Synthesis of substituted 4-azaisoindoles — New tacrine analogues

Henri Bekolo and Gilbert Kirsch

Abstract: The regioselective Friedländer reaction of 3-amino-4-cyanopyrroles with a series of cyclic ketones has enabled the first reported synthesis of substituted 4-azaisoindoles. Structurally, this new class of compounds stands for the first reported 4-azaisoindole tacrine analogues. A reaction mechanism for the formation of the reported 4-azaisoindoles is proposed.

Key words: 4-azaisoindoles, tacrine, Friedländer reaction, pyrroles, mechanism.

Résumé : La réaction de Friedländer des 3-amino-4-cyanopyrroles avec une série de cétones cycliques a permis la synthèse d'une nouvelle famille de composés: les 4-azaisoindoles substituées. Ces nouveaux composés sont de nouveaux analogues de la tacrine soit les 4-azaisoindoles analogues de la tacrine dont nous proposons aussi le mécanisme de formation.

Mots-clés : 4-azaisoindoles, tacrine, réaction de Friedländer, pyrroles, mécanisme.

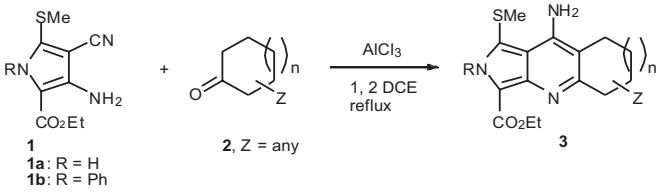
Introduction

We have previously developed an efficient synthesis of 3-amino-4-cyanopyrrole derivatives (1–3) and have set out to investigate their reactivity. Herein we give a preliminary account of our investigations, since pyrroles **1a** (1) and **1b** (3) have proven to be good synthons for the preparation of substituted 4-azaisoindoles **3** (Scheme 1).

While the derivatives of 4-azaindole have been extensively synthesized (4), the synthesis of the derivatives of the isomeric 4-azaisoindole seems to have been neglected despite their possible potential as bioactive molecules. A related example is the potent antitumor agent camptothecin, whose B and C rings system is a reduced tautomeric form of 4-azaisoindole (5). This lack of interest in the synthesis of 4-azaisoindoles stems from the current research endeavour aimed at developing a potent side effect free anti-Alzheimers's disease drug based on a tacrine analogue lead compound. Many research groups have been synthesizing and screening various kinds of heterocyclic system tacrine analogues for biological activities, but none has ever reported a synthesis nor a biological evaluation of 4-azaisoindole tacrine analogues, or any other "pyrrolo" tacrines (6–14), i.e., tacrine analogues having a pyrrole ring in place of the benzene ring of tacrine **4** (Fig. 1).

Tacrine was the first drug approved in the USA for the palliative treatment of Alzheimer's disease. However, its severe side effects, such as hepatotoxicity and gastrointestinal upset, represent an important drawback. Despite these limitations, tacrine appears as an important reference (9). So, a great synthetic and pharmacological research effort has been undertaken to design a tacrine analogue, which would be a more potent and side effect free drug.

Scheme 1. Friedländer synthesis of **3** from **1** and **2**.



Results and discussion

We have prepared 4-azaisoindole tacrine analogues **3a**–**3q** (Tables 1–8) in which, as in the previously reported analogues, the cyclohexane-fused ring (**3b**, **3h**) has been contracted (**3a**), enlarged (**3c**, **3d**), and replaced by functionalized cyclohexane rings (**3e**, **3f**, **3g**, **3l**, **3m**, **3n**, and **3p**) (14), a nitrogen-containing six-membered heterocyclic ring (**3j**) (14), and unlike the previously reported analogues, replaced by a pyran (**3q**) and a thiopyran ring (**3i**).

In most cases the Friedländer cyclizations (9) (Scheme 1) were complete within 2 h, yielding the 4-azaisoindoles **3** in good to quantitative yields, which is noteworthy as the primary amino group of **1** is expected to be weakly nucleophilic (15) and the "pyridine ring" might form at either substituent ortho to the primary amino group.

The α tetralone-type ketones **2e**, **2f**, **2n**, and **2o** were slow to react and required higher reagent–reactant concentrations. Considering the mechanistic pathway 2 (Scheme 2) that we have postulated, this slowness is probably the result of the

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Fig 1. Tacrine **4**.

