, 1277, 1255, 1130, 1050. ^{1}H-NMR ((D$_6$)DMSO): 12.88 (br. *s*, COOH); 10.88 (*s*, NH); 8.36 (*s*, N=CH); 7.73 (*d*, *J* = 1.9, =CH); 7.23 (br. *t*, *J* = 8.4, =CH); 7.04 (br. *d*, *J* = 8.6, =CH); 6.80 (br. *t*, *J* = 7.3, =CH); 6.75 (*d*, *J* = 1.9, =CH). ^{13}C-NMR ((D$_6$)DMSO): 164.0; 153.7; 144.4; 142.8; 129.1; 125.9; 119.6; 115.1; 112.3; 111.7. Anal. calc. for $C_{12}H_{10}N_2O_3$ (230.22): C 62.60, H 4.38, N 12.17; found: C 62.21, H 4.40, N 11.82.

2-{[(4-Methylphenyl)hydrazono]methyl}furan-3-carboxylic Acid (**14d**). The ester **12d** (0.24 g, 0.93 mmol) was hydrolyzed at r.t. for 6 h as described above. **14d** (0.20 g, 88%). Brown solid. M.p. 188–190°. IR (ATR): 3725, 3690, 3293, 2988, 2900, 2565, 1670, 1581, 1508, 1434, 1308, 1271, 1252, 1051, 1024. ^{1}H-NMR ((D$_6$)DMSO): 12.89 (br. *s*, COOH); 10.85 (*s*, NH); 8.37 (*s*, 1 H); 7.77 (*d*, *J* = 1.9, N=CH); 7.12–7.10 (br. *d*, *A* of *AA′BB′*, *J* = 8.0, =CH); 7.02–7.00 (br. *d*, *B* of *AA′BB′*, *J* = 8.0, =CH); 6.80 (*d*, *J* = 1.9, =CH); 2.27 (*s*, Me). ^{13}C-NMR ((D$_6$)DMSO): 164.1; 153.9; 142.6; 142.1; 129.5; 128.3; 125.2; 114.8; 112.4; 111.7; 20.2. Anal. calc. for $C_{13}H_{12}N_2O_3$ (244.25): C 63.93, H 4.95, N 11.97; found: C 63.54, H 4.85, N 11.62.

2-{[(4-Methoxyphenyl)hydrazono]methyl}furan-3-carboxylic Acid (**14e**). The ester **12e** (0.26 g, 0.95 mmol) was hydrolyzed at reflux temp. for 18 h as described above: **14e** (0.22 g, 89%). Brown solid. M.p. 169–171°. IR (ATR): 3735, 3690, 3649, 2988, 2900, 2837, 1693, 1506, 1454, 1405, 1237, 1191, 1079, 1038. ^{1}H-NMR ((D$_6$)DMSO): 12.75 (br. *s*, COOH); 10.73 (*s*, NH); 8.29 (*s*, N=CH); 7.70 (*d*, *J* = 1.9, =CH); 7.00–6.98 (br. *d*, *A* of *AA′BB′*, *J* = 7.9, =CH); 6.87–6.84 (br. *d*, *B* of *AA′BB′*, *J* = 7.9, =CH); 6.74

(*d*, *J* = 1.9, =CH); 3.69 (*s*, MeO). ^{13}C-NMR ((D$_6$)DMSO): 164.0; 154.0; 153.2; 142.5; 138.3; 124.6; 114.6; 114.3; 113.4; 111.6; 55.2. Anal. calc. for $C_{13}H_{12}N_2O_4$ (260.25): C 60.00, H 4.65, N 10.76; found: C 60.01, H, 4.65, N 10.43.

