Synthesis of Camalexin and Related Analogues

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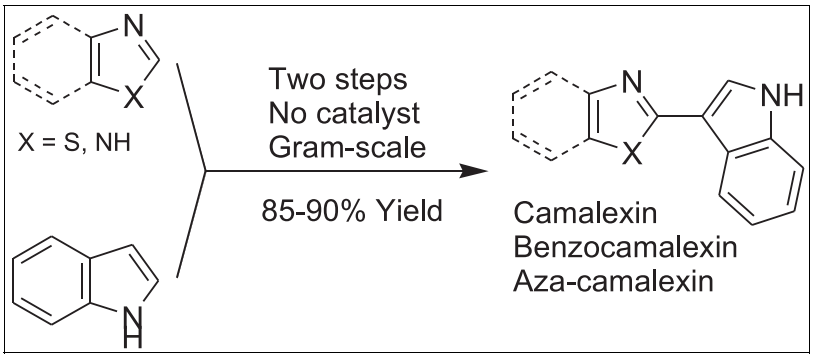

Camalexin is synthesized on a gram scale by coupling of thiazole and indole in an amidoalkylation–oxidation sequence. Several high-yielding implementations of this two-step approach are demonstrated with variation of either the intermediate acyliminium reagent or the oxidation conditions. Benzo-analogues and aza-analogues of the natural product are also obtained by this method. As a side result, a new formylation of indole is demonstrated.

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INTRODUCTION

Camalexin (Fig. 1) is a phytoalexin [1], first isolated from *Camelina sativa* infected with *Alternaria brassicae* [2] and later found in other *Cruciferae* plants [3]. In addition to its important role in plant immunity, this natural product has interesting biological profile, showing antibacterial,3a antifungal [4], and cytotoxic activity [5]. Camalexin has also attracted interest from purely chemical standpoint and has been synthesized by various methods, including organometallic approaches [6], Suzuki–Miyaura coupling [7], Masuda borylation/Suzuki arylation sequence [8], and a biomimetic approach [9]. Despite the apparent simplicity of this natural product, its synthesis has proved challenging, and all of the published syntheses have their drawbacks with regard to yield, scale-up potential, or availability of necessary reagents.

The α-amidoalkylation is a well-established method for C—C bond formation in which an imine is reacted with acid chloride to generate electrophilic acyliminium species, reactive enough to alkylate a broad range of substrates in either intramolecular or intermolecular manner [10]. In a variation of this method, pioneered by the Reissert reaction [11], the acyliminium reagent is generated from aromatic *N*-heterocycle [12] instead of simple imine. We have previously used such approach to obtain various heterocyclic compounds [13]. In view of this experience, we reckoned that a sequence of amidoalkylation of indole with *N*-acylthiazolium reagent, followed by removal of the auxiliary alkoxycarbonyl group, would be an efficient method for coupling of thiazole and indole and may provide straightforward access to camalexin and related analogues. Although several syntheses of camalexin have already been published, our approach offers significant advantages by avoiding expensive catalysts and sensitive organometallic reagents.

RESULTS AND DISCUSSION

First, we tried activation of thiazole and benzothiazole with alkyl chloroformates. As illustrated on Scheme 1, this proved successful and the obtained acyliminium reagents **2** reacted in situ with indole in the presence of triethylamine as HCl scavenger to give **3** in excellent yields (Table 1). The activation was also tried with acid chlorides such as acetylchloride and benzoylchloride but was successful only in the case of benzothiazole and gave significantly lower yields (Table 1, **3bd**–**3be**).

During the optimization of the synthetic procedure, we observed that products **3b** were often accompanied by triindolylmethane **4**. This side product was isolated in varying amounts, depending mostly on the acidity of the reaction mixture. In the case of **3be**, for example, when the reaction was tried in the absence of Et_3N, triindolylmethane became the major product (76% yield based on indole). This led us to a hypothesis that

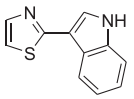


Figure 1. Structure of the natural product camalexin.

Scheme 1. Amidoalkylation of indole with acylthiazolium reagents. Reagents and conditions: (a) RCOCl (1.15 equiv.), dichloroethane (3–7 mL/mmol), see Table 1 for temperature; (b) indole (1 equiv.), then slowly Et_3N (1 equiv.), see Table 1 for duration.

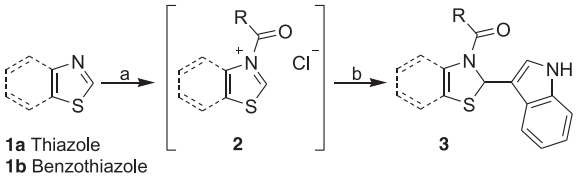


Table 1

Reaction conditions and yields of amidoalkylated indoles **3**.

