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_2-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.[1] 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.[2,3] 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[4–6] being potent sedative,[6–8] anticonvulsant,[7,8] myorelaxant,[8,9] and psychotropic[9–11] agents. Moreover, pyrrolo[1,2-*a*][1,4]benzodiazepine derivatives showed antiinflammatory,[6] analgesic,[11,12] and fungicidal[13] 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),[7,11,13–15] 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*).[17] Not only α-aminoalkyl group but also imines (methods *d* and *e*),[18] oximes (method *f*)[18c,19] and amides[20] 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*),[8,21] this process has been also realized under conditions of four-component Ugi reaction (method *h*).[22] 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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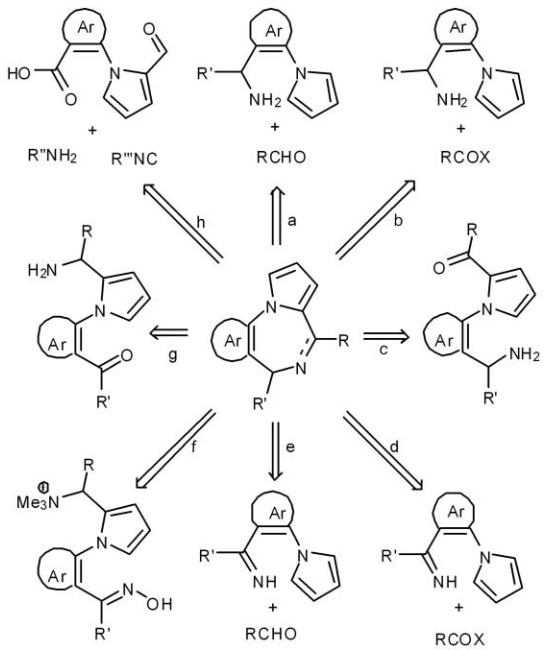
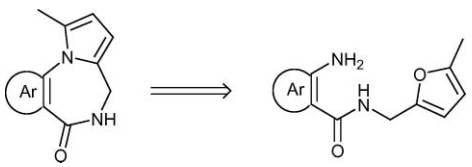


Scheme 1 The main methods of pyrrolo[1,2-*a*][1,4]benzodiazepine unit synthesis.

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).[24] 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 α-carbon atom. Herein, we describe the results of this investigation in detail.



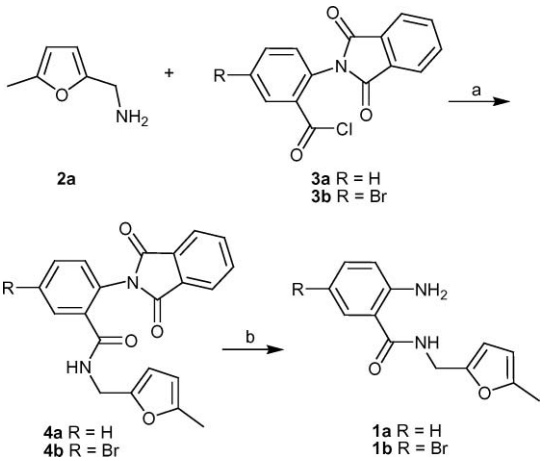
Scheme 2 Synthesis of pyrrolo[1,2-*a*][1,4]benzodiazepines *via* *N*-(furfuryl)anthranilamide recyclizations.

Results and discussion

Synthesis of *N*-(furfuryl)anthranilamides

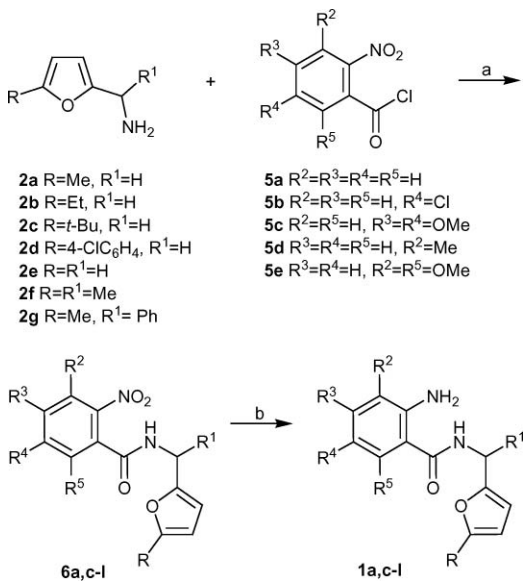
The proposed method for the pyrrolo[1,2-*a*][1,4]benzodiazepine synthesis consists of acid-catalyzed recyclization of *N*-(furfuryl)-anthranilamides **1**. These substrates were synthesized from furfurylamines **2**[25] by two procedures. The first one is based on the transformation of anthranilic acid 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[26] (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) $N_2H_4 \cdot H_2O$, EtOH, rt, 15 min, 90% **1a**, 92% **1b**.

further reduced to anthranilamides **1** by hydrazine hydrate in the presence of RANEY®® 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) $N_2H_4 \cdot H_2O$, RANEY®® Ni, EtOH, reflux, 30 min.

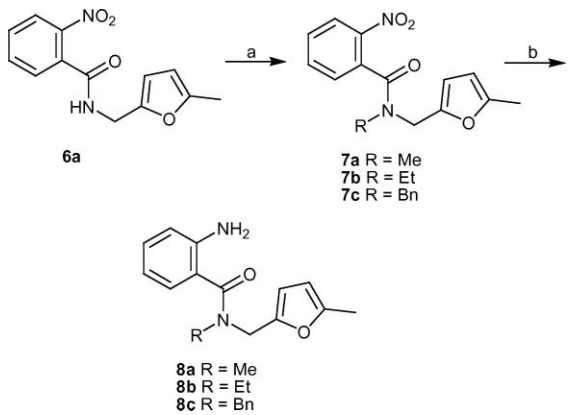
To the better understanding the title recyclization, we also synthesized *N*-substituted-*N*-(furfuryl)anthranilamides **8**. *N*-Alkyl derivatives **8a–c** were obtained by reaction of **6a** with the corresponding alkyl halides in the presence of sodium hydride followed by reduction of the formed adducts **7a–c** with a hydrazine hydrate/RANEY®® 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	R^1	R^2	R^3	R^4	R^5	Yield of **6**, %[a]	Yield of **1**, %[a]
1	**6a/1a**	Me	H	H	H	H	H	94	95
2	**6c/1c**	Me	H	H	H	Cl	H	91	89
3	**6d/1d**	Me	H	H	OMe	OMe	H	84	89
4	**6e/1e**	Me	H	Me	H	H	H	73	75
5	**6f/1f**	Me	H	OMe	H	H	OMe	68	89
6	**6g/1g**	Et	H	H	H	H	H	82	94
7	**6h/1h**	*t*-Bu	H	H	H	H	H	86	92
8	**6i/1i**	H	H	H	H	H	H	92	90
9	**6j/1j**	*p*-ClC_6H_4	H	H	H	H	H	82	93
10	**6k/1k**	Me	Me	H	H	H	H	63	96
11	**6l/1l**	Me	Ph	H	H	H	H	90	91

[a] Isolated yield.

