# Furan ring opening-pyrrole ring closure: a new synthetic route to aryl(heteroaryl)-annulated pyrrolo[1,2-*a*][1,4]diazepines†

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A method of synthesis of pyrrolo[1,2-a][1,4]benzodiazepines is described. This method is based on the recyclization of N-(furfuryl)anthranilamides under treatment with an aq. HCl/AcOH system and allows one to form both diazepine and pyrrole rings in one step. The reaction proceeds *via* furan ring opening into a diketone moiety followed by consecutive interaction of the NH<sub>2</sub>-group with both carbonyl functions. The process is not efficient in the presence of alkyl or aryl groups on amide nitrogen due to competitive furfuryl cation elimination. But alkylation of pyrrolo[1,2-a][1,4]benzodiazepines yields efficiently the corresponding N-alkyl derivatives. Steric effects also prevent cyclization due to reversibility of diazepine ring formation under these reaction conditions. However, the corresponding pyrrolo[1,2-a][1,4]benzodiazepines can be obtained by a stepwise process, *i.e.*, 1) furan ring opening with aq. HCl/AcOH and 2) cyclization of isolated aminodiketones under treatment with glacial acetic acid. Another efficient procedure for the synthesis of pyrrolo[1,2-a][1,4]benzodiazepines consists of acid-catalyzed furan ring opening of N-(furfuryl)-2-nitrobenzamides followed by treatment of the formed nitrodiketone with Fe/AcOH. It leads to a one pot reduction of nitro group to amine, cyclization into diazepine and pyrrole ring formation. This procedure is efficient both for substrates with steric demands and for N-alkyl- or N-aryl-N-(furfuryl)amides. The proposed approach can be also applied to the synthesis of parent pyrrolo[1,2-a][1,4]diazepines or their analogues annulated to heterocycles.

#### Introduction

[1,4]Benzodiazepines are psychoactive drugs showing anxiolytic, sedative, hypnotic, amnesic, muscle relaxant, and other kinds of physiological activities.<sup>1</sup> On the other hand, the pyrrole moiety is an important part of various medicines, such as Atorvastatin, Dividol, Ketorolac, Pyrvinium, Sunitinib, Tolmetin, *etc.* The combination of [1,4]benzodiazepine and pyrrole fragments in one molecule might both increase the known activities of these pharmacophores and induce some other physiological effects. One of the methods for this combination is annulation of the pyrrole ring to the [1,4]benzodiazepine moiety. Among these compounds, the most studied ones are "anthramycins" produced by *Streptomyces* sp.<sup>2,3</sup> These antitumor antibiotics are pyrrolo[2,

1-*c*][1,4]benzodiazepine derivatives. While isomeric pyrrolo[1, 2-*a*][1,4]benzodiazepines have been less studied, it has been demonstrated that these compounds have CNS activity<sup>4-6</sup> being potent sedative,<sup>6-8</sup> anticonvulsant,<sup>7,8</sup> myorelaxant,<sup>8,9</sup> and psychotropic<sup>9-11</sup> agents. Moreover, pyrrolo[1,2-*a*][1,4]benzo-diazepine derivatives showed antiinflammatory,<sup>6</sup> analgesic,<sup>11,12</sup> and fungicidal<sup>13</sup> activity.

The methods of pyrrolo[1,2-a][1,4]benzodiazepines synthesis are mainly based on the use of 1-[2-(α-aminoalkyl)phenyl]pyrroles which form the target diazepines by Pictet-Spengler condensation with aldehydes (method a on Scheme 1),<sup>7,11,13-15</sup> Bischler-Napieralski reaction of the corresponding amide (method b), 4-6,15,16 or the intramolecular condensation with carbonyl moiety at C2 atom of the pyrrole ring (method *c*).<sup>17</sup> Not only  $\alpha$ -aminoalkyl group but also imines (methods d and e),<sup>18</sup> oximes (method f)<sup>18c,19</sup> and amides<sup>20</sup> might participate in these reactions. An analogous reaction can be also performed when the pyrrole ring consists of nucleophilic fragment and N-aryl substituent has an electrophilic moiety (method g),<sup>8,21</sup> this process has been also realized under conditions of four-component Ugi reaction (method h).<sup>22</sup> Some other methods of the synthesis of pyrrolo[1, 2-a][1,4]benzodiazepines and their analogues wherein benzene ring is replaced by heterocycles have been described too.23

All these methods include the formation of diazepine ring from 1-arylpyrroles. However, pyrroles are very susceptible to acids and other electrophilic agents. Moreover, the use of these approaches is restricted due to the complexity of 1-arylpyrrole synthesis. Recently we proposed a principally new approach to the construction of pyrrolo[1,2-*a*][1,4]benzodiazepine scaffold

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**Scheme 1** The main methods of pyrrolo[1,2-*a*][1,4]benzodiazepine unit synthesis.

based on the acid-catalyzed recyclization of *N*-(2-aminobenzoyl)-5-methylfurfurylamine which allows one to form simultaneously both diazepine and pyrrole rings (Scheme 2).<sup>24</sup> This method allows us to obtain a broad scope of pyrrolo[1,2-*a*][1,4]benzodiazepines from cheap starting compounds. Now we have applied this method to a broad range of substrates bearing various substituents in the furan moiety, in benzoyl group, at the amide nitrogen and at  $\alpha$ carbon atom. Herein, we describe the results of this investigation in detail.



**Scheme 2** Synthesis of pyrrolo[1,2-*a*][1,4]benzodiazepines *via N*-(furfuryl)anthranilamide recyclizations.

#### **Results and discussion**

#### Synthesis of N-(furfuryl)anthranilamides

The proposed method for the pyrrolo[1,2-*a*][1,4]benzodiazepine synthesis consists of acid-catalyzed recyclization of *N*-(furfuryl)anthranilamides **1**. These substrates were synthesized from furfurylamines  $2^{25}$  by two procedures. The first one is based on the transformation of anthranilic acid derivatives into 2-(phthalimido)benzoyl chlorides **3** followed by reaction with 5-methylfurfurylamine (**2a**) with formation of amides **4**. The target anthranilamides **1a**,**b** were obtained from **4a**,**b** by amine deprotection using a common procedure<sup>26</sup> (Scheme 3).

The second method consists of acylation of furfurylamines 2 with 2-nitrobenzoyl chlorides 5 yielding amides 6 which were



Scheme 3 Synthesis of *N*-(furfuryl)anthranilamides 1 from furfurylamine 2a and 2-(phthalimido)benzoyl chlorides 3. *Reagents and conditions:* a) benzene, rt, 1.5 h, 66% 4a, 72% 4b; b)  $N_2H_4$ · $H_2O$ , EtOH, rt, 15 min, 90% 1a, 92% 1b.

further reduced to anthranilamides 1 by hydrazine hydrate in the presence of RANEY®<sup>®</sup> nickel (Scheme 4). Both approaches allow one to synthesize amides 1 in good yields. Therefore, the selection of the synthetic method is determined by the accessibility of the starting *ortho*-substituted benzoic acids only. The obtained results are summarized in Table 1.



Scheme 4 Synthesis of 1 from furfurylamines 2 and *o*-nitrobenzoyl chlorides 5. *Reagents and conditions*: a) benzene, rt, 1.5 h; b)  $N_2H_4$ ·H<sub>2</sub>O, RANEY <sup>®</sup> Ni, EtOH, reflux, 30 min.

To the better understanding the title recyclization, we also synthesized *N*-substituted-*N*-(furfuryl)anthranilamides **8**. *N*-Alkyl derivatives **8a–c** were obtained by reaction of **6a** with the corresponding alkyl halides in the presence of sodium hydride followed by reduction of the formed adducts **7a–c** with a hydrazine hydrate/RANEY( $\mathbb{R}^{\mathbb{R}}$  nickel system (Scheme 5).

*N*-(4-Chlorophenyl)-*N*-(5-methylfurfuryl)anthranilamide **8d** was synthesized from 5-methylfurfural **9** using the sequence presented in Scheme 6.

