Substituted Indole-2-carboxylates as Potent Antagonists of the Glycine Binding Site Associated with the NMDA Receptor

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Summary

A novel series of indole-2-carboxylate analogues of GV150526 (**1**) in which the propenoic double bond was substituted with different "probes" or replaced by a isosteric cyclopropyl moiety were synthesized and evaluated for their affinity profile in order to obtain further information on the pharmacophoric model of the glycine binding site associated to the NMDA receptor.

Introduction

Glutamate is the most abundant excitatory neurotransmitter present in the CNS. It is now widely recognized that in pathological conditions[1–4], such as stroke, abnormal amounts of glutamate are released into synaptic clefts causing an over-stimulation of N-methyl-D-aspartate (NMDA) receptor which, ultimately, leads to a significant increase of the intracellular level of Ca^{++} in the post-synaptic neurons, causing the activation of several neurotoxic cascades responsible for irreversible neuronal damage [5].

Modulating the influx of Ca^{2+} through the ion channel associated with the NMDA receptor[6] using competitive and non-competitive NMDA antagonists[7,8] led to potential therapeutic benefit according to animal models of stroke. Recently, the glycine binding site has become one of the most attractive targets for neuroprotection after stroke, in view of the role of glycine as a co-agonist of the glutamate[9–12] in the activation of this ionotropic receptor complex and the favorable therapeutic index seen for glycine-antagonists[13–21].

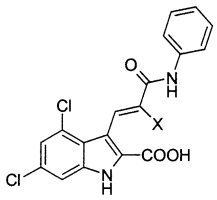
The indole-2-carboxylate derivative GV150526 (Entry 1**,** Table 1) was identified by GlaxoWellcome[22–27] as a potent and selective glycine antagonist endowed with nanomolar affinity *in vitro* and excellent *in vivo* activity in the MCAo model in rats both pre and post-ischemia. The present paper deals with the synthesis and the pharmacological characterization of a novel series of analogues of the compound **1**, bearing different "probes" on the propenoic double bond or with its replacement with a bioisosteric cyclopropyl group. This new series of indole-2-carboxylates showed nanomolar affinity for the glycine binding site coupled with high receptor selectivity. Some analogues prepared in our laboratories were not reported because of disclosure in a patent reporting novel 3-(indol-3-yl)propenoic acid derivatives analogues[28].

Results and Discussion

Synthesis

The derivatives of the new series carrying the different "probes" on the α,β-unsaturated double bond are listed below (Table 1, **2–6**) and were prepared exploiting alternatively Horner-Emmons-Wittig or Knoevenagel reactions to insert on the vinylic double bond different groups endowed with steric and/or stereoelectonic differentiation in order to allow a possible further mapping of the glycine binding site. The stereochemistry of the double bond in the various derivatives represented in the Schemes shown below was determined using NMR techniques (namely $J_{C,H}$ and NOES experiments).

Table 1



Entry	X	pKi	ED_{50} (*i.v.*) mg/kg	ED_{50} (*p.o.*) mg/kg
1	H	8.5	0.06	6.0
2	Me	8.3	0.9	13.2
3	Cl	7.7	0.055	3.98
4	F (Z)	8.0	0.14	18.4
4a	F(E)	6.6	*n.t.*	*n.t.*
5	NHAc	7.6	0.2	10
6	CN	7.3	*n.t.*	*n.t.*

As depicted in Scheme 1, the starting point for the reactions based on Horner-Wittig reaction was the aldehyde **7** which was easily obtained in high yield submitting 2-ethoxycarbonyl-4,6-dichloroindole to Vilsmeyer-Haack ($POCl_3$/DMF) conditions. This derivative was protected as (2-trimethylsilyl)ethoxymethyl (SEM) derivative using SEM chloride in DMF at low temperature to give in almost quantitative yield the intermediate **7c**. This intermediate was submitted to Horner-Wittig reaction at RT with different phosphonates using DiazoBicycloUndecene (DBU) as base [29]. The desired methyl derivative was obtained as an *E:Z* mixture and the

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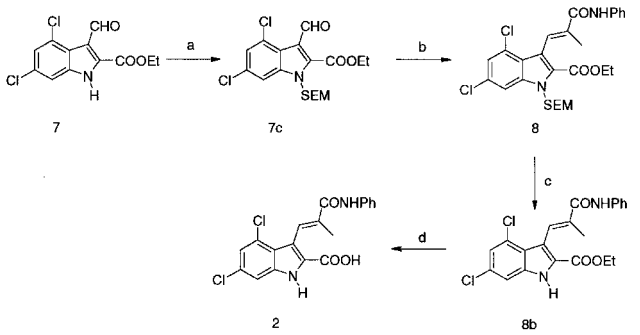
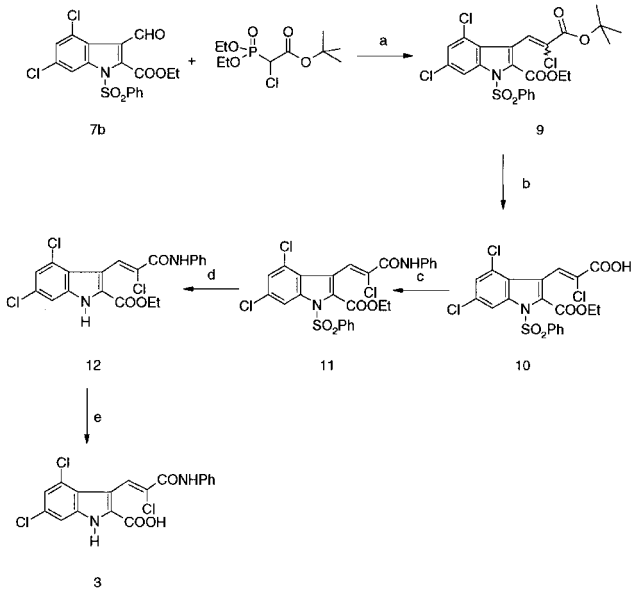


Scheme 1. a) LHMDS, SEMCl, DMF, 0 °C; b) LHMDS, (EtO)2OPC(H)(Me)CONHPh, DMF, 0 °C followed by chromatographic separation; c) HCl 5M, reflux; d) LiOH·H_2O, EtOH, 50 °C followed by acid quenching.

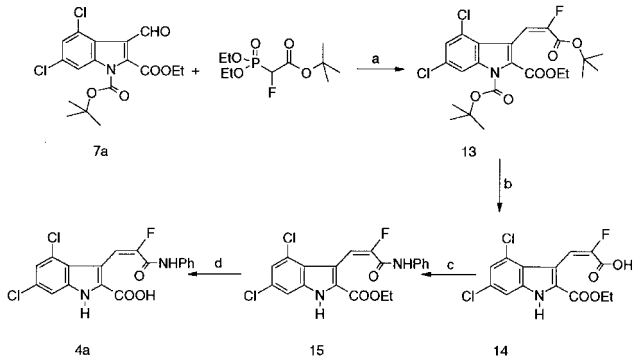
isomer percentage was dependent on the equivalents of base used and the reaction temperature; however, the desired pure isomer was easily obtained by flash chromatography.

