

Synthetic studies towards the development of a novel class of acitretin-type retinoids

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Dedicated to Professor Anastasios Varvoglis on the occasion of his 65th birthday

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Abstract

3,4,5-Trimethoxyaniline, indole-3-carboxylic acid and the dicarboxylic acids fumaric, maleic, succinic and phthalic have been combined to produce novel analogs of the aromatic retinoid acitretin. These analogs are characterized by a highly electron-rich benzene ring in the lipophilic part and two amide bonds, replacing the C7-C8 and C11-C12 double bonds, with simultaneous restriction of the C9-C10 double bond, in the spacer compared to acitretin. In addition, the terminal *trans* C13-C14 double bond has been either retained or isomerized or reduced or incorporated within an indole nucleus with simultaneous replacement of the carboxy group by the indole imine function. The related syntheses involved coupling of the *N*-Boc protected indole-3-carboxylic acid with 3,4,5-trimethoxyaniline, acid-mediated removal of the Boc group, coupling of the thus obtained anilide with the anhydrides or suitable monoesters of the above mentioned dicarboxylic acids in liquid or on solid phase and finally deprotection.

Keywords: Acitretin analogs, anilines, dicarboxylic acids, indole-3-carboxylic acid, protecting groups, retinoids

Introduction

Retinoids, a large family of natural and synthetic compounds structurally related to vitamin A (retinol, **1**), play an important role in a variety of biological functions, including vision, development, reproduction and cell differentiation and have been applied successfully to the management of severe and recalcitrant skin disorders and more recently to cancer prevention and therapy. In particular, the synthetic analogs of *all-trans*-retinoic acid (**2**) 13-*cis*-retinoic acid (isotretinoin, **3**) and acitretin (**4**) are presently regarded as the drugs of choice for the treatment of acne and rosacea and psoriasis, ichthyosis, Darier's disease and other keratinization disorders, respectively. However, retinoids are toxic compounds in large doses, cause skin inflammation, hyperlipidemia and severe neurological abnormalities and are teratogenic. In order to improve the therapeutic efficacy to toxicity index as well as to develop better selectivities for various

therapeutic applications, e.g. in dermatology, oncology, rheumatology, immunology etc, a huge array of analogs has been synthesized and their biological activity determined. These analogs incorporate changes in one or more of the three discrete structural parts of the parent retinoid **2**, namely the lipophilic part (the polymethylated cyclohexene ring), the hydrophilic part (the carboxy function) and the spacer (the polyene chain). For example, in isotretinoin (**3**) the natural (*trans*) configuration of the 13-double bond has changed to *cis*, in acitretin (**4**) the lipophilic part has been replaced by a lipophilic/electron rich aromatic ring, in amide **5** a double bond has been replaced by its isosteric amide bond whereas in both the amide **5** and the arotinoid Ro13-7410 (**6**, Figure 1) conformational restrains have been introduced into the molecules in the form of aromatic rings.¹

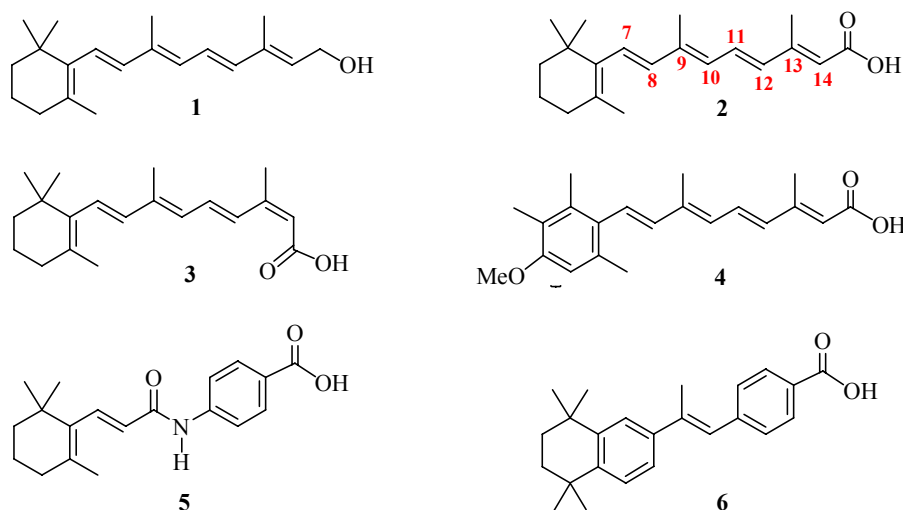


Figure 1. Structures of natural and synthetic retinoids relevant to this work.

The current practice to develop new retinoid-type drugs involves the synthesis of ligands for the nuclear receptors of retinoic acid $RAR_{\alpha,\beta,\gamma}$ and $RXR_{\alpha,\beta,\gamma}$ and the orphan receptors through which gene expression is regulated.² Recent studies, however, have shown that natural (**1** and **2**) and synthetic (**3** and **4**) retinoids, currently used as antipsoriatic agents, inhibit the enzyme RNase P isolated from the slime mold *Dictyostelium discoideum*, the most potent inhibitor being acitretin (**4**). Arotinoid Ro13-7410 is also a strong inhibitor of this enzyme. These studies showed that the retinoids also regulate, most possibly through allosteric interactions with lipophilic site(s) of RNase P, the activity of enzymes playing a decisive role in the biosynthesis of macromolecules and that important structural features for stronger interactions are the hydrophilic carboxy function and the hydrophobic substituted aromatic ring, whereas the configuration of the double bond in position 13 seemed not to play an important role.³ We now wish to report on our initial synthetic efforts to develop a new class of retinoids, in which the parent structure of acitretin is changed in the following ways. One or more methoxy groups are introduced in the lipophilic part of the molecule to increase the electron density of the aromatic nucleus, two of the double bonds, namely C7-C8 and C11-C12, of the spacer are replaced by isosteric amide bonds whereas one of the double bonds, namely C9-C10, is restrained within an

heterocyclic ring (Figure 2). The structural diversity projected for this class of acitretin analogs can be secured by a combination of (a) polymethoxylated anilines (e.g. 2,4-dimethoxy- and 3,4,5-trimethoxyaniline) to provide the lipophilic part of the molecules, (b) suitable heterocyclic amino acids (e.g. indole- or pyrrole-3-carboxylic acid) to build on the spacer and incorporate a conformational restriction (e.g. structures **7-9a**)⁴ and (c) an unsaturated 1,4-dicarboxylic acid to complete the spacer and provide the carboxy group (e.g. structures **7a-c**). The latter could be furthermore replaced by the relatively acidic NH group of the indole nucleus (structure **7e**) whereas the double bond next to the carboxy group can be replaced by an ethylene group to increase conformational freedom in this part of the molecule (structure **7d**). For the purpose of the present studies we chose to use the commercially available 3,4,5-trimethoxyaniline and indole-3-carboxylic acid to build up the right half part of the molecules, whereas the other half was provided by the also commercially available fumaric, maleic, succinic and phthalic acids.

