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# A novel synthesis of pyrrolo[1,2-*d*][1,4]diazocines from tetrahydropyrrolo[1,2-*a*] pyrazines using activated alkynes in pyrazine ring expansion

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ABSTRACT

A novel and efficient one-pot synthesis of pyrrolo[1,2-*d*][1,4]diazocines based on tandem transformation of tetrahydropyrazine ring was elaborated.



## 1. Introduction

Among numerous biologically active aryl- and heteroaryl-fused six and seven-membered 1,4-diazaheterocycles—piperazines[1] and diazepines,[2] their eight- and nine-membered congeners represent an apparently underexplored group with immense therapeutic potential. In many cases their structures strongly resemble the whole composition of low-membered analogues in accordance to the fundamental bioisosteric rules.[3]

The few pathways towards benzoannulated pyrrolodiazocines include Ugi-type reaction and Dieckman condensation[4] of adequately substituted pyrroles and a multi-step synthesis of fully hydrogenated pyrrolo[1,2-*a*][1,4]diazocines and pyrrolo[1,2-*a*][1,5] diazocines starting from proline and pyroglutamic acid.[5] It was shown that pyrrolo[1,2-*a*][1,4]diazocines could be used as dipeptide reverse-turn mimetics[6] exhibiting cognition enhancing activity.

We have previously developed an original and efficient method for the synthesis of tetrahydropyrrolo[3,2-*d*]azocines based on the transformation of tetrahydropyrrolo[3,2-*c*]pyridines under the action of activated alkynes.[7] Subsequent research of the tandem transformations of tetrahydropyrrolo[1,2-*a*]pyrimidines,[8] tetrahydro-β and γ-carbolines,[9] tetrahydrothieno[3,2-*c*] and [2,3-*c*]pyridines and their benzo analogues[10] showed that this reaction is a general one for the annulated tetrahydropyridine system.

In this paper we report on the reactivity of 1-methyl-2-aryl-6-*R*-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines in the reaction with activated alkynes. The main goal of this study was to elaborate a new method for the synthesis of pyrrolo[1,2-*d*][1,4]diazocines.

## 2. Results and discussion

Based on the obtained data we could presume that the pathway of the reaction is defined by different factors: (a) the nature of the solvent; (b) the electronic effects of the substituents both on the tetrahydropyridines fragment and on the fused aromatic ring; (c) the type of the linkage between tetrahydropyridine and aromatic rings.

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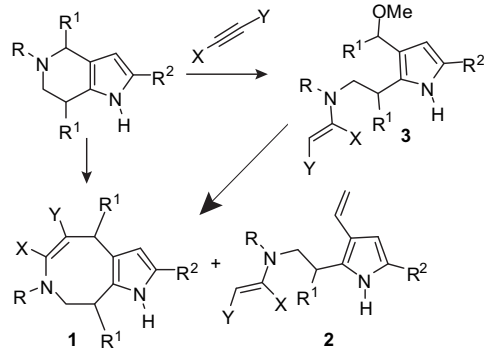
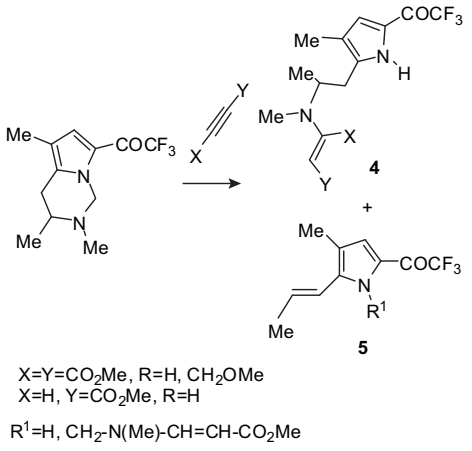
In aprotic solvents tetrahydropyrrolo[3,2-*c*]pyridines produce mixtures containing tetrahydropyrrolo[2,3-*d*]azocines **1** and 3-vinyl substituted pyrroles **2** in the various ratio. In the case of reactions in methanol the main products are 3-alkoxy(hydroxy) alkyl-pyrroles **3**, the latter compounds can be cyclized into pyrroloazocine by the action of electrophilic agents (yield 70–75%) (Scheme 1).




**Scheme 1.**

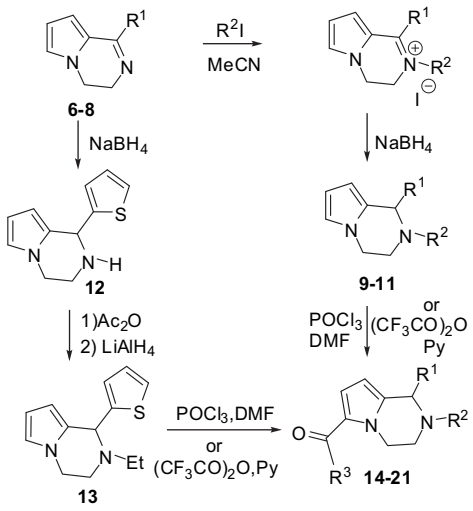
Tetrahydropyrrolo[1,2-*a*]pyrimidines under the action of alkynes in protic solvents undergo the cleavage process of tetrahydropyrimidine ring thus forming only substituted pyrroles **4** and **5** (Scheme 2).




**Scheme 2.**

The synthesis of starting tetrahydropyrrolo[1,2-*a*]pyrazines **14**–**21** required for the present study is shown in Scheme 3. Dihydropyrrolopyrazines **6**–**8** were obtained according to the previously described procedure.[11] The subsequent quaternization of compounds **6** and **7** by methyl or ethyl iodide and reduction of the obtained quaternary salts by the action of $NaBH_4$ led to the formation of *N*-alkyl substituted intermediate tetrahydropyrrolo [1,2-*a*]pyrazines **9**–**11**. *N*-Ethyl tetrahydropyrrolopyrazine **13** were synthesized via acylation of corresponding dihydropyrrolopyrazine **12** followed by reduction with $LiAlH_4$ in THF. The required pyrrolopyrazines **14**–**21** were obtained by formylation or trifluoroacylation of corresponding tetrahydropyrrolopyrazines **9**–**11** and **13** (Scheme 3, Table 1).

Unlike pyrrolopyridines and pyrrolopyrimidines reactions of formyl substituted pyrrolopyrazines **14**–**16** with methyl propiolate

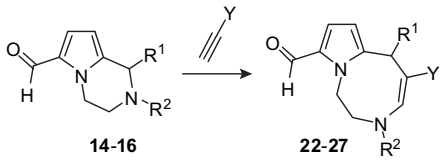


**Scheme 3.**

**Table 1**
Pyrrolo[1,2-*a*]pyrazines **14**–**21**

| Compound | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **9** | Ph | Me | — |
| **10** | Ph | Et | — |
| **11** | *p*-Me–$C_6H_4$ | Me | — |
| **14** | Ph | Me | H |
| **15** | Ph | Et | H |
| **16** | *p*-Me–$C_6H_4$ | Me | H |
| **17** | Th | Et | H |
| **18** | Ph | Me | $CF_3$ |
| **19** | Ph | Et | $CF_3$ |
| **20** | *p*-Me–$C_6H_4$ | Me | $CF_3$ |
| **21** | Th | Et | $CF_3$ |

both in methanol and in acetonitrile require an excess of the alkyne (from 2 upto 10-fold molar excess) and more forcing conditions (reflux). At room temperature reactions proceeded very slowly. In the case of reactions with acetylacetylene pyrrolopyrazines **14** and **16** reacted smoothly at 30 °C but pyrrolopyrazine **15** required reflux. However in all cases tandem transformation leads to the enlargement of tetrahydropyrazine ring yielding pyrrolodiazocines **22**–**27** (Scheme 4, Table 2). The time of the reactions varies from 4 to 100 h.



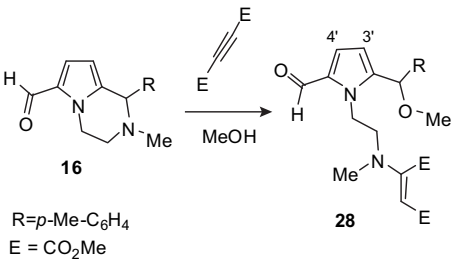
**Scheme 4.**

**Table 2**
Tetrahydropyrrolo[1,2-*d*][1,4]diazocines **22**–**27**

| Compound | $R^1$ | $R^2$ | Y |
|---|---|---|---|
| **22** | Ph | Me | $CO_2Me$ |
| **23** | Ph | Et | $CO_2Me$ |
| **24** | *p*-Me–$C_6H_4$ | Me | $CO_2Me$ |
| **25** | Ph | Me | COMe |
| **26** | Ph | Et | COMe |
| **27** | *p*-Me–$C_6H_4$ | Me | COMe |

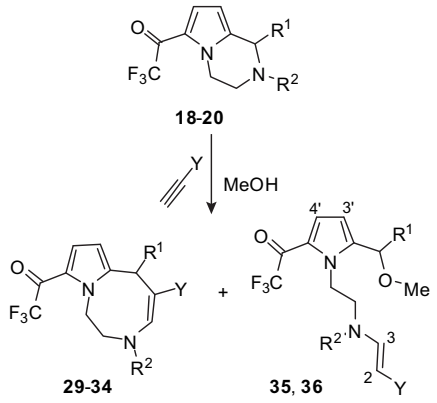
Reaction of compound **14** with DMAD in refluxing acetonitrile for 3 weeks yielded only a multi-component mixture.

The reaction of compounds **16** with DMAD in methanol led to the cleavage process involving one molecule of the solvent thus giving substituted pyrrole **28** in yield 65% (Scheme 5).




**Scheme 5.**

Trifluoroacetyl substituted pyrrolopyrazines **18**–**20** do not react with activated alkynes in acetonitrile even under reflux. In the case of reactions with methyl propiolate and acetylacetylene in refluxing methanol two concurrent processes—enlargement and cleavage of tetrahydropyrazine ring—took place producing the mixtures of pyrrolodiazocines **29**–**34** and methoxyalkyl substituted pyrroles **35** and **36** (Scheme 6 and Table 3).



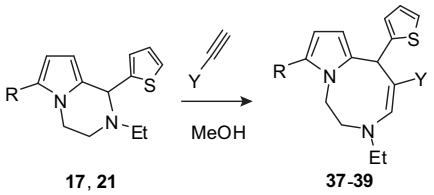

**Scheme 6.**

**Table 3**
Tetrahydropyrrolo[1,2-*d*][1,4]diazocines **29**–**34** and pyrrole **35**–**36**

| Compound | $R^1$ | $R^2$ | Y |
|---|---|---|---|
| **29** | Ph | Me | $CO_2Me$ |
| **30** | Ph | Et | $CO_2Me$ |
| **31** | *p*-Me–$C_6H_4$ | Me | $CO_2Me$ |
| **32** | Ph | Me | COMe |
| **33** | Ph | Et | COMe |
| **34** | *p*-Me–$C_6H_4$ | Me | COMe |
| **35** | Ph | Me | $CO_2Me$ |
| **36** | Ph | Me | COMe |

1-Thienyl substituted tetrahydropyrrolo[1,2-*a*]pyrazines **17** and **21** did not react with alkynes even in refluxing acetonitrile and with the use of excess of the reagent. In methanol at 55 °C formyl pyrrolopyrazine **17** reacted with methyl propiolate and acetylacetylene smoothly in 48 and 32 h, respectively, yielding only pyrrolodiazocines **37** and **38**. Analogously, under the same conditions trifluoroacetyl substituted pyrrolopyrazine **21** in the presence of methyl propiolate gave pyrrolodiazocine **39** (Scheme 7, Table 4).