Thiazole	Product	R	Conditions	Yield, %
1a	**3aa**	CH_3CH_2O	0–25°C, 1.5 h	83
	3ab	CH_3O	0–25°C, 1.5 h	90
	3ac	CCl_3CH_2O	0°C, 1 h	96
1b	**3ba**	CH_3CH_2O	25°C, 4 h	75
	3bb	CH_3O	25°C, 4 h	85
	3bc	CCl_3CH_2O	0°C, 1 h	92
	3bd	CH_3	0°C, 2 h	63
	3be	C_6H_5	25°C, 2 h	60

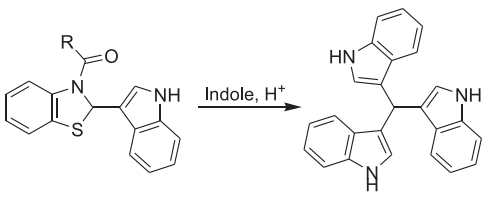
compounds **3b** may undergo acid-catalyzed opening of the thiazoline ring and turn into electrophilic species, which quickly reacts with the indole still available in the solution to give **4** eventually (see ESI for proposed mechanism). To test this hypothesis, we mixed clean **3ba** with indole (2 equiv) in dichloroethane/TFA (10:1 vol.) and kept the solution for 24 h at 25°C. Indeed, under these conditions, triindolylmethane was obtained and isolated in 37% yield (Scheme 2).

After the successful coupling of the heterocyclic rings, we proceeded with experiments to remove the auxiliary acyl or alkoxycabonyl group and rearomatize the thiazole moiety in **3**. Similar task, although in different context, has been accomplished before by Beveridge et al. under oxidative conditions [14], using *o*-chloranil in acetonitrile at 85°C. Following this literature precedent, and after some experimentation to adjust the reaction conditions, we successfully oxidized compounds **3** with *o*-chloranil and obtained excellent yields of camalexin or benzocamalexin, respectively. Comparable yields were obtained with DDQ as the oxidant (Scheme 3, Table 2). The melting points and spectral data of the obtained compounds are in complete agreement with those published earlier [6–9]. The synthesis of camalexin was repeated on a gram scale via intermediate **3ac**, starting with 7 mmol thiazole and again was found to work with excellent yield of 88% over two steps (1.232 g).

Experiments to obtain dihydro derivatives of camalexin and benzocamalexin by removing the *Troc* group from **3ac** and **3bc** under reductive conditions were not successful, although they led to a rather interesting result in the case of **3ac**. While the reaction of the benzo derivative **3bc** with Zn/NH_4Cl in refluxing MeOH gave messy outcome, **3ac** on the other hand gave indole-3-carboxaldehyde (**7**) in 70% yield (Scheme 4). We assume that dihydrocamalexin **6** is formed under these conditions, but the thiazoline ring is then easily hydrolyzed upon work up to reveal a formyl group (see ESI for proposed mechanism). This reaction, along with the aforementioned formation of triindolylmethane, suggests potential use of the *N*-alkoxycarbonyl thiazoline moiety as a masked formyl equivalent.

With camalexin and benzocamalexin in hand, we turned our attention to the possibility of using imidazole as the starting material in order to prepare an aza-analogue of the natural product. The activation of the imidazole ring required two equivalents of alkylchloroformate and was carried out in one pot, without isolation of the monoacyl derivative. Then indole and Et_3N were added to the same reaction vessel, and the mixture was stirred for 30 min at 0°C and for one more hour at r.t. Thus, compounds **10** were obtained with excellent yields in a one-pot multicomponent manner. The oxidation of **10** with *o*-chloranil at r.t. was successful and gave 72–88% yield of

Scheme 2. Formation of triindolylmethane **4** from **3b** and indole in acidic media. See ESI for proposed mechanism.



Scheme 3. Oxidation of amidoalkylated indoles **3** to (benzo)camalexin **5**. See Table 2 for reagents and conditions.

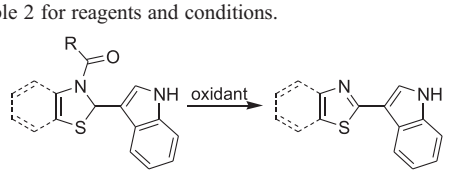
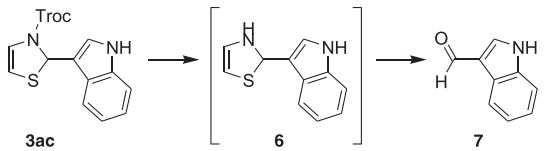


Table 2

Reaction conditions and yields of camalexin **5**, obtained according to Scheme 3.

Starting material	Product	*o*-Chloranil oxidation			DDQ oxidation		
		T, °C	Time, h	Yield 5, %	T, °C	Time, h	Yield 5, %
3aa	**5a**	0	1	97	0	1	74
3ab	**5a**	0	1	95	0	1	83
3ac	**5a**	0	1	93	0	1	92
3ba	**5b**	85	4	81	25	2	70
3bb	**5b**	85	1	85	25	1	72
3bc	**5b**	25	2	80	25	2	83
3bd	**5b**	25	2	88	–	–	–
3be	**5b**	25	2	96	–	–	–

Scheme 4. Formation of indole-3-carboxaldehyde upon removal of the *Troc* group from **3ac**. Reagents and conditions: Zn (10 equiv.), NH_4Cl (10 equiv.), CH_3OH, reflux, 3 h, H_2O.



aza-camalexin **11** (Scheme 5, Table 3). At higher temperature, a [4 + 2]-cycloaddition between **10** and *o*-chloranil took precedence over the desired aromatization, and the Diels–Alder adducts **12** were isolated in 50–60% yield (Scheme 6). Compounds **12** were obtained as single diastereoisomers and the lack of any NOE to the proton at position 2 in the imidazolidine ring suggests *trans*-configuration.