The synthesis of the chloro derivative is shown in Scheme 2 for the same aldehyde protected as phenylsulphonyl derivative **7b**; on the vinyl derivative the acidic deprotection (HCO_2H, RT) of the α,β-unsaturated *tert*-butyl ester gave in high yield the corresponding acid which could be obtained as pure isomer after crystallization from ethyl ether. The pure *Z* isomer was subsequently transformed into the phenyl amide in high yield using EDC and aniline. Finally, a two step[1)] deprotection was performed with ethanolic lithium hydroxide to obtain the desired 2-carboxylic acid in quantitative yield.

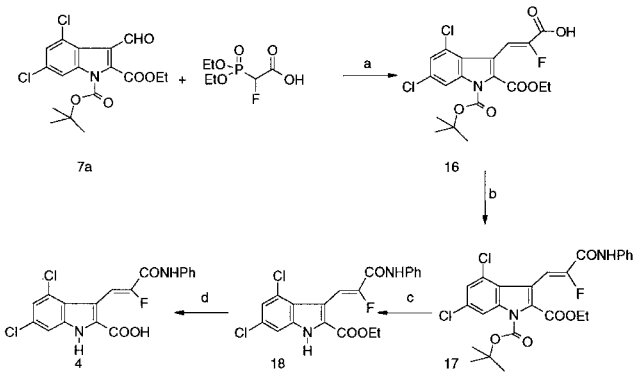
As far as the vinylic fluoro derivative is concerned, two approaches were followed and they are reported in Schemes 3 and 4. It is worth noting that, as reported in Scheme 3, only the pure *E* isomer was obtained using the phosphonate *tert*-butyl ester on the protected aldehyde **7a**, while to obtain the



Scheme 2. a) LHMDS, THF, 0 °C; b) HCO_2H, r.t.followed by crystallization from Et_2O; c) $(PyS)_2$, PPh_3, THF, Aniline, reflux; d)LiOH·H_2O, EtOH, r.t.; e) LiOH·H_2O, EtOH, r.t. followed by acid quenching.



Scheme 3. a) t-BuOK, CH_2Cl_2 from -70 °C to r.t.; b) HCO_2H, 40 °C; c) EDC, HOBT, Aniline, CH_3CN, r.t.; d) LiOH·H_2O, THF/H_2O, r.t. followed by acid quenching.



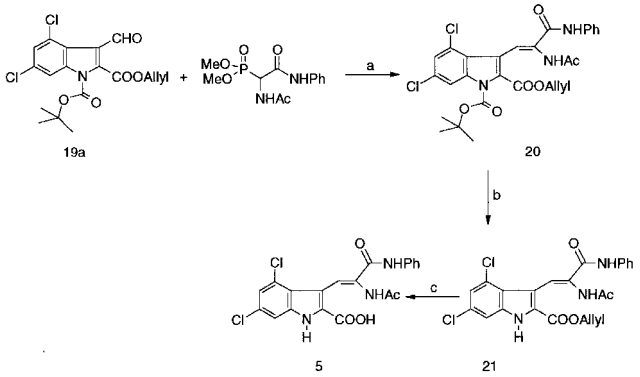
Scheme 4. a) LHMDS, THF, –70 °C followed by chromatographic separation b) EDC, HOBT, Aniline, CH_3CN, reflux; c) HCO_2H, 40 °C; d) LiOH·H_2O, THF/H_2O, 60 °C followed by acid quenching.

desired *Z* product, the Horner-Emmons reaction had to be performed using the phosphonate carrying the free carboxylic acid as shown in Scheme 4, according to literature references[30–32]. The *E*/*Z* mixture obtained was then easily separated and the *Z* acid **16** was coupled to aniline using EDC in THF. Deprotection of the N-BOC derivative **17** with formic acid and basic hydrolysis (LiOH/EtOH) of the esteric moiety in position C-2 gave the desired product **4**.

In order to obtain the acetamido derivative **5** without problems in the final basic hydrolysis, the 2-carboethoxy aldehyde **7a** was replaced by the corresponding allyl ester derivative **19a** as depicted in Scheme 5. The neutral deprotection of intermediate **21** with Pd-tetrakis(triphenylphosphine) and dimedone allowed a quantitative recovery of the desired pure isomer.

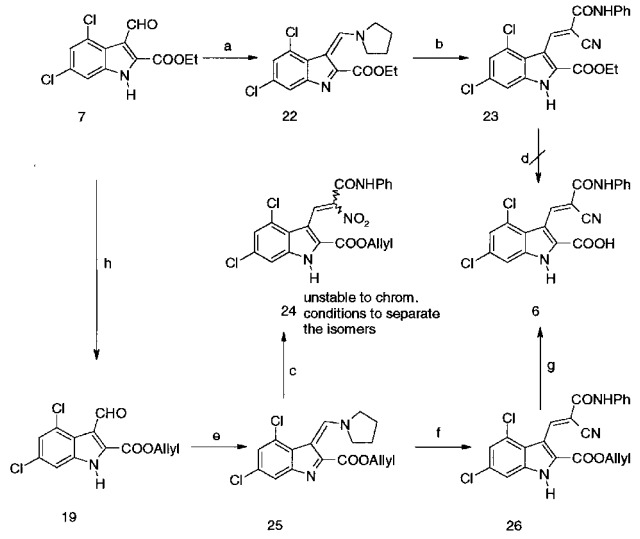
As far the Knoevenagel reaction described in Scheme 6 is concerned, the enamino intermediate **22** was obtained by refluxing 3-formyl-2-ethoxycarbonyl-4,6-dichloroindole with pyrrolidine in benzene under Dean-Stark conditions. This intermediate could easily be separated and remained

[1)] It is worth noting that the transformation to give derivative **3** could have been performed in a single step from intermediate **11** but this attempt allowed the recovery of some propargylic derivative too because of a possible β-elimination reaction. On the other hand, the two-step procedure allowed a chromatographic purification of intermediate **12** and no elimination reaction was observed on this substrate, thus permitting synthesis of the desired derivative **3** as pure compound.



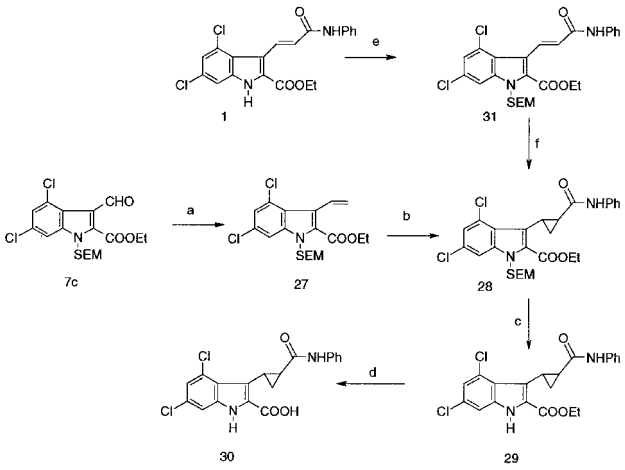
Scheme 5. a) DBU, CH_2Cl_2, r.t. b) TFA, CH_2Cl_2, r.t.; c) Dimedone, $Pd(PPh_3)_4$, THF, r.t.

stable for weeks if stored at low temperature. The reaction of **22** with the *N*-phenyl 2-cyanoacetamide in pyridine led to the isolation of the desired *E* product **23** only. Basic hydrolysis of the ethyl ester with lithium hydroxide monohydrate unfortunately led to a complete isomerization of the double bond producing a 1:1 *E*:*Z* mixture of the desired 2-carboxylic acid derivative **6**. This problem was overcome using the corresponding 2-allyl ester **19** to give intermediate **25** which, after reaction with cyanophenylacetamide in pyridine led to the isolation of the desired *E* product only also in this case. Neutral hydrolysis of the allyl ester **26** using Pd tetrakis triphenyl phosphine allowed the recovery the desired pure 2-carboxylic acid **6** as single *E* isomer. When intermediate **25** were submitted to Knoevenagel reaction using the nitrophenyl acetamide in pyridine, *E*/*Z* mixture of the desired product were immediately obtained. Unfortunately, the nitro derivative proved unstable to the different chromatographic conditions used to isolate the pure *E* isomer; furthermore, any attempt at deprotection on the isomeric mixture led to extensive decomposition.