Table 1 Synthesis of amides 6 and 1

	Products	R	$\mathbf{R}^1$	R <sup>2</sup>	<b>R</b> <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Yield of <b>6</b> , % <sup><i>a</i></sup>	Yield of <b>1</b> , % <sup><i>a</i></sup>
1	6a/1a	Me	Н	Н	Н	Н	Н	94	95
2	6c/1c	Me	Н	Н	Н	Cl	Н	91	89
3	6d/1d	Me	Н	Н	OMe	OMe	Н	84	89
4	6e/1e	Me	Н	Me	Н	Н	Н	73	75
5	6f/1f	Me	Н	OMe	Н	Н	OMe	68	89
6	6g/1g	Et	Н	Н	Н	Н	Н	82	94
7	6h/1h	t-Bu	Н	Н	Н	Н	Н	86	92
8	6i/1i	Н	Н	Н	Н	Н	Н	92	90
9	6j/1j	$p-ClC_6H_4$	Н	Н	Н	Н	Н	82	93
10	6k/1k	Me	Me	Н	Н	Н	Н	63	96
11	6l/1l	Me	Ph	Н	Н	Н	Н	90	91

" Isolated yield.



Scheme 5 Synthesis of amides 8a–c. *Reagents and conditions*: a) RHal, NaH, THF, rt, 24 h; 86% 7a (MeI), 83% 7b (EtBr), 62% 7c (BnCl); b)  $N_2H_4$ · $H_2O$ , RANEY  $\mathbb{R}^{\otimes}$  Ni, EtOH, reflux, 30 min; 82% 8a, 76% 8b, 85% 8c.

#### Recyclization of N-(furfuryl)anthranilamides

Earlier we have shown that furan derivatives containing nucleophilic centers recyclized under treatment with Brønsted acids into new heterocyclic systems.<sup>27</sup> We investigated the possibility of the related recyclization of *N*-(furfuryl)anthranilamides using the model substrate **1a**. We found that **1a** rearranged into pyrrolo[1, 2-*a*][1,4]benzodiazepine **13a** in moderate yield under heating at 60–70 °C in AcOH in the presence of conc. HCl for 4–5 h.<sup>24</sup> At room temperature this reaction proceeded much more slowly and went to completion after 24 h only but the temperature decrease influenced by-processes even more efficiently. It allowed us to obtain product **13a** in 72% yield. The structure of **13a** was assigned from <sup>1</sup>H and <sup>13</sup>C NMR spectra and unambiguously proved by single crystal X-ray data<sup>28</sup> (Fig. 1).<sup>†</sup>

To determine the scope of this reaction, we studied the recyclization of the synthesized *N*-(furfuryl)amides 1 into pyrrolo[1, 2-*a*][1,4]benzodiazepines 13 under the optimized reaction conditions (Table 2). We found that compounds 1b–d,g were transformed into the corresponding pyrrolobenzodiazepines in 65–78% yield. However, in the case of substrate 1e, which has a methyl group at the C3 atom of the anthranilic acid moiety, the yield of the target diazepine 13e was 11% only. The main product in this reaction was uncyclized diketone 14e. Only traces of pyrrolodiazepine 13f were found in the reaction mixture formed after treatment



Scheme 6 Synthesis of amide 8d. *Reagents and conditions*: a) TsOH, benzene, reflux, 2 h; b) NaBH<sub>4</sub>, EtOH, rt, 35 min, 55% over two steps; c) 5a, benzene, rt, 1.5 h, 86%; d)  $N_2H_4$ ·H<sub>2</sub>O, RANEY®<sup>®</sup> Ni, EtOH, reflux, 30 min, 72%.

8d



Fig. 1 Single-crystal X-ray structure of 13a.

of *N*-furfurylamide **1f** with aq. HCl/AcOH. Diketone **14f** was isolated in this reaction in a yield of 32%. Amide **1h** failed to form diazepine at all, diketone **14h** being the single reaction product in this case. When we used *N*-furfurylamides **1i–l** as substrates, neither pyrrolodiazepines **13** nor diketones **14** were isolated from the reaction mixtures. Products of destruction were only formed from these substrates under the studied reaction conditions.

The isolation of diketones 14 in the reactions of *N*-furfurylamides 1e,f,h allows us to suppose that these compounds are intermediates in the transformation of 1 into 13. To prove it, we investigated the reaction mixtures under the conditions



 Table 2
 Acid-catalyzed recyclization of N-(furfuryl)anthranilamides 1

of the partial conversion of 1. Indeed, we isolated diketone 14c under these conditions and assigned its structure using spectral data. Using this compound as reference, we found by TLC analysis that diketones 14 are present in the reaction mixtures for all the studied processes of diazepines 13 formation. Therefore, we can state that the first step of the title recyclization is furan ring opening leading to 14. The formed diketones react with the amine function of the anthranilic acid moiety by intramolecular Paal–Knorr reaction yielding pyrrolodiazepines 13 (Scheme 7).



Scheme 7 The possible mechanism of pyrrolodiazepine 13 formation.

This sequence of transformation (furan–diketone–pyrrole) is quite standard but usually it is realized as the stepwise procedure with isolation of the intermediate diketones.<sup>29</sup> To the best of our knowledge, there are only two examples of similar intramolecular furan into pyrrole transformations without isolation of dicarbonyl intermediates.<sup>30</sup>

We failed to isolate imines 15 from the reaction mixtures. We believe it is a result of the reversibility of the diazepine ring formation when the reactions were performed in the presence of hydrochloric acid. As a result, the lifetime of this intermediate is small enough. The formed diazepines 15 can either further cyclize with the formation of the pyrrole ring leading to 13, or can decompose back to aminodiketones 14. Indeed, when the anthranilic acid moiety has a substituent in the position ortho to the amine function (amides 1e,f), the yields of pyrrolodiazepines drop significantly. The cyclizations of 15e,f proceeded slowly than their hydrolysis, and the main products in these reactions were diketones 14e,f. Similarly, the hydrolysis of 15h to 14h is faster than its cyclization into 13h. These results can be explained by the steric effects of the substituents which can influence both kinetic and thermodynamic characteristics of the reaction. To shed more light on this problem, we performed ab initio quantum chemical calculations on 13, 15 and tetrahedral intermediates 16 (Fig. 2) at MP2/6-311G\*\* level.31 The selected method of calculation allows one to reproduce well the experimental geometry of 13a (Fig. 1). For example, according to our calculations, the pyrrole ring is tilted vs. the benzene ring by  $47.7^{\circ}$ , with the corresponding experimental value being 47.6°.28



Fig. 2 Structures optimized at MP2/6-311G\*\* level.

According to our calculations, the cyclization of 15a into 16a is a slightly exothermic process ( $\Delta E = -2.8 \text{ kJ mol}^{-1}$ ). Oppositely, the transformations of 15e into 16e and 15h into 16h are slightly endothermic (+5.5 and +0.4 kJ mol<sup>-1</sup>, respectively). The tilting angle between the pyrrole and benzene rings can be also considered as a measure of the steric effects in 16 and 13. This angle is  $28.3^{\circ}$ in the most stable conformer of 16a, 37.8° in 16e, and 59.2° in 16h. Dehydration of 16 into 13 is exothermic for all studied substrates (-17.5, -17.8 and -9.7 kJ mol<sup>-1</sup> for **16a**, **16e**, and **16h**, respectively). Therefore, it is possible to conclude that the steric effects definitely influence the stability of the intermediates 16 and the products 13 but these effects are relative small. The total energy changes in the transformations of 15 into 13 were calculated to be  $-20.3 \text{ kJ mol}^{-1}$ , -12.3 kJ mol<sup>-1</sup>, and -9.3 kJ mol<sup>-1</sup> for 13a, 13e, and 13h, respectively. It means that the obtained results cannot be explained on the basis of thermodynamic effects only. At least, the formation of 13 from 15 is exothermic and, therefore, can be realized for all studied substrates. We supposed that hydrolysis of imines 15 to aminodiketones 14 should compete with their cyclizations to 13 to a small extent only if hydrochloric acid is absent in the reaction mixture. Indeed, the treatment of diketones **14e**,**f** with glacial acetic acid for 2 h leads to **13e**,**f** in high yield (Scheme 8).



Scheme 8 Transformation of diketones 14e, f into pyrrolodiazepines 13e, f.

