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Straightforward protocol for the efficient synthesis of varied N^1-acylated (aza) indole 2-/3-alkanoic acids and esters: optimization and scale-up

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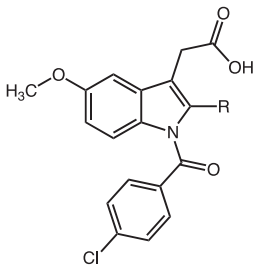
ABSTRACT

A library of approximately 40 N^1-acylated (aza)indole alkanoic esters and acids was prepared employing a microwave-assisted approach. The optimized synthetic route allows for parallel synthesis, variation of the indole substitution pattern, and high overall yield. Additionally, the procedure has been scaled up to yield multi-gram amounts of preferred indole compounds, e.g.: 2′-*des*-methyl indomethacin **2**. The reported compounds were designed as biomedical tools for primary and secondary in vitro and in vivo studies at relevant molecular targets.

1. Introduction

N-Acylated indole acetic acids are drawing continued attention due to their wide-ranging pharmacological activities.[1–5] For example, indomethacin (INDO, **1**, Fig. 1), a traditional non-steroidal anti-inflammatory drug (NSAID), is a potent, time-dependent inhibitor of cyclooxygenases (COX-1 and COX-2) with a long history of clinical use in human subjects.[6] It promotes anti-inflammatory, anti-pyretic, and analgesic activities, but also contributes to severe stomach irritation and ulcers due to secondary pharmacodynamic effects.[7,8] Recently, **1** and some of its derivatives have been shown to hold interesting and potentially useful 'off-target' activities, e.g., regulation of Th2-mediated asthma and other allergic diseases or chemoprevention of tumors by addressing targets different from COX.[9–14] Of these INDO derivatives, those that do not (strongly) interfere with arachidonic acid (AA) metabolism, have greater potential to be valuable drug candidates because of their presumably lower gastrointestinal toxicity. Very recently we have probed 2′-*des*-methyl indomethacin (2′-DM-INDO, **2**, Fig. 1),[15] a structurally edited version of **1**, which exhibits drastically reduced inhibitory potency against both COX enzymes and reduced gastric toxicity relative to **1** in C57BL6 mice.[16,10] To further probe the effects of indoles related to **1** and **2**, we required rapid production of iterative series of *N*-acyl indole alkanoic acids and esters in good overall yield.



1 Indomethacin (INDO): R = CH_3
2 2′-*Des*-methyl INDO: R = H

Fig. 1. Structure of indomethacin derivatives.

In the present manuscript we report a very efficient indolization/acylation approach toward *N*-substituted (aza)indole compounds and we describe the successful scale-up of the synthesis of two prototype indole analogues.

2. Results and discussion

2.1. Small-scale approach

We accomplished a robust synthetic routine and generated a series of novel INDO (**1**) analogues **18**–**31** (Tables 2 and 3) with individual compounds emerging in milligram or multi-gram quantities and good overall yield (>55%). The general reaction

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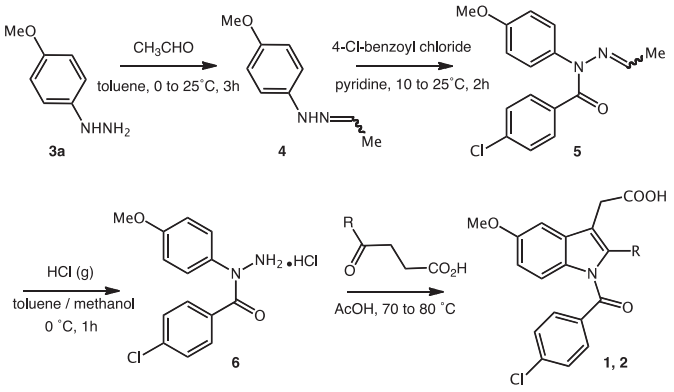
sequence leading to indoles **18** through **31**, followed three simple steps: (a) Fischer indolization of substituted phenylhydrazine hydrochlorides condensed with selected ketoacids/esters, (b) base-catalyzed indole N^1-acylation reactions (S_N2 substitutions) with different acid chlorides, and (c) ester hydrolysis of the intermediate methyl or cleavage of allyl *N*-acyl indole alkanoates in the presence of a metal organic catalyst. Structural modifications with respect to **1** (and **2**) were made at the C^2, C^3, C^5, COOH, and N^1-position of the indole ring. Previous procedures using similar synthetic strategies have not been reported on large-scale and oftentimes proceed in low overall yield.

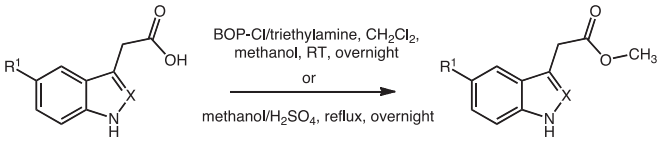
Several creative methods for assembly of N^1-substituted indole compounds have been reported. These include one-pot Stille couplings of *N*-acyl-2-iodoanilines,[17] catalytic dehydrogenative N^1-couplings of indoles with primary alcohols,[18] distinct indolization reactions with cyclic enol ethers and enol lactones,[19] and variations of the Fischer Indole synthesis.[20]

In the refined standard procedure of Yamamoto for compound **1** (Scheme 1),[21,22] an arylhydrazone precursor **4** is benzoylated at the N^1-position to give the N^1,N^1-disubstituted hydrazine **5**. Typically, commercial hydrazine hydrochloride starting materials **3** need to be deprotonated prior to reaction. The intermediate **5** is then hydrolyzed with hydrogen chloride to give the hydrazine hydrochloride salt **6**, which is cyclized in the final reaction step with levulinic acid to afford **1**.[23] The synthesis of 2′-*des*-methyl INDO **2** has been conducted accordingly with the exception that succinic semialdehyde was used for the ring-closure.



Scheme 1. Yamamoto's procedure for the synthesis of (2′-*des*-methyl) indomethacin; R=CH_3 or H.

Isolated product yields are often unsatisfactory using this literature procedure due to multiple reaction steps, the formation of by-products, and the requirement for extensive purification of intermediates.[19] The early insertion of the N^1-acyl moiety in the reaction sequence is another limitation of this entry, which involves the addition and subsequent displacement of an ethylidene protection group (N^2). Therefore, in order to vary the *N*-acyl substituent for a series of indole analogues **18**–**21** (Table 2), each derivative needed to be constructed individually. To overcome this limitation and enhance the flexibility toward the introduction of multiple substituents in the indole scaffold, we pursued a strategy (Scheme 2) that has not been intensively investigated for the serial production of substituted indoles because it has proven to be rather uneconomical, especially for larger scales. This strategy employs indolization first followed by late-stage N^1-substitution and release of the carboxylic acid under optimized reaction conditions. Cyclization reactions of arylhydrazines with different ketoacids/esters were conducted in AcOH or refluxing methanol/H_2SO_4. We used methyl or allyl esters for our small-scale and large-scale reactions, respectively, because of their stability to the reaction conditions and ease of removal. Utilization of ^{t}BuONa in THF or DMAP/Et_3N in DCM as reaction medium facilitated indole *N*-acylation with select aryl acid chlorides. Final ester cleavage was done in 1,2-DCE with trimethyltin hydroxide[24] (methyl esters) or in THF using $Pd(PPh_3)_4$/morpholine as catalyst complex (allyl esters). Concurrent *N*-deacylation was not observed with these expedient procedures, which clearly privileges them over standard saponification methods with metal alkaline hydroxide/water. We also investigated the synthesis under microwave irradiation for numerous compounds with a view to speed up reaction rates and increase isolable yields.



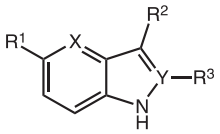
7a: R^1 = OMe, X = CCH_3
7b: R^1 = OMe, X = CH
8: R^1 = H, X = N

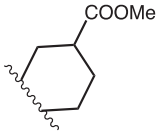
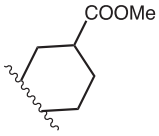
9a: R^1 = OMe, X = CCH_3
9b: R^1 = OMe, X = CH
10: R^1 = H, X = N

Scheme 2. Esterification of (2′-aza-/2′-*des*-methyl) indole-3′-acetic acids.

2.1.1. Preparation of different indole methyl alkanoates. Initially, we generated a set of 10 different C^2/C^3/C^5-substituted (aza)indole intermediates. The structures, specific conditions, and yields are summarized in Table 1. Detailed experimental data can be also found in Supplementary data.