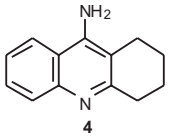
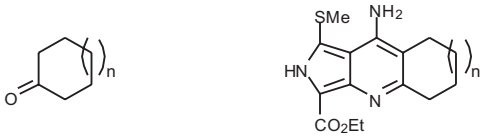


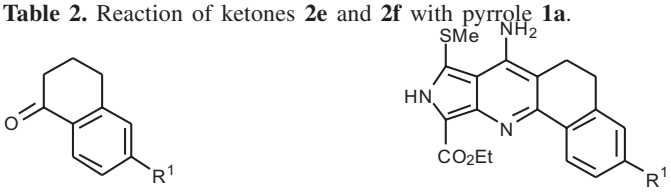
Table 1. Reaction of ketones **2a–2d** with pyrrole **1a**.



Ketone	Time (h)	Product	Yield (%)[a]
2a: n = 0	1	**3a**: n = 0	81
2b: n = 1	1	**3b**: n = 1	92
2c: n = 2	2	**3c**: n = 2	80
2d: n = 3	2	**3d**: n = 3	100

[a]Isolated yields.

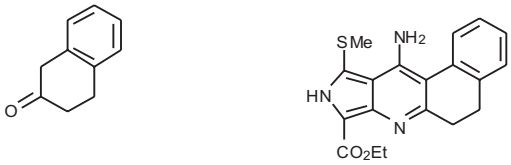
Table 2. Reaction of ketones **2e** and **2f** with pyrrole **1a**.



Ketone	Time (h)	Product	Yield (%)[a,b]
2e: R^1 = H	8	**3e**: R^1 = H	50
2f: R^1 = OMe	15	**3f**: R^1 = OMe	55

[a]Isolated yields.
[b]1,2 DCE (5 mL) was used.

Table 3. Reaction of ketone **2g** with pyrrole **1a**.



Ketone	Time (h)	Product	Yield (%)[a]
2g	2	**3g**	73

[a]Isolated yield.

reduced electrophilicity of the corresponding aluminium chloride coordinated carbonyls **5** whose α aromatic rings act by mesomeric effects as electron suppliers to the developing positive charge induced at the benzylic position by $AlCl_3$, thus slowing the enamine formation steps. As can be seen in Tables 2 and 7, the formations of azaisoindoles **3e** and **3f** assembled from **1a**, and **3n** and **3o** assembled from **1b**, required longer reaction times than those of **3b** and **3h**, respectively.

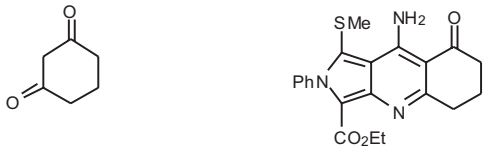
In the case of the formation of **3e** and **3f**, many unidentified by-products were detected, which would account for the modest obtained isolated yields of 50% and 55%, respectively.

Table 4. Reaction of ketones **2b–2j** with pyrrole **1b**.

Ketone	Time (h)	Product	Yield (%)[a]
2b: X = CH_2	1	**3h**: X = CH_2	76
2i: X = S	1	**3i**: X = S	77
2j: X = N-Ts	2	**3j**: X = N-Ts	70

[a]Isolated yields.

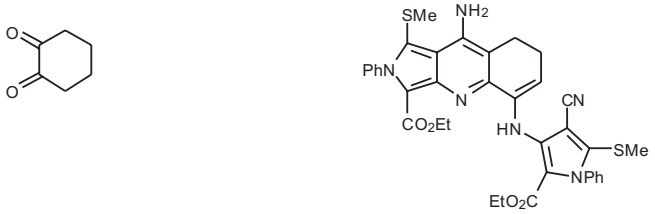
Table 5. Reaction of ketone **2l** with pyrrole **1b**.



Ketone	Time (h)	Product	Yield (%)[a]
2l	2	**3l**	80

[a]Isolated yields.

Table 6. Reaction of ketone **2m** with pyrrole **1b**.



Ketone	Time (h)	Product	Yield (%)[a]
2m	2	**3m**	25

[a]Isolated yields.

Table 7. Reaction of ketones **2n–2p** with pyrrole **1b**.

Ketone	Time (h)	Product	Yield (%)[a,b]
2n: X = O	15	**3n**: X = O	67
2o: X = NH	24	**3o**: X = NH	5
2p: X = N-SO_2Ph	2	**3p**: X = N-SO_2Ph	40

[a]Isolated yield.
[b]1,2 DCE (5 mL) was used.

In line with our reasoning, ketone **2o**, whose α pyrrole ring has a greater electron supplying ability than the furan ring of **2n**, reacted poorly with **1b** even after 24 h of reflux

Scheme 2. Possible mechanistic pathways for the Friedländer cyclization of α tetralone-type ketones.