Similarly to the reaction of the thia-analogue **3ac** described earlier, reductive removal of the *Troc* groups in **10c** gave indole-3-carboxaldehyde again (Scheme 7), but

Scheme 5. Reagents and conditions: (a) Et_3N (1 equiv), ROCOCl (2.2 equiv), 0°C; (b) indole (1 equiv), then slowly Et_3N, 90 min, 0°C to r.t.; (c) *o*-chloranil (1 equiv.), CH_3CN, r.t., 4 h.

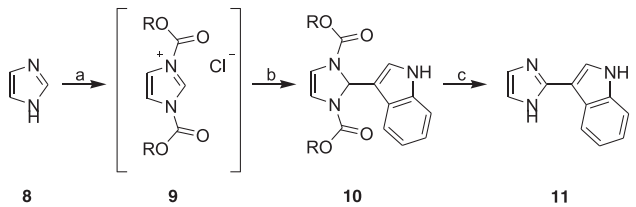
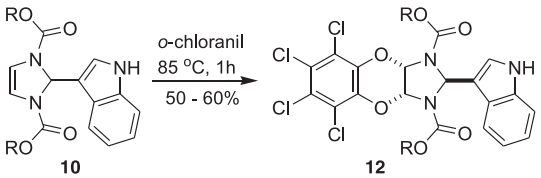


Table 3

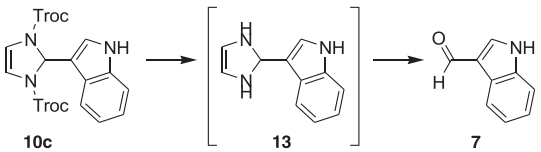
Yields of compounds **10** and **11**, obtained according to Scheme 5.

Entry	R	Yield 10, %	Yield 11, %
a	CH_3CH_2O	94	88
b	CH_3O	95	80
c	CCl_3CH_2O	92	72

Scheme 6. Competing Diels–Alder cycloaddition of *o*-chloranil to compounds **10**.



Scheme 7. Formation of indole-3-carboxaldehyde upon removal of the *Troc* group from **10c**. Reagents and conditions: Zn (10 equiv.), NH_4Cl (10 equiv.), CH_3OH/H_2O (8:2 vol.), 60°C, 2 h.



in lower yield. However, addition of water (20% vol.) to the reaction mixture boosted the yield of the aldehyde **7** to 82% – a result suggesting that the imidazoline intermediate **13** here is more stable to hydrolysis than its thiazoline counterpart **6**.

CONCLUSION

In conclusion, a robust and scalable synthesis of camalexin and related analogues has been developed. The amidoalkylation–oxidation sequence does not require expensive catalysts or sensitive organometallic reagents and offers significant advantages over other methods of heteroaromatic ring coupling. Also, a new method of indole formylation has been demonstrated. The potential of introducing masked formyl group in other substrates via acyliminium reagents of imidazole or thiazole is currently under investigation, and the results will be reported in due course.

EXPERIMENTAL

General information. All reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich, St. Louis, MO or Merck, Kenilworth, NJ) and were used without further purification. Melting points were taken on Boetius hot stage apparatus and are not corrected. Nuclear magnetic resonance (NMR) spectra were measured on Bruker Avance AV600 or DRX250 spectrometers, and chemical shifts (δ, ppm) are downfield from TMS. To average out the rotamers observed in compounds **3**, **10**, and **12**, some spectra were measured at 80°C, as indicated in the succeeding text. Mass spectral measurements were performed on a Thermo Scientific Q Exactive hybrid quadrupole-orbitrap mass spectrometer.

Synthesis of amidoalkylated indoles (3). general procedure. The corresponding acid chloride or chloroformate (1.15 mmol) is slowly added with magnetic stirring to a solution of the corresponding thiazole (1 mmol) in 1,2-dichloroethane (3–7 mL) at the temperature indicated in Table 1. Immediately after that, indole (1 mmol) is added. Then gradually, in the course of 30 min, triethylamine (1 mmol), dissolved in 1,2-dichloroethane (2 mL), is added. The reaction mixture is stirred for the time and at the temperature specified in Table 1. After completion of the reaction, the mixture is transferred to a separatory funnel with dichloromethane (10 mL) and is consecutively extracted with equal volumes of aqueous HCl (1:10), Na_2CO_3 (3%), and brine. The combined organic layers are dried (Na_2SO_4), and the solvent is removed under reduced pressure. The residue is then triturated with small amount of hexane to induce crystallization. The product obtained in this way is usually sufficiently clean to be taken to the next stage without further purification. Analytically pure samples can be obtained by column chromatography on neutral alumina, using mixtures of diethyl ether/petroleum ether as eluents.