2-{[(4-Chlorophenyl)hydrazono]methyl}furan-3-carboxylic Acid (**14f**). The ester **12f** (0.76 g, 2.73 mmol) was hydrolyzed at reflux temp. for 18 h as described above: **14f** (0.57 g, 79%). Brown solid. M.p. 198–200°. IR (ATR): 3734, 3675, 3231, 3174, 3100, 2988, 2900, 1697, 1582, 1488, 1418, 1266, 1194, 1075. ^{1}H-NMR ((D$_6$)DMSO): 12.93 (br. *s*. COOH); 10.99 (*s*, NH); 8.36 (*s*, N=CH); 7.75 (*d*, *J* = 1.9, =CH); 7.29–7.25 (br. *d*, *A* of *AA′BB′*, *J* = 8.1, =CH); 7.06–7.02 (br. *d*, *B* of *AA′BB′*, *J* = 8.1, =CH); 6.76 (*d*, *J* = 1.9, =CH). ^{13}C-NMR ((D$_6$)DMSO): 164.0; 153.4; 143.3; 143.1; 128.9; 126.6; 122.9; 115.6; 113.7; 111.8. Anal. calc. for $C_{12}H_9ClN_2O_3$ (264.66): C 54.46, H 3.43, N 10.58; found: C 54.33, H 3.43, N 10.19.

2-{[(4-Fluorophenyl)hydrazono]methyl}furan-3-carboxylic Acid (**14g**).The ester **12g** (0.69 g, 2.63 mmol) was hydrolyzed at 75° for 6 h as described above: **14g** (0.49 g, 75%). Brown solid. M.p. 199–200°. IR (ATR): 3241, 3213, 3041, 2961, 2562, 1696, 1556, 1505, 1455, 1316, 1223, 1189, 1076, 1025. ^{1}H-NMR ((D$_6$)DMSO): 12.87 (br. *s*, COOH); 10.89 (*s*, NH); 8.34 (*s*, N=CH); 7.73 (*d*, *J* = 1.9, =CH); 7.11–7.01 (*m*, =CH); 6.75 (*d*, *J* = 1.9, =CH). ^{13}C-NMR ((D$_6$)DMSO): 164.1; 156.4 (*d*, *J* = 234.9); 153.7; 142.9; 141.0 (*d*, *J* = 1.0); 125.9; 115.7 (*d*, *J* = 22.5); 115.2; 113.4 (*d*, *J* = 7.6); 111.8. Anal. calc. for $C_{12}H_9FN_2O_3$ (248.21): C 58.07, H 3.65, N 11.29; found: C 58.16, H 3.87, N 10.91.

2-{[(2,4-Difluorophenyl)hydrazono]methyl}furan-3-carboxylic Acid (**14h**). The ester **12h** (0.50 g, 1.78 mmol) was hydrolyzed at 50° for 4 h as described above: **14h** (0.35 g, 74%). Brown solid. M.p. 241–243°. IR (ATR): 3363, 3002, 2970, 2571, 1738, 1679, 1595, 1506, 1441, 1365, 1216, 1204, 1136. ^{1}H-NMR ((D$_6$)DMSO): 12.91 (br. *s*, COOH); 10.77 (*s*, NH); 8.60 (*s*, N=CH); 7.75 (*d*, *J* = 1.9, =CH); 7.41 (*dt*, *J* = 6.0, 9.3, =CH); 7.22 (*ddd*, *J* = 11.8, 8.9, 2.8, =CH); 7.03–6.98 (br. *t*, *J* = 8.6, =CH); 6.76 (*d*, *J* = 1.9, =CH). ^{13}C-NMR ((D$_6$)DMSO): 163.9; 155.3 (*dd*, *J* = 238.0, 10.9); 153.3; 148.7 (*dd*, *J* = 243.7, 12.2); 143.2; 129.7 (*dd*, *J* = 9.9, 3.0); 128.7; 116.1; 114.4 (*dd*, *J* = 8.9, 4.2); 111.9; 111.5 (*dd*, *J* = 22.0, 3.3); 103.9 (*dd*, *J* = 27.0, 22.3). Anal. calc. for $C_{13}H_{12}N_2O_3$ (266.20): C 63.93, H 4.95, N 11.97; found: C 63.54, H 4.85, N 11.45.