The structures of pyrrolodiazocines **22**–**27**, **29**–**34** and **37**–**39** and pyrroles **28**, **35**, **36** were confirmed by spectral data. The $^1H$ NMR spectra of pyrrolodiazocines **22**–**27**, **29**–**34** and **37**–**39** have similar characteristic signals: the enamine protons resonate as



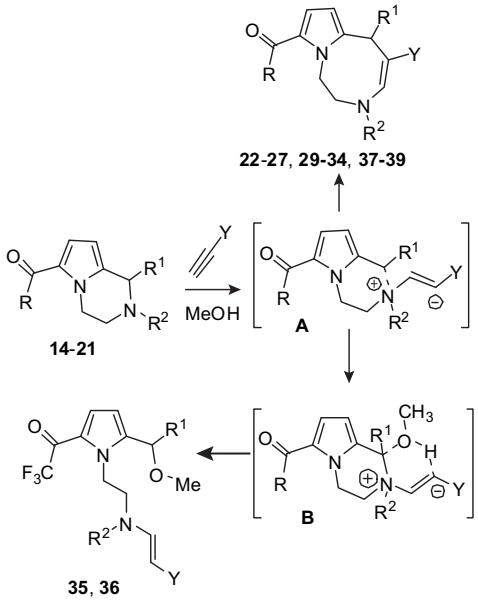

**Scheme 7.**

**Table 4**
Tetrahydropyrrolo[1,2-*d*][1,4]diazocines **37**–**39**

| Compound | R | Y |
|---|---|---|
| **37** | CHO | $CO_2Me$ |
| **38** | CHO | COMe |
| **39** | $COCF_3$ | $CO_2Me$ |

singlets at $\delta$=7.43–7.69 ppm. In the $^1H$ NMR spectra of pyrroles **28**, **35**, **36** characteristic protons resonate: as singlets for three protons at $\delta$=4.75–5.32 ppm from methoxy group and as singlet at $\delta$=4.77–5.39 ppm (**28**) or two broad singlets at $\delta$=4.64–5.09 and $\delta$=7.27–7.53 ppm (**35** and **36**) from enamine fragment.

We presume that the tandem transformation starts with the formation of zwitterion **A**. Intramolecular substitution in the zwitterion **A** leads to the enlargement of the tetrahydropyrazine fragment thus forming 1,2,3,6-tetrahydropyrrolo[1,2-*d*][1,4]diazocines **22**–**27**, **29**–**34** and **37**–**39**. In the case of reactions in methanol intermediate, **B** could be stabilized by the nucleophilic assistance of the solvent resulting into the cleavage of the pyrazine ring (Scheme 8).

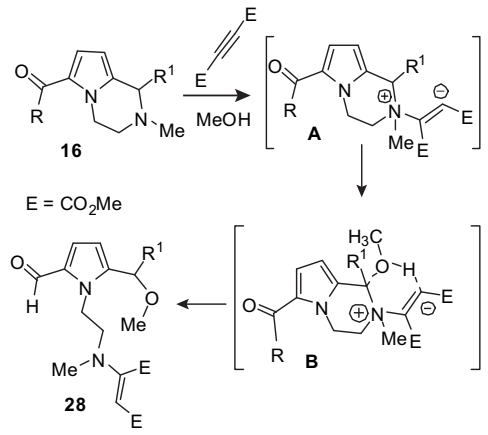



**Scheme 8.**

In the case of reaction with DMAD we consider the possibility of delocalization of anionic center between two ester groups. This process diminishes nucleophilicity of anionic center facilitating the cleavage process of tetrahydropyrazine ring via the intermediate **B** (Scheme 9).

## 3. Conclusion

We have elaborated a new method for the synthesis of tetrahydropyrrolodiazocines based on tandem cleavage-cyclization reaction of easy available tetrahydropyrrolpyrazine derivatives.




**Scheme 9.**

## 4. Experimental section

### 4.1. General

All solvents were distilled and dried before use, DMAD, acetylacetylene and methyl propiolate were purchased from ACROC ORGANICS and were used without any additional purification. Column chromatography was performed with aluminium oxide, activated, neutral, Brockmann I purchased from ACROS ORGANIC. $^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ solutions, at 25 °C, using a 400 or 600 MHz NMR spectrometer, peak positions are given in parts per million ($\delta$) with tetramethylsilane used as the internal standard. Mass-spectra were registered using ESI or EI techniques. IR spectra were recorded with a Perkin–Elmer Spectrum One instrument. Only noteworthy IR absorptions [$cm^{-1}$] are listed. Melting points were determined in capillary tube and are uncorrected.

### 4.2. General procedure for the synthesis of tetrahydropyrrolopyrazines 9–11

A solution of alkyl iodide (12 mmol) in acetonitrile (5 mL) was added dropwise to a stirred solution of dihydropyrrolopyrazine (10 mmol) in acetonitrile (7 mL). The reaction mixture was heated at reflux for 3 h (TLC monitoring). After completion of the reaction the solvent was evaporated in vacuo to give the corresponding salt. The salt (12 mmol) was dissolved in methanol (17 mL) and the resulting solution was stirred. $NaBH_4$ (1.89 g, 50 mmol) was added to the stirred solution by small portions. The stirring was continued for 5 days (TLC monitoring). The solvent was evaporated in vacuo. The resulting mixture was dissolved in water (30 mL) and extracted with ether (3×50 mL). The combined organic layers were dried with $MgSO_4$. The solvent was evaporated in vacuo to give the target tetrahydropyrrolopyrazines **9**–**11**.

*4.2.1. 2-Methyl-1-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (**9**).* Yield 1.63 g (77%) as white solid, mp 73–75 °C (ethyl acetate/hexane); [Found: C, 78.9; H, 7.9; N, 13.1. $C_{14}H_{16}N_2$ requires C, 79.21; H, 7.60; N, 13.20%]; $R_f$ (1:1, ethyl acetate/hexane) 0.70; $\delta_H$ (400 MHz $CDC1_3$) 7.39–7.29 (5H, m, Ph), 6.57 (1H, s, 6-H), 6.07 (1H, t, *J* 2.7 Hz, 7-H), 5.33–5.31 (1H, m, 8-H), 4.25 (1H, td, *J* 11.8, 4.3 Hz, 4-$CH_2$), 4.16 (1H, s, 1-H), 4.04–4.00 (1H, m, 3-$CH_2$), 3.19–3.14 (1H, m, 4-$CH_2$), 2.82 (1H, td, *J* 11.8, 3.9 Hz, 3-$CH_2$), 2.22 (3H, s, NMe); $\delta_C$ (150.9 MHz, $CDCl_3$) 141.9, 131.5, 128.9 (2C), 128.2 (2C), 127.6, 118.3, 108.1, 105.2, 68.4, 53.0, 44.7, 43.6; *m*/*z* (EI, 70 eV) 212 (14, $M^+$), 211 (17), 168 (15), 167 (10), 135 (100), 77 (24), 51 (16), 42 (33), 39 (10%).

*4.2.2. 2-Ethyl-1-phenyl-1,2,3,4-tetrahydropyrrolopyrazine (**10**).* Yield 1.47 g (65%), as yellowish solid, mp 52–53 °C (ethyl acetate/hexane); [Found: C, 79.3; H, 7.9; N, 12.2. $C_{15}H_{18}N_2$ requires C, 79.61; H, 8.02; N, 12.38%]; $R_f$ (1:2 ethyl acetate/hexane) 0.36; $\delta_H$ (400 MHz, $CDCl_3$) 7.40–7.29 (5H, m, Ph), 6.57–6.56 (1H, m, 6-H), 6.08 (1H, dd, *J* 3.4, 2.8 Hz, 7-H), 5.37–5.36 (1H, m, 8-H), 4.49 (1H, s, 1-H), 4.21 (1H, td, *J* 11.2, 4.4 Hz, 4-$CH_2$), 4.05 (1H, ddd, *J* 11.6, 3.9, 2.9 Hz, 4-$CH_2$), 3.31 (1H, ddd, *J* 12.1, 4.3, 2.9 Hz, 3-$CH_2$), 2.75 (1H, ddd, *J* 12.1, 11.1, 3.9 Hz, 3-$CH_2$), 2.72–2.64 (1H, m, NC*H*$_2$Me), 2.26 (1H, qd, *J* 13.8, 7.0 Hz, NC*H*$_2$Me), 1.05 (3H, t, *J* 7.0 Hz, NCH$_2$*Me*); $\delta_C$ (150.9 MHz, $CDCl_3$) 142.5, 131.6, 128.8 (2C), 128.2 (2C), 127.3, 118.1, 108.0, 105.3, 65.6, 47.9, 47.7, 44.6, 11.7; *m*/*z* (EI, 70 eV) 226 (9, $M^+$), 225 (10), 168 (17), 167 (10), 149 (100), 94 (10), 91 (11), 77 (20), 56 (9), 51 (22), 42 (25), 41 (17), 39 (18%).

*4.2.3. 2-Methyl-1-(4-methylphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (**11**).* Yield 2.06 g (91%), as brown oil; [Found: C, 79.4; H, 8.3; N, 12.2. $C_{15}H_{18}N_2$ requires C, 79.61; H, 8.02; N, 12.38%]; $R_f$ (silufol, ethyl acetate) 0.46; $\delta_H$ (400 MHz, $CDCl_3$) 7.21 (2H, d, *J* 7.8 Hz, CH–Ar), 7.11 (2H, d, *J* 7.8 Hz, CH–Ar), 6.52 (1H, s, 6-H), 6.02 (1H, t, *J* 2.6 Hz, 7-H), 5.28 (1H, s, 8-H), 4.20 (1H, td, *J* 11.7, 4.3 Hz, 4-$CH_2$), 4.09 (1H, s, 1-H), 4.00–3.95 (1H, m, 4-$CH_2$), 3.12 (1H, dd, *J* 11.9, 2.9 Hz, 3-$CH_2$), 2.77 (1H, dd, *J* 11.9, 3.8 Hz, 3-$CH_2$), 2.33 (3H, s, NMe), 2.18 (3H, s, $C_6H_4$–*Me-p*); $\delta_C$ (150.9 MHz, $CDCl_3$) 138.9, 137.1, 131.8, 128.9 (2C), 128.8 (2C), 118.2, 108.1, 105.1, 68.1, 53.0, 44.7, 43.5, 21.1; *m*/*z* (EI, 70 eV) 226 (2, $M^+$), 211 (11), 210 (100), 209 (53), 208 (5), 195 (27), 182 (13), 181 (7), 168 (8), 167 (9), 91 (7), 65 (9), 42 (7), 41 (7), 39 (7%).

