JOC The Journal of Organic Chemistry



Article

# Synthesis and intramolecular azo coupling of 4-diazopyrrole-2-carboxylates: selective approach to benzo and hetero [c]-fused 6H-pyrrolo[3,4-c]pyridazine-5-carboxylates

Ekaterina E. Galenko, Alexey V. Galenko, Alexander F. Khlebnikov, Mikhail Sergeevich Novikov, and Julia R. Shakirova

*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01662 • Publication Date (Web): 22 Aug 2016



ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

# Synthesis and intramolecular azo coupling of 4-diazopyrrole-2-carboxylates: selective approach to benzo and hetero [*c*]-fused 6*H*-pyrrolo[3,4-*c*]pyridazine-5-carboxylates

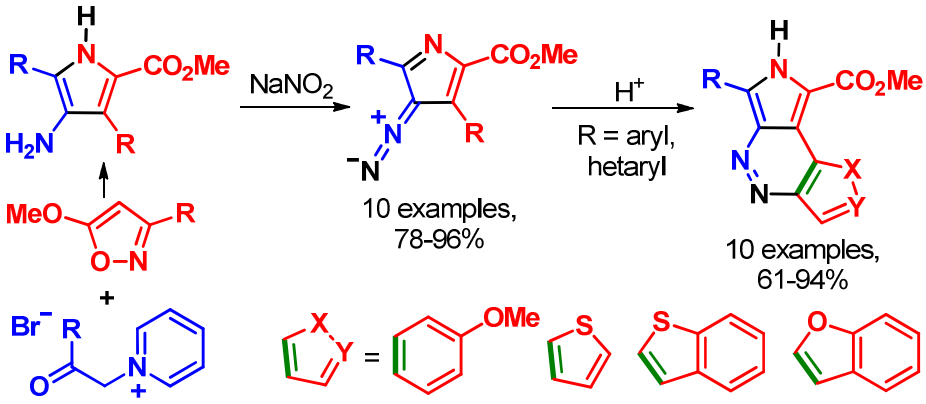
Ekaterina E. Galenko, Alexey V. Galenko, Alexander F. Khlebnikov,* Mikhail S. Novikov,

Julia R. Shakirova

St. Petersburg State University, Institute of Chemistry, 7/9 Universitetskaya nab., St. Petersburg, 199034 Russia

*Corresponding author e-mail: a.khlebnikov@spbu.ru*

## Abstract Graphic



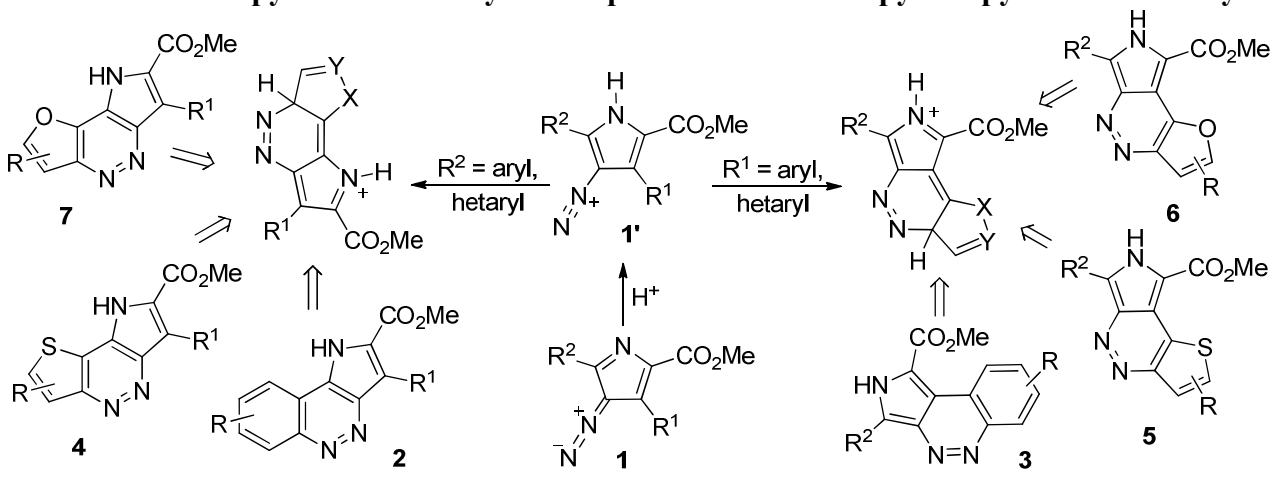

## Abstract:

A high yield synthesis of fluorescent benzo, thieno and furo [*c*]-fused methyl 7-aryl-6*H*-pyrrolo[3,4-*c*]pyridazine-5-carboxylates, including unprecedented heterocyclic skeletons, was performed by the transformation of methyl 4-aminopyrrole-2-carboxylate into the corresponding diazo compound, followed by intramolecular azo coupling under acid conditions onto a nucleophilic aryl or hetaryl group in the 3-position. Azo coupling is completely regioselective and, according to DFT calculations, kinetically controlled reaction. N-Methylation of 1,3-disubstituted 2*H*-pyrrolo[3,4-*c*]cinnolines occurs selectively at N5 under kinetic control, leading exclusively to 5-methyl-5*H*-pyrrolo[3,4-*c*]cinnoline derivatives.

## INTRODUCTION

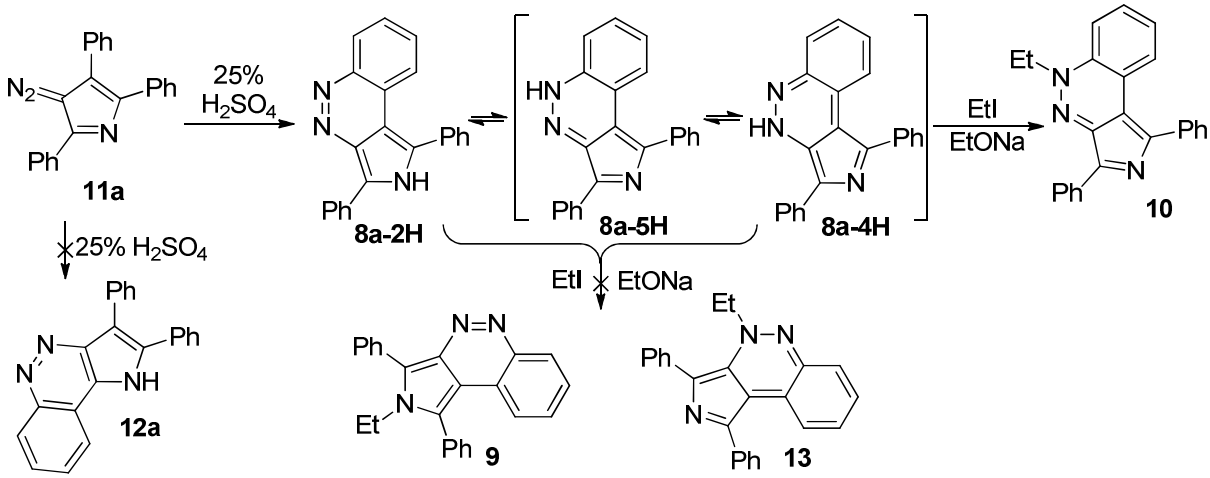
Diazoazoles have demonstrated high potential for the synthesis of practically useful polynitrogen compounds.[1] Thus, for example, the preparation of temozolomide, 3-methyl-4-oxoimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxamide, which is used as a treatment of some brain cancers,[2] involves reactions of 4-diazo-4*H*-imidazole-5-carboxamide.[3] β-Aminopyrroles, efficient synthesis of which was recently described,[4] are potentially convenient precursors of β-diazopyrroles **1**. Analysis of the literature showed that while chemistry of β-diazoindoles is developing widely, for example, 6 articles were published only during 2015,[5] the chemistry of β-diazopyrroles was studied only in one work for the same period.[6] Moreover, only about 20 articles were published[1d, 7] for the time since the release in 1908 of the first work[7a] on β-diazopyrrole chemistry, and this despite the fact that some β-diazopyrroles showed antimicrobial[8] and mutagenic[9] activity. One of the reasons for this may be the relative inaccessibility of the corresponding β-aminopyrroles, which are convenient precursors of β-diazopyrroles. With an effective method for the preparation of alkyl 4-aminopyrrole-2-carboxylates in hand that allows the introduction of a variety of aryl and hetaryl substituents at positions 3 and 5,[4] we decided to synthesize the corresponding diazopyrroles **1** with the aim of studying their intramolecular azo coupling. Such azo coupling could potentially serve as a method for the preparation of 1*H*-pyrrolo[3,2-*c*]cinnoline **2**, 2*H*-pyrrolo[3,4-*c*]cinnoline **3**, 8*H*-pyrrolo[3,2-*c*]thieno[2,3-*e*]pyridazine **4**, 7*H*-pyrrolo[3,4-*c*]thieno[2,3-*e*]pyridazine **5**, 7*H*-furo[3,2-*c*]pyrrolo[3,4-*e*]pyridazine **6**, 8*H*-furo[3,2-*c*]pyrrolo[2,3-*e*]pyridazine **7** and other fused heterocycles (Scheme 1). It is notable that about thirty substituted 1*H*-pyrrolo[3,2-*c*]cinnolines (backbone **2**) are known,[7e,10] while only three compounds with the skeleton 2*H*-pyrrolo[3,4-*c*]cinnoline **3** were reported: (1,3-diphenyl-, 1,3-diphenyl-2-ethyl-2*H*-pyrrolo[3,4-*c*]cinnoline (**8a, 9**) and 1,3-diphenyl-5-ethyl-5*H*-pyrrolo[3,4-*c*]cinnoline (**10**).[7a,b,d] The remaining mentioned heterocyclic systems are until now unknown. Meanwhile fused heteroaromatic molecules containing a pyrrole core have a significant importance in the development of new perspective materials, especially luminophores for bioimaging applications.[11]

**Scheme 1. 4-Diazopyrrole-2-carboxylates as precursors of fused pyrrolopyridazinecarboxylates**




1,3-Diphenyl-2*H*-pyrrolo[3,4-*c*]cinnoline **8a** was obtained for the first time by prolonged boiling of diazo compound **11a** in 25% sulfuric acid (Scheme 2).[7a] The formation of the second isomer, 1*H*-pyrrolo[3,2-*c*]cinnoline **12a** as a result of competitive intramolecular azo coupling reaction on the 2-phenyl group was not reported.[7a,d] It has also been shown that compound **8a** occurs as the 2*H*-tautomer, and its alkylation with EtI/EtONa leads to the formation of only 5-ethyl-5*H*-substituted tautomer **10** (Scheme 2).[7d] It is noteworthy that compound **9**, **8a**, and **10** is yellow, red and blue, respectively.[7d] Such a possibility of managing the color of the heterocyclic system by protonation, alkylation, or complexation of a certain skeletal nitrogen atom of the heterocycle is very useful for their application in modern technologies.

**Scheme 2. Synthesis of pyrrolo[3,4-*c*]cinnolines 8a, 10**



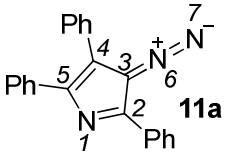
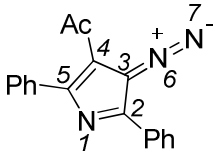
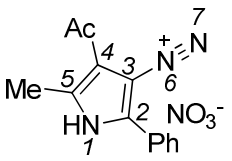
## RESULTS AND DISCUSSION

First we tried to reproduce the intramolecular azo coupling for diazo compound **11a** under conditions[7a] published in 1908 to make sure that the reaction actually proceeds selectively. The synthesis of aminopyrrole **14a** was carried out according to our method from azirine **15a** and the pyridinium salt **16a**.[4] Aminopyrrole **14a** was transformed into diazo compound **11a** by treating with excess of sodium nitrite in acetic acid at about 10 °C for 15 minutes. Diazo compound **11b**, without the 5-phenyl group, was synthesized analogously (Scheme 3).

The structure of 3-diazopyrroles has virtually not been investigated by X-ray analysis, probably because of difficulties in obtaining suitable crystals.[1d] The only, but very inaccurate, structural data was mentioned in a review[1d] for 4-acetyl-3-diazo-2,5-diphenylpyrrole. Moreover, 4-acetyl-5-methyl-2-phenyl-1*H*-pyrrole-3-diazonium nitrate instead of the corresponding diazopyrrole was obtained under diazotization of 3-acetyl-4-amino-2-methyl-5-phenyl-1*H*-pyrrole with $NaNO_2$/AcOH.[6] Taking all this into account, crystals of **11a**, suitable for performing a single crystal X-ray analysis, were grown and the X-ray study was performed (see Supporting Information) to be sure of the diazopyrrole structure. The selected X-ray structural data for **11a**, as well as the corresponding data for the mentioned compounds, available from the publications[1d,6] are listed in Table 1. The $N^1$-$C^2$and $C^3$-$N^6$ bond in diazopyrrole **11a** are much shorter than the corresponding bonds in the 1*H*-pyrrole-3-diazonium nitrate, however the $N^6$-$N^7$ in the diazo compound is much longer. The CNN fragment of diazo compound **11a** has linear geometry. The X-ray bond length and angle are in good accordance with the corresponding data from DFT B3LYP/6-31+g(d,p) calculations.

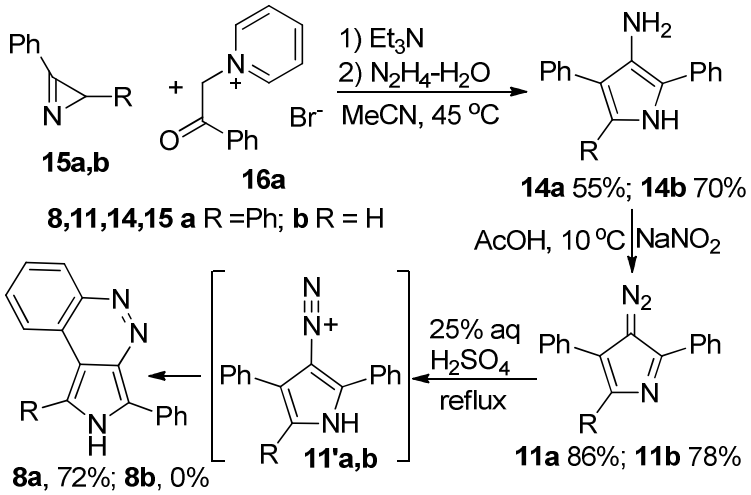
Refluxing compound **11a** in 25% sulfuric acid for 8 days resulted in the formation of cinnoline **8a** isolated in 72% yield. Analysis of the reaction by TLC and NMR showed the absence of a second possible isomer.

**Table 1. The selected structural data for 3-diazopyrrole derivatives**

| Bond length, Å; bond angle, grad |  **11a** | **11a [B3LYP/6-31+g(d,p)]** |  |  |
|---|---|---|---|---|
| $l_{1-2}$ | 1.315(2) | 1.315 | - | 1.352(3) |
| $l_{2-3}$ | 1.442(2) | 1.459 | - | 1.381(3) |
| $l_{3-4}$ | 1.437(2) | 1.452 | - | 1.433(3) |
| $l_{4-5}$ | 1.385(2) | 1.390 | - | 1.366(3) |
| $l_{5-1}$ | 1.400(1) | 1.395 | - | 1.375(3) |
| $l_{3-6}$ | 1.324(2) | 1.313 | 1.31(3) | 1.353(3) |
| $l_{6-7}$ | 1.129(2) | 1.136 | 1.13(3) | 1.101(3) |
| $a_{3-6-7}$ | 179.3(1) | 179.3 | 171(1) | 179.1(3) |

Use of 20% aq $HBF_4$ or glacial acetic acid in place of 25% aq sulfuric acid did not lead to a reduction of the reaction time or to an increase of the reaction yield (55 and 57%, respectively).