General Procedure for the Synthesis of Furo-pyridazinone Derivatives **13c**–**13h**. $SOCl_2$ (0.15–0.28 ml, 2 mol equiv.) was added dropwise to a stirred soln. of acid **14c**–**14h** (0.27–0.44 g, 1.02–1.91 mmol) in THF (20 ml), and the mixture was stirred at reflux temp. for 18 h (TLC monitoring). After the completion of the reaction, the solvent and excess $SOCl_2$ were evaporated, and the crude product was purified by CC (SiO; hexaneAcOEt) to give **13c**–**13h**.

*5-Phenylfuro[2,3-*d*]pyridazin-4(5*H*)-one* (**13c**). The acid **14c** (0.46 g, 2 mmol) was reacted as described above: **13c** (0.38 g, 93%). White solid. M.p. 93–94°. IR (ATR): 3156, 3105, 3057, 1674, 1581, 1493, 1456, 1379, 1297, 1266, 1152, 1116. ^{1}H-NMR ($CDCl_3$): 8.35 (*d*, *J* = 0.7, N=CH); 7.73 (*d*, *J* = 1.9, =CH); 7.58 (*m*, =CH); 7.49 (*m*, =CH); 7.40 (*tt*, *J* = 7.4, 1.2, =CH); 7.13 (*dd*, *J* = 1.9, 0.7, =CH). ^{13}C-NMR ($CDCl_3$): 158.4; 152.6; 146.9; 141.7; 128.8; 128.1; 127.0; 126.0; 123.5; 107.8. Anal. calc. for $C_{12}H_8N_2O_2$ (212.20): C 67.92, H 3.80, N 13.20; found: C 67.88, H 3.72, N 12.96.

*5-(4-Methylphenyl)furo[2,3-*d*]pyridazin-4(5*H*)-one* (**13d**). The acid **14d** (0.46 g, 1.88 mmol) was reacted as described above. CC was performed with hexane/AcOEt (2:1). **13d** (0.29 g, 68%). White powder. M.p. 92–94°. IR (ATR): 3113, 3042, 2987, 2901, 1681, 1584, 1498, 1380, 1296, 1274, 1152, 1119, 1062, 1024. ^{1}H-NMR ($CDCl_3$): 8.33 (*d*, *J* = 0.6, N=CH); 7.73 (*d*, *J* = 2.0, =CH); 7.46–7.43 (br. *d*, *A* of *AA′BB′*, *J* = 8.3, =CH); 7.31–7.27 (br. *d*, *B* of *AA′BB′*, *J* = 8.3, =CH); 7.13 (*dd*, *J* = 2.0, 0.6 =CH); 2.41 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 158.5; 152.6; 146.8; 139.2; 138.0; 129.4; 126.9; 125.8; 123.4; 107.8; 21.1. Anal. calc. for $C_{13}H_{10}N_2O_2$ (226.23): C 69.02, H 4.46, N 12.38 found: C 68.72, H 4.48, N 11.99.

*5-(4-Methoxyphenyl)furo[2,3-*d*]pyridazin-4(5*H*)-one* (**13e**). The acid **14e** (0.30 g, 1.15 mmol) was reacted as described above. CC was performed with hexane/AcOEt (3:1). **13e** (0.21 g, 75%). White powder. M.p. 116–118°. IR (ATR): 3145, 2965, 2900, 1680, 1509, 1498, 1252, 1173, 1143, 1110, 1058, 1032, 1011. ^{1}H-NMR ($CDCl_3$): 8.33 (*d*, *J* = 0.7, N=CH); 7.73 (*d*, *J* = 2.0, =CH); 7.50–7.46 (br. *d*, *A* of *AA′BB′*, *J* = 8.1, =CH); 7.12 (*dd*, *J* = 2.0, 0.7, =CH); 7.02–6.98 (br. *d*, *B* of *AA′BB′*, *J* = 8.1, =CH); 3.85 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 159.1; 158.6; 152.6; 146.9; 134.6; 127.1; 126.9; 123.4; 114.0; 107.8; 55.5. Anal. calc. for $C_{13}H_{10}N_2O_3$ (242.23): C 64.46, H 4.16, N 11.56; found: C 64.03, H 4.20, N 11.23.