The moderate yields of the target pyrrolodiazepines by HCl/AcOH-catalyzed recyclizations of 1e,f are the result of the concurrent decomposition of N-furfurylamides. The presence of a substituent in the position ortho to the amine function decreases the rate of 14 into 13 cyclization. As a result, the back reaction of 14 into 1 competes efficiently with this process. But different sites of 1 can be protonated by acid. The protonation at the C5 atom of the furan ring leads to cation 17 and, after its hydrolysis, to diketone 14. The protonation of the  $NH_2$  group (formation of 18) is the preferable process but fails to give any product. And lastly, the protonation of the amide oxygen yields cation 19. This process is very important as it is accompanied by N-C bond breaking which yields anthranilamide 20 and furfuryl cation 21 (Scheme 9) and, as a result, leads to the tar formation. When we tried to perform the recyclizations of 1j–l, we isolated only anthranilamide 20a ( $R^2 =$  $R^5 = H$ ). This can be explained by the increased stability of cations 21b-d in comparison to 21a (Chart 1).

In other words, the formation of these relatively stable cations was competing efficiently with the transformation of **1**j–**1** into pyrrolobenzodiazepines but this process was not important when



Chart 1 Furfuryl cations formed from 1a-f (21a), 1j (21b), 1k (21c) and 1l (21d).

**1a–f** were treated with acid. We also failed to obtain the recyclization products for substrates **8a–d** bearing alkyl or aryl substituents at the amide nitrogen atom. The significant tar formation due to  $\alpha$ -C–N bond fragmentation leading to cation **21a** formation was found in these cases. The detailed analysis of the reaction mixture for **8b** transformation allowed one to identify *N*-ethylanthranilamide.

The intermediate **21a** is formed in the reactions of **8a–d** but not in the transformations of **1a–f**. We believe it is related to the nature of the second substituent at the amide nitrogen atom. Indeed, protonation of amide oxygen atom can be accompanied by N–C bond breaking with formation of cation **21** and amide **20** or by N deprotonation yielding hydroxyimine **22** (Scheme 9).

The last process is predominant for reactions of **1a–f**. However, this deprotonation is impossible for products of the amide oxygen protonation in **8a–d**. As a result, the intermediate decomposes into amide and  $ArCH_2^+$  cation which leads to realization of various by-processes.

This problem can be solved in a straightforward manner. *N*-Alkylpyrrolobenzodiazepines **23a**–c,e can be easily synthesized



Scheme 9 The possible acid-catalyzed transformations of *N*-(furfuryl)anthranilamides 1.

from the corresponding *NH*-analogues **13** by treatment with alkyl halides in the presence of sodium hydride. We demonstrated the efficiency of this approach using **13a** and a series of alkylating agents. The synthesized **23** were isolated in good to excellent yields (Scheme 10).



Scheme 10 Synthesis of *N*-alkylpyrrolo[1,2-*a*][1,4]benzodiazepines 23a–c,e by alkylation of compound 13a. *Reagents and conditions*: a) RX, NaH, THF, rt, 95% 23a (MeI, 6 h), 93% 23b (EtBr, 6 h); 85% 23c (BnCl, 48 h); 67% 23e (ICH<sub>2</sub>CO<sub>2</sub>Et, 24 h).

## Synthesis of pyrrolo[1,2-*a*][1,4]benzodiazepines from *N*-(furfuryl)-2-nitrobenzamides

The recyclizations of the substrates 1e,f,h-l and 8a-d were not efficient due to their protonation at the amide oxygen atom with the formation of cations 21 and their decomposition to the anthranilamides and furfuryl cations. We supposed that this protonation would be depressed if an electron releasing ortho amino group could be changed for an electron withdrawing substituent. To prove it, we treated N-(5-methylfurfuryl)-2-nitrobenzamide (6a) with HCl/AcOH under the same reaction conditions. Indeed, we isolated diketone 24a in 75% yield. Encouraged by this result, we performed similar transformations with nitrobenzamides 6e,h,k,l. All of them have substituents which prevented the efficient recyclization of the corresponding anthranilamides 1. Some quantity of 2-nitrobenzamide was formed in these reactions but we isolated nitrodiketones 24 in moderate yields too (Table 3). When a solution of 24 in AcOH was heated with Fe to reflux and then the reaction mixture kept for 1 h at room temperature, the target pyrrolobenzodiazepines 13 were formed via reduction to 14 and their one pot cyclization (Table 3).

The structure of **13h** was unambiguously proved by single crystal X-ray analysis<sup>†</sup> (Fig. 3).<sup>28</sup> The angle between the planes of the benzene and pyrrole rings in this structure is 56.6°, in good accordance with the calculated value (58.0°). The steric effect of the *tert*-butyl group is also revealed by significant elongation of some bonds in **13h** vs. **13a**. For example, the N2–C6 (using numeration on Fig. 1 and 3) bond length is 1.420 Å in **13a** but 1.431 Å in **13h**. Similar elongation was also found for N2–C12, C10–C11, C11–C12, and, especially, for the C12–C13 bond, namely C–CH<sub>3</sub> distance in **13a** is 1.486 Å and C–CMe<sub>3</sub> bond length is 1.528 Å.

This approach was found to be also efficient for the direct synthesis of N-alkylpyrrolo[1,2-a][1,4]benzodiazepines 23 from N,N-disubstituted o-nitrobenzamides 7 (Scheme 11).

#### Synthesis of other pyrrolo[1,2-a][1,4]diazepines

To determine the scope of the applicability of the proposed method, we studied the recyclization of heterocyclic analogues of N-(furfuryl)anthranilamides. We selected 1-methyl-4-

Table 3Transformation of N-(furfuryl)-2-nitrobenzamides 6 into nitrodiketones24 and then to pyrrolo[1,2-a][1,4]benzodiazepines13



<sup>a</sup> Isolated yield.



Fig. 3 Single-crystal X-ray structure of 13h.

nitropyrazole-5-carbonyl chlorides  $26^{32}$  as the starting compounds. They were transformed into the corresponding *N*-(furfuryl)amides **27** which were further reduced to 4-aminopyrazol-5-carboxamides **28**. We found that **28** recyclized smoothly into pyrazolo[3,4-*f*]pyrrolo[1,2-*a*][1,4]diazepines **29** in good yields under treatment with hydrochloric acid in AcOH (Scheme 12). The bulky *tert*-butyl substituent at the C3 atom of the pyrazole ring in **28b** has no significant effect on this transformation. This is explained by the larger distance between *ortho* substituents in five-membered pyrazole cycle in comparison with six-membered benzene ring.



Scheme 11 Synthesis of *N*-substituted pyrrolo[1,2-*a*][1,4]benzodiazepines 23 from nitrobenzamides 7. *Reagents and conditions*: a) HCl, AcOH, rt, 24 h, 70% 25a, 80% 25d; b) Fe, AcOH, heating to reflux, then rt, 1 h, 63% 23a, 77% 23d.



Scheme 12 Synthesis of pyrazolo[3,4-*f*]pyrrolo[1,2-*a*][1,4]diazepines 29. *Reagents and conditions*: a) benzene, 1.5 h, 63% 27a, 88% 27b; b)  $N_2H_4$ · $H_2O$ , RANEY®<sup>®</sup> Ni, EtOH, reflux, 30 min; 79% 28a, 87% 28b; c) HCl, AcOH, rt, 24 h, 83% 29a, 76% 29b.

Moreover, we applied the developed approach to the synthesis of a pyrrolo[1,2-a][1,4]diazepine which is not annulated to other rings. To realize this idea, we acylated 5-methylfurfurylamine (2a) with 3-(phthalimido)propionyl chloride (30). Phthalimide protecting group was then changed for the acid-labile Boc substituent using a standard two-step procedure. The treatment of the obtained carbamate 32 with HCl/AcOH yields 5-methyl-1,2,4,5-tetrahydro-3*H*-pyrrolo[1,2*a*][1,4]diazepin-3-one (**33**) (Scheme 13).

