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First synthesis of methyl 3-amino-4-(het)aryl-1*H*-pyrrole-2-carboxylates as useful scaffolds in medicinal chemistry

Christophe Rochais, Vincent Lisowski, Patrick Dallemagne* and Sylvain Rault

CERMN, UFR des Sciences Pharmaceutiques, Université de Caen Basse-Normandie, 5, rue Vaubénard, Caen 14032, France

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Abstract—The preparation of new methyl 4-(het)aryl-3-amino-1*H*-pyrrole-2-carboxylates was achieved starting from commercial arylacetonitriles. This four steps synthesis afforded with good yields interesting building-blocks useful in the access to many nitrogen heterocycles with potential therapeutic interest.

1. Introduction

The anthranilic acids are widely used as interesting building-blocks in the field of medicinal chemistry and allow, for example, the synthesis of several antiinflammatory drugs like mefenamic acid, and more recently some protein tyrosine phosphatase inhibitors.[1] With the aim of investigating new heterocyclic bioisosters of the latter, our group has recently developed furane[2] and thiophene[3] analogs of anthranilic acids and we wish to extend herein this study to the pyrrole derivatives. In fact the latter are often reported as crucial intermediates in the synthesis of various potent heterocycles.[4] Although some groups have published work about 3-aminopyrrole-2-carboxylates, none of these papers were concerned with the title 4-(het)aryl compounds **1**, since only 4,5-unsubstituted **2**, 5-aryl **3** or 4-arylmethyl **4** derivatives were reported (Fig. 1).[5–7] We therefore decided to investigate a convenient route towards these potential useful scaffolds.

2. Results and discussion

During our previous work in thiophene series, we focused on the preparation, by formylation of commercial arylacetonitriles **5**, of stable enolates **6** which were involved, after activation by a sulfonylbenzene leaving group, in a Kirsch's cyclisation.[8] The latter was performed by treatment with methyl thioglycolate and sodium methoxide and led to the attempted methyl amino-4-arylthiophene-3-carboxylates **8** (Scheme 1). With the aim to apply this pathway to the synthesis of the pyrrole analogs of **8**, we first replaced thiophene thioglycolate in the previous sequence by diethylaminomalonate (DEAM), according to the Chen's procedure used for the access to 5-substituted 3-amino-1*H*-pyrrole-2-carboxylates.[6]

This method, involved in *p*-methoxyphenyl series led to the first methyl 3-amino-4-aryl-1*H*-pyrrole-2-carboxylate **9a**, but in very poor yield (Scheme 2).

In order to improve this sequence, we focused on the isolation of the enamine **10a** as a key intermediate in the synthesis of **9a**, since Elliot alleged it was possible to isolate it with a benzyl substituent in the place of the aryl one.[7] We

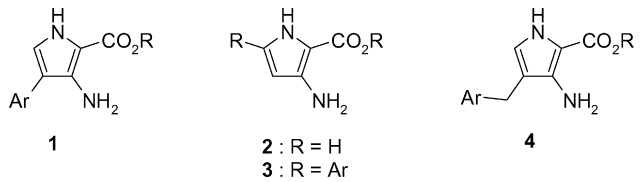
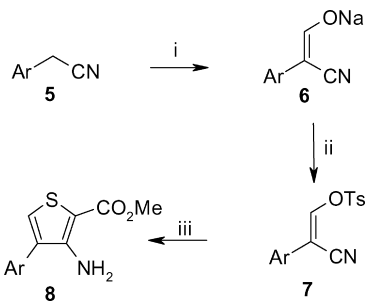


Figure 1.



Scheme 1. (i) HCO_2Et, NaH, THF; (ii) $ClSO_2C_6H_5$, DMF; (iii) $HSCH_2CO_2Me$, MeONa, MeOH.