Table 1
Preparation of different (aza)indole alkanoic acid ester precursors



#	X	Y	R^1	R^2	R^3	Method	Yield[a] (%)
9a	C	C	OMe	$CH_2C(O)OMe$	Me	A1	>99
9b	C	C	OMe	$CH_2C(O)OMe$	H	A1	85
9c	C	C	F	$CH_2C(O)OMe$	Me	B2	84
9d	C	C	F	$CH_2CH_2C(O)OMe$	Me	B2	76
9e	C	C	F	$CH_2C(O)OMe$	H	B2[b]	86
14	C	C	F	Me	$CH_2CH_2C(O)OMe$	B2	46
15a	C	C	OMe			B1	90
15b	C	C	F			B2	99
10	C	N	H	$CH_2C(O)OMe$	—	A2	77
17	N	C	OMe	$CH_2C(O)OMe$	H	Other	60

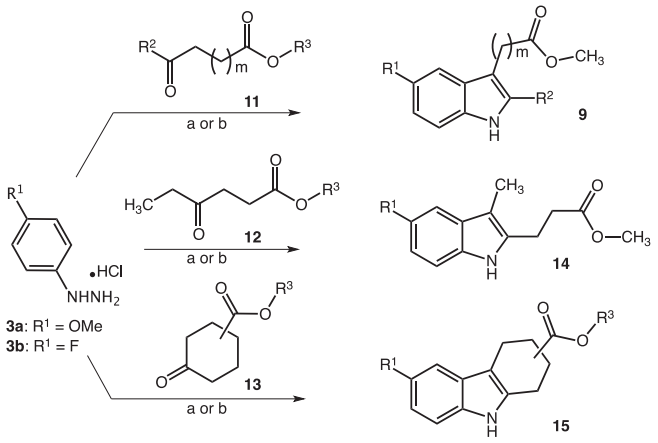
Reagents and conditions: [method A1]: BOP–Cl, triethylamine, CH_2Cl_2, MeOH, rt, overnight; [method A2]: MeOH, H_2SO_4, reflux, overnight; [method B1]: arylhydrazine HCl, ketoacid ester, AcOH, 80 °C, 3 h; [method B2]: arylhydrazine HCl, ketoacid or ketoacid ester, MeOH, H_2SO_4, microwave, 120 °C, 10 min.

[a] Isolated yield.

[b] Conventional heating, 3 h instead of microwave.

Methyl esters **9a**, and **9b** of commercial 5-methoxy-2-methylindole-3-acetic acid **7a**, and 5-methoxyindole-3-acetic acid **7b** were generated overnight at room temperature in yields >85% using BOP–Cl/triethylamine and methanol (Scheme 2).[25]

The preparation of different C^2/C^3-substituted indole compounds **9c**–**e**, **14**, and **15** is summarized in Scheme 3. Substituted arylhydrazine hydrochlorides **3** were directly subjected to reaction with selected ketoacids or esters **11** through **13**. Particularly, indole compound **15a** was generated in 90% yield under standard reaction conditions (AcOH, 80 °C, 3 h) using 4-methoxyphenyl hydrazine hydrochloride **3a** and methyl 4-ketocyclohexanecarboxylate. Next, in order to allow investigation of the significance of a fluoro substitution at the indole 5-position, we pursued Fischer indole synthesis of C^2/C^3-substituted indole analogues **9c**–**e**, **14**, and **15b**. Whereas *para*-methoxylated phenylhydrazine hydrochloride **3a** (e.g., for compound **15a**) readily dissolved in AcOH upon heating, this was not the case for fluorinated starting material **3b** (leaving unreacted starting materials). Therefore, AcOH was replaced by methanol/H_2SO_4 as solvent mixture for better solubility of the fluorinated precursors. In this case, selected 'ketoacids' rather than their low alkyl esters were employed in the reaction, as clean COOH-esterification usually occurred alongside the 'indole' ring-closure (compare Experimental section for **9c** vs **9e**). Reactions were accelerated by microwave irradiation and ran approx. 50 times faster (5–10 min instead 3–6 h) than with conventional heating affording consistently high and reproducible yields (~80%). In many cases products precipitated upon pouring the reaction mixture on crushed ice or could be extracted from the resulting aqueous mixture, washed and obtained in acceptable quality after removal of solvent in vacuo and trituration with hexanes.



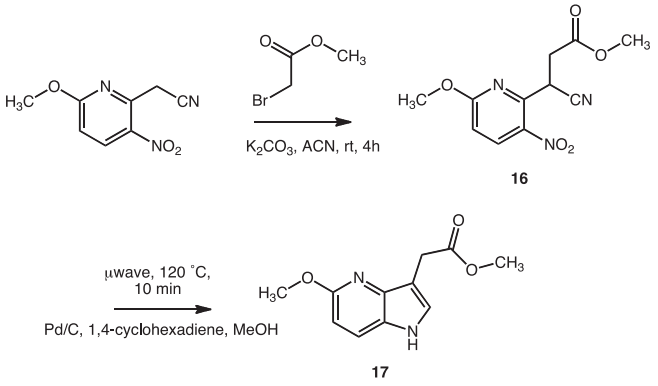
Scheme 3. Fischer cyclization reactions toward different indole 2-/3-alkylcarboxylic acid methyl ester intermediates. Reagents and conditions: (a) AcOH, 80 °C, 3h; (b) MeOH/H_2SO_4, 5 min (microwave) to 3 h (conventional heating).

The same results were achieved when using ketoacids whose carboxylic acid group had been esterified beforehand (see experimental details for **9c**). (Partial) re-esterification to the corresponding methyl esters **9** even occurred when starting, for example, with ethyl esters of **11** (data not shown). For compound **9d** bearing an extended exocyclic alkyl chain on position C^3 of the indole, 4-F-phenylhydrazine hydrochloride was converted with 5-oxohexanoic acid under the conditions described. Finally a 2-propionic acid derivative was realized with indole **14**, using 4-oxohexanoic acid as cyclization reagent. In this case, however, the desired product could be isolated only in 46% yield.

Not only did this reaction eliminate the need for an *N*-protection, it also allowed the variation of all relevant substituents R^1 through R^3 as well as the length and position of the carboxyalkyl chain at the indole framework within only one reaction step. Generally, linear ketones **11** or **12** were of importance for the later configuration of the carboxyalkyl substituted indoles. Certain 'keto' alkanoic acids/esters provided high regioselectivity in the 3,3-sigmatropic rearrangement in the course of the Fischer indole synthesis. In the case of **11** (acetyl or formyl tail end), the alkyl acid functionality was solely directed to position 3 of the indole product, whereas reagents **12** (ethylcarbonyl tail end) typically produce the alkyl acid functionality at position 2 (isolated products).[26] Structure examples are given in Scheme 2 and Table 1.[26] Elongation of the alkyl chain in between the two functional groups with respect to reagents **11** was tolerated and didn't affect the selectivity (e.g., **9d**). On the contrary, the inclusion of one or more extra methylene units into the terminal alkyl chain (beyond carbonyl) and/or extension of the alkyl spacer (between CO and COOH) of **12** continuously yielded isomeric mixtures (C^2/C^3). Such compounds are not part of the current work.

Poor regioselectivity is a general problem of Fischer indole reactions as evidenced in the use of unsymmetrical cyclic ketones. Interestingly, there have been a few examples for the selective cyclization of phenylhydrazones with, e.g., 3-ketocyclo-hexanecarboxylic acid or 5-aryldihydro-3(2*H*)-thiophenones.[27,28] To simplify matters in our present study we used symmetrical 4-ketocyclohexanecarboxylic acid to produce indole derivatives **15a** (6′-methoxy, see above) and **15b** (6′-fluoro) and to demonstrate the later availability for use of similar intermediates in subsequent *N*-acylation/ester cleavage reactions. In practice, indole derivative **15b** could be isolated quantitatively after short reaction times using microwave-aided synthesis.

In order to demonstrate the feasibility of additional heteroatoms and to modify the hydrophilicity of the core skeletons, we also produced a 2-aza (**10**) and a 4-aza indole-3-acetic acid methyl ester analogue (**17**) (Schemes 2 and 4). The reaction for **10** was completed in 77% yield according to a patent method starting from 2-(1*H*-indazol-3-yl)acetic acid (14 h reflux in methanol/H_2SO_4).[29] In this case the originally attempted esterification with BOP–Cl/methanol did not succeed. Another literature method allowed for the synthesis of the 4-aza indole derivative **17**.[30,31] In contrast to the published procedure, we adopted the reaction under microwave irradiation with the respective methyl ester. Customized one-pot catalytic reduction/cyclization of a 3-cyano-3-(nitropyridin-2-yl)-methyl propionate precursor **16** in methanol using Pd/C and cyclohexadiene as hydrogen source (10 min at 120 °C) readily afforded **17** in 60% yield.