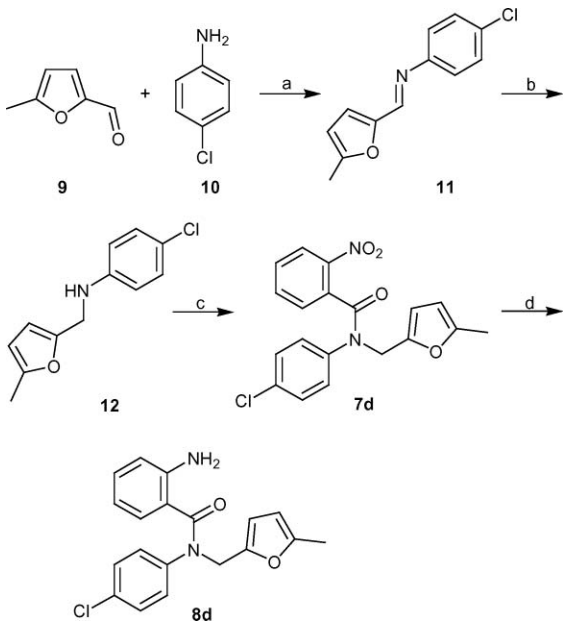


Scheme 5 Synthesis of amides **8a–c**. *Reagents and conditions*: a) RHal, NaH, THF, rt, 24 h; 86% **7a** (MeI), 83% **7b** (EtBr), 62% **7c** (BnCl); b) $N_2H_4{\cdot}H_2O$, RANEY®® Ni, EtOH, reflux, 30 min; 82% **8a**, 76% **8b**, 85% **8c**.

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.[27] 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.[24] 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 ^1H and ^{13}C NMR spectra and unambiguously proved by single crystal X-ray data[28] (Fig. 1).†

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) $NaBH_4$, EtOH, rt, 35 min, 55% over two steps; c) **5a**, benzene, rt, 1.5 h, 86%; d) $N_2H_4{\cdot}H_2O$, RANEY®® Ni, EtOH, reflux, 30 min, 72%.

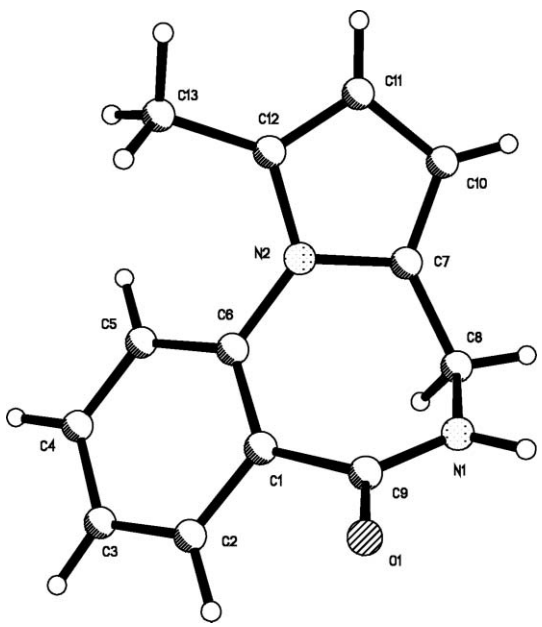
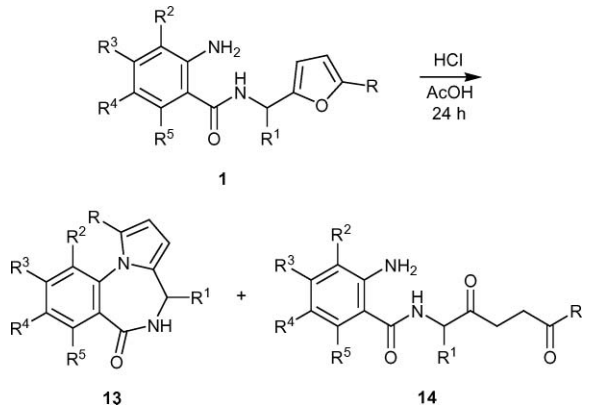


Fig. 1 Single-crystal X-ray structure of **13a**.

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

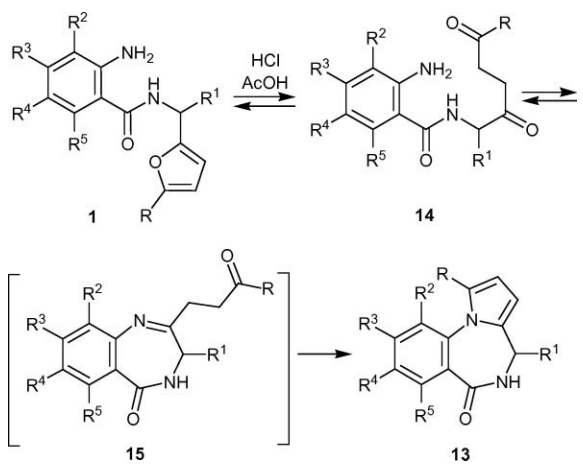
Table 2 Acid-catalyzed recyclization of *N*-(furfuryl)anthranilamides **1** into pyrrolo[1,2-*a*][1,4]benzodiazepines **13**



	Substrate	R	R^1	R^2	R^3	R^4	R^5	Yield of **13**, %[a]	Yield of **14**, %[a]
1	**1a**	Me	H	H	H	H	H	72	—
2	**1b**	Me	H	H	H	Br	H	65	—
3	**1c**	Me	H	H	H	Cl	H	75	—
4	**1d**	Me	H	H	OMe	OMe	H	78	—
5	**1e**	Me	H	Me	H	H	H	11	20
6	**1f**	Me	H	OMe	H	H	OMe	*traces*	32
7	**1g**	Et	H	H	H	H	H	70	—
8	**1h**	*t*-Bu	H	H	H	H	H	—	57
9	**1i**	H	H	H	H	H	H	—	—
10	**1j**	*p*-ClC_6H_4	H	H	H	H	H	—	—
11	**1k**	Me	Me	H	H	H	H	—	—
12	**1l**	Me	Ph	H	H	H	H	—	—

[a] Isolated yield.

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.[29] To the best of our knowledge, there are only two examples of similar intramolecular furan into pyrrole transformations without isolation of dicarbonyl intermediates.[30]

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°, with the corresponding experimental value being 47.6°.[28]

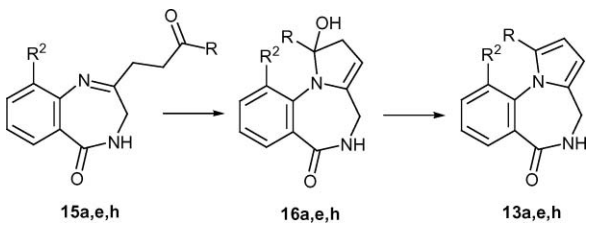
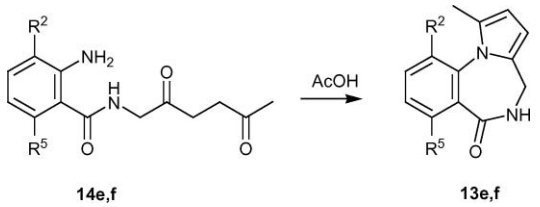


Fig. 2 Structures optimized at MP2/6-311G** level.