### 4.3. 1-(2-Thienyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (12)

To a stirred solution of pyrrolopyrazine **8** (5.8 g, 219 mmol) in methanol (20 mL), $NaBH_4$ (2.7 g, 73 mmol) was added in small portions. The stirring was continued for 48 h at 50 °C (TLC monitoring). After completion of the reaction, the solvent was evaporated in vacuo, the residue was dissolved in water (15 mL) and extracted with ether (3×20 mL). The combined organic layers were dried with $MgSO_4$. The solvent was evaporated in vacuo to give pyrrolopyrazine **12** (2.23 g, 45%) as yellow solid, mp 92–93 °C (ethyl acetate/hexane); [Found: C, 64.5; H, 5.8; N, 13.5. $C_{11}H_{12}N_2S$ requires C, 64.67; H, 5.92; N, 13.71%]; $R_f$ (alufol, 20:1, *i*-PrOH/$NH_3$) 0.69; $\delta_H$ (400 MHz, $CDCl_3$) 7.21 (1H, d, *J* 4.9 Hz, CH–Th), 7.01 (1H, d, *J* 3.0 Hz, 6-H), 6.92 (1H, dd, *J* 4.9, 3.7 Hz, CH–Th), 6.55 (1H, s, CH–Th), 6.09 (1H, t, *J* 3.0 Hz, 7-H), 5.77–5.76 (1H, m, 8-H), 5.39 (1H, s, 1-H), 4.04–3.88 (2H, m, 4-$CH_2$), 3.37–3.29 (1H, m, 3-$CH_2$), 3.24–3.15 (1H, m, 3-$CH_2$), 2.10 (1H, s, NH); $\delta_C$ (150.9 MHz, $CDCl_3$) 144.4, 141.0, 126.5, 126.2, 125.7, 116.1, 106.1, 104.0, 55.7, 47.9, 46.7; *m*/*z* (EI, 70 eV) 204 (57, $M^+$), 203 (75), 174 (18), 121 (65), 94 (20), 92 (26), 67 (18), 65 (20), 51 (17), 45 (41), 42 (20), 41 (39), 39 (100), 38 (18%).

### 4.4. 2-Ethyl-1-(2-thienyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (13)

Freshly distilled acetic anhydride (5.4 g, 53 mmol) was added to pyrrolopyrazine **12** (2.2 g, 11 mmol). The reaction mixture was stirred for 2 h (TLC monitoring). After completion of the reaction, the pH was adjusted to 9–10 by addition of 40% aqueous $Na_2CO_3$. The resulting solution was extracted with $CH_2Cl_2$ (3×20 mL). The combined organic layers were dried with $MgSO_4$. The solvent was evaporated in vacuo to give intermediate *N*-acetyl substituted pyrrolopyrazine (1.8 g, 68%) as white solid, mp 100–102 °C.

To a stirred suspension of $LiAlH_4$ (2.34 g, 61.6 mmol) in THF (100 mL) *N*-acetyl substituted pyrrolopyrazine (1.9 g, 7.7 mmol) was added by small portions. The reaction was carried out under an argon atmosphere. The reaction completed in 3 h (TLC monitoring). After completion ethyl acetate (10 mL), water (7 mL) and 30% aqueous solution of NaOH (25 mL) were added to the stirred

reaction mixture. The resulting solution was poured into a funnel and extracted with ethyl acetate (3×100 mL). The combined organic layers were dried with $MgSO_4$. The solvent was evaporated in vacuo to give pyrrolopyrazine **13** (1.0 g, 59%) as white solid, mp 45–46 °C (ethyl acetate/hexane); [Found: C, 66.9; H, 6.8; N, 11.9. $C_{13}H_{16}N_2S$ requires C, 67.20; H, 6.94; N, 12.06%]; $R_f$ (sorbfil, 2:3, ethyl acetate/hexane) 0.73; $\delta_H$ (400 MHz, $CDCl_3$) 7.25 (1H, d, *J* 4.9 Hz, CH–Th), 7.03 (1H, d, *J* 2.9 Hz, 6-H), 6.94 (1H, dd, *J* 4.9, 3.2 Hz, CH–Th), 6.55 (1H, s, CH–Th), 6.10 (1H, t, *J* 2.9 Hz, 7-H), 5.64–5.63 (1H, m, 8-H), 4.92 (1H, s, 1-H), 4.13–3.99 (2H, m, 4-$CH_2$), 3.31 (1H, td, *J* 12.4, 4.3 Hz, 3-$CH_2$), 2.85–2.72 (2H, m, 3-$CH_2$ and N*CH*$_2$Me), 2.38 (1H, qd, *J* 13.7, 7.0 Hz, N*CH*$_2$Me), 1.10 (3H, t, *J* 7.0 Hz, NCH$_2$*Me*); $\delta_C$ (150.9 MHz, $CDCl_3$) 146.8, 143.3, 126.0, 125.8, 125.3, 118.3, 108.0, 105.4, 59.7, 47.6, 47.2, 44.0, 12.0; *m*/*z* (EI, 70 eV) 232 (46, $M^+$), 231 (38), 203 (9), 174 (34), 149 (100), 121 (14), 97 (20), 94 (20), 77 (11), 65 (13), 56 (17), 51 (14), 45 (30), 42 (48), 41 (31), 39 (71%).

### 4.5. General procedure for the synthesis of pyrrolo[1,2-*a*] pyrazines 14–17

Freshly distilled $POCl_3$ (1.54 g, 10 mmol) was added dropwise to cooled (−5 °C) DMF (2.31 ml, 30 mmol) maintaining the temperature. The resulting solution was stirred for 40 min at room temperature and pyrrolopyrazine (5 mmol) dissolved in DMF (3 mL) was added. The stirring was continued for 8 h (TLC monitoring). The pH of the reaction mixture was adjusted to 9–10 (10% aqueous NaOH). The resulting solution was extracted with ether (3×20 mL). The combined organic layers were dried with $MgSO_4$. The solvent was evaporated in vacuo to give the target pyrrolopyrazines **14**–**17**.

*4.5.1. 2-Methyl-1-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbaldehyde (**14**).* Yield 0.60 g (50%), yellowish solid, mp 138–139 °C (ethyl acetate/hexane); [Found: C, 74.7; H, 6.6; N, 11.5. $C_{15}H_{16}N_2O$ requires C, 74.97; H, 6.71; N, 11.66%]; $R_f$ (alufol, 1:3, ethyl acetate/hexane) 0.49; $\nu_{max}$ (KBr) 1646 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.46 (1H, s, CHO), 7.37–7.32 (5H, m, Ph), 6.78 (1H, d, *J* 4.1 Hz, 7-H), 5.48 (1H, d, *J* 4.1 Hz, 8-H), 4.75 (1H, dd, *J* 13.5, 2.5 Hz, 4-$CH_2$), 4.42–4.32 (1H, m, 4-$CH_2$), 4.21 (1H, s, 1-H), 3.20 (1H, ddd, *J* 12.1, 4.4, 1.3 Hz, 3-$CH_2$), 2.80 (1H, td, *J* 12.1, 4.0 Hz, 3-$CH_2$), 2.23 (3H, s, NMe); $\delta_C$ (150.9 MHz, $CDCl_3$) 179.1, 141.4, 140.5, 130.4, 128.8 (2C), 128.6 (2C), 128.1, 124.0, 108.3, 68.1, 52.2, 45.5, 43.5; *m*/*z* (EI, 70 eV) 240 (31, $M^+$), 239 (16), 211 (17), 196 (8), 167 (6), 164 (9), 163 (100), 77 (12), 51 (7), 42 (19%).

*4.5.2. 2-Ethyl-1-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbaldehyde (**15**).* Yield 0.61 g (48%), yellow solid, mp 87–89 °C (ether); [Found: C, 75.9; H, 7.1; N, 10.7. $C_{16}H_{18}N_2O$ requires C, 75.56; H, 7.13; N, 11.01%]; $R_f$ (alufol, 1:3, ethyl acetate/hexane) 0.55; $\nu_{max}$ (KBr) 1654 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.46 (1H, s, CHO), 7.35–7.30 (5H, m, Ph), 6.78 (1H, d, *J* 4.1 Hz, 7-H), 5.50 (1H, dd, *J* 4.1, 0.5 Hz, 8-H), 4.76–4.71 (1H, m, 4-$CH_2$), 4.51 (1H, s, 1-H), 4.33 (1H, ddd, *J* 13.6, 11.1, 4.5 Hz, 4-$CH_2$), 3.33 (1H, ddd, *J* 12.4, 4.5, 2.6 Hz, 3-$CH_2$), 2.72 (1H, ddd, *J* 12.4, 11.1, 4.0 Hz, 3-$CH_2$), 2.70–2.61 (1H, m, N*CH*$_2$Me), 2.26 (1H, qd, *J* 13.7, 7.0 Hz, N*CH*$_2$Me), 1.03 (3H, t, *J* 7.0 Hz, NCH$_2$*Me*); $\delta_C$ (100.6 MHz, $CDCl_3$) 178.9, 141.6, 140.9, 130.3, 128.8 (2C), 128.5 (2C), 127.9, 123.8, 108.5, 65.5, 47.7, 47.2, 45.5, 11.5; *m*/*z* (EI, 70 eV) 254 (16, $M^+$), 253 (7), 225 (9), 196 (7), 178 (11), 177 (100), 167 (5), 91 (5), 77 (8), 56 (6), 42 (10%).

*4.5.3. 2-Methyl-1-(4-methylphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a] pyrazine-6-carbaldehyde (**16**).* Yield 0.80 g (63%), white solid, mp 134–135 °C (ethyl acetate/hexane); [Found: C, 75.4; H, 7.3; N, 10.9. $C_{16}H_{18}N_2O$ requires C, 75.56; H, 7.13; N, 11.01%]; $R_f$ (silufol, ethyl acetate) 0.66; $\nu_{max}$ (KBr) 1645 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.45 (1H, s, CHO), 7.20 (2H, d, *J* 8.0 Hz, CH–Ar), 7.15 (2H, d, *J* 8.0 Hz, CH–Ar), 6.77 (1H, d, *J* 4.0 Hz, 7-H), 5.48 (1H, d, *J* 4.0 Hz, 8-H), 4.73 (1H, dd, *J* 13.5, 3.0 Hz, 4-$CH_2$), 4.40–4.31 (1H, m, 4-$CH_2$), 4.17 (1H, s, 1-H), 3.19 (1H, dd, *J* 11.8, 3.9 Hz, 3-$CH_2$), 2.78 (1H, td, *J* 11.8, 4.0 Hz, 3-$CH_2$), 2.35 (3H, s, NMe), 2.21 (3H, s, $C_6H_4$–*Me-p*); $\delta_C$ (100.6 MHz, $CDCl_3$) 178.9, 141.7, 137.8, 137.5, 130.4, 129.2 (2C), 128.7 (2C), 123.8, 108.3, 67.8, 52.2, 45.3, 43.4, 21.1; *m*/*z* (EI, 70 eV) 254 (40, $M^+$), 253 (35), 225 (26), 210 (6), 196 (7), 167 (6), 164 (11), 163 (100), 132 (9), 112 (6), 42 (7%).

*4.5.4. 2-Ethyl-1-(2-thienyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbaldehyde (**17**).* Yield 1.0 g (78%), yellow oil; [Found: C, 64.3; H, 6.0; N, 10.6. $C_{14}H_{16}N_2OS$ requires C, 64.58; H, 6.19; N, 10.76%]; $R_f$ (silufol, 1:2, ethyl acetate/hexane) 0.73; $\nu_{max}$ (KBr) 1663 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.46 (1H, s, CHO), 7.28–7.26 (1H, m, CH–Th), 7.04 (1H, d, *J* 3.5 Hz, CH–Th), 6.95 (1H, dd, *J* 5.1, 3.5 Hz, CH–Th), 6.81 (1H, d, *J* 4.0 Hz, 7-H), 5.76 (1H, d, *J* 4.0 Hz, 8-H), 4.95 (1H, s, 1-H), 4.64 (1H, td, *J* 13.6, 4.0 Hz, 4-$CH_2$), 4.32 (1H, ddd, *J* 13.7, 9.5, 4.5 Hz, 4-$CH_2$), 3.31 (1H, td, *J* 12.6, 4.3 Hz, 3-$CH_2$), 2.82–2.69 (2H, m, 3-$CH_2$ and N*CH*$_2$Me), 2.36 (1H, qd, *J* 13.8, 7.0 Hz, N*CH*$_2$Me), 1.09 (3H, t, *J* 7.0 Hz, NCH$_2$*Me*); $\delta_C$ (150.9 MHz, $CDCl_3$) 179.1, 144.7, 140.2, 130.4, 126.6, 126.1, 126.0, 123.8, 108.4, 59.8, 47.7, 46.6, 44.9, 11.8; *m*/*z* (EI, 70 eV) 260 (75, $M^+$), 231 (100), 202 (40), 177 (94), 174 (10), 147 (8), 122 (10), 108 (13), 97 (18), 56 (8%).