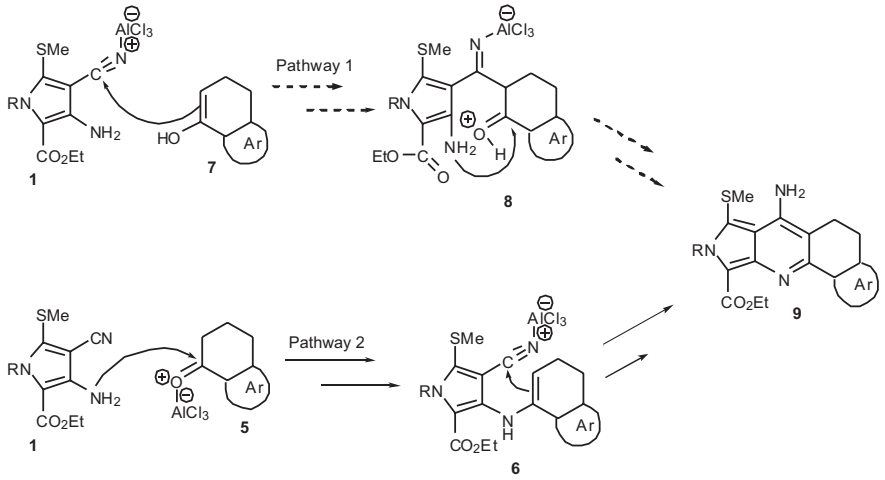
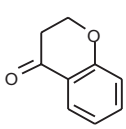
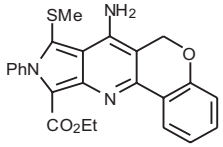


Table 8. Reaction of ketone **2q** with pyrrole **1b**.





Ketone	Time (h)	Product	Yield (%)[a]
2q	2	**3q**	86

[a]Isolated yield.

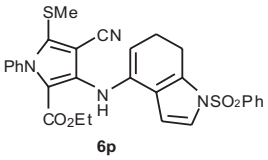
to yield traces (5%) of the corresponding azaisoindole **3o** along with the remaining starting materials **1b** and **2o**. A prolonged reaction time (5 days) resulted in recovering **1b** and **2o**; the expected product **3o** was not detected under these reaction conditions.

To gain further insight into the mechanistic pathway 2, we made the pyrrole ring of **2o** electron-deficient by protecting its NH group as the benzenesulfonylamide **2p**, which, as expected, reacted with **1b** within 2 h, more rapidly than did **2o**. All these facts have supported our proposed mechanistic pathway 2 for the formation of the 4-azaisoindoles of type **9**, and we have made it general for the formation of compounds **3**.

The 4-azaisoindole **3p** was isolated in only 40% yield. This is propably due to the slow intramolecular cyclization of the presumed enamine intermediate **6p** (Fig. 2), whose benzenesulfonyl group raises the energy barrier for the cyclization. Therefore, the uncyclized enamine **6p** might have enough time to undergo competing side reactions. A similar reasoning would account for the low isolated yield (25%) obtained in the case of **3m**; the CO group α to the corresponding enamine intermediate (**6m**) double bond would compare to the benzenesulfonyl group in **6p**. For similar reasons, the "pyridine ring" nitrogen atom might have prevented the possible further intramolecular cyclization of **3m** by raising the energy barrier for cyclization.

The good reactivity of the α tetralone-type ketone **2q** may then be surprising. We believe that the presumed corresponding enamine intermediate might have formed from **2q**

Fig 2. The likely intermediates **6p** and **6m**.



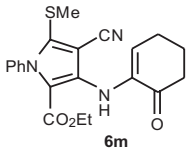
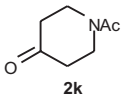
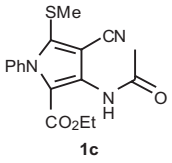


Fig 3. Ketone **2k** and pyrrole **1c**.





coordinated to $AlCl_3$ on both oxygen atoms. The aluminium chloride coordinated pyran ring oxygen would have made the carbonyl group somewhat more electrophilic by an electron-withdrawing inductive effect. The subsequent intramolecular enamine cyclization would have occured within an enamine species whose pyran ring oxygen was free of $AlCl_3$. This presumed positive electronic effect was probably less beneficial to the reactivity of ketone **2f** whose *p*-methoxy group oxygen is relatively far from the carbonyl group.