#### Conclusions

We developed a principally new approach to the synthesis of the biologically active pyrrolo[1,2-a][1,4]diazepines. Contrary to the known methods of synthesis of these compounds, diazepine and pyrrole rings are formed in *one pot* as a result of a domino reaction sequence "furan ring opening–diazepine ring closure–pyrrole ring closure". The proposed method allows one to synthesize pyrrolo[1,2-a][1,4]diazepines and their derivatives annulated to aromatic and heteroaromatic rings in good yields. Yields of pyrrolobenzodiazepines are lower if the starting compounds contain substituents hampering cyclizations due to steric effects. However, the corresponding pyrrolobenzodiazepines were synthesized in good yields by furan ring opening of *N*-(furfuryl)-2-nitrobenzamides followed by nitro group reduction and *in situ* cyclization of the formed aminodiketones.

#### Experimental

#### General procedures

NMR spectra were recorded with a Bruker DPX 300 (300 MHz for <sup>1</sup>H and 75 MHz for <sup>13</sup>C NMR) spectrometer in CDCl<sub>3</sub> or DMSO- $d_6$  at room temperature; the chemical shifts ( $\delta$ ) were measured in ppm with respect to the solvent (CDCl<sub>3</sub>: <sup>1</sup>H:  $\delta$  = 7.25 ppm, <sup>13</sup>C:  $\delta = 77.0$  ppm; DMSO- $d_6$ : <sup>1</sup>H:  $\delta = 2.50$  ppm, <sup>13</sup>C:  $\delta = 39.5$  ppm). Coupling constants (J) are given in Hz. Multiplicities of signals are described as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, dd =double doublet, dq = double quadruplet, br = broadened. IR spectra were measured as KBr plates on InfraLUM FT-02 and InfraLUM FT-801 instruments. Mass spectra were recorded on a Kratos MS-30 instrument with 70 eV electron impact ionization at 200 °C. Melting points (uncorrected) were determined in open capillaries with Electrothermal 9100 melting point apparatus. Column chromatography was performed on silica gel KSK (50-160 µm, LTD Sorbpolymer). Acyl chlorides 3, 5, and 30 were obtained by treatment of the corresponding acids with thionyl chloride according to published procedure.<sup>33</sup> Amines 2a-d,f,g were synthesized by published methods.<sup>25</sup> Other starting compounds



Scheme 13 Synthesis of pyrrolo[1,2-*a*][1,4]diazepine 33 from furfurylamine 2a and  $\beta$ -alanine derivative 30. *Reagents and conditions*: a) benzene, rt, 1.5 h, 93%; b) N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>O, EtOH, rt, 2 h; c) Boc<sub>2</sub>O, rt, 1 h, 76% over two steps; d) HCl, AcOH, rt, 8 h, 41%.

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are available commercially. All reactions were carried out using freshly distilled and dry solvents.

# General procedure A for synthesis of *N*-(furfuryl)amides 4, 6, 27, and 31

To benzene solution of furfurylamine (2) was added dropwise under stirring a solution of acyl chloride (1.1 equiv) in benzene (for *ca.* 30 min). The reaction mixture was stirred for 1 h at room temperature. Saturated NaHCO<sub>3</sub> solution (100 mL) was added, mixture was vigorously stirred for 30 min. The formed precipitate was filtered off; filtrate was extracted with benzene ( $3 \times 30$  mL). The combined organic phases were washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was evaporated under reduced pressure. Residue and precipitate were combined. The crude product was purified by flash chromatography on silica gel using the specified eluent or recrystallization from the specified solvents.

2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-N-[(5-methyl-2-furyl)methyllbenzamide (4a). Synthesized according to General procedure A from 5-methylfurfurylamine (2a) (5 g, 45 mmol; solution in 50 mL of benzene) and 2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)benzoyl chloride (3a) (14.15 g, 49.5 mmol; solution in 100 mL of benzene); eluent: CH<sub>2</sub>Cl<sub>2</sub>-petroleum ether (1:2); 66% (10.7 g); colorless needles; mp 146-147 °C (CH<sub>2</sub>Cl<sub>2</sub>-petroleum ether);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.19 (3H, s, Me), 4.38 (2H, d,  ${}^{3}J = 5.4$  Hz, CH<sub>2</sub>), 5.81 (1H, d,  ${}^{3}J = 3.0$  Hz,  $H_{Fur}$ ), 6.05 (1H, d,  ${}^{3}J = 3.0$  Hz,  $H_{Fur}$ ), 6.30 (1H, br t,  ${}^{3}J = 5.4$  Hz, NH), 7.35–7.38 (1H, m, H<sub>Ar</sub>), 7.45–7.50 (1H, m, H<sub>Ar</sub>), 7.56–7.61 (1H, m, H<sub>Ar</sub>), 7.63–7.66 (1H, m, H<sub>Ar</sub>), 7.72–7.79 (2H, m, H<sub>Pht</sub>), 7.87–7.93 (2H, m,  $H_{Pht}$ );  $\delta_{C}$  (75 MHz, CDCl<sub>3</sub>) 13.4, 36.9, 106.2, 108.3, 123.7 (2C), 128.1, 129.0, 129.8, 129.9, 131.3, 131.9 (2C), 133.9, 134.2 (2C), 148.8, 151.7, 166.4, 167.4 (2C);  $v_{max}$  (KBr)/cm<sup>-1</sup> 3346, 1711, 1665, 1524, 1381, 1299, 1111, 1083, 1017, 804, 720; *m*/*z* (EI) 360 (M<sup>+</sup>, 5%), 250 (7), 110 (100), 76 (11), 43 (8); Found: C, 70.14; H, 4.44; N, 7.80. Calc. for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 69.99; H, 4.48; N, 7.77%.

N-[(5-Methyl-2-furyl)methyl]-2-nitrobenzamide (6a). Obtained according to General procedure A from (2a) (5 g, 45 mmol; solution in 50 mL of benzene) and 2-nitrobenzoyl chloride (5a) (9.3 g, 49.5 mmol, solution in 50 mL of benzene); 94% (10.96 g); white solid; mp 117-118 °C (CH<sub>2</sub>Cl<sub>2</sub>-petroleum ether);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.21 (3H, s, Me), 4.47 (2H, d,  ${}^{3}J = 5.4$  Hz, CH<sub>2</sub>), 5.87 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Fur</sub>), 6.14 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Eur</sub>), 6.45 (1H, br t,  ${}^{3}J = 5.4$  Hz, NH), 7.43–7.46 (1H, m, H<sub>Ar</sub>), 7.48–7.54 (1H, m, H<sub>Ar</sub>), 7.57–7.63 (1H, m, H<sub>Ar</sub>), 7.95–7.98 (1H, m,  $H_{Ar}$ );  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 13.4, 37.2, 106.3, 108.7, 124.4, 128.7, 130.4, 132.5, 133.6, 146.3, 148.4, 152.0, 166.1;  $v_{\text{max}}$  (KBr)/cm<sup>-1</sup> 3281, 1640, 1543, 1523, 1353, 1297, 786, 750; m/z (EI) 242 (M<sup>+</sup>-18, 44), 169 (50), 155 (45), 150 (16), 141 (24), 134 (64), 110 (66), 104 (47), 95 (69), 76 (80), 65 (38), 51 (100), 43 (98); Found: C, 60.03; H, 4.67; N, 10.80. Calc. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C, 60.00; H, 4.65; N, 10.76%.

### General procedure B for synthesis of *N*-(furfuryl)anthranilamides 1a,b

Hydrazine hydrate (5 mL) was added to solution of 4 in ethanol (50 mL). The reaction mixture was heated until dissolution of

starting compound and stirred at room temperature until full conversion (15 min, TLC monitoring). The main part of solvent was evaporated under reduced pressure. Residue was poured into cold water (50 mL). Precipitate was filtered, washed with water, dried and recrystallized from aqueous ethanol.