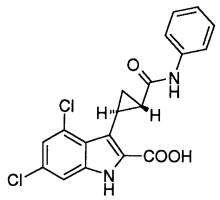
Scheme 6. a) pyrrolidine, benzene, reflux; b) $NCCH_2CONHPh$, Py, r.t.; c) $O_2NCH_2CONHPh$, Py, r.t; d) $LiOH \cdot H2O$, EtOH, r.t. followed by acid quenching; e) pyrrolidine, benzene, reflux; f) $NCCH_2CONHPh$, Py, r.t.; g) Dimedone, $Pd(PPh_3)_4$, THF, r.t. h) AllylOH, pTSA, reflux.

Finally, the removal of the vinylic double bond and its substitution with an isosteric cyclopropyl moiety (**30**) was performed as described in Scheme 7. Aldehyde **7** was protected as SEM derivative (**7c**) using SEMCl in DMF, the formyl group transformed into the corresponding vinyl derivative **27** which was then subjected to the cyclopropanation reaction using rhodium acetate in dimethoxyethane. The resulting amide **28** was then hydrolyzed to the ester derivative **29** using HCl and finally transformed into the desired product **30** using monohydrated lithium hydroxide. In order to overcome the low yield obtained for the production of intermediate **28** from **27**, an alternative route through intermediate **31** was set up and the product obtained in acceptable yield via diazomethane cyclopropanation.



Scheme 7. a) LHMDS, $MePPh_3I$, THF, 60 °C; b) $Rh_2(OAc)_4$, DME, N-phenyl-diazoacetamide, r.t.; c) HCl 5M, reflux; d) $LiOH \cdot H2O$, EtOH, 50 °C followed by acid quenching; e) LHMDS, SEMCl, DMF, 0 °C; f) CH_2N_2; Et_2O; $Rh_2(OAc)_4$.

Table 2



Entry	pK_i	ED_{50} (*i.v.*) mg/kg	ED_{50} (*p.o.*) mg/kg
30	6.7	0.27	n.t.

Biology

The biological evaluation of the new chemical entities (NCE) was performed using the following screening sequence previously described[22]: a) binding assay[33] to evaluate the affinity for the glycine site ; b) selectivity for the

glutamate receptors (NMDA/AMPA/KA); c) *in vivo* anticonvulsant activity in the NMDA induced convulsions model in mice (*iv* and *po*)[34].

Discussion

Different "probes" in terms of steric hindrance and stereoelectronic properties were used to evaluate the effect of the substitution in the α position to the phenylamidic moiety of the derivative **1**. The results of this study are reported in Table 1.

The replacement of a vinylic proton with a group exhibiting a moderately increased steric bulk but with poor electronic properties like a methyl probe (**2**) led to minimal variations in terms of *in vitro* affinity.

On the other hand, compounds endowed with approximately the same steric hindrance of the methyl derivative **2**, but with electron-withdrawing properties (**3**, **5**, **6**) led to a significant decrease of the in vitro affinity (K_i).

This marked effect could be minimized using an electron-withdrawing substituent but endowed with reduced steric hindrance. Accordingly, when the vinylic proton was replaced by a fluorine atom as in derivative **4** a reversed effect was observed.

A possible explanation (for this effect) could be offered in accordance with the pharmacophoric interaction proposed in ref. [22]. In particular, it was proposed that the carbonyl group belonging to the phenylamidic moiety of **1** could behave as a H-bonding acceptor group. Therefore, the introduction of EWG in position α to this carbonyl group should reduce its ability to interact with the receptor, resulting in a lower affinity. Moreover, the increase of the steric hindrance in this position probably should represent an additional penalty for this series of compounds, making it more difficult to achieve the right spatial orientation of the carbonyl.

Obviously, when the C-3 side chain cannot direct the phenylamidic moiety to correctly achieve the above mentioned interaction, as in derivative **4a**, a dramatic reduction in affinity is observed.

To further evaluate the stereoelectronic effect of this olefin moiety, the cyclopropyl derivative **29** was prepared. According to modeling studies, this compound showed the correct spatial requirements necessary for the alignment with derivative **1** within the pharmacophoric model[22]. Despite that, a marked decrease in terms of *in vitro* affinity was observed as reported in Table 2, suggesting once more the "ideal" features of GV150526 (**1**).

Finally, these compounds were tested for their ability to inhibit the convulsions caused by "in vivo" administration of NMDA[34] , a surrogate for stroke models, starting form the basic assumption that NMDA receptor overactivation is the key event in neurodegeneration following cerebral ischemia. The ability of the new chemical entities to counteract NMDA-induced convulsions was used as the end point of the model. Some of the product described in Table 1, despite their reduced affinity, showed excellent ED_{50}s in inhibiting convulsions in mice. In particular, derivative **3** showed properties quite similar to those of the lead compound **1**, making it very attractive in terms of further characterization.

Conclusions

Different "probes" were used to test the ability of the receptor to tolerate substitution on the double bond of analogues of **1**. The receptor seems to be extremely sensitive to hindered EGW, leading to a reduced affinity. Among the different compound tested, derivative **3**, despite the reduced *in vitro* affinity with respect to the unsubstituted analogue **1**, showed a promising preliminary *in vivo* pharmacological profile.

Acknowledgments

We would like to thank Mr. S. Costa for the *in vivo* profiling. We also thank the spectrometry and spectroscopy labs of GlaxoWellcome S.p.A. for their fruitful collaboration in MS and NMR studies and Mrs. Maria Passarini for her valuable support.

Experimental

Infrared spectra were recorded on a Bruker IFS 48 spectrometer. ^{1}H NMR spectra were recorded on a Varian Unity 400 (400 MHz); the data are reported as follows: chemical shift in ppm from the Me_4Si line as external standard, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants.

Chromatography was carried out by use of the Merck Silica Gel 60 (230–400 mesh) as described by Still *et al*. Mass spectra were performed on a Triple Quadrupole (VG-4 Fison Instrument, UK) equipped with Fast Atom Bombardment (FAB) ionization . Elemental analyses were determined by a EA 1108 Carlo Erba elemental analyzer and the analyses of the reported compounds are in agreement with the calculated values. Melting points were determined on a Büchi 530 apparatus (scale 0 °C–250 °C) and are uncorrected. All the reactions were carried out under a controlled atmosphere in flame dried glassware. Anhydrous DMF was purchased from Aldrich; THF was used after distillation over K/benzophenone; CH_2Cl_2 and CH_3CN were used after distillation over P_2O_5. Reactions were monitored by analytical thin-layer chromatography (TLC) using Merck Silica Gel 60 F-254 glass plates (0.25 mm).