### 4.6. General procedure for the synthesis of pyrrolo[1,2-*a*] pyrazines 18–21

Trifluoroacetic anhydride (2.78 ml, 20 mmol) was added dropwise to a stirred solution of pyrrolopyrazine (10 mmol) and pyridine (2.00 ml, 25 mmol) in dry $CH_2Cl_2$ (40 mL). The stirring was continued at 35 °C (TLC monitoring). After completion, the pH of the reaction mixture was adjusted to 9–10 by addition of 40% aqueous $Na_2CO_3$. The resulting solution was extracted with $CH_2Cl_2$ (3×50 mL). The combined organic layers were dried with $MgSO_4$. The solvent was evaporated in vacuo to crude product, which was purified by column chromatography or recrystalization to give pyrrolopyrazines **18**–**21**.

*4.6.1. 2,2,2-Trifluoro-1-(2-methyl-1-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-6-yl)ethanone (**18**).* Purified by column chromatography (ethyl acetate/hexane, 1:8), yield 1.66 g (54%), as yellowish solid, mp 111–113 °C (ethyl acetate/hexane); [Found: C, 62.0; H, 4.8; N, 8.9. $C_{16}H_{15}F_3N_2O$ requires C, 62.33; H, 4.90; N, 9.09%]; $R_f$ (sorbfil, 1:2, ethyl acetate/hexane) 0.64; $\nu_{max}$ (KBr) 1651 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.37–7.32 (5H, m, Ph), 7.09–7.06 (1H, m, 7-H), 5.55 (1H, d, *J* 4.5 Hz, 8-H), 4.73 (1H, dd, *J* 13.7, 2.7 Hz, 4-$CH_2$), 4.45–4.35 (1H, m, 4-$CH_2$), 4.22 (1H, s, 1-H), 3.24 (1H, dd, *J* 12.2, 4.6 Hz, 3-$CH_2$), 2.81 (1H, dd, *J* 12.2, 4.0 Hz, 3-$CH_2$), 2.24 (3H, s, NMe); $\delta_C$ (100.6 MHz, $CDCl_3$) 169.4 (q, $^2J_{C,F}$ 35 Hz), 144.4, 140.0, 128.8 (2C), 128.7 (2C), 128.4, 123.6 (q, $^3J_{C,F}$ 4 Hz), 123.5, 117.2 (q, $^1J_{C,F}$ 291 Hz), 109.5, 68.3, 52.1, 46.3, 43.4; *m*/*z* (EI, 70 eV) 308 (17, $M^+$), 307 (10), 232 (10), 231 (100), 211 (9), 134 (8), 118 (7), 91 (6), 77 (16), 69 (7), 51 (9), 42 (21%).

*4.6.2. 1-(2-Ethyl-1-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-6-yl)-2,2,2-trifluoroethanone (**19**).* Purified by recrystallization (ethyl acetate/hexane), yield 1.64 g (51%), as yellowish solid, mp 74–75 °C (ethyl acetate/hexane); [Found: C, 63.1; H, 5.2; N, 8.5. $C_{17}H_{17}F_3N_2O$ requires C, 63.35; H, 5.32; N, 8.69%]; $R_f$ (sorbfil, 1:2, ethyl acetate/hexane) 0.59; $\nu_{max}$ (KBr) 1661 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 7.37–7.31 (5H, m, Ph), 7.07 (1H, dd, *J* 4.4, $^5J_{H,F}$ 1.7 Hz, 7-H), 5.57 (1H, d, *J* 4.4 Hz, 8-H), 4.73 (1H, td, *J* 13.7, 2.9 Hz, 4-$CH_2$), 4.51 (1H, s, 1-H), 4.38–4.33 (1H, m, 4-$CH_2$), 3.37 (1H, ddd, *J* 12.4, 4.7, 2.9 Hz, 3-$CH_2$), 2.74–2.70 (1H, m, 3-$CH_2$), 2.69–2.63 (1H, m, N*CH*$_2$Me), 2.25 (1H, qd, *J* 13.5, 6.9 Hz, N*CH*$_2$Me), 1.03 (3H, t, *J* 6.9 Hz, NCH$_2$*Me*); $\delta_C$ (100.6 MHz, $CDCl_3$) 169.3 (q, $^2J_{C,F}$ 35 Hz), 144.7, 140.4, 128.8 (2C), 128.7 (2C), 128.2, 123.5 (q, $^3J_{C,F}$ 4 Hz), 123.4, 117.2 (q, $^1J_{C,F}$

290 Hz), 109.7, 65.8, 47.7, 47.2, 46.4, 11.5; *m*/*z* (EI, 70 eV) 322 (7, $M^+$), 246 (11), 245 (100), 225 (9), 168 (8), 167 (15), 166 (9), 148 (9), 147 (11), 127 (7), 119 (7), 104 (8), 91 (25), 77 (13), 69 (8), 56 (17), 51 (7), 42 (14%).

*4.6.3. 2,2,2-Trifluoro-1-[2-methyl-1(4-methylphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-6-yl]ethanone (**20**).* Purified by column chromatography (ethyl acetate/ether, 1:1), yield 1.80 g (56%), as white solid, mp 108–109 °C (ethyl acetate/hexane); [Found: C, 63.0; H, 5.2; N, 8.5. $C_{17}H_{17}F_3N_2O$ requires C, 63.35; H, 5.32; N, 8.69%]; $R_f$ (sorbfil, 1:2, ethyl acetate/hexane) 0.57; $\nu_{max}$ (KBr) 1658 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.21 (2H, d, *J* 8.2 Hz, CH–Ar), 7.16 (2H, d, *J* 8.2 Hz, CH–Ar), 7.08 (1H, dd, *J* 4.3, $^5J_{H,F}$ 2.0 Hz, 7-H), 5.56 (1H, d, *J* 4.3 Hz, 8-H), 4.72 (1H, dd, *J* 13.9, 2.8 Hz, 4-$CH_2$), 4.44–4.34 (1H, m, 4-$CH_2$), 4.19 (1H, s, 1-H), 3.23 (1H, ddd, *J* 12.2, 4.6, 1.6 Hz, 3-$CH_2$), 2.79 (1H, td, *J* 12.2, 4.1 Hz, 3-$CH_2$), 2.36 (3H, s, NMe), 2.23 (3H, s, $-C_6H_4-$*Me-p*); $\delta_C$ (100.6 MHz, $CDCl_3$) 169.4 (q, $^2J_{C,F}$ 35 Hz), 144.7, 138.2, 137.0, 129.4 (2C), 128.8 (2C), 123.6 (q, $^3J_{C,F}$ 4 Hz), 123.4, 117.2 (q, $^1J_{C,F}$ 290 Hz), 109.5, 68.0, 52.2, 46.3, 43.4, 21.2; *m*/*z* (EI, 70 eV) 322 (35, $M^+$), 321 (28), 232 (11), 231 (100), 225 (14), 132 (7), 42 (6%).

*4.6.4. 1-[2-Ethyl]-1-(2-thienyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-6-yl]-2,2,2-trifluoroethanone (**21**).* Purified by column chromatography (ethyl acetate, 1:15), yield 2.62 g (80%), as yellow oil; [Found: C, 54.7; H, 4.8; N, 8.4. $C_{15}H_{15}F_3N_2OS$ requires C, 54.87; H, 4.90; N, 8.53%]; $R_f$ (sorbfil,1:7, ethyl acetate/hexane) 0.54; $\nu_{max}$ (KBr) 1660 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 7.30 (1H, d, *J* 5.2 Hz, CH–Th), 7.12 (1H, dd, *J* 4.3, $^5J_{H,F}$ 2.0 Hz, 7-H), 7.07 (1H, d, *J* 3.5 Hz, CH–Th), 6.97 (1H, dd, *J* 5.2, 3.5 Hz, CH–Th), 5.81 (1H, d, *J* 4.3 Hz, 8-H), 4.96 (1H, s, 1-H), 4.65 (1H, td, *J* 13.9, 4.0 Hz, 4-$CH_2$), 4.36 (1H, ddd, *J* 13.9, 9.6, 5.0 Hz, 4-$CH_2$), 3.36 (1H, td, *J* 12.9, 4.0 Hz, 3-$CH_2$), 2.81–2.73 (2H, m, 3-$CH_2$ and N*C*$H_2$Me), 2.36 (1H, qd, *J* 13.7, 6.90 Hz, N*C*$H_2$Me), 1.10 (3H, t, *J* 6.9 Hz, NCH$_2$*Me*); $\delta_C$ (150.9 MHz, $CDCl_3$) 169.4 (q, $^2J_{C,F}$ 36 Hz), 143.9, 143.2, 126.8, 126.2 (2C), 123.5 (q, $^3J_{C,F}$ 4 Hz), 123.4, 117.1 (q, $^1J_{C,F}$ 290 Hz), 109.6, 60.0, 47.7, 46.6, 45.9, 11.7; *m*/*z* (EI, 70 eV) 328 (28, $M^+$), 327 (26), 270 (16), 245 (100), 231 (74), 202 (19), 200 (15), 174 (19), 147 (18), 110 (18), 97 (56), 89 (15), 69 (59), 57 (15), 56 (45), 45 (36), 42 (77), 41 (22), 39 (69%).

### 4.7. Experimental procedure for the synthesis of pyrrolodiazocine 22 in acetonitrile

Methyl propiolate (440 mg, 5.3 mmol) was added to a solution of pyrrolopyrazine **14** (370 mg, 1.5 mmol) in acetonitrile (15 mL). The reaction was heated for 5 days at reflux (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give pyrrolodiazocine **22**.

*4.7.1. Methyl 9-formyl-3-methyl-6-phenyl-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-5-carboxylate (**22**).* Yield 250 mg (51%) as yellowish solid, mp 163–164 °C (ethyl acetate/hexane); [Found: C, 70.0; H, 6.1; N, 8.5. $C_{19}H_{20}N_2O_3$ requires C, 70.35; H, 6.21; N, 8.64%]; $R_f$ (silufol, 1:1, ethyl acetate/hexane) 0.87; $\nu_{max}$ (KBr) 1683, 1653, 1600 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.47 (1H, s, CHO), 7.68 (1H, s, 4-H), 7.31–7.01 (5H, m, Ph), 6.98 (1H, d, *J* 3.8 Hz, 8-H), 6.25 (1H, d, *J* 3.8 Hz, 7-H), 6.17 (1H, s, 6-H), 5.42 (1H, ddd, *J* 14.9, 13.1, 5.4 Hz, 1-$CH_2$), 3.90–3.71 (5H, m, 2-$CH_2$ and 1-$CH_2$ and $CO_2$Me), 2.99 (3H, s, NMe), 3.82 (1H, dd, *J* 15.4, 4.6 Hz, 2-$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 179.4, 170.3, 153.0, 145.1, 144.6, 133.5, 129.7 (2C), 126.8, 126.4, 126.0 (2C), 114.2, 96.7, 51.7, 49.5, 46.3, 43.7, 42.3; *m*/*z* (EI, 70 eV) 324 (60, $M^+$), 293 (5), 281 (7), 265 (30), 235 (6), 208 (14), 192 (8), 180 (11), 167 (8), 154 (9), 152 (12), 115 (12), 91 (9), 78 (9), 77 (2), 59 (100), 57 (23), 52 (12), 43 (14), 42 (93), 41 (12%).