Ethyl 2-(1H-indol-3-yl)thiazole-3(2H)-carboxylate (3aa). Chromatographed on neutral alumina with petroleum/diethyl ether (2,1); Yield: 83%; mp = 111–113°C; IR (KBr, cm^{-1}): 3393, 2983, 1690, 1589, 1552, 1257, 1460, 741; ^{1}H-NMR (600 MHz, 80°C, DMSO-d_6, δ ppm, *J* Hz): 1.12 (t, *J* = 7.0, 3H), 4.05 (t, *J* = 7.0, 2H), 5.99 (d, *J* = 4.7, 1H), 6.65 (d, *J* = 4.7, 1H), 6.91 (s, 1H), 7.03 (m, 1H), 7.12 (m, 1H), 7.30 (d, *J* = 2.4, 1H), 7.39 (d, *J* = 8.2, 1H), 7.64 (d, *J* = 8.2, 1H), 10.88 (s, 1H); ^{13}C-NMR (150 MHz, 80°C, DMSO-d_6, δ ppm): 14.6, 60.5, 61.9, 104.4, 112.2, 116.6, 119.4, 119.7, 121.5, 121.8, 123.8, 124.9, 137.3, 152.7; HRMS *m/z* (ESI): calcd for $C_{14}H_{14}N_2NaO_2S^+$ $[M + Na]^+$ 297.0668, found 297.0667; calcd for $C_{14}H_{13}N_2O_2S^-$ $[M - H]^-$ 273.0703, found 273.0698.

Methyl 2-(1H-indol-3-yl)thiazole-3(2H)-carboxylate (3ab). Chromatographed on neutral alumina with petroleum/diethyl ether (2:1); Yield: 90%; mp = 132–134°C; IR (KBr, cm^{-1}): 3331, 2953, 1691, 1599, 1544, 1446, 1250, 741; ^{1}H-NMR (600 MHz, 80°C, DMSO-d_6, δ ppm, *J* Hz): 3.61 (s, 3H), 6.00 (d, *J* = 4.7, 1H), 6.65 (d, *J* = 4.1, 1H), 6.90 (s, 1H), 7.02 (m, 1H), 7.11 (m, 1H), 7.29 (d, *J* = 2.4, 1H), 7.38 (d, *J* = 8.2, 1H), 7.62 (d, *J* = 8.2, 1H), 10.87 (s, 1H); ^{13}C-NMR (150 MHz, 80°C, DMSO-d_6, δ ppm): 53.1, 60.5, 104.5, 112.1, 116.4, 119.3, 119.6, 121.3, 121.8, 123.6, 124.7, 137.3, 153.1; HRMS *m/z* (ESI): calcd for $C_{13}H_{12}N_2NaO_2S^+$ $[M + Na]^+$ 283.0512, found 283.0512; calcd for $C_{13}H_{11}N_2O_2S^-$ $[M - H]^-$ 259.0547, found 259.0555.

2,2,2-Trichloroethyl 2-(1H-indol-3-yl)thiazole-3(2H)-carboxylate (3ac). Yield: 96%; mp = 135–137°C; IR (KBr, cm^{-1}): 3362, 3061, 2952, 1695, 1546, 1460, 1430, 1248, 744; ^{1}H-NMR (250 MHz, 80°C, DMSO-d_6, δ ppm, *J* Hz): 4.83 (s, 2H), 6.17 (d, *J* = 4.7, 1H), 6.72 (d, *J* = 4.7, 1H), 6.99 (s, 1H), 7.00–7.06 (m, 1H), 7.09–7.16 (m, 1H), 7.34 (d, *J* = 2.7, 1H), 7.40 (d, *J* = 8.1, 1H), 7.65 (d, *J* = 8.1, 1H), 10.90 (br s, 1H, NH); ^{13}C-NMR (62.5 MHz, 80°C, DMSO-d_6, δ ppm): 60.9, 75.1, 95.9, 106.5, 112.3, 115.8, 119.5, 119.7, 120.7, 121.9, 124.1, 124.8, 132.1, 137.4; HRMS *m/z* (ESI): calcd for $C_{14}H_{11}Cl_3N_2NaO_2S^+$ $[M + Na]^+$ 398.9499, found 398.9495.

Ethyl 2-(1H-indol-3-yl)benzo[d]thiazole-3(2H)-carboxylate (3ba). Chromatographed on neutral alumina with petroleum/diethyl ether (4:1); Yield: 75%; mp = 151–152°C; IR (KBr, cm^{-1}): 3383, 2983, 1695, 1577, 1548, 1466, 1248, 740; ^{1}H-NMR (600 MHz, 20°C, DMSO-d_6, δ ppm, *J* Hz): 1.18 (t, *J* = 7.0, 3H), 4.12–4.21 (m, 2H), 6.89 (t, *J* = 7.6, 1H), 7.05–7.09 (m, 2H), 7.16–7.19 (m, 2H), 7.18 (s, 1H), 7.24 (d, *J* = 2.3, 1H), 7.30 (d, *J* = 8.2, 1H), 7.35 (d, *J* = 8.2, 1H), 7.75 (s, 1H), 11.08 (s, 1H); ^{13}C-NMR (150 MHz, 20°C, DMSO-d_6, δ ppm): 14.7, 61.9, 62.4, 112.3, 116.3, 117.5, 119.5, 122.0, 122.8, 123.9, 124.5, 124.8, 125.7, 137.2, 152.7; HRMS *m/z* (ESI): calcd for $C_{18}H_{16}N_2NaO_2S^+$ $[M + Na]^+$ 347.0825, found 347.0826; $[2\ M + Na]^+$ calcd. 671.1757, found 671.1759.