*1-tert-Butoxycarbonyl-3-formyl-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (***7a***)*

To a solution of aldehyde **7** (prepared according to the procedure reported in ref. [22]) (858 mg, 3.0 mmol) in dry THF, DMAP (74 mg, 0.6 mmol) and bis(*tert*-butoxy carbonate (380 mg, 3.6 mmol) were added at room temperature and stirred for 24 h. The solution was evaporated to dryness and the crude product crystallized by cold AcOEt to give the desired product in 80% yield.– Mp 141 °C.– IR (Nujol) ν = 3305–3288 cm^{-1} (NH).– ^{1}H NMR ($CDCl_3$): δ = 10.77 (s, 1H), 8.24 (d, 1H), 7.42 (d, 1H), 4.50 (q, 2H), 1.65 (s, 9H), 1.43 (t, 3H).– MS *m/z* 386 $[M]^+$.

*1-(2-(Trimethylsilyl)ethoxymethyl)-3-formyl-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (***7c***)*

To a solution of aldehyde **7** (prepared according to the procedure reported in ref. [22]) (860 mg, 3.0 mmol) in dry DMF, LHMDS (sol. 1 M in hexanes) (3.6 mL, 3.6 mmol) was slowly added at 0 °C; SEMCl (0.64 mL, 3.6 mmol) was subsequently added at the same temperature and the solution was allowed to warm to room temperature and stirred for an additional two hours. The solution was quenched with aq. NH_4Cl, extracted with AcOEt, and the organic phase was dried over sodium sulphate; the solution was filtered and the organic phase evaporated. The crude product was purified by flash chromatography (CyH/AcOEt 90:10) to produce the desired product in 93% yield.–. ^{1}H NMR ([D6]DMSO): δ = 10.54 (s, 1H), 7.991 (d, 1H), 7.57 (d, 1H), 5.73 (s, 2H), 4.41 (q, 2H), 3.44 (t, 2H), 1.32 (t, 3H), 0.78 (t, 2H), –0.12 (s, 9H).

*E-1-(2-(Trimethylsilyl)ethoxymethyl)-3-(2-methyl-2-phenylcarbamoyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**8**)*

To a solution of $(EtO)_2PO(CH)(Me)CONHPh$ (430 mg, 1.5 mmol) in dry DMF, KHMSD (0.5 M in toluene) (0.75 mL, 1.5 mmol) were slowly added at 0 °C and the solution was left under stirring at the same temperature for 1 h. Aldehyde **7c** (430 mg, 1 mmol) was slowly added the solution was allowed to warm to room, quenched with aq. NH_4Cl, extracted with AcOEt and the organic phase was dried over sodium sulphate; the solution was filtered and the organic phase evaporated. The crude product was purified by flash chromatography (CyH/AcOEt 85:15) to isolate the desired *E* product in 56% yield.– IR (Nujol) ν = 1678 cm^{-1} (C=O).– ^1H NMR ([D6]DMSO): δ = 12.48 (bs, 1H), 9.70 (s, 1H), 7.80–7.72 (m, 3H), 7.48 (d, 1H), 7.33 (t, 2H), 7.26 (d, 1H), 7.08 (m, 1H), 5.71 (s, 2H), 4.32 (q, 2H), 3.31 (t, 2H), 1.79 (d, 3H), 1.30 (t, 3H), –0.11 (s, 9H).

*E-3-(2-Methyl-2-phenylcarbamoyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**8b**)*

Derivative **8** (1.65g, 3 mmol) was suspended in 95% EtOH (10 mL) and 5N HCl (3 mmol) was slowly added. The resulting suspension was refluxed for 3 h. AcOEt was added and the mixture extracted. The crude product was dried over sodium sulphate and after evaporation it was chromatographed (CyH/AcOEt 75:25) to give the desired product **8b** in 80% yield.– IR (Nujol) ν = 3317–3288 cm^{-1} (NH), 1678 (C=O).– ^1H NMR ([D6]DMSO): δ = 12.48 (bs, 1H), 9.70 (s, 1H), 7.80–7.72 (m, 3H), 7.48 (d, 1H), 7.33 (t, 2H), 7.26 (d, 1H), 7.08 (m, 1H), 4.32 (q, 2H), 1.79 (d, 3H), 1.30 (t, 3H).

*E-3-(2-Methyl-2-phenylcarbamoyl)-4,6-dichloroindole-2-carboxylic Acid (**2**)*

Intermediate **8b** (835 mg, 2 mmol) was suspended in 80% EtOH (10 mL) and LiOH monohydrated (144 mg, 6 mmol) was added; the mixture was warmed at 50 °C for 3 h, acidified to pH = 3 and extracted with AcOEt. The organic solution was dried and the crude product precipitated from cold EtOH to give the desired product **2** in 90% yield.– IR (Nujol) ν = 3838 cm^{-1} (NH), 2725–2000 (COOH), 1703 (C=O).– ^1H NMR ([D6]DMSO): δ = 13.45 (bs, 1H), 12.38 (s, 1H), 9.69 (s, 1H0, 7.76 (dd, 1H), 7.74 (d, 1H), 7.31 (t, 2H), 7.22 (d, 1H), 7.06 (tt, 1H), 1.78 (bs, 3H). MS *m/z* 389 $[M]^+$.

*E- and Z-1-Benzenesulfonyl-3-(2-tert-butoxycarbonyl-2-chlorovinyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**9**)*

A solution of 2-chloro-(diethoxyphosphonyl)acetic acid *tert*-butyl ester (prepared in 94% overall yield from the commercially available (diethoxyphosphonyl)acetic acid *tert*-butyl ester in two steps according to ref. [35]) (0.9 g, 3.5 mmol) in dry THF (15 mL) was cooled to 0 °C and 1 M LHMDS (3.5 mL, 3.5 mmol) was added dropwise. The reaction was stirred for 0.75 h at this temperature, then a suspension of **7b** (prepared as reported in ref. [36]) (1.5 g, 3.5 mmol) in dry THF (30 mL) was added. Stirring was continued for 3 h at 0 °C resulting in the gradual formation of a clear solution to which was added saturated NH_4Cl (10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with brine, dried, and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography (CyH/EtOAc 85:15) to give **9** (68% yield, 62/38 mixture of isomers of unassigned stereochemistry) as a white solid. – IR (Nujol) ν = 1736 and 1718 cm^{-1} (C=O)$^{-}$ ^1H NMR ($CDCl_3$): Major isomer δ = 8.04 (dd, 2H), 8.01 (d, 1H), 8.00 (s, 1H), 7.65 (tt, 1H), 7.55 (td, 2H), 7.28 (d, 1H), 4.41 (q, 2H), 1.56 (s, 9H), 1.37 (t, 3H); Minor isomer: 8.09 (dd, 2H), 8.0 (d, 1H), 7.55 (td, 2H), 4.41 (q, 2H), 1.37 (t, 3H). MS *m/z* 558 $[M + H]^+$.