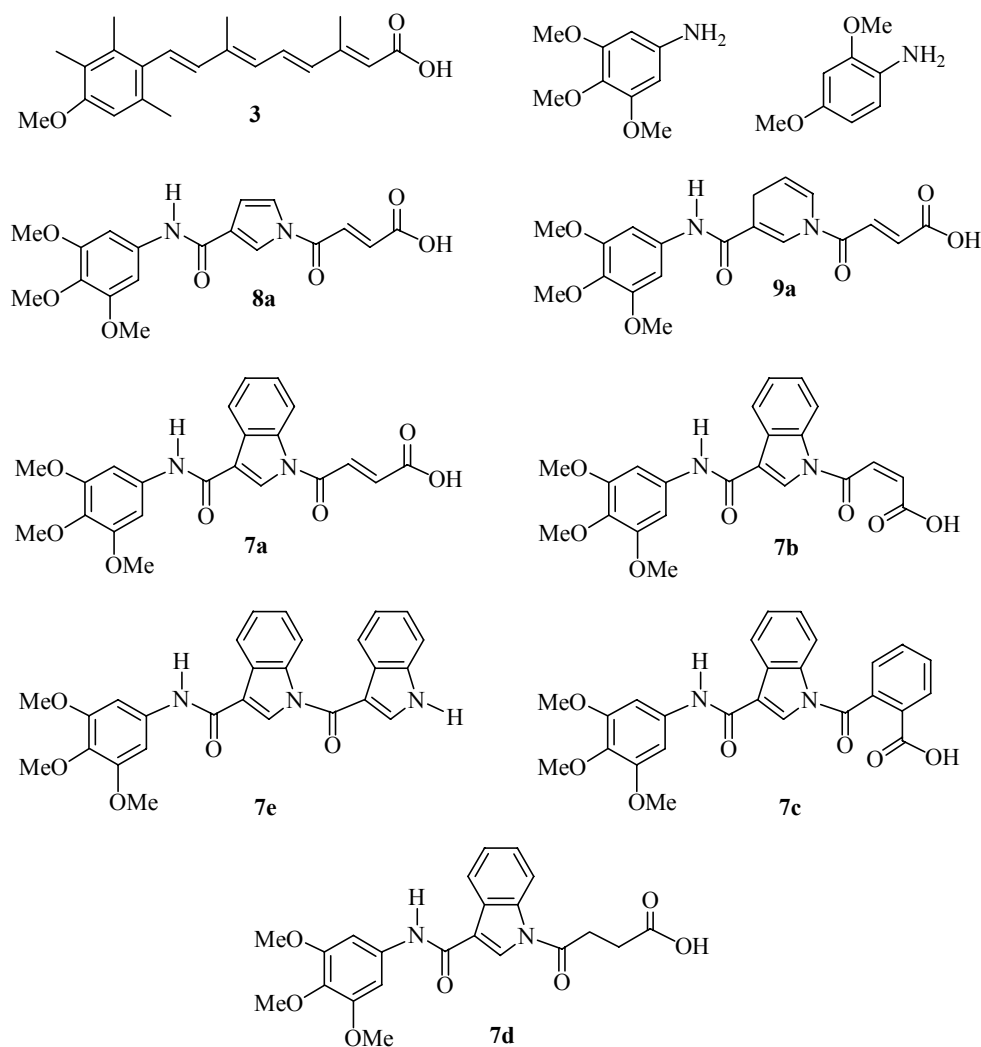
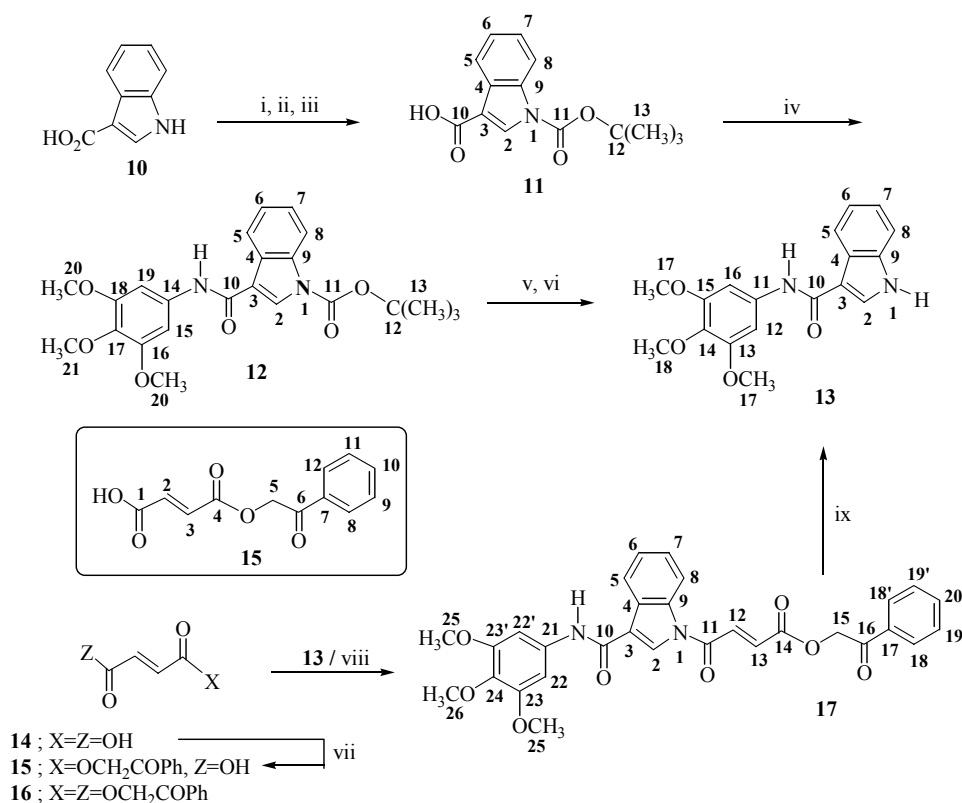


Figure 2. Structures of the new acitretin analogs described in this work.

Results and Discussion

Synthesis of the key-intermediate anilide **13** and the acitretin analog **7a**

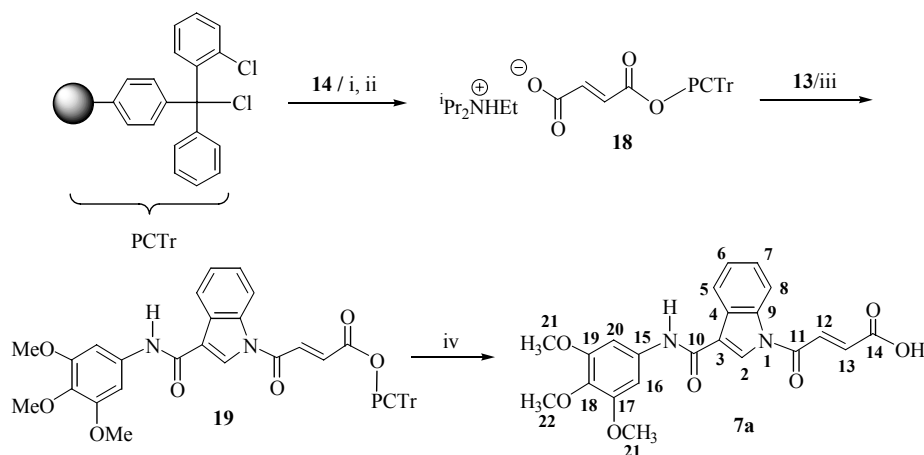
Taking into consideration that all projected synthetic targets **7a-e** share as the common structural feature the anilide **13** (see Scheme 1), we decided to develop first an efficient method for the preparation of this key-intermediate. We envisaged that coupling of 3,4,5-trimethoxyaniline with a suitably *N*-protected derivative of indole-3-carboxylic acid (**10**), followed by deprotection, would provide an ease access to anilide **13**. The imino function in pyrroles or indole and derivatives, e.g. amino acids incorporating the indole heterocycle, has been traditionally protected with the *tert*-butoxycarbonyl (Boc) group. This protecting group is cleanly introduced in such molecules using di-*tert*-butyl dicarbonate (Boc₂O) in the presence of 4-dimethylaminopyridine (DMAP) and MeCN as the solvent and can be then readily removed by trifluoroacetic acid (TFA)-mediated acidolysis.⁵



Scheme 1. Synthesis of the key-intermediate anilide **13**. *Reagents and conditions* : (i) Me₃SiCl/ⁱPr₂NEt, CHCl₃/MeCN (3:2), reflux, 30 min; (ii) Boc₂O/cat. DMAP, reflux, 2.5 h then 25°C, 16 h; (iii) MeOH, 60%; (iv) 3,4,5-trimethoxyaniline/PyBrOP/ⁱPr₂NEt, CHCl₃, 25°C, 16 h, 81%; (v) CF₃CO₂H/CH₂Cl₂ (1:1), 25°C, 1 h; (vi) 5% aqueous NaHCO₃, 60%; (vii) PhCOCH₂Br/ⁱPr₂NEt, DMF, 25°C, 16 h, 34%; (viii) PyBrOP/ⁱPr₂NEt/cat. DMAP, CHCl₃/MeCN (1:1), 25°C, 5 min, 70%; (ix) PhSH/NaH/cat. imidazole, DMF, 25°C, 4 h, 85%.