Methyl 2-(1H-indol-3-yl)benzo[d]thiazole-3(2H)-carboxylate (3bb). Chromatographed on neutral alumina with petroleum/diethyl ether (3:1); Yield: 85%; mp = 184–185°C; IR (KBr, cm^{-1}): 3313, 2955, 1683, 1575, 1537, 1471, 1252, 749; ^{1}H-NMR (600 MHz, 20°C, DMSO-d_6, δ ppm, *J* Hz): 3.72 (s, 3H), 6.90 (t, *J* = 7.6, 1H), 7.06–7.09 (m, 2H), 7.17–7.21 (m, 2H), 7.18 (s, 1H), 7.23 (d, *J* = 2.3, 1H), 7.30 (d, *J* = 8.2, 1H), 7.36 (d, *J* = 8.2, 1H), 7.75 (s, 1H), 11.08 (s, 1H); ^{13}C-NMR (150 MHz, 20°C, DMSO-d_6, δ ppm): 53.7, 62.0, 112.3, 116.3, 117.5, 119.5, 122.0, 122.8, 123.7, 124.4, 124.9, 125.7, 137.2, 153.2; HRMS *m/z* (ESI): calcd for $C_{17}H_{14}N_2NaO_2S^+$ $[M + Na]^+$ 333.0668, found 333.0660; calcd for $C_{17}H_{13}N_2O_2S^-$ $[M - H]^-$ 309.0703, found 309.0705.

2,2,2-Trichloroethyl 2-(1H-indol-3-yl)benzo[d]thiazole-3(2H)-carboxylate (3bc). Chromatographed on neutral alumina

with petroleum/diethyl ether (2:1 increasing polarity to 1:1); Yield: 92%; Oil; IR (KBr, cm^{-1}): 3405, 3060, 2953, 1720, 1578, 1546, 1470, 1241, 743; ^{1}H-NMR (250 MHz, 80°C, DMSO-d_6, δ ppm, J Hz): 4.94 (d, ^2J = 12.2, 1H) 5.03 (d, ^2J = 12.2, 1H), 6.90 (m, 1H), 7.05–7.23 (m, 4H), 7.25 (s, 1H), 7.27 (d, J = 2.7, 1H), 7.36 (m, 2H), 7.83 (m, 1H), 10.88 (br s, 1H); ^{13}C-NMR (62.5 MHz, 80°C, DMSO-d_6, δ ppm): 62.5, 75.4, 95.8, 112.3, 115.9, 117.9, 119.4, 119.6, 122.0, 122.9, 124.0, 124.6, 125.5, 125.8, 126.6, 130.1, 137.4, 143.6; HRMS *m/z* (ESI): calcd for $C_{18}H_{13}Cl_3N_2NaO_2S^+$ $[M + Na]^+$ 448.9655, found 448.9647.

1-(2-(1H-indol-3-yl)benzo[d]thiazol-3(2H)-yl)ethanone (3bd). Chromatographed on neutral alumina with petroleum/diethyl ether (1:1); Yield: 63%; mp = 108–110°C; IR (KBr, cm^{-1}): 3297, 3057, 1651, 1575, 1541, 1465, 744; ^{1}H-NMR (600 MHz, 80°C, DMSO-d_6, δ ppm, J Hz): 2.25 (s, 3H), 6.92 (m, 1H), 7.09 (m, 2H), 7.15–7.19 (m, 2H), 7.26 (m, 2H), 7.33 (s, 1H), 7.36 (d, J = 8.2, 1H), 7.96 (m, 1H), 10.88 (s, 1H); ^{13}C-NMR (150 MHz, 80°C, DMSO-d_6, δ ppm): 23.7, 62.5, 112.2, 116.2, 119.3, 119.5, 122.0, 122.8, 123.3, 125.2, 134.9, 169.1; HRMS *m/z* (ESI): calcd for $C_{17}H_{14}N_2NaOS^+$ $[M + Na]^+$ 317.0719, found 317.0711; calcd for $C_{17}H_{13}N_2OS^-$ $[M - H]^-$ 293.0754, found 293.0755.

(2-(1H-indol-3-yl)benzo[d]thiazol-3(2H)-yl)(phenyl) methanone (3be). Chromatographed on neutral alumina with petroleum/diethyl ether (1:1); Yield: 60%; mp = 190–193°C; IR (KBr, cm^{-1}): 3303, 3057, 1659, 1627, 1574, 1547, 1463, 748; ^{1}H-NMR (600 MHz, 80°C, DMSO-d_6, δ ppm, J Hz): 7.02–7.50 (m, 14H) 7.34 (s, 1H), 8.28 (br s, 1H); ^{13}C-NMR (150 MHz, 80°C, DMSO-d_6, δ ppm): 64.1, 111.6, 116.7, 119.3, 120.0, 120.2, 122.6, 122.7, 123.4, 124.1, 124.9, 125.7, 127.1, 127.6, 128.5, 128.9, 131.0, 132.4, 135.3, 136.7, 138.2, 165.1; HRMS *m/z* (ESI): calcd for $C_{22}H_{16}N_2NaOS^+$ $[M + Na]^+$ 379.0876, found 379.0873.