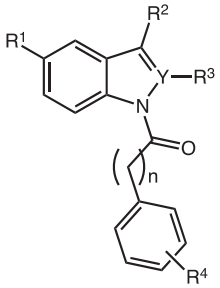


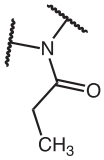
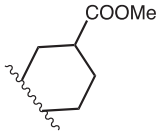
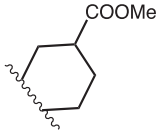
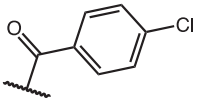
Scheme 4. Synthesis of a 4-aza-indole-3-acetic acid ester analogue.

2.1.2. Substitution at nitrogen (N^1). *N*-Substitution of indoles, **9** and **15**, yielded a series of *N*-acyl indole methyl alkanoates, **18** and **19**, respectively (Table 2). Different benzoyl/aryl acid chlorides were chosen as acylating reagents. However, direct *N*-acylation of an indole nucleus is demanding and necessitates deprotonation of the N–H center, as neutral indoles are non-nucleophilic at the nitrogen atom. Due to the low acidity of the indole-N^1, full deprotonation to the reactive anion can be only realized under strong base catalysis in (polar) aprotic solvents.

For the small-scale one-pot reactions on indole **9** we first tried sodium hydride (powdered material) in DMF, though, with less

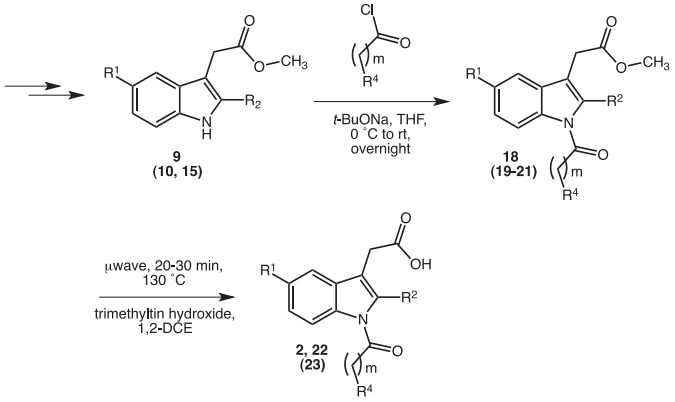
Table 2
Synthesis of *N*-acyl methyl (aza)indole(cyclo)alkanoates



#	Y	R^1	R^2	R^3	*n*	R^4	Method	Yield[a] (%)
18a	C	OMe	$CH_2C(O)OMe$	Me	0	*p*-F	C2	25
18b	C	OMe	$CH_2C(O)OMe$	Me	0	*m*-CF_3	C2	32
18c	C	OMe	$CH_2C(O)OMe$	Me	0	*p*-CF_3	C2	33
18d	C	OMe	$CH_2C(O)OMe$	Me	0	*p*-Me	C2	57
18e	C	OMe	$CH_2C(O)OMe$	Me	0	*p*-CH_2Cl	C2	42
18f	C	OMe	$CH_2C(O)OMe$	Me	0	*p*-OMe	C2	32
18g	C	OMe	$CH_2C(O)OMe$	H	0	*p*-Cl	C1	18
18h	C	OMe	$CH_2C(O)OMe$	H	0	*p*-F	C2	22
18i	C	OMe	$CH_2C(O)OMe$	H	0	*m*-CF_3	C2	13
18j	C	OMe	$CH_2C(O)OMe$	H	0	*p*-CF_3	C2	29
18k	C	OMe	$CH_2C(O)OMe$	H	1	*p*-OMe	C1	(13)[c]
18l	C	OMe	$CH_2C(O)OMe$	H	0		C1	21
18m	C	F	$CH_2C(O)OMe$	Me	0	*p*-Cl	C2	42
18n	C	F	$CH_2C(O)OMe$	Me	0	*m*-CF_3	C2	33
18o	C	F	$CH_2CH_2C(O)OMe$	Me	0	*p*-Cl	C2	49
18p	C	F	$CH_2C(O)OMe$	Me	1	*p*-Cl	C2	4
18q	C	F	$CH_2C(O)OMe$	H	0	*p*-Cl	C2	42
19a	C	OMe			0	*m*-CF_3	C2	24
19b	C	F			0	*p*-Cl	C2	14
20a	C	OMe	H	Me	0	*p*-Cl	C2	25
20b	C	OMe		Me	0	*p*-Cl	C2	8[b]
21	N	OMe	$CH_2C(O)OMe$	—	0	*p*-Cl	C2	37

Reagents and conditions: [method C1]: NaH, DMF, acyl chloride, 0 °C to rt, overnight; [method C2]: ^{t}BuONa, THF, acyl chloride, 0 °C to rt, overnight.
[a] Isolated yield.
[b] Compound **20b** emerged as one side product in the synthesis of **20a**.
[c] Compound after repeated chromatography only about 50% pure.

satisfying results due to several handling issues (e.g., with compounds **18g**, **18k** or **18l**). Then we switched to sodium *tert*-butoxide and used a 2 M commercial solution in THF to produce a larger series of compounds **18**–**21** having different benzoyl (*p*-Cl, *p*-CH_2Cl, *p*-F, *p*-Me, *p*-OMe, *m*/*p*-CF_3) and other acyl moieties (Scheme 5, first step). Not only did we observe higher yields and reproducibility with this base (yields ranging from 20 to 60% for numerous analogues), but also total reaction processing and workup were cleaner than with NaH/DMF (pipetting volumes



Scheme 5. N-Acylation and ester cleavage reactions.

instead of weighing moisture-sensitive solids; phase separation after water quench). Reactions were run on a small-scale (80–100 mg each) under argon on a parallel synthesis apparatus. *N*-Acylation with different acid chlorides occurred best at temperatures between 0 °C and 25 °C. Therefore, in a typical experiment, we pipetted the base to an ice-cold stirred solution of the indole in THF and after 20 min we added the acid chloride and let the mixture react at ambient temperature until the starting material was consumed or no further product formation could be detected (usually overnight). Progress of the reactions was monitored by LCMS and TLC. In most cases, one major product was detected. By-products were predominantly unreacted or *N*-deacylated/hydrolyzed indole starting materials and the carboxyl counterparts of the applied benzoyl chlorides.

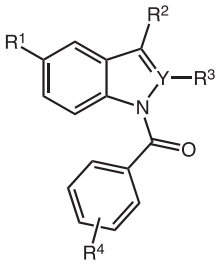
Isolated amounts of products with varied *meta*- and *para*-substituted *N*-benzoyl moieties appeared to be better (24–57%), when a 2-methyl group was present on the indole ring (**18a**–**f** and **18m**–**o**) and were lower (13–29%) among the 2-*des*-methyl indole analogues (**18g**–**k**), except for **18q** (42%). In compounds **18k** and **18p** the acyl substituent was 'extended' by an additional methylene unit, which further reduced the percent yields [**18k**: 13% (impure) and **18q**: 4%, respectively]. A simple aliphatic *N*-propanoyl substituent was realized with indole acetic acid ester analogue **18l**. C^2/C^3-Cyclized indole intermediates, **12a** and **12b** could be substituted on their nitrogens with a *m*-CF_3- and *p*-Cl-benzoyl substituent in 24 and 14% yields, respectively (**19a**, **19b**). Acylation of an N^1,C^2,C^3-unsubstituted 5-methoxyindole precursor using sodium *tert*-butoxide and *p*-Cl-benzoyl chloride afforded a mixture of three compounds, two of which were isomers with the benzoyl moiety on either position C^3 (faint, not isolated) or N^1 (**20a**, 25%). The other isolated product **20b** (8%) was analyzed to be an N^1/C^3-dibenzoylated indole derivative. These reactions reflect the enhanced reactivity of the unsubstituted indole 3-position upon hydrogen abstraction at the nitrogen via the conjugated double-bond system (conjugate-like substitution) and in turn the facilitated N^1-deprotonation reaction by the 3-acyl ring substituent.

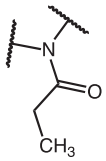
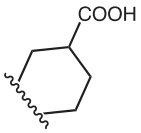
The initial attempt to acylate a 2-propionic acid ester indole derivative (e.g., **11**) with 4-chlorobenzoyl chloride using similar conditions failed and considerable amounts of starting material were detected beside some undefined products by LCMS. Nevertheless, N-substitution of a comparable indole derivative was successfully followed up later under larger scale and with optimized reaction conditions (compound **30**, see below).