### 4.8. Experimental procedure for the synthesis of pyrrolodiazocine 24 in acetonitrile

Methyl propiolate (920 mg, 10.9 mmol) was added to a solution of pyrrolopyrazine **16** (400 mg, 1.6 mmol) in acetonitrile (20 mL). The reaction was heated for 14 days at reflux (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give pyrrolodiazocine **24**.

*4.8.1. Methyl 9-formyl-3-methyl-6-(4-methylphenyl)-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-5-carboxylate (**24**).* Yield 290 mg (55%) as white solid, mp 193–195 °C (ethyl acetate/hexane); [Found: C, 70.6; H, 6.4; N, 8.0. $C_{20}H_{22}N_2O_3$ requires C, 70.99; H, 6.55; N, 8.28%]; $R_f$ (silufol, ethyl acetate) 0.69; $\nu_{max}$ (KBr) 1686, 1654, 1602 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.47 (1H, s, CHO), 7.49 (1H, s, 4-H), 7.08 (2H, d, *J* 7.8 Hz, CH–Ar), 6.98 (1H, d, *J* 3.9 Hz, 8-H), 6.82 (2H, d, *J* 7.8 Hz, CH–Ar), 6.44 (1H, s, 6-H), 6.23 (1H, d, *J* 3.9 Hz, 7-H), 5.49 (1H, td, *J* 15.0, 5.2 Hz, 1-$CH_2$), 3.77 (1H, td, *J* 15.8, 5.2, Hz, 2-$CH_2$), 3.77 (1H, dd, *J* 15.0, 3.8 Hz, 1-$CH_2$), 3.04 (3H, s, $CO_2$Me), 2.88 (1H, dd, *J* 15.8, 5.2 Hz, 2-$CH_2$), 2.35 (3H, s, NMe), 2.29 (3H, s, $C_6H_4-$*Me-p*); $\delta_C$ (100 MHz, $CDCl_3$) 179.3, 170.3, 152.9, 144.8, 142.0, 135.9, 133.4, 129.7 (2C), 126.7, 125.8 (2C), 114.1, 96.8, 51.6, 49.6, 46.2, 43.6, 41.9, 21.0; *m*/*z* (EI, 70 eV) 338 (100, $M^+$), 307 (15), 295 (13), 279 (90), 249 (16), 247 (15), 222 (30), 42 (11%).

### 4.9. Experimental procedure for the synthesis of pyrrolodiazocine 25 in acetonitrile

Acetylacetylene (260 mg, 3.9 mmol) was added to a solution of pyrrolopyrazine **14** (74 mg, 0.32 mmol) in acetonitrile (8 mL). The reaction was heated for 3 days at reflux (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give pyrrolodiazocine **25**.

*4.9.1. 5-Acetyl-3-methyl-6-phenyl-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-9-carbaldehyde (**25**).* Yield 290 mg (55%) as brown solid, mp 170–171 °C (ethyl acetate/hexane); [Found: C, 73.7; H, 6.4; N, 8.9. $C_{19}H_{20}N_2O_2$ requires C, 74.00; H, 6.54; N, 9.08%]; $R_f$ (silufol, 1:1, ethyl acetate/hexane) 0.30; $\nu_{max}$ (KBr) 1658, 1580 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 9.43 (1H, s, CHO), 7.45 (1H, s, 4-H), 7.22 (2H, t, *J* 7.7 Hz, CH–Ar), 7.13–7.11 (1H, m, CH–Ar), 6.93 (1H, d, *J* 3.9 Hz, 8-H), 6.88 (2H, d, *J* 8.3 Hz, CH–Ar), 6.45 (1H, s, 6-H), 6.18 (1H, d, *J* 3.9 Hz, 7-H), 5.44 (1H, ddd, *J* 15.3, 13.7, 5.7 Hz, 1-$CH_2$), 3.90–3.85 (1H, m, 2-$CH_2$), 3.70 (1H, ddd, *J* 15.3, 4.4, 1.3 Hz, 1-$CH_2$), 3.00 (3H, s, COMe), 2.81 (1H, ddd, *J* 15.7, 5.7, 1.3 Hz, 2-$CH_2$), 2.31 (3H, s, NMe); $\delta_C$ (100 MHz, $CDCl_3$) 194.3, 179.3, 154.8, 144.8, 144.6, 133.4, 129.0 (2C), 126.8, 126.2, 125.8 (2C), 114.4, 111.3, 49.4, 46.0, 43.8, 40.1, 25.1; *m*/*z* (EI, 70 eV) 308 (45, $M^+$), 265 (37), 222 (5), 115 (5), 82 (5), 78 (5), 43 (100), 42 (28%).

### 4.10. General procedure for the synthesis of pyrrolodiazocines 25 and 34 in methanol

Acetylacetylene (177 mg, 2.6 mmol) was added to a stirred solution of pyrrolopyrazine **14** or **20** (2 mmol) in methanol (20 mL). The stirring was continued at 30 °C (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give the target pyrrolodiazocine **25** or **34**.

*4.10.1. 5-Acetyl-3-methyl-6-phenyl-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-9-carbaldehyde (**25**).* Yield 120 mg (31%).

*4.10.2. 1-[5-Acetyl-3-methyl-6-(4-methylphenyl)-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocin-9-yl]-2,2,2-trifluoroethanone (**34**).*

Yield 270 mg (70%) as white solid, mp 112–114 °C (ethyl acetate/hexane); [Found: C, 64.4; H, 5.3; N, 7.0. $C_{21}H_{21}F_3N_2O_2$ requires C, 64.61; H, 5.42; N, 7.18%]; $R_f$ (sorbfil, 1:1, ethyl acetate/hexane) 0.63; $\nu_{max}$ (KBr) 1662, 1590 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 7.50 (1H, s, 4-H), 7.32–7.31 (1H, m, 8-H), 7.07 (2H, d, *J* 7.7 Hz, CH–Ar), 6.80 (2H, d, *J* 7.7 Hz, CH–Ar), 6.51 (1H, s, 6-H), 6.27 (1H, d, *J* 4.4 Hz, 7-H), 5.39 (1H, ddd, *J* 15.2, 13.4, 5.5 Hz, 1-$CH_2$), 4.07–4.01 (1H, m, 2-$CH_2$), 3.81 (1H, ddd, *J* 15.2, 4.4, 1.7 Hz, 1-$CH_2$), 3.05 (3H, s, $CO_2Me$), 2.88 (1H, ddd, *J* 15.7, 5.5, 1.7 Hz, 2-$CH_2$), 2.35 (3H, s, NMe), 2.29 (3H, s, $C_6H_4$–*Me-p*); $\delta_C$ (100 MHz, $CDCl_3$) 194.2, 169.5 (q, $^2J_{C,F}$ 34 Hz), 154.8, 147.8, 141.3, 136.0, 129.8 (2C), 126.2, 125.9 (q, $^3J_{C,F}$ 4 Hz), 125.6 (2C), 117.5 (q, $^1J_{C,F}$ 290 Hz), 115.4, 110.9, 49.6, 46.9, 43.9, 40.0, 25.1, 21.0; *m*/*z* (EI, 70 eV) 390 (45, $M^+$), 347 (27), 271 (4), 43 (100), 42 (21%).

### 4.11. General procedure for the synthesis of pyrrolodiazocines 22–24, 31 and 39

Methyl propiolate (420 mg, 5 mmol) was added to a solution of pyrrolopyrazine **14**–**16**, or **20**, **21** (2 mmol) in methanol (20 mL). The reaction was heated at reflux (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give pyrrolodiazocines **22**–**24**, **31** or **39**.

*4.11.1. Methyl 9-formyl-3-methyl-6-phenyl-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-5-carboxylate (**22**).* Yield 240 mg (57%).

*4.11.2. Methyl 3-ethyl-9-formyl-6-phenyl-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-5-carboxylate (**23**).* Yield 340 mg (71%) as yellowish solid, mp 154–156 °C (ethyl acetate/hexane); [Found: C, 70.8; H, 6.5; N, 8.1. $C_{20}H_{22}N_2O_3$ requires C, 70.99; H, 6.55; N, 8.28%]; $R_f$ (sorbfil, 1:2, ethyl acetate/hexane) 0.43; $\nu_{max}$ (KBr) 1656, 1604 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 9.46 (1H, s, CHO), 7.72 (1H, s, 4-H), 7.29 (2H, t, *J* 7.7 Hz, CH–Ar), 7.20–7.17 (1H, m, CH–Ar), 7.06–7.04 (2H, m, CH–Ar), 6.97 (1H, d, *J* 3.9 Hz, 8-H), 6.25 (1H, d, *J* 3.9 Hz, 7-H), 6.16 (1H, s, 6-H), 5.44 (1H, ddd, *J* 16.2, 14.7, 6.1 Hz, 1-$CH_2$), 3.75 (3H, s, $CO_2Me$), 3.75–3.69 (2H, m, 2-$CH_2$ and 1-$CH_2$), 3.28–3.23 (1H, m, N$CH_2$Me), 3.18–3.12 (1H, m, N$CH_2$Me), 2.96 (1H, dd, *J* 14.7, 5.5 Hz, 2-$CH_2$), 1.08 (3H, t, *J* 7.2 Hz, $NCH_2Me$); $\delta_C$ (100 MHz, $CDCl_3$) 179.3, 170.3, 152.5, 144.9, 144.7, 133.1, 129.0 (2C), 126.8, 126.4, 126.1 (2C), 114.0, 96.9, 51.9, 51.6, 48.1, 46.9, 42.2, 15.0; *m*/*z* (EI, 70 eV) 338 (14, $M^+$), 279 (9), 115 (4), 91 (4), 77 (17), 59 (100), 56 (12%).

*4.11.3. Methyl 9-formyl-3-methyl-6-(4-methylphenyl)-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-5-carboxylate (**24**).* Yield 230 mg (44%).