According to our calculations, the cyclization of **15a** into **16a** is a slightly exothermic process ($\Delta E = -2.8$ kJ mol^{-1}). Oppositely, the transformations of **15e** into **16e** and **15h** into **16h** are slightly endothermic (+5.5 and +0.4 kJ mol^{-1}, 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° 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^{-1} 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 kJ mol^{-1}, –12.3 kJ mol^{-1}, and –9.3 kJ mol^{-1} 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 **1j–l** into pyrrolobenzodiazepines but this process was not important when

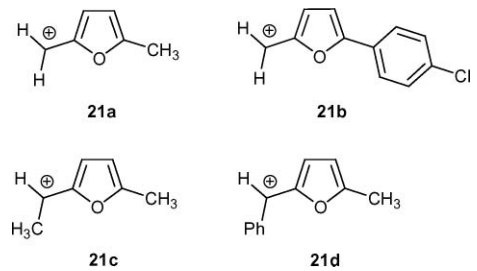


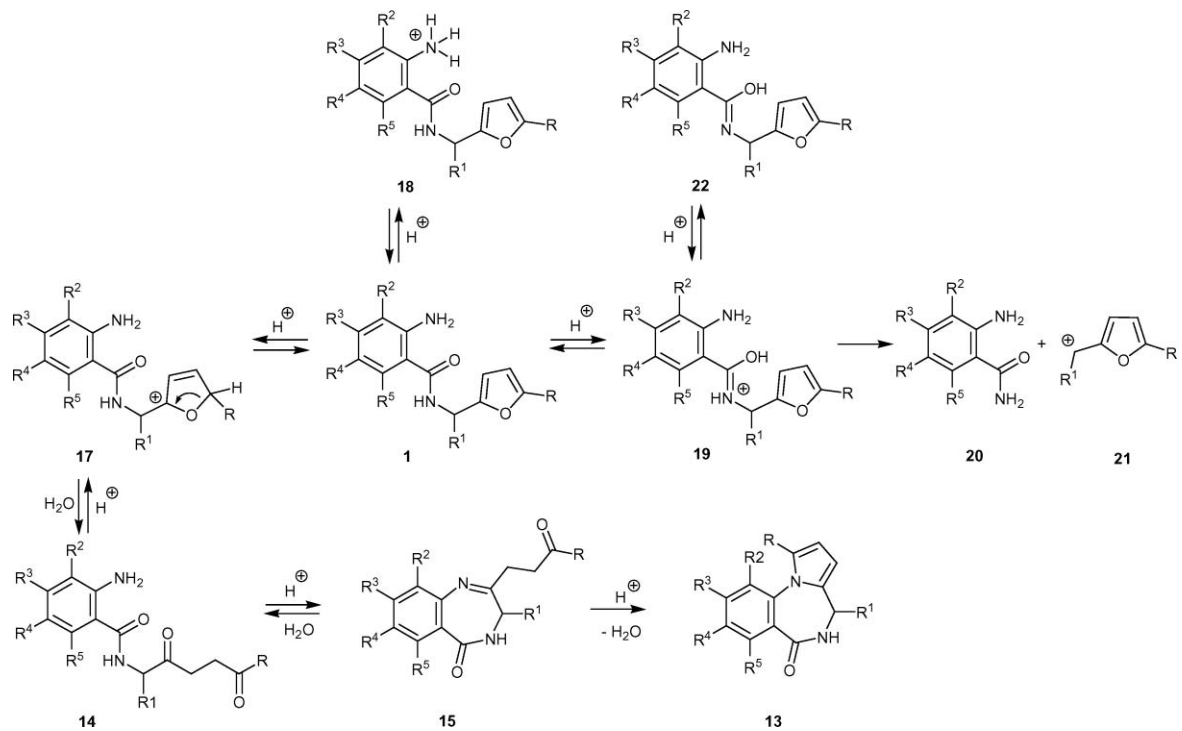
Chart 1 Furfuryl cations formed from **1a–f** (**21a**), **1j** (**21b**), **1k** (**21c**) and **1l** (**21d**).

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 α-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).

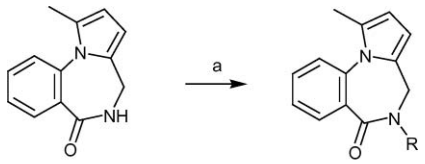
The last process is predominant for reactions of **1a–f**. However, this deprotonation is impossible for products of the amide oxygen protonation in **8a–d**. As a result, the intermediate decomposes into amide and $ArCH_2^+$ cation which leads to realization of various by-processes.

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_2CO_2Et, 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).

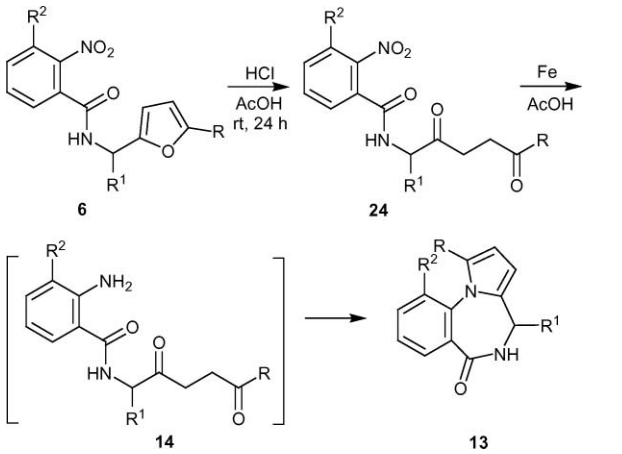
The structure of **13h** was unambiguously proved by single crystal X-ray analysis† (Fig. 3).[28] The angle between the planes of the benzene and pyrrole rings in this structure is 56.6°, in good accordance with the calculated value (58.0°). The steric effect of the *tert*-butyl group is also revealed 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_3 distance in **13a** is 1.486 Å and C–CMe_3 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 3 Transformation of *N*-(furfuryl)-2-nitrobenzamides **6** into nitrodiketones **24** and then to pyrrolo[1,2-*a*][1,4]benzodiazepines **13**



Entry	Substrate	R	R^1	R^2	Yield of **24**, %[a]	Yield of **13**, %[a]
1	**6a**	Me	H	H	75	81
2	**6e**	Me	H	Me	79	80
3	**6h**	*t*-Bu	H	H	43	19
4	**6k**	Me	Me	H	42	81
5	**6l**	Me	Ph	H	40	67

[a] Isolated yield.