**Scheme 3. Synthesis and reactivity of diazopyrroles 11a,b**




An attempt to synthesize the 1-unsubstituted analogue **8b** by intramolecular azo coupling of diazo compound **11b** under the same conditions resulted in the formation of a complex mixture of unidentified products and significant resinification of the reaction mixture. To clarify the reasons for the selectivity of cyclization of diazo compound **11a** and the failure in the synthesis of pyrrolocinnoline **8b** the DFT

calculations of cyclization of the corresponding diazonium cations **11'** were performed (Fig. 1). According to the calculation results the barrier for the cyclization of the diazonium cation **11'a**, generated from diazo compound **11a**, on the 4-Ph group, leading eventually to the formation of compound **8a,** is 4.8 kcal/mol lower than the barrier for the cyclization on the 2-Ph group (product **12a**). This difference is large enough to provide complete selectivity of the intramolecular azo coupling. The minimal barrier for the cyclization of diazonium cation **11'b** (from diazo compound **8b**) is 1.7 kcal/mol higher than that of diazonium cation **11'a**. This should result in a relatively lower rate of intramolecular reaction of diazo compound **8b**, but it should not principally change the reactivity. At the same time, unlike compound **8a**, compound **8b** is able to enter into intermolecular azo coupling on the unsubstituted position of the pyrrole ring. For example, the intermolecular reaction of 2,5-diphenylpyrrole-3-diazonium chloride with α-unsubstituted pyrroles, leading to the corresponding azo compounds, have been implemented by Kreutzberg and Kalter.[7c] Formation of a complex mixture of products and resinification of the reaction mixture in the case of compound **11b** is therefore most likely due to the occurrence of intermolecular azo coupling leading to oligomeric products.

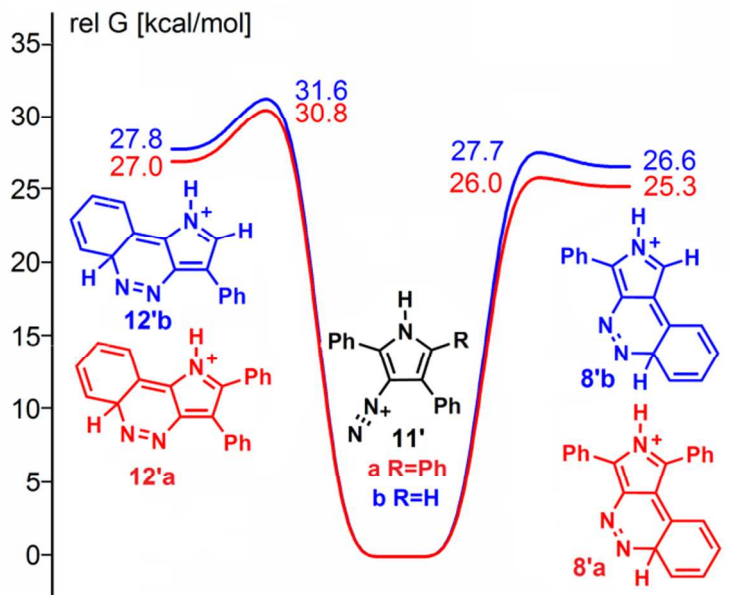



**Fig. 1.** Energy profiles for the intramolecular azo coupling of diazonium cations **11'**. Relative free *Gibbs* energies (in kcal $mol^{-1}$, 298 K, PCM model for $H_2O$) computed at the B3LYP/6-31+g(d,p) level.

From this standpoint, the use of diazo compounds **1**, containing substituents in the 2,3,5-positions, as starting material for intramolecular azo coupling is promising. The presence of a methoxycarbonyl group could potentially preclude the implementation of the intramolecular azo coupling in the harsh reaction conditions mentioned above, due to hydrolysis or decarboxylation of the ester group. To outline the ways of rational choice of diazo compounds **1** for selective intramolecular azo coupling, we performed DFT calculations for the cyclization of diazonium cations **1'** (Fig. 2).

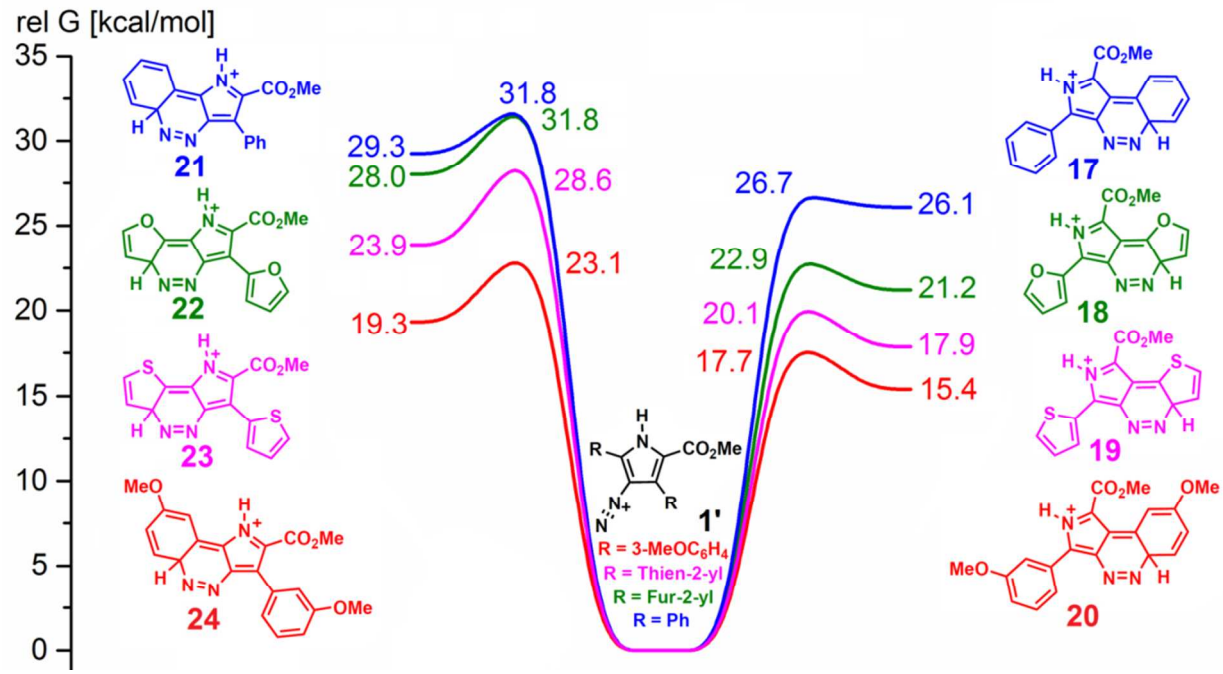
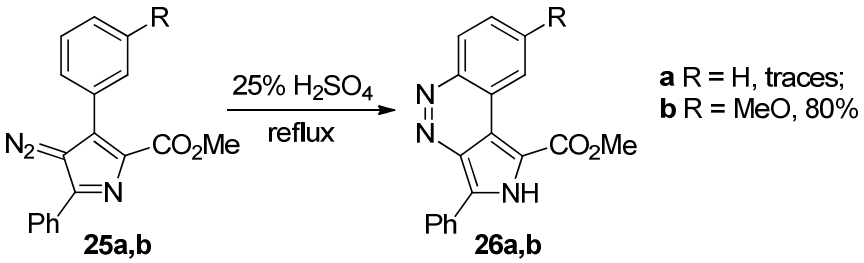



**Fig. 2.** Energy profiles for the intramolecular azo coupling of diazonium cations **1'**. Relative free *Gibbs* energies (in kcal $mol^{-1}$, 298 K, PCM model for $H_2O$) computed at the B3LYP/6-31+g(d,p) level.

According to the calculation the barrier for cyclization of diazonium cation **1'**, generated from diazo compound **1a** (R = Ph), on the 3-Ph group, leading to intermediate **17**, is 5.1 kcal/mol lower than the barrier for cyclization on the 5-Ph group (intermediate **21**). This difference should provide the selective cyclization onto the 3-Ph exclusively. On the other hand, the barrier for the formation of intermediate **17** from **1'a** is little higher than that for the cyclization of diazonium cation **11'a** into **8'a**. From the latter it follows that the diazonium cation **1'a** needs even harsher conditions for the cyclization than **11'a**. This may make it impossible the intramolecular azo coupling starting from compound **1a**, which is potentially

less stable in boiling acid due to the ester group. Since the azo coupling is an electrophilic reaction, an introduction of an electron donating group into the respective benzene ring or replacement of the phenyl group with a more nucleophilic group should lead to a reduction of the cyclization barrier, thus decreasing the reaction time and increasing the probability of obtaining the desired products. According to the calculation, the introduction of a *meta*-methoxy group into the 3-phenyl substituent or replacing the 3-phenyl group with the thiophene-2-yl or fur-2-yl group significantly reduces the cyclization barrier. Similar changes with the 5-phenyl substituent also lead to lowering the respective barriers, which however, are still higher than that for the cyclization on the identical aryl/hetaryl substituent at the 3-position of diazo compound **1**. Then diazo compounds **25a,b** were synthesized (vide infra) and introduced into the azo coupling reaction in order to check reliability of our theoretical predictions for the rational design of pyrrolo[3,4-*c*]pyridazine systems.

**Scheme 4. Intramolecular azo coupling of diazopyrroles 25a,b**

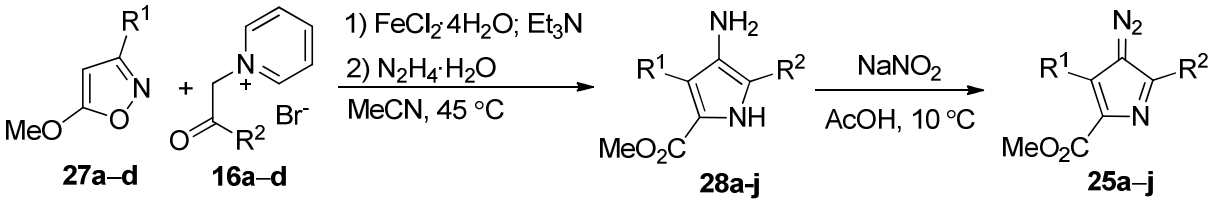



Refluxing of the solution of diazo compound **25a** in 25% aqueous sulfuric acid during 4 d was required for the complete consumption of the starting material. This was accompanied by intensive resinification of the reaction mixture and afforded only trace amounts of cinnoline **26a** (according to $^1$H NMR spectroscopy of the reaction mixture). In contrast, cyclization of diazo **25b** proceeded 5 times faster than the cyclization of diazo compound **11a** under the same conditions and cinnoline **26b** was isolated in 80%yield (Scheme 4).

Based on the above theoretical and experimental results, we synthesized a series of diazo pyrroles **25** (Table 2), containing 3-aryl- and hetaryl-substituents which are suitable for intramolecular azo coupling.

Pyrroles **28a-j** were prepared in one-pot mode by the reaction of 5-methoxyisoxazoles **27a-d** with pyridinium ylides **16a-d** under relay catalysis with $FeCl_2/Et_3N$ leading to 1-(5-methoxycarbonyl-1*H*-pyrrol-3-yl)pyridinium salts, followed by hydrazinolysis, according to published procedure (Table 2).[4] All new compounds were characterized by $^1H$ and $^{13}C$ NMR, IR spectroscopy, and mass-spectrometry.

**Table 2. Synthesis of 4-aminopyrroles 28a-j and 4-diazopyrroles 25a-j**

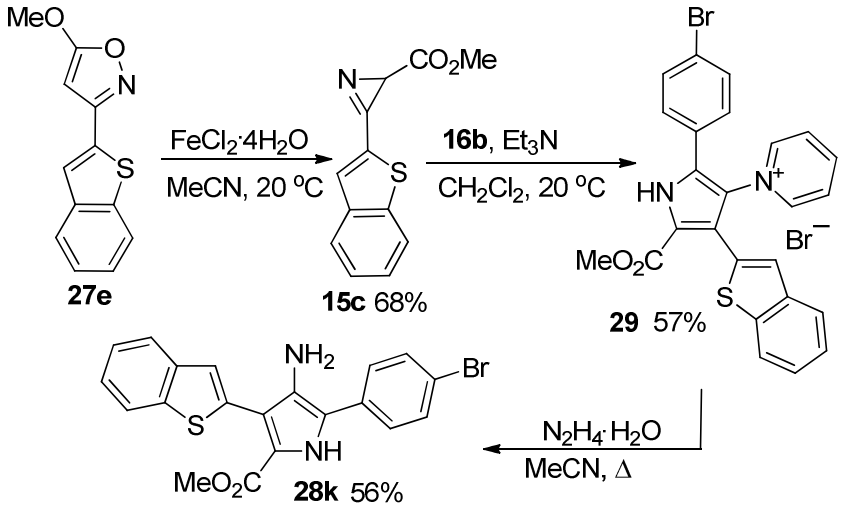



**27a–d** **16a–d** **28a-j** **25a–j**

| Entry | $R^1$ | $R^2$ | 27+16 | 28, yield % | 25, yield % |
|---|---|---|---|---|---|
| 1 | Ph | Ph | **27a+16a** | **a**, 63 | **a**, 89 |
| 2 | 3-$MeOC_6H_4$ | Ph | **27b+16a** | **b**, 67 | **b**, 76 |
| 3 | 3-$MeOC_6H_4$ | 4-$BrC_6H_4$ | **27b+16b** | **c**, 78 | **c**, 98 |
| 4 | 3-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | **27b+16c** | **d**, 47 | **d**, 88 |
| 5 | 3-$MeOC_6H_4$ | 4-$NO_2C_6H_4$ | **27b+16d** | **e**, 58 | **e**, 99 |
| 6 | thiophen-2-yl | Ph | **27c+16a** | **f**, 47 | **f**, 94 |
| 7 | thiophen-2-yl | 4-$BrC_6H_4$ | **27c+16b** | **g**, 52 | **g**, 92 |
| 8 | thiophen-2-yl | 4-$MeOC_6H_4$ | **27c+16c** | **h**, 71 | **h**, 79 |
| 9 | thiophen-2-yl | 4-$NO_2C_6H_4$ | **27c+16d** | **i**, 15 | **i**, 99 |
| 10 | benzofuran-2-yl | Ph | **27d+16a** | **j**, 44 | **j**, 84 |

The one-pot procedure for the preparation of 4-aminopyrrolole **28k** having a benzo[*b*]thiophen-2-yl substituent at the C3 atom gave unsatisfactory results, and therefore this compound was synthesized in a stepwise manner (Scheme 5).[4,12]

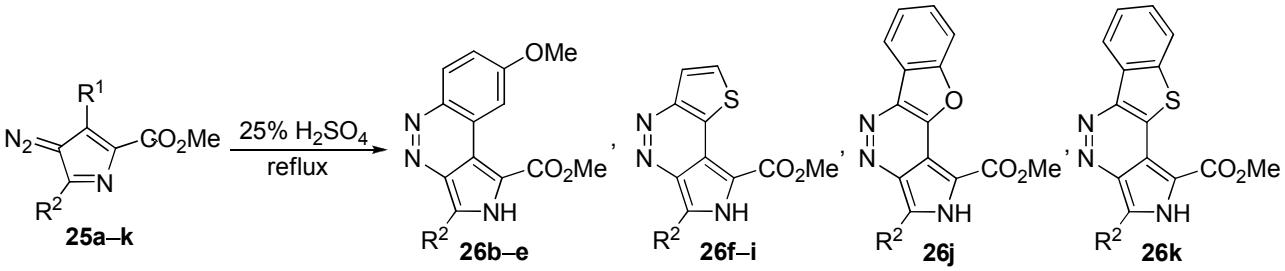
**Scheme 5. Stepwise synthesis of diazopyrrole 28k**




Aminopyrroles **28** were easily converted into diazopyrroles **25** by the reaction with sodium nitrite in acetic acid (Table 3). The reaction is completed within 15 minutes at a temperature of about 10 °C to give 3-diazopyrroles **25a-j** in high yields. Diazopyrroles are usually bright orange crystals that are stable in the solid state in the absence of light. Compound **25k** with 3-(benzo[*b*]thiophen-2-yl) substituent was not isolated in pure form. According to NMR, the reaction mixture along with the diazotization product contained a significant amount of the intramolecular azo coupling product. Apparently the activation barrier for the azo coupling reaction in this case is sufficiently low and the reaction proceeds already in acetic acid at low temperature.