Lastly, compound **21** exemplifies an N^1-benzoylated 2-aza-indole acetic acid methyl ester emerging in 37% yield from the parallel routine described above.

2.1.3. Methyl ester cleavage. In order to obtain the free acid derivatives **2**, **22**, **23**, and **24** (Table 3) of the *N*-acylated indole

Table 3
Synthesis of *N*-acyl indole(cyclo)alkanoic acids



#	Y	R^1	R^2	R^3	R^4	Method	Yield[a] (%)
2	C	OMe	$CH_2C(O)OH$	H	*p*-Cl	D	81
22a	C	OMe	$CH_2C(O)OH$	Me	*p*-F	D	90
22b	C	OMe	$CH_2C(O)OH$	Me	*m*-CF_3	D	97
22c	C	OMe	$CH_2C(O)OH$	Me	*p*-CF_3	D	90
22d	C	OMe	$CH_2C(O)OH$	Me	*p*-Me	D	82
22e	C	OMe	$CH_2C(O)OH$	Me	*p*-CH_2Cl	D	98
22f	C	OMe	$CH_2C(O)OH$	Me	*p*-OMe	D	93[b]
22g	C	OMe	$CH_2C(O)OH$	H	*p*-F	D	76
22h	C	OMe	$CH_2C(O)OH$	H	*m*-CF_3	D	96
22i	C	OMe	$CH_2C(O)OH$	H	*p*-CF_3	D	99
22j	C	OMe	$CH_2C(O)OH$	H		D	94
22k	C	F	$CH_2C(O)OH$	Me	*p*-Cl	D	87
22l	C	F	$CH_2C(O)OH$	Me	*m*-CF_3	D	95
22m	C	F	$CH_2CH_2C(O)OH$	Me	*p*-Cl	D	95
22n	C	F	$CH_2C(O)OH$	H	*p*-Cl	D	78
23	C	OMe			*m*-CF_3	D	98[b]
24	N	OMe	$CH_2C(O)OH$	—	Cl	D	No product (decomposition)

Reagents and conditions: [method D]: trimethyltin hydroxide, 1,2-DCE, microwave, 130 °C, 30 min.
[a] Isolated yield.
[b] Crude educts used; impurity of the starting material taken into account for the calculation of the percent yield (see Supplementary data)!

compounds **18**, **19**, and **21**, the methyl ester groups had to be hydrolyzed. Different standard 'saponification' methods exist to achieve this task, however, common drawbacks include elimination reactions induced by the aqueous-basic conditions.[32] This circumstance became particularly significant, as the *N*-acyl bonds of our indole derivatives were perceptibly fragile toward basic (and strong acidic) treatment and easily hydrolyzed to liberate *N*-unsubstituted indole alkanoic acids. This was true for numerous 2-*des*-methyl indole analogues and also for the sterically more demanding 2-propionic acid derivatives (see below), notwithstanding a limited number of literature instances for successful ester saponification toward *N*-acyl 2-methylindole acetic acids.[20]

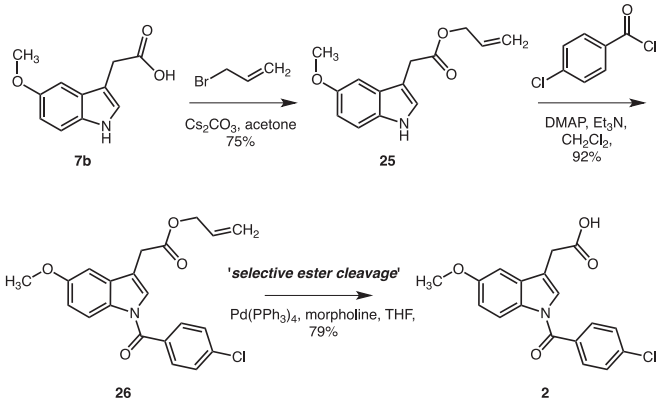
We attempted a recently reported non-aqueous metal catalytic method for the mild and selective hydrolysis of esters with trimethyltin hydroxide.[24] It had been illustrated for many (complex) aromatic and aliphatic systems that methyl, allyl, and benzyl esters are hydrolyzed in quantitative yields using this reagent. For our current study, we once more transferred the stated settings to microwave conditions (for detailed parameters see Experimental part) and consistently applied 5 equiv of Me_3SnOH beside our starting methyl esters in 1,2-dichloroethane for the expedited ester hydrolysis. Reactions normally ran to completion within 20–30 min (IPC by TLC and LCMS) and workup was quite simple, as products could be extracted into dichloromethane after addition of 50% acetic acid. Residual Me_3SnOH was removed with water or brine; the organic layer was dried over Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel afforded the pure *N*-acyl indole alkanoic acids **2**, **22**, and **23** quantitatively. As shown in Table 3, this technique proved truly valuable in getting the selective and high-yielding (76–99%) hydrolysis of methyl esters within the sensitive substrates **18** and **19**. Unfortunately, this procedure failed with the 2-aza derivative **21** to obtain the corresponding free acid derivative **24**. The latter compound repeatedly decomposed into several unidentified products, regardless of whether the reaction was conducted with microwave or under conventional heating conditions (60–80 °C).

To extend this strategy to the large-scale synthesis of individual *N*-acyl indole derivatives, we further optimized the reaction conditions as described below, particularly with a view to improving capacities of the N-acylation step.

2.2. Large-scale synthesis

New synthetic methodology was adopted for the scale-up to multi-gram scale. Beside the efforts with N-substitution, the major problematic step in the synthesis remained the final hydrolysis of the ester in the presence of the *N*-acyl functional group. As mentioned above, the *N*-benzoyl bond is labile under basic conditions, so it was hydrolyzed easily at normal hydrolysis condition for the ester hydrolysis step.[32] Therefore we considered using allyl,[33,34] benzyl,[35,36] and *tert*-butyl ester[37] to overcome the side reaction and allyl ester **26** was evaluated.

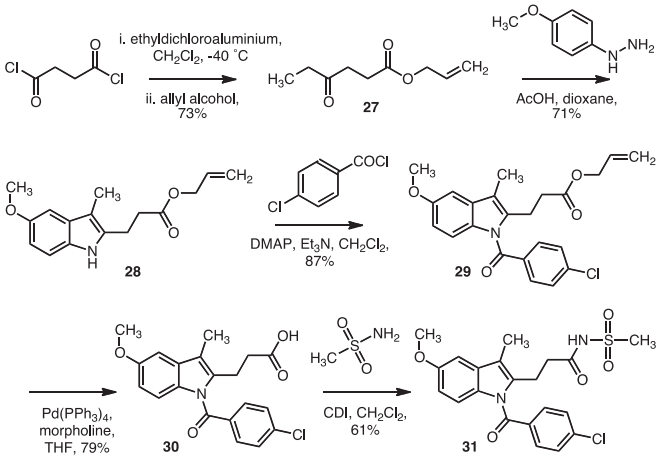
A large quantity of **2** was prepared from the commercially available 2-(5-methoxy-1*H*-indol-3-yl)acetic acid **7b** in three steps starting with esterification with allyl bromide to afford allyl ester **25** in 75% yield (Scheme 6). Efficient acylation of **25** followed by treatment with triethylamine and DMAP then gave *N*-benzoate **26** (92% yield). Subsequently, cleavage of the allyl ester was examined. Optimal conditions employed tetrakis(triphenylphosphine) palladium in combination with morpholine in THF to quantitatively provide **2** without unwanted hydrolysis of the *N*-acyl group.[38]



Scheme 6. Large-scale synthesis of compound **2**.

From the result of the synthesis for **2**, allyl ester was projected as an advanced intermediate in our synthesis so it was applied to another large-scale synthesis of a 2-propionic acid derivative **30** en route to a more complex sulfonimide derivative (COOH bioisostere) **31** (Scheme 7).

Indole **28** was not commercially available and therefore should be prepared from succinyl chloride using Boger's synthesis.[39] Succinyl chloride was treated with ethyldichloroaluminum and allyl alcohol in dichloromethane to provide allyl-4-oxohexanoate **27**. Fischer indolization of **27** with 4-methoxyphenyl hydrazine followed by treatment with acetic acid then gave indole compound **28** in 71% yield. Acylation (87%) and ester cleavage (79%) produced carboxylic acid, **30**.[15] Finally compound **31** was obtained by amide coupling between methylsulfonylamine and acid **30** using CDI coupling reagent (Scheme 7).