The mixture of **1b**, $AlCl_3$, and *N*-acetyl-4-piperidone (**2k**) (Fig. 3) was insoluble in refluxing 1,2 dichloroethane (1,2 DCE) and had to be heated for 24 h for complete consumption of pyrrole **1b**. We postulated that the amide functionality (Lewis base) part of piperidone **2k** was sufficiently basic to coordinate to $AlCl_3$ (Lewis acid) to form an insoluble complex, which plagued the reaction and led to the acylation of pyrrole **1b** as we isolated pyrrole **1c** (Fig. 3) as the major product (25%) among numerous by-products we could not separate. Not surprisingly, the basic 1-methyl-4-piperidone and 2,2,6,6-tetramethyl-4-piperidone that we attempted to react with **1b** and $AlCl_3$ in refluxing 1,2 DCE formed insoluble mixtures from which we could isolate what seemed to be degradation products from the ^{1}H NMR of the material we obtained after flash chromatography. We then prepared the less basic *N*-tosyl-4-piperidone (**2j**), which refluxed in a

homogeneous reaction mixture to provide **3j** cleanly in 70% isolated yield within 2 h.

In our effort to improve the yield (5%) of **3o**, the reaction was run in nitrobenzene as solvent at a higher temperature (130 °C) for 1 h, and we isolated some undentified material besides the remaining pyrrole **1b** and ketone **2o**. The use of extra pure H_2SO_4 as the catalyst, instead of $AlCl_3$, in refluxing 1,2 DCE led to complete consumption of **1b** and **2o** and the formation of a presumed new product, whose structure could not be determined by ^{1}H NMR. The acid catalyst, *p*-toluenesulfonic, did not help effect the desired transformation; **1b** and **2o** were recovered after 6 h of reflux in 1,2 DCE.

Attempts to improve the reactivity of 1-methyl-4-piperidone were made. Thus, acetic acid was used as cosolvent. It was believed that its presumed in situ protonated amino group would not coordinate to $AlCl_3$. Unfortunately, the expected cyclization did not proceed under these conditions as **1b** and the piperidone were recovered essentially after a 3 h reflux in CH_3CO_2H–1,2 DCE (1.5:8.5). The mixture of 1-methyl-4-piperidone, **1b,** and $AlCl_3$ in nitrobenzene as solvent at 110 °C resulted in complete disappearance of both reactants within 1 h, and no product was detected by TLC analysis. The use of polyphosphoric acid, instead of $AlCl_3$, in refluxing 1,2 DCE for 3 h was not helpful; only the two reactants were detected in the crude mixture by TLC analysis.

Conclusion

In summary, the standard Friedländer cyclization has enabled the first reported preparation of substituted 4-azaisoindoles and the first reported 4-azaisoindole tacrine analogues that we plan to have tested for biological evaluation.

Experimental

General

Melting points were determined on a Stuart Scientific SMP 3 capillary melting apparatus and were uncorrected. ^{1}H and ^{13}C spectra were recorded on a Brucker AC250 spectrometer using $CHCl_3$ as internal standard. The chemical shifts (δ) are reported in ppm. Commercially available ketones and $AlCl_3$ were used as purchased. Ketones **2j** (16) and **2p** were prepared using standard procedures. Pyrroles **1a** (1) and **1b** (3) were prepared as previously reported. For indications on the preparation of **1b**, please see the following.

Typical procedure for the preparation of 4-azaisoindoles 3

A mixture of pyrrole **1** (0.62 mmol), ketone **2** (3.1 mmol), and $AlCl_3$ (anhyd. granules, 99%, 3.1 mmol) in distilled 1,2 DCE (10 mL) was placed in an oil bath held at 115–120 °C for 2 h. After cooling to RT, a solution of aq. NaOH (pH 14) – THF (1:2, 15 mL) was added. The mixture was stirred for 15 min. Solvents were removed under reduced pressure. To the residue, CH_2Cl_2 (15 mL) and aq. NaOH (20 mL, pH 14) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (FC) on silica gel (MeOH–CH_2Cl_2, 6:94) afforded **3**.

8-Amino-1-methylsulfanyl-2,5,6,7-tetrahydro-2,4-diaza-s-indacene-3-carboxylic acid ethyl ester (3a)

Yield 81%; yellow crystals; mp 170 °C. ^{1}H NMR ($CDCl_3$) δ: 6.51 (br s, 2H, NH_2), 4.35 (q, *J* = 7.12 Hz, 2H), 2.99 (t, *J* = 7.62, 2H), 2.75 (t, *J* = 7.32 Hz, 2H), 2.48 (s, 3H), 2.25–2.05 (m, 2H), 1.35 (t, *J* = 7.01 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 149.2, 138.4, 114.2, 111.3, 110.8, 59.6, 32.0, 26.5, 22.6, 20.5, 13.9. HRMS calcd. for $C_{14}O_2N_3H_{17}S$ $[MH]^+$: 292.111 42; found: 292.1116.