**2-Amino-5-bromo-***N***-I(5-methyl-2-furyl)methyl]benzamide (1b).** Obtained according to General procedure B from **4b** (5 g, 11.4 mmol); 92% (3.25 g); white solid; mp 126–127 °C (EtOH);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.28 (3H, s, Me), 4.50 (2H, d, <sup>3</sup>*J* = 5.1 Hz, CH<sub>2</sub>), 5.54 (2H, br s, NH<sub>2</sub>), 5.91 (1H, d, <sup>3</sup>*J* = 3.3 Hz, H<sub>Fur</sub>), 6.16 (1H, d, <sup>3</sup>*J* = 3.3 Hz, H<sub>Fur</sub>), 6.23 (1H, br t, <sup>3</sup>*J* = 5.1 Hz, NH), 6.51 (1H, d, <sup>3</sup>*J* = 8.7 Hz, H<sub>Ar</sub>), 7.26 (1H, dd, <sup>3</sup>*J* = 8.7 Hz, <sup>4</sup>*J* = 2.1 Hz, H<sub>Ar</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 13.5, 36.8, 106.3, 107.5, 108.7, 117.1, 118.8, 129.6, 135.0, 147.7, 148.9, 152.2, 167.7;  $v_{\rm max}$  (KBr)/cm<sup>-1</sup> 3457, 3354, 3283, 1623, 1573, 1537, 1250, 1017, 894, 819, 787; *m*/*z* (EI) 310/308 (M<sup>+</sup>, 17/18%), 200/198 (12/12), 110 (90), 95 (100), 43 (22); Found: C, 50.64; H, 4.22; N, 9.12. Calc. for C<sub>13</sub>H<sub>13</sub>BrN<sub>2</sub>O<sub>2</sub>: C, 50.51; H, 4.24; N, 9.06%.

#### General procedure C for synthesis of amides 1

Hydrazine hydrate (1.5 mL) and RANEY  $\mathbb{R}^{\otimes}$  nickel (0.5 g) was added to a solution of amide **6** (1 g) in ethanol (20 mL); reaction mixture was refluxed until full conversion of substrate (30 min, TLC control). Nickel was filtered off. Filtrate was evaporated to volume of *ca*. 5 mL and poured into water (30 mL). The precipitate was filtered, air-dried and purified by flash chromatography on silica gel using the specified eluent or by recrystallization from the specified solvents.

**2-Amino-***N***-[(5-methyl-2-furyl)methyl]benzamide** (1a). Synthesized according to General procedure C from **6a** (1 g, 3.84 mmol); 95% (0.84 g); white solid; mp 62–63 °C (aq. EtOH);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.25 (3H, s, Me), 4.50 (2H, d,  ${}^{3}J =$ 5.4 Hz, CH<sub>2</sub>), 5.50 (2H, br s, NH<sub>2</sub>), 5.89 (1H, d,  ${}^{3}J =$  3.0 Hz, H<sub>Fur</sub>), 6.12 (1H, d,  ${}^{3}J =$  3.0 Hz, H<sub>Fur</sub>), 6.44 (1H, br t,  ${}^{3}J =$  5.4 Hz, NH), 6.56–6.62 (1H, m, H<sub>Ar</sub>), 6.63–6.66 (1H, m, H<sub>Ar</sub>), 7.14–7.20 (1H, m, H<sub>Ar</sub>), 7.29–7.32 (1H, m, H<sub>Ar</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 13.4, 36.6, 106.2, 108.3, 115.6, 116.4, 117.2, 127.2, 132.3, 148.7, 149.3, 151.9, 168.9;  $v_{\rm max}$  (KBr)/cm<sup>-1</sup> 3370, 3300, 3271, 1635, 1528, 1447, 1300, 1255, 782, 749; *m*/*z* (EI) 230 (M<sup>+</sup>, 30%), 120 (45), 110 (100), 95 (68), 92 (38), 65 (59), 43 (37); Found: C, 67.60; H, 6.24; N, 12.19. Calc. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 67.81; H, 6.13; N, 12.17%.

#### General procedure D for alkylation of N-(furfuryl)amide 6a

Sodium hydride (0.7 g, 60% dispersion in mineral oil) was added portionwise at 15 °C to a solution of **6a** (3 g, 11.5 mmol) in THF (60 mL). Reaction mixture was stirred for 10 min, then alkyl halide (23 mmol) was added. Mixture was stirred for 1 d (TLC control), poured carefully into water (150 mL) and kept overnight for THF evaporation. Product was extracted with ethyl acetate ( $5 \times 30$  mL, TLC control). The combined organic phases were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>; solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using the specified eluent and recrystallized from the specified solvents.

*N*-Methyl-*N*-[(5-methyl-2-furyl)methyl]-2-nitrobenzamide (7a). Synthesized according to General procedure D using methyl iodide (3.26 g, 23 mmol); eluent: benzene-petroleum ether (1:1). Product was isolated as white solid by recrystallization from petroleum ether below 0 °C; 86% (2.72 g); mp 73-74 °C;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) (two rotamers) 2.24/2.29 (3H, s, Me), 2.77/3.11 (3H, s, NMe), 4.17/4.72 (2H, br s/s, CH<sub>2</sub>), 5.86/5.94  $(1H, d, {}^{3}J = 3.0 \text{ Hz}, H_{\text{Eur}}), 6.01/6.27 (1H, d, {}^{3}J = 3.0 \text{ Hz}, H_{\text{Eur}}),$ 7.39-7.42/7.51-7.54 (1H, m, H<sub>Ar</sub>), 7.52-7.58/7.54-7.60 (1H, m,  $H_{Ar}$ ), 7.67–7.73/7.68–7.74 (1H, m,  $H_{Ar}$ ), 8.17–8.20/8.20–8.23 (1H, m, H<sub>Ar</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) (two rotamers) 13.5/13.6, 32.3/35.6, 43.2/47.7, 106.2/106.4, 109.7/109.9, 124.6/124.7, 128.2/128.7, 129.7/129.8, 132.9/133, 134.3/134.5, 144.9/145.3, 147.0/147.9, 152.2/152.7, 167.7/167.7;  $v_{\text{max}}$  (KBr)/cm<sup>-1</sup> 1648, 1564, 1520, 1488, 1424, 1400, 1348, 1284, 1224, 1028, 800; m/z (EI) 274 (M<sup>+</sup>, 15%), 257 (22), 150 (10), 134 (15), 123 (82), 104 (14), 95 (100), 76 (26), 65 (13), 51 (39), 43 (46); Found: C, 61.68; H, 5.26; N, 10.26. Calc. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 61.31; H, 5.14; N, 10.21%.

**2-Amino-N-methyl-N-[(5-methyl-2-furyl)methyl]benzamide (8a).** Synthesized according to General procedure C from **7a** (1 g, 3.65 mmol); eluent: CH<sub>2</sub>Cl<sub>2</sub>-petroleum ether (1 : 1). Aniline **8a** was isolated as light-yellow oil in 82% yield (0.73 g).  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.25 (3H, s, Me), 2.97 (3H, s, N*Me*), 4.33 (2H, s, CH<sub>2</sub>), 4.50 (2H, br s, NH<sub>2</sub>), 5.88 (1H, d, <sup>3</sup>*J* = 3.0 Hz, H<sub>Fur</sub>), 6.10 (1H, d, <sup>3</sup>*J* = 3.0 Hz, H<sub>Fur</sub>), 6.65–6.71 (2H, m, H<sub>Ar</sub>), 7.09–7.15 (2H, m, H<sub>Ar</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>, 40 °C) 13.5, 32.9/36.4, 43.6/47.9, 106.2, 109.3, 116.5, 117.3, 120.0, 127.9, 130.5, 145.4, 148.4, 152.1, 171.1; *v*<sub>max</sub> (KBr)/cm<sup>-1</sup> 3456, 3352, 1624, 1592, 1496, 1456, 1400, 1264, 1220, 1064, 1020, 784, 756; *m/z* (EI) 244 (M<sup>+</sup>, 10%), 124 (100), 120 (39), 95 (80), 92 (25), 65 (29), 43 (20); Found: C, 68.87; H, 6.72; N, 11.28. Calc. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: C, 68.83; H, 6.60; N, 11.47%.

#### 4-Chloro-N-[(5-methyl-2-furyl)methyl]aniline (12)

A solution of 4-chloroaniline (10) (11.5 g, 90 mmol), 5-methylfurfural (9) (9.91 g, 90 mmol) and TsOH (0.4 g) in benzene (90 mL) was refluxed with a Dean–Stark trap for 2 h. Solvent was evaporated under reduced pressure. The formed imine 11 was dissolved in ethanol (100 mL). Sodium borohydride (2 g) was added to this solution portionwise for 5 min. Reaction mixture was stirred at room temperature for 30 min (TLC control), poured into cold water (100 mL) and neutralized with aqueous acetic acid (1:1) to pH ~ 7. Product was extracted with ethyl acetate (3 × 50 mL); the combined organic fractions were dried over Na<sub>2</sub>SO<sub>4</sub>. Solvent was removed using rotary evaporator. Residue was distilled under vacuum. Product 12 was obtained as lightyellow oil (11 g, 55%); bp 205–210 °C/10 Torr. It was used for further transformations without additional purification.