The cyclization of diazopyrroles **25** to pyrrolo[3,4-*c*]pyridazines **26c-k** was performed by refluxing solutions of the diazopyrroles in 25% sulfuric acid. Typically, the reaction requires 30-36 h, except the synthesis of compound **26k**, which requires only 0.5 h. Compounds **26b-k** were isolated in good yields by a simple workup: the sulphate salt of the product was filtered off, converted to free base by suspending in an aqueous sodium bicarbonate solution, the base obtained was filtered, washed with water and dried (Table 3). Pyrrolo[3,4-*c*]pyridazines **26** are solid, coloured, high-melting compounds .

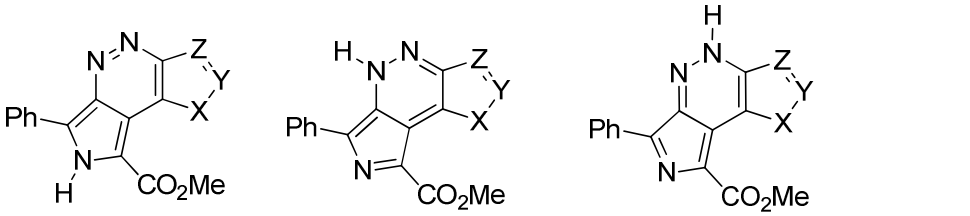
**Table 3. Synthesis of pyrrolo[3,4-*c*]pyridazines 26**




| Entry | $R^1$ | $R^2$ | 25 | 26, yield % |
|---|---|---|---|---|
| 1 | Ph | Ph | **a** | **a**, 0 |
| 2 | 3-$MeOC_6H_4$ | Ph | **b** | **b**, 80 |
| 3 | 3-$MeOC_6H_4$ | 4-$BrC_6H_4$ | **c** | **c**, 85 |
| 4 | 3-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | **d** | **d**, 73 |
| 5 | 3-$MeOC_6H_4$ | 4-$NO_2C_6H_4$ | **e** | **e**, 84 |
| 6 | thiophen-2-yl | Ph | **f** | **f**, 70 |
| 7 | thiophen-2-yl | 4-$BrC_6H_4$ | **g** | **g**, 89 |
| 8 | thiophen-2-yl | 4-$MeOC_6H_4$ | **h** | **h**, 61 |
| 9 | thiophen-2-yl | 4-$NO_2C_6H_4$ | **i** | **i**, 82 |
| 10 | benzofuran-2-yl | Ph | **j** | **j**, 94 |
| 11 | benzo[*b*]thiophen-2-yl | 4-$BrC_6H_4$ | **k** | **k**, 79 |

Compounds **26** may in principle exist in the three tautomeric forms, as shown in the scheme 6.

**Scheme 6. Tautomeric forms of compounds 26b,f,j**




**26b-2H** **26b-4H** **26b-5H** X-Y=Z = CH=C(OMe)CH=CH

**26f-7H** **26f-5H** **26f-4H** X = S, Y=Z = CH=CH

**26j-2H** **26j-4H** **26j-5H** X = O, Y=Z =

According to calculations (Table 4) the tautomer with hydrogen at the pyrrole nitrogen is much more stable than the other two tautomers in solution. The most stable tautomers (**26b-2H**, **26f-7H**, **26j-2H**) have

also a long-wave maximum at ~400 nm in the visible absorption spectra whereas tautomers **26b-4H**, **26f-4H**, **26j-4H** and **26b-5H**, **26f-2H**, **26j-5H** have a maximum at ~550 and ~ 530 nm, respectively (Table 4).

**Table 4. Relative free *Gibbs* energies (298K), the long-wave maximums and the oscillator strengths of tautomers 26b,f,j, (DFT and TD-DFT B3LYP/6-31+g(d,p), PCM model for the corresponding solvents)**

| | EtOH | | MeOH | | $CH_2Cl_2$ | |
|---|---|---|---|---|---|---|
| | **rel ΔG, kcal/mol** | **$\lambda_{max}$, nm; *f*** | **rel ΔG, kcal/mol** | **$\lambda_{max}$, nm; *f*** | **rel ΔG, kcal/mol** | **$\lambda_{max}$, nm; *f*** |
| **26b-2H** | 0.0 | 392; 0.478 | 0.0 | 392; 0.468 | 0.0 | 393; 0.509 |
| **26b-4H** | 9.6 | 569; 0.089 | 9.5 | 568; 0.088 | 9.8 | 578; 0.090 |
| **26b-5H** | 5.3 | 527; 0.254 | 5.2 | 525; 0.250 | 5.4 | 534; 0.260 |
| **26f-7H** | 0.0 | 403; 0.317 | 0.0 | 402; 0.309 | 0.0 | 402; 0.338 |
| **26f-5H** | 7.5 | 563; 0.044 | 7.5 | 562; 0.043 | 7.7 | 569; 0.044 |
| **26f-4H** | 4.0 | 533; 0.165 | 3.9 | 527; 0.163 | 4.6 | 534; 0.169 |
| **26j-2H** | 0.0 | 404; 0.356 | 0.0 | 404; 0.349 | 0.0 | 405; 0.374 |
| **26j-4H** | 6.2 | 540; 0.075 | 6.2 | 539; 0.074 | 6.4 | 546; 0.075 |
| **26j-5H** | 4.8 | 524; 0.269 | 4.8 | 522; 0.269 | 4.7 | 533; 0.281 |

UV-VIS spectra in the region 230-700 nm for dichloromethane solutions of compounds **26b,f,j** are shown in Fig. 3. The long-wave absorption band maxima of compounds **26b,f,j** are at 392, 401, 403 nm, respectively (Table 5). This is in accordance with the results of TD-DFT B3LYP/6-31+g(d,p) calculations for the electronic transition from the HOMO to the LUMO of the most stable tautomers **26b-2H**, **26f-7H**, **26j-2H** in dichloromethane (Table 4).

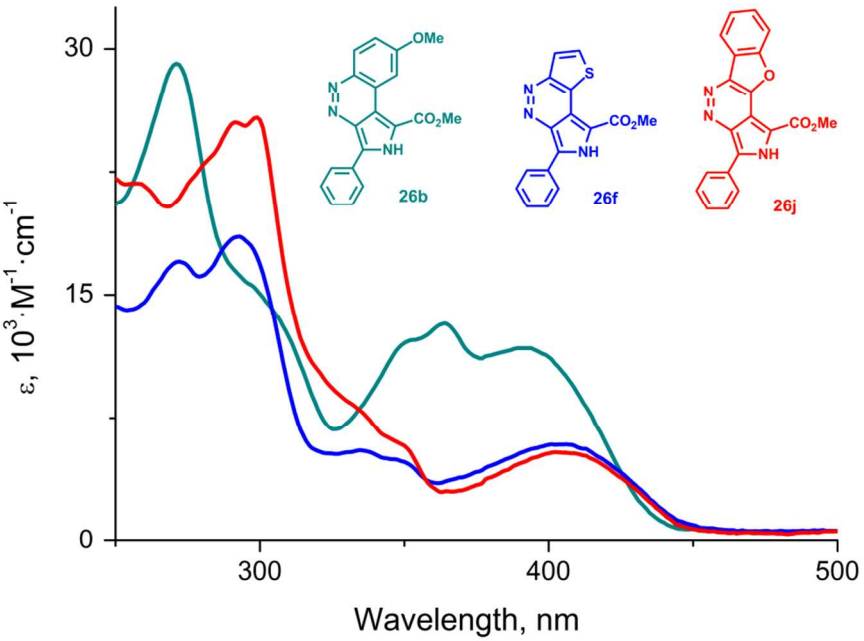



**Fig. 3**. UV-VIS spectra of compounds **26b,f,j** in dichloromethane.

The compounds **26** are luminescent in solution. The photophysical data are given in Table 5 and representative examples of excitation and emission spectra are depicted in Fig. 4. Typically small values of Stokes shifts, together with excited state lifetime in nanosecond domain, clearly indicate that the emission observed originates from the singlet excited state, i.e. fluorescence.

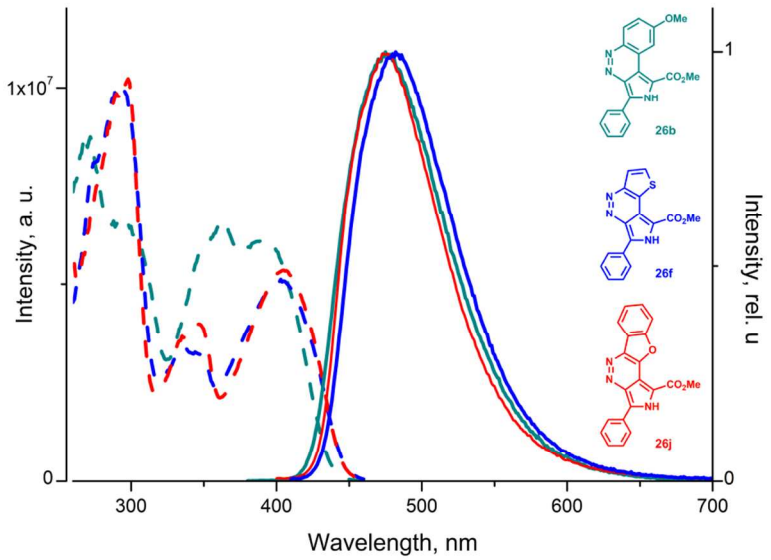



**Fig**. **4**. Room temperature excitation and emission spectra of **26b,f,j** in dichloromethane.

It was found that the fluorescence properties of **26b,c,d,e** are sensitive to the substituent in the para position of the phenyl group (Fig. 5, Table 5). The Br-substituent does not change the position of the emission maxima but increases the fluorescence quantum yield. The MeO and $NO_2$ substituents shift emission to redder wavelengths by 29 or 74 nm, respectively, and increase the fluorescence quantum yield more than an order of magnitude.

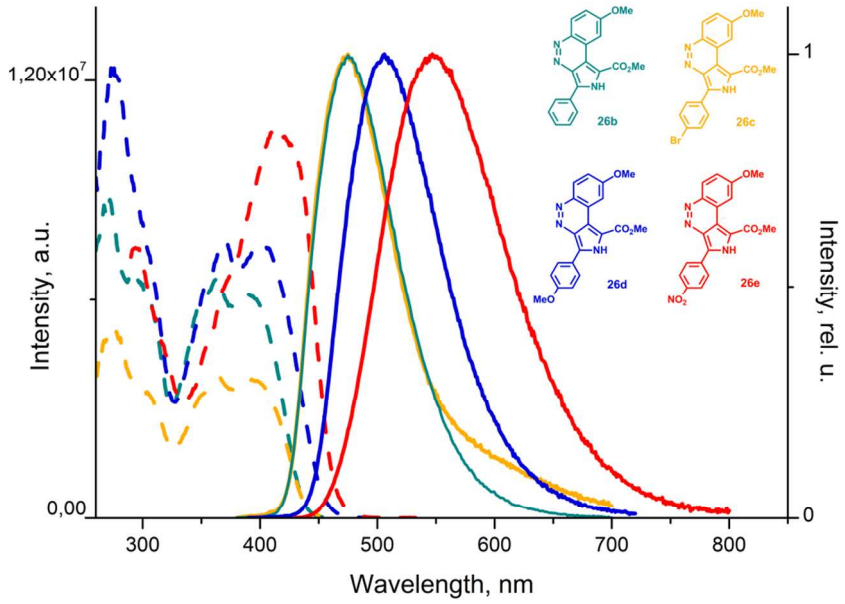



**Fig**. **5**. Room temperature excitation and emission spectra of **26b,c,d,e** in dichloromethane.

**Table 5. Photophysical characteristics of 26b,c,d,e,f,j and 26b-5Me in dichloromethane solutions at room temperature, $\lambda_{ex}$ = 383-415 nm (corresponds to the most wavelength maximum of excitation spectrum). Lifetimes (τ) were measured at $\lambda_{max}$ of the emission bands**

| Compound | Absorbance, $\lambda_{max}$, nm ($\varepsilon$, $10^3 \cdot M^{-1} \cdot cm^{-1}$) | Emission $\lambda_{max}$, nm | Excitation $\lambda_{max}$, nm | τ, ns | QY, % |
|---|---|---|---|---|---|
| **26b** | 271 (29), 297 (16), 353 (12), 364 (13), 392 (12) | 475 | 272, 297, 350, 363, 390 | 2.23 | 2.07 |
| **26c** | 276 (34), 302 (17), 346 (12), 365 (14), 395 (14) | 475 | 274, 298, 349, 364, 393 | 0.58 | 11.37 |
| **26d** | 277 (27), 302 (15), 356 (11), 370 (12), 401 (11) | 504 | 275, 298, 356, 367, 400 | 6.10 | 28.23 |
| **26e** | 298 (15), 371 (11), 413 (22), 436 (18) | 549 | 295, 375, 415 | 2.44 | 26.19 |

| | | | | | |
|---|---|---|---|---|---|
| **26f** | 272 (17), 293(19), 335 (6), 350 (5), 401 (6) | 478 | 273, 292, 333, 344, 403 | 2.13 | 11.05 |
| **26j** | 260 (22), 290 (25), 299 (26), 331 (8), 347 (6), 403 (5) | 473 | 291, 297, 336, 348, 408 | 3.36 | 16.72 |
| **26b-5Me** | 257 (29), 281 (21), 297 (18), 335 (10), 345 (13), 371 (5), 397 (4), 533 (6) | 482 | 268, 291, 341, 359, 383 | 2.71 | 1.86 |

Fixing other tautomeric forms of the compounds **26**, which should have significantly different VIS properties from the most stable, may be realized by alkylation of the nitrogens of the pyridazine fragment of **26**. Alkylation of pyrrolocinnoline **8a**, existing in 2*H*-tautomeric form, proceeded selectively under the action of EtI/EtONa in EtOH and led to the formation of the 5-ethyl-5*H*-tautomer **10**.[7a] To understand the reasons for this selectivity and to evaluate the prospects of the selective alkylation of compounds **26**, we performed DFT calculations for the model compounds listed in the Table 6.

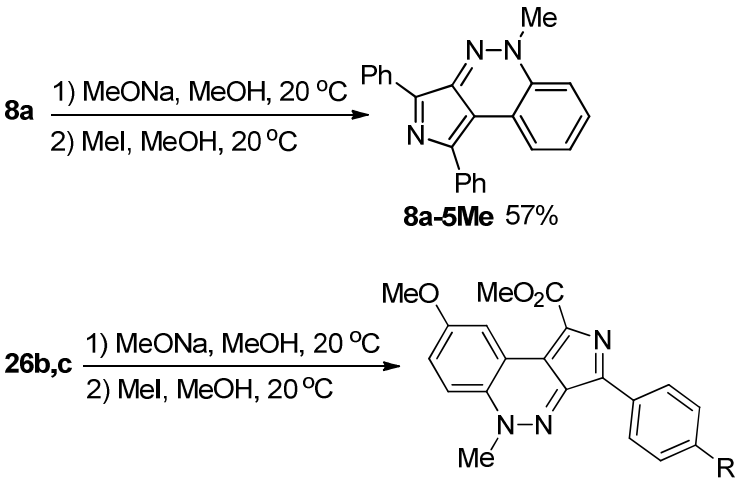
**Table 6. Relative free *Gibbs* energies (298K) of tautomers 8a, 26b, their Me-derivatives 8a-nMe, 26b-nMe (DFT B3LYP/6-31+g(d,p), PCM for MeOH) and barrier for nucleophilic substitution of Br in MeBr with anion derived from 8a or 26b (DFT B3LYP/6-31+g(d,p){CNH}/LANL2DZ{Br}, 298K, PCM for MeOH)**

| | **Compound** | **rel ΔG, kcal/mol** | **Compound** | **rel ΔG, kcal/mol** | **rel $\Delta G^{\#}$, kcal/mol** |
|---|---|---|---|---|---|
| 2*H*-tautomer | **8a-2H** | 0.0 | **8a-2Me** | 0.0 | 33.3 |
| 4*H*-tautomer | **8a-4H** | 10.7 | **8a-4Me** | 8.1 | 34.6 |
| 5*H*-tautomer | **8a-5H** | 3.7 | **8a-5Me** | 0.3 | 31.1 |
| 2*H*-tautomer | **26b-2H** | 0.0 | **26b-2Me** | 2.2 | 34.4 |
| 4*H*-tautomer | **26b-4H** | 9.5 | **26b-4Me** | 5.2 | 34.9 |
| 5*H*-tautomer | **26b-5H** | 5.2 | **26b-5Me** | 0 | 30.6 |

The existence of pyrrolocinnoline **8a** as 2*H*-tautomer corresponds to its greater stability compared with 5*H*- and 4*H*- tautomers (Table 6). Since the relative thermodynamic stabilities of 2-methyl-1,3-diphenyl-2*H*-pyrrolo[3,4-*c*]cinnoline **8a-2Me** and 5-methyl-1,3-diphenyl-5*H*-pyrrolo[3,4-*c*]cinnoline **8a-5Me** are

almost equal (Table 6), the selective alkylation the cinnoline N5 atom is a kinetically controlled process. The DFT calculations of the thermodynamic parameters for the reaction of MeBr with the anion, formed from pyrrolocinnoline **8a** under deprotonation, showed that the free Gibbs energies of the transition states for N2 and N4 alkylation were by 2.2 and 3.5 kcal/mol greater than for N5 alkylation and ensures the dominant alkylation of the N5 atom of the backbone (Table 6). This result can be explained by steric hindrances for attack of the alkylating agent caused by the Ph-groups in the case of N2 attack and by the 3-Ph-group in the case of N4 attack (Table S8, Supporting Information). In accordance with the calculation results methylation of **8a** by MeI/MeONa in MeOH gave **8a-5Me** as the only product (Scheme 7).