Scheme 7. Large-scale synthesis of compounds **30** (free acid) and **31** (COOH bioisostere).

3. Conclusions

In summary, we have found that different INDO analogues, including 2′-*des*-methyl INDO **2** are efficiently prepared in a parallel approach via their *N*-unsubstituted indole methyl-/allylalkanoate intermediates starting from commercially available arylhydrazine hydrochlorides and a variety of ketoacids/esters. Substituted phenylhydrazine precursors were subjected to Fischer cyclization in a one-pot procedure to provide respective indole products. The *N*-unsubstituted indole alkanoic acid esters (optimally methyl or allyl esters) were deprotonated and further elaborated by N-acylation followed by aqueous-free ester cleavage in the presence of different metal-based catalyst systems. Concomitant N-deacylation was not observed with the applied technique. The synthetic strategy enabled assembly and variation of all relevant substituents within only three reaction steps. Target compounds were readily formed under optimized settings and could be isolated in good to high overall yields and in acceptable analytical quality. The procedure also allowed for scale-up to afford large amounts of selected compounds of interest for further derivatization reactions and/or direct use in in vitro and in vivo experiments. The range of indole analogues will be evaluated for activity against peroxisome proliferator activated receptor γ, induction of tumor cell apoptosis, and inhibition of aldo-keto reductase enyzmes.[10,40]

4. Experimental part

4.1. General

All commercial reagents, solvents, and other materials were used as received without further purification. Flash chromatography was conducted on a Biotage SP1 automated flash chromatography system equipped with a fixed wavelength UV detector (λ=254 nm) using prefabricated 'Flash KP-SIL' columns (size according to requirements). Thin-layer chromatography was performed on precoated fluorescent silica gel 60 F_{254} plates (250 um) from Whatman (Partisil® LK6D, cat. no. 4865-821). Spots were visualized under natural light, and UV illumination at λ=254 and 365 nm. Microwave reactions were performed in an automated Biotage Initiator Eight Synthesizer. NMR spectra were recorded with a Bruker AV-400 instrument with sample changer (BACS 60) (400 MHz for ^{1}H, 100 MHz for ^{13}C) or a Bruker AV-300 system (282 MHz for 19F) and calibrated with DMSO-d_6 as solvent and TMS as internal standard signal. Chemical shifts (δ) are reported in parts per million (ppm). Coupling constants (J) are given in hertz. Low-resolution mass spectra were obtained on an Agilent 1200 series liquid chromatography – mass spectrometry (LCMS) system with electrospray ionization. High-resolution mass spectra (HRMS) were recorded on a Waters QTof-API-US Plus Acquity system with ES as the ion source. Analytical high-pressure liquid chromatography (HPLC) was performed on an Agilent 1200 analytical LCMS with UV detection at 214 and 254 nm along with ELSD detection. General methods are specified in Supplementary data. Compounds **9a**, **9b**, **10**, and **17** were prepared according to literature procedures.[25,31,41,30]

Synthesis of exemplified intermediates and target compounds:

4.2. Methyl 2-(5-fluoro-1*H*-indol-3-yl)acetate 9e

According to general procedure B_variant2 (conventional heating), (4-fluorophenyl)hydrazine hydrochloride (100 mg, 0.62 mmol), 4-oxobutanoic acid (79 mg, 0.68 mmol), and 160 μL H_2SO_4 in 2 mL methanol were refluxed for 3 h under argon to afford 110 mg (86%) of **9e** as brownish viscous mass. $C_{11}H_{10}FNO_2$, M_r=207.20; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.60 (s, 3H), 3.72 (s, 2H), 6.91 (td, J=2.6/9.2 Hz, 1H), 7.22 (dd, J=2.4/10.0 Hz, 1H), 7.31–7.35 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: −123.52 (5′-F); LCMS (ESI) t_R: 2.16 min (>99%, ELSD), m/z: 208.2 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{11}H_{10}FNO_2$ $[M+H]^+$ calcd mass 208.0774, found 208.0772.

4.3. Methyl 2-(1*H*-indazol-3-yl)acetate 10

According to general procedure A_variant2, 2-(1*H*-indazol-3-yl)acetic acid (300 mg, 1.70 mmol) was refluxed in methanol (15 mL) for 14 h. The reaction mixture was worked up as described to afford 250 mg (77%) of **10**. $C_{10}H_{10}N_2O_2$, M_r=190.20; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.62 (s, 3H), 4.01 (s, 2H), 7.09 (td, J=0.8/7.4 Hz, 1H), 7.33 (td, J=1.0/7.7 Hz, 1H), 7.48 (d, J=8.4 Hz, 1H), 7.69 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 33.04 (s, $-CH_2-$), 52.17 (s, $-OCH_3$), 110.49 (s, C7′), 120.29 (s), 120.43 (s), 122.20 (s, C4a′), 126.40 (s, C6′), 138.83 (s, C7a′), 141.20 (s, C3′), 171.03 (s, >C=O); LCMS (ESI) t_R: 1.65 min (>99%, UV254), m/z: 191.2 $[M+H]+$; HRMS (TOF, ES$^+$) $C_{10}H_{10}N_2O_2$ $[M+H]^+$ calcd mass 191.0821, found 191.0821.

4.4. Methyl 3-(5-fluoro-3-methyl-1*H*-indol-2-yl)propanoate 14

According to general procedure B_variant2, the title compound was obtained from (4-fluorophenyl)hydrazine hydrochloride (100 mg, 0.62 mmol), 4-oxohexanoic acid (88.8 g, 0.68 mmol), and 80 μL H_2SO_4 in 3 mL methanol after 10 min at 120 °C in 46% yield (67 mg) as brownish viscous mass. $C_{13}H_{14}FNO_2$, M_r=235.25; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.12 (s, 3H), 2.66 (t, J=8.0 Hz, 2H), 2.93 (t, J=7.6 Hz, 2H), 3.58 (s, 3H), 6.80 (td, J=2.8/9.2 Hz, 1H), 7.10 (dd, J=2.4/10.2 Hz, 1H), 7.20 (dd, J=4.6/8.6 Hz, 1H), 10.74 (br s, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: −124.03 (d, 5′-F); LCMS (ESI) t_R: 2.58 min (>99%, UV220), m/z: 236.2 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{13}H_{14}FNO_2$ $[M+H]^+$ calcd mass 236.1087, found 236.1085.

4.5. Methyl 6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylate 15a

According to general procedure B_variant1, the title compound was obtained from (4-methoxyphenyl)hydrazine hydrochloride (80.0 mg, 0.46 mmol) and methyl 4-oxocyclohexanecarboxylate (85.9 mg, 0.55 mmol) in 0.5 mL glacial acetic acid after 3 h at 80 °C in 90% yield (107 mg) as an off-white solid. $C_{15}H_{17}NO_3$, M_r=259.30; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.81–1.91 (m, 1H), 2.15–2.19 (m, 1H), 2.66–2.84 (m, 4H), 2.90 (dd, J=4.6/14.2 Hz, 1H), 3.65 (s, 3H), 3.72 (s, 3H), 6.61 (dd, J=2.4/8.8 Hz, 1H), 6.86 (d, J=2.4 Hz, 1H), 7.11 (d, J=8.8 Hz, 1H), 10.51 (s, 1H); LCMS (ESI) t_R: 2.27 min (>99%, ELSD), m/z: 260.2 $[M+H]^+$; HRMS (TOF, ES^+) $C_{15}H_{17}NO_3$ $[M+H]^+$ calcd mass 260.1287, found 260.1285.

4.6. Methyl 2-(5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)acetate 17

A 2 mL microwave process vial with a stir bar was charged with crude methyl 3-cyano-3-(6-methoxy-3-nitropyridin-2-yl)propanoate **16** (50 mg, 0.19 mmol), 10% Pd/C (5 mol %, 20 mg, 0.01 mmol), and methanol (1.5 mL). An excess of 1,4-cyclohexadiene (91 mg, 1.13 mmol) was added and the vessel flooded with argon, capped, and heated under microwave conditions at 120 °C for 5 min. The reaction mixture was filtered through Celite® and the solvent was evaporated in vacuo. The crude material was purified by flash chromatography (SiO_2, ethyl acetate/hexane gradient) to yield the product as greenish oil (25 mg, 60%). $C_{11}H_{12}N_2O_3$, M_r=220.22; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.61 (s, 3H), 3.72 (s, 2H), 3.83 (s, 3H), 6.53 (d, J=8.8 Hz, 1H), 7.38 (d, J=2.8 Hz, 1H), 7.66 (d, J=8.4 Hz, 1H), 11.01 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 29.41 (s, $-CH_2-$), 51.86 (s, $-C(O)OCH_3$), 52.83 (s, $-OCH_3$), 104.86 (s, C6′), 107.19 (s, C3′), 122.78 (s, C2′), 124.60 (s, C7a′), 126.80 (s, C7′), 141.29 (s, C3a′), 159.16 (s, C5′), 172.47 (s, >C=O); LCMS (ESI) t_R: 0.69 min (>97%, UV220, ELSD), m/z: 221.2 $[M+H]^+$; HRMS (TOF, ES^+) $C_{11}H_{12}N_2O_3$ $[M+H]^+$ calcd mass 221.0926, found 221.0926.