#### *N*-(4-Chlorophenyl)-*N*-[(5-methyl-2-furyl)methyl]-2nitrobenzamide (7d)

Solution of 2-nitrobenzoyl chloride (**5a**) (2.05 g, 11 mmol) in 30 mL of benzene was added dropwise for 30 min to benzene solution (50 mL) of furfurylaniline **12** (2.22 g, 10 mmol) under stirring. The reaction mixture was stirred for 1 h at room temperature. Saturated NaHCO<sub>3</sub> solution (100 mL) was added, mixture was vigorously stirred for 30 min. Organic phase was separated, aqueous phase was extracted with benzene ( $3 \times 30$  mL). The combined organic phases were washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was evaporated under reduced pressure. Residue was

dissolved in benzene–petroleum ether (1:1) mixture and filtered through pad of silica gel. Solvent was evaporated under reduced pressure. The obtained product (3.2 g, 86%) was used for further transformations without additional purification.

## General procedure E for acid-catalyzed recyclization of amides 1 into pyrrolo[1,2-*a*][1,4]benzodiazepine-6-ones 13

Mixture of amide 1 (1 g), glacial acetic acid (20 mL) and conc. HCl (3 mL) was stirred at room temperature for 24 h (TLC control). Then reaction mixture was poured into water (100 mL) and neutralized to pH ~ 7 with NaHCO<sub>3</sub>. The formed precipitate was filtered, washed with water and air-dried. Residue was purified by flash chromatography on silica gel using the specified eluent and crystallized from the specified solvents.

**1-Methyl-4,5-dihydro-6***H***-pyrrolo[1,2-***a***][1,4]benzodiazepin-6one (13a). Synthesized according to General procedure E from 1a (1 g, 4.34 mmol); eluent: benzene; 72% (0.66 g); white solid; mp 235–236 °C (benzene–petroleum ether); \delta\_{\rm H} (300 MHz, CDCl<sub>3</sub>) 2.30 (3H, s, Me), 4.09 (2H, d, <sup>3</sup>***J* **= 6.0 Hz, CH<sub>2</sub>), 5.98 (1H, d, <sup>3</sup>***J* **= 3.3 Hz, H<sub>Pyr</sub>), 6.01 (1H, d, <sup>3</sup>***J* **= 3.3 Hz, H<sub>Pyr</sub>), 7.25–7.28 (1H, m, H<sub>Ar</sub>), 7.35–7.41 (1H, m, H<sub>Ar</sub>), 7.52–7.57 (1H, m, H<sub>Ar</sub>), 7.92 (1H, br t, <sup>3</sup>***J* **= 6.0 Hz, NH), 7.93–7.97 (1H, m, H<sub>Ar</sub>); \delta\_{\rm C} (75 MHz, CDCl<sub>3</sub>) 14.0, 38.0, 104.9, 109.5, 124.9, 126.2, 129.4 (2C), 131.2, 131.4, 132.7, 135.8, 170.7;** *v***<sub>max</sub> (KBr)/cm<sup>-1</sup> 3260, 1656, 1628, 1584, 1492, 1464, 1444, 1408, 1336, 1208, 796, 764;** *m/z* **(EI) 212 (M<sup>+</sup>, 100%), 197 (69), 183 (31), 168 (36), 154 (48), 77 (24), 63 (16), 51 (37); Found: C, 73.52; H, 5.45; N, 13.19. Calc. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O: C, 73.57; H, 5.70; N, 13.20%.** 

#### Cyclization of aminodiketones 14 into pyrrolo[1,2*a*][1,4]benzodiazepine-6-ones 13

7,10-Dimethoxy-1-methyl-4,5-dihydro-6H-pyrrolo[1,2-a][1,4]-(13f). 2-Amino-3,6-dimethoxy-N-(2,5benzodiazepin-6-one dioxohexyl)benzamide (14f) (0.2 g, 0.65 mmol) was dissolved in glacial acetic acid (5 mL) and stirred at room temperature for 2 h (TLC control). Then reaction mixture was poured into water (20 mL) and neutralized to pH ~ 7 with NaHCO<sub>3</sub>. The formed precipitate was filtered, washed with water and air-dried. The residue was purified by flash chromatography on silica gel using benzene-petroleum ether (1:1) as eluent. Product 13f was isolated as a beige solid in 62% yield (0.11 g). Mp 166-167 °C (ethyl acetate-petroleum ether);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.12 (3H, s, Me), 3.73 (3H, s, OMe), 3.89 (3H, s, OMe), 3.93 (1H, dd,  ${}^{3}J = 6.3 \text{ Hz}, {}^{2}J = 15.9 \text{ Hz}, \text{CH}_{2}, 4.07 (1\text{H}, \text{dd}, {}^{3}J = 6.3 \text{ Hz}, {}^{2}J =$ 15.9 Hz, CH<sub>2</sub>), 5.89 (1H, d,  ${}^{3}J = 3.3$  Hz, H<sub>Pyr</sub>), 6.01 (1H, d,  ${}^{3}J =$ 3.3 Hz, H<sub>Pvr</sub>), 6.40 (1H, br t,  ${}^{3}J = 6.3$  Hz, NH), 6.94 (1H, d,  ${}^{3}J =$ 9.3 Hz, H<sub>Ar</sub>), 7.03 (1H, d,  ${}^{3}J = 9.3$  Hz, H<sub>Ar</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 13.0, 38.5, 55.9, 56.5, 105.4, 107.1, 110.8, 114.0, 121.1, 125.9, 132.4, 133.1, 146.8, 151.3, 167.9;  $v_{\text{max}}$  (KBr)/cm<sup>-1</sup> 3229, 1647, 1519, 1490, 1445, 1265, 1114, 1054, 1004, 796, 751; m/z (EI) 272 (M<sup>+</sup>, 100%), 257 (37), 242 (37), 228 (44), 213 (36), 199 (27), 170 (12), 154 (11), 45 (14); Found: C, 66.29; H, 6.05; N, 10.19. Calc. for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C, 66.16; H, 5.92; N, 10.29%.

#### General procedure F for alkylation of 13a

Sodium hydride (0.56 g, 60% dispersion in mineral oil) was added portionwise at 15 °C to a solution of **13a** (2 g, 9.42 mmol) in

THF (40 mL). Reaction mixture was stirred for 10 min, then alkyl halide (18.84 mmol) was added. Mixture was stirred until full conversion of substrate (6–48 h, TLC control), poured carefully into water (100 mL) and kept overnight for THF evaporation. The formed precipitate was filtered off, air-dried and purified by flash chromatography on silica gel using the specified eluent and recrystallized from the specified solvents.

**1,5-Dimethyl-4,5-dihydro-6***H***-pyrrolo[1,2-***a***][1,4]benzodiazepin-<b>6-one (23a).** Synthesized according to General procedure F using methyl iodide (2.67 g, 18.84 mmol); 6 h; eluent: ethyl acetate– petroleum ether (1:1), 95% (2.02 g); colorless plates; mp 156– 157 °C (ethyl acetate–petroleum ether);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.31 (3H, s, Me), 3.13 (3H, s, NMe), 3.92 (1H, d, <sup>2</sup>*J* = 15.6 Hz, CH<sub>2</sub>), 4.32 (1H, d, <sup>2</sup>*J* = 15.6 Hz, CH<sub>2</sub>), 6.01 (1H, d, <sup>3</sup>*J* = 3.3 Hz, H<sub>Pyr</sub>), 6.07 (1H, d, <sup>3</sup>*J* = 3.3 Hz, H<sub>Pyr</sub>), 7.24–7.27 (1H, m, H<sub>Ar</sub>), 7.34– 7.39 (1H, m, H<sub>Ar</sub>), 7.48–7.54 (1H, m, H<sub>Ar</sub>), 7.90–7.94 (1H, m, H<sub>Ar</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 13.9, 34.6, 46.0, 105.1, 109.2, 124.2, 126.1, 129.3, 130.6, 130.8, 131.2, 135.1(2C), 167.7;  $v_{\rm max}$  (KBr)/cm<sup>-1</sup> 1628, 1520, 1488, 1456, 1408, 1392, 1336, 1232, 1148, 784, 760, 712; *m*/*z* (EI) 226 (M<sup>+</sup>, 96%), 211 (100), 197 (10), 184 (25), 168 (36), 154 (52), 99 (13), 84 (15), 77 (21), 51 (26), 42 (43); Found: C, 74.32; H, 6.41; N, 12.33. Calc. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O: C, 74.31; H, 6.24; N, 12.38%.