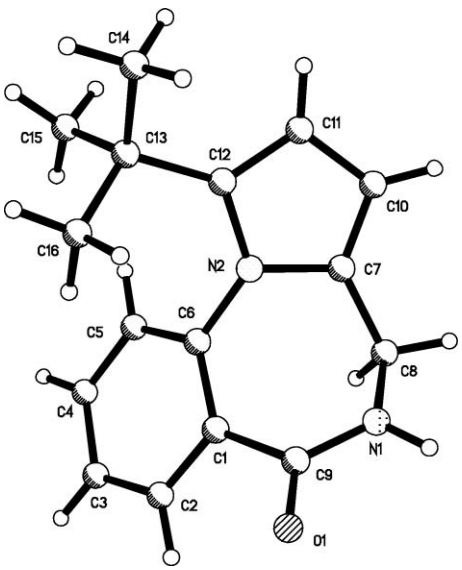
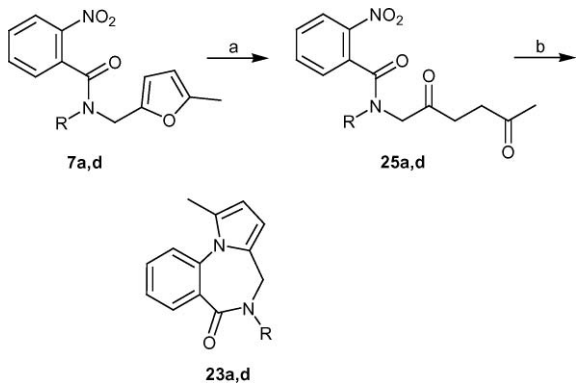
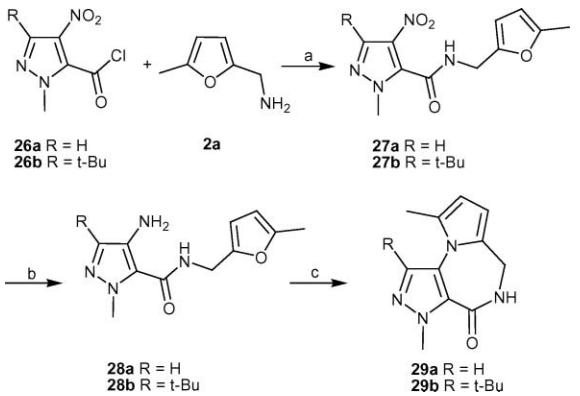


Fig. 3 Single-crystal X-ray structure of **13h**.

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) $N_2H_4 \cdot H_2O$, RANEY®® 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).

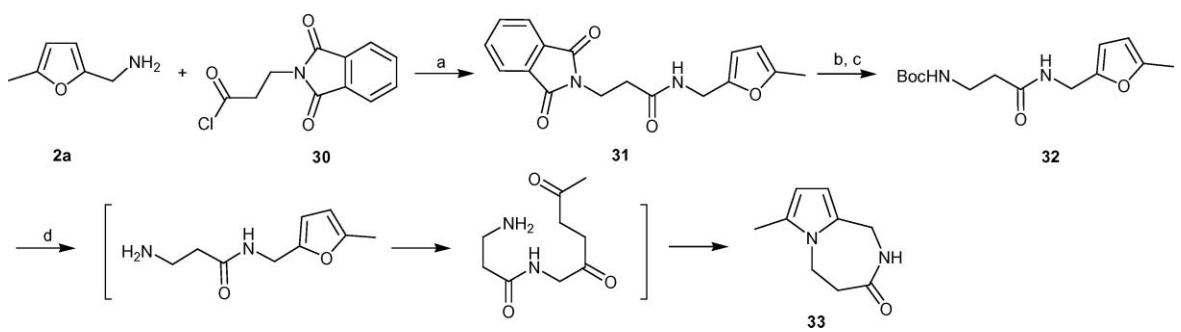
Conclusions

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 ^{1}H and 75 MHz for ^{13}C NMR) spectrometer in $CDCl_3$ or DMSO-d_6 at room temperature; the chemical shifts (δ) were measured in ppm with respect to the solvent ($CDCl_3$: ^{1}H: δ = 7.25 ppm, ^{13}C: δ = 77.0 ppm; DMSO-d_6: ^{1}H: δ = 2.50 ppm, ^{13}C: δ = 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.[33] Amines **2a–d**,**f**,**g** were synthesized by published methods.[25] Other starting compounds



Scheme 13 Synthesis of pyrrolo[1,2-*a*][1,4]diazepine **33** from furfurylamine **2a** and β-alanine derivative **30**. *Reagents and conditions*: a) benzene, rt, 1.5 h, 93%; b) $N_2H_4 \cdot H_2O$, EtOH, rt, 2 h; c) Boc_2O, rt, 1 h, 76% over two steps; d) HCl, AcOH, rt, 8 h, 41%.

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 $NaHCO_3$ solution (100 mL) was added, mixture was vigorously stirred for 30 min. The formed precipitate was filtered off; filtrate was extracted with benzene (3 × 30 mL). The combined organic phases were washed with water and dried over anhydrous Na_2SO_4. 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-2*H*-isoindol-2-yl)-*N*-[(5-methyl-2-furyl)-methyl]benzamide (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-2*H*-isoindol-2-yl)benzoyl chloride (**3a**) (14.15 g, 49.5 mmol; solution in 100 mL of benzene); eluent: CH_2Cl_2–petroleum ether (1 : 2); 66% (10.7 g); colorless needles; mp 146–147 °C (CH_2Cl_2-petroleum ether); δ_H (300 MHz, $CDCl_3$) 2.19 (3H, s, Me), 4.38 (2H, d, ^3J = 5.4 Hz, CH_2), 5.81 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.05 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.30 (1H, br t, ^3J = 5.4 Hz, NH), 7.35–7.38 (1H, m, H_{Ar}), 7.45–7.50 (1H, m, H_{Ar}), 7.56–7.61 (1H, m, H_{Ar}), 7.63–7.66 (1H, m, H_{Ar}), 7.72–7.79 (2H, m, H_{Pht}), 7.87–7.93 (2H, m, H_{Pht}); δ_C (75 MHz, $CDCl_3$) 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); ν_{max} (KBr)/cm^{-1} 3346, 1711, 1665, 1524, 1381, 1299, 1111, 1083, 1017, 804, 720; *m*/*z* (EI) 360 (M^+, 5%), 250 (7), 110 (100), 76 (11), 43 (8); Found: C, 70.14; H, 4.44; N, 7.80. Calc. for $C_{21}H_{16}N_2O_4$: 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_2Cl_2–petroleum ether); δ_H (300 MHz, $CDCl_3$) 2.21 (3H, s, Me), 4.47 (2H, d, ^3J = 5.4 Hz, CH_2), 5.87 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.14 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.45 (1H, br t, ^3J = 5.4 Hz, NH), 7.43–7.46 (1H, m, H_{Ar}), 7.48–7.54 (1H, m, H_{Ar}), 7.57–7.63 (1H, m, H_{Ar}), 7.95–7.98 (1H, m, H_{Ar}); δ_C (75 MHz, $CDCl_3$) 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; ν_{max} (KBr)/cm^{-1} 3281, 1640, 1543, 1523, 1353, 1297, 786, 750; *m*/*z* (EI) 242 (M^+–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 $C_{13}H_{12}N_2O_4$: 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*-[(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); δ_H (300 MHz, $CDCl_3$) 2.28 (3H, s, Me), 4.50 (2H, d, ^3J = 5.1 Hz, CH_2), 5.54 (2H, br s, NH_2), 5.91 (1H, d, ^3J = 3.3 Hz, H_{Fur}), 6.16 (1H, d, ^3J = 3.3 Hz, H_{Fur}), 6.23 (1H, br t, ^3J = 5.1 Hz, NH), 6.51 (1H, d, ^3J = 8.7 Hz, H_{Ar}), 7.26 (1H, dd, ^3J = 8.7 Hz, ^4J = 2.1 Hz, H_{Ar}), 7.40 (1H, d, ^4J = 2.1 Hz, H_{Ar}); δ_C (75 MHz, $CDCl_3$) 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; ν_{max} (KBr)/cm^{-1} 3457, 3354, 3283, 1623, 1573, 1537, 1250, 1017, 894, 819, 787; *m*/*z* (EI) 310/308 (M^+, 17/18%), 200/198 (12/12), 110 (90), 95 (100), 43 (22); Found: C, 50.64; H, 4.22; N, 9.12. Calc. for $C_{13}H_{13}BrN_2O_2$: C, 50.51; H, 4.24; N, 9.06%.