Keywords: Aminoarylpyrrolecarboxylates; Enamine; Diethylaminomalonate; Cyclisation.
* Corresponding author. Tel.: +33-2-31-56-59-10; fax: +33-2-31-93-11-88; e-mail address: dallemagne@pharmacie.unicane.fr

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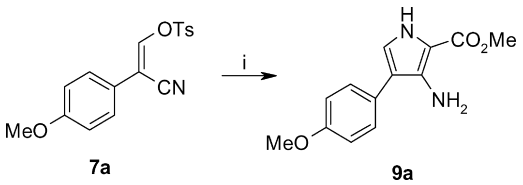
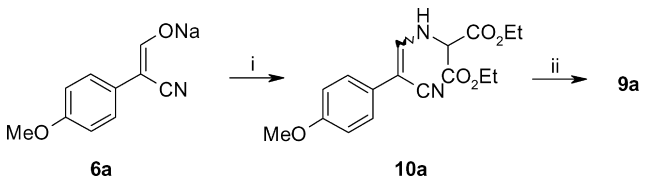


Scheme 2. (i) DEAM, MeONa, MeOH.

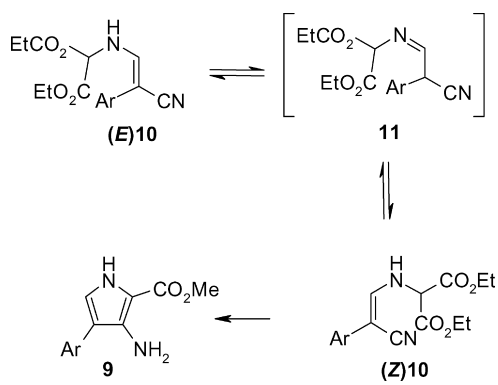
first tried to reach this goal by treatment of the tosyl derivative **7a** with DEAM, but all the attempts in various experimental conditions failed. The reaction involving the enol displaced from its sodium salt **6a** and DEAM in diluted methanol was also unsuccessful, whereas utilization in this sequence of the hydrochloric salt of DEAM in anhydrous methanol and in the presence of triethylamine afforded the attempted enamine **10a** in 95% yield (Scheme 3). The latter was subsequently cyclised and transesterified into **9a** using sodium methoxide in methanol with 43% yield.



Scheme 3. (i) (1) AcOH, H_2O, (2) DEAM–HCl, Et_3N, MeOH; (ii) MeONa, MeOH.

This relative poor yield could have been explained by the two isomeric forms *E* and *Z* observed in ^{1}H NMR for **10a** in 1/5 respective proportions as already demonstrated by Lim.[9] In fact we first though that only the *Z* isomer could be cyclised as it was recently demonstrated by Redman[10] in furane series. According to this hypothesis, the unreacted *E* isomer should be recovered in the reaction mixture, but none trace of the latter was observed. So we alleged that an *E*/*Z* isomerisation occurred during intramolecular cyclisation through an imine form **11**, the equilibrium being displaced by the formation of **9** from (*Z*) **10** (Scheme 4).

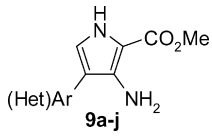
Eight other methyl 3-amino-4-(het)aryl-1*H*-pyrrole-2-carboxylates **9b–j** have been synthesized according to this pathway with 41–80% overall yields from **6** (Table 1).



Scheme 4.

Table 1.

(Het)Ar	Product	Overall yield (%)
4-Methoxyphenyl	**9a**	41
Phenyl	**9b**	66
4-Methylphenyl	**9c**	58
4-Fluorophenyl	**9d**	49
4-Chlorophenyl	**9e**	74
4-Bromophenyl	**9f**	68
3,4-Dichlorophenyl	**9g**	66
3,4-Dimethoxyphenyl	**9h**	65
2-Thienyl	**9i**	46
3-Thienyl	**9j**	80



In summary, we have developed an efficient preparation of new methyl 3-amino-4-(het)aryl-1*H*-pyrrole-2-carboxylates, in four steps from commercially available inexpensive starting materials. These products constitute building-blocks useful in the access to many nitrogen heterocycles with potential therapeutic interest.

3. Experimental

3.1. General

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer spectrum BX FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) spectra were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from TMS as an internal standard. Mass Spectra were recorded on a JEOL JMS GCMate with ionising potential of 70 eV and with pfk as internal standard for high-resolution procedure.