*4.11.4. Methyl 3-methyl-6-(4-methylphenyl)-9-(trifluoroacetyl)-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-5-carboxylate (**31**).* Yield 276 mg (34%) as yellow solid, mp 95–97 °C (ethyl acetate/hexane); [Found: C, 61.9; H, 5.1; N, 6.7. $C_{21}H_{21}F_3N_2O_3$ requires C, 62.06; H, 5.21; N, 6.89%]; $R_f$ (sorbfil, 1:2, ethyl acetate/hexane) 0.56; $\nu_{max}$ (KBr) 1686, 1666, 1597 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.68 (1H, s, 4-H), 7.34–7.32 (1H, m, 8-H), 7.10 (2H, d, *J* 7.9 Hz, CH–Ar), 6.90 (2H, d, *J* 7.9 Hz, CH–Ar), 6.30 (1H, d, *J* 4.2 Hz, 7-H), 6.18 (1H, s, 6-H), 5.33 (1H, ddd, *J* 15.0, 13.1, 5.4 Hz, 1-$CH_2$), 4.01–3.90 (1H, m, 2-$CH_2$), 3.81 (1H, ddd, *J* 15.0, 3.4, 1.6 Hz, 1-$CH_2$), 3.75 (3H, s, $CO_2Me$), 3.00 (3H, s, NMe), 2.85 (1H, ddd, *J* 15.8, 5.4, 1.6 Hz, 2-$CH_2$), 2.31 (3H, s, $C_6H_4$–*Me-p*); $\delta_C$ (100 MHz, $CDCl_3$) 170.1, 169.5 (q, $^2J_{C,F}$ 35 Hz), 153.0, 147.7, 141.4, 136.1, 129.8 (2C), 126.2, 125.8 (q, $^3J_{C,F}$ 4 Hz), 125.7 (2C), 117.1 (q, $^1J_{C,F}$ 290 Hz), 115.1, 96.2, 51.7, 49.7, 47.1, 43.7, 42.1, 21.0; *m*/*z* (EI, 70 eV) 406 (21, $M^+$), 347 (20), 91 (10), 69 (6), 59 (100), 42 (59%).

*4.11.5. Methyl 3-ethyl-6-(2-thienyl)-9-(trifluoroacetyl)-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-5-carboxylate (**39**).* Yield 140 mg (22%) as white solid, mp 88–90 °C (ethyl acetate/hexane); [Found: C, 55.0; H, 4.5; N, 6.6. $C_{19}H_{19}F_3N_2O_3S$ requires C, 55.33; H, 4.64; N, 6.79%]; $R_f$ (sorbfil, 1:7, ethyl acetate/hexane) 0.22; $\nu_{max}$ (KBr) 1664, 1606 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.72 (1H, s, 4-H), 7.31 (1H, dd, *J* 4.3, $^5J_{H,F}$ 2.0 Hz, 8-H), 7.16 (1H, d, *J* 5.0 Hz, CH–Th), 6.91 (1H, dd, *J* 5.0, 3.7 Hz, CH–Th), 6.61–6.60 (1H, m, CH–Th), 6.31 (1H, d, *J* 4.3 Hz, 7-H), 6.30 (1H, s, 6-H), 5.20 (1H, ddd, *J* 15.4, 12.3, 5.1 Hz, 1-$CH_2$), 4.20 (1H, td, *J* 15.4, 3.4 Hz, 1-$CH_2$), 4.05 (1H, ddd, *J* 16.1, 12.3, 3.4 Hz, 2-$CH_2$), 3.76 (3H, s, $CO_2Me$), 3.32–3.19 (2H, m, N$CH_2$Me), 3.14 (1H, ddd, *J* 16.1, 5.1, 3.4 Hz, 2-$H_a$), 1.13 (3H, t, *J* 7.2 Hz, $NCH_2Me$); $\delta_C$ (100.6 MHz, $CDCl_3$) 170.0, 169.4 (q, $^2J_{C,F}$ 38 Hz), 152.2, 149.6, 146.7, 127.3, 126.0, 125.5 (q, $^3J_{C,F}$ 4 Hz), 124.3, 122.7, 117.3 (q, $^1J_{C,F}$ 291 Hz), 114.3, 96.6, 52.1, 51.6, 48.5, 48.1, 38.8, 14.8; *m*/*z* (EI, 70 eV) 412 (55, $M^+$), 354 (13), 353 (72), 352 (11), 282 (10), 255 (14), 226 (13), 200 (20), 199 (17), 198 (13), 186 (16), 172 (15), 160 (14), 154 (21), 142 (17), 140 (25), 121 (16), 111 (13), 97 (31), 98 (15), 84 (15), 82 (19), 71 (18), 69 (19), 68 (14), 59 (100), 58 (43), 56 (63), 54 (15), 53 (17), 45 (29), 42 (25), 41 (13), 39 (23%).

### 4.12. General procedure for the synthesis of pyrrolodiazocine 26 and 33

Acetylacetylene (272 mg, 4 mmol) was added to a solution of pyrrolopyrazine **15** or **19** (2 mmol) in methanol (20 mL). The reaction was heated at reflux (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give pyrrolodiazocines **26** or **33**.

*4.12.1. 5-Acetyl-3-ethyl-6-phenyl-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-8-carbaldehyde (**26**).* Yield 406 mg (63%), as yellow solid, mp 182–183 °C (ethyl acetate/hexane); [Found: C, 74.2; H, 6.7; N, 8.5. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88; N, 8.69%]; $R_f$ (sorbfil, 1:1, ethyl acetate/hexane) 0.45; $\nu_{max}$ (KBr) 1650, 1578 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 9.46 (1H, s, CHO), 7.53 (1H, s, 4-H), 7.29–7.25 (2H, m, CH–Ar), 7.19–7.15 (1H, m, CH–Ar), 6.97–6.95 (3H, m, CH–Ar and 8-H), 6.49 (1H, s, 6-H), 6.23 (1H, d, *J* 4.0 Hz, 7-H), 5.50 (1H, ddd, *J* 14.9, 13.3, 6.1 Hz, 1-$CH_2$), 3.80 (1H, ddd, *J* 15.3, 13.3, 5.0 Hz, 2-$CH_2$), 3.75–3.70 (1H, m, 1-$CH_2$), 3.27 (2H, qd, *J* 13.9, 7.2 Hz, N$CH_2$Me), 2.99 (1H, ddd, *J* 15.3, 6.1, 0.9 Hz, 2-$CH_2$), 2.36 (3H, s, COMe), 1.14 (3H, t, *J* 7.2 Hz, $NCH_2Me$); $\delta_C$ (100 MHz, $CDCl_3$) 194.3, 179.3, 154.3, 144.8, 144.6, 133.1, 129.0 (2C), 126.9, 126.2, 126.0 (2C), 114.2, 111.7, 52.2, 48.1, 46.6, 40.2, 25.2, 15.0; *m*/*z* (EI, 70 eV) 322 (33, $M^+$), 279 (30), 249 (7), 208 (8), 56 (11), 43 (100%).

*4.12.2. 1-(5-Acetyl-3-methyl-6-phenyl-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocin-9-yl)-2,2,2-trifluoroethanone (**33**).* Yield 164 mg (21%) as white solid, mp 137–139 °C (ethyl acetate/hexane); [Found: C, 64.3; H, 5.3; N, 7.0. $C_{21}H_{21}F_3N_2O_2$ requires C, 64.61; H, 5.42; N, 7.18%]; $R_f$ (sorbfil, 1:3, ethyl acetate/hexane) 0.38; $\nu_{max}$ (KBr) 1661, 1580 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.55 (1H, s, 4-H), 7.34–7.27 (3H, m, 8-H and CH–Ar), 7.21–7.17 (1H, m, CH–Ar), 6.96–6.94 (2H, m, CH–Ar), 6.57 (1H, s, 6-H), 6.28 (1H, d, *J* 4.3 Hz, 7-H), 5.43 (1H, ddd, *J* 15.1, 13.2, 6.0 Hz, 1-$CH_2$), 3.88 (1H, ddd, *J* 15.7, 13.2, 4.7 Hz, 2-$CH_2$), 3.78 (1H, ddd, *J* 15.1, 4.7, 1.4 Hz, 1-$CH_2$), 3.35–3.21 (2H, m, N$CH_2$Me), 3.01 (1H, ddd, *J* 15.7, 6.0, 1.4 Hz, 2-$CH_2$), 2.36 (3H, s, COMe), 1.14 (3H, t, *J* 7.2 Hz, $NCH_2Me$); $\delta_C$ (100 MHz, $CDCl_3$) 194.2, 169.5 (q, $^2J_{C,F}$ 35 Hz), 154.3, 147.6, 144.1, 129.1 (2C), 126.4, 126.0 (q, $^3J_{C,F}$ 4 Hz), 125.9, 125.8 (2C), 117.4 (q, $^1J_{C,F}$ 290 Hz), 115.2, 110.9, 52.1, 48.0, 47.3, 40.3, 25.1, 14.9; *m*/*z* (EI, 70 eV) 390 (24, $M^+$), 347 (23), 165 (5), 115 (8), 91 (10), 77 (7), 56 (8), 43 (100), 42 (11%).

### 4.13. Experimental procedure for the synthesis of pyrrolodiazocine 27

Acetylacetylene (290 mg, 3.4 mmol) was added to a stirred solution of pyrrolopyrazine **16** (350 mg, 1.4 mmol) in methanol

(20 mL). The stirring was continued for 3 days at 30 °C (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give pyrrolodiazocine **27**.

*4.13.1. 5-Acetyl-3-methyl-6-(4-methylphenyl)-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-9-carbaldehyde (**27**).* Yield 130 mg (30%) as white solid, mp 175–176 °C (ethyl acetate/hexane); [Found: C, 74.3; H, 6.8; N, 8.6. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88; N, 8.69%]; $R_f$ (silufol, ethyl acetate) 0.48; $\nu_{max}$ (KBr) 1661, 1589 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 9.45 (1H, s, CHO), 7.47 (1H, s, 4-H), 7.04 (2H, d, *J* 7.6 Hz, CH–Ar), 6.95 (1H, d, *J* 3.9 Hz, 8-H), 6.78 (2H, d, *J* 7.6 Hz, CH–Ar), 6.41 (1H, s, 6-H), 6.19 (1H, d, *J* 3.9 Hz, 7-H), 5.46 (1H, ddd, *J* 14.8, 13.7, 5.5 Hz, 1-$CH_2$), 3.97–3.92 (1H, m, 2-$CH_2$), 3.73 (1H, ddd, *J* 14.8, 4.4, 1.3 Hz, 1-$CH_2$), 3.02 (3H, s, COMe), 2.84 (1H, ddd, *J* 15.7, 5.5, 1.3 Hz, 2-$CH_2$), 2.33 (3H, s, NMe), 2.27 (3H, s, $C_6H_4$–*Me-p*); $\delta_C$ (100 MHz, $CDCl_3$) 194.4, 179.3, 154.9, 144.9, 141.8, 135.7, 133.4, 129.7 (2C), 126.8, 125.8 (2C), 114.4, 111.5, 49.6, 46.0, 43.9, 39.9, 25.2, 21.0; *m*/*z* (EI, 70 eV) 322 (100, $M^+$), 293 (6), 279 (39), 248 (9), 223 (10), 203 (9), 167 (9), 129 (5), 105 (6), 57 (5), 43 (56), 42 (18)%.

### 4.14. Experimental procedure for the synthesis of pyrrole 28

DMAD (690 mg, 4.7 mmol) was added to a stirred solution of pyrrolopyrazine **16** (400 mg, 1.6 mmol) in methanol (20 mL). The reaction was heated at reflux (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give pyrrole **28**.