We preferred to use an alternative method for the introduction of the Boc group into amino acid **10** which involved persilylation of the latter with Me_3SiCl in CHCl_3 and MeCN in the presence of *N,N*-diisopropylethylamine (DIPEA) and DMAP, followed by Boc_2O -mediated N-Si bond splitting and finally methanolysis of the resulting trimethylsilyl ester.⁶ Accordingly, the Boc-protected derivative **11** was obtained in 66% yield. Coupling of this acid with 3,4,5-trimethoxyaniline was best performed in the presence of the strong coupling agent bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) and DIPEA in CHCl_3 to give the expected anilide **12** in 81 % yield. Finally, treatment of Boc-protected anilide **12** with a 50% solution of TFA in CH_2Cl_2 for 1 h at ambient temperature effected its complete deprotection. From the thus obtained trifluoroacetate salt, the free anilide **13** was obtained in 60% yield after routine neutralization with a 5% aqueous NaHCO_3 solution.

Attachment of the fumaryl unit to anilide **13** required the selective protection of one of its carboxy functions. Based on previous work of our group on the selective protection of α,ω -dicarboxylic acids and their use to effect intermolecular bridging of polyamine moieties,⁷ we decided to use the phenacyl group for this purpose. This group is readily introduced into the carboxy function, monoprotected derivatives are readily separated by flash column chromatography (FCC) from the undesired byproducts from diesterification and finally it is efficiently removed under mild reaction conditions with sodium thiophenolate. Thus, reaction of fumaric acid (**14**) with phenacyl bromide in DMF in the presence of DIPEA provided the anticipated monophenacyl ester **15** along with the diphenacyl ester **16**. From this reaction mixture, monoester **15** was readily isolated in 34% yield through routine FCC. Coupling of this compound with anilide **13** in $\text{CHCl}_3/\text{MeCN}$ (1:1) in the presence of PyBrOP, DIPEA and a catalytic quantity of DMAP proceeded unexceptionally to provide the phenacyl ester **17** in 70% yield. However, the sodium thiophenolate-mediated attempted removal of the phenacyl group resulted instead to the removal of the fumaryl moiety, due to an unexpected cleavage of the N^{ind} -CO amide bond, as evidenced by the recovery of the anilide **13** in 85% yield.

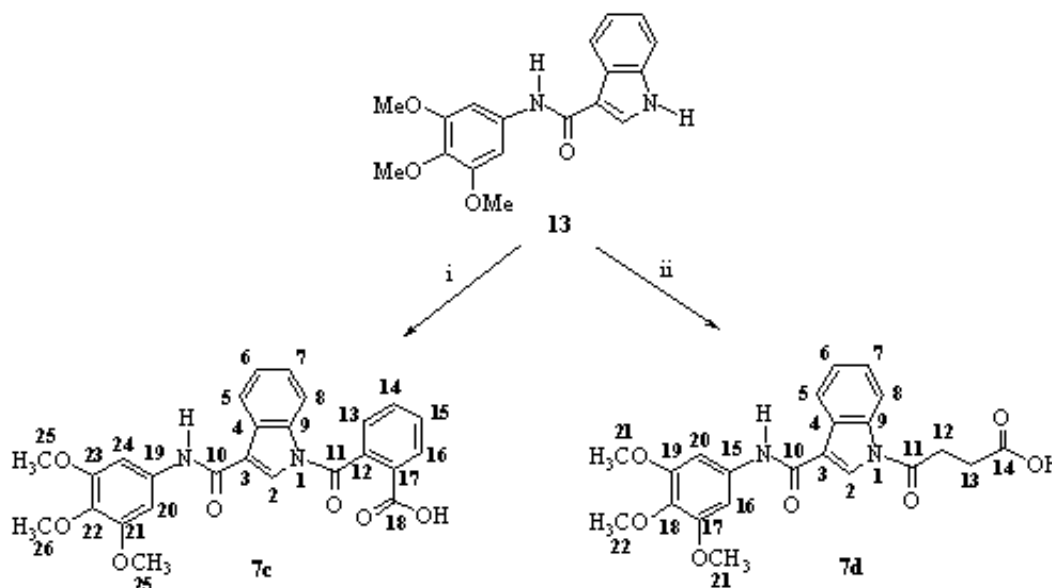


Scheme 2. Solid phase synthesis of acitretin analog **7a**. *Reagents and conditions* : (i) $^i\text{Pr}_2\text{NHEt}$, DMF, 0°C , 30 min then 25°C , 16 h; (ii) MeOH, 25°C , 1 h; (iii) PyBrOP/ $^i\text{Pr}_2\text{NHEt}$, $\text{CH}_2\text{Cl}_2/\text{DMF}$ (9:1), 25°C , 16 h; (iv) $\text{CH}_2\text{Cl}_2/\text{CF}_3\text{CH}_2\text{OH}/\text{CF}_3\text{CO}_2\text{H}$ (8:4:1), CH_2Cl_2 , 25°C , 1 h, 85%.

Prompted by this result we then turned our attention to carboxy protecting groups cleaved by acids and in particular of the triphenylmethyl (trityl) type, e.g. the *o*-chlorotrityl group known to be cleaved under very mild acidic conditions. In addition, we decided to use its polymeric version, namely the *o*-chlorotrityl resin (PCTr),⁸ in order to further improve its selectivity towards monoesterification. Indeed, treatment of PCTr-Cl resin (1.5 meq Cl/g resin) with fumaric acid in DMF in the presence of excess DIPEA at ambient temperature for overnight provided the polymeric monoester **18** (Scheme 2) with a calculated substitution of *ca.* 0.5 mmol fumarate/g resin. Ester **18** was further reacted with the anilide **13** in CH₂Cl₂/DMF (12:1) in the presence of PyBrOP and DIPEA to give the expected polymeric bisamide **19**. Finally, this resin was swallowed in CH₂Cl₂ and then treated with a solution consisted of CH₂Cl₂, trifluoroethanol (TFE) and TFA (*ca.* 8:4:1) for 1h at ambient temperature to split off the resin the acitretin analog **7a**, free of byproducts. Analog **7a** was thus obtained in 85% overall yield based on the calculated substitution of resin **18**.

Reaction of anilide **13** with anhydrides *en route* to acitretin analogs **7c** and **d**

We have recently developed a methodology to bridge polyamine moieties inter- or intramolecularly using as the key-step the reaction of suitably *N*-trityl protected polyamines with anhydrides of dicarboxylic acids, e.g succinic anhydride.^{7,9} We therefore reasoned that the acitretin analog **7d** could be readily accessed through the reaction of anilide **13** with succinic anhydride. Indeed, reaction of anilide **13** with succinic anhydride in CH₂Cl₂ in the presence of Et₃N and a catalytic quantity of DMAP produced unexceptionally the acitretin analog **7d** in 47% yield (Scheme 3). Unfortunately, attempts to apply this reaction to maleic anhydride in order to produce the acitretin analog **7b**, resembling isotretinoin, failed to produce any isolable product.