*5-(4-Chlorophenyl)furo[2,3-*d*]pyridazin-4(5*H*)-one* (**13f**). The acid **14f** (0.27 g, 1.02 mmol) was reacted as described above. **13f** (0.23 g, 92%). White solid. M.p. 166–188°. IR (ATR): 3152, 3105, 2929, 1679, 1490, 1380, 1301, 1259, 1141, 1108, 1088, 1013. ^{1}H-NMR ($CDCl_3$): 8.35 (*d*, *J* = 0.6, N=CH); 7.74 (*d*,

$J = 2.0$, =CH); 7.58 – 7.54 (*m*, *A* of *AA′BB′*, =CH), 7.48 – 7.44 (*m*, *B* of *AA′BB′*, =CH), 7.13 (*dd*, $J = 2.0$, 0.6, =CH). ^{13}C-NMR ($CDCl_3$): 158.3; 152.6; 147.1; 140.1; 133.8; 128.9; 127.4; 127.2; 123.5; 107.8. Anal. calc. $C_{12}H_7ClN_2O_2$ (246.65): C 58.43, H 2.86, N 11.36; found: C 58.79, H 2.81, N 11.02.

*5-(4-Fluorophenyl)furo[2,3-*d*]pyridazin-4(5*H*)-one* (**13g**). The acid **14g** (0.4 g, 1.61 mmol) was reacted as described above. CC was performed with hexane/AcOEt (2 : 1). **13g** (0.26 g, 70%). White powder. M.p. 122 – 123°. IR (ATR): 2922, 1739, 1688, 1507, 1496, 1381, 1262, 1216, 1141, 1106, 1060, 1012, 1012. ^{1}H-NMR ($CDCl_3$): 8.35 (*d*, $J = 0.6$, N=CH); 7.74 (*d*, $J = 2.0$, =CH); 7.59 – 7.54 (*m*, *A* of *AA′BB′X*, =CH); 7.20 – 7.15 (*m*, *B* of *AA′BB′X*, =CH); 7.13 (*dd*, $J = 2.0$, 0.6, =CH). ^{13}C-NMR ($CDCl_3$): 163.2; 159.6 (*d*, $J = 228.3$); 152.6; 147.1; 137.6 (*d*, $J = 3.2$); 127.8 (*d*, $J = 8.5$); 127.2; 123.5; 115.7 (*d*, $J = 22.8$); 107.8. Anal. calc. for $C_{12}H_7FN_2O_2$ (230.19) C 62.61, H 3.07, N 12.17: found: C 62.44, H 3.00, N 12.05.

*5-(2,4-Difluorophenyl)furo[2,3-*d*]pyridazin-4(5*H*)-one* (**13h**). The acid **14h** (0.3 g, 1.13 mmol) was reacted as described above. CC was performed with hexane/AcOEt (3 : 2). **13h** (0.20 g, 70%). White powder. M.p. 183 – 185°. IR (ATR): 3059, 2988, 2900, 1683, 1614, 1510, 1497, 1253, 1147, 1056. ^{1}H-NMR ($CDCl_3$): 8.35 (*d*, $J = 0.6$, N=CH); 7.76 (*d*, $J = 2.0$, =CH); 7.43 (*dt*, $J = 9.3, 5.7$, =CH); 7.13 (*dd*, $J = 2.0, 0.6$, =CH); 7.05 – 6.98 (*m*, =CH). ^{13}C-NMR ($CDCl_3$): 162.7 (*dd*, $J = 251.1, 10.9$); 158.0; 157.6 (*dd*, $J = 255.5$, 12.7); 152.7; 147.1; 129.9 (*dd*, $J = 10.2, 1.7$); 127.7; 125.7 (*dd*, $J = 12.8, 3.7$); 123.1; 111.7 (*dd*, $J = 22.6, 3.6$); 107.7; 105.0 (*dd*, $J = 26.3, 23.8$). Anal. calc. for $C_{12}H_6F_2N_2O_2$ (248.19): C 58.07, H 2.44, N 11.29; found: C 57.66, H 2.35, N 11.07.

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