General procedure C for synthesis of amides 1

Hydrazine hydrate (1.5 mL) and RANEY®® 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); δ_H (300 MHz, $CDCl_3$) 2.25 (3H, s, Me), 4.50 (2H, d, ^3J = 5.4 Hz, CH_2), 5.50 (2H, br s, NH_2), 5.89 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.12 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.44 (1H, br t, ^3J = 5.4 Hz, NH), 6.56–6.62 (1H, m, H_{Ar}), 6.63–6.66 (1H, m, H_{Ar}), 7.14–7.20 (1H, m, H_{Ar}), 7.29–7.32 (1H, m, H_{Ar}); δ_C (75 MHz, $CDCl_3$) 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; ν_{max} (KBr)/cm^{-1} 3370, 3300, 3271, 1635, 1528, 1447, 1300, 1255, 782, 749; *m*/*z* (EI) 230 (M^+, 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 $C_{13}H_{14}N_2O_2$: 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 (5×30 mL, TLC control). The combined organic phases were dried with anhydrous Na_2SO_4; 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; δ_H (300 MHz, $CDCl_3$) (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_2), 5.86/5.94 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.01/6.27 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 7.39–7.42/7.51–7.54 (1H, m, H_{Ar}), 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_{Ar}); δ_C (75 MHz, $CDCl_3$) (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; ν_{max} (KBr)/cm^{-1} 1648, 1564, 1520, 1488, 1424, 1400, 1348, 1284, 1224, 1028, 800; *m*/*z* (EI) 274 (M^+, 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 $C_{14}H_{14}N_2O_4$: 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_2Cl_2–petroleum ether (1 : 1). Aniline **8a** was isolated as light-yellow oil in 82% yield (0.73 g). δ_H (300 MHz, $CDCl_3$) 2.25 (3H, s, Me), 2.97 (3H, s, N*Me*), 4.33 (2H, s, CH_2), 4.50 (2H, br s, NH_2), 5.88 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.10 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.65–6.71 (2H, m, H_{Ar}), 7.09–7.15 (2H, m, H_{Ar}); δ_C (75 MHz, $CDCl_3$, 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; ν_{max} (KBr)/cm^{-1} 3456, 3352, 1624, 1592, 1496, 1456, 1400, 1264, 1220, 1064, 1020, 784, 756; *m*/*z* (EI) 244 (M^+, 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 $C_{14}H_{16}N_2O_2$: 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_2SO_4. Solvent was removed using rotary evaporator. Residue was distilled under vacuum. Product **12** was obtained as light-yellow 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]-2-nitrobenzamide (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 $NaHCO_3$ solution (100 mL) was added, mixture was vigorously stirred for 30 min. Organic phase was separated, aqueous phase was extracted with benzene (3 × 30 mL). The combined organic phases were washed with water and dried over anhydrous Na_2SO_4. 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 $NaHCO_3$. 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-6-one (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); δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, Me), 4.09 (2H, d, ^3J = 6.0 Hz, CH_2), 5.98 (1H, d, ^3J = 3.3 Hz, H_{Pyr}), 6.01 (1H, d, ^3J = 3.3 Hz, H_{Pyr}), 7.25–7.28 (1H, m, H_{Ar}), 7.35–7.41 (1H, m, H_{Ar}), 7.52–7.57 (1H, m, H_{Ar}), 7.92 (1H, br t, ^3J = 6.0 Hz, NH), 7.93–7.97 (1H, m, H_{Ar}); δ_C (75 MHz, $CDCl_3$) 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; ν_{max} (KBr)/cm^{-1} 3260, 1656, 1628, 1584, 1492, 1464, 1444, 1408, 1336, 1208, 796, 764; *m*/*z* (EI) 212 (M^+, 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 $C_{13}H_{12}N_2O$: 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-6*H*-pyrrolo[1,2-*a*][1,4]-benzodiazepin-6-one (13f). 2-Amino-3,6-dimethoxy-*N*-(2,5-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 $NaHCO_3$. 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); δ_H (300 MHz, $CDCl_3$) 2.12 (3H, s, Me), 3.73 (3H, s, OMe), 3.89 (3H, s, OMe), 3.93 (1H, dd, ^3J = 6.3 Hz, ^2J = 15.9 Hz, CH_2), 4.07 (1H, dd, ^3J = 6.3 Hz, ^2J = 15.9 Hz, CH_2), 5.89 (1H, d, ^3J = 3.3 Hz, H_{Pyr}), 6.01 (1H, d, ^3J = 3.3 Hz, H_{Pyr}), 6.40 (1H, br t, ^3J = 6.3 Hz, NH), 6.94 (1H, d, ^3J = 9.3 Hz, H_{Ar}), 7.03 (1H, d, ^3J = 9.3 Hz, H_{Ar}); δ_C (75 MHz, $CDCl_3$) 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; ν_{max} (KBr)/cm^{-1} 3229, 1647, 1519, 1490, 1445, 1265, 1114, 1054, 1004, 796, 751; *m*/*z* (EI) 272 (M^+, 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 $C_{15}H_{16}N_2O_3$: 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-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); δ_H (300 MHz, $CDCl_3$) 2.31 (3H, s, Me), 3.13 (3H, s, NMe), 3.92 (1H, d, ^2J = 15.6 Hz, CH_2), 4.32 (1H, d, ^2J = 15.6 Hz, CH_2), 6.01 (1H, d, ^3J = 3.3 Hz, H_{Pyr}), 6.07 (1H, d, ^3J = 3.3 Hz, H_{Pyr}), 7.24–7.27 (1H, m, H_{Ar}), 7.34–7.39 (1H, m, H_{Ar}), 7.48–7.54 (1H, m, H_{Ar}), 7.90–7.94 (1H, m, H_{Ar}); δ_C (75 MHz, $CDCl_3$) 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; ν_{max} (KBr)/cm^{-1} 1628, 1520, 1488, 1456, 1408, 1392, 1336, 1232, 1148, 784, 760, 712; *m*/*z* (EI) 226 (M^+, 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 $C_{14}H_{14}N_2O$: 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 $NaHCO_3$. 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_2SO_4 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); δ_H (300 MHz, $CDCl_3$) 2.18 (3H, s, Me), 2.71–2.75 (2H, m, CH_2), 2.81–2.85 (2H, m, CH_2), 4.43 (2H, d, ^3J = 4.5 Hz, CH_2), 6.64 (1H, br t, ^3J = 4.5 Hz, NH), 7.53–7.61 (2H, m, H_{Ar}), 7.65–7.70 (1H, m, H_{Ar}), 8.04–8.07 (1H, m, H_{Ar}); δ_C (75 MHz, $CDCl_3$) 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; ν_{max} (KBr)/cm^{-1} 3276, 1732, 1712, 1648, 1520, 1412, 1364, 1312, 1240, 856, 792, 716; *m*/*z* (EI) 248 (M^+–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 $C_{13}H_{14}N_2O_5$: 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 $NaHCO_3$. The formed precipitate was filtered off and carefully washed with hot ethyl acetate (5 × 30 mL). The combined organic fractions were dried over Na_2SO_4. 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); δ_H (300 MHz, $CDCl_3$) 1.63 (3H, d, ^3J = 6.9 Hz, CH*Me*), 2.28 (3H, s, Me), 4.31 (1H, dq, ^3J = 6.0 Hz, ^3J = 6.9 Hz, *CH*Me), 5.99 (1H, d, ^3J = 3.3 Hz, H_{Pyr}), 6.02 (1H d, ^3J = 3.3 Hz, H_{Pyr}), 6.90 (1H, br d, ^3J = 6.0 Hz, NH), 7.24–7.27 (1H, m, H_{Ar}), 7.35–7.41 (1H, m, H_{Ar}), 7.51–7.57 (1H, m, H_{Ar}), 7.93–7.96 (1H, m, H_{Ar}); δ_C (75 MHz, $CDCl_3$) 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; ν_{max} (KBr)/cm^{-1} 3160, 1648, 1604, 1520, 1488, 1460, 1404, 1320, 1288, 1160, 772, 704; *m*/*z* (EI) 226 (M^+, 67%), 211 (100), 184 (57), 167 (18), 77 (22), 43 (50); Found: C, 74.48; H, 6.59; N, 12.22. Calc. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38%.