4.7. Methyl 2-(5-methoxy-2-methyl-1-(4-methylbenzoyl)-1*H*-indol-3-yl)acetate 18d

According to general procedure C_variant2, the title compound was obtained from methyl 2-(5-methoxy-2-methyl-1*H*-indol-3-yl) acetate (80 mg, 0.34 mmol), 4-methylbenzoyl chloride (63.6 mg, 0.41 mmol), and ^{t}BuONa (2 M in THF, 206 μL, 0.41 mmol) in anhydrous THF (2.5 mL). The crude residue was subjected to flash chromatography (SiO_2, ethyl acetate/hexane gradient) to afford the pure title compound in 57% yield (68.5 mg). $C_{21}H_{21}NO_4$, M_r=351.40; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.22 (s, 3H), 2.42 (s, 3H), 3.62 (s, 3H), 3.74 (s, 3H), 3.77 (s, 2H), 6.68 (dd, J=2.6/9.0 Hz, 1H), 6.85 (d, J=8.8 Hz, 1H), 7.01 (d, J=2.4 Hz, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.54 (pseudo-d, J=8.4 Hz, 2H); LCMS (ESI) t_R: 2.74 min (>95%, ELSD), m/z: 352.2 $[M+H]^+$; HRMS (TOF, ES^+) $C_{21}H_{21}NO_4$ $[M+H]^+$ calcd mass 352.1549, found 352.1548.

4.8. Methyl 3-(1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1*H*-indol-3-yl)propanoate 18o

According to general procedure C_variant2, the title compound was obtained from methyl 3-(5-fluoro-2-methyl-1*H*-indol-3-yl) propanoate (80 mg, 0.34 mmol), 4-chlorobenzoyl chloride (71.4 mg, 0.41 mmol), and ^{t}BuONa (2 M in THF, 204 μL, 0.41 mmol) in anhydrous THF (2.5 mL). The crude residue was subjected to flash chromatography (SiO_2, ethyl acetate/hexane gradient) to afford the pure title compound as yellow oil in 49% yield (62 mg). $C_{20}H_{17}ClFNO_3$, M_r=373.81; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.19 (s, 3H), 2.59 (t, J=7.4 Hz, 2H), 2.92 (t, J=7.6 Hz, 2H), 3.56 (s, 3H), 6.94 (td, J=2.4/9.2 Hz, 1H), 7.08 (dd, J=4.6/9.0 Hz, 1H), 7.39 (dd, J=2.4/9.2 Hz, 1H), 7.63–7.68 (m, 4H); LCMS (ESI) t_R: 3.21 min (>95%, ELSD), m/z: 374.3 $[M+H]^+$; HRMS (TOF, ES^+) $C_{20}H_{17}ClFNO_3$ [M+H]+ calcd mass 374.0959, found 374.0962.

4.9. Methyl 6-methoxy-9-(3-(trifluoromethyl)benzoyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylate 19a

According to general procedure C_variant2, the title compound was obtained from methyl 6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylate (80 mg, 0.31 mmol), 3-(trifluoromethyl) benzoyl chloride (77.2 mg, 0.37 mmol), and ^{t}BuONa (2 M in THF, 185 μL, 0.37 mmol) in anhydrous THF (2.5 mL). The crude residue was subjected to flash chromatography (SiO_2, ethyl acetate/hexane gradient) to afford the pure title compound in 24% yield (32 mg). $C_{23}H_{20}F_3NO_4$, M_r=431.40; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.70–1.80 (m, 1H), 2.03–2.07 (m, 1H), 2.47 (m, 2H, partly overlayed by DMSO signal), 2.73–2.79 (m, 1H), 2.82–2.89 (m, 1H), 2.94 (dd, J=5.0/15.8 Hz, 1H), 3.65 (s, 3H), 3.77 (s, 3H), 6.73 (dd, J=2.6/9.0 Hz, 1H), 7.04 (d, J=2.4 Hz, 1H), 7.08 (d, J=9.2 Hz, 1H), 7.79 (t, J=8.0 Hz, 1H), 7.93 (d, J=8.0 Hz, 1H), 7.99 (s, 1H), 8.04 (d, J=8.0 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: −59.41 (m-CF_3); LCMS (ESI) t_R: 0.95 min (>95%, UV254), m/z: 432.0 $[M+H]^+$; HRMS (TOF, ES^+) $C_{23}H_{20}F_3NO_4$ $[M+H]^+$ calcd mass 432.1423, found 432.1422.

4.10. Methyl 2-(1-(4-chlorobenzoyl)-1*H*-indazol-3-yl)acetate 21

According to general procedure C_variant2, methyl 2-(1*H*-indazol-3-yl)acetate (80 mg, 0.42 mmol) was subjected to reaction with 4-chlorobenzoyl chloride (88.3 mg, 0.50 mmol) (252 μL ^{t}BuONa). The crude product was purified by flash chromatography (SiO_2, ethyl acetate/hexane gradient) to afford 13.5 mg (52%) of the title compound as bright yellow solid. The compound permanently crystallized upon drying at high vacuum and storage at −20 °C. Yield: 51 mg (37%). $C_{17}H_{13}ClN_2O_3$, M_r=328.75; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.65 (s, 3H), 4.16 (s, 2H), 7.50 (td, J=0.8/7.6 Hz, 1H), 7.63–7.66 (m, 2H), 7.71 (td, J=1.0/7.6 Hz, 1H), 7.91 (d, J=8.0 Hz, 1H), 8.00–8.03 (m, 2H), 8.41 (d, J=8.4 Hz, 1H); LCMS (ESI) t_R: 2.80 min (>99%, ELSD), m/z: 329.0 $[M+H]^+$; HRMS (TOF, ES^+) $C_{17}H_{13}ClN_2O_3$ $[M+H]^+$ calcd mass 329.0693, found 329.0693.

4.11. 2-(1-(4-(Chloromethyl)benzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid 22e

According to general procedure D, methyl 2-(1-(4-(chloromethyl) benzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (15 mg, 0.039 mmol) was subjected to reaction with trimethyltin hydroxide (35 mg, 0.194 mmol) in 1,2-DCE (1 mL). The crude product was chromatographed on a short silica gel column using 1:1 ethyl acetate/hexane (0.5% AcOH) mixtures of increasing polarity as eluants to afford the title compound quantitatively as off-white solid. Yield: 14.1 mg (98%). $C_{20}H_{18}ClNO_4$, M_r=371.81; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.19 (s, 3H), 3.65 (br s, 2H), 3.75 (s, 3H), 4.88 (s, 2H), 6.68 (dd, J=2.4/9.2 Hz, 1H), 6.90 (d, J=8.8 Hz, 1H), 7.02 (d, J=2.4 Hz, 1H), 7.61–7.67 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.34 (s), 29.93 (s), 45.23 (s), 55.72 (s), 101.14 (s), 111.68 (s), 115.08 (s), 128.79 (s, 2C), 130.14 (s, 2C), 130.41 (s), 130.85 (s), 135.38 (s), 136.27 (s), 142.26 (s), 156.02 (s), 168.79 (s), 176.3 (s), one signal invisible; LCMS (ESI) t_R: 2.48 min (>99%, UV220, UV254), m/z: 372.0 $[M+H]^+$; HRMS (TOF, ES^+) $C_{20}H_{18}ClNO_4$ $[M+H]^+$ calcd mass 372.1003, found 372.1003.