**Scheme 7. Methylation of cinnolines 8a, 26b,c**




Replacing the 1-Ph group with a $CO_2Me$ group when passing from compound **8a** to compounds **26** can potentially alter the selectivity of the alkylation. The DFT calculation showed, however, that the free Gibbs energy of the transition states of N2- and N4-methylation of the anion, formed by deprotonation of **26b**, with MeBr are 3.8 and 4.3 kcal/mol greater than that for N5-methylation and that ensures complete selectivity of the reaction. Increasing energy of the transition states under the attack N2 and N4 on MeBr is caused by obstacles for the approach of the alkylating agent, created by the Ph and the $MeO_2C$ groups in the case of N2, and the 3-Ph-group in the case of N4 (Table S8, Supporting Information). Methylation of

pyrrolocinnoline **26b** by MeI/MeONa in MeOH in accordance with the theoretical prediction led to the isolation of compound **26b-5Me** as the only product (Scheme 7). The structure of the alkylation product was proven by 2D-NOESY.

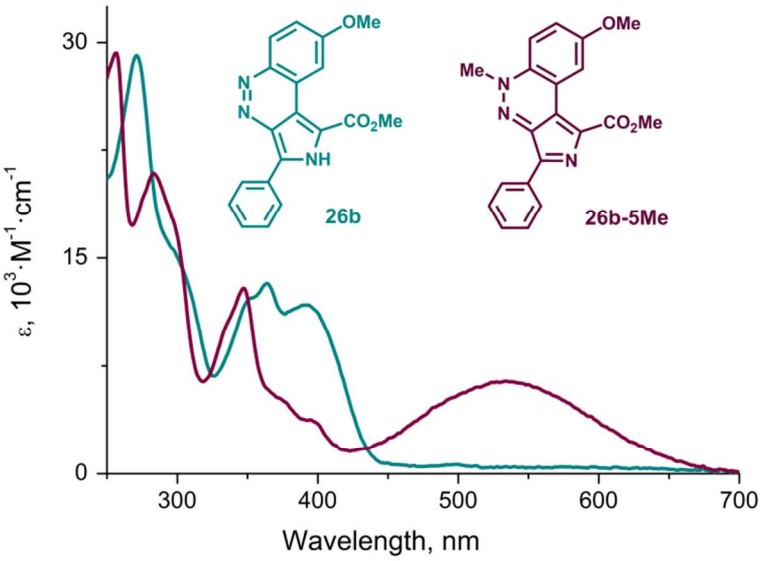



**Fig. 6**. UV-VIS spectra of compounds **26b** and **26b-5Me** in dichloromethane.

Since the alkylation of compound **26b** occurs at the N5, a substantial change of the electronic structure takes place. This is reflected in the difference between both the structure and the energies of HOMO and LUMO of the compounds **26b** and **26b-5Me**. Fixing the 5*H*-tautomer of compound **26b** via methylation increases the energy of the HOMO and lowers the LUMO energy in the compound **26b-5Me**, the latter changes larger than the former. From a comparison of FMO energies of compounds **26b-5H** and **26b-5Me** (Table S9, Supporting Information) it can be concluded, that this change is not an effect of a methyl group. As a result, the alkylation should lead to a large bathochromic shift of the long-wave band in the absorption spectrum (Table 4), which is observed experimentally (533 nm **26b-5Me** compared to 392 nm **26b**) (Fig. 6).

In conclusion:

Methyl 4-aminopyrrole-2-carboxylates are excellent precursors of methyl 4-diazopyrrole-2-carboxylates. According to DFT calculations cyclization of the diazonium cations derived from 4-diazopyrrole-2-carboxylates in acid should proceed selectively on the nucleophilic 3-aryl/heteroaryl group rather than on the same group in the 5-position of the pyrrole ring. This led to the easy performing high yield synthesis of benzo, thieno and furo [*c*]-fused 7-aryl-6*H*-pyrrolo[3,4-*c*]pyridazine-5-carboxylates, including first representatives of new heterocyclic systems, from the corresponding 4-diazopyrrole-2-carboxylates. The synthesised derivatives of pyrrolo[3,4-*c*]pyridazine fluoresce in solutions. N-Methylation of 1,3-disubstituted 2*H*-pyrrolo[3,4-*c*]cinnolines, which occurs selectively at N5 under kinetic control, leads to a large bathochromic shift of the long-wave band in the VIS absorption spectra.

## EXPERIMENTAL SECTION

**General Information and Methods.** Melting points were determined on a capillary melting point apparatus. $^{1}$H (400 MHz) and $^{13}$C (100 MHz) NMR spectra were determined in $CDCl_3$ and DMSO-$d_6$. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane (TMS δ = 0.00). $^{1}$H NMR spectra were calibrated according to the residual peak of $CDCl_3$ (7.26 ppm) or DMSO-$d_6$ (2.50 ppm). For all new compounds $^{13}$C{$^{1}$H} and $^{13}$C DEPT135 were recorded and calibrated according to the peak of $CDCl_3$ (77.00 ppm) or DMSO-$d_6$ (39.51 ppm). Mass spectra were recorded on a HRMS-ESI-QTOF, electrospray ionization, positive mode. IR-spectra were recorded for tablets in KBr, only characteristic absorption is indicated. The photophysical measurements in solution were carried out using $CH_2Cl_2$, which was distilled prior to use. UV/Vis spectra were recorded on a UV-spectrophotometer Emission and excitation spectra in solution were recorded on a spectrofluorimeter. The absolute emission quantum yield in solutions was determined by a comparative method. Fluorescence lifetimes were determined by the TCSPC (Time-Correlated Single Photon Counting) method. The lifetime data were fit

using the Jobin-Yvon software package. Direct quantum yield measurements of the samples were performed at room temperature with an integrating sphere. Single crystal X-ray diffraction experiment was performed on diffractometer at 100K using monochromated Cu*Kα* radiation. Thin-layer chromatography (TLC) was conducted on aluminium sheets with 0.2 mm silica gel with fluorescent indicator. Synthesis of 3-substituted-3-oxopropanoates was performed according to published procedure.[13]

**Methyl 3-(benzo[*b*]thiophen-2-yl)-3-oxopropanoate (30)**. A hexane solution of BuLi (2.5 M, 20.8 mL, 52 mmol) was added to a solution of DIPA (3.85 g, 52 mmol) in absolute THF (10 mL) at -78 °C under an argon atmosphere and the mixture was stirred for 10 min. Methyl acetate (3.85 g, 52 mmol), and then, after an additional 10 min, a solution of methyl benzo[*b*]thiophen-2-carboxylate (5.00 g, 26 mmol) in absolute THF (20 mL) was added. The reaction mixture was stirred for 30 min and quenched by saturated aqueous $NH_4Cl$. The organic layer was separated and the water layer extracted with ether (30 mL). The combined organic solution was washed with brine and dried over $Na_2SO_4$. The solvents were evaporated and the residue purified by column chromatography on silica gel (light petroleum/EtOAc 6:1). Light yellow oil, 4.21 g (69%, 97% on consumed methyl benzo[*b*]thiophen-2-carboxylate). $^1$H NMR ($CDCl_3$): δ = 3.76 (s, 3H), 4.03 (s, 2H), 7.39-7.46 (m, 1H), 7.46-7.50 (m, 1H), 7.85-7.91 (m, 2H), 7.98 (s, 1H). Spectrum demonstrated the presence of about 8 % of the enol form with characteristic signals δ = 5.65 (s, 1H) и 12.35 (s, 1H) – CH and OH. $^{13}$C NMR ($CDCl_3$): δ = 46.1 ($CH_2$), 52.6 ($CH_3$), 122.9 (CH), 125.2 (CH), 126.2 (CH), 127.9 (CH), 130.6 (CH), 138.9 (C), 142.5 (C), 142.9 (C), 167.2 (C), 186.2 (C). ESI/HRMS (m/z): 235.0423 calcd for $C_{12}H_{11}O_3S$ $[M + H]^+$, found 235.0419. IR (KBr, $cm^{-1}$): ν 3469, 2557, 1744, 1667.

**General method for 3-arylisoxazol-5-ones synthesis.**[14] A mixture of alkyl 3-aryl-3-oxopropanoate (1.00 mol) and $H_2NOH{\cdot}HCl$ (2.50-3.00 mol, 2.50-3.00 eq.) in water (100 mL) was brought to boiling while stirring and boiled for 5 minutes. The mixture was diluted with ethanol (100 mL), and boiled for 40-60 minutes. After cooling, the precipitate was filtered, washed with a mixture EtOH/$H_2O$ 1:1 and dried.

**3-(3-Methoxyphenyl)isoxazol-5(4*H*)-one (31a)**. Compound **31a** (6.10 g , 87%) was obtained from ethyl 3-(3-methoxylphenyl)-3-oxopropanoate (8.17 g, 36.76 mmol) and $H_2NOH{\cdot}HCl$ (7.70 g, 110.00 mmol). Colorless solid, mp 112-113 °C (EtOH-$H_2O$). $^1$H NMR ($CDCl_3$): δ = 3.78 (s, 2H), 3.85 (s, 3H), 7.05-7.08 (m, 1H), 7.16-7.18 (m, 1H), 7.25-7.26 (m, 1H), 7.36-7.40 (m, 1H). $^{13}$C NMR ($CDCl_3$): δ = 34.1 ($CH_2$), 55.5 ($CH_3$), 111.0 (CH), 118.4 (CH), 119.3 (CH), 128.8 (C), 130.2 (CH), 160.0 (C), 163.0 (C), 174.6 (C). ESI/HRMS (m/z): 214.0480 calcd for $C_{10}H_9NNaO_3$ $[M + Na]^+$, found 214.0485. IR (KBr, $cm^{-1}$): ν 2924, 1806.

**3-(Benzofuran-2-yl)isoxazol-5(4*H*)-one (31b)**. Compound **31b** (1.64 g, 25%) was obtained from ethyl 3-(3-benzofuran-2-yl)-3-oxopropanoate (7.30 g, 31.4 mmol) and $H_2NOH{\cdot}HCl$ (6.95 g, 100.0 mmol). Colorless solid, mp 140-165°C (dec.) (EtOH). $^1$H NMR (DMSO-$d_6$): δ = 4.33 (br s, 0.6H), 5.72 (br s, 0.6H), 7.32-7.36 (m, 1H), 7.43-7.45 (m, 1H), 7.53-7.55 (m, 1H), 7.68-7.70 (m, 1H), 7.75-7.77 (m, 1H), 13.13 (br s, 0.3H); tautomer ratio: 1:2. $^{13}$C NMR spectrum consisted of very wide signals due to the tautomeric equilibrium. ESI/HRMS (m/z): 202.0499 calcd for $C_{11}H_8NO_3$ $[M + H]^+$, found 202.0495. IR (KBr, $cm^{-1}$): ν 3108, 1794, 1607.

**3-(Benzo[*b*]thiophen-2-yl)isoxazol-5(4*H*)-one (31c)**. Compound **31c** (2.33 g, 66%) was obtained from compound **30** (3.90 g, 16.6 mmol) and $H_2NOH{\cdot}HCl$ (3.06 g, 44 mmol) in ethanol (without addition of water). Colorless solid, mp > 188 °C (dec) (EtOH). $^1$H NMR (DMSO-$d_6$): δ = 4.41 (br s, 0.95H), 5.79 (br s, 0.44H), 7.45-7.46 (m, 2H), 7.95 (*pseudo*-s, 2H), 8.03-8.05 (m, 1H), 13.35 (br s, 0.32H); tautomer ratio: 1:1. $^{13}$C NMR spectrum consisted of very wide signals due to the tautomeric equilibrium. ESI/HRMS (m/z): 240.0090 calcd for $C_{11}H_7NO_2S$ $[M + Na]^+$, found 240.0096. IR (KBr, $cm^{-1}$): ν 1809, 1792.

**General method of 5-methoxyisoxazoles 27.**[14] Isoxazolone (1.00 mmol) was added in small portions to a stirred solution of diazomethane in ether, prepared by reaction of *N,N*-nitrosomethylcarbamide (2.50-3.00 mmol, 2.50-3.00 eq) with KOH (40% water solution). The reaction mixture was stirred for 30 min and

excess of diazomethane was quenched with acetic acid. The solvent was removed in vacuo and the residue was purified by column chromatography (light petroleum/EtOAc 6:1 – 4:1).

**5-Methoxy-3-(3-methoxyphenyl)isoxazole (27b)**. Compound **27b** (2.95 g, 74%) was obtained from compound **31a** (3.71 g, 19.40 mmol) and *N,N*-nitrosomethylcarbamide (6.00 g, 58.00 mmol). Light yellow oil. $^{1}$H NMR ($CDCl_3$): δ = 3.84 (s, 3H), 4.03 (s, 3H), 5.51 (s, 1H), 6.96-6.99 (m, 1H), 7.26-7.36 (m, 3H). $^{13}$C NMR ($CDCl_3$): δ = 55.3 ($CH_3$), 58.8 ($CH_3$), 75.5 (CH), 111.3 (CH), 116.1 (CH), 119.0 (CH), 129.8 (CH), 130.8 (C), 159.8 (C), 164.1 (C), 174.4 (C). ESI/HRMS (m/z): 228.0632 calcd for $C_{11}H_{11}NNaO_3$ [M + Na]$^+$, found 228.0626. IR (KBr, cm$^{-1}$): ν 2950, 1615.

**5-Methoxy-3-(thiophen-2-yl)isoxazole (27c)**. Compound **27c** (2.98 g, 81%), was obtained from 3-(thiophen-2-yl)isoxazol-5(4*H*)-one (3.39 g, 20.29 mmol) and *N,N*-nitrosomethylcarbamide (5.44 g, 53.00 mmol). Colorless solid, mp 64-65 °C (hexane-EtOAc). $^{1}$H NMR ($CDCl_3$): δ = 4.03 (s, 3H), 5.47 (s, 1H), 7.08-7.10 (m, 1H), 7.39-7.41 (m, 2H). $^{13}$C NMR ($CDCl_3$): δ = 58.9 ($CH_3$), 75.6 (CH), 127.2 (CH), 127.4 (CH), 127.5 (CH), 131.3 (C), 159.4 (C), 174.3 (C). ESI/HRMS (m/z): 182.0271 calcd for $C_8H_8NO_2S$ [M + H]$^+$, found 182.0269. IR (KBr, cm$^{-1}$): ν 3134, 1612.

**3-(Benzofuran-2-yl)-5-methoxyisoxazole (27d)**. Compound **27d** (535 mg, 99%) was obtained from compound **31b** (503 mg, 2.50 mmol), suspended in THF, and *N,N*-nitrosomethylcarbamide (620 mg, 6.00 mmol). Colorless solid, mp 92-95 °C (MeOH). $^{1}$H NMR ($CDCl_3$): δ = 4.07 (s, 3H), 5.65 (s, 1H), 7.21-7.22 (m, 1H), 7.26-7.29 (m, 1H), 7.34-7.38 (m, 1H), 7.54-7.56 (m, 1H), 7.62-7.64 (m, 1H). $^{13}$C NMR ($CDCl_3$): δ = 59.0 ($CH_3$), 75.7 (CH), 106.2 (CH), 111.6 (CH), 121.7 (CH), 123.4 (CH), 125.7 (CH), 127.9 (C), 146.1 (C), 155.1 (C), 156.8 (C), 174.5(C). ESI/HRMS (m/z): 216.0657 calcd for $C_{12}H_{10}NO_3$ [M + H]$^+$, found 216.0660. IR (KBr, cm$^{-1}$): ν 3121, 2924, 1737, 1621, 1600.