*Z-1-Benzenesulfonyl-3-(2-carboxy-2-chlorovinyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**10**)*

A suspension of **9** (3.1 g, 5.42 mmol) in formic acid (150 mL) was stirred overnight at room temperature. After evaporation of the formic acid, product **10** (100% yield, mixture of *E*- and *Z*-isomers) was obtained as a white solid. The pure *Z*-isomer was obtained by trituration with diethyl ether.– Mp 229.5–232.1 °C.– IR (Nujol) ν = 2900–2790 cm^{-1} (OH), 1736 (C=O).– ^1H NMR ([D_6]DMSO): δ = 8.09 (dd, 2H), 8.06 (s, 1H), 8.04 (d, 1H), 7.82 (m, 1H), 7.71 (m, 2H), 7.65 (d, 1H), 4.34 (q, 2H), 1.23 (t, 3H). MS *m/z* 502 $[M + H]^+$.

*Z-1-Benzenesulfonyl-3-(2-phenylcarbamoyl-2-chlorovinyl)-4,6-dichloroindole-2-Carboxylic Acid Ethyl Ester (**11**)*

To a solution of **10** (1.05 g, 2 mmol) in dry THF were added 2,2'-dipyridyl disulfide (506 mg, 2.3 mmol) and triphenyl phosphine (600 mg, 2.3 mmol) and the resulting yellow solution was stirred at room temperature for 2.5 h. Aniline (0.25 mL, 2.7 mmol) was added and the mixture heated at reflux for 24 h, then 1N hydrochloric acid was added and the mixture extracted with EtOAc The combined organic phase was washed with brine, dried and concentrated under reduced pressure. The resulting residue was adsorbed onto silica and purified by flash chromatography to give the desired product **11**.– IR (Nujol) ν = 3240 cm^{-1} (NH), 1724 (C=O).– ^1H NMR ([D6]DMSO): δ = 10.17 (bs, 1H), 8.08 –8.05 (m, 4H), 7.83–7.70 (m, 6H), 7.37 (m, 2H), 7.16 (m, 1H), 4.36 (q, 2H), 1.25 (t, 3H).

*Z-3-(2-Phenylcarabamoyl-2-chlorovinyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**12**)*

Intermediate **11** (276 mg, 0.5 mmol) was suspended in 80% EtOH and $LiOH{\cdot}H_2O$ (18 mg, 0.75 mmol) was added. The mixture was stirred for 6 h and AcOEt was subsequently added. The organic phase was dried over sodium sulphate and evaporated to dryness. The crude product was purified by flash chromatography (CyH/AcOEt 75:25) to give the desired intermediate **12** in 88% yield.– ^1H NMR ([D6]DMSO): δ = 12.67 (bs, 1H), 10.07 (s, 1H), 8.25 (s, 1H), 7.73 (d, 2H), 7.48–7.13 (m, 5H), 4.32 (q, 2H), 1.3 (t, 3H).

*Z-3-(2-Phenylcarabamoyl-2-chlorovinyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**3**)*

Intermediate **12** (164 mg, 0.4 mmol) was suspended in 80% EtOH and $LiOH{\cdot}H_2O$ (14 mg, 0.6 mmol) was added. The mixture was stirred for 6 h and subsequently acidified to pH = 3. AcOEt was subsequently added, and the desired product **3** was precipitated as solid in 70% yield.– IR (Nujol) ν = 3267 cm^{-1} NH, 1684 (C=O), 1599 (C=C).– ^1H NMR ([D6]DMSO): δ = 13.5 (bs, 1H), 12.5 (s, 1H),10.00 (s, 1H), 8.26 (s, 1H), 7.75 (d, 2H), 7.48–7.37 (m, 3H), 7.29, (d, 1H), 7.03 (t, 1H). MS *m/z* 375 $[M + H]^+$.

*Z-1-tert-Butoxycarbonyl-3-(2-fluoro-2-carboxy)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**16**)*

A 1 M solution of LHMDS in THF (0.92 mL) was added dropwise to a solution of diethyl 2-fluoro-(diethoxyphosphonyl)acetic acid (0.1 g, 0.46 mmol) in dry THF (4 mL) at –70 °C, and the reaction was stirred at –40 °C for 15 min. After cooling at –70 °C, a solution of aldehyde **7a** (0.15 g, 0.39 mmol) in THF (6 mL) was added dropwise and the stirring was continued at –40 °C for 1.5 h. Ethyl acetate was added and the organic phase was washed with a 2N solution of HCl and brine, dried and concentrated under reduced pressure to give a crude *E*/*Z* mixture and the isomers were separated by flash chromatography (CyH/AcOEt 85:15). to give the desired isomer **16** in 57% yield.

Isomer *E*: mp > 220 °C. ^1H NMR ([D6]DMSO): δ = 7.93 (d, 1H), 7.41 (d, 1H), 6.39 (d, 1H), 4.24 (q, 2H), 1.53 (s, 9H), 1.24 (t, 3H). MS *m/z* 447 $[M+H]^+$.

Isomer *Z* (**16**): mp > 220 °C. ^1H NMR ([D6]DMSO): δ = 8.03 (d, 1H), 7.54 (d, 1H), 6.90 (d, 1H), 4.28 (q, 2H), 1.58 (s, 9H), 1.27 (t, 3H). MS *m/z* 447 $[M+H]^+$.

*Z-1-tert-Butoxycarbonyl-3-(2-fluoro-2-phenylcarbamoyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**17**)*

1-Hydroxybenzotriazole hydrate (0.047 g, 0.35 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.085 g, 0.43 mmol) and aniline (0.04 g, 0.43 mmol) were added to a suspension of the compound **16** (0.13 g, 0.29 mmol) in acetonitrile (15 mL) and the reaction was refluxed for 1.5 h. Ethyl acetate was added and the organic phase was washed with a 2N solution of HCl and brine, dried and concentrated under reduced pressure. The crude product which was purified by flash chromatography to yield the desired compound **17** in 66% yield.– Mp> 220 °C.– IR (Nujol) ν = 3360 cm^{-1} (NH), 1745 and 1676 (C=O), 1603 (C=C).– ^1H NMR ([D6]Acetone): δ =

9.68 (s, 1H), 8.15 (d, 1H), 7.84 (m, 1H), 7.52 (d, 1H), 7.47 (d, 1H), 7.38 (t, 2H), 7.17 (tt, 1H), 4.41 (q, 2H), 1.65 (s, 9H), 1.35 (s, 3H MS *m/z* 552 $[M+H]^+$.

*Z-3-(2-Fluoro-2-phenylcarbamoyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (***18***)*

A suspension of compound **17** (0.1 g, 0.19 mmol) in formic acid (5 mL) was heated at 40 °C for 2 h. The precipitate was filtered and washed with diethyl ether to give the desired compound **18** in 62% yield.– Mp > 200 °C.– IR (Nujol) ν = 3312 cm^{-1} (NH), 1678 and 1659 (C=O),1600 (C=C) cm^{-1}.– ^{1}H NMR ([D6]Acetone): δ = 11.63 (bs, 1H), 9.71 (bs, 1H), 7.86 (d, 2H), 7.62 (s, 1H), 7.58 (d, 1H), 7.37 (t, 2H), 7.25 (d, 1H), 7.15 (t, 1H), 4.38 (q, 2H), 1.35 (t, 3H). MS *m/z* 421 $[M+H]^+$.