1-Methyl-*N*-[(5-methyl-2-furyl)methyl]-4-nitro-1*H*-pyrazole-5-carboxamide (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_2Cl_2–petroleum ether (1 : 1); 63% (3.02 g); beige plates; mp 109–110 °C (CCl_4); δ_H (300 MHz, $CDCl_3$) 2.24 (3H, s, Me), 4.11 (3H, s, Me), 4.55 (2H, d, ^3J = 5.4 Hz, CH_2), 5.88 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.17 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 8.05 (1H, s, H_{Het}), 8.22 (1H, br t, ^3J = 5.4 Hz, NH); δ_C (75 MHz, $CDCl_3$) 13.5, 37.0, 41.3, 106.3, 109.0, 132.2, 133.1, 136.3, 147.7, 152.4, 156.5; ν_{max} (KBr)/cm^{-1} 3296, 1640, 1572, 1564, 1532, 1508, 1468, 1396, 1392, 1316, 1192, 828, 796; *m*/*z* (EI) 246 (M^+–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 $C_{11}H_{12}N_4O_4$: 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); δ_H (300 MHz, $CDCl_3$) 2.24 (3H, s, Me), 2.92 (2H, br s, NH_2), 4.12 (3H, s, Me), 4.49 (2H, d, ^3J = 5.7 Hz, CH_2), 5.88 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.11 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 7.17 (1H, s, H_{Het}), 8.55 (1H, br t, ^3J = 5.7 Hz, NH); δ_C (75 MHz, $CDCl_3$) 13.5, 35.8, 40.2, 106.2, 108.1, 127.0, 127.1, 133.1, 149.4, 151.9, 159.9; ν_{max} (KBr)/cm^{-1} 3348, 3280, 1652, 1640, 1616, 1568, 1548, 1424, 1356, 1312, 1292, 1204, 1024, 980, 912, 812; *m*/*z* (EI) 234 (M^+, 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 $C_{11}H_{14}N_4O_2$: 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); δ_H (300 MHz, $CDCl_3$) 2.37 (3H, s, Me), 4.16 (3H, s, Me), 4.17 (2H, d, ^3J = 6.0 Hz, CH_2), 5.96–5.99 (2H, m, H_{Pyr}), 7.24 (1H, br t, ^3J = 6.0 Hz, NH), 7.60 (1H, s, H_{Het}); δ_C (75 MHz, $CDCl_3$)

13.9, 38.2, 39.6, 105.7, 108.6, 123.8, 126.5, 129.0, 129.4, 129.9, 162.5; ν_{max} (KBr)/cm^{-1} 3200, 1656, 1564, 1528, 1432, 1412, 1392, 1340, 1328, 1208, 788, 748, 692; *m/z* (EI) 216 (M$^+$, 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 $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91%.

3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-*N*-[(5-methyl-2-furyl)-methyl]propanamide (31). Obtained according to General procedure A from **2a** (5 g, 45.05 mmol; solution in 50 mL of benzene) and 3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-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); δ_H (300 MHz, $CDCl_3$) 2.20 (3H, s, Me), 2.60–2.65 (2H, m, CH_2), 3.98–4.02 (2H, m, CH_2), 4.33 (2H, d, ^3J = 5.4 Hz, CH_2), 5.83 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 5.95 (1H, br t, ^3J = 5.4 Hz, NH), 6.05 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 7.66–7.72 (2H, m, H_{Pht}), 7.78–7.85 (2H, m, H_{Pht}); δ_C (75 MHz, $CDCl_3$) 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); ν_{max} (KBr)/cm^{-1} 3416, 1720, 1647, 1026, 998, 866, 803, 717; *m/z* (EI) 312 (M$^+$, 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 $C_{17}H_{16}N_2O_4$: 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 $CHCl_3$ (3 × 20 mL); filtrate was evaporated under reduced pressure. The formed residue was treated with Boc_2O (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_2Cl_2—petroleum ether (1 : 1) as eluent. Product was crystallized as white solid (6.83 g, 76%). Mp 89—90 °C (petroleum ether); δ_H (300 MHz, $CDCl_3$) 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, ^3J = 5.4 Hz, CH_2), 5.18 (1H, br s, NH), 5.86 (1H, d, ^3J = 3.0 Hz, H_{Fur}), 6.03 (1H, br s, NH), 6.07 (1H, d, ^3J = 3.0 Hz, H_{Fur}); δ_C (75 MHz, $CDCl_3$) 13.5, 28.3 (3C), 36.0, 36.5 (2C), 79.2, 106.2, 108.3, 149.1, 151.9, 156.0, 171.1; ν_{max} (KBr)/cm^{-1} 3344, 3318, 1685, 1633, 1530, 1452, 1366, 1325, 1283, 1253, 1231, 1174, 1023, 786; *m/z* (EI) 282 (M$^+$, 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 $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92%.