*4.14.1. Dimethyl (2E)-2-[(2-{2-formyl-5-[methoxy(4-methylphenyl)methyl]-1H-pyrrol-1-yl}ethyl)(methyl)amino]but-2-enedioate (**28**).* Yield 440 mg (65%) as white solid, mp 125–127 °C (ethyl acetate/hexane); [Found: C, 64.2; H, 6.6; N, 6.4. $C_{23}H_{28}N_2O_6$ requires C, 64.47; H, 6.59; N, 6.54%]; $R_f$ (sorbfil, 1:4 ethyl acetate/hexane) 0.32; $\nu_{max}$ (KBr) 1738, 1683, 1664, 1578 $cm^{-1}$; $\delta_H$ (400 MHz, DMSO-$d_6$) 9.48 (1H, s, CHO), 7.27 (2H, d, *J* 7.9 Hz, CH–Ar), 7.19 (2H, d, *J* 7.9 Hz, CH–Ar), 6.88 (1H, d, *J* 4.0 Hz, 3′-H), 5.98 (1H, d, *J* 4.0 Hz, 4′-H), 5.31 (1H, s, C*H*(OMe)Ph), 4.76 (1H, s, 3-H), 4.53–4.35 (2H, m, β-$CH_2$), 3.97 (3H, s, $CO_2$Me), 3.66 (3H, s, $CO_2$Me), 3.48 (2H, t, *J* 6.7 Hz, α-$CH_2$), 3.38 (3H, s, CH(O*Me*)Ph), 2.74 (3H, s, NMe), 2.36 (3H, s, $C_6H_4$–*Me*); $\delta_C$ (100.6 MHz, $CDCl_3$) 179.4, 168.0, 166.0, 154.6, 143.6, 138.3, 135.1, 132.4, 129.4 (3C), 127.7 (2C), 124.9, 111.5, 85.1, 77.5, 56.9, 53.1, 50.8, 43.8, 38.0, 21.2; *m*/*z* (EI, 70 eV) 428 (8, $M^+$), 412 (11), 325 (100), 293 (9), 281 (9), 266 (15), 265 (58), 247 (13), 235 (12), 234 (10), 186 (36), 167 (16), 154 (9), 129 (11), 104 (10), 91 (26), 82 (22), 81 (12), 80 (11), 78 (10), 77 (16), 68 (11), 59 (78), 58 (18), 57 (26), 51 (11), 45 (13), 42 (55), 41 (18%).

### 4.15. Experimental procedure for the synthesis of pyrrolodiazocine 29 and pyrrole 35

Methyl propiolate (140 mg, 1.6 mmol) was added to a solution of pyrrolopyrazine **18** (250 mg, 0.8 mmol) in methanol (8 mL). The reaction was heated for 7 h at reflux (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:3) to give pyrrolodiazocine **29** (100 mg, 31%) as white solid and pyrrole **35** (50 mg, 32%) as white solid.

*4.15.1. Methyl 3-methyl-6-phenyl-9-(trifluoroacetyl)-1,2,3,6-tetrahydro[1,2-d][1,4]diazocine-5-carboxylate (**29**).* Yield 100 mg (32%), white solid, mp 159–161 °C (ethyl acetate/hexane); [Found: C, 61.0; H, 4.8; N, 7.0. $C_{20}H_{19}F_3N_2O_3$ requires C, 61.22; H, 4.88; N, 7.14%]; $R_f$ (sorbfil, 1:3, ethyl acetate/hexane) 0.34; $\nu_{max}$ (KBr) 1666, 1620 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.70 (1H, s, 4-H), 7.33–7.28 (3H, m, CH–Ar and 8-H), 7.21 (1H, t, *J* 7.3 Hz, CH–Ar), 7.02 (2H, d, *J* 8.1 Hz, CH–Ar), 6.31 (1H, d, *J* 4.4 Hz, 7-H), 6.24 (1H, s, 6-H), 5.34 (1H, ddd, *J* 15.1, 13.0, 5.4 Hz, 1-$CH_2$), 3.98–3.78 (2H, m, 1-$CH_2$ and 2-$CH_2$), 3.76 (3H, s, $CO_2$Me), 3.01 (3H, s, NMe), 3.87 (1H, ddd, *J* 15.8, 5.4, 1.6 Hz, 2-$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 170.2, 169.7 (q, $^2J_{C,F}$ 35 Hz), 153.1, 147.5, 144.6, 129.3 (2C), 126.6, 126.3, 126.0 (2C), 125.9 (q, $^3J_{C,F}$ 4 Hz), 117.5 (q, $^1J_{C,F}$ 290 Hz), 115.3, 96.1, 51.8, 49.6, 47.2, 43.8, 42.5; *m*/*z* (EI, 70 eV) 392 (86, $M^+$), 377 (7), 261 (11), 333 (100), 315 (14), 302 (7), 276 (21), 235 (7), 229 (7), 180 (7), 115 (10), 42 (14%).

*4.15.2. Methyl (2E)-3-[{2-[2-[methoxy(phenyl)methyl]-5-(trifluoroacetyl)-1H-pyrrol-1-yl]ethyl}(methyl)amino]acrylate (**35**).* Yield 51 mg (15%), white solid, mp 115–117 °C (ethyl acetate/hexane); [Found: C, 59.1; H, 5.3; N, 6.4. $C_{21}H_{23}F_3N_2O_4$ requires C, 59.43; H, 5.46; N, 6.60%]; $R_f$ (sorbfil, 1:3, ethyl acetate/hexane) 0.27; $\nu_{max}$ (KBr) 1670, 1612 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.47–7.31 (6H, m, Ph and 3-H), 7.21 (1H, dd, *J* 4.3, $^5J_{H,F}$ 2.1 Hz, 4′-H), 6.07 (1H, d, *J* 4.3 Hz, 3′-H), 5.32 (1H, s, *CH*(OMe)Ph), 4.61 (1H, d, *J* 13.6 Hz, 2-H), 4.46–4.31 (2H, m, β-$CH_2$), 3.69 (3H, s, $CO_2$Me), 3.42 (3H, s, CH(O*Me*)Ph), 3.30–3.18 (2H, m, α-$CH_2$), 2.83 (3H, s, NMe); $\delta_C$ (100.6 MHz, $CDCl_3$) 170.0 (q, $^2J_{C,F}$ 35 Hz), 169.6, 152.1, 145.6, 137.7, 129.1 (2C), 128.8, 127.2 (2C), 125.8, 125.4, 124.1 (q, $^3J_{C,F}$ 4 Hz), 117.0 (q, $^1J_{C,F}$ 291 Hz), 112.7, 85.5, 78.4, 57.2, 56.0, 50.5, 45.2; *m*/*z* (EI, 70 eV) 424 (6, $M^+$), 409 (10), 393 (13), 392 (40), 378 (7), 377 (41), 294 (7), 129 (6), 128 (100), 45 (11%).

### 4.16. Experimental procedure for the synthesis of pyrrolodiazocine 30

Methyl propiolate (310 mg, 3.7 mmol) was added to a solution of pyrrolopyrazine **19** (400 mg, 1.2 mmol) in methanol (20 mL). The reaction was heated for 6 h at reflux (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give diazocine **30**.

*4.16.1. Methyl 3-ethyl-6-phenyl-9-(trifluoroacetyl)1,2,3,6-tetrahydropyrrolo[1,2-a][1,4]diazocine-5-carboxylate (**30**).* Yield 240 mg (49%) as yellow solid, mp 126–127 °C (ethyl acetate/hexane); [Found: C, 61.8; H, 5.1; N, 6.7. $C_{21}H_{21}F_3N_2O_3$ requires C, 62.06; H, 5.21; N, 6.89%]; $R_f$ (sorbfil, 1:3, ethyl acetate/hexane) 0.64; $\nu_{max}$ (KBr) 1656, 1604 $cm^{-1}$; $\delta_H$ (600 MHz, $CDCl_3$) 7.73 (1H, s, 4-H), 7.33 (1H, dd, *J* 4.3, $^5J_{H,F}$ 2.2 Hz, 8-H), 7.30 (2H, t, *J* 7.7 Hz, CH–Ar), 7.20 (1H, t, *J* 7.2 Hz, CH–Ar), 7.04 (2H, d, *J* 7.7 Hz, CH–Ar), 6.30 (1H, d, *J* 4.3 Hz, 7-H), 6.22 (1H, s, 6-H), 5.39–5.32 (1H, m, 1-$CH_2$), 3.81–3.75 (2H, m, 1-$CH_2$ and 2-$CH_2$), 3.75 (3H, s, $CO_2$Me), 3.21 (2H, qd, *J* 14.3, 7.2 Hz, N*CH*$_2$Me), 2.99–2.96 (1H, m, 2-$CH_2$), 1.08 (3H, t, *J* 7.2 Hz, NCH$_2$*Me*); $\delta_C$ (100 MHz, $CDCl_3$) 170.1, 169.5 (q, $^2J_{C,F}$ 35 Hz), 152.5, 147.5, 144.3, 129.1 (2C), 126.5, 125.9 (3C), 125.8 (q, $^3J_{C,F}$ 4 Hz), 117.4 (q, $^1J_{C,F}$ 290 Hz), 114.9, 96.2, 51.8, 51.7, 48.0, 47.5, 42.3, 14.8; *m*/*z* (EI, 70 eV) 406 (15, $M^+$), 347 (37), 276 (11), 220 (9), 205 (10), 192 (18), 180 (18), 154 (20), 139 (19), 115 (39), 91 (38), 77 (60), 69 (28), 59 (100), 42 (80%).

### 4.17. Experimental procedure for the synthesis of pyrrolodiazocine 32 and pyrrole 36

Acetylacetylene (180 mg, 2.6 mmol) was added to a solution of pyrrolopyrazine **18** (400 mg, 1.3 mmol) in methanol (15 mL). The reaction was heated for 7 h at reflux (TLC monitoring). After completion the solvent was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 1:15) to give pyrrolodiazocine **32** (120 mg, 23%) as yellow solid and pyrrole **36** (100 mg, 19%) as yellow solid.

*4.17.1. 1-(5-Acetyl-3-methyl-6-phenyl-1,2,3,6-tetrahydropyrrolo[1,2-a][1,4]diazocin-9-yl)-2,2,2-trifluoroethanone (**32**).* Yield 120 mg

(23%) as yellow solid, mp 184–186 °C (ethyl acetate/hexane); [Found: C, 63.5; H, 5.0; N, 7.3. $C_{20}H_{19}F_3N_2O_2$ requires C, 63.82; H, 5.09; N, 7.44%]; $R_f$ (sorbfil, 1:3, ethyl acetate/hexane) 0.42; $\nu_{max}$ (KBr) 1660, 1589 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.52 (1H, s, 4-H), 7.33–7.26 (4H, m, 8-H and CH–Ar), 6.93–6.90 (1H, m, CH–Ar), 6.92 (2H, d, *J* 7.8 Hz, CH–Ar) 6.57 (1H, s, 6-H), 6.28 (1H, d, *J* 4.3 Hz, 7-H), 5.40 (1H, ddd, *J* 15.2, 13.8, 5.5 Hz, 1-$CH_2$), 4.06–3.95 (1H, m, 2-$CH_2$), 3.80 (1H, dd, *J* 15.2, 2.5 Hz, 1-$CH_2$), 3.06 (3H, s, COMe), 2.88 (1H, dd, *J* 15.9, 4.2 Hz, 2-$CH_2$), 2.36 (3H, s, NMe); $\delta_C$ (150.9 MHz, $CDCl_3$) 194.1, 169.5 (q, $^2J_{C,F}$ 35 Hz), 154.8, 147.4, 144.3, 129.1 (2C), 126.3, 126.2, 125.8 (q, $^3J_{C,F}$ 4 Hz), 125.7 (2C), 117.4 (q, $^1J_{C,F}$ 292 Hz), 115.4, 110.6, 49.4, 46.8, 43.9, 40.2, 25.0; *m*/*z* (EI, 70 eV) 376 (100, $M^+$), 361 (6), 333 (83), 285 (8), 276 (14), 271 (8), 229 (9), 193 (8), 180 (7), 115 (7), 91 (7), 43 (16), 42 (11%).