*9-Amino-1-methylsulfanyl-5,6,7,8-tetrahydro-2**H**-pyrrolo[3,4-**b**]quinoline-3-carboxylic acid ethyl ester (3b)*

Yield 92%; yellow crystals; mp 195 °C. ^{1}H NMR ($CDCl_3$) δ: 4.36 (q, *J* = 7.12 Hz, 2H), 2.80–2.60 (m, 2H), 2.44 (s, 5H), 1.95–1.75 (m, 4H), 1.37 (t, *J* = 7.01 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 164.9, 151.6, 144.0, 136.3, 127.7, 114.0, 110.6, 104.5, 59.5, 28.7, 21.9, 21.4, 21.3, 20.4, 14.7. HRMS calcd. for $C_{15}O_2N_3H_{19}S$ $[MH]^+$: 306.127 07; found: 306.1271.

*10-Amino-1-methylsulfanyl-2,5,6,7,8,9-hexahydro-2,4-diaza-cyclohepta[**f**]indene-3-carboxylic acid ethyl ester (3c)*

Yield 80%; yellow crystals; mp 185 °C. ^{1}H NMR ($CDCl_3$) δ: 6.84 (br s, 2H, NH_2), 4.37 (q, *J* = 7.12 Hz, 2H), 2.95–2.80 (m, 2H), 2.75–2.60 (m, 2H), 2.47 (s, 3H), 1.83 (m, 2H), 1.71 (m, 2H), 1.59 (m, 2H), 1.38 (t, *J* = 7.01 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 164.9, 150.9, 150.6, 135.6, 127.5, 114.3, 111.0, 109.7, 59.5, 35.7, 31.5, 26.5, 25.8, 24.4, 20.6, 14.7. HRMS calcd. for $C_{16}O_2N_3H_{21}S$ $[MH]^+$: 320.142 72; found: 320.1427.

8-Amino-6-methylsulfanyl-2,5-diaza-tricyclo[7.6.0.0^{3,7}]-pentadeca-1,3,6,8-tetraene-4-carboxylic acid ethyl ester (3d)

Yield quant; yellow crystals; mp 205 °C. ^{1}H NMR ($CDCl_3$) δ: 6.69 (br s, 2H, NH_2), 4.38 (q, *J* = 7.12 Hz, 2H), 2.85 (t, *J* = 6.10 Hz, 2H), 2.70 (t, *J* = 6.40 Hz, 2H), 2.49 (s, 3H), 1.79 (m, 2H), 1.68 (m, 2H), 1.49 (m, 2H), 1.43–1.25 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 165.0, 151.1, 148.0, 136.4, 127.7, 114.3, 110.9, 106.8, 59.4, 33.0, 30.6, 27.8, 25.9, 25.7, 23.0, 20.4, 14.7. HRMS calcd. for $C_{17}O_2N_3H_{23}S$ $[MH]^+$: 334.158 37; found: 334.1583.

*7-Amino-8-methylsulfanyl-5,9-dihydro-6**H**-benzo[**h**]pyrrolo[3,4-b]quinoline-10-carboxylic acid ethyl ester (3e)*

The reaction was carried out in 1,2 DCE (5 mL). FC (MeOH–CH_2Cl_2, 3:97). Yield 50%; yellow crystals; mp 185 °C. ^{1}H NMR ($CDCl_3$) δ: 7.75 (m, 1H), 7.45–7.25 (m, 3H), 6.77 (br s, 2H, NH_2), 4.41 (q, *J* = 7.12 Hz, 2H), 2.96 (t, *J* = 7.31 Hz, 2H), 2.76 (t, *J* = 6.97 Hz, 2H), 2.49 (s, 3H), 1.42 (t, *J* = 7.31 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 138.5, 130.6, 128.6, 127.4, 122.7, 114.7, 111.2, 104.8, 59.7, 29.6, 27.8, 20.7, 20.2, 14.7. HRMS calcd. for $C_{19}O_2N_3H_{19}S$ $[MH]^+$: 354.127 07; found: 354.1271.

7-Amino-3-methoxy-8-methylsulfanyl-5,9-dihydro-6H-benzo[h]pyrrolo[3,4-b]quinoline-10-carboxylic acid ethyl ester (3f)

The reaction was carried out in 1,2 DCE (5 mL). FC (MeOH–CH_2Cl_2, 3:97). Yield 55%; reddish crystals; mp 184 °C. ^{1}H NMR ($CDCl_3$) δ: 7.70 (d, J = 7.92 Hz, 1H), 6.95–6.80 (m, 2H), 6.65 (br s, 2H, NH_2), 4.42 (q, J = 7.12 Hz, 2H), 3.85 (s, 3H), 2.95 (t, J = 7.01 Hz, 2H), 2.73 (t, J = 7.01 Hz, 2H), 2.50 (s, 3H), 1.43 (t, J = 7.02 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 161.4, 150.6, 140.7, 136.5, 124.1, 121.0, 114.4, 113.8, 112.7, 110.7, 103.6, 59.5, 55.3, 28.1, 20.5, 20.0, 14.7. HRMS calcd. for $C_{20}O_3N_3H_{21}S$ $[MH]^+$: 384.137 64; found: 384.1377.