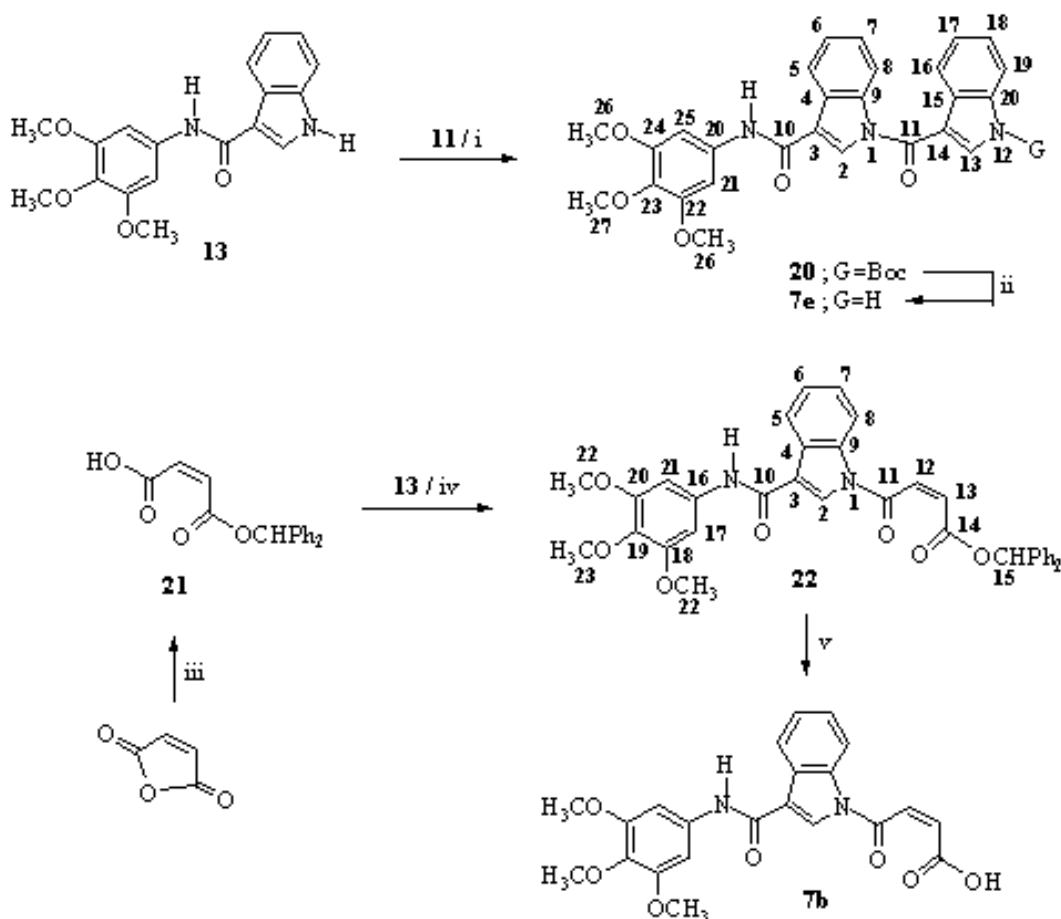


Scheme 3. Synthesis of acitretin analogs **7c** and **d**. *Reagents and conditions* : (i) phthalic anhydride/^tPr₂NEt/cat. DMAP, CH₂Cl₂/MeCN (1:1), 25°C, 15 min, 84%; (ii) succinic anhydride/Et₃N/cat. DMAP, CH₂Cl₂, 25°C, 1 h, 47%.

In sharp contrast was, however, the reaction of anilide **13** with phthalic anhydride. That reaction proceeded in $\text{CH}_2\text{Cl}_2/\text{MeCN}$ (1:1), in the presence of DIPEA and a catalytic quantity of DMAP, at ambient temperature fast and smoothly and produced the anticipated acitretin analog **7c** in 84% yield.

Reaction of anilide **13** with monoprotected dicarboxylic or amino acids *en route* to the acitretin analogs **7b** and **e**

Taking into consideration the fact that acitretin analog **7b** was inaccessible through the direct reaction of anilide **13** with maleic anhydride, we decided to use a suitable monoester of maleic acid in order to introduce the maleyl moiety to the target molecule. We thought that the monodiphenylmethyl ester **21** would be a good candidate because the benzhydryl protecting group is readily removed from a carboxy function under mild acidic conditions. Indeed, reaction of benzhydrol with maleic anhydride in CH_2Cl_2 in the presence of Et_3N and a catalytic quantity of DMAP produced monoester **21** in 74% yield (Scheme 4).



Scheme 4. Synthetic pathways to acitretin analogs **7b** and **e**. *Reagents and conditions* : (i) $\text{PyBrOP}/^i\text{Pr}_2\text{NEt}/\text{cat. DMAP}$, CHCl_3 , 25°C , 1 h, 83%; (ii) $\text{CF}_3\text{CO}_2\text{H}/\text{CH}_2\text{Cl}_2$ (1:1), 25°C , 1 h, 77%; (iii) $\text{Ph}_2\text{CHOH}/\text{Et}_3\text{N}/\text{cat. DMAP}$, CH_2Cl_2 , 0°C , 30 min then 25°C , 16 h, 74%; (iv) $\text{PyBrOP}/^i\text{Pr}_2\text{NEt}/\text{cat. DMAP}$, CH_2Cl_2 , 25°C , 16 h, 56%; (v) $\text{CF}_3\text{CO}_2\text{H}/\text{CH}_2\text{Cl}_2$ (1:3), 25°C , 5 min, 60%.

Furthermore, condensation of **21** and the anilide **13** in CH₂Cl₂ in the presence of PyBrOP and Et₃N and a catalytic quantity of DMAP proceeded smoothly at ambient temperature and produced the benzhydryl ester **22** in 56% yield. Finally, treatment of this ester with a 25% solution of TFA in CH₂Cl₂ for 5 min at ambient temperature produced the desired acitretin analog **7b** in 60% yield. On the other hand, condensation of anilide **13** with the *N*-Boc protected indole-3-carboxylic acid (**11**) in CHCl₃ in the presence of PyBrOP, DIPEA and a catalytic quantity of DMAP for 1 h at ambient temperature produced the intermediate **20** in 83% yield. This was then treated with a 50% solution of TFA in CH₂Cl₂ for 1 h at ambient temperature to produce the acitretin analog **7e**, incorporating two adjacent indole-3-carboxylic acid units, in 77% yield.

Conclusions

The present studies have shown that novel analogs of the aromatic retinoid acitretin can be readily synthesized by using (a) commercially available compounds, such as the 3,4,5-trimethoxyaniline, indole-3-carboxylic acid and the dicarboxylic acids fumaric, maleic, succinic and phthalic or their anhydrides as building blocks, (b) acid-labile, widely used, amino or carboxy protecting groups like the Boc, the diphenylmethyl and the polymeric *o*-chlorotriptyl groups and (c) the powerful coupling agent PyBrOP to effect amide bond formation. Further applications of this methodology are currently under investigation whereas the biological evaluation of the synthesized analogs as potential RNase P inhibitors and the determination, by detailed NMR studies, of their preferred conformations in solution are now in progress.