3.2. General procedure for the preparation of the enamine 10a–j

3.2.1. {[2-Cyano-2-(*p*-methoxyphenyl)vinyl)]amino}-diethyl malonate (10a). Diethylaminomalonate hydrochloride (1.81 g, 8.56 mmol) and TEA (873 μL, 6.28 mmol) were added to a solution of **6a** (1 g, 5.7 mmol) in methanol (20 mL). The reaction mixture was then heated for 4 h. Methanol was then removed and the residue was diluted in dichloromethane (100 mL). The organic layer was washed with water, and then dried over calcium chloride. Filtration and evaporation afforded the title compound **10a** (1.88 g, 99%), as an unstable yellow oil which was used without further purification, IR (KBr): 3382; 2199; 1743; 1630 cm^{-1}. ^{1}H NMR *Z*/*E* mixture 5/1 ($CDCl_3$): δ=7.36 (d, 2H$_{phenyl}$, *J*=8.8 Hz, *E*), 7.23 (d, 2H$_{phenyl}$, *J*=8.8 Hz, *Z*), 7.01 (d, 1H, *J*=13.0 Hz, CHN, *Z*), 6.95 (d, 2H$_{phenyl}$, *J*=8.8 Hz, *E*), 6.86 (d, 2H$_{phenyl}$, *J*=8.8 Hz, *Z*), 6.75 (d,

1H, J=13.3 Hz, CHN, *E*), 5.70 (m, 1H, NH, *E*), 5.65 (dd, 1H, J=13.0, 8.3 Hz, NH, *Z*), 4.65 (d, 1H, J=8.3 Hz, $CH(CO_2Et)_2$, *Z*), 4.55 (d, 1H, J=8.4 Hz, $CH(CO_2Et)_2$, *E*), 4.31 (m, 4H, CH_2, *Z*+*E*), 3.82 (s, 3H, OCH_3, *E*), 3.80 (s, 3H, OCH_3, *Z*), 1.32 (t, 6H, J=7.1 Hz, CH_3, *Z*+*E*); MS *m*/*z*: 332.0.

3.2.2. {[2-Cyano-2-(phenylvinyl)]amino}diethylmalonate (10b). From 2-phenyl-3-hydroxyacrylonitrile (3 g); yellow oil **10b** (5.9 g, 95%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.32 (m, $4H_{phenyl}$), 7.11 (d, 1H, J=12.9 Hz, CHN), 5.82 (dd, 1H, J=12.9, 8.3 Hz, NH), 4.70 (d, 1H, J=8.3 Hz, $CH(CO_2Et)_2$), 4.30 (m, 4H, CH_2), 1.32 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 302.1.

3.2.3. {[2-Cyano-2-(*p*-methylphenyl)vinyl)]amino}-diethyl malonate (10c). From 2-(*p*-methylphenyl)-3-hydroxyacrylonitrile (2 g); yellow oil **10c** (3.9 g, 97%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.20 (d, $2H_{phenyl}$, J=8.2 Hz), 7.12 (d, 1H, J=12.9 Hz, CHN), 7.10 (d, $2H_{phenyl}$, J=8.2 Hz), 5.73 (dd, 1H, J=12.9, 8.2 Hz, NH), 4.69 (d, 1H, J=8.2 Hz, $CH(CO_2Et)_2$), 4.31 (m, 4H, CH_2), 2.31 (s, 3H, CH_3), 1.32 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 316.1.

3.2.4. {[2-Cyano-2-(*p*-fluorophenyl)vinyl)]amino}diethyl malonate (10d). From 2-(*p*-fluorophenyl)-3-hydroxyacrylonitrile (1.75 g); yellow oil **10d** (3.4 g, 98%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.24–6.79 (m, 5H), 6.13 (dd, 1H, J=12.6, 8.4 Hz, NH), 4.66 (d, 1H, J=8.4 Hz, $CH(CO_2Et)_2$), 4.30 (m, 4H, CH_2), 1.32 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 308.1.