Tris-(3-indolyl)-methane (4). The general procedure for preparation of **3be**, but without any Et_3N, gave **4** in 76% isolated yield (based on indole). Chromatographed on neutral alumina with petroleum/diethyl ether (1:1); mp = 232–235°C (El-Sayed et al. [15] 235–240°C); IR (KBr, cm^{-1}): 3402, 3051, 2929, 1578, 1456, 1420; ^{1}H-NMR (600 MHz, 20°C, DMSO-d_6, δ ppm, J Hz): 6.06 (s, 1H), 6.86 (t, J = 7.6, 3H), 6.95 (d, J = 1.8, 3H), 7.02 (t, J = 7.6, 3H), 7.34 (d, J = 8.2, 3H), 7.41 (d, J = 8.2, 3H), 10.73 (s, 3H); ^{13}C-NMR (150 MHz, 20°C, DMSO-d_6, δ ppm): 36.1, 116.6, 123.2, 123.5, 124.5, 125.8, 128.4, 132.0, 141.8; HRMS *m/z* (ESI): calcd for $C_{25}H_{18}N_3^-$ $[M - H]^-$ 360.1506, found 360.1499.

Synthesis of amidoalkylated indoles (10), general procedure. The corresponding chloroformate (4.4 mmol) is slowly added to a cooled (0°C) and magnetically stirred solution of imidazole (2 mmol, 0.136 mg) and Et_3N (2 mmol, 0.28 mL) in 1,2-dichloroethane (10 mL). Immediately after that, indole (2 mmol, 0.234 g) is added. In the course of the next 30 min, Et_3N (2 mmol) in 1,2-dichloroethane (4 mL) is gradually added, then the ice bath is removed, and the reaction mixture is stirred for 60 more minutes at r.t. After completion of the reaction, the mixture is transferred to a separatory funnel with dichloromethane (50 mL) and is successively extracted with equal volumes of aqueous HCl (1:10), Na_2CO_3 (3%), and brine. The combined organic layers are dried (Na_2SO_4), and the solvent is removed under reduced pressure. The solid residue is then triturated and washed with small amount of petrol/diethyl ether (4:1) to remove any unreacted indole. Analytically pure samples were obtained by column chromatography on neutral alumina, using diethyl ether as the eluent, and the yields are indicated in Table 3.

Diethyl 2-(1H-indol-3-yl)-1H-imidazole-1,3(2H)-dicarboxylate (10a). Yield 94%; mp = 141–143°C; IR (KBr, cm^{-1}): 3334, 3062, 2985, 1713, 1681, 1551, 1480, 1467, 1278; ^{1}H-NMR (600 MHz, 80°C, DMSO-d_6, δ ppm, J Hz): 1.15 (br s, 6H, 2 × CH_3), 4.07 (q, J = 7.0, 4H, 2 × CH_2), 6.58 (s, 2H), 6.94 (s, 1H), 7.06 (m, 1H), 7.15 (m, 1H), 7.45 (m, 2H), 7.62 (d, J = 8.2, 1H), 11.00 (s, 1H); ^{13}C-NMR (150 MHz, 80°C, DMSO-d_6, δ ppm): 14.5, 61.5, 70.3, 112.1, 112.9, 113.3, 119.4, 119.5, 121.5, 124.8, 125.6, 136.8, 150.6; HRMS *m/z* (ESI): calcd for $C_{17}H_{19}N_3NaO_4^+$ $[M + Na]^+$ 352.1268, found 352.1260.

Dimethyl 2-(1H-indol-3-yl)-1H-imidazole-1,3(2H)-dicarboxylate (10b). Yield 97%; mp = 182–184°C; IR (KBr, cm^{-1}): 3341, 3048, 2958, 1723, 1698, 1577, 1550, 1450, 1265; ^{1}H-NMR (600 MHz, 80°C, DMSO-d_6, δ ppm, J Hz): 3.58 (s, 6H, 2 × CH_3), 6.51 (s, 2H), 6.88 (s, 1H), 7.00 (m, 1H), 7.10 (m, 1H), 7.40 (m, 2H), 7.56 (d, J = 8.2, 1H), 10.96 (br s, 1H); ^{13}C-NMR (150 MHz, 80°C, DMSO-d_6, δ ppm): 52.9, 70.5, 112.3, 113.1, 113.2, 119.5, 119.6, 121.7, 124.9, 125.7, 137.0, 151.2; HRMS *m/z* (ESI): calcd for $C_{15}H_{15}N_3NaO_4^+$ $[M + Na]^+$ 324.0955, found 324.0942.