4.12. 2-(1-(4-Chlorobenzoyl)-5-fluoro-1*H*-indol-3-yl)acetic acid 22n

According to general procedure D, methyl 2-(1-(4-chlorobenzoyl)-5-fluoro-1*H*-indol-3-yl)acetate (15 mg, 0.043 mmol) was subjected to

reaction with trimethyltin hydroxide (39 mg, 0.216 mmol) in 1,2-DCE (1 mL). The crude product was chromatographed on a short silica gel column using 1:1 ethyl acetate/hexane (0.5% AcOH) mixtures of increasing polarity as eluants to afford the title compound quantitatively as off-white solid. Yield: 11.2 mg (78%). $C_{17}H_{11}ClFNO_3$, M_r=331.73; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.66 (br s, 2H), 7.23 (td, J=2.6/9.2 Hz, 1H), 7.40–7.43 (m, 2H), 7.65–7.69 (m, 2H), 7.75–7.79 (m, 2H), 8.28 (dd, J=4.8/9.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 30.62 (s), 104.99 (d, J=24.3 Hz, 1C), 113.34 (d, J=24.9 Hz, 1C), 113.92 (s), 117.76 (d, J=8.9 Hz, 1C), 127.35 (s), 129.08 (s, 2C), 130.57 (s, 2C), 131.38 (d, J=9.7 Hz, 1C), 132.37 (s), 132.47 (s), 138.58 (s), 159.96 (d, J=242 Hz, 1C), 167.09 (s), 175.85 (s); ^{19}F NMR (282 MHz, DMSO-d_6) δ: −116.72 (5′-F); LCMS (ESI) t_R: 2.54 min (>99%, UV215, UV254, ELSD), m/z: 332.0 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{17}H_{11}ClFNO_3$ $[M+H]^+$ calcd mass 332.0490, found 332.0490.

4.13. 6-Methoxy-9-(3-(trifluoromethyl)benzoyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid 23

According to general procedure D, methyl 6-methoxy-9-(3-(trifluoromethyl)benzoyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylate (15 mg, 0.035 mmol; ~60% pure) was subjected to reaction with trimethyltin hydroxide (31 mg, 0.174 mmol) in 1,2-DCE (1 mL). The crude product was chromatographed on a short silica gel column using 1:1 ethyl acetate/hexane (0.5% AcOH) mixtures of increasing polarity as eluants to afford the title compound quantitatively as bright yellow solid. Yield: 8.5 mg (98%). $C_{22}H_{18}F_3NO_4$, M_r=417.38; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.69–1.75 (m, 1H), 2.02–2.06 (m, 1H), ~2.47 (m, 2H, partially overlaid by DMSO signal), 2.71–2.74 (m, 2H), 2.89–2.92 (m, 1H), 3.78 (s, 3H), 6.73 (dd, J=2.6/9.0 Hz, 1H), 7.03 (d, J=2.4 Hz, 1H), 7.10 (d, J=9.2 Hz, 1H), 7.78 (t, J=7.8 Hz, 1H), 7.93 (d, J=7.6 Hz, 1H), 7.99 (s, 1H), 8.03 (d, J=7.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.51 (s), 24.73 (s), 25.81 (s), 38.74 (s), 55.68 (s), 101.09 (s), 111.96 (s), 115.49 (s), 116.78 (s), 123.48 (d, J=272 Hz, 1C), 126.18 (s), 128.81 (s), 129.34 (s), 130.63 (s), 130.95 (s), 131.37 (d, J=29.0 Hz, 1C), 132.42 (s), 135.55 (s), 136.53 (s), 156.35 (s), 167.29 (s), 179.92 (s); ^{19}F NMR (282 MHz, DMSO-d_6) δ: −59.38 (m-CF_3); LCMS (ESI) t_R: 2.74 min (>99%, UV254, ELSD), m/z: 418.0 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{22}H_{18}F_3NO_4$ $[M+H]^+$ calcd mass 418.1266, found 418.1267.

4.14. Allyl 2-(5-methoxy-1*H*-indol-3-yl)acetate 25

To a solution of 2-(5-methoxy-1*H*-indol-3-yl)acetic acid **7b** (15.25 g, 74.3 mmol) in 250 mL of acetone was added 29 g of cesium carbonate (89.2 mmol) and allyl bromide (7.1 mL, 81.74 mmol). The reaction mixture was stirred at room temperature for 12 h. The residual cesium carbonate was removed by filtration and solvent was concentrated in vacuo. The residue was purified by column chromatography using Hex/EtOAc (gradient: 0–30% EtOAc) to afford allyl 2-(5-methoxy-1*H*-indol-3-yl)acetate 25 (13.6 g, 75%). $C_{14}H_{15}NO_3$, M_r=245.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.8 (s, 2H), 3.89 (s, 3H), 4.64 (dt, J=1.2, 5.7, 2H), 5.2 (dd, J=1.2, 10.4, 1H), 5.32 (dd, J=1.5, 17.2, 1H), 6.0–5.90 (m, 1H), 6.89 (dd, J=2.4, 8.8 Hz, 1H), 7.09 (d, J=2.4 Hz, 1H), 7.17 (s, 1H), 7.26 (d, J=8.8 Hz, 1H).

4.15. Allyl 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl) acetate 26

To a solution of allyl 2-(5-methoxy-1*H*-indol-3-yl)acetate **25** (10 g, 40.8 mmol) in dichloromethane (150 mL) were added triethylamine (17.1 mL, 122. 4 mmol) and DMAP (4.9 g, 40.8 mmol) at 0 °C. After stirring for 30 min, 4-chlorobenzoyl chloride (7.9 mL, 61.2 mmol) was added to the reaction mixture, which was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was then quenched with saturated ammonium chloride (200 mL), extracted with dichloromethane (3×150 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography using Hex/EtOAc (gradient: 0–30% EtOAc) to afford a yellow solid of allyl 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetate **26** (14.3 g, 92%). $C_{21}H_{18}ClNO_4$, M_r=383.82; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 2H), 3.88 (s, 3H), 4.62 (d, J=6.0 Hz, 2H), 5.23 (dd, J=1.2, 10.4 Hz, 1H), 5.29 (dd, J=1.2, 17.2 Hz, 1H), 5.95–5.84 (m, 1H), 7.01 (d, J=7.6 Hz, 2H), 7.25 (s, 1H), 7.50 (d, J=8.4 Hz, 2H), 7.67 (d, J=8.4 Hz, 2H), 8.28 (d, J=10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.97 (s), 55.70 (s), 65.74 (s), 101.93 (s), 113.76 (s), 114.68 (s), 117.39 (s), 118.69 (s), 126.31 (s), 128.92 (s, 2C), 130.50 (s, 2C), 130.73 (s), 131.43 (s), 131.78 (s), 132.85 (s), 138.15 (s), 156.89 (s), 166.96 (s), 170.25 (s); LCMS (ESI), single peak, t_R: 0.92 min (>99%, UV, ELSD), m/z: 384.0 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{21}H_{18}ClNO_4$ $[M+H]^+$ calcd mass 384.1003, found 384.1003.

4.16. 2-(1-(4-Chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid 2

To a solution of allyl 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetate **3** (14.3 g, 37.3 mmol) in THF (200 mL) were added morpholine (32.5 mL, 373 mmol) and $Pd(PPh_3)_4$ (2.3 g, 1.9 mmol) under argon at room temperature. Stirring was continued until LCMS analysis indicated starting material has disappeared. The mixture was filtered and concentrated in vacuo. The residue was redissolved in dichloromethane and acidified with 2 N HCl (50 mL) to afford white solid **2** (10 g, 79%). $C_{18}H_{14}ClNO_4$, M_r=343.76; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.67 (s, 2H), 3.81 (s, 3H), 6.99 (dd, J=2.4/9.2 Hz, 1H), 7.12 (d, J=2.4 Hz, 1H), 7.32 (s, 1H), 7.65–7.77 (m, 4H), 8.17 (d, J=9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 30.15 (s), 55.47 (s), 102.70 (s), 113.05 (s), 115.70 (s), 116.70 (s), 126.84 (s), 128.82 (s, 2C), 129.99 (s), 130.69 (s, 2C), 131.87 (s), 133.00 (s), 136.57 (s), 156.30 (s), 166.60 (s), 171.97 (s); LCMS (ESI) t_R: 2.60 min (>99%, ELSD), m/z: 344.0 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{18}H_{14}ClNO_4$ $[M+H]^+$ calcd mass 344.0690, found 344.0687.