3.2.5. {[2-Cyano-2-(*p*-chlorophenyl)vinyl)]amino}diethyl malonate (10e). From 2-(*p*-chlorophenyl)-3-hydroxyacrylonitrile (4 g); yellow oil **10e** (7.5 g, 99%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.39 (d, 1H, J=13 Hz, CHN), 7.28–7.16 (m, $4H_{phenyl}$), 5.84 (dd, 1H, J=13, 8.0 Hz, NH), 4.70 (d, 1H, J=8.0 Hz, $CH(CO_2Et)_2$), 4.34 (m, 4H, CH_2), 1.31 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 336.1.

3.2.6. {[2-Cyano-2-(*p*-bromophenyl)vinyl)]amino}-diethyl malonate (10f). From 2-(*p*-bromophenyl)-3-hydroxyacrylonitrile (4.3 g); yellow oil **10f** (7.3 g, 99%); IR (KBr): 3378; 2198; 1754; 1633 cm^{-1}. ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.41 (d, $2H_{phenyl}$, J=8.3 Hz), 7.20 (d, 1H, J=13 Hz, CHN), 7.17 (d, $2H_{phenyl}$, J=8.3 Hz), 5.92 (dd, 1H, J=13, 8.1 Hz, NH), 4.71 (d, 1H, J=8.1 Hz, $CH(CO_2Et)_2$), 4.26 (m, 4H, CH_2), 1.31 (m, 6H, CH_3); MS *m*/*z*: 381.9.

3.2.7. {[2-Cyano-2-(3,4-dichlorophenyl)vinyl)]amino}-diethyl malonate (10g). From 2-(3,4-dichlorophenyl)-3-hydroxyacrylonitrile (2.5 g); yellow solid **10g** (4.3 g, 99%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.54–7.13 (m, 4H), 5.97 (dd, 1H, J=12.9, 8.1 Hz, NH), 4.72 (d, 1H, J=8.1 Hz, $CH(CO_2Et)_2$), 4.36 (m, 4H, CH_2), 1.33 (t, 6H, J=7.2 Hz, CH_3); MS *m*/*z*: 371.1.

3.2.8. {[2-Cyano-2-(3,4-dimethoxyphenyl)vinyl)]amino}-diethyl malonate (10h). From 2-(3,4-dimethoxyphenyl)-3-hydroxyacrylonitrile (8 g); yellow oil **10h** (4.46 g, 78%); IR (KBr): 3301; 2195; 1760; 1637 cm^{-1}. ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.06 (d, 1H, J=12.9 Hz, CHN), 6.82 (m, $3H_{phenyl}$), 5.72 (dd, 1H, J=12.9, 8.3 Hz, NH), 4.70 (d, 1H, J=8.3 Hz, $CH(CO_2Et)_2$), 4.31 (m, 4H, CH_2), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 1.32 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 362.1.

3.2.9. {[2-Cyano-2-(2-thienyl)vinyl)]amino}diethylmalonate (10i). From 2-(2-thienyl)-3-hydroxyacrylonitrile (3 g); black oil **10i** (4.97 g, 81%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.30–6.78 (m, 4H), 5.90 (dd, 1H, J=12, 6.8 Hz, NH), 4.66 (d, 1H, J=6.8 Hz, $CH(CO_2Et)_2$), 4.30 (m, 4H, CH_2), 1.32 (m, 6H, CH_3); MS *m*/*z*: 308.1.

3.2.10. {[2-Cyano-2-(3-thienyl)vinyl)]amino}diethylmalonate (10j). From 2-(3-thienyl)-3-hydroxyacrylonitrile (3.8 g); yellow syrup **10j** (7.7 g, 98%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.40–6.77 (m, 4H), 5.88 (dd, 1H, J=12.4, 8.0 Hz, NH), 4.67 (d, 1H, J=8.0 Hz, $CH(CO_2Et)_2$), 4.31 (m, 4H, CH_2), 1.32 (t, 6H, J=7.2 Hz, CH_3); MS *m*/*z*: 308.1.