### General procedure G for furan ring opening in *N*-(furfuryl)-2-nitrobenzamides 6

Mixture of *N*-(furfuryl)-2-nitrobenzamide **6** (1 g), glacial acetic acid (20 mL) and conc. HCl (3 mL) was stirred at room temperature until full conversion of starting compound (24 h, TLC control). Then reaction mixture was poured into water (100 mL) and neutralized to pH ~ 7 with NaHCO<sub>3</sub>. The formed precipitate was filtered off, washed with water and air-dried. If product was not precipitated, it was extracted with ethyl acetate (4×30 mL), the combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated. In both cases residue was purified by flash chromatography on silica gel using the specified eluent. Solvent was evaporated under reduced pressure to 1/3 of the initial volume. Mixture was kept until crystallization of product.

*N*-(2,5-Dioxohexyl)-2-nitrobenzamide (24a). Synthesized according to General procedure G from **6a** (1 g, 3.84 mmol); eluent: ethyl acetate–petroleum ether (1 : 1); 75% (0.8 g); colorless needles; mp 119–120 °C (ethyl acetate–petroleum ether);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.18 (3H, s, Me), 2.71–2.75 (2H, m, CH<sub>2</sub>), 2.81–2.85 (2H, m, CH<sub>2</sub>), 4.43 (2H, d, <sup>3</sup>*J* = 4.5 Hz, CH<sub>2</sub>), 6.64 (1H, br t, <sup>3</sup>*J* = 4.5 Hz, NH), 7.53–7.61 (2H, m, H<sub>Ar</sub>), 7.65–7.70 (1H, m, H<sub>Ar</sub>), 8.04–8.07 (1H, m, H<sub>Ar</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 29.6, 33.5, 36.9, 49.5, 124.5, 128.7, 130.6, 132.2, 133.7, 146.4, 166.3, 203.8, 206.8; *v*<sub>max</sub> (KBr)/cm<sup>-1</sup> 3276, 1732, 1712, 1648, 1520, 1412, 1364, 1312, 1240, 856, 792, 716; *m*/*z* (EI) 248 (M<sup>+</sup>–30, 4%), 162 (22), 150 (100), 134 (40), 120 (94), 104 (66), 99 (85), 92 (54), 76 (46), 65 (25), 51 (93), 43 (32); Found: C, 56.26; H, 5.13; N, 10.19. Calc. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>: C, 56.11; H, 5.07; N, 10.07%.

# General procedure H for synthesis of pyrrolo[1,2-*a*][1,4]benzodiazepine-6-ones 13 from nitrodiketones 24

Iron powder (3 g) was added to solution of nitrodiketone 24(1 g) in glacial acetic acid (20 mL). Reaction mixture was heated to reflux and then stirred at room temperature for 1 h (TLC control). Then

mixture was poured into cold water (100 mL) and neutralized to pH ~ 7 with NaHCO<sub>3</sub>. The formed precipitate was filtered off and carefully washed with hot ethyl acetate (5 × 30 mL). The combined organic fractions were dried over Na<sub>2</sub>SO<sub>4</sub>. Solvent was evaporated under reduced pressure. Residue was purified by flash chromatography on silica gel using the specified eluent and crystallized from the specified solvents.

**1,4-Dimethyl-4,5-dihydro-6***H*-**pyrrolo**[**1,2**-*a*][**1,4**]**benzodiazepin-6-one (13k).** Synthesized according to General procedure H from (**24k**) (1 g, 3.42 mmol); eluent: ethyl acetate–petroleum ether (1 : 2); colorless prisms; 81% (0.62 g); mp 201–202 °C (ethyl acetate–petroleum ether);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 1.63 (3H, d,  ${}^{3}J$  = 6.9 Hz, CH*Me*), 2.28 (3H, s, Me), 4.31 (1H, dq,  ${}^{3}J$  = 6.0 Hz,  ${}^{3}J$  = 6.9 Hz, *CHMe*), 5.99 (1H, d,  ${}^{3}J$  = 6.0 Hz, NH), 7.24–7.27 (1H, m, H<sub>Ar</sub>), 7.35–7.41 (1H, m, H<sub>Ar</sub>), 7.51–7.57 (1H, m, H<sub>Ar</sub>), 7.93–7.96 (1H, m, H<sub>Ar</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 13.9, 15.7, 43.8, 102.1, 109.2, 125.0, 126.2, 129.4, 129.9, 130.9, 131.2, 135.7, 137.6, 169.6;  $v_{\rm max}$  (KBr)/cm<sup>-1</sup> 3160, 1648, 1604, 1520, 1488, 1460, 1404, 1320, 1288, 1160, 772, 704; *m*/*z* (EI) 226 (M<sup>+</sup>, 67%), 211 (100), 184 (57), 167 (18), 77 (22), 43 (50); Found: C, 74.48; H, 6.59; N, 12.22. Calc. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O: C, 74.31; H, 6.24; N, 12.38%.

**1-Methyl-***N*-**[(5-methyl-2-furyl)methyl]-4-nitro-**1*H*-**pyrazole-5carboxamide (27a).** Synthesized according to General procedure A from **2a** (2 g, 18 mmol; solution in 30 mL of benzene) and 1-methyl-4-nitro-1*H*-pyrazole-5-carbonyl chloride (**26a**) (3.76 g, 19.8 mmol; solution in 30 mL of benzene); eluent: CH<sub>2</sub>Cl<sub>2</sub>petroleum ether (1 : 1); 63% (3.02 g); beige plates; mp 109–110 °C (CCl<sub>4</sub>);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.24 (3H, s, Me), 4.11 (3H, s, Me), 4.55 (2H, d,  ${}^{3}J = 5.4$  Hz, CH<sub>2</sub>), 5.88 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Fur</sub>), 6.17 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Fur</sub>), 8.05 (1H, s, H<sub>Het</sub>), 8.22 (1H, br t,  ${}^{3}J = 5.4$  Hz, NH);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 13.5, 37.0, 41.3, 106.3, 109.0, 132.2, 133.1, 136.3, 147.7, 152.4, 156.5;  $v_{\rm max}$  (KBr)/cm<sup>-1</sup> 3296, 1640, 1572, 1564, 1532, 1508, 1468, 1396, 1392, 1316, 1192, 828, 796; *m*/*z* (EI) 246 (M<sup>+</sup>–18, 30%), 136 (82), 108 (25), 95 (52), 83 (46), 67 (39), 53 (50), 43 (100); Found: C, 49.71; H, 4.50; N, 21.08. Calc. for C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub>: C, 50.00; H, 4.58; N, 21.20%.

**4-Amino-1-methyl-***N***-[(5-methyl-2-furyl)methyl]**-1*H***-pyrazole-5-carboxamide (28a).** Synthesized according to General procedure C from **27a** (1 g, 3.79 mmol); 79% (0.7 g); colorless needles; mp 101–102 °C (aq. EtOH);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.24 (3H, s, Me), 2.92 (2H, br s, NH<sub>2</sub>), 4.12 (3H, s, Me), 4.49 (2H, d,  ${}^{3}J = 5.7$  Hz, CH<sub>2</sub>), 5.88 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Fur</sub>), 6.11 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Fur</sub>), 7.17 (1H, s, H<sub>Hel</sub>), 8.55 (1H, br t,  ${}^{3}J = 5.7$  Hz, NH);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 13.5, 35.8, 40.2, 106.2, 108.1, 127.0, 127.1, 133.1, 149.4, 151.9, 159.9;  $v_{\rm max}$  (KBr)/cm<sup>-1</sup> 3348, 3280, 1652, 1640, 1616, 1568, 1548, 1424, 1356, 1312, 1292, 1204, 1024, 980, 912, 812; *m*/*z* (EI) 234 (M<sup>+</sup>, 17%), 124 (11), 110 (52), 95 (100), 69 (10), 53 (11), 42 (36); Found: C, 56.43; H, 6.16; N, 24.03. Calc. for C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>: C, 56.40; H, 6.02; N, 23.92%.