Experimental Section

General Procedures. Melting points were determined with a Büchi SMP-20 apparatus and are uncorrected. IR spectra were recorded for KBr pellets on a Perkin Elmer 16PC FT-IR spectrophotometer. ¹H-NMR spectra were obtained at 400.13 MHz and ¹³C-NMR spectra at 100.62 MHz on a Bruker DPX spectrometer. CDCl₃ and tetramethylsilane (TMS) were used as the solvent and internal standard, respectively, unless otherwise stated. Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS. The assignments of the ¹H spectra are based on chemical shift arguments, analysis of coupling patterns and signal intensities whereas the ¹³C spectra were assigned taking into consideration chemical shift arguments. Electron-spray ionization (ESI) mass spectra were recorded on a Micromass-Platform LC spectrometer using MeOH or MeCN as solvents. Microanalyses were performed on a Carlo Erba EA 1108 CHNS elemental analyzer in the Center for Instrumental Analysis of the University of Patras.

Flash column chromatography (FCC) was performed on Merck silica gel 60 (230-400 mesh) and TLC on 60 Merck 60F₂₅₄ films (0.2 mm) precoated on aluminium foil. The solvent or solvent systems used for elution were: (A) CHCl₃/MeOH/conc. NH₃ (9:1:0.1), (B) CHCl₃/MeOH

(8:2), (C) CHCl₃/MeOH (9.5:0.5), (D) EtOAc, (E) PhMe/EtOAc (1:1), (F) PhMe/EtOAc (7:3), (G) PhMe/EtOAc (8:2), (H) CHCl₃/MeOH/gl. AcOH (8:2:0.5).

Spots were visualized with UV light at 254 nm and the charring agent (NH₄)₂SO₄-conc. H₂SO₄-H₂O (20 g - 4 mL - 100 mL). All solvents (Merck) were dried and/or purified according to standard procedures prior to use. Anhydrous Na₂SO₄ was used for drying organic solvents and subsequently solvents were routinely removed at ca. 40 °C under reduced pressure (water aspirator). All reagents employed in the present work were purchased from Aldrich and used without further purification. The *o*-chlorotriptyl chloride resin (PCTr-Cl) was purchased from CBL Patras and had a substitution of 1.5 meq Cl/g resin. With the exception of TFA-mediated deprotections, all other reactions were routinely carried out under an atmosphere of Ar. Yields of the reactions described below are not optimized.

***N*-(*tert*-Butoxycarbonyl)-indole-3-carboxylic acid (11).** To an ice-cold (0 °C), magnetically stirred, suspension of indole-3-carboxylic acid (6 g, 37.2 mmol) in anhydrous CHCl₃ (55 mL) and MeCN (37 mL) Me₃SiCl (10.4 mL, 82 mmol) and DIPEA (14.6 mL, 84 mmol) were added sequentially. The reaction mixture was allowed to attain ambient temperature and then refluxed for 30 min. The resulting solution allowed to attain ambient temperature, treated sequentially with DMAP (0.9 g, 7.4 mmol) and Boc₂O (12.2 g, 55.8 mmol), then refluxed for 2.5 h and finally left at ambient temperature for overnight. The thus obtained reaction mixture was treated with MeOH (10 mL) and then evaporated to dryness. The residue was treated with 100 mL of 5% aqueous citric acid and extracted twice with 80 mL of ethyl acetate (EtOAc). The organic layers were combined and sequentially washed twice with H₂O and once with saturated aqueous NaCl (brine). The organic phase was dried and evaporated to dryness. The crude product was crystallized from EtOAc to give 3.86 g of pure acid **11**. An additional quantity (2.54 g) of pure acid **11** is obtained on concentrating the mother liquid to dryness and subjecting the residue to FCC using the solvent system C as eluant raising the yield to 66%. Acid **11** had m.p. 240-41 °C, R_f (C) 0.36. Anal. Calcd for C₁₄H₁₅NO₄ (261.28): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.47; H, 5.45, N, 5.20. IR: 3200-2400 (OH), 1751 (N-CO-O), 1684 (CO-OH) cm⁻¹. ESI-MS (m/z): 284.39 (MNa), 262.28 (MH). ¹H NMR: δ 8.428 (1H, s, H-2), 8.258 and 8.242 (2H, two dd, *J* 6.62 and 1.83 Hz, H-5 and H-8), 7.441 and 7.414 (2H, two td, *J* 7.31 and 1.53 Hz, H-6 and H-7), 1.748 (9H, s, H-13) ppm. ¹³C NMR: δ 169.84 (C-10), 149.27 (C-11), 136.07 (C-9), 133.78 (C-2), 127.94 (C-3), 125.65 (C-5), 124.52 (C-8), 122.16 (C-6), 115.62 (C-7), 112.17 (C-4), 85.69 (C-12) 28.50 (C-13) ppm.

***N*-(*tert*-Butoxycarbonyl)-3',4',5'-trimethoxy-indole-3-carboxanilide (12).** To a magnetic-ally stirred solution of acid **11** (3.6 g, 13.8 mmol) and 3,4,5-trimethoxyaniline (2.52 g, 13.8 mmol) in dry CHCl₃ (20 mL) anhydrous DIPEA (9.6 mL, 55.2 mmol) and PyBrOP (9.78 g, 21 mmol) were added sequentially. The thus obtained dark colored solution was kept at ambient temperature for overnight, then diluted with CHCl₃ and finally washed sequentially once with a 5% aqueous NaHCO₃ solution, twice with H₂O and brine. Drying and evaporation to dryness left a residue, from which pure amide **12** (4.77 g, 81% yield) was obtained through FCC using solvent system F as eluant. Amide **12** had m.p. 165-66 °C, R_f (F) 0.43. Anal. Calcd for C₂₃H₂₆N₂O₆ (426.47): C, 64.78; H, 6.15; N, 6.57. Found: C, 64.50; H, 6.46, N, 6.71.

IR: 3300 (*NH-CO*), 1737 (*N-CO-O*), 1636 (*NH-CO*) cm^{-1} . ESI-MS (*m/z*): 875.50 ($2M+\text{Na}$), 449.18 ($M\text{Na}$), 427.12 (*MH*). ^1H NMR: δ 8.191 (1H, d, $J = 8.40$ Hz, H-8), 8.180 (1H, s, H-2), 8.115 (1H, d, $J = 7.6$ Hz, H-5), 7.710 (1H, s, NH), 7.412 (1H, t, $J = 7.2$ Hz, H-7), 7.371 (1H, t, $J = 7.2$ Hz, H-6), 6.971 (2H, s, H-15 and H-19), 3.886 (6H, s, H-20), 3.842 (3H, s, H-21), 1.701 (9H, s, H-13) ppm. ^{13}C NMR: δ 162.52 (C-10), 153.88 (C-11), 149.51 (C-16 and C-18), 136.03 (C-17), 134.35 (C-14 and C-2), 128.19 (C-9), 127.69 (C-3), 125.79 (C-5), 124.36 (C-8), 121.25 (C-6), 116.86 (C-4), 115.88 (C-7), 98.53 (C-15 and C-19), 85.61 (C-12), 61.35 (C-21), 56.62 (C-20), 28.52 (C-13) ppm.

3',4',5'-Trimethoxy-indole-3-carboxanilide (13). A solution of the amide **12** (2.86 g, 6.7 mmol) in CH_2Cl_2 (10 mL) and TFA (10 mL) was kept at ambient temperature for 1 h and then evaporated to dryness. Addition of Et_2O and overnight refrigeration gave a precipitate, which upon filtration, washing with more Et_2O and drying gave anilide **13** as its trifluoroacetate salt. This was then added to an excess of a 5% aqueous NaHCO_3 solution and extracted twice with EtOAc . The organic layers were combined and washed twice with H_2O , dried and evaporated to leave a residue. Addition of Et_2O and overnight refrigeration gave pure free anilide **12** (1.32 g, 60%).