**3-(Benzo[*b*]thiophen-2-yl)-5-methoxyisoxazole (27e)**. Compound **27e** (1.21 g, 86%) was obtained from compound **31c** (1.30 g, 6.00 mmol), suspended in THF, and *N,N*-nitrosomethylcarbamide (1.61 g, 15.6 mmol). Colorless solid, mp 125-126 °C (MeOH). $^{1}$H NMR ($CDCl_3$): δ = 4.05 (s, 3H), 5.58 (s, 1H), 7.35-

7.40 (m, 2H), 7.63 (s, 1H), 7.78-7.82 (m, 1H), 7.84-7.87 (m, 1H). $^{13}$C NMR ($CDCl_3$): δ = 58.9 ($CH_3$), 75.8 (CH), 122.5 (CH), 124.1 (CH), 124.1 (CH), 124.7 (CH), 125.6 (CH), 131.5 (C), 139.2 (C), 140.1 (C), 159.7 (C), 174.5 (C). ESI/HRMS (m/z): 232.0427 calcd for $C_{12}H_{10}NO_2S$ $[M + H]^+$, for 232.0431. IR (KBr, $cm^{-1}$): ν 3132, 1614, 1601.

**Methyl 3-(benzo[*b*]thiophen-2-yl)-2*H*-azirine-2-carboxylate (15c)** was prepared according to the published procedure.[15] A mixture of compound **27e** (880 mg, 3.80 mmol), $FeCl_2 \cdot 4H_2O$ (152 mg, 0.76 mmol, 20 mol.%) in absolute acetonitrile (25 mL) was stirred for 20h at room temperature under Ar, then filtered and the solvent removed in vacuo. The residue was purified by column chromatography (light petroleum/EtOAc 6:1). Colorless solid, 598 mg (68%), mp 101-102 °C (pentane). $^1$H NMR ($CDCl_3$): δ = 2.97 (s, 1H), 3.77 (s, 3H), 7.16-7.54 (m, 2H), 7.93 (s, 1H), 7.93-7.95 (m, 2H). $^{13}$C NMR ($CDCl_3$): δ = 30.8 (CH), 52.4 ($CH_3$), 122.9 (CH), 124.3 (C), 125.5 (CH), 125.8 (CH), 127.7 (CH), 133.3 (CH), 138.3 (C), 143.5 (C), 153.3 (C), 171.5 (C). ESI/HRMS (m/z): 232.0427 calcd for $C_{12}H_{10}NO_2S$ $[M + H]^+$, found 232.0432. IR (KBr, $cm^{-1}$): ν 1767, 1721.

**One-pot synthesis of 4-aminopyrroles 28.**[4] A mixture of isoxazole **27** (1.2-1.5 mmol), phenacylpyridinium bromide **16** (1.0 mmol), $FeCl_2 \cdot 4H_2O$ (0.06–0.08 mmol, 5 mol.% on isoxazole) and $NEt_3$ (3.0 mmol, 3 eq) in absolute acetonitrile (4 mL) was stirred at 45 °C for 6-7 h. (monitoring by TLC). Hydrazine hydrate (10.0 mmol, 10 eq) was added to the reaction mixture when bromide **16** was consumed. The mixture was stirred at 45 °C for 6-7 h until the completion of the reaction (monitoring by TLC). The solvent was removed in vacuo and the residue was purified by column chromatography ($CH_2Cl_2$ or $CH_2Cl_2$/MeOH 40:1).

**Methyl 4-amino-3-(3-methoxyphenyl)-5-phenyl-1*H*-pyrrole-2-carboxylate (28b)**. Compound **28b** (498 mg, 67%) was obtained from compounds **27b** (513 mg, 2.50 mmol), **16a** (639 mg, 2.30 mmol), $FeCl_2 \cdot 4H_2O$ (26 mg, 0.13 mmol, 5 mol.%), $Et_3N$ (700 mg, 6.90 mmol) and $NH_2NH_2 \cdot H_2O$ (1150 mg, 23.00 mmol). Light yellow solid, mp 57-58 °C (hexane). $^1$H NMR ($CDCl_3$): δ = 3.29 (br s, 2H), 3.72 (s,

3H), 3.84 (s, 3H), 6.89-6.92 (m, 1H), 7.02-7.06 (m, 2H), 7.28-7.31 (m, 1H), 7.34-7.38 (m, 1H), 7.44-7.48 (m, 2H), 7.61-7.63 (m, 2H), 8.87 (br s, 1H). $^{13}$C NMR ($CDCl_3$): δ = 51.2 ($CH_3$), 55.3 ($CH_3$), 113.1 (CH), 115.6 (CH), 116.6 (C), 120.7 (C), 121.8 (C), 122.6 (CH), 125.5 (CH), 126.9 (CH), 129.1 (C), 129.16 (CH), 129.22 (CH), 131.7 (C), 134.4 (C), 159.5 (C), 161.5 (C). ESI/HRMS (m/z): 323.1390 calcd for $C_{19}H_{19}N_2O_3$ $[M + H]^+$, found 323.1391. IR (KBr, $cm^{-1}$): ν 3304, 2952, 1712, 1670, 1604.

**Methyl 4-amino-5-(4-bromophenyl)-3-(3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (28c)**. Compound **28c** (624 mg, 78%) was obtained from compounds **27b** (472 mg, 2.30 mmol), **16b** (714 mg, 2.00 mmol), $FeCl_2·4H_2O$ (24 mg, 0.12 mmol, 5 mol.%), $Et_3N$ (400 mg, 6.00 mmol) and $NH_2NH_2·H_2O$ (1150 mg, 23.00 mmol). Colorless solid, mp 177-178 °C ($CH_2Cl_2$). $^1$H NMR (DMSO-$d_6$): δ = 3.62 (s, 3H), 3.72 (s, 2H), 3.77 (s, 3H), 6.89-6.92 (m, 3H), 7.31-7.35 (m, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6Hz, 2H), 11.44 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 50.7 ($CH_3$), 55.0 ($CH_3$), 112.4 (CH), 115.7 (CH), 116.7 (C), 118.8 (C), 119.9 (C), 121.2 (C), 122.4 (CH), 128.1 (CH), 128.9 (CH), 130.0 (C), 131.0 (C), 131.2 (CH), 134.8 (C), 158.9 (C), 160.7 (C). ESI/HRMS (m/z): 401.0495 calcd for $C_{19}H_{18}BrN_2O_3$ $[M + H]^+$, found 401.0502. IR (KBr, $cm^{-1}$): ν 3314, 1665, 1603.

**Methyl 4-amino-3-(3-methoxyphenyl)-5-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (28d)**. Compound **28d** (414 mg, 47%) was obtained from compounds **27b** (606 mg, 2.95 mmol), **16c** (770 mg, 2.50 mmol), $FeCl_2·4H_2O$ (30 mg, 0.15 mmol, 5 mol.%), $Et_3N$ (758 mg, 7.50 mmol) and $NH_2NH_2·H_2O$ (1150 mg, 23.00 mmol). Colorless solid, mp 61-64 °C (hexane). $^1$H NMR ($CDCl_3$): δ = 3.21 (br s, 2H), 3.71 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 6.88-6.91 (m, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.02-7.06 (m, 2H), 7.33-7.37 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 8.80 (br s, 1H). $^{13}$C NMR ($CDCl_3$): δ = 51.2 ($CH_3$), 55.3 ($CH_3$), 55.4 ($CH_3$), 113.0 (CH), 114.7 (CH), 115.6 (CH), 115.9 (C), 121.0 (C), 121.9 (C), 122.6 (CH), 124.3 (C), 127.1 (CH), 128.2 (C), 129.1 (CH), 134.5 (C), 158.7 (C), 159.4 (C), 161.6 (C). ESI/HRMS (m/z): 375.1315 calcd for $C_{20}H_{20}N_2NaO_4$ $[M + Na]^+$, found 375.1311. IR (KBr, $cm^{-1}$): ν 3309, 2949, 1709, 1669, 1610.

**Methyl 4-amino-3-(3-methoxyphenyl)-5-(4-nitrophenyl)-1*H*-pyrrole-2-carboxylate (28e)**. Compound **28e** (322 mg (58%) was obtained from compounds **27b** (369 mg, 1.80 mmol), **16d** (484 mg, 2.50 mmol), $FeCl_2 \cdot 4H_2O$ (18 mg, 0.09 mmol, 5 mol.%), $Et_3N$ (455 mg, 4.50 mmol) and $NH_2NH_2 \cdot H_2O$ (751 mg, 15.00 mmol). Red solid, mp 208 °C. ($CH_2Cl_2$). $^1$H NMR (DMSO-$d_6$): δ = 3.65 (s, 3H), 3.78 (s, 3H), 4.07 (s, 2H), 6.89-6.91 (m, 3H), 7.32-7.38 (m, 1H), 8.05(d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 11.64 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.0 ($CH_3$), 55.0 ($CH_3$), 112.6 (CH), 115.6 (CH), 118.6 (C), 119.1 (C), 120.9 (C), 122.4 (CH), 123.7 (CH), 125.9 (CH), 129.0 (CH), 132.8 (C), 134.2 (C), 138.5 (C), 144.1 (C), 159.0 (C), 160.6 (C). ESI/HRMS (m/z): 368.1241 calcd for $C_{19}H_{18}N_3O_5$ $[M + H]^+$, found 368.1247. IR (KBr, $cm^{-1}$): ν 3318, 1671.

**Methyl 4-amino-5-phenyl-3-(thiopen-2-yl)-1*H*-pyrrole-2-carboxylate (28f)**. Compound **28f** (135 mg, 47%) was obtained compounds **27c** (208 mg, 1.15 mmol), **16a** (271 mg, 0.97 mmol), $FeCl_2 \cdot 4H_2O$ (20 mg, 0.10 mmol, 5 mol.%)), $Et_3N$ (300 mg, 3.00 mmol) and $NH_2NH_2 \cdot H_2O$ (500 mg, 10.00 mmol). Colorless solid, mp 153-154 °C ($Et_2O$-hexane). $^1$H NMR (DMSO-$d_6$): δ = 3.67 (s, 3H), 3.82 (s, 2H), 7.12-7.14 (m, 2H), 7.24-7.27 (m, 1H), 7.40-7.43 (m, 2H), 7.56-7.57 (m, 1H), 7.73-7.75 (m, 2H), 11.50 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 50.8 ($CH_3$), 113.2 (C), 116.8 (C), 120.9 (C), 125.9 (CH), 126.2 (CH), 126.3 (CH), 126.9 (CH), 127.4 (CH), 128.4 (CH), 130.3 (C), 131.6 (C), 134.1 (C), 160.4 (C). ESI/HRMS (m/z): 299.0849 calcd for $C_{16}H_{15}N_2O_2S$ $[M + H]^+$, found 299.0857. IR (KBr, $cm^{-1}$): ν 3303, 1670, 1604.

**Methyl 4-amino-5-(4-bromophenyl)-3-(thiopen-2-yl)-1*H*-pyrrole-2-carboxylate (28g)**. Compound **28g** (429 mg, 52%) was obtained from compounds **27c** (453 mg, 2.50 mmol), **16b** (785 mg, 2.20 mmol), $FeCl_2 \cdot 4H_2O$ (25 mg, 0.13 mmol, 5 mol.%), $Et_3N$ (668 mg, 6.60 mmol) and $NH_2NH_2 \cdot H_2O$ (1100 mg, 22.00 mmol). Colorless solid, mp 168 °C ($CH_2Cl_2$). $^1$H NMR (DMSO-$d_6$): δ = 3.67 (s, 3H), 3.88 (s, 2H), 7.10-7.14 (m, 2H), 7.56-7.57 (m, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 11.59 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 50.8 ($CH_3$), 113.3 (C), 117.3 (C), 119.0 (C), 119.8 (C), 126.0 (CH), 126.9

(CH), 127.5 (CH), 128.2 (CH), 130.7 (C), 130.8 (C), 131.2 (CH), 133.9 (C), 160.4 (C). ESI/HRMS (m/z): 376.9959 calcd for $C_{16}H_{14}BrN_2O_2S$ $[M + H]^+$, found 376.9961. IR (KBr, $cm^{-1}$): ν 3300, 1679.

**Methyl 4-amino-5-(4-methoxyphenyl)-3-(thiopen-2-yl)-1*H*-pyrrole-2-carboxylate (28h)**. Compound **28h** (515 mg, 71%) was obtained from compounds **27c** (453 mg, 2.50 mmol), **16c** (678 mg, 2.20 mmol), $FeCl_2·4H_2O$ (25 mg, 0.13 mmol, 5 mol.%), $Et_3N$ (668 mg, 6.60 mmol) and $NH_2NH_2·H_2O$ (1100 mg, 22.00 mmol). Colorless solid, mp 156 °C ($CH_2Cl_2$). $^1H$ NMR (DMSO-$d_6$): δ = 3.66 (s, 3H), 3.72 (s, 2H), 3.79 (s, 3H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.11-7.12 (m, 2H), 7.56-7.57 (m, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 11.43 (br s, 1H). $^{13}C$ NMR (DMSO-$d_6$): δ = 50.7 ($CH_3$), 55.1 ($CH_3$), 113.5 (C), 113.9 (CH), 115.9 (C), 121.4 (C), 124.1 (C), 125.8 (CH), 126.8 (CH), 127.3 (CH), 127.8 (CH), 129.4 (C), 134.3 (C), 157.9 (C), 160.5 (C). ESI/HRMS (m/z): 329.0960 calcd for $C_{17}H_{17}N_2O_3S$ $[M + H]^+$, found 329.0962. IR (KBr, $cm^{-1}$): ν 3290, 1672, 1614.

**Methyl 4-amino-5-(4-nitrophenyl)-3-(thiopen-2-yl)-1*H*-pyrrole-2-carboxylate (28i)**. Compound **28i** (115 mg, 15%) was obtained from compounds **27c** (453 mg, 2.50 mmol), **16d** (710 mg, 2.20 mmol), $FeCl_2·4H_2O$ (25 mg, 0.13 mmol, 5 mol.%), $Et_3N$ (668 mg, 6.60 mmol) and $NH_2NH_2·H_2O$ (1100 mg, 22.00 mmol). Orange solid, mp 201-202 °C ($CH_2Cl_2$). $^1H$ NMR (DMSO-$d_6$): δ = 3.69 (s, 3H), 4.22 (s, 2H), 7.09-7.10 (m, 1H), 7.15-7.16 (m, 1H), 7.60-7.61 (m, 1H), 8.04 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 11.79 (s, 1H). $^{13}C$ NMR (DMSO-$d_6$): δ = 51.1 ($CH_3$), 113.0 (C), 118.5 (C), 119.7 (C), 123.7 (CH), 126.0 (CH), 126.3 (CH), 127.0 (CH), 127.8 (CH), 133.2 (C), 133.5 (C), 138.2 (C), 144.3 (C), 160.3 (C). ESI/HRMS (m/z): 344.0700 calcd for $C_{16}H_{14}N_3O_4S$ $[M + H]^+$, found 344.0705. IR (KBr, $cm^{-1}$): ν 3338, 1679.