11-Amino-10-methylsulfanyl-5,9-dihydro-6H-7,9-diaza-cyclopenta[b]phenanthrene-8-carboxylic acid ethyl ester (3g)

$AlCl_3$ (4 equiv.) and ketone (2 equiv.) were used. Yield 73%; greenish crystals; mp 190 °C. ^{1}H NMR ($CDCl_3$) δ: 7.81 (d, J = 7.95 Hz, 1H), 7.36–7.04 (m, 3H), 6.86 (br s, 2H, NH_2), 4.38 (q, J = 7.12 Hz, 2H), 3.05–2.70 (m, 4H), 2.50 (s, 3H), 1.36 (t, J = 7.01 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 137.0, 131.3, 128.3, 126.9, 126.4, 124.0, 114.5, 112.0, 105.2, 59.8, 28.2, 20.5, 14.5. HRMS calcd. for $C_{19}O_2N_3H_{19}S$ $[MH]^+$: 354.127 07; found: 354.1271.

9-Amino-1-methylsulfanyl-2-phenyl-5,6,7,8-tetrahydro-2H-pyrrolo[3,4-b]quinoline-3-carboxylic acid ethyl ester (3h)

The reaction mixture refluxed for 1 h. Yield 76%; yellow crystals; mp 100 °C. ^{1}H NMR ($CDCl_3$) δ: 7.55–7.40 (m, 3H), 7.35–7.20 (m, 2H), 4.15 (q, J = 7.12 Hz, 2H), 3.00 (t, J = 5.8 Hz, 2H), 2.53 (t, J = 6.10 Hz, 2H), 2.08 (s, 3H), 1.98–1.75 (m, 4H), 1.08 (t, J = 7.01 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 159.0, 154.7, 151.8, 136.4, 131.9, 129.8, 128.7, 127.6, 110.1, 109.4, 108.7, 61.1, 29.4, 22.9, 21.5, 20.9, 20.8, 13.7. HRMS calcd. for $C_{21}O_2N_3H_{23}S$ $[MH]^+$: 382.158 37; found: 382.1585.

9-Amino-1-methylsulfanyl-2-phenyl-2,5,6,8-tetrahydro-7-thia-2,4-diaza-cyclopenta[b]naphthalene-3-carboxylic acid ethyl ester (3i)

Yield 77%; yellow crystals; mp 105 °C. ^{1}H NMR ($CDCl_3$) δ: 7.52 (m, 3H), 7.26 (m, 2H), 5.86 (br s, 2H, NH_2), 4.14 (q, J = 6.72 Hz, 2H), 3.65 (s, 2H), 3.32 (t, J = 6.10 Hz, 2H), 2.97 (t, J = 6.41 Hz, 2H), 2.12 (s, 3H), 0.84 (t, J = 6.40 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 159.6, 159.3, 144.4, 141.3, 138.6, 128.2, 127.8, 127.7, 119.8, 115.5, 112.0, 105.6, 59.9, 35.3, 25.2, 22.5, 21.4, 13.7. HRMS calcd. for $C_{20}O_2N_3H_{21}S$ $[MH]^+$: 400.1148; found: 400.1148.

9-Amino-1-methylsulfanyl-2-phenyl-7-(toluene-4-sulfonyl)-5,6,7,8-tetrahydro-2H-2,4,7,-triaza-cyclopenta[b]naphthalene-3-carboxylic acid ethyl ester (3j)

After refluxing, CH_2Cl_2 (15 mL) and aq. NaOH (pH 14, 15 mL) were added, respectively. The two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. FC (MeOH–CH_2Cl_2, 3:97). Yield 70%; yellow crystals; mp 162 °C. ^{1}H NMR ($CDCl_3$) δ: 7.74 (d, J = 8.52 Hz, 2H), 7.60–7.40 (m, 3H), 7.35–7.05 (m, 4H), 5.90 (br s, 2H, NH_2), 4.21 (s, 2H), 4.12 (q, J = 7.32 Hz, 2H), 3.43 (t, J = 5.80 Hz, 2H), 3.15 (t, J = 5.80 Hz, 2H), 2.39 (s, 3H), 2.06 (s, 3H), 0.90 (t, J = 7.32 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 159.6, 156.2, 144.4, 143.7, 142.1, 138.7, 133.2, 129.7, 128.8, 128.3, 127.9, 127.6, 119.4, 116.0, 111.6, 102.0, 60.0, 43.6, 43.2, 33.7, 21.5, 13.8. HRMS calcd. for $C_{27}O_4N_4H_{28}S_2$ $[MH]^+$: 537.162 47; found: 537.1624.