Anilide **13** had m.p. 201-02 $^\circ\text{C}$, $R_f(\text{A})$ 0.33. Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$ (326.36): C, 66.25; H, 5.56; N, 8.59. Found: C, 66.17; H, 5.60; N, 8.79.

IR: 3339 (*NH-CO*), 3170 (NH), 1646 (*NH-CO*) cm^{-1} . ESI-MS (*m/z*): 675.35 ($2M+\text{Na}$), 349.28 ($M\text{Na}$), 327.32 (*MH*). ^1H NMR: δ 10.962 (1H, br. s, NH), 9.002 (1H, s, *NHCO*), 8.261 (1H, m, H-8), 8.070 (1H, d, J 2.92 Hz, H-2), 7.453 (1H, m, H-5), 7.236 (2H, m, H-6 and H-7), 7.173 (2H, s, H-12 and H-16) ppm. ^{13}C NMR: δ 166.52 (C-10), 153.35 (C-13 and C-15), 135.99 (C-11), 134.01 (C-2), 128.70 (C-3), 126.34 (C-4), 122.81 (C-9), 121.46 (C-6), 121.37 (C-7), 112.29 (C-5), 111.87 (C-8), 98.17 (C-12 and C-16), 61.15 (C-18), 56.31 (C-17) ppm.

Fumaric acid monophenacyl ester (15). To a magnetically stirred solution of fumaric acid (**14**) (4.64 g, 40 mmol) and DIPEA (8 mL, 44 mmol) in anhydrous DMF (40 mL) phenacyl bromide (7.96 g, 40 mmol) was added in small portions within 1 h at ambient temperature. Stirring was continued overnight and then the resulting reaction mixture was diluted with EtOAc . Following filtration, the organic phase was washed sequentially twice with a 5% aqueous citric acid solution, H_2O and brine and dried. Evaporation of the solvent left a residue which was crystallized with EtOAc to give 3.18 g (34% yield) of pure product. Monoester **15** had m.p. 154-55 $^\circ\text{C}$, $R_f(\text{D})$: 0.2. Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{O}_5$ (234.21): C, 61.54; H, 4.30. Found: C, 61.42; H, 4.47.

IR: 3260-2500 (*CO-OH*), 1734 (*CO-O*), 1710 (*Ph-CO*) cm^{-1} . ^1H NMR (DMSO-d_6): δ 8.006 (2H, d, J 7.51 Hz, H-8 and H-12), 7.729 (1H, t, J 7.35 Hz, H-10), 7.598 (2H, t, J 7.60 Hz, H-9 and H-11), 6.869 (1H, d, J 15.7 Hz, H-2), 6.616 (1H, d, J 15.7 Hz, H-3), 5.639 (2H, s, H-5) ppm. ^{13}C NMR: δ 193.34 (C-6), 167.54 (C-4), 165.84 (C-1), 141.77 (C-7), 134.87 (C-2), 134.68 (C-3), 129.80 (C-8 and C-2), 128.74 (C-10), 128.66 (C-9 and C-11), 67.82 (C-5) ppm.

***N*-(*O*-Phenacylfumaryl)-3',4',5'-trimethoxy-indole-3-carboxanilide (17).** To a magnetically stirred solution of anilide **13** (0.66 g, 2 mmol), fumaric acid derivative **15** (0.46 g, 2 mmol), a catalytic quantity of DMAP (2.5 mg, 0.02 mmol) and DIPEA (1 mL, 6 mmol) in anhydrous CHCl_3 (2 mL) and MeCN (2 mL) PyBrOP (1.16 g, 2.5 mmol) was added. From the resulting solution a yellow precipitate is formed after 5 min at ambient temperature. The yellow

precipitate, namely pure product **17**, is obtained by filtration and washing with cold CHCl_3 . The filtrate was washed sequentially once with a 5% aqueous NaHCO_3 solution and twice with H_2O , dried and evaporated to leave a residue. From this residue a further quantity of product **17** is obtained through FCC using as eluant the solvent system E. Totally 0.76 g (70% yield) of product **17** were obtained which had $R_f(\text{E})$ 0.51. Anal. Calcd for $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_8$ (542.55): C, 66.41; H, 4.83; N, 5.16. Found: C, 66.75; H, 4.62; N, 4.93. ESI-MS (m/z): 565.46 ($M\text{Na}$), 543.52 ($M\text{H}$). ^1H NMR (DMSO-d_6): δ 10.160 (1H, s, NH), 9.023 (1H, s, H-2), 8.533 (1H, d, J 7.8 Hz, H-8), 8.378 (1H, d, J 6.96 Hz, H-5), 8.094 (3H, two d, J 7.67 Hz, H-18 and H-18' and J 15.09 Hz, H-12), 7.769 (1H, t, J 7.4 Hz, H-20), 7.665 (2H, t, J 7.64 Hz, H-19 and H-19'), 7.541 and 7.498 (2H, two t, J 6.56 Hz, H-6 and H-7), 7.296 (1H, d, J 15.28 Hz, H-13), 7.235 (2H, s, H-22 and H-22'), 5.835 (2H, s, H-15), 3.869 (6H, s, H-25), 3.719 (3H, s, H-26) ppm. ^{13}C NMR: δ 192.96 (C-16), 164.95, 163.76 and 162.51 (C-10/C-11/C-14), 153.59 (C-23 and C-23'), 136.19-116.74 (aromatic and vinylic carbons), 98.71 (C-6 and C-7), 68.47 (C-15), 67.88 (C-25), 56.69 (C-26) ppm.

Attempted dephenacylation of 17-recovery of anilide (13). To an ice-cold (0°C) magnetically stirred suspension of NaH (30 mg, 0.75 mmol) in anhydrous DMF thiophenol (0.08 mL, 0.75 mmol) and a catalytic quantity of imidazole were added. Following complete dissolution of NaH, the bisamide **17** (0.27 g, 0.5 mmol) was added and the resulting solution was allowed to attain ambient temperature where it left to stand for 4 h. It was then diluted with an ice-cold 5% aqueous solution citric acid, extracted twice with EtOAc and the organic layers were combined washed twice with H_2O , dried and evaporated to give an oily residue. From this, 0.14 g (85 % yield) of anilide **13** was obtained through FCC using as eluant the solvent system E.

Polymeric *N,N*-diisopropylethylammonium salt of fumaric acid mono-*o*-chlorotryl ester (18). PCTr-Cl resin (2.0130 g, 3.02 meq Cl) was swallowed with DMF (10 mL), ice-cooled (0°C) and treated sequentially with DIPEA (2.8 mL, 16 mmol) and fumaric acid (**14**) (0.70 g, 6 mmol). The resulting reaction mixture was shaken at that temperature for 30 min and then for overnight at ambient temperature. MeOH (1 mL) was then introduced into the reaction mixture, shaking was continued for a further 1 h and then filtered. Resin was then washed on the filter sequentially twice with DMF, MeOH, CH_2Cl_2 and again twice DMF, MeOH and finally Et_2O . Drying overnight under high vacuum gave resin **18** (2.2118 g) with a calcd substitution of 0.476 mmol/g resin. IR : 1720 (CO-O), 1644 (C=C) cm^{-1} .

Polymeric *N*-[*O*-(*o*-chloro)tritylfumaryl]-3',4',5'-trimethoxy-indole-3-carboxanilide (19). To resin **18** (1.4834 g, 0.706 mmol), swallowed with CH_2Cl_2 (8.5 mL), was added sequentially DIPEA (0.6 mL, 3.5 mmol), the anilide **13** (0.57 g, 1.75 mmol) and DMF (0.7 mL) and finally PyBrOP (0.82 g, 1.75 mmol). The resulting reaction mixture was shaken overnight and then the resin was filtered off and washed on the filter sequentially twice with DMF, MeOH, CH_2Cl_2 and again twice with DMF and MeOH and finally Et_2O . Drying under high vacuum for overnight gave 1.626 g of resin **19**. IR : 1736 (CO-O), 1706 (CO-N), 1654 (C=C and CO-NH) cm^{-1} .