**Methyl 4-amino-3-(benzofuran-2-yl)-5-phenyl-1*H*-pyrrole-2-carboxylate (28j)**. Compound **28j** (220 mg, 44%) was obtained from compounds **27d** (405 mg, 1.88 mmol), **16a** (417 mg, 1.50 mmol), $FeCl_2·4H_2O$ (20 mg, 0.10 mmol, 5 mol.%), $Et_3N$ (450 mg, 4.50 mmol) and $NH_2NH_2·H_2O$ (751 mg, 15.00 mmol). Colorless solid, mp 174-175 °C ($CH_2Cl_2$). $^1H$ NMR (DMSO-$d_6$): δ = 3.76 (s, 3H), 4.38 (s, 2H),

7.25-7.30 (m, 4H), 7.43-7.46 (m, 2H), 7.59-7.61 (m, 1H), 7.64-7.7.66 (m, 1H), 7.73-7.75 (m, 2H), 11.73 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.1 ($CH_3$), 105.1 (CH), 108.9 (C), 110.8 (CH), 116.6 (C), 120.6 (CH), 120.7 (C), 122.7 (CH), 123.6 (CH), 126.4 (CH), 126.6 (CH), 128.5 (CH), 128.7 (C), 131.0 (C), 131.3 (C), 150.7 (C), 153.6 (C), 160.2 (C). ESI/HRMS (m/z): 333.1234 calcd for $C_{20}H_{17}N_2O_3$ $[M + H]^+$, found 333.1240. IR (KBr, $cm^{-1}$): ν 3315, 1666.

**Methyl 4-amino-3-(benzo[*b*]thiophen-2-yl)-5-(4-bromophenyl)-1*H*-pyrrole-2-carboxylate (28k)**. Hydrazine hydrate (165 mg, 3.3 mmol) was added to a suspension of salt **29** (190 mg, 0.33 mmol) in MeCN/DMSO (20:1, 5 mL) and the reaction mixture was stirred for 10 h at 45-50 °C. The solvents were removed in vacuo, and the residue was purified by column chromatography ($CH_2Cl_2$) to give compound **28k** (80 mg, 56%). Light yellow solid, mp 184-185 °C ($CH_2Cl_2$). $^1$H NMR (DMSO-$d_6$): δ = 3.68 (s, 3H), 4.04 (s, 2H), 7.32-7.40 (m, 3H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.84-7.87 (m, 1H), 7.94-7.96 (m, 1H), 11.74 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.0 ($CH_3$), 113.2 (C), 117.6 (C), 119.2 (C), 120.1 (C), 122.0 (CH), 123.4 (CH), 123.9 (CH), 124.0 (CH), 124.1 (CH), 128.3 (CH), 130.5 (C), 130.5 (C), 131.3 (CH), 134.8 (C), 139.7 (C), 139.8 (C), 160.2 (C). ESI/HRMS (m/z): 427.0110 calcd for $C_{20}H_{16}BrN_2O_2S$ $[M + H]^+$, found 427.0108. IR (KBr, $cm^{-1}$): ν 3309, 1680.

**1-(4-(Benzo[*b*]thiophen-2-yl)-2-(4-bromophenyl)-5-(methoxycarbonyl)-1*H*-pyrrole-3-yl)pyridine-1-ium bromide (29)**. A mixture of azirine **15c** (200 mg, 0.86 mmol), salt **16b** (268 mg, 0.75 mmol) and $NEt_3$ (152 mg, 1.50 mmol) in $CH_2Cl_2$ (5 mL) was stirred for 2 days at room temperature. Precipitate was filtered, washed with $CH_2Cl_2$, and dried on air to give compound **29** (245 mg, 57%). Light yellow solid, mp 292 °C (dec.) ($CH_2Cl_2$). $^1$H NMR (DMSO-$d_6$): δ = 3.61 (s, 3H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.15 (s, 1H), 7.23-7.28 (m, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.67-7.68 (m, 1H), 7.76-7.78 (m, 1H), 8.07-8.10 (m, 2H), 8.58-8.62 (m, 1H), 9.01-9.03 (m, 2H). $^{13}$C NMR (DMSO-$d_6$): δ = 50.0 ($CH_3$), 118.1 (C), 118.5 (C), 121.8 (CH), 123.00 (CH), 123.03 (CH), 123.5 (CH), 124.0 (CH), 125.5 (C), 127.6 (CH), 128.1 (C), 128.2 (CH), 131.2 (CH), 134.0 (C), 134.8 (C), 136.2 (C), 139.5 (C), 139.7 (C), 145.8 (CH), 147.3 (CH), 164.5 (C).

ESI/HRMS (m/z): 489.0267 calcd for $C_{25}H_{18}BrN_2O_2S$ $[M - Br]^+$, found 489.0258. IR (KBr, $cm^{-1}$): ν 1693,1618.

**Synthesis of 4-aminopyrroles from 2*H*-azirines and phenacylpyridinium salts.** A mixture of phenacylpyridinium salts **16** (1.00 mmol), azirine (1.20-1.50 mmol, 1.2-1.5 eq) and $NEt_3$ (3.00 mmol, 3.0 eq). in absolute acetonitrile (8 mL) was stirred at 45-50 °C for 6-8 h until complete consumption of the starting salt (monitoring by TLC). Hydrazine hydrate (10.00 mmol, 10.0 eq) was added to the reaction mixture and stirring continued at 45-50 °C for 6-8 h until the pyridylpyridinium salt (monitoring by TLC) was consumed. The solvent was removed in vacuo and the residue was purified by column chromotography ($CH_2Cl_2$).

**3-Amino-2,4,5-triphenyl-1*H*-pyrrole (14a)**. Compound **14a** (750 mg, 55%) was obtained from azirine **15a** (971 mg, 5.03 mmol), bromide **16a** (1224 mg, 4.40 mmol), $Et_3N$ (1333 mg, 13.20 mmol) and $NH_2NH_2 \cdot H_2O$ (2200 mg, 44.00 mmol). Light yellow solid, mp 178-180 °C (EtOH-$H_2O$) (lit.[7c] data 182-183 °C (benzene)). $^1H$ NMR ($CDCl_3$): δ = 3.42 (br. s, 2H), 7.15-7.32 (m, 7H), 7.35-7.40 (m, 4H), 7.41-7.46 (m, 2H), 7.57-7.61 (m, 2H), 7.85 (s, 1H). $^{13}C$ NMR ($CDCl_3$): δ =115.4 (C), 116.6 (C), 124.5 (CH), 125.3 (CH), 126.5 (CH), 126.6 (CH), 128.2 (C), 128.6 (CH), 128.8 (CH), 129.2 (CH), 130.2 (CH), 132.8 (C), 133.0 (C), 134.4 (C). ESI/HRMS (m/z): 311.1534 calcd for $C_{22}H_{19}N_2$ $[M + H]^+$, found 311.1531. IR (KBr, $cm^{-1}$): ν 3416, 3357, 1598, 1503.

**3-Amino-2,4-diphenyl-1*H*-pyrrole (14b)**. Compound **14b** (355 mg, 70%) was obtained from azirine **15b** (470 mg, 4.00 mmol), bromide **16a** (600 mg, 2.15 mmol), $Et_3N$ (780 mg, 7.70 mmol) and $NH_2NH_2 \cdot H_2O$ (1500 mg, 30.00 mmol). Light yellow solid, mp 176-177 °C (EtOH-$H_2O$) (lit.[16] data 181°C (EtOH)). $^1H$ NMR ($CDCl_3$): δ = 3.41 (br. s, 2H), 6.79 (d, *J* = 3.0 Hz, 1H), 7.19-7.22 (m, 1H), 7.25-7.29 (m, 1H), 7.39-7.45 (m, 4H), 7.49-7.57 (m, 4H), 7.87 (br. s, 1H). $^{13}C$ NMR ($CDCl_3$): δ = 115.4 (CH), 116.9 (C), 118.2 (C), 124.7 (CH), 125.3 (CH), 125.9 (CH), 126.6 (C), 127.5 (CH), 128.8 (CH), 129.1 (CH), 133.3 (C),

135.1 (C). ESI/HRMS (m/z): 235.1226 calcd for $C_{16}H_{15}N_2$ $[M + H]^+$, found 235.1230. IR (KBr, $cm^{-1}$): ν 3391, 3163, 3046, 1603, 1568.

**Synthesis β-diazopyrroles.** Aminopyrrole (1.00 mmol) was dissolved (or suspended) in minimal volume of acetic acid, the mixture cooled to 10 °C and saturated aqueous $NaNO_2$ (2.00-3.00 mmol, 2.0-3.0 eq) was added dropwise. The mixture was stirred for 15-20 min at room temperature, and then diluted with water (20 mL). The precipitate was filtered, washed with water and dried in vacuo. If the product did not crystallize, it was extracted with ether, the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$ and the solvent removed in vacuo.

**3-Diazo-2,4,5-triphenyl-3*H*-pyrrole (11a)**. Compound **11a** (325 mg, 86%) was obtained from compound **14a** (360 mg, 1.20 mmol) and $NaNO_2$ (166 mg, 2.40 mmol) in 4 mL of AcOH. Orange solid, mp 151-153 °C (EtOH, dec.) (lit.[7c] data 157-158°C (ether, dec.)). $^1$H NMR ($CDCl_3$): δ = 7.19-7.33 (m, 3H), 7.34-7.50 (m, 6H), 7.51-7.62 (m, 4H), 7.85-7.89 (m, 2H). $^{13}$C NMR ($CDCl_3$): δ = 122.5 (C), 126.1 (CH), 127.0 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 128.7 (CH), 129.1 (CH), 129.1 (CH), 129.2 (CH), 131.9 (C), 133.4 (C), 135.3 (C), 139.2 (C), 156.0 (C). ESI/HRMS (m/z): 322.1339 calcd for $C_{22}H_{17}N_3$ $[M + H]^+$, found 322.1341. IR (KBr, $cm^{-1}$): ν 2089.

**3-Diazo-2,4-diphenyl-3*H*-pyrrole (11b)**. Compound **11b** (290 mg, 78%) was obtained from compound **14b** (350 mg, 1.50 mmol) and $NaNO_2$ (210 mg, 3.00 mmol) in 4 mL of AcOH. Brick-red solid, mp 171-172 °C ($Et_2O$-hexane) (lit.[17] data 170 (dec) °C). $^1$H NMR ($CDCl_3$): δ = 3.85 (s, 3H), 7.41-7.51 (m, 8H), 7.77-7.80 (m, 2H). $^{13}$C NMR ($CDCl_3$): δ = 51.8 ($CH_3$), 126.7 (CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 129.2 (CH), 129.8 (CH), 130.3 (C), 131.1 (C), 132.8 (C), 132.8 (C), 136.1 (C), 156.0 (C), 163.1 (C). ESI/HRMS (m/z): 246.1026 calcd for $C_{16}H_{13}N_3$ $[M + H]^+$, found 246.1015. IR (KBr, $cm^{-1}$): ν 2105.

**Methyl 3-diazo-2,4-diphenyl-3*H*-pyrrole-5-carboxylate (25a)**. Compound **25a** (427 mg, 89%) was obtained from compound **28a** (464 mg, 1.59 mmol) and $NaNO_2$ (276 mg, 4.00 mmol) in 4 mL of AcOH.

Orange solid, mp 134-134 °C (AcOH-$H_2O$). $^1$H NMR ($CDCl_3$): δ = 3.85 (s, 3H), 7.41-7.51 (m, 8H), 7.77-7.80 (m, 2H). $^{13}$C NMR ($CDCl_3$): δ = 51.8 ($CH_3$), 126.7 (CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 129.2 (CH), 129.8 (CH), 130.3 (C), 131.1 (C), 132.8 (C), 132.8 (C), 136.1 (C), 156.0 (C), 163.1 (C). ESI/HRMS (m/z): 326.0900 calcd for $C_{18}H_{13}N_3NaO_2$ $[M + Na]^+$, found 326.0906. IR (KBr, $cm^{-1}$): ν 2115, 1712.

**Methyl 3-diazo-4-(3-methoxyphenyl)-2-phenyl-3*H*-pyrrole-5-carboxylate (25b)**. Compound **25b** (335 mg, 76%) was obtained from compound **28b** (424 mg, 1.32 mmol) and $NaNO_2$ (228 mg, 3.30 mmol) in 3 mL of AcOH. Orange solid, mp 116-118 °C (AcOH-$H_2O$). $^1$H NMR ($CDCl_3$): δ = 3.85 (*pseudo*-s, 6H), 6.95-6.98 (m, 1H), 7.05-7.06 (m, 2H), 7.37-7.42 (m, 1H), 7.44-7.50 (m, 3H), 7.77-7.79 (m, 2H). $^{13}$C NMR ($CDCl_3$): δ = 51.8 ($CH_3$), 55.3 ($CH_3$), 114.5 (CH), 115.0 (CH), 121.4 (CH), 126.7 (CH), 129.1 (CH), 129.6 (CH), 129.8 (CH), 131.1 (C), 131.5 (C), 132.8 (C), 135.7 (C), 156.0 (C), 159.6 (C), 163.1 (C). ESI/HRMS (m/z): 356.1006 calcd for $C_{19}H_{15}N_3NaO_3$ $[M + Na]^+$, found 356.1012. IR (KBr, $cm^{-1}$): ν 2115, 1708.

**Methyl 2-(4-bromophenyl)-3-diazo-4-(3-methoxyphenyl)-3*H*-pyrrole-5-carboxylate (25c)**. Compound **25c** (511 mg (98%) was obtained from compound **28c** (507 mg, 1.26 mmol) and $NaNO_2$ (276 mg, 4.40 mmol) in 6 mL of AcOH. Orange solid, mp 88-93 °C (AcOH-$H_2O$). $^1$H NMR ($CDCl_3$): δ = 3.87 (s, 3H), 3.88 (s, 3H), 6.96-6.99 (m, 1H), 7.03-7.05 (m, 2H), 7.37-7.41 (m, 1H), 7.60-7.69 (m, 4H). $^{13}$C NMR ($CDCl_3$): δ = 51.9 ($CH_3$), 55.4 ($CH_3$), 114.6 (CH), 115.0 (CH), 121.4 (CH), 124.2 (C), 124.2 (C), 128.1 (CH), 129.7 (CH), 131.3 (C), 131.4 (C), 131.6 (C), 132.3 (CH), 136.0 (C), 154.5 (C), 159.6 (C), 163.0 (C). ESI/HRMS (m/z): 434.0111 calcd for $C_{19}H_{14}BrN_3NaO_3$ $[M + Na]^+$, found 434.0120. IR (KBr, $cm^{-1}$): ν 2157, 1723, 1699.

**Methyl 3-diazo-4-(3-methoxyphenyl)-2-(4-methoxyphenyl)-3*H*-pyrrole-5-carboxylate (25d)**. Compound **25d** (345 mg, 88%) was obtained from compound **28d** (380 mg, 1.08 mmol) and $NaNO_2$ (150 mg, 2.20 mmol) in 5 ml of AcOH. Orange solid, dec. > 115 °C (AcOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.74 (m, 3H), 3.81 (m, 3H), 3.87 (m, 3H), 7.06-7.08 (m, 1H), 7.17-7.19 (m, 3H), 7.23 (s, 1H), 7.43-7.7.47

(m, 1H), 7.86-7.88 (m, 2H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.9 ($CH_3$), 55.4 ($CH_3$), 55.8 ($CH_3$), 106.3 (CH), 111.1 (C), 113.8 (C), 114.1 (CH), 119.7 (CH), 120.9 (C), 121.2 (C), 129.9 (CH), 130.6 (CH), 133.2 (C), 137.7 (C), 160.4 (C), 160.6 (C), 160.8 (C). ESI/HRMS (m/z): 364.1292 calcd. for $C_{20}H_{18}N_3O_4$ $[M + H]^+$, found 364.1292. IR (KBr, $cm^{-1}$): ν 2206, 2217, 1734.

**Methyl 3-diazo-4-(3-methoxyphenyl)-2-(4-nitrophenyl)-3*H*-pyrrole-5-carboxylate (25e)**. Compound **25e** (110 mg, 99%) was obtained from compound **28e** (108 mg, 0.29 mmol) and $NaNO_2$ (41 mg, 0.60 mmol) in 2 ml of AcOH. Orange solid, mp 93-98 °C (AcOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.71 (s, 3H), 3.80 (s, 3H), 7.02-7.06 (m, 1H), 7.14-7.16 (m, 1H), 7.18-7.20 (m, 1H), 7.41-7.45 (m, 1H), 8.10 (d, *J* = 8.8 Hz, 2H), 8.38 (d, *J* = 8.8 Hz, 2H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.2 ($CH_3$), 55.3 ($CH_3$), 114.4 (CH), 114.7 (CH), 121.4 (CH), 121.4 (C), 124.4 (CH), 127.2 (CH), 129.6 (CH), 129.6 (C), 131.3 (C), 131.3 (C), 147.3 (C), 149.6 (C), 149.6 (C), 159.1 (C), 162.6 (C). ESI/HRMS (m/z): 401.0856 calcd. for $C_{19}H_{14}N_4NaO_5$ $[M + Na]^+$, found 401.0863. IR (KBr, $cm^{-1}$): ν 2159, 1716, 1702.