7-Methyl-1,2,4,5-tetrahydro-3*H*-pyrrolo[1,2-*a*][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 $NaHCO_3$. 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; δ_H (300 MHz, $CDCl_3$) 2.19 (3H, s, Me), 2.90–2.94 (2H, m, CH_2), 4.00–4.05 (2H, m, CH_2), 4.31 (2H, d, ^3J = 5.7 Hz, CH_2), 5.79 (1H, d, ^3J = 3.3 Hz, H_{Pyr}), 5.85 (1H, d, ^3J = 3.3 Hz, H_{Pyr}), 7.16 (1H, br t, ^3J = 5.7 Hz, NH); δ_C (75 MHz, $CDCl_3$) 12.2, 34.1, 39.3, 40.9, 105.3, 105.8, 126.9, 129.9, 174.3; ν_{max} (KBr)/cm^{-1} 3200, 1664, 1508, 1476, 1440, 1424, 1388, 1348, 1312, 1248, 1200, 1172, 1100, 776; *m/z* (EI) 164 (M$^+$, 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 $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06%.

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References

1 (*a*) E. Usdin, J. F. Tallman, P. Skolnick, D. Greenblatt and S. M. Paul, *Pharmacology of benzodiazepines*, Wiley, New York, 1983; (*b*) *Benzodiazepines: Current Concepts - Biological, Clinical and Social Perspectives*, ed. by I. Hindmarch, G. Beaumont, S. Brandon and B. L. Leonard, Wiley, New York, 1990; (*c*) S. J. Salamons, *Benzodiazepines and GHB: Detection and Pharmacology*, Humana Press, 2001.
2 For reviews, see: (*a*) W. A. Remers, in *Chemistry of Antitumor Antibiotics*, Wiley, New York, 1988, **2**, 28-92; (*b*) D. E. Thurston and D. S. Bose, *Chem. Rev.*, 1994, **94**, 433–465.
3 Some recent examples: (*a*) T. Hadjivassileva, D. E. Thurston and P. W. Taylor, *J. Antimicrob. Chemother.*, 2005, **56**, 513–518; (*b*) R. Kumar and J. W. Lown, *Eur. J. Med. Chem.*, 2005, **40**, 641–654; (*c*) A. M. Venkatesan, G. T. Grosu, A. A. Failli, P. S. Chan, J. Coupet, T. Saunders, H. Mazandarani and X. Ru, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5003–5006; (*d*) L. A. Masterson, V. J. Spanswick, J. A. Hartley, R. H. Begent, P. W. Howard and D. E. Thurston, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 252–256; (*e*) J.-J. Wang, Y.-K. Shen, W.-P. Hu, M.-C. Hsieh, F.-L. Lin, M.-K. Hsu and M.-H. Hsu, *J. Med. Chem.*, 2006, **49**, 1442–1449; (*f*) D. Antonow, T. C. Jenkins, P. W. Howard and D. E. Thurston, *Bioorg. Med. Chem.*, 2007, **15**, 3041–3053; (*g*) A. Kamal, M. N. A. Khan, K. S. Reddy, S. K. Ahmed, M. S. Kumar, A. Juvekar, S. Sen and S. Zingde, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5345–5348; (*h*) A. Kamal, P. P. Kumar, B. N. Seshadri, O. Srinivas, M. S. Kumar, S. Sen, N. Kurian, A. S. Juvekarb and S. M. Zingde, *Bioorg. Med. Chem.*, 2008, **16**, 3895–3906.
4 (*a*) G. W. H. Cheeseman and S. G. Greenberg, *Chem. Ind. (London)*, 1974, 916–917; (*b*) F. Corelli, S. Massa, G. C. Pantaleoni, G. Palumbo and D. Fanini, *Farmaco*, 1984, **39**, 707–717.
5 A. Mai, R. Di Santo, S. Massa, M. Artico, G. C. Pantaleoni, R. Giorgi, M. F. Coppolino and A. Barracchini, *Eur. J. Med. Chem.*, 1995, **30**, 593–601.
6 F. Corelli, S. Massa, G. Stefancich, G. Ortenzi, M. Artico, G. C. Pantaleoni, G. Palumbo, D. Fanini and R. Giorgi, *Eur. J. Med. Chem.-Chim. Ther.*, 1986, **21**, 445–449.
7 S. Massa, F. Corelli, M. Artico, A. Mai, R. Silvestri, G. C. Pantaleoni, G. Palumbo, D. Fanini and R. Giorgi, *Farmaco*, 1989, **44**, 109–123.
8 T. Hara, Y. Kayama, T. Mori, K. Itoh, H. Fujimori, T. Sunami, Y. Hashimoto and S. Ishimoto, *J. Med. Chem.*, 1978, **21**, 263–268.
9 S. Massa, M. Artico, A. Mai, F. Corelli, M. Botta, A. Tafi, G. C. Pantaleoni, R. Giorgi, M. F. Coppolino, A. Cagnotto and M. Skorupska, *J. Med. Chem.*, 1992, **35**, 4533–4541.
10 E. G. Glamkowski and Y. Chiang, *J. Heterocycl. Chem.*, 1987, **24**, 1599–1604.
11 S. Massa, M. Artico, A. Mai, F. Corelli, G. C. Pantaleoni, R. Giorgi, D. Ottaviani and A. Cagnotto, *Farmaco*, 1990, **45**, 1265–1281.

12 S. Saito, H. Umemiya, Y. Suga, M. Sato and N. Kawashima, WO Pat., 2003, WO 2003095427; *Chem. Abstr.*, **139**, 395821.

13 (*a*) T. Gilkerson, R. J. Nash, J. F. E. Van Gestel and L. Meerpoel, WO Pat., 2002, WO 2002034752; *Chem. Abstr.*, **136**, 340708; (*b*) L. Meerpoel, J. Van Gestel, F. Van Gerven, F. Woestenborghs, P. Marichal, V. Sipido, G. Terence, R. Nash, D. Corens and R. D. Richards, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3453–3458.

14 (*a*) S. Raines, S. Y. Chai and F. P. Palopoli, *J. Heterocycl. Chem.*, 1976, **13**, 711–716; (*b*) G. W. H. Cheeseman and S. G. Greenberg, *J. Heterocycl. Chem.*, 1979, **16**, 241–244; (*c*) S. Massa, A. Mai, M. Artico, F. Corelli and M. Botta, *Tetrahedron*, 1989, **45**, 2763–2772; (*d*) S. Massa, A. Mai and M. Artico, *Synth. Commun.*, 1990, **20**, 3537–3545; (*e*) S. Vega and M. S. Gil, *J. Heterocycl. Chem.*, 1991, **28**, 945–950; (*f*) X. Feng, J.-C. Lancelot, H. Prunier and S. Rault, *J. Heterocycl. Chem.*, 1996, **33**, 2007–2011.

15 (*a*) S. Vomero, R. Giuliano, M. Artico and G. Stefancich, *Farmaco*, 1980, **35**, 110–119; (*b*) S. Massa, A. Mai, R. Di Santo and M. Artico, *J. Heterocycl. Chem.*, 1993, **30**, 897–903; (*c*) F. Esser, K.-H. Pook, A. Carpy and J.-M. Leger, *Synthesis*, 1994, 77–82.

16 (*a*) S. Massa, R. Di Santo, R. Costi and M. Artico, *J. Heterocycl. Chem.*, 1993, **30**, 749–753; (*b*) I. Rault, S. Rault and M. Robba, *Heterocycles*, 1994, **38**, 811–817; (*c*) X. Feng, J.-C. Lancelot, A.-C. Gillard, H. Landelle and S. Rault, *J. Heterocycl. Chem.*, 1998, **35**, 1313–1316.