Bis(2,2,2-trichloroethyl) 2-(1H-indol-3-yl)-1H-imidazole-1,3(2H)-dicarboxylate (10c). Yield 92%; Oil; IR (KBr, cm^{-1}): 3398, 3061, 2956, 1711, 1577, 1551, 1410, 1276; ^{1}H-NMR (600 MHz, 80°C, DMSO-d_6, δ ppm, J Hz): 4.79 (s, 4H, 2 × CH_2), 6.68 (s, 2H), 7.00 (m, 1H), 7.03 (s, 1H), 7.09 (m, 1H, Ar), 7.39 (d, J = 8.2, 1H), 7.48 (d, J = 2.9, 1H), 7.56 (d, J = 8.2, 1H), 11.01 (s, 1H); ^{13}C-NMR (150 MHz, 80°C, DMSO-d_6, δ ppm): 71.1, 75.0, 95.9, 112.3, 113.4, 115.4, 119.4, 119.7, 121.8, 123.1, 137.1, 147.7, 152.7; HRMS *m/z* (ESI): calcd for $C_{17}H_{13}Cl_6N_3NaO_4^+$ $[M + Na]^+$ 555.8929, found 555.8923.

Oxidation of amidoalkylated indoles (3) to camalexin (5a) and benzocamalexin (5b). The corresponding compound **3** (1 mmol) is dissolved in CH_3CN (5–15 mL/mmol), then the corresponding oxidant (1 mmol for the thiazole derivatives **3a** or 1.5 mmol for benzothiazole derivatives

3b) is added, and the reaction mixture is magnetically stirred under the conditions specified in Table 2. After completion of the reaction, the solvent is evaporated under reduced pressure, and the mixture is then dry-loaded onto neutral alumina. Chromatography on a short alumina column with diethyl ether/petroleum as the eluent gave camalexin **5a** or benzocamalexin **5b** in yields indicated in Table 2.

Camalexin, 2-(1H-indol-3-yl)thiazole (5a). Chromatographed on neutral alumina with petroleum/diethyl ether (2:1, increasing polarity to 1:1); Yield: 74–97%; mp = 137–138°C; IR (KBr, cm^{-1}): 3149, 2980, 1587, 1561, 1455, 738; ^{1}H-NMR (600 MHz, 20°C, DMSO-d_6, δ ppm, *J* Hz): 7.17–7.23 (m, 2H), 7.48 (d, *J* = 8.2, 1H), 7.54 (d, *J* = 3.5, 1H), 7.81 (d, *J* = 3.5, 1H), 8.08 (s, 1H), 8.19 (d, *J* = 8.2, 1H), 11.72 (s, 1H); ^{13}C-NMR (150 MHz, 20°C, DMSO-d_6, δ ppm): 111.1, 112.6, 116.7, 120.7, 121.1, 122.8, 124.7, 126.8, 137.0, 143.0, 163.4; HRMS *m/z* (ESI): calcd for $C_{11}H_9N_2S^+$ $[M + H]^+$ calcd 201.0481, found 201.0488, calcd for $C_{11}H_7N_2S^-$ $[M - H]^-$ 199.0335, found 199.0330.

Benzocamalexin, 2-(1H-indol-3-yl)benzo[d]thiazole (5b). Chromatographed on neutral alumina with petroleum/diethyl ether (3:1, increasing polarity to 2:1); Yield: 81–96%; mp = 171–172°C (Harris [16a] 171–172°C, Dzurilla et al. [16b] 124–127°C from ethanol); IR (KBr, cm^{-1}): 3218, 2963, 1594, 1552, 1443, 749; ^{1}H-NMR (600 MHz, 20°C, DMSO-d_6, δ ppm, *J* Hz): 7.27 (m, 2H), 7.36 (m, 1H), 7.48 (m, 1H), 7.53 (m, 1H), 7.97 (d, *J* = 8.2, 1H), 8.05 (d, *J* = 8.2, 1H), 8.28 (s, 1H), 8.39 (m, 1H), 11.97 (s, 1H); ^{13}C-NMR (150 MHz, 20°C, DMSO-d_6, δ ppm): 110.9, 112.8, 121.2, 121.6, 122.1, 122.2, 123.2, 124.7, 125.0, 126.6, 129.4, 133.5, 137.3, 154.2, 163.4; HRMS *m/z* (ESI): calcd for $C_{15}H_{11}N_2S^+$ $[M + H]^+$ 251.0637, found 251.0634, calcd for $C_{15}H_9N_2S^-$ $[M - H]^-$ 249.0492, found 249.0485.

Oxidation of amidoalkylated indoles (10) to aza-camalexin (11). *o*-Chloranil (1 mmol, 246 mg) is added to a solution of the corresponding compound **10** (1 mmol) in CH_3CN (15–20 mL), and the mixture is stirred for 4 h at r.t. After completion of the reaction, the solvent is evaporated under reduced pressure, the residue is redissolved in dichloromethane and is dry-loaded onto neutral alumina. Chromatography on a short alumina column with diethyl ether/petroleum (1:1) as the eluent gave aza-camalexin **11** in yields specified in Table 3. The Diels–Alder adducts **12** are obtained as competing side products when the reaction is carried out at 85°C.

Aza-camalexin, 3-(1H-imidazol-2-yl)-1H-indole (11). Chromatographed on neutral alumina with petroleum/diethyl ether (1:1); Yield: 80–88%; ^{1}H-NMR (600 MHz, 20°C, DMSO-d_6, δ ppm, *J* Hz): 6.57 (s, 2H), 6.63 (d, *J* = 1.2, 1H) 6.71 (s, 1H), 6.86 (m, 1H), 6.98 (m, 1H), 7.22 (d, *J* = 8.2, 1H), 7.35 (d, *J* = 8.2, 1H), 10.78 (br s, 1H); ^{3}C-NMR (150 MHz, 20°C, DMSO-d_6, δ ppm): 112.0, 118.4, 119.4, 121.4, 121.9, 125.2, 126.0, 126.4, 136.4, 141.0, 152.4; 3215, 2995, 1590, 1570, 1460; HRMS *m/z* (ESI): calcd for $C_{11}H_{10}N_3^+$ $[M + H]^+$ 184.0869, found 184.0864.