**Methyl 3-diazo-2-phenyl-4-(thiophen-2-yl)-3*H*-pyrrole-5-carboxylate (25f)**. Compound **25f** (219 mg, 94%) was obtained from compound **28f** (224 mg, 1.08 mmol) and $NaNO_2$ (150 mg, 2.20 mmol) in 2 ml AcOH. Orange solid, mp 118-123 °C (dec.) (AcOH-$H_2O$). $^1$H NMR ($CDCl_3$): δ = 3.90 (s, 3H), 7.14-7.16 (m, 1H), 7.37-7.38 (m, 1H), 7.43-7.49 (m, 4H), 7.75-7.77 (m, 2H). $^{13}$C NMR ($CDCl_3$): δ = 52.0 ($CH_3$), 126.7 (CH), 127.5 (CH), 127.8 (CH), 128.2 (C), 128.7 (CH), 129.1 (CH), 129.9 (CH), 130.7 (C), 131.4 (C), 132.5 (C), 132.5 (C), 156.2 (C), 163.1(C). ESI/HRMS (m/z): 332.0464 calcd. for $C_{16}H_{11}N_3NaO_2S$ $[M + Na]^+$, found 332.0455. IR (KBr, $cm^{-1}$): ν 2120, 1712.

**Methyl 2-(4-bromophenyl)-3-diazo-4-(thiophen-2-yl)-3*H*-pyrrole-5-carboxylate (25g)**. Compound **25g** (326 mg, 92%) was obtained from compound **28g** (343 mg, 0.91 mmol) and $NaNO_2$ (172 mg, 2.50 mmol) in 5 ml of AcOH. Orange solid, dec. > 114 °C (AcOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.75 (s, 3H), 7.19-7.21 (m, 1H), 7.44-7.45 (m, 1H), 7.72-7.79 (m, 5H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.2 ($CH_3$), 122.8 (C), 127.3 (CH) 127.9 (C), 128.2 (CH), 128.5 (CH), 128.5 (C), 128.6 (CH), 130.0 (C), 130.6 (CH),

131.9 (C), 132.1 (CH), 151.9 (C), 162.7 (C). ESI/HRMS (m/z): 387.9750 calcd. for $C_{16}H_{11}BrN_3O_2S$ [M + H]$^+$, found 387.9755. IR (KBr, cm$^{-1}$): ν 2129, 1713.

**Methyl 3-diazo-2-(4-methoxyphenyl)-4-(thiophen-2-yl)-3*H*-pyrrole-5-carboxylate (25h)**. Compound **25h** (335 mg, 79%) was obtained from compound **28h** (410 mg, 1.25 mmol) and $NaNO_2$ (310 mg, 4.50 mmol) in 4 ml of AcOH. Orange solid, mp 104 °C (dec.) (AcOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.78 (s, 3H), 3.85 (s, 3H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.21-7.23 (m, 1H), 7.48-7.49 (m, 1H), 7.79-7.80 (m, 1H), 7.82 (d, *J* = 8.8 Hz, 2H). $^{13}$C NMR (DMSO-$d_6$) could not be registered due to low solubility and instability of the substance in solution. ESI/HRMS (m/z): 340.0750 calcd. for $C_{17}H_{14}N_3O_3S$ [M + H]$^+$, found 340.0746. IR (KBr, cm$^{-1}$): ν 2188, 2159, 2122, 1732, 1717, 1607.

**Methyl 3-diazo-2-(4-nitrophenyl)-4-(thiophen-2-yl)-3*H*-pyrrole-5-carboxylate (25i)**. Compound **25i** (138 mg, 89%) was obtained from compound **28i** (151 mg, 0.44 mmol) and $NaNO_2$ (76 mg, 1.10 mmol) in 2 ml of Ac OH. Orange solid, dec. > 100 °C (AcOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.77 (s, 3H), 7.21-7.23 (m, 1H), 7.47-7.48 (m, 1H), 7.79-7.80 (m, 1H), 8.10 (d, *J* = 8.8 Hz, 2H), 8.37 (d, *J* = 8.8 Hz, 2H). $^{13}$C NMR could not be registered due to low solubility and instability of the substance in solution. ESI/HRMS (m/z): 377.0315 calcd. for $C_{16}H_{10}N_4NaO_4S$ [M + Na]$^+$, found 377.0317. IR (KBr, cm$^{-1}$): ν 2133, 1712.

**Methyl 4-(benzofuran-2-yl)-3-diazo-2-phenyl-3*H*-pyrrole-5-carboxylate (25j)**. Compound **25j** (160 mg, 84%) was obtained from compound **28j** (185 mg, 0.56 mmol) and $NaNO_2$ (104 mg, 1.50 mmol) in 3 ml of AcOH. Orange solid, dec. > 100 °C (AcOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.88 (s, 3H), 7.29-7.33 (m, 1H), 7.36-7.40 (m, 1H), 7.48-7.57 (m, 3H), 7.60-7.62 (m, 1H), 7.75-7.77 (m, 1H), 7.86-7.87 (m, 2H), 7.94 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): 51.6 ($CH_3$), 108.1 (CH), 110.9 (CH), 121.9 (CH), 122.8 (C), 123.6 (CH), 125.6 (CH), 126.6 (CH), 128.2 (C), 129.1 (CH), 129.6 (CH), 129.6 (C), 129.9 (C), 132.5 (C), 147.4 (C), 153.5 (C), 154.0 (C), 163.1(C). ESI/HRMS (m/z): 366.0855 calcd. for $C_{20}H_{13}N_3NaO_3$ [M + Na]$^+$, found 366.0859. IR (KBr, cm$^{-1}$): ν 2134, 1700.

**Cyclization of 3-diazopyrroles 25 to pyrrolopyridazines 26.** The suspension of β-diazopyrrole **25** in 25% $H_2SO_4$ was refluxed (107 °C, monitored by TLC) until complete conversion of the starting material. After cooling to room temperature the reaction mixture was filtered and the filter-cake was thoroughly washed with water, suspended in aqueous ethanol and treated with 5% aqueous sodium carbonate solution. The precipitate was filtered off, thoroughly washed with water and dried on air prior to trituration with boiling ether.

**1,3-Diphenyl-2*H*-pyrrolo[3,4-*c*]cinnoline (8a)**. Compound **8a** (104 mg, 72%) was obtained from pyrrole **11a** (145 mg, 0.45 mmol). Red crystals, mp 327-330 °C (dec.) (EtOH-$H_2O$) (lit.[7f] mp. 330-335°C). $^1$H NMR (DMSO-$d_6$): δ = 7.35-7.39 (m, 1H), 7.57-7.67 (m, 7H), 7.80-7.82 (m, 2H), 8.07 (d, J = 7.6 Hz, 1H), 8.43 (d, *J* = 7.6 Hz, 1H), 8.56-8.58 (m, 2H), 13.37 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 104.9 (C), 120.2 (C), 121.2 (CH), 126.7 (CH), 126.7 (C), 126.8 (CH), 126.8 (C), 127.1 (CH), 128.1 (CH), 128.6 (CH), 128.6 (C), 128.7 (CH), 128.7 (C), 129.8 (CH), 129.8 (C), 130.3 (CH), 130.4 (CH), 142.9 (C). ESI/HRMS (m/z): 322.1344 calcd. for $C_{22}H_{16}N_3$ $[M + H]^+$, found 322.1325. IR (KBr, $cm^{-1}$): ν 3048, 1604, 1467.

**Methyl 8-methoxy-3-phenyl-2*H*-pyrrolo[3,4-*c*]cinnoline-1-carboxylate (26b)**. Compound **26b** (269 mg, 80%) was obtained from compound **25b** (335 mg, 1.00 mmol). Yellow-brown crystals, mp 212-213 °C (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.98 (s, 3H), 3.99 (s, 3H), 7.43-7.45 (m, 1H), 7.48-7.52 (s, 1H), 7.57-7.61 (m, 2H), 8.41-8.43 (m, 1H), 8.48-8.49 (m, 2H), 8.91 (s, 1H), 13.74 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.8 ($CH_3$), 55.6 ($CH_3$), 106.2 (CH), 111.3 (C), 113.6 (C), 118.9 (CH), 120.3 (C), 128.5 (CH), 128.9 (CH), 128.9 (CH), 129.0 (C), 131.4 (C), 132.0 (CH), 138.3 (C), 140.7 (C), 160.5 (C), 160.7 (C). ESI/HRMS (m/z): 334.1192 calcd. for $C_{19}H_{16}N_3O_3$ $[M + H]^+$, found 334.1197. IR (KBr, $cm^{-1}$): ν 3271, 1703, 1667, 1614.

**Methyl 3-(4-bromophenyl)-8-methoxy-2*H*-pyrrolo[3,4-*c*]cinnoline-1-carboxylate (26c)**. Compound **26c** (411 mg, 85%) was obtained from compound **25c** (483 mg, 1.17 mmol). Brown crystals, mp 222-223 °C (dec.) (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.96 (s, 3H), 3.97 (s, 3H), 7.40-7.43 (m, 1H), 7.76 (d, *J*

= 8.4 Hz, 2H), 8.37-8.39 (m, 1H), 8.46 (d, *J* = 8.4 Hz, 2H), 8.83 (s, 1H), 13.71 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.5 ($CH_3$), 55.4 ($CH_3$), 106.2 (CH), 111.7 (C), 113.3 (C), 118.5 (CH), 120.0 (C), 122.1 (C), 128.1 (C), 130.3 (C), 130.4 (CH), 131.2 (CH), 131.9 (C), 132.6 (CH), 138.2 (C), 160.4 (C). ESI/HRMS (m/z): 412.0291 calcd. for $C_{19}H_{15}BrN_3O_3$ $[M + H]^+$, found 412.0291. IR (KBr, $cm^{-1}$): ν 3092, 1710, 1615.

**Methyl 8-methoxy-3-(4-methoxyphenyl)-2*H*-pyrrolo[3,4-*c*]cinnoline-1-carboxylate (26d)**. Compound **26d** (219 mg, 73%) was obtained from compound **25d** (300 mg, 0.83 mmol). Brown crystals, mp 201 °C (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.88 (s, 3H), 4.01 (*pseudo-s*, 6H), 7.15 (d, *J* = 8.9 Hz, 2H), 7.45 (dd, *J* = 9.0, 2.8 Hz, 1H), 8.42 (d, *J* = 9.0 Hz, 1H), 8.49 (d, *J* = 8.9 Hz, 2H), 8.94 (d, *J* = 2.8 Hz, 1H), 13.41 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.4 ($CH_3$), 55.1 ($CH_3$), 55.4 ($CH_3$), 106.3 (CH), 110.4 (C), 113.4 (C), 113.9 (CH), 118.5 (CH), 120.2 (C), 121.4 (C), 130.1 (CH), 131.6 (C), 131.7 (CH), 138.0 (C), 140.6 (C), 159.9 (C), 160.2 (C), 160.5 (C). ESI/HRMS (m/z): 364.1292 calcd. for $C_{20}H_{18}N_3O_4$ $[M + H]^+$, found 364.1301. IR (KBr, $cm^{-1}$): ν 2951, 1699, 1664, 1613.

**Methyl 8-methoxy-3-(4-nitrophenyl)-2*H*-pyrrolo[3,4-*c*]cinnoline-1-carboxylate (26e)**. Compound **26e** (94 mg (84%) was obtained from compound **25e** (300 mg, 0.83 mmol). Dark purple crystals, dec. > 240 °C (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 4.03 (s, 3H), 4.04 (s, 3H), 7.47-7.50 (m, 1H), 8.40 (d, *J* = 8.9 Hz, 2H), 8.47-8.49 (m, 1H), 8.90 (d, *J* = 8.9 Hz, 2H), 8.99 (s, 1H), 14.04 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.4 ($CH_3$), 55.4 ($CH_3$), 106.1 (CH), 113.4 (C), 114.4 (C), 118.5 (CH), 120.1 (C), 123.2 (CH), 128.3 (C), 128.5 (CH), 131.6 (CH), 136.0 (C), 139.4 (C), 140.4 (C), 146.3 (C), 160.5 (C), 160.9 (C). ESI/HRMS (m/z): 379.1042 calcd. for $C_{19}H_{15}N_4O_5$ $[M + H]^+$, found 379.1049. IR (KBr, $cm^{-1}$): ν 1689, 1616, 1597.

**Methyl 6-phenyl-7*H*-pyrrolo[3,4-*c*]thieno[2,3-*e*]pyridazine-8-carboxylate (26f)**. Compound **26f** (149 mg, 70%) was obtained from compound **25f** (208 mg, 0.67 mmol). Dark green crystals, mp 228-230°C (dec.) (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 4.02 (s, 3H), 7.50-7.53 (m, 1H), 7.59-7.61 (m, 2H), 8.08-

8.12 (m, 2H), 8.59-8.61 (m, 2H), 14.42 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.5 ($CH_3$), 107.9 (C), 114.9 (C), 124.9 (C), 126.0 (CH), 128.58 (CH), 128.64 (CH), 129.1 (CH), 129.8 (CH), 129.9 (C), 132.0 (C), 138.2 (C), 152.5 (C), 160.3(C). ESI/HRMS (m/z): 310.0650 calcd. for $C_{16}H_{12}N_3O_2S$ $[M + H]^+$, found 310.0646. IR (KBr, $cm^{-1}$): ν 3235, 1673, 1597.

**Methyl 6-(4-bromophenyl)-7*H*-pyrrolo[3,4-*c*]thieno[2,3-*e*]pyridazine-8-carboxylate (26g)**. Compound **26g** (264 mg, 89%) was obtained from methyl compound **25g** (295 mg, 0.76 mmol). Dark purple crystals, mp 218-221 °C (dec.) (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 4.01 (s, 3H), 7.79 (d, *J* = 8.6 Hz, 2H), 8.07 (d, *J* = 5.5 Hz, 1H), 8.11 (d, *J* = 5.5 Hz, 1H), 8.57 (d, *J* = 8.6 Hz, 2H), 14.45 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.5 ($CH_3$), 108.5 (C), 114.9 (C), 122.5 (C), 124.7 (CH), 126.2 (C), 128.3 (C), 130.1 (CH), 130.2 (CH), 130.6 (C), 131.6 (CH), 138.1 (C), 152.2 (C), 160.2 (C). ESI/HRMS (m/z): 387.9750 calcd. for $C_{16}H_{11}BrN_3O_2S$ $[M + H]^+$, found 387.9757. IR (KBr, $cm^{-1}$): ν 3086, 1698, 1676.

**Methyl 6-(4-methoxyphenyl)-7*H*-pyrrolo[3,4-*c*]thieno[2,3-*e*]pyridazine-8-carboxylate (26h)**. Compound **26h** (178 mg, 61%) was obtained from compound **25h** (290 mg, 0.86 mmol). Green crystals, mp 225-227 °C (dec.) (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 3.88 (s, 3H), 4.02 (s, 3H), 7.16 (d, *J* = 8.5 Hz, 2H), 8.05 (*pseudo*-s, 2H), 8.59 (d, *J* = 8.5 Hz, 2H), 14.06 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 50.9 ($CH_3$), 55.1 ($CH_3$), 114.0 (CH), 114.8 (C), 114.8 (C), 121.6 (C), 124.6 (CH), 125.6 (C), 125.6 (C), 129.3 (CH), 129.8 (CH), 137.8 (C), 137.8 (C), 160.0 (C), 160.1 (C). ESI/HRMS (m/z): 340.0756 calcd. for $C_{17}H_{14}N_3O_3S$ $[M + H]^+$, found 340.0765. IR (KBr, $cm^{-1}$): ν 3214, 1664,1610.