8-Tetrahydro-2H-pyrrolo[3,4-b]quinoline-3-carboxylic acid ethyl ester (3l)

FC (MeOH–CH_2Cl_2, 1:99). Yield 80%; white crystals; mp 164 °C. ^{1}H NMR ($CDCl_3$) δ: 7.60–7.35 (m, 3H), 7.24–7.14 (m, 2H), 7.09 (br s, 2H, NH_2), 3.98 (q, J = 7.31 Hz, 2H), 2.55 (t, J = 6.10 Hz, 2H), 2.47–2.25 (m, 5H), 2.20–2.00 (m, 2H), 0.89 (t, J = 7.31 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 198.2, 160.4, 159.1, 137.6, 130.5, 129.5, 128.8, 104.0, 60.8, 36.4, 29.3, 21.6, 18.4, 13.4. HRMS calcd. for $C_{21}O_3N_3H_{21}S$ $[MH]^+$: 396.137 64; found: 396.1376.

9-Amino-5-(4-cyano-5-ethoxycarbonyl-2-methylsulfanyl-1-phenyl-1H-pyrrol-3-ylamino)-1-methylsulfanyl-2-phenyl-7,8-dihydro-2H-pyrrolo[3,4-b]quinoline-3-carboxylic acid ethyl ester (3m)

FC (100% CH_2Cl_2). Yield 25%; viscous yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.45 (br s, 1H, NH), 7.60–7.35 (m, 6H), 7.25–7.10 (m, 4H), 6.54 (t, J = 4.57 Hz, 1H), 5.06 (br s, 2H, NH_2), 4.10–3.90 (m, 4H), 2.59 (t, J = 6.40 Hz, 2H), 2.39 (s, 3H), 2.32 (s, 3H), 2.20–2.00 (m, 2H), 1.10–0.80 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 194.8, 159.6, 145.7, 139.5, 138.0, 134.5, 128.8, 128.7, 128.4, 128.3, 127.9, 127.8, 126.3, 60.0, 59.4, 37.4, 24.2, 23.0, 18.5, 17.9, 13.6, 13.5, 12.8.

6-Amino-7-methylsulfanyl-8-phenyl-5,8-dihydro-4H-3-oxa-8,10-diaza-dicyclopenta[a,g]naphthalene-9-carboxylic acid ethyl ester (3n)

The reaction was carried out in 1,2 DCE (5 mL). FC (MeOH–CH_2Cl_2, 3:97). Yield 67%; yellow crystals; mp 180 °C. ^{1}H NMR ($CDCl_3$) δ: 7.85–7.64 (m, 3H), 7.58 (d, J = 1.82 Hz, 1H), 7.55–7.40 (m, 2H), 7.25 (d, J = 1.82 Hz, 1H), 5.90 (br s, 2H, NH_2), 4.44 (q, J = 7.12 Hz, 2H), 3.35–3.00 (m, 4H), 2.32 (s, 3H), 1.48 (t, J = 7.01 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 160.2, 156.3, 152.9, 143.8, 142.5, 141.9, 138.8, 128.6, 128.3, 128.0, 121.2, 119.7, 116.4, 112.6, 107.7, 103.1, 60.0, 21.6, 21.3, 14.0. HRMS calcd. for $C_{23}O_3N_3H_{21}S$ $[MH]^+$: 420.137 64; found: 420.1375.

6-Amino-7-methylsulfanyl-8-phenyl-3,4,5,8-tetrahydro-3,8,10-triaza-dicyclopenta[a,g]naphthalene-9-carboxylic acid ethyl ester (3o)

The reaction was carried out in 1,2 DCE (5 mL). FC (MeOH–CH_2Cl_2, 1.5:98.5). Yield 5%, white crystals. ^{1}H NMR ($CDCl_3$) δ: 8.52 (br s, 1H, NH), 7.55–7.40 (m, 4H), 7.30–7.15 (m, 2H), 6.67 (d, J = 1.85 Hz, 1H), 3.96 (q, J = 7.12 Hz, 2H), 2.75 (t, J = 6.10 Hz, 2H), 2.50 (t, J = 6.10 Hz, 2H), 2.40 (s, 3H), 0.93 (t, J = 7.01 Hz, 3H). ^{13}C NMR δ: 167.2, 159.3, 138.6, 138.0, 129.0, 128.9, 128.6, 128.5, 128.0, 127.9, 119.1, 114.5, 105.5, 59.8, 37.8, 29.6, 23.9, 23.5, 22.6, 18.4, 13.7.