Diethyl 5,6,7,8-tetrachloro-2-(1H-indol-3-yl)-3a,9a-dihydro-1H-benzo[5,6][1,4]dioxino[2,3-d]imidazole-1,3(2H)-dicarboxylate (12a). Chromatographed on neutral alumina with petroleum/diethyl ether (1:1, increasing polarity to neat diethyl ether) Yield: 62%; IR (KBr, cm^{-1}): 3329, 3062, 2986, 1718, 1599, 1558, 1466, 1278; ^{1}H-NMR (600 MHz, 80°C, DMSO-d_6, δ ppm, *J* Hz): 0.87 (br s, 6H, 2 × CH_3), 3.87 (br s, 4H, 2 × CH_2), 6.31 (s, 1H), 6.78 (s, 2H), 7.00 (m, 1H), 7.07 (m, 1H), 7.35 (d, *J* = 7.6, 1H), 7.38 (d, *J* = 2.3, 1H), 7.48 (d, *J* = 7.6, 1H), 10.91 (s, 1H); ^{13}C-NMR (150 MHz, 80°C, DMSO-d_6, δ ppm): 14.0, 61.8, 69.8, 84.4, 112.0, 113.2, 118.4, 119.4, 121.4, 121.9, 125.2, 126.0, 126.4, 136.4, 141.0, 152.3; HRMS *m/z* (ESI): calcd for $C_{23}H_{19}Cl_4N_3NaO_6^+$ $[M + Na]^+$ 597.9896, found 597.9890.

Dimethyl 5,6,7,8-tetrachloro-2-(1H-indol-3-yl)-3a,9a-dihydro-1H-benzo[5,6][1,4]dioxino[2,3-d]imidazole-1,3(2H)-dicarboxylate (12b). Chromatographed on neutral alumina with petroleum/diethyl ether (1:1, increasing polarity to neat diethyl ether); Yield: 54%; IR (KBr, cm^{-1}): 3402, 3059, 2990, 1699, 1598, 1549, 1450, 1276; ^{1}H-NMR (600 MHz, 80°C, DMSO-d_6, δ ppm, *J* Hz): 3.47 (s, 6H, 2 × CH_3), 6.30 (s, 1H), 6.79 (s, 2H), 7.00 (m, 1H), 7.08 (m, 1H), 7.35 (d, *J* = 8.2, 1H), 7.39 (s, 1H), 7.47 (d, *J* = 8.2, 1H), 10.91 (s, 1H); ^{13}C-NMR (150 MHz, 80°C, DMSO-d_6, δ ppm): 52.9, 69.9, 84.6, 112.1, 112.6, 118.4, 119.5, 121.4, 124.9, 125.6, 126.2, 126.7, 136.5, 141.1, 152.6; HRMS *m/z* (ESI): calcd for $C_{21}H_{15}Cl_4N_3NaO_6^+$ $[M + Na]^+$ 569.9583, found 569.9590.

Synthesis of indole-3-carboxaldehyde (7) from either 3ac or 10c. Zinc (325 mg, 5 mmol) is added to a solution of the corresponding *Troc*-derivative **3ac** or **10c** (0.5 mmol) and NH_4Cl (265 mg, 5 mmol) in methanol/water (8:2, 10 mL), and the mixture is heated for 2 h at 60°C (**10c**) or at reflux temperature (**3ac**). The solids are then filtered off, and the filtrate is diluted with water (50–60 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The organic layers are dried with Na_2SO_4, and the solvent is evaporated under reduced pressure, dry-loading the crude indole-3-carboxaldehyde onto neutral alumina. Column chromatography on neutral alumina with diethyl ether/petroleum (1:1) as the eluent gave pure indole-3-carboxaldehyde in 82% yield (from **10c**) or 74% yield (from **3ac**). mp = 194–196°C (Guillon et al. and Wang et al. [17] 195–196°C); IR (KBr, cm^{-1}): 3167, 2931, 1634, 1577, 1521, 1445; ^{1}H-NMR (600 MHz, 20°C, DMSO-d_6, δ ppm, *J* Hz): 7.22 (m, 1H), 7.26 (m, 1H), 7.51 (d, *J* = 8.2, 1H), 8.09 (d, *J* = 8.2, 1H), 8.29 (s, 1H), 9.93 (s, 1H), 12.14 (s, 1H); ^{13}C-NMR (150 MHz, 20°C, DMSO-d_6, δ ppm): 112.9, 118.6, 121.3, 122.6, 123.9,

124.6, 137.5, 139.0, 185.5; HRMS *m/z* (ESI): calcd for $C_9H_7NNaO^+$ $[M + Na]^+$ 168.0425, found 168.0420; calcd for $C_9H_6NO^-$ $[M - H]^-$ 144.0449, found 144.0425.

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