***N*-Fumaryl-3',4',5'-trimethoxy-indole-3-carboxanilide (7a).** Resin **19** (1.6260 g) was swallowed with CH_2Cl_2 (8 mL) and then shaken with a solution made-up of CH_2Cl_2 (10.75 mL), TFE (5 mL) and TFA (1.25 mL) for 1 h at ambient temperature. The resin was then filtered and washed on the filter sequentially twice with a solution made-up of CH_2Cl_2 (16 mL) and TFE (4 mL) and DMF (2 x 10 mL). Volatile solvents were removed under reduced pressure and the

residual DMF solution was refrigerated overnight to afford a yellow precipitate. The precipitate was discarded by filtration and the filtrate was diluted with EtOAc and washed twice with H₂O and once with brine. Drying and evaporation gave 0.17 g (85% overall yield based on the calcd substitution of resin **18**) of pure product **7a**. Acid **7a** had m.p. 253-54 °C, R_f (B) 0.14. Anal. Calcd for C₂₂H₂₀N₂O₇ (424.41): C, 62.26; H, 4.75; N, 6.60. Found: C, 61.95; H, 4.83; N, 6.79.

IR: 3349 (NH-CO), 3200-2400 (CO-OH), 1710 (N-CO and CO-OH), 1650 (C=C), 1615 (NH-CO) cm⁻¹. ESI-MS (m/z): 463.07 (MK), 447.06 (MNa), 425.07 (MH). ¹H NMR: δ 11.707 (1H, s, OH), 10.056 (1H, s, NH), 8.922 (1H, s, H-2), 8.415 (1H, d, *J* 7.60 Hz, H-8), 8.281 (1H, d, *J* 7.60 Hz, H-5), 7.835 (1H, d, *J* 15.20 Hz, H-12), 7.431 (1H, t, *J* 7.20 Hz, H-7), 7.392 (1H, t, *J* 7.20 Hz, H-6), 7.144 (2H, s, H-16 and H-20), 6.986 (1H, d, *J* 15.20 Hz, H-13), 3.786 (6H, s, H-21), 3.631 (3H, s, H-22) ppm. ¹³C NMR: δ 166.75, 164.14 and 162.42 (C-10/C-11/C-14), 153.61 (C-17 and C-19), 136.86-117.03 (12 C, aromatic and vinylic carbons), 98.76 (C-6 and C-7) 61.01 (C-22), 56.70 (C-21) ppm

N-Phthalyl-3',4',5'-trimethoxy-indole-3-carboxanilide (7c). To a magnetically stirred solution of anilide **13** (0.26 g, 0.80 mmol), DIPEA (0.18 mL, 1 mmol) and DMAP (12 mg, 0.1 mmol) in anhydrous CH₂Cl₂ (0.8 mL) and MeCN (0.8 mL) phthalic anhydride (0.14 g, 0.88 mmol) was added. After 15 min at ambient temperature the reaction mixture was diluted with CHCl₃ and washed once with an ice-cold 5% aqueous citric acid solution and twice with H₂O. Drying and evaporation to dryness left a residue from which 0.32 g (84% yield) pure product **7c** was obtained as a white powder through FCC using the solvent system A, pooling the fractions containing the product, washing them with 5% aqueous citric acid solution and H₂O and finally drying, evaporation and trituration with Et₂O. Product **7c** had m.p. 200-01 °C, R_f(A) 0.11. Anal. Calcd for C₂₆H₂₂N₂O₇ (474.47): C, 65.82; H, 4.67; N, 5.90. Found: C, 65.52; H, 4.93; N, 6.08.

IR: 3342 (NH-CO), 3200-2400 (OH), 1639 (CO), 1606 (Ar C=C) cm⁻¹. ESI-MS (m/z): 971.58 (2M+Na), 497.31 (MNa), 475.38 (MH). ¹H NMR: δ 10.407 (1H, s, OH), 8.379 (1H, s, NH), 8.146 (1H, d, *J* 7.28 Hz, H-8), 7.909 (1H, s, H-2), 7.752 (1H, d, *J* 7.41 Hz, H-5), 7.562 (1H, d, *J* 7.29 Hz, H-16), 7.381 (3H, m, H-13, H-14 and H-15), 7.216 (1H, t, *J* 7.23 Hz, H-7), 7.183 (1H, t, *J* 6.88 Hz, H-6), 7.064 (2H, s, H-20 and H-24), 3.808 (6H, s, H-25), 3.793 (3H, s, H-26) ppm.

N-Succinyl-3',4',5'-trimethoxy-indole-3-carboxanilide (7d). To a magnetically stirred solution of anilide **13** (0.2 g, 0.6 mmol), Et₃N (0.09 mL, 0.66 mmol) and a catalytic quantity of DMAP in anhydrous CH₂Cl₂ (1.5 mL) succinic anhydride (0.07 g, 0.66 mmol) was added. After 1 h at ambient temperature the reaction mixture was diluted with CH₂Cl₂ and washed with an ice-cold 5% aqueous citric acid solution. The resulting white precipitate was filtered and washed on the filter sequentially twice with H₂O, MeOH and Et₂O and dried under vacuum to give 0.12 g (47 %) of pure product **7d**. Product **7d** had m.p. 202-03 °C, R_f (B) 0.24. Anal. Calcd for C₂₂H₂₂N₂O₇ (426.43): C, 61.97; H, 5.20; N, 6.57. Found: C, 61.77; H, 5.31; N, 6.77.

IR: 3280 (NH-CO), 3200-2400 (CO-OH), 1740 (N-CO), 1648 (CO-OH) cm⁻¹. ESI-MS (m/z): 876.71 (2M+Na), 853.67 (2M+H), 449.43 (MNa), 427.42 (MH). ¹H NMR (DMSO-d₆): δ 12.367 (1H, br. s, OH), 10.009 (1H, s, NH), 8.838 (1H, s, H-2), 8.350 (1H, d, *J* 8.00 Hz, H-8), 8.183 (1H, d, *J* 7.60 Hz, H-5), 7.392 (1H, t, *J* 7.20 Hz, H-7), 7.349 (1H, d, *J* 7.20 Hz, H-6), 7.159 (2H, s, H-16 and H-20), 3.790 (6H, s, H-21), 3.637 (3H, s, H-22), 3.363 (2H, t, *J* 6.40 Hz, H-12), 2.736 (2H, t, *J* 6.00 Hz, H-13) ppm. ¹³C NMR: δ 173.90, 172.38 and 164.04 (C-10/C-11/C-14),

153.61 (C-17 and C-19), 137.08-111.38 (10 C, aromatic and vinylic carbons), 98.26 (C-6 and C-7) 61.00 (C-22), 56.60 (C-21), 29.62 (C-12 and C-13) ppm

***N*-(Indole-3-carboxyl)-3',4',5'-trimethoxy-indole-3-carboxanilide (7e)**. To a magnetically stirred suspension of acid **11** (0.21 g, 0.8 mmol), anilide **13** (0.26 g, 0.8 mmol), anhydrous DIPEA (0.42 mL, 2.4 mmol) and a catalytic quantity of DMAP in anhydrous CHCl₃ (1.5 mL) PyBrOP (0.47 g, 1 mmol) was added. After 1 h at ambient temperature the resulting solution is diluted with more CHCl₃ and washed once with a 5% aqueous NaHCO₃ solution and twice with H₂O. Drying and evaporation left a residue from which 0.38 g (83% yield) of pure intermediate **20** was obtained as an oil following purification by FCC using as eluant the solvent system G. This compound had R_f (G) 0.37. ESI-MS (m/z) : 592.43 (MNa), 570.50 (MH). It was subsequently dissolved into a 50% solution (8 ml) of TFA in CH₂Cl₂ and kept at ambient temperature for 1 h. Evaporation to dryness, trituration with Et₂O, overnight refrigeration and finally filtration gave **7b** as its corresponding trifluoroacetate salt. This was then added to a 5% aqueous NaHCO₃ solution and extracted twice with EtOAc. The combined organic layers were washed twice with H₂O, dried and evaporated to give 0.24 g (77% yield) of pure **7b**. Bisamide **7b** had m.p. 245-46 °C, R_f (F) 0.22. Anal. Calcd for C₂₇H₂₃N₃O₅ (469.5): C, 69.07; H, 4.94; N, 8.95. Found: C, 68.88; H, 5.12; N, 9.08.