6-Amino-3-benzenesulfonyl-7-methylsulfanyl-8-phenyl-3,4,5,8-tetrahydro-3,8,10-triaza-dicyclopenta[a,g]naphthalene-9-carboxylic acid ethyl ester (3p)

The reaction was carried out in 1,2 DCE (5 mL). After refluxing, the same work-up is used as for **3j**. FC (cyclohexane–

CH_2Cl_2, 2:8). Yield 40%; white crystals; mp 185 °C. ^{1}H NMR ($CDCl_3$) δ: 7.87 (d, *J* = 7.32 Hz, 2H), 7.75–7.40 (m, 6H), 7.29 (d, *J* = 3.65 Hz, 1Hz), 7.25–7.10 (m, 2H), 6.80 (d, *J* = 3.67 Hz, 1H), 3.92 (q, *J* = 7.12 Hz, 2H), 2.50–2.35 (m, 5H), 0.85 (t, *J* = 7.01 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 194.2, 166.0, 159.0, 138.8, 138.5, 137.9, 134.5, 134.3, 129.6, 129.1, 128.8, 128.7, 128.5, 127.8, 127.0, 126.9, 124.6, 122.3, 114.1, 109.0, 60.0, 37.3, 28.9, 22.6, 13.6.

7-Amino-8-methylsulfanyl-9-phenyl-6H,9H-5-oxa-9,11-diaza-cyclopenta[b]phenanthrene-10-carboxylic acid ethyl ester (3q)

FC (MeOH–CH_2Cl_2, 3:97). Yield 86%; yellow crystals; mp 215 °C. ^{1}H NMR ($CDCl_3$) δ: 8.44 (d, *J* = 7.92 Hz, 1H), 7.60–7.45 (m, 3H), 7.40–7.20 (m, 3H), 7.10 (t, *J* = 7.62 Hz, 1H), 6.96 (d, *J* = 8.52 Hz, 1H), 5.72 (br s, 2H, NH_2), 5.20 (s, 2H), 4.28 (q, *J* = 7.12 Hz, 2H), 2.11 (s, 3H), 1.33 (t, *J* = 7.01 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 160.2, 156.6, 142.7, 138.5, 131.1, 128.9, 128.5, 128.0, 125.8, 122.0, 120.3, 116.6, 112.4, 102.0, 63.6, 60.2, 21.6, 14.1. HRMS calcd. for $C_{24}O_3N_3H_{21}S$ $[MH]^+$: 432.137 64; found: 432.1377.

1-Benzenesulfonyl-1,5,6,7-tetrahydro-indol-4-one (2p)

To a solution of **2o** (0.3 g, 2.2 mmol, 1 equiv.) in 1,2 DCE (1 mL) was added benzenesulfonyl chloride (1.6 g, 8.8 mmol, 4 equiv.), Et_3N (1.8 g, 17.6 mmol, 8 equiv.) in 1,2 DCE (2 mL). The mixture was placed in an oil bath held at 93 °C for 1 h. HCl 1N (3 mL) and CH_2Cl_2 (10 mL) were added. The 2 layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by FC (cyclohexane–CH_2Cl_2, 1:99) afforded **2p**. Yield 73%; beige solid; mp 122 °C. ^{1}H NMR ($CDCl_3$) δ: 7.85 (d, *J* = 7.92 Hz, 2H), 7.75–7.45 (m, 3H), 7.23 (d, *J* = 3.05 Hz, 1H), 6.60 (d, *J* = 3.05 Hz, 1H), 2.95 (t, *J* = 6.10 Hz, 2H), 2.39 (t, *J* = 6.40 Hz, 2H), 2.07 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 194.1, 143.6, 138.0, 134.5, 129.7, 126.9, 124.7, 122.2, 108.2, 37.2, 23.1, 22.7.

3-Amino-4-cyano-5-methylsulfanyl-1-phenyl-1H-pyrrole-2-carboxylic acid ethyl ester (1b)

This compound, fully described in ref. 3, was made according to the methodology we developed in ref. 2 for the preparation of compound 3 (see ref.2, Scheme 3) therein. The ketene phenylaminomethylthioacetal (see ref. 2, Table 3, entry e) was used. The mixture was refluxed in acetone for 5 days. Yield 70%; white crystals; mp 147–149 °C. ^{1}H NMR ($CDCl_3$) δ: 7.17–7.50 (m, 5H), 5.06 (br s, 2H, NH_2), 4.01 (q, *J* = 7.20 Hz, 2H), 2.40 (s, 3H), 0.94 (t, *J* = 7.20 Hz, 3H).

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