*Z-3-(2-Fluoro-2-phenylcarbamoyl)-4,6-dichloroindole-2-carboxylic Acid (***4***)*

Lithium hydroxide monohydrate (0.024 g, 0.57 mmol) was added to a solution of the compound **18** (0.04 g, 0.095 mmol) in THF/H_2O (6 mL/4 mL) and the reaction was stirred at 60 °C for 7 h and at r.t. for 15 h. Ethyl acetate was added and the solution was washed with a 2N solution of HCl and brine. The organic layer was dried and concentrated at reduced pressure to give the crude product which was purified by trituration in diethyl ether/petroleum ether to give the desired product **(4)** in 60% yield.– IR (Nujol) ν = 3418–3315cm^{-1} (NH, OH), 1664 (C=O).– ^{1}H NMR ([D6]DMSO): δ = 13.67 (bs, 1H), 12.54 (bs, 1H), 10.33 (s, 1H), 7.77 (d, 2H), 7.48 (s, 1H), 7.46 (d, 1H), 7.34 (t, 2H), 7.28 (d, 1H), 7.12 (t, 1H). MS *m/z* 392 $[M]^+$.

*E-1-tert-Butoxycarbonyl-3-(2-fluoro-2-tert-butoxycarbonyl)-4,6-dichloro-indole-2-carboxylic Acid Ethyl Ester (***13***)*

A solution of diethyl 2-fluoro-(diethoxyphosphonyl)acetic acid *tert*-butyl ester (0.2 g, 0.74 mmol) in dry dichloromethane (5 mL) was added to a suspension of potassium *tert*-butoxyde (0.09 g; 0.74 mmol) in dry dichloromethane (5 mL) at –70 °C; the reaction was stirred for 20 min and a solution of the aldehyde **7a** (0.23 g; 0.62 mmol) in dry dichloromethane (10 mL) was added. The temperature was raised to r.t. and after 1.5 h the solution washed with a 2N solution of HCl and brine, dried and concentrated under reduced pressure to give the crude compound which was purified by flash chromatography (CyH/AcOEt 70:30) to give the desired product **13** in 75% yield.– Isomer *Z*: ^{1}H NMR ([D6]Acetone): δ = 8.12 (d, 1H), 7.44 (d, 1H), 7.03 (d, 1H), 4.38 (q, 2H), 1.63 (s, 9H), 1.34 (t, 3H), 1.12 (s, 9H). MS *m/z* 502 $[M+H]^+$.

*E-3-(2-Fluoro-2-carboxy)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (***14***)*

A solution of the compound **13** (0.23 g, 0.46 mmol) in formic acid (5 mL) was heated at 40 °C for 1.5 h. The formed precipitated was filtered and washed with diethyl ether to give the desired compound **14** in 94% yield. – Mp > 238–240 °C.– IR (Nujol) ν = 3321 cm^{-1} (NH), 1711 and 1672 (C=O).– ^{1}H NMR ([D6]Acetone): δ = 13.35 (bs, 1H), 12.45 (s, 1H), 7.44 (d, 1H), 7.23 (d, 1H), 7.23 (s, 1H), 4.30 (q, 2H), 1.29 (t, 3H). MS *m/z* 345 $[M]^+$.

*E-3-(2-Fluoro-2-phenylcarbamoyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (***15***)*

1-Hydroxybenzotriazole hydrate (0.071 g, 0.53 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.1 g, 0.5 mmol) and aniline (0.52 g, 0.56 mmol) were added to a suspension of the compound **14** (0.13 g, 0.43 mmol) in acetonitrile (15 mL) and the reaction was stirred at r.t. overnight. Ethyl acetate was added and the organic phase was washed with a 2N solution of HCl and brine, dried and concentrated at reduced pressure. The crude product was purified by flash chromatography (CyH/AcOEt 80:20) to give the desired compound **15** in 50% yield.– Mp> 199–201 °C.– IR (Nujol) ν = 3342 cm^{-1} (NH), 1707 and 1661 (C=O), 1601 (C=C).– ^{1}H NMR ([D6]acetone): δ = 11.43 (bs, 1H), 9.46 (bs, 1H), 7.66 (dd, 2H), 7.54 (d, 1H), 7.28 (t, 2H), 7.16 (d, 1H), 7.15 (d, 1H), 7.08 (tt, 1H), 4.31 (q, 2H), 1.32 (t, 3H). MS *m/z* 421 $[M+H]^+$.

*E-3-(2-Fluoro-2-phenylcarbamoyl)-4,6-dichloroindole-2-carboxylic Acid (***4a***)*

Lithium hydroxide monohydrated (0.015 g, 0.36 mmol) was added to a solution of the compound **15** (0.04 g, 0.095 mmol) in THF/H_2O (6 mL/4 mL) and the reaction mixture was stirred at r.t. overnight. Ethyl acetate was added and the solution was washed with a 2N solution of HCl and brine. The organic layer was dried and concentrated under reduced pressure. The crude product was purified by trituration in diethyl ether to give the desired compound **4a** in 40% yield.– Mp >220 °C.– IR (Nujol) ν = 3427 and 3317 cm^{-1} (NH + OH), 1699 and 1670 (C=O), 1600 (C=C).– ^{1}H NMR ([D6]DMSO): δ = 13.38 (bs, 1H), 12.28 (bs, 1H), 10.34 (bs, 1H), 7.56 (d, 2H), 7.41 (d, 1H), 7.25 (t, 2H), 7.17 (d, 1H), 7.12 (d, 1H), 7.05 (t, 1H). MS *m/z* 393 $[M+H]^+$.

*Z-1-tert-Butoxycarbonyl-3-(2-phenylcarbamoyl-2-acetamido)-4,6-dichlor oindole-2-carboxylic Acid Allyl Ester (***20***)*

DBU (0.12 mL, 0.8 mmol) was added to a solution of commercially available N-acetyl-(dimethoxyphosphonyl)phenylacetamide (0.12 g, 0.39 mmol) in dry dichloromethane (10 mL) and the reaction mixture was stirred at r.t. for 30 min. After cooling at –20 °C, a solution of aldehyde **19a** (115 mg, 0.3 mmol) in dry dichloromethane (10 mL) was added dropwise and the stirring was continued at –20 °C for 7 h. The reaction mixture was washed with a 2N solution of HCl and brine, then dried and concentrated under reduced pressure. The crude product was purified by flash chromatography (CyH/AcOEt 85:15) to give the desired compound **20** in 52% yield.– Mp > 250 °C . IR (Nujol) ν = 3302 cm^{-1} (NH), 1745 and 1695 and 1648 (C=O).– ^{1}H NMR ([D6]Acetone): δ = 9. 26 (bs, 1H), 8.77 (bs, 1H), 8.11 (d, 1H), 7.75 (d, 2H), 7.41 (d, 1H), 7.32 (t, 2H), 7.19 (s, 1H), 7.08 (t, 1H), 6.06 (m, 1H), 5.5–5.2 (m, 2H), 4.79 (m, 1H), 1.89 (s, 3H), 1.64 (s, 9H). MS *m/z* 572 $[M+H]^+$.