ESI-MS (m/z): 492.27 (MNa), 470.14 (MH). ¹H NMR (DMSO-d₆): δ 12.376 (1H, br. S, H-20), 9.898 (1H, s, NH), 8.883 (1H, s, H-2), 8.333 (1H, d, *J* 8.00 Hz, H-8), 8.323 (1H, s, H-13), 8.228 (1H, d, *J* 8.00 Hz, H-5), 8.073 (1H, d, *J* 7.60 Hz, H-16), 7.593 (1H, d, *J* 8.00 Hz, H-19), 7.390 (1H, t, *J* 6.80 Hz, H-7), 7.355 (1H, t, *J* 6.40 Hz, H-6), 7.313 (1H, t, *J* 7.20 Hz, H-17), 7.390 (1H, t, *J* 6.80 Hz, H-18), 7.157 (2H, s, H-22 and H-26), 3.766 (6H, s, H-27), 3.626 (3H, s, H-28) ppm. ¹³C NMR: δ 164.43 (C-10), 163.02 (C-11), 153.55 (C-23 and C-25), 137.40-108.88 (18 C, aromatic and vinylic carbons), 98.51 (C-6 and C-7) 61.00 (C-28), 56.70 (C-27) ppm

Maleic acid monodiphenylmethyl ester (21). To an ice-cold, magnetically stirred, solution of diphenylmethanol (1.48 g, 8 mmol), anhydrous Et₃N (1.24 mL, 8.8 mmol) and a catalytic quantity of DMAP in anhydrous CH₂Cl₂ (24 mL) maleic anhydride (0.78 g, 8 mmol) was added and the reaction mixture was allowed to stand at that temperature for 30 min and then for overnight at ambient temperature. The resulting solution was diluted with more CH₂Cl₂, washed once with an ice-cold 5% aqueous citric acid solution and twice with H₂O. Drying and evaporation left 1.68 g (74% yield) of the product **21** as an oil. Acid **21** had R_f(D) 0.31. Anal. Calcd for C₁₇H₁₄O₄ (282.30): C, 72.33; H, 5.00. Found: C, 72.57; H, 4.86.

IR: 3200-2400 (CO-OH), 1727 (br., CO-O and CO-OH), 1646 (C=C) cm⁻¹. ¹H NMR: δ 7.36-7.30 (10H, m, Ph-H), 6.977 (1H, s, Ph₂CH), 6.446 (2H, Abq, *J* 12.40 Hz, CH=CH) ppm.

***N*-(*O*-Diphenylmethylmaleyl)-3',4',5'-trimethoxy-indole-3-carboxanilide (22)**. To a magnetically stirred solution of acid **22** (0.28 g, 1 mmol), the anilide **13** (0.30 g, 0.91 mmol) and DIPEA (0.48 mL, 2.74 mmol) in anhydrous CH₂Cl₂ (4 mL) PyBrOP (0.61 g, 1.3 mmol) was added. The resulting solution was kept at ambient temperature for overnight and then diluted with more CH₂Cl₂. Washing once with a 5% aqueous NaHCO₃ solution and twice with H₂O, followed by drying and evaporation gave a yellowish foam. FCC of crude product, using the solvent system E for elution, gave 0.30 g (56% yield) of intermediate **22** as a white solid. Ester **22** had m.p. 195-97 °C, R_f (E) 0.5. Anal. Calcd for C₃₅H₃₀N₂O₇ (590.64): C, 71.18; H, 5.12; N, 4.74. Found: C, 71.40; H, 5.01; N, 4.55.

IR: 3383 (*NH-CO*), 1719 (*CO-O*), 1687 (*N-CO*), 1656 (*NH-CO*), 1623 (*C=C*) cm^{-1} . ESI-MS (*m/z*): 1203.28 (*2M+Na*), 630.65 (*MK*), 613.58 (*MNa*), 591.79 (*MH*). ^1H NMR (*DMSO-d*₆): 9.992 (1H, s, *NH*), 8.544 (1H, s, *H-2*), 8.353 (1H, br. d, *J* 7.20 Hz, *H-8*), 8.297 (1H, d, *J* 7.60 Hz, *H-5*), 7.469 (1H, d, *J* 12.00 Hz, *H-12*), 7.417 (2H, m, *H-6* and *H-7*), 7.143 (10H, m, *Ph-H*), 7.109 (2H, s, *H-17* and *H-21*), 6.772 (1H, s, *H-15*), 6.677 (1H, d, *J* 12.00 Hz, *H-13*) ppm. ^{13}C NMR: δ 166.32, 163.47 and 161.95 (*C-10/C-11/C-14*), 153.61 (*C-18* and *C-20*), 140.14-116.14 (22 *C*, aromatic and vinylic carbons), 98.61 (*C-6* and *C-7*), 78.224 (*C-15*), 60.61 (*C-23*), 56.70 (*C-22*) ppm

***N*-Maleyl-3',4',5'-trimethoxy-indole-3-carboxanilide (7b)**. A solution of ester **22** (0.28 g, 0.47 mmol) in CH_2Cl_2 (4.5 mL) and TFA (1.5 mL) was prepared and allowed to stand at ambient temperature for 5 min, whereby deprotection was found complete (TLC). Dilution with more CH_2Cl_2 , followed by washing with H_2O twice, drying and evaporation left an oily residue. Product **7b** was finally obtained pure (0.12 g, 60% yield) as a white solid through FCC using as eluant the solvent system H. Compound **7b** had m.p. 108-09 °C, *R*_f (B) 0.24. Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_7$ (424.41): C, 62.26; H, 4.75; N, 6.60. Found: C, 61.95; H, 4.83; N, 6.79.

IR: 3600-2800 (br., *NH-CO* and *CO-OH*), 1642 (br., *N-CO*, *NH-CO*, *CO-OH*) cm^{-1} . ^1H NMR (*DMSO-d*₆): δ 11.911 (1H, s, *OH*), 9.678 (1H, s, *NH*), 8.304 (1H, s, *H-2*), 8.183 (1H, d, *J* 7.60 Hz, *H-8*), 7.453 (1H, d, *J* 8.00 Hz, *H-5*), 7.217 (2H, s, *H-16* and *H-20*), 7.137 (2H, m, *H-6* and *H-7*), 6.225 (1H, d, *J* 12.00 Hz, *H-12*), 5.662 (1H, d, *J* 12.00 Hz, *H-13*), 3.765 (6H, s, *H-21*), 3.616 (3H, s, *H-22*) ppm. ^{13}C NMR: δ 170.12, 167.74 and 164.09 (*C-10/C-11/C-14*), 153.83 (*C-17* and *C-19*), 137.12-111.34 (12 *C*, aromatic and vinylic carbons), 98.32 (*C-6* and *C-7*) 62.57 (*C-22*), 56.62 (*C-21*) ppm

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