**Methyl 6-(4-nitrophenyl)-7*H*-pyrrolo[3,4-*c*]thieno[2,3-*e*]pyridazine-8-carboxylate (26i)**. Compound **26i** (94 mg, 82%) was obtained from compound **25i** (114 mg, 0.33 mmol). Dark purple crystals, dec. > 205 °C (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 4.04 (s, 3H), 8.10 (d, *J* = 5.5 Hz, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 8.41 (d, *J* = 8.8 Hz, 2H), 8.93 (d, *J* = 8.8 Hz, 2H), 14.72 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.7 ($CH_3$), 110.4 (C), 114.9 (C), 123.8 (CH), 123.8 (CH), 124.9 (C), 126.3 (C), 128.4 (C), 128.7 (CH), 130.4

(CH), 135.4 (C), 138.8 (C), 146.6 (C), 160.2 (C). ESI/HRMS (m/z): 355.0496 calcd. for $C_{16}H_{11}N_4O_4S$ [M + H]$^+$, found 355.0501. IR (KBr, cm$^{-1}$): ν 3106, 1699.

**Methyl 3-phenyl-2*H*-benzofuro[3,2-*c*]pyrrolo[3,4-*e*]pyridazine-1-carboxylate (26j)**. Compound **26j** (119 mg, 94%) was obtained from compound **25j** (126 mg, 0.37 mmol). Brown crystals, mp 256-257 °C (dec.) (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 4.05 (s, 3H), 7.50-7.54 (m, 1H), 7.60-7.64 (m, 3H), 7.69-7.73 (m, 1H), 7.94-7.96 (m, 1H), 8.41-8.43 (m, 1H), 8.58-8.60 (m, 2H), 14.73 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 51.8 ($CH_3$), 106.8 (C), 107.6 (C), 112.5 (CH), 120.2 (CH), 121.8 (C), 124.8 (CH), 128.59 (CH), 128.63 (CH), 128.8 (CH), 128.9 (C), 129.2 (CH), 131.9 (C), 138.0 (C), 142.1 (C), 143.6 (C), 154.7 (C), 160.0 (C). ESI/HRMS (m/z): 366.0849 calcd. for $C_{20}H_{13}N_3NaO_3$ [M + Na]$^+$, found 366.0855. IR (KBr, cm$^{-1}$): ν 3193, 1673.

**Methyl 3-(4-bromophenyl)-2*H*-benzo[4,5]thieno[3,2-*c*]pyrrolo[3,4-*e*]pyridazine-1-carboxylate (26k)**. Compound **26k** (30 mg, 79%) was obtained from the mixture of compound **25k** and **26k** mixture (38 mg, 0.09 mmol). Brown crystals, mp 266-268 °C (dec.) (EtOH-$H_2O$). $^1$H NMR (DMSO-$d_6$): δ = 4.07 (s, 3H), 7.69-7.74 (m, 2H), 7.80 (d, *J* = 8.6 Hz, 2H), 8.19-8.22 (m, 1H), 8.63 (d, *J* = 8.6 Hz, 2H), 8.72-8.73 (m, 1H), 14.46 (br. s, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 53.3 ($CH_3$), 121.9 (CH), 123.2 (C), 123.9 (CH), 124.3 (C), 125.9 (C), 126.7 (C), 126.9 (C), 130.26 (CH), 130.29 (C), 131.4 (CH), 131.7 (CH), 132.1 (CH), 132.8 (C), 140.4 (C), 154.2 (C), 154.5 (C), 167.6 (C). ESI/HRMS (m/z): 437.9920 calcd. for $C_{20}H_{13}BrN_3O_2S$ [M + H]$^+$, found 437.9906. IR (KBr, cm$^{-1}$): 3222, 1679.

**Methylation of pyrrolocinnolines.** Cinnoline **26** was dissolved in a solution of NaOMe in methanol, prepared from Na (2.00-4.00 eq) and absolute MeOH (5 mL), and then methyl iodide (3.00-10.00 equiv) was added. The reaction mixture was stirred for 12 hours at room temperature. All the volatiles were removed in vacuo and the residue was treated with aqueous ammonium chloride. The precipitate formed was filtered off, washed with water and dried prior to column chromatography on silica (light

petroleum/EtOAc 6:1 - 0:1). The substance obtained was treated with boiling ether, filtered and dried on air.

**5-Methyl-1,3-diphenyl-5*H*-pyrrolo[3,4-*c*]cinnoline** (**8a-5Me**). Compound **8a-5Me** (73 mg, 57%) was obtained from cinnoline **8a** (124 mg, 0.39 mmol) sodium (31 mg, 1.35 mmol) and methyl iodide (570 mg, 4.00 mmol). Dark blue crystals, mp 225-227 °C (hexane-EtOAc). $^1$H NMR (DMSO-$d_6$): δ = 4.54 (s, 3H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.48-7.61 (m, 5H), 7.64-7.67 (m, 1H), 7.87 (d, *J* = 7.2 Hz, 2H), 8.05-8.07 (m, 1H), 8.32-8.34 (m, 1H), 8.49 (d, *J* = 7.2 Hz, 2H). $^{13}$C NMR (DMSO-$d_6$): δ = 46.5 ($CH_3$), 104.0 (CH), 117.5 (CH), 121.5 (CH), 122.4 (CH), 127.0 (CH), 127.3 (CH), 127.6 (CH), 127.8 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 132.2 (C), 134.7 (C), 137.1 (C), 137.8 (C), 143.6 (C), 145.2 (C). ESI/HRMS (m/z): 336.1495 calcd for $C_{23}H_{18}N_3$ $[M + H]^+$, found 336.1505. IR (KBr, $cm^{-1}$): ν 3446, 1679, 1602.

**Methyl 8-methoxy-5-methyl-3-phenyl-5*H*-pyrrolo[3,4-*c*]cinnoline-1-carboxylate** (**26b-5Me**). Compound **26b-5Me** (87 mg, 64%) was obtained from compound **26b** (131 mg, 0.39 mmol), sodium (36 mg, 1.57 mmol) and methyl iodide (560 mg, 3.95 mmol). Dark violet crystals, mp 227-229 °C (hexane-EtOAc). $^1$H NMR (DMSO-$d_6$): δ = 4.08 (s, 3H), 4.10 (s, 3H), 4.56 (s, 3H), 7.30-7.33 (m, 1H), 7.35-7.39 (m, 1H), 7.46-7.50 (m, 2H), 7.74-7.76 (m, 1H), 8.51-8.53 (m, 2H), 9.57-9.58 (m, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 48.2 ($CH_3$), 51.3 ($CH_3$), 55.8 ($CH_3$), 107.2 (CH), 115.4 (C), 120.1 (CH), 120.3 (CH), 123.9 (C), 127.0 (CH), 127.8 (CH), 127.8 (C), 128.5 (CH), 128.9 (C), 134.6 (C), 140.9 (C), 142.9 (C), 159.5 (C), 165.4 (C). ESI/HRMS (m/z): 348.1343 calcd for $C_{20}H_{18}N_3O_3$ $[M + H]^+$, found 348.1351. IR (KBr, $cm^{-1}$): ν 2944, 1683, 1618.

**Methyl 3-(4-bromophenyl)-8-methoxy-5-methyl-5*H*-pyrrolo[3,4-*c*]cinnoline-1-carboxylate** (**26c-5Me**). Compound **26c-5Me** (57 mg, 55%) was obtained from compound **26c** (100 mg, 0.24 mmol), sodium (51 mg, 2.22 mmol) and methyl iodide (340 mg, 2.40 mmol). Dark violet crystals, mp 227-229 °C (hexane-EtOAc). $^1$H NMR (DMSO-$d_6$): δ = 3.96 (s, 3H), 4.06 (s, 3H), 4.74 (s, 3H), 7.54(dd, *J* = 9.5, 2.9

Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 8.30 (d, *J* = 9.5 Hz, 1H), 8.44 (d, *J* = 8.6 Hz, 2H), 9.44 (d, *J* = 2.9 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$): δ = 47.6 ($CH_3$), 50.7 ($CH_3$), 55.5 ($CH_3$), 107.3 (CH), 114.9 (C), 119.6 (CH), 119.8 (CH), 120.5 (C), 123.6 (C), 124.7 (C), 128.5 (CH), 128.7 (C), 131.0 (CH), 133.6 (C), 140.6 (C), 141.4 (C), 159.3 (C), 165.0 (C). ESI/HRMS (m/z): 426.0448 calcd for $C_{20}H_{17}BrN_3O_3$ $[M + H]^+$, found 426.0455. IR (KBr, $cm^{-1}$): ν 3436, 2091, 1668, 1618.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc…

NMR spectra for all new compounds, crystallographic data for compound **11a**, computation details: energies of the reactants, transition states, their Cartesian coordinates. (PDF). Crystallographic data for **11a** (CIF)

## ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the Russian Science Foundation (Grant No. 16-13-10036). This research was carried out using resources of the X-ray Diffraction Centre, the Centre for Magnetic Resonance, the Computer Centre, the Centre for Optical and Laser Materials Research and the Centre for Chemical Analysis and Materials of St. Petersburg State University.

## REFERENCES

1. (a) Mokrushin, V. S.; Sadchikova, E. V. Chemistry of heterocyclic diazo compounds, St. Petersburg, Russia: Prospekt Nauki, 2013, 224 p.; (b) da Silva, F. C.; Jordão, A. K.; da Rocha, D. R.; Ferreira, S. B.; Cunha, A. C.; Ferreira, V. F. *Curr. Org. Chem*. **2012**, 16, 224-251; (c) Zollinger, H. Diazo Chemistry. I. Aromatic and heteroaromatic compounds, VCH: Weinheim, Germany, 1994, 454 p.; (d) Cirrincione, G.; Almerico, A. M.; Aiello, E.; Dattolo, G., *Adv. Heterocycl. Chem*. **1990**, *48*, 65-175 (and references cited therein); (e) Elnagdi, M.H.; Zayed, E.M.; Abdou, S. *Heterocycles* **1982**, *19*, 559-

578; (f) Tišler, M.; Stanovik, B. *Chem. Heterocycle. Compd*. **1980**, 443-463; (g) Butler, R.N. *Chem. Rev*. **1975**, *75*, 241–257.

2. (a) Tatar, Z.; Thivat, E.; Planchat, E.; Gimbergues, P.; Gadea, E.; Abrial, C.; Durando, X. *Cancer. Treat. Rev*. **2013**, *39*, 125-135; (b) Hansen, N.; Wittig, A.; Hense, J.; Kastrup, O.; Gizewski, E. R.; Van de Nes, J. A. P. *Eur. J. Med. Res.* **2011**,*16*, 415-419; (c) Kizilarslanoglu, M. C.; Aksoy, S.; Yildirim, N. O.; Ararat, E.; Sahin, I.; Altundag, K. *J. BION* 2011, 16, 547-550.
3. (a) Stevens, M. F. G.; Hickman, J. A.; Stone, R.; Gibson, N. W.; Baig, G. U.; Lunt, E.; Newton, C. G. *J. Med. Chem*., **1984**, *27*, 196–201; (b) Wheelhouse, R. T.; Wilman, D. E. V.; Thomson, W.; Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 249–252.
4. Galenko, E. E.; Tomashenko, O. A.; Khlebnikov, A. F., Novikov, M. S. *Org. Biomol. Chem*. **2015**, *13*, 9825-9833.
5. (a) Wang, C.; Zhang, H.; Lang, B.; Ren, A.; Lu, P.; Wang, Y. *Org. Lett*. **2015**, *17*, 4412-4415; (b) Wu, M.-Y.; He, W.-W.; Liu, X.-Y.; Tan, B. *Angew. Chem. Int. Ed*. **2015**, *54*, 9409-9413; (c) Sheng, G.; Huang, K.; Ma, S.; Qian, J.; Lu, P.; Wang, Y. *Chem. Commun*. **2015**, *51*, 11056-11059; (d) Jing, C.; Xing, D.; Wang, C.; Hu, W. *Tetrahedron* **2015**, *71*, 3597-3602; (e) Coffey, K. E.; Moreira, R.; Abbas, F. Z.; Murphy, G. K. *Org. Biomol. Chem*. **2015**, *13*, 682-685; (f) Karthik, G.; Rajakaran, T.; Sridhar, B.; Reddy, B. V. S. *Tetrahedron Lett*. **2015**, *55*, 7064-7067.
6. Parrino, B.; Spanò, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Màtyus, P.; Cirrincione, G.; Diana, P. *Tetrahedron*. **2014**, *70*, 7318-7321.
7. (a) Angelico, F. *Atti. Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nut*. **1908**, *17*, 655-662; (b) Angelico, F.; Labisi, C. Gazzetta **1910**, *40*, 411-417; (c) Kreutzberg, A.; Kalter, P. A. *J. Org. Chem*. **1961**, *26*, 3790-3796; (e) Bartholomew, R. F.; Tedder J. M. *J. Chem. Soc*. **1968**, 1601; (d) Ames, D. E.; Ansari, H. R.; Ellis, A. W. *J. Chem. Soc. (C)* **1969**, 1795-1798; (e) Dattolo, G.; Cirrincione, G.; Almerico, A. M.; Presti, G.; Aiello, E. *Heterocycles* **1984**, *22*, 2269-2276; (f) Dattolo, G.; Cirrincione,

G.; Almerico, A. M.; Aiello, E. *J. Heterocycl. Chem*. **1989**, *26*, 1747-1749; (g) Ceraulo, L.; Agozzino, P.; Ferrugia, M.; Plescia, S.; Sprio, V. *J. Heterocycl. Chem*. **1990**, *27*, 135-138; (h) Buscemi, S.; Pace, A.; Cirrincione, G.; Diana, P. *Heterocycles* **1999**, *51*, 1631-1638.

8. Cirrincione, G.; Almerico, A. M.; Dattolo, G.; Aiello, E.; Grimaudo, S.; Diana, P.; Misuraca, F. *Farmaco* **1992**, *47*, 1555-1562.
9. Cirrincione, G.; Almerico, A. M.; Grimaudo, S.; Diana, P.; Mingoia, F.; Barraja, P.; Misuraca, F. *Farmaco* **1996**, 51, 49-52.
10. (a) Cirrincione, G.; Dattolo, G.; Almerico, A.;M.; Aiello, E. *Heterocycles* **1985**, *23*, 2635-2638; (b) Dattolo, G.; Cirrincione, G.; Almerico A. M.; Lamartina, L.; Aiello, E. A. *J. Chem. Res. Synop*. **1985**, 164-165; (c) Ames, D. E.; Bull, D. *Tetrahedron* **1982**, *38*, 383-387.
11. For recent examples see: (a) Yu, C.; Wu, Q.; Wang, J.; Wei, Y.; Hao, E.; Jiao, *J. Org. Chem*. **2016**, *81*, 3761-3770; (b) Sareen, D.; Lee, J. H.; Hwang, H.; Yoo, S.; Lee, C.-H. *Chem. Commun*. **2016**, *52*, 5852-5855; (c) Kim, L. E**.;** Lee, Y**.;** Lee, S**.;** Park**,** S**.** B**.** *Acc. Chem. Res*. **2015**, *48*, 538−547; (d) Tomashenko, O. A.; Khlebnikov, A. F.; Mosiagin, I. P.; Novikov, M. S.; Grachova, E. V.; Shakirova, J. R.; Tunik, S. P. *RSC Adv.*, **2015**, *5*, 94551-94561**;**(e) Yang, D.-T.; Radtke, J.; Mellerup, S. K.; Yuan, K.; Wang, X.; Wagner, M.; Wang, S. *Org. Lett*., **2015**, *17*, 2486-2489; (f) Liu, G.; Chen, D.; Kong, L.; Shi, J.; Tong, B.; Zhi, J.; Feng, X.; Dong, Y. *Chem. Commun*., **2015**, *51*, 8555-8558.
12. Khlebnikov, A. F.; Golovkina, M. V.; Novikov, M. S.; Yufit, D. S. *Org. Lett*. **2012**, *14*, 3768-3771.
13. Clark, A. D.; Ha, U. T.; Prager, R. H.; Smith, J. A. *Aust. J. Chem*. **1999**, *52*, 1029-1033.
14. Clark, A. D.; Janowski, W. K.; Prager, R. H. Tetrahedron, **1999**, *55*, 3637-3647.
15. Auricchio, S.; Bini, A.; Pastormelo, E.; Truscello, A. M. Tetrahedron, **1997**, *53*, 10911-10920.
16. Nomine, G.; Penassel, L.; Dalaroff, V. *Annales Pharm. Franc*. **1958**, *16*, 436-441.
17. Moore, R. G. D.; Woitach, P. T. Light-sensitive layers for photomechanical reproduction. GB Pat. 816382, **1959**.