4.17. Allyl 4-oxohexanoate 27

Succinyl dichloride **4** (4.6 mL, 41.6 mmol) in dichloromethane (200 mL) was cooled to −40 °C and ethylaluminum dichloride (50 mL, 50 mmol) was added at −40 °C. The reaction mixture was stirred at −40 °C for 3.5 h and quenched with the addition of anhydrous allyl alcohol (100 mL). The reaction mixture was concentrated to dryness and redissolved in dichloromethane (100 mL). The organic layer was washed with aqueous sodium potassium tartrate (2×50 mL), water (50 mL), and saturated aqueous NaCl (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to provide pure allyl 4-oxohexanoate **27** (5.2 g, 73%). $C_9H_{14}O_3$, M_r=170.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, J=7.2 Hz, 3H), 2.47 (q, J=7.2 Hz, 2H), 2.62 (t, J=6.4 Hz, 2H), 2.73 (t, J=6.4 Hz, 2H), 4.57 (d, J=5.6 Hz, 2H), 5.23 (dd, J=1.2, 10.4 Hz, 1H), 5.31 (dd, J=1.2, 18.0 Hz, 1H), 5.96–5.84 (m, 1H).

4.18. Allyl 3-(5-methoxy-3-methyl-1*H*-indol-2-yl)propanoate 28

To a mixture of (4-methoxyphenyl)hydrazine (10.4 g, 59.7 mmol) and allyl 4-oxohexanoate 5 (10.2 g, 59.7 mmol) in 1,4-dioxane (60 mL) was added acetic acid (30 mL) at room temperature. The reaction mixture was heated at 80 °C for 6 h then quenched with saturated $NaHCO_3$ (150 mL), extracted with EtOAc (3×60 mL), and dried over $MgSO_4$. The residue was purified by column chromatography using Hex/EtOAc (gradient: 0–40% EtOAc) to afford brown oil allyl 3-(5-methoxy-3-methyl-1*H*-indol-2-yl)propanoate **28** (11.6 g, 71%). $C_{16}H_{19}NO_3$, M_r=273.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.68 (t, J=6.4 Hz, 2H), 3.03 (t, J=6.4 Hz, 2H), 3.86 (s, 3H), 4.60 (d, J=7.2 Hz, 2H), 5.23 (dd, J=1.2, 10.4 Hz, 1H), 5.29 (dd, J=1.2, 17.2 Hz,

1H), 5.95–5.83 (m, 1H), 6.78 (dd, J=2.4, 8.8 Hz, 1H), 6.93 (d, J=2.4 Hz, 1H), 7.16 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.43 (s), 20.91 (s), 34.09 (s), 55.95 (s), 65.47 (s), 100.50 (s), 106.91 (s), 111.04 (s), 111.08 (s), 118.54 (s), 129.32 (s), 130.39 (s), 131.85 (s), 134.45 (s), 153.73 (s), 173.45 (s); LCMS (ESI), single peak, t_R: 0.79 min, m/z: 274.0 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{16}H_{19}NO_3$ $[M+H]^+$ calcd mass 274.1443, found 274.1441.

4.19. Allyl 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoate 29

To a solution of allyl 3-(5-methoxy-3-methyl-1*H*-indol-2-yl) propanoate **28** (16 g, 61.8 mmol) in 1,2-dichloroethane (200 mL) were added triethylamine (34.5 mL, 247.2 mmol) and DMAP (7.55 g, 61.8 mmol) at 0 °C. After stirring for 30 min, 4-chlorobenzoyl chloride (19.7 mL, 154.6 mmol) was added to the reaction mixture, which was allowed to stir for 12 h under reflux condition. The reaction mixture was cooled down, quenched with saturated ammonium chloride (200 mL), extracted with dichloromethane (3×150 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography using Hex/EtOAc (gradient: 0–30% EtOAc) to afford brown oil of allyl 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoate **29** (22.2 g, 87%). $C_{23}H_{22}ClNO_4$, M_r=411.88; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.69 (t, J=7.6 Hz, 2H), 3.29 (t, J=7.6 Hz, 2H), 3.83 (s, 3H), 4.53 (d, J=6.0 Hz, 2H), 5.18 (dd, J=1.2, 10.4 Hz, 1H), 5.25 (dd, J=1.2, 17.2 Hz, 1H), 5.93–5.78 (m, 1H), 6.44 (d, J=9.2 Hz, 1H), 6.59 (dd, J=2.8, 8.4 Hz, 1H), 6.89 (d, J=2.8 Hz, 1H), 7.46 (d, J=8.4 Hz, 2H), 7.65 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.67 (s), 21.67 (s), 34.14 (s), 55.65 (s), 65.18 (s), 101.38 (s), 111.48 (s), 114.78 (s), 116.38 (s), 118.28 (s), 129.10 (s, 2C), 129.33 (s), 130.76 (s), 131.15 (s, 2C), 131.66 (s), 131.84 (s), 132.06 (s), 133.88 (s), 136.71 (s), 139.15 (s), 155.77 (s), 168.13 (s), 172.23 (s); LCMS (ESI), single peak, t_R: 0.99 min, m/z: 412.0 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{23}H_{22}ClNO_4$ $[M+H]^+$ calcd mass 412.1316, found 412.1320.

4.20. 3-(1-(4-Chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid 30

To a solution of allyl 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoate **29** (11.1 g, 26.9 mmol) in THF (200 mL) were added morpholine (23.0 mL, 269 mmol) and $Pd(PPh_3)_4$ (1.67 g, 1.35 mmol) under argon at room temperature. Stirring was continued until LCMS analysis indicated starting material has disappeared. The mixture was filtered and concentrated in vacuo. The residue was redissolved in dichloromethane, acidified with 2 N HCl (50 mL), concentrated in vacuo, and purified by column chromatography using Hex/EtOAc (gradient: 0–100% EtOAc) to afford yellow solid of 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid **30** (7.9 g, 79%). $C_{20}H_{18}ClNO_4$, M_r=371.81; ^{1}H NMR (400 MHz, $CDCl_3$,) δ 2.24 (s, 3H), 2.72 (t, J=7.6 Hz, 2H), 3.29 (t, J=7.6 Hz, 2H), 3.83 (s, 3H), 6.42 (d, J=9.2 Hz, 1H), 6.59 (dd, J=2.8, 9.2 Hz, 1H), 6.90 (d, J=2.8 Hz, 1H), 7.45 (d, J=8.4 Hz, 2H), 7.64 (d, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 8.40 (s), 21.24 (s), 33.74 (s), 55.42 (s), 101.55 (s), 111.58 (s), 114.38 (s), 115.74 (s), 129.15 (s, 2C), 130.26 (s), 131.24 (s, 2C), 134.04 (s), 136.72 (s), 137.78 (s), 155.46 (s), 167.77 (s), 173.40 (s), one signal invisible; LCMS (ESI), single peak, t_R: 0.82 min, m/z: 372.0 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{20}H_{18}ClNO_4$ $[M+H]^+$ calcd mass 372.1003, found 372.1005.

4.21. 3-(1-(4-Chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)-*N*-(methylsulfonyl)propanamide 31

The reaction mixture of 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid **30** (7 g, 18.8 mmol) and methanesulfonamide (1.97 g, 20.7 mmol) in dichloromethane (94 mL) was treated with 1,1′-carbonyldiimidazole (3.05 g, 18.8 mmol) and DBU (3.4 mL, 22.6 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h then quenched with acetic acid (5 mL) and washed with brine (3×40 mL). The organic layer was then dried over $MgSO_4$ and the solvent was removed in vacuo. The yellow solid **31** (5.6 g, 61%) was obtained after column chromatography purification using Hex/EtOAc (gradient: 0–100% EtOAc with 0.5% of acetic acid). $C_{21}H_{21}ClN_2O_5S$, M_r=170.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.54 (dd, J=7.2, 7.6 Hz, 2H), 3.10 (dd, J=7.2, 7.6 Hz, 2H), 3.14 (s, 3H), 3.75 (s, 3H), 6.42 (d, J=9.2 Hz, 1H), 7.70–7.64 (m, 4H), 6.63 (dd, J=2.4, 9.2 Hz, 1H), 7.01 (d, J=2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 8.42 (s), 20.57 (s), 35.30 (s), 40.96 (s), 55.42 (s), 101.59 (s), 111.66 (s), 114.45 (s), 116.01 (s), 129.13 (s, 2C), 130.25 (s), 131.20 (s), 131.27 (s, 2C), 134.00 (s), 136.31 (s), 137.77 (s), 155.48 (s), 167.74 (s), 171.42 (s); LCMS (ESI), single peak, 0.81 min, m/z: 449.08 $[M+H]^+$; HRMS (TOF, ES$^+$) $C_{21}H_{21}ClN_2O_5S$ $[M+H]^+$ calcd mass 449.0938, found 449.0941.

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Supplementary data

Detailed synthetic procedures, routine spectroscopic and spectrometric data, and HPLC data, as well as exemplified ^{1}H and ^{13}C NMR spectra of intermediates and final compounds are available. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.08.044.

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