**3,9 - Dimethyl-5,6 - dihydropyrazolo**[**3,4**-*f*]**pyrrolo**[**1,2**-*a*][**1,4**]**diazepin-4(3H)-one (29a).** Synthesized according to General procedure E from **28a** (1 g, 4.27 mmol); eluent: benzene; 83% (0.77 g); white solid; mp 179–180 °C (benzene–petroleum ether);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.37 (3H, s, Me), 4.16 (3H, s, Me), 4.17 (2H, d, <sup>3</sup>J = 6.0 Hz, CH<sub>2</sub>), 5.96–5.99 (2H, m, H<sub>Pyr</sub>), 7.24 (1H, br t, <sup>3</sup>J = 6.0 Hz, NH), 7.60 (1H, s, H<sub>Het</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 13.9, 38.2, 39.6, 105.7, 108.6, 123.8, 126.5, 129.0, 129.4, 129.9, 162.5;  $v_{max}$  (KBr)/cm<sup>-1</sup> 3200, 1656, 1564, 1528, 1432, 1412, 1392, 1340, 1328, 1208, 788, 748, 692; *m*/*z* (EI) 216 (M<sup>+</sup>, 100%), 201 (20), 187 (25), 172 (10), 109 (11), 93 (11), 77 (15), 65 (16), 52 (23), 42 (24); Found: C, 61.44; H, 5.82; N, 25.99. Calc. for C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O: C, 61.10; H, 5.59; N, 25.91%.

3-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-vl)-N-I(5-methyl-2-furyl)methylpropanamide (31). Obtained according to General procedure A from 2a (5 g, 45.05 mmol; solution in 50 mL 3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2benzene) and of yl)propanoyl chloride (30) (11.77 g, 49.56 mmol, solution in 50 mL of benzene); eluent: ethyl acetate-petroleum ether (1:1). Compound 31 was isolated as colorless needles in 93% yield (13.07 g). Mp 176–177 °C (EtOH);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.20 (3H, s, Me), 2.60-2.65 (2H, m, CH<sub>2</sub>), 3.98-4.02 (2H, m, CH<sub>2</sub>), 4.33 (2H, d,  ${}^{3}J = 5.4$  Hz, CH<sub>2</sub>), 5.83 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Fur</sub>), 5.95 (1H, br t,  ${}^{3}J = 5.4$  Hz, NH), 6.05 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Fur</sub>), 7.66–7.72 (2H, m,  $H_{Pht}$ ), 7.78–7.85 (2H, m,  $H_{Pht}$ );  $\delta_{C}$  (75 MHz, CDCl<sub>3</sub>) 13.4, 34.2, 34.6, 36.5, 106.2, 108.3, 123.2 (2C), 131.9, 133.9 (2C), 149.0, 151.8, 168.0, 169.2 (2C);  $v_{\text{max}}$  (KBr)/cm<sup>-1</sup> 3416, 1720, 1647, 1026, 998, 866, 803, 717; m/z (EI) 312 (M<sup>+</sup>, 42%), 160 (34), 110 (100), 95 (16), 76 (12), 55 (10), 43 (18); Found: C, 65.39; H, 5.30; N, 8.94. Calc. for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 65.38; H, 5.16; N. 8.97%.

3-(tert-Butoxycarbonylamino)-N-[(5-methyl-2-furyl)methyl]propanamide (32). Hydrazine hydrate (10 mL) was added to a solution of compound 31 (10 g, 32.05 mmol) in ethanol (20 mL). Reaction mixture was stirred at room temperature for 2 h (TLC control). The formed precipitate was filtered, washed with CHCl<sub>3</sub>  $(3 \times 20 \text{ mL})$ ; filtrate was evaporated under reduced pressure. The formed residue was treated with Boc<sub>2</sub>O (8 g) at room temperature for 1 h. Then water (50 mL) was added to reaction mixture, precipitate was filtered off, washed with water and air-dried. The residue was purified by flash chromatography on silica gel using CH<sub>2</sub>Cl<sub>2</sub>—petroleum ether (1:1) as eluent. Product was crystallized as white solid (6.83 g, 76%). Mp 89—90 °C (petroleum ether);  $\delta_{\rm H}$ (300 MHz, CDCl<sub>3</sub>) 1.40 (9H, s, t-Bu), 2.24 (3H, s, Me), 2.37–2.41  $(2H, m, CH_2), 3.35-3.41 (2H, m, CH_2), 4.34 (2H, d, {}^{3}J = 5.4 Hz,$ CH<sub>2</sub>), 5.18 (1H, br s, NH), 5.86 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Fur</sub>), 6.03 (1H, br s, NH), 6.07 (1H, d,  ${}^{3}J = 3.0$  Hz, H<sub>Fur</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 13.5, 28.3 (3C), 36.0, 36.5 (2C), 79.2, 106.2, 108.3, 149.1, 151.9, 156.0, 171.1;  $v_{\text{max}}$  (KBr)/cm<sup>-1</sup> 3344, 3318, 1685, 1633, 1530, 1452, 1366, 1325, 1283, 1253, 1231, 1174, 1023, 786; m/z (EI) 282 (M<sup>+</sup>, 16%), 227 (24), 226 (100), 208 (42), 182 (66), 152 (24), 137 (21), 122 (25), 110 (55), 95 (51), 70 (21), 57 (46), 42 (26); Found: C, 59.70; H, 7.68; N, 9.78. Calc. for C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C, 59.56; H, 7.85; N, 9.92%.

**7-Methyl-1,2,4,5-tetrahydro-3***H***-pyrrolo[1,2-***a***]<b>[1,4]diazepin-3-one (33).** A mixture of **32** (1 g, 3.55 mmol), glacial acetic acid (20 mL) and conc. HCl (3 mL) was stirred at room temperature for 8 h. Reaction mixture was poured into water (100 mL) and neutralized to pH ~ 7 with NaHCO<sub>3</sub>. The formed solution was heated to reflux and then kept at room temperature overnight. The precipitate was filtered and air-dried. The residue was purified by flash chromatography on silica gel using benzene–petroleum ether (1:1) as eluent. Solvent was evaporated under reduced pressure. Residue was recrystallized from acetone–petroleum ether mixture.

Pyrrolodiazepine **33** was obtained as white solid (0.24 g, 41%). Mp 194–195 °C;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 2.19 (3H, s, Me), 2.90–2.94 (2H, m, CH<sub>2</sub>), 4.00–4.05 (2H, m, CH<sub>2</sub>), 4.31 (2H, d,  ${}^{3}J = 5.7$  Hz, CH<sub>2</sub>), 5.79 (1H, d,  ${}^{3}J = 3.3$  Hz, H<sub>Pyr</sub>), 5.85 (1H, d,  ${}^{3}J = 3.3$  Hz, H<sub>Pyr</sub>), 7.16 (1H, br t,  ${}^{3}J = 5.7$  Hz, NH);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 12.2, 34.1, 39.3, 40.9, 105.3, 105.8, 126.9, 129.9, 174.3;  $v_{\rm max}$  (KBr)/cm<sup>-1</sup> 3200, 1664, 1508, 1476, 1440, 1424, 1388, 1348, 1312, 1248, 1200, 1172, 1100, 776; *m*/*z* (EI) 164 (M<sup>+</sup>, 60%), 162 (51), 149 (39), 136 (30), 120 (67), 109 (100), 106 (90), 95 (42), 93 (48), 77 (47), 66 (41), 59 (29), 55 (66), 42 (46); Found: C, 65.67; H, 7.30; N, 17.06. Calc. for C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>O: C, 65.83; H, 7.37; N, 17.06%.

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