3.3. General procedure for the intramolecular ring closure

3.3.1. Methyl 3-amino-4-(*p*-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (9a). To a solution of **10a** (1.80 g, 5.7 mmol) in methanol (10 mL) was added sodium methoxide (330 mg, 6.2 mmol). The reaction mixture was then stirred for 30 min at room temperature, then heated for 3 h. Methanol was then partially removed and water added. The resulted precipitate was then filtered off, washed with petroleum ether and dry to afford the title product **9a** (580 mg, 41%), white powder. Mp 140 °C. IR (KBr): 3431; 3123; 2913; 2833; 1684; 1604 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.12 (br s, 1H, NH); 7.37 (d, $2H_{phenyl}$, J=8.7 Hz); 6.95 (d, $2H_{phenyl}$, J=8.7 Hz); 6.80 (s, 1H, CHNH); 4.51 (br s, 2H, NH_2); 3.83 (s, 6H, OCH_3). ^{13}C NMR ($CDCl_3$): 158.22; 158.05; 144.24; 128.42; 126.04; 124.98; 118.10; 114.43; 114.38; 55.33; 50.77. HRMS *m*/*z* (EI) 246.1004 (M^+, 43.4, $C_{13}H_{14}N_2O_3$ required 246.1000).

3.3.2. Methyl 3-amino-4-phenyl-1*H*-pyrrole-2-carboxylates (9b). From **10b** (5.60 g), yellow solid (2.76 g, 69%). Mp 152 °C. IR (KBr): 3379; 3304; 3035; 2879; 1691; 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.40 (br s, 1H, NH), 7.43 (m, $5H_{phenyl}$), 6.80 (s, 1H, CHNH), 4.67 (br s, 2H, NH_2), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.72; 142.08; 134.06; 128.96; 127.11; 127.31; 126.23; 120.97; 114.84; 50.80. MS *m*/*z*: 216.1.

3.3.3. Methyl 3-amino-4-(*p*-methylphenyl)-1*H*-pyrrole-2-carboxylate (9c). From **10c** (3.69 g), yellow solid (1.60 g, 60%). Mp 142 °C. IR (KBr): 3398; 3318; 3203; 3022; 1688; 1595 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.40 (br s, 1H, NH), 7.34 (d, $2H_{phenyl}$, J=7.8 Hz), 7.21 (d, $2H_{phenyl}$, J=7.8 Hz), 6.83 (s, 1H, CHNH), 4.50 (br s, 2H, NH_2), 3.86 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 160.71; 143.13; 135.90; 130.97; 129.63; 127.05; 126.45; 120.84; 114.78; 50.77; 21.08. MS *m*/*z*: 230.1.

3.3.4. Methyl 3-amino-4-(*p*-fluorophenyl)-1*H*-pyrrole-2-carboxylate (9d). From **10d** (3.4 g), yellow solid (1.25 g, 50%). Mp 156 °C. IR (KBr): 3392; 3310; 3217; 3120; 1665; 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.42 (br s, 1H, NH), 7.41 (d, $2H_{phenyl}$, J=8.4 Hz), 7.09 (d, $2H_{phenyl}$, J=8.4 Hz), 6.82 (s, 1H, CHNH), 4.40 (br s, 2H, NH_2), 3.87 (s, 3H, OCH_3). ^{13}C

NMR ($CDCl_3$): 162.75; 160.72; 160.30; 146.38; 129.95; 129.92; 128.83; 128.79; 128.70; 117.06; 115.94; 115.72; 113.63; 50.83. MS *m*/*z*: 234.0.

3.3.5. Methyl 3-amino-4-(*p*-chlorophenyl)-1*H*-pyrrole-2-carboxylate (9e). From **10e** (7 g), yellow solid (3.90 g, 75%). Mp 180 °C. IR (KBr): 3396; 3314; 3195; 2954; 1684; 1584 cm^{-1}. ^1H NMR ($CDCl_3$): 8.40 (br s, 1H, NH), 7.39 (d, $2H_{phenyl}$, *J*=8.8 Hz), 7.36 (d, $2H_{phenyl}$, *J*=8.8 Hz), 6.84 (s, 1H, CHNH), 4.35 (br s, 2H, NH_2), 3.87 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.72; 143.52; 132.48; 131.95; 129.09; 128.29; 120.91; 113.77; 100.56; 50.87. MS *m*/*z*: 250.1.