*Z-3-(2-Phenylcarbamoyl-2-acetamido)-4,6-dichloroindole-2-carboxylic Acid Allyl Ester (***21***)*

Trifluoroacetic acid (6 mL) was added dropwise to a solution of the compound **20** (0.125 g, 0.21 mmol) in dry dichloromethane (6 mL) at 0 °C, then the reaction mixture was stirred at r.t. for 1 h. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed with a saturated solution of $NaHCO_3$. The organic layer was dried and concentrated under reduced pressure. The crude product was purified by trituration in diethyl ether to give the compound **21** in 60% yield.– Mp> 200 °C.– IR (Nujol) ν = 3331 cm^{-1} (NH), 1720 and1656 (C=O).– ^{1}H NMR ([D6]DMSO): δ = 12.48 (s, 1H), 9.74 (s, 1H), 9.05 (s, 1H), 7.75 (d, 2H), 7.48 (d, 1H), 7.32 (t, 2H), 7.25 (d, 1H), 7.13 (s, 1H), 7.07 (t, 1H), 6.03 (m, 1H), 5.40 (dq, 1H), 5.25 (dq, 1H), 4.80 (d, 2H), 1.78 (s, 3H). MS *m/z* 472 $[M+H]^+$.

*Z-3-(2-Phenylcarbamoyl-2-acetamido)-4,6-dichloroindole-2-carboxylic Acid (***5***)*

Dimedone (0.023 g, 0.17 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.024 g, 0.011 mmol) were added to a solution of compound **21** (0.02 g, 0.042 mmol) in THF (2 mL) and the reaction was stirred for 1 h. Ethyl acetate was added and the solution was washed with a saturated solution of $NaHCO_3$, a 2N solution of HCl and brine. The organic layer was dried and concentrated under reduced pressure to give a crude product which was purified by trituration in diethyl ether to give compound **5** in 55% yield.– IR (Nujol) ν = 3321 cm^{-1} (NH).– ^{1}H NMR ([D6]DMSO): δ = 13.44 (bs, 1H), 12.32 (bs, 1H), 9.73 (s, 1H), 9.02 (bs, 1H), 7.76 (d, 2H), 7.45 (d, 1H), 7.32 (t, 2H), 7.21 (s, 1H), 7.3–7.1 (bs, 1H), 7.06 (t, 1H), 1.80 (s, 3H). MS *m/z* 432 $[M+H]^+$.

*4,6-Dichloropyrrolidin-1-ylmethylene-3H-indole-2-carboxylic Acid Ethyl Ester (***22***)*

Intermediate **7** (2.0 g, 7 mmol) was treated with pyrrolidine (0.71 mL, 1.2 mmol) in refluxing benzene under Dean-Stark conditions for 2 h. The solution was cooled to room temperature and evaporated to dryness to give the desired product **22** in 80% yield.– ^{1}H NMR ([D6]DMSO): δ = 9.29 (s, 1H), 7.68 (d, 1H), 7.21 (d, 1H), 4.40 (m, 2H), 4.01–3.50 (m, 4H), 2.05 (m, 4H), 1.38 (t, 3H).

*E-3-(2-Phenylcarbamoyl-2-cyano)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**23**)*

Intermediate **22** (500 mg, 1.48 mmol) was treated with $NCCH_2CONHPh$ (237 mg, 1.48 mmol) in pyridine at room temperature for 1 h. The solution was evaporated to dryness and the residue precipitated from 95% EtOH to give the desired product **23** in 85% yield.– IR (Nujol) ν = 3414–3283 cm^{-1} (NH), 1700–1676 (C=O), 1606 (C=C).– ^1H NMR ([D6]DMSO): δ = 13.07 (bs, 1H), 10.38 (bs, 1H), 8.83 (s, 1H), 7.68 (d, 2H), 7.54 (d, 1H), 7.41–7.36 (m, 3H), 7.14 (t, 1H), 4.37 (q, 2H), 1.31 (t, 3H).

*E/Z-3-(2-Phenylcarbamoyl-2-nitro)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**24**)*

Intermediate **25** (370 mg; 1.24 mmol) was treated with $O_2NCH_2CONHPh$ (225 mg, 1.24 mmol) in pyridine at room temperature for 12 h. The product was isolated as a crude *E*/*Z* mixture, but the desired *E* product was not obtained because of the chromatographic instability of the mixture to any of the attempted purification conditions.

*3-Formyl-4,6-dichloroindole-2-carboxylic Acid Allyl Ester (**19**)*

Intermediate **7** (1 g, 3.5 mmol) was suspended in allyl alcohol, *p*-toluenesulphonic acid monohydrate (665 mg, 3.5 mmol) was added and the mixture refluxed for 2h. The resulting solution was evaporated to dryness and the crude product was purified by precipitation from CyH to give the desired product **19** in 60% yield.– IR (Nujol) ν = 3305–3288 cm^{-1} (NH).– ^1H NMR ([D6]DMSO): δ = 11.4 (s, 1H), 7.41 (d, 1H), 7.05 (d, 1H), 6.1–5.9 (m, 1H), 5.4–5.2 (m, 2H), 4.8 (m, 2H).

*4,6-Dichloropyrrolidin-1-ylmethylene-3H-indole-2-carboxylic Acid Allyl Ester (**25**)*

Intermediate **19** (450 mg, 1.51 mmol) was refluxed in benzene under Dean-Stark conditions with pyrrolidine (0.16 mL, 1.8 mmol) for 4 h. The solution was evaporated to dryness to give the desired intermediate **25** in 80% yield.– ^1H NMR ([D6]DMSO): δ = 9.12 (s, 1H), 7.70 (d, 1H), 7.20 (d, 1H), 6.20 (m, 1H), 5.50-5.20 (m, 2H), 4.85 (m, 2H), 4.00–3.50 (m, 2H), 2.05 (m, 4H).

*E-3-(2-Phenylcarbamoyl-2-cyano)-4,6-dichloroindole-2-carboxylic Acid Allyl Ester (**26**)*

Intermediate **25** (420 mg, 1.51 mmol) was treated with $NCCH_2CONHPh$ (350 mg, 1.8 mmol) in pyridine at room temperature for 1 h. The solution was evaporated to dryness and the crude product purified by flash chromatography (CyH/AcOEt 50:50) to give the desired product **26** in 60% yield.– IR (Nujol) ν = 3283 cm^{-1} (NH), 1676 (C=O), 1599 (C=C).– ^1H NMR ([D6]DMSO): δ = 13.1 (bs, 1H), 10.4 (bs, 1H), 8.83 (s, 1H), 7.70 (d, 2H), 7.55 (d, 1H), 7.41–7.36 (m, 3H), 7.14 (t, 1H), 6.02 (m, 1H), 5.35 (m, 2H), 4.86 (m, 2H).