*4.17.2. (3E)-4-[{2-[2-[Methoxy(phenyl)methyl]-5-(trifluoroacetyl)-1H-pyrrol-1-yl]ethyl}(methyl)amino]but-3-en-2-one (**36**).* Yield 101 mg (19%), yellow solid, mp 120–122 °C (ethyl acetate/hexane); [Found: C, 61.5; H, 5.6; N, 6.7. $C_{21}H_{23}F_3N_2O_3$ requires C, 61.76; H, 5.68; N, 6.86%]; $R_f$ (sorbfil, 1:3, ethyl acetate/hexane) 0.25; $\nu_{max}$ (KBr) 1668, 1569 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.44–7.32 (6H, m, Ph and 3-H), 7.22–7.21 (1H, m, 4′-H), 6.09 (1H, d, *J* 4.3 Hz, 3′-H), 5.32 (1H, s, C*H*(OMe)Ph), 5.08 (1H, d, *J* 13.7 Hz, 2-H), 4.46–4.30 (2H, m, β-$CH_2$), 3.42 (3H, s, CH(O*Me*)Ph), 3.30–3.18 (2H, m, α-$CH_2$), 2.85 (3H, s, NMe), 2.11 (3H, s, COMe); $\delta_C$ (100.6 MHz, $CDCl_3$) 195.2, 170.0 (q, $^2J_{C,F}$ 35 Hz), 151.7, 145.4, 137.7, 128.9 (2C), 128.8, 127.0 (2C), 125.6, 124.1 (q, $^3J_{C,F}$ 4 Hz), 116.9 (q, $^1J_{C,F}$ 291 Hz), 112.8, 98.2, 78.3, 57.2, 56.6, 45.5, 35.8, 27.9; *m*/*z* (EI, 70 eV) 408 (31, $M^+$), 393 (100), 294 (16), 287 (17), 277 (8), 112 (80), 84 (8), 70 (11) 43 (10%).

### 4.18. Experimental procedure for the synthesis of pyrrolodiazocine 37

Methyl propiolate (170 mg, 2.0 mmol) was added to a stirred solution of pyrrolopyrazine **17** (310 mg, 1.2 mmol) in methanol (15 mL). The stirring was continued for 6 days at 55 °C (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give pyrrolodiazocine **37**.

*4.18.1. Methyl 3-ethyl-9-formyl-6-(2-thienyl)-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-5-carboxylate (**37**).* Yield 240 mg (57%) as yellow solid, mp 125–127 °C (ethyl acetate/hexane); [Found: C, 62.5; H, 5.8; N, 8.0. $C_{18}H_{20}N_2O_3S$ requires C, 62.77; H, 5.85; N, 8.13%]; $R_f$ (sorbfil, 1:4, ethyl acetate/hexane) 0.50; $\nu_{max}$ (KBr) 1653, 1610 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.47 (1H, s, CHO), 7.71 (1H, s, 4-H), 7.16–7.14 (1H, m, CH–Th), 6.95 (1H, d, *J* 4.0 Hz, 8-H), 6.90 (1H, dd, *J* 5.1, 3.5 Hz, CH–Th), 6.60–6.59 (1H, m, CH–Th), 6.26 (1H, d, *J* 4.0 Hz, 7-H), 6.23 (1H, s, 6-H), 5.29 (1H, ddd, *J* 14.9, 12.7, 5.3 Hz, 1-$CH_2$), 4.13 (1H, ddd, *J* 14.9, 4.2, 2.5 Hz, 1-$CH_2$), 3.99 (1H, ddd, *J* 15.8, 12.7, 4.2 Hz, 2-$CH_2$), 3.75 (3H, s, $CO_2$Me), 3.35–3.33 (2H, m, NC$H_2$Me), 3.11 (1H, ddd, *J* 15.8, 5.3, 2.5 Hz, 2-$CH_2$), 1.12 (3H, t, *J* 7.2 Hz, NC$H_2$*Me*); $\delta_C$ (100 MHz, $CDCl_3$) 179.4, 169.9, 152.2, 150.3, 144.0, 133.2, 127.2, 126.4, 124.1, 122.6, 113.3, 97.2, 52.1, 51.5, 48.2, 47.8, 38.7, 14.9; *m*/*z* (EI, 70 eV) 344 (85, $M^+$), 312 (9), 285 (100), 255 (22), 240 (15), 214 (27), 186 (15), 173 (12), 140 (16), 97 (17), 71 (15), 56 (11%).

### 4.19. Experimental procedure for the synthesis of pyrrolodiazocine 38

Acetylacetylene (100 mg, 1.5 mmol) was added to a stirred solution of pyrrolopyrazine **17** (330 mg, 1.2 mmol) in methanol (15 mL). The stirring was continued for 4 days at 55 °C (TLC monitoring). After completion the solvent was evaporated in vacuo to give crude product, which was purified by recrystallization (ethyl acetate/hexane) to give pyrrolodiazocine **38**.

*4.19.1. 5-Acetyl-3-ethyl-6-(2-thienyl)-1,2,3,6-tetrahydropyrrolo[1,2-d][1,4]diazocine-9-carbaldehyde (**38**).* Yield 160 mg (38%) as yellow solid, mp 134–136 °C (ethyl acetate/hexane); [Found: C, 65.5; H, 6.0; N, 8.3. $C_{18}H_{20}N_2O_2S$ requires C, 65.83; H, 6.14; N, 8.53%]; $R_f$ (sorbfil, 1:2, ethyl acetate/hexane) 0.33; $\nu_{max}$ (KBr) 1650, 1579 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.46 (1H, s, CHO), 7.51 (1H, s, 4-H), 7.11 (1H, d, *J* 5.1 Hz, CH–Th), 6.94 (1H, d, *J* 4.0 Hz, 8-H), 6.88 (1H, dd, *J* 5.1, 3.5 Hz, CH–Th), 6.54 (1H, s, 6-H), 6.53–6.50 (1H, m, CH–Th), 6.23 (1H, d, *J* 4.0 Hz, 7-H), 5.45–5.33 (1H, m, 1-$CH_2$), 4.13–4.04 (2H, m, 1-$CH_2$ and 2-$CH_2$), 3.37–3.19 (2H, m, NC$H_2$Me), 3.17–3.10 (1H, m, 2-$CH_2$), 2.32 (3H, s, COMe), 1.16 (3H, t, *J* 7.2 Hz, NC$H_2$*Me*); $\delta_C$ (100 MHz, $CDCl_3$) 193.7, 179.5, 154.0, 150.0, 144.1, 133.3, 127.3, 126.6, 124.0, 122.6, 113.7, 112.1, 52.4, 48.2, 47.6, 36.8, 25.1, 15.0; *m*/*z* (EI, 70 eV) 328 (100, $M^+$), 299 (7), 285 (45), 257 (8), 240 (11), 214 (17), 178 (10), 140 (10), 97 (12), 71 (7), 43 (23%).

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### Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.104. These data include MOL files and InchIkeys of the most important compounds described in this article.

### References and notes

1. (a) Askew, B. C.; Bednar, R. A.; Bednar, B.; Claremon, D. A.; Cook, J. J.; McIntyre, C. J.; Hunt, C. A.; Gould, R. J.; Lynch, R. J.; Lynch, J. J., Jr.; Gaul, S. L.; Stranieri, M. T.; Sitko, G. R.; Holahan, M. A.; Glass, J. D.; Hamill, T.; Gorham, L. M.; Prueksaritanont, T.; Baldwin, J. J.; Hartman, G. D. *J. Med. Chem.* **1997**, *40*, 1779–1788; (b) Tapia, R. A.; Prieto, Y.; Pautet, F.; Domard, M.; Sarciron, M.-E.; Walchshofer, N.; Fillion, H. *Eur. J. Org. Chem.* **2002**, *23*, 4005–4010; (c) Cafieri, F.; Fattorusso, E.; Taglialatela Scafati, O. *J. Nat. Prod.* **1998**, *61*, 122–125; (d) Poullennec, K.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344–6345.
2. (a) Higgins, G. A.; Joharchi, N.; Wang, Y.; Corrigall, W. A.; Sellers, E. M. *Brain Res.* **1994**, *640*, 246–254; (b) De Dios, I.; Urucuela, A.; Orfao, A.; Manso, M. A. *Dig. Dis. Sci.* **2002**, *47*, 1800–1809; (c) Gonzlez-Puga, C.; Garcна-Navarro, A.; Escames, G.; Leyn, J.; Lypez-Cantarero, M.; Ros, E.; Acuca-Castroviejo, D. *J. Pineal. Res.* **2005**, *39*, 243–250; (d) Palm, C.; Pistrosch, F.; Herbrig, K.; Gross, P. *Am. J. Med.* **2006**, *119*, S87–S92; (e) Rabinstein, A. A. *Clin. Neuropharmacol.* **2006**, *29*, 87–93; (f) Albright, J. D.; Reich, M. F.; Delos Santos, E. G.; Dusza, J. P.; Sum, F. W.; Venkatesan, A. M.; Coupet, J.; Chan, P. S.; Ru, X.; Mazandarani, H.; Bailey, T. *J. Med. Chem.* **1998**, *41*, 2442–2444; (g) Tari, A.; Hamada, M.; Kamiyasu, T.; Fukino, Y.; Sumii, M.; Haruma, K.; Sumii, K. J. *Gastroenterology* **1996**, *31*, 167–170.
3. Potapov, V. V.; Fetisova, N. A.; Niktin, A. V.; Ivachtchenko, A. V. *Tetrahedron Lett.* **2009**, *50*, 2790–2792.
4. Koriatopoulou, K.; Karousis, N.; Varvounis, G. *Tetrahedron* **2008**, *64*, 10009–10013.
5. Mazurov, A. A.; Andronati, S. A.; Korotenko, T. I.; Sokolenko, N. I.; Dyadenko, A. I.; Shapiro, Y. E.; Gorbatyuk, V. Y.; Voronina, T. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2595–2600.
6. Mazurov, A. A.; Andronati, S. A.; Korotenko, T. I.; Sokolenko, N. I.; Dyadenko, A. I.; Shapiro, Y. E.; Gorbatyuk, V. Y.; Voronina, T. A. *Bioorg. Med. Chem.* **1997**, *5*, 2029–2040.
7. Varlamov, A. V.; Borisova, T. N.; Voskressensky, L. G.; Kulikova, L. N.; Soklakova, T. A.; Chernyshev, A. I.; Alexandrov, G. G. *Tetrahedron Lett.* **2002**, *43*, 6767–6769.
8. Voskressensky, L. G.; Borisova, T. N.; Kulikova, L. N.; Varlamov, A. V. *Chem. Heterocycl. Comp.* **2007**, *43*, 913–918.
9. Voskressensky, L. G.; Borisova, T. N.; Kulikova, L. N.; Varlamov, A. V.; Catto, M.; Altomare, C.; Carotti, A. *Eur. J. Org. Chem.* **2004**, 3128–3135.
10. Voskressensky, L. G.; Listratova, A. V.; Borisova, T. N.; Kovaleva, S. A.; Borisov, R. S.; Varlamov, A. V. *Tetrahedron* **2008**, *64*, 10443–10452.
11. Likhosherstov, A. M.; Peresada, V. P.; Vinokurov, V. G.; Skoldinov, A. P. *Zh. Org. Khim.* **1986**, *22*, 2610–2614.