3.3.6. Methyl 3-amino-4-(*p*-bromophenyl)-1*H*-pyrrole-2-carboxylate (9f). From **10f** (7.31 g), yellow solid (3.90 g, 69%). Mp 198 °C. IR (KBr): 3395; 3315; 3196; 1686; 1600 cm^{-1}. ^1H NMR ($CDCl_3$): 8.42 (br s, 1H, NH), 7.51 (d, $2H_{phenyl}$, *J*=8.2 Hz), 7.33 (d, $2H_{phenyl}$, *J*=8.2 Hz), 6.85 (s, 1H, CHNH), 4.58 (br s, 2H, NH_2), 3.87 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.72; 143.52; 132.96; 132.05; 131.80; 128.63; 120.79; 119.95; 113.79; 50.87. MS *m*/*z*: 295.9.

3.3.7. Methyl 3-amino-4-(3,4-dichlorophenyl)-1*H*-pyrrole-2-carboxylate (9g). From **10g** (4 g), yellow solid (2.05 g, 67%). Mp 170 °C. IR (KBr): 3392; 3310; 3206; 2951; 1668; 1565 cm^{-1}. ^1H NMR ($CDCl_3$): 8.38 (br s, 1H, NH), 7.45 (d, $2H_{phenyl}$, *J*=8.2 Hz), 7.29 (d, $2H_{phenyl}$, *J*=8.2 Hz), 6.86 (s, 1H, CHNH), 4.40 (br s, 2H, NH_2), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.72; 140.54; 134.19; 132.95; 131.06; 130.81; 129.90; 128.59; 127.20; 126.15; 112.68; 50.93. MS *m*/*z*: 285.1.

3.3.8. Methyl 3-amino-4-(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carboxylate (9h). From **10h** (3.85 g), off-white solid (2.58 g, 85%). Mp 169 °C. IR (KBr): 3463; 3358; 3275; 1661; 1597 cm^{-1}. ^1H NMR ($CDCl_3$): 8.31 (br s, 1H, NH), 6.94 (m, $2H_{phenyl}$), 6.86 (d, $1H_{phenyl}$, *J*=8.2 Hz), 6.77 (s, 1H, CHNH), 4.53 (br s, 2H, NH_2), 3.84 (s, 9H, OCH_3). ^{13}C NMR ($CDCl_3$): 162.32; 149.91; 147.48; 128.61; 128.52; 127.79; 126.73; 119.47; 114.65; 111.72; 110.73; 55.91; 55.84; 50.91. MS *m*/*z*: 276.1.

3.3.9. Methyl 3-amino-4-(2-thienyl)-1*H*-pyrrole-2-carboxylate (9i). From **10i** (1.64 g), brown solid (0.68 g, 57%). Mp 170 °C. IR (KBr): 3395; 3316; 3195; 2960; 1670; 1569 cm^{-1}. ^1H NMR ($CDCl_3$): 8.31 (br s, 1H, NH), 7.22 (d, $1H_{thiophene}$, *J*=5.0 Hz), 7.08 (m, $2H_{thiophene}$), 6.91 (s, 1H, CHNH), 3.87 (s, 3H, OCH_3), 3.51 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): 160.50; 144.57; 137.25; 125.70; 125.27; 123.41; 123.19; 122.71; 112.61; 50.87. MS *m*/*z*: 222.1.

3.3.10. Methyl 3-amino-4-(3-thienyl)-1*H*-pyrrole-2-carboxylate (9j). From **10j** (7.74 g), off-white solid (4.58 g, 82%). Mp 180 °C. IR (KBr): 3379; 3304; 3106; 1686; 1595 cm^{-1}. ^1H NMR ($CDCl_3$): 8.30 (br s, 1H, NH), 7.39 (m, $1H_{thiophene}$), 7.21 (s, $1H_{thiophene}$), 7.20 (d, $1H_{thiophene}$, *J*=4.75 Hz), 6.88 (s, 1H, CHNH), 4.61 (br s, 2H, NH_2), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.50; 143.04; 134.08; 126.81; 125.99; 124.94; 121.62; 118.94; 109.16; 50.82. MS *m*/*z*: 222.1.

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References and notes

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