*E-3-(2-Phenylcarbamoyl-2-cyano)-4,6-dichloroindole-2-carboxylic Acid (**6**)*

Intermediate 26 (20 mg, 0.046 mmol) were dissolved in dry THF under nitrogen and dimedone (7.5 mg, 0.06 mmol) and $Pd(PPh3)_4$ (1.3 mg, 0.001 mmol) were subsequently added at room temperature. The solution was left under stirring for 2 h, poured into AcOEt, extracted with 0.5 N NaOH. The aqueous phase was acidified with 0.5 N HCl and extracted with AcOEt, the organic phase dried over sodium sulphate, filtered and evaporated to dryness to give the desired product **6** in 80% yield.– ^1H NMR ([D6]DMSO): δ = 14. 0 (bs, 1H), 12.95 (bs, 1H), 10.39 (bs, 1H), 8.82 (s, 1H), 7.70 (m, 2H), 7.52 (d, 1H), 7.39–7.36 (m, 3H), 7.14 (m, 1H). MS *m/z* 401 $[M + H]^+$.

*1-(2-(Trimethylsilyl)ethoxymethyl)-3-vinyl-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**27**)*

To a 1M solution of LHMDS (0.3 mL, 0.3 mmol) in dry THF, methyltriphenylphosphonium bromide (107 mg, 0.3 mmol) was added at room temperature and the mixture stirred for 4 h. Intermediate **7c** (125 mg, 0.3 mmol) was subsequently added and the reaction warmed to 60 °C for 9 h. The reaction was cooled to room temperature, poured into water, and extracted with AcOEt. The organic phase dried over sodium sulphate, filtered and evaporated to dryness. The crude product was purified by flash chromatography (CyH/AcOEt 75:25) to give the desired product **27** in 42% yield.– ^1H NMR ([D6]DMSO): δ = 7.89 (d, 1H), 7.32 (d, 1H), 7.14 (dd, 1H), 5.77 (s, 2H), 5.48 (dd, 1H), 5.33 (dd, 1H), 4.32 (q, 2H), 3.36 (t, 2H), 1.24 (t, 3H), 0.74 (t, 2H), –0.13 (s, 9H).

*E-1-(2-(Trimethylsilyl)ethoxymethyl)-3-(2-phenylcarbamoylcyclopropyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**28**)*

To a solution of compound **27** (120 mg, 0.29 mmol) and $Rh_2(OAc)_4$ (2.6 mg, 0.0058 mmol) in 1,2 – dimethoxyethane was added a solution of N-phenyl diazoacetamide (70 mg, 0.435 mmol) in 1,2-dimethoxyethane by a motor-driven syringe pump over a 4 h period. The solvent was evaporated and the crude product was purified by a gradient elution to give the desired intermediate **28** in 7% yield. – IR ($CDCl_3$) ν = 1720–1709 cm^{-1} (C=O), 1601 (C=C).– ^1H NMR ($CDCl_3$): δ = 7.55 (d, 2H), 7.42 (d, 1H), 7.34 (t, 2H), 7.18 (d, 1H), 7.12 (t, 1H), 5.73 (d, 1H), 5.65 (d, 1H), 4.55–4.10 (m, 2H), 3.50–3.40 (m, 2H), 2.83 (m, 1H), 1.80 (m, 1H), 1.70 (m, 1H), 1. 42 (t, 3H), 1.15 (m, 1H), 0.86 (m, 2H), –0.06 (s, 9H).

*Alternative Procedure to Prepare E-1-(2-(Trimethylsilyl)ethoxymethyl)-3-(2-phenylcarbamoylcyclopropyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**28**)*

Intermediate **31** (602 mg, 1.13 mmol) was dissolved in dry Et_2O under an argon atmosphere, $Pd(OAc)_2$ (10%) and an ethereal solution of diazomethane was added at 0 °C. The mixture was carefully warmed at room temperature and stirring continued for 1 h. The solution was evaporated using a stream of dry nitrogen, the crude product was washed carefully with dry Et_2O and dry DCM and finally purified by flash chromatography to give the desired product in 82% yield.

*E-3-(2-Phenylcarbamoylcyclopropyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**29**)*

5N HCl (2 mL) was added to a suspension of intermediate **28** (201 mg, 0.5 mmol) in 95% EtOH and the resulting mixture was refluxed for 5 h. The mixture was cooled to room temperature, concentrated at reduced pressure and extracted with AcOEt. The organic phase dried over sodium sulphate, filtered and evaporated to dryness. The crude product was purified by flash chromatography (CyH /AcOEt 50:50) to give the desired product **29** in 70% yield.– IR (Nujol) ν = 3312 cm^{-1} (NH), 1672 and 1649 (C=O).– ^1H NMR ([D6]DMSO): δ = 12.1 (bs, 1H), 10.2 (bs, 1H), 7.60 (d, 2H), 7.40 (d, 1H), 7.28 (t, 2H), 7.20 (d, 1H), 7.01 (m, 1H), 4.4–4.25 (m, 2H), 2.55 (m, 1H), 1.98 (m, 1H), 1.49 (m, 1H), 1.27 (t, 3H), 1.22 (m, 1H).

*E-3-(2-Phenylcarbamoylcyclopropyl)-4,6-dichloroindole-2-carboxylic Acid (**30**)*

$LiOH \cdot H_2O$ (21 mg, 0.9 mmol) was added to a suspension of intermediate **29** (125 mg, 0.3 mmol) in 80% EtOH and the resulting mixture was stirred at 50 °C for 3 h. The mixture was cooled to room temperature, the pH adjusted to 3 and the desired product 30 was obtained for precipitation in almost quantitative yield.– IR (Nujol) ν = 3400–3150 cm^{-1} (NH), 1670 and 1597 (C=O).– ^1H NMR ([D6]DMSO): δ = 11.2 (bs, 1H), 10.8 (bs, 1H), 7.59 (d, 2H), 7.29 (d, 1H), 7.26 (t, 2H), 6.97(t, 1H), 6.95 (d, 1H), 2.32 (m, 1H), 2.21 (m, 1H), 1.40 (m, 1H), 1.31 (m, 1H). MS *m/z* 390 $[M + H]^+$.

*E-1-(2-(Trimethylsilyl)ethoxymethyl)-3-(2-phenylcarbamoylvinyl)-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (**31**)*

To a solution of **1** (120 mg, 0.3 mmol) (prepared according to ref. [22] in dry DMF, a 1 M solution of LHMDS in THF (0.36 mL, 0.36 mmol) was added at 0 °C followed by SEMCl (0.0 64 mL, 0.36 mmol). The solution was left under stirring at room temperature for 1h, concentrated, poured onto water and extracted with AcOEt. The organic phase dried over sodium sulphate, filtered and evaporated to dryness. The crude product was purified by flash chromatography (CyH/AcOEt 90:10) to give the desired product **31** in 80% yield.– IR (Nujol) ν = 3206 cm^{-1} (NH), 1703 and 1659 (C=O), 1618 and 1603 (C=C).– ^1H NMR ([D6]DMSO): δ = 10.22 (s, 1H), 8.13 (d, 1H),

7.97 (d, 1H), 7.70 (d, 2H), 7.44 (d, 1H), 7.33 (t, 2H), 7.07 (t, 1H), 6.44 (d, 1H), 5.83 (s 2H), 4. 39 (q, 2H), 3.41 (t, 2H), 1.29 (t, 3H), 0.77 (t, 2H), -0.12 (s, 9H).

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