17 (*a*) G. De Martino, M. Scalzo, S. Massa, R. Giuliano and M. Artico, *Farmaco*, 1972, **27**, 980–989; (*b*) S. Rault, M. Cugnon de Sevricourt M. and M. Robba, *Compt. Rend. Acad. Sc.*, 1978, **287C**, 117–120; (*c*) H. Stetter and P. Lappe, *Liebigs Ann. Chem.*, 1980, 703–714.

18 (*a*) I. Rault, S. Rault and M. Robba, *Tetrahedron Lett.*, 1993, **34**, 1929–1930; (*b*) I. Rault, M.-P. Foloppe, S. Rault and M. Robba, *Heterocycles*, 1993, **36**, 2059–2066; (*c*) M. P. Foloppe, P. Sonnet, S. Rault and M. Robba, *Tetrahedron Lett.*, 1995, **36**, 3127–3128; (*d*) M.-P. Foloppe, P. Sonnet, I. Bureau, S. Rault and M. Robba, *J. Heterocycl. Chem.*, 1996, **33**, 75–80.

19 E. E. Garcia, J. G. Riley and R. I. Fryer, *J. Org. Chem.*, 1968, **33**, 1359–1363.

20 (*a*) S. Rault, M. Cugnon de Sevricourt M. and M. Robba, *Heterocycles*, 1979, **12**, 1009–1011; (*b*) M. Boulouard, S. Rault, P. Dallemagne and M. Robba, *Heterocycles*, 1995, **41**, 515–522; (*c*) M. Boulouard, S. Rault, A. Alsaidi, P. Dallemagne and M. Robba, *J. Heterocycl. Chem.*, 1995, **32**, 1719–1724; (*d*) M. Boulouard, S. Rault, P. Dallemagne, A. Alsaidi and M. Robba, *J. Heterocycl. Chem.*, 1996, **33**, 87–91; (*e*) M. Boulouard, P. Dallemagne, A. Alsaidi and S. Rault, *J. Heterocycl. Chem.*, 1996, **33**, 1743–1749.

21 (*a*) Y. Kayama, T. Hara, K. Itoh and T. Sunami, *J. Heterocycl. Chem.*, 1977, **14**, 171–172; (*b*) H. Fujimori, Y. Kayama, T. Hara, K. Itoh and T. Sunami, *J. Heterocycl. Chem.*, 1977, **14**, 235–240; (*c*) D. Korakas and G. Varvounis, *J. Heterocycl. Chem.*, 1994, **31**, 1317–1320; (*d*) D. Korakas and G. Varvounis, *Synthesis*, 1994, 164–166.

22 A. P. Ilyn, A. S. Trifilenkov, J. A. Kuzovkova, S. A. Kutepov, A. V. Nikitin and A. V. Ivachtchenko, *J. Org. Chem.*, 2005, **70**, 1478–1481.

23 (*a*) J. S. Duceppe and J. Gauthier, *J. Heterocycl. Chem.*, 1984, **21**, 1685–1687; (*b*) S. Massa, A. Mai and F. Corelli, *Tetrahedron Lett.*, 1988, **29**, 6471–6474; (*c*) S. Massa, M. Artico, A. Mai and A. Mancuso, *J. Heterocycl. Chem.*, 1992, **29**, 1851–1854; (*d*) L.-H. Zhang, W. Meier, E. Wats, T. D. Costello, P. Ma, C. L. Ensinger, J. M. Rodgers, I. C. Jacobson and P. Rajagopalan, *Tetrahedron Lett.*, 1995, **36**, 8387–8390; (*e*) D. Korakas, A. Kimbaris and G. Varvounis, *Tetrahedron*, 1996, **52**, 10751–10760; (*f*) M. Othman, P. Pigeon, P. Netchitailo, A. Daich and B. Decroix, *Heterocycles*, 2000, **52**, 273–281.

24 T. A. Stroganova, A. V. Butin, V. K. Vasilin, T. A. Nevolina and G. D. Krapivin, *Synlett*, 2007, 1106–1108.

25 Y.-A. Kuo and K.-S. Shih, *Chem. Pharm. Bull.*, 1991, **39**, 181–183.

26 R. Y. F. Manske, W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 1927, 1–14.

27 (*a*) A. V. Butin, S. K. Smirnov and T. A. Stroganova, *J. Heterocycl. Chem.*, 2006, **43**, 623–628; (*b*) V. T. Abaev, A. S. Dmitriev, A. V. Gutnov, S. A. Podelyakin and A. V. Butin, *J. Heterocycl. Chem.*, 2006, **43**, 1195–1204; (*c*) A. V. Butin, S. K. Smirnov, T. A. Stroganova, W. Bender and G. D. Krapivin, *Tetrahedron*, 2007, **63**, 474–491; (*d*) A. V. Butin, A. S. Dmitriev, O. N. Kostyukova, V. T. Abaev and I. V. Trushkov, *Synthesis*, 2007, 2208–2214; (*e*) A. S. Dmitriev, V. T. Abaev, W. Bender and A. V. Butin, *Tetrahedron*, 2007, **63**, 9437–9447; (*f*) A. V. Butin, V. T. Abaev, V. V. Mel'chin, A. S. Dmitriev, A. S. Pilipenko and A. S. Shashkov, *Synthesis*, 2008, 1798–1804.

28 CCDC 761545 (**13a**) and CCDC 761546 (**13h**) contain the supplementary crystallographic data for this paper†. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

29 (*a*) J. F. Haley, Jr. and P. M. Keehn, *Tetrahedron Lett.*, 1973, 4017–4020; (*b*) J. F. Haley, Jr., S. M. Rosenfeld and P. M. Keehn, *J. Org. Chem.*, 1977, **42**, 1379–1386; (*c*) P. S. Hammond and D. T. Longone, *Tetrahedron Lett.*, 1978, 415–418; (*d*) I. K. Khanna, R. M. Weier, Y. Yu, P. W. Collins, J. M. Miyashiro, C. M. Koboldt, A. W. Veenhuizen, J. L. Currie, K. Seibert and P. C. Isakson, *J. Med. Chem.*, 1997, **40**, 1619–1633; (*e*) F. W. Lichtenthaler, A. Brust and E. Cuny, *Green Chem.*, 2001, **3**, 201–209; (*f*) G. Cafeo, F. H. Kohuke, M. F. Parisi, R. P. Nascone, G. L. Torre and D. J. Williams, *Org. Lett.*, 2002, **4**, 2695–2697.

30 (*a*) Y. Takeuchi, K. Azuma, H. Abe and T. Harayama, *Heterocycles*, 2000, **53**, 2247–2252; (*b*) I. M. Skvortsov, N. A. Buntyakova, M. I. Kuramshin and S. A. Filimonov, *Chem. Heterocycl. Compd.*, 1983, **19**, 1139; *Khim. Geterosikl. Soedin.*, 1983, 1424–1425.

31 *Gaussian 98, Revision A.11*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 2001.

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33 L. F. Tietze, T. Eicher, *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, Thieme, Stuttgart, 1991.