Molecules **2006**, *11*, 867-889

molecules

ISSN 1420-3049
http://www.mdpi.org

Full Paper

Synthesis and Structural Characterization of 1- and 2-Substituted Indazoles: Ester and Carboxylic Acid Derivatives

Fátima C. Teixeira [1,*], Hélène Ramos [1], Inês F. Antunes [1], M. João M. Curto [1], M. Teresa Duarte [2] and Isabel Bento [3]

[1] INETI - Departamento de Tecnologia de Indústrias Químicas, Estrada do Paço do Lumiar, 22, 1649-038 Lisboa, Portugal
[2] Instituto Superior Técnico, Centro de Química Estrutural, Complexo I, Av. Rovisco Pais, 1049-001 Lisboa, Portugal
[3] Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Apartado 127, 2781-901 Oeiras, Portugal

* Author to whom correspondence should be addressed; E-mail: fatima.teixeira@ineti.pt

Received: 4 October 2006; in revised form: 30 October 2006 / Accepted: 13 November 2006 / Published: 14 November 2006

Abstract: A series of indazoles substituted at the N-1 and N-2 positions with ester-containing side chains -$(CH_2)_nCO_2R$ of different lengths (n = 0-6, 9, 10) are described. Nucleophilic substitution reactions on halo esters ($X(CH_2)_nCO_2R$) by 1*H*-indazole in alkaline solution lead to mixtures of N-1 and N-2 isomers, in which the N-1 isomer predominates. Basic hydrolysis of the ester derivatives allowed the synthesis of the corresponding indazole carboxylic acids. All compounds were fully characterised by multinuclear NMR and IR spectroscopies, MS spectrometry and elemental analysis; the NMR spectroscopic data were used for structural assignment of the N-1 and N-2 isomers. The molecular structure of indazol-2-yl-acetic acid (**5b**) was determined by X-ray diffraction, which shows a supramolecular architecture involving O2-H...N1 intermolecular hydrogen bonds.

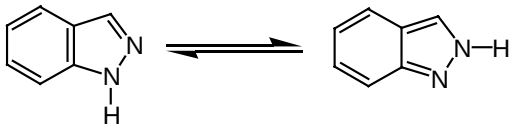
Keywords: Indazole, N-1 and N-2 isomers, Spectroscopic characterization, X-ray diffraction studies.

Introduction

Indazoles constitute an important class of heterocycles that display interesting biological properties [1,2], such as anti-depressant [3], anti-inflammatory [4,5], analgesic and antipyretic [6], dopamine antagonistic [7], anti-tumor [8], anti-emetic [9] and anti-HIV activities [10]. The indazole ring system is also present in many other compounds such as herbicides, dyes or sweeteners like guanidine-1*H*-indazole [1,2,11]. Despite the many useful applications of indazole derivatives, indazole chemistry remains less studied compared to other heteroaromatic compounds, such as indole or benzimidazole.

Indazole is a ten-π electron aromatic heterocyclic system. Like the pyrazole molecule, indazole resembles both pyridine and pyrrole and its reactivity reflects this dual behaviour [1]. The indazole ring has two nitrogen atoms and presents annular tautomerism with regards to the position of the NH hydrogen atom. Due to the difference in energy between the tautomers, the 1*H*-tautomer (the benzenoid form **1a**) predominates in the gas-phase, solution and solid state, and its derivatives are usually thermodynamically more stable than the corresponding 2*H*-forms (the quinonoid form **1b**) (Figure 1) [1,2,12,13].

Figure 1. Annular tautomerism of indazole (**1a**: benzenoid 1*H*-indazole tautomer; **1b**: quinonoid 2*H*-indazole tautomer).



1a **1b**

Several studies concerning the alkylation of 1*H*-indazole (**1**) reveal that the acidity or basicity of the medium, use of protic or aprotic solvents, as well as electronic and steric effects all affect the ratio of N-1 and N-2 alkylated isomers formed. Generally, the N-1 isomers are thermodynamically more stable, whereas the N-2 isomers are kinetically favoured [14]. Yamazaki [15] and Elguero [16] have reported the formation of both N-1 and N-2-acyl indazole derivatives, but they readily isomerize to afford the most stable isomer after equilibration. The regioselectivity of the reaction is also dependent on the nature of the alkylating agents used; recently Cheung *et al.* reported an efficient and regioselective synthesis of N-2 alkylated isomers using trimethyloxonium tetrafluoroborate or triethyloxonium hexafluorophosphonate as alkylating agents [17].

NMR spectroscopy is very useful to assign the structures of 1- and 2-substituted indazoles, as the ^{1}H-NMR and ^{13}C-NMR spectra of the two isomers are usually sufficiently different to be used as diagnostic tools to establish the position of substitution. ^{13}C-NMR spectroscopy is usually a particularly good method to perform this assignment [1,2,14,16-18].

As part of a continuing effort to develop novel heterocyclic compounds with potential therapeutic biological activity, we are currently involved in the synthesis of a large number of indazole derivatives. The substitution at the different atoms of the six- and five membered rings with side chains with different length and functionalisation, can afford a large number of indazole derivatives, presenting a promising field to provide new derivatives with biological/therapeutical properties.

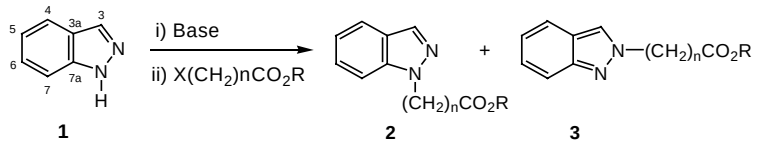
Here we report the synthesis, starting from 1*H*-indazole (**1**), of several indazole derivatives substituted at the N-1 and N-2 positions with side chains of different lengths and functionalised with ester or carboxylic acid groups. Their full characterization was achieved by IR and multinuclear NMR, mass spectrometry, mp and elemental analysis. The recrystallization of indazol-2-yl-acetic acid **5b** afforded crystals suitable for X-ray diffraction studies, which confirm the proposed structure. Application of these compounds to the synthesis of novel biologically active compounds is under investigation and will be reported in due course.

Results and Discussion

Synthesis

The indazole ester derivatives **2** and **3** were obtained in different yields and ratios starting from 1*H*-indazole (**1**) by nucleophilic substitution reactions of the corresponding halo esters with different hydrocarbon chain lengths (Table 1).

Table 1. Synthesis of indazole derivatives substituted at N-1 and N-2 (**2** and **3**).



1 **2** **3**

Series	n	Base (solvent)	$X(CH_2)_nCO_2R$		2	3	2 + 3
			X	R	(%)	(%)	(%)
a	0	K*t*-BuO (THF)	Cl	Me	99	-	99
b	1	K*t*-BuO (THF)	Cl	Et	(45)[a]	(10)[a]	
		K*t*-BuO(THF)	Br	Et	55	13	68
		K_2CO_3 (DMF)	Br	Et	67	22	89
c	2	K*t*-BuO (THF)	Br	Et	(15)[a]	(15)[a]	
		NaH (THF)	Br	Et	47	39	86
		K_2CO_3 (DMF)	Br	Et	49	46	95
d[b]	3	K*t*-BuO (THF)	Br	Et	(26)[a]	(18)[a]	
		K*t*-BuO (DMSO)	Br	Et	49	12	61[c]
		K_2CO_3 (DMF)	Br	Et	59	37	96
e[b]	4	K_2CO_3 (DMF)	Br	Et	59	31	90
f[b]	5	K*t*-BuO (THF)	Br	Et	(39)[a]	(39)[a]	
		K_2CO_3 (DMF)	Br	Et	62	34	96
g	6	K_2CO_3 (DMF)	Br	Et	61	36	97
h	9	K_2CO_3 (DMF)	Br	Me	63	34	97
i	10	K_2CO_3 (DMF)	Br	Me	60	38	98

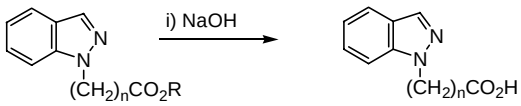
[a] Determined from the ^{1}H-NMR spectra; [b] For the same reagents, the reactions were also performed using bases such as NaH (THF) (n = 3-5), *n*BuLi (THF) (n = 3, 5), KOH (MeOH) (n = 3) and pyridine (n = 3), but indazole **1** remained unreacted; [c] A complex mixture of products was also obtained.

For best results, the reaction was carried out on the anionic form of the 1*H*-indazole, readily obtained *in situ* by the action of a base (K*t*-BuO, NaH, *n*BuLi, KOH, pyridine or K_2CO_3), in different solvents (THF, DMSO, MeOH or DMF). Compounds **2** and **3** were separated by column chromatography to provide the pure compounds, usually as pale yellow oils, in good to excellent yield. The N-1 isomers **2** were eluted first in each case and in all cases the N-1 isomers were the major isomers formed.

In these common nucleophilic displacement reactions, X in the compounds $X(CH_2)_nCO_2R$ corresponds to chloro or bromo atoms. When n≥1, the reactivity of chloroesters was lower than that of the corresponding bromoesters, so the latter were used. For n> 3 only the use of K_2CO_3 as base in DMF allows complete reactions. The reaction of indazole **1** with $ClCO_2Me$ in the presence of K*t*-BuO, at room temperature, gave only the N-1 isomer **2a** in excellent yield (99%). The synthesis of **2a** was previously reported by Kingsbury *et al*. [19], who showed that the reaction of $ClCO_2Me$ with indazole **1** in the presence of an amine, such as pyridine or triethylamine, gave the N-1 isomer **2a** (57%) at room temperature and the N-2 isomer at -78 ºC. The synthesis of **2b**, **2c**, **3b** and **3c**, using also a nucleophilic displacement reactions with bromo esters, was first reported by Auwers in 1926 [20], but no spectroscopic characterisation has been described. During the course of this work, a patent referring to compounds **2d**, **2e**, **3d** and **3e** was published, but no spectroscopic data was given [21].

The esters **2** and **3** were subject to basic hydrolysis to afford the corresponding N-1 and N-2 indazole carboxylic acid derivatives (compounds **4** and **5**, respectively), as white crystalline solids in good to excellent yields (Table 2 and 3). Indazol-2-yl-acetic acid **5b** gave crystals suitable for an X-ray structural analysis (see Figure 2, below).

Table 2. Physical-chemical characteristics and elemental analysis of indazole carboxylic acids **4b-i.**



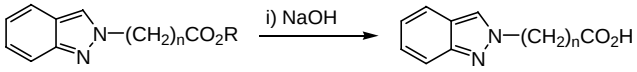
2 **4**

Nº	n	R	Yield (%)	mp (ºC)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4b	1	Et	97	186-188 [1]	$C_9H_8N_2O_2$	61.36	4.58	15.90	61.32	4.52	15.85
4c	2	Et	98	106-107 [2]	$C_{10}H_{10}N_2O_2$	63.15	5.30	14.73	62.96	5.34	14.49
4d	3	Et	93	60-62	$C_{11}H_{12}N_2O_2$	64.69	5.92	13.72	64.71	5.97	13.74
4e	4	Et	99	82-83	$C_{12}H_{14}N_2O_2$	66.04	6.47	12.84	66.11	6.58	12.86
4f	5	Et	100	69-70	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	67.42	6.99	11.97
4g	6	Et	74	54-58	$C_{14}H_{18}N_2O_2$	68.27	7.37	11.37	68.46	7.25	11.36
4h	9	Me	93	78-81	$C_{17}H_{24}N_2O_2$	70.80	8.39	9.71	70.67	8.49	9.65
4i	10	Me	95	73-74	$C_{18}H_{26}N_2O_2$	71.49	8.67	9.26	71.39	8.91	9.29

[1] (Lit. [20] (H_2O) 185-186 ºC)

[2] (Lit. [20] (C_6H_6/petroluem ether 105.5-106.5 ºC)

Table 3. Physical-chemical characteristics and elemental analyses of indazole carboxylic acids **5a-i.**



3 **5**

Nº	n	R	Yield (%)	mp (ºC)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
5b	1	Et	96	254-256 [1]	$C_9H_8N_2O_2$	61.36	4.58	15.90	61.24	4.51	15.90
5c	2	Et	98	147-149 [2]	$C_{10}H_{10}N_2O_2$	63.15	5.30	14.73	63.05	5.37	14.70
5d	3	Et	97	132-134	$C_{11}H_{12}N_2O_2$	64.69	5.92	13.72	64.71	5.99	13.64
5e	4	Et	98	112-114	$C_{12}H_{14}N_2O_2$	66.04	6.47	12.84	65.92	6.18	12.74
5f	5	Et	59	86-87	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	66.97	7.31	11.66
5g	6	Et	62	77-78	$C_{14}H_{18}N_2O_2$	68.27	7.37	11.37	68.15	7.38	11.27
5h	9	Me	90	68	$C_{17}H_{24}N_2O_2$	70.80	8.39	9.71	70.69	8.68	9.76
5i	10	Me	93	82	$C_{18}H_{26}N_2O_2$	71.49	8.67	9.26	71.53	8.68	9.15

[1] (Lit. [20] dec. 257 ºC) ; [2] (Lit. [20] (H_2O) 148 ºC)

Spectroscopic Characterization

The unambiguous assignment of indazole derivatives substituted at N-1 and N-2 was carried out by ^{1}H- and ^{13}C-NMR spectroscopy, DEPT and two-dimensional NMR techniques. The main resonances in the ^{1}H-NMR spectra of 1*H*-indazole ester derivatives **2b-i** in $CDCl_3$ are: i) three resonances in the δ = 7.12-7.73 ppm region, usually as a two proton multiplet, a one proton doublet and a one proton triplet, which correspond to the 4-H to 7-H protons, ii) a singlet (or a doublet with *J* = 0.6 Hz) at δ = 7.98-8.04 ppm, which corresponds to the 3-H proton, iii) a triplet for the the NC*H*$_2$ protons at δ = 4.36-5.13 ppm, and iv) resonances at δ = 1.22-3.65 ppm for the C*H*$_2$ protons. The ^{1}H-NMR spectrum of 1*H*-indazole ester derivative **2a** (n = 0), with the ester carbonyl group bonded to the nitrogen atom of the indazole, shows all the resonances at higher frequency than those of compounds **2b-i**, in particular the resonance of the 7-H proton, which appears at δ = 8.26 ppm, due to the deshielding effect of the ester carbonyl group.

The ^{1}H-NMR spectra of the N-1 and N-2 isomers are very different. Spectral comparison shows that the resonances of the 3-H to 6-H protons in the N-2 isomers appear at lower frequency than in the corresponding 1N-isomers, but the resonance of the 7-H proton of the N-2 isomers appears at higher frequency, due to the deshielding effect of the N-1 lone pair. The 3-H proton in the N-2 isomers is shielded relative to the same proton in the N-1 isomer. The main resonances of the N-2 ester derivatives **3** are: i) four resonances in the δ = 7.06-7.71 ppm region, usually as two one proton doublets (4-H and 7-H) and two one proton triplets (5-H and 6-H), ii) a singlet (or a doublet, *J* = 0.6 Hz) at δ = 7.88-8.00 ppm, which corresponds to the 3-H proton, iii) a triplet for the the NC*H*$_2$ protons at δ = 4.39-5.19 ppm, and iv) resonances at δ = 1.35-3.65 ppm for the C*H*$_2$ protons.

The chemical shifts of the indazole protons in carboxylic acids **4** and **5** do not differ substantially from those in the corresponding esters **2** and **3**, respectively. This is also the case for the side-chain protons.

The main resonances in the ^{1}H-NMR spectra of the 1*H*-indazole carboxylic acid derivatives **4** in MeOD are: i) four resonances at δ = 7.12-7.76 ppm, usually as two one proton doublets (4-H and 7-H) and two one proton triplets (5-H and 6-H), ii) a singlet (or a doublet with *J* = 0.6 Hz) at δ = 7.98-8.04 ppm corresponding to the 3-H proton, iii) a triplet for the NC*H*$_2$ protons at δ = 4.38-5.22 ppm, and iv) resonances at δ = 1.23-2.91 ppm for the C*H*$_2$ protons. The ^{1}H-NMR spectra of compounds **4d**, **4e** and **4f** were also recorded in $CDCl_3$. It was observed that the chemical shifts depend on solvents used, in particular the resonance of 7-H: in MeOD, it appears as a doublet at δ ≈ 7.53 ppm and in $CDCl_3$ it appears as a two proton multiplet at δ ≈ 7.40 ppm (with the same chemical shift as the 6-H proton). The ^{1}H-NMR spectrum of compound **4f** was also recorded in DMSO and it showed no significant differences compared to the spectrum recorded in MeOD.

The main resonances in the ^{1}H-NMR spectra of the 2*H*-indazole carboxylic acid derivatives **5c-i** in MeOD are: i) four resonances in the δ = 7.03-7.74 ppm region, usually as two one proton doublets (4-H and 7-H) and two one proton triplets (5-H and 6-H), ii) a singlet (or a doublet with *J* = 0.6 Hz) at δ = 8.16-8.36 ppm, corresponding to the 3-H proton, iii) a triplet for the NC*H*$_2$ protons at δ = 4.40-5.28 ppm, and iv) resonances at δ = 1.27-3.00 ppm for the C*H*$_2$ protons. The ^{1}H-NMR spectrum of carboxylic acid **5b** was recorded in DMSO, but comparison with the spectra of **5c-i** recorded in MeOD showed no significant differences. As observed for the N-1 isomer, the N-2 carboxylic acid derivatives **5** present ^{1}H-NMR spectra similar to those of the corresponding ester derivatives **3**, with the exception of the 3-H proton which is deshielded compared to the corresponding esters and N-1 isomers.

The main resonances in the ^{13}C-NMR spectra in $CDCl_3$ of 1*H*-indazole ester derivatives **2b-i** (with the exception **2a**) are: i) the resonances of C4 and C5 appear at δ ≈ 120-121 ppm, ii) C6 has a chemical shift of δ = 126 ppm, iii) C7 is the more shielded atom, with a chemical shift at δ = 108-109 ppm, iv) C3 appears at higher frequency, with a chemical shift at δ = 132-134 ppm; v) the quaternary C3a and C7a carbon atoms present different chemical shifts, with C7a at higher frequency (δ = 139 ppm) than C3a (δ = 123-125 ppm), vi) the CH_2 carbon atom resonances appear at δ = 22.2-34.5 ppm, as expected, and vii) the CO carbon atom has a chemical shift of δ = 167-174 ppm and becomes more deshielded in compounds with longer hydrocarbon chains. In the case of compound **2a** (n = 0), the chemical shift of carbon C7 is deshielded relative to the free indazole due to the ester group (Table 4).

Table 4. ^{13}C-NMR chemical shifts (δ in ppm) of 1*H*-indazole **1,** 1*H*-indazole esters **2a-i** and 2*H*-indazole esters **3b-i** in $CDCl_3$.

Nº	**n**	**R**	**C7**	**C4**	**C5**	**C6**	**C3**	**C3a**	**C7a**	**CO**	**NCH_2**	**CH_2**	**OCH_2CH_3**	**OCH_3**
1			110.0	120.4	120.1	125.8	133.4	122.8	139.9					
2a	0	Me	114.3	121.1	124.0	129.2	140.2	125.7	139.7	151.0				54.3
2b	1	Et	108.6	121.1	120.8	126.6	134.1	124.1	140.0	167.8	50.1		61.6, 13.9	
2c	2	Et	109.0	120.9*	120.5*	126.3	133.5	123.9	139.5	171.1	44.1	34.5	60.8, 14.0	
2d	3	Et	108.8	121.0*	120.4*	126.1	133.0	123.9	139.4	172.7	47.6	24.9, 30.9	60.4, 14.1	
2e	4	Et	108.9	121.1*	120.4*	126.1	132.8	124.0	139.3	173.2	48.4	22.2, 29.2, 33.7	60.3, 14.2	
2f	5	Et	108.8	121.0*	120.3*	126.0	132.7	123.9	139.3	173.4	48.5	24.5, 26.3, 29.4, 34.0	60.1, 14.1	

Table 4. Cont.

Nº	n	R	C7	C4	C5	C6	C3	C3a	C7a	CO	NCH_2	CH_2	OCH_2CH_3	OCH_3
2g	6	Et	108.9	121.1*	120.3*	126.0	132.7	123.9	139.3	173.7	48.7	24.7, 26.5, 28.7, 29.6, 34.2	60.2, 14.2	
2h	9	Me	108.9	121.0	120.3	126.0	132.6	123.9	139.3	174.2	48.8	24.8, 26.8, 29.0, 29.1, 29.2, 29.8, 34.0		51.4
2i	10	Me	109.0	121.1*	120.3*	126.0	132.6	124.0	139.3	174.3	48.9	24.9, 26.8, 29.05, 29.13, 29.26, 29.31, 29.8, 34.1		51.4
3b	1	Et	117.6	120.3	122.1	126.4	124.4	122.2	149.2	167.2	54.5		62.2, 14.1	
3c	2	Et	117.1	120.1	121.51	125.9	123.5	121.5	148.9	170.7	48.7	34.9	60.8, 13.9	
3d	3	Et	117.2	119.9	121.47	125.7	122.8	121.5	148.8	172.4	52.3	25.5, 30.7	60.4, 14.0	
3e	4	Et	117.2	120.0	121.5	125.7	122.6	121.6	148.7	173.0	53.2	21.9, 29.8, 33.5	60.3, 14.1	
3f	5	Et	117.3	119.9	121.5	125.7	122.5	121.6	148.8	173.4	53.4	24.3, 26.0, 30.2, 33.9	60.2, 14.1	
3g	6	Et	117.3	120.0	121.5	125.7	122.5	121.7	148.8	173.6	53.6	24.7, 26.3, 28.5, 30.4, 34.1	60.2, 14.2	
3h	9	Me	117.3	120.0*	121.4*	125.6	122.4	121.7	148.7	174.2	53.7	24.8, 26.6, 28.96, 28.98, 29.0, 29.1, 30.6, 34.0		51.4
3i	10	Me	117.4	120.0*	121.5*	125.7	122.5	121.7	148.8	174.3	53.8	24.9, 26.6, 29.04, 29.12, 29.24, 29.28, 30.6, 34.1		51.4

* These assignments may be reversed. The NMR assignment of the other compounds was done using two-dimensional NMR techniques.

Compared to the N-1 isomer **2** the N-2 isomers **3** present similar chemical shifts for CH_2, CO, C6, C4 and C5 (Table 4). Other carbon atoms present large differences that allow the unequivocal assignment of both isomers: i) C7 ($\delta \approx 117$ ppm) and C7a ($\delta \approx 148$-149 ppm) are more deshielded in the N-2 isomer, with $\Delta\delta \approx 8$-9 and 9-10 ppm, respectively, ii) C3 ($\delta \approx 122$-124 ppm) and C3a ($\delta \approx 121$-122 ppm) are more shielded in these N-2 isomers, with $\Delta\delta \approx 10$ ppm (C3) and $\Delta\delta \approx 2$-3 ppm (C3a).

In the ^{13}C-NMR spectra in MeOD, the differences between the N-1 and N-2 indazole carboxylic acids **4** and **5** are similar to those observed in the spectra of the ester derivatives: i) CH_2, CO, C6, C5 and C4 have similar chemical shifts in both isomers, ii) C7 and C7a are deshielded in the N-2 isomers with $\Delta\delta \approx 7$ ppm (C7) and $\Delta\delta \approx 10$-11 ppm (C7a), iii) the C3 ($\delta \approx 135$ ppm in N-1 and $\delta \approx 125$ ppm in N-2 isomer) and C3a ($\delta \approx 125$ ppm in N-1 and $\delta \approx 122$-123 ppm in N-2 isomer) are more shielded in the N-2 than in the N-1 isomers (Table 5).

The ^{13}C-NMR spectra in different deuterated solvents show similar patterns, with small differences in the chemical shifts, as were observed at higher frequencies in MeOD. Comparison of the spectra of indazole carboxylic acid derivatives **4d**, **4e** and **4f** and indazole esters **2d**, **2e** and **2f** in the same solvent ($CDCl_3$), reveal no differences between their ^{13}C-NMR spectra, with the exception of the CO carbon atom. These observations confirm that, despite the change in the functional groups of indazole derivatives (with no mesomeric effect towards the indazole ring) the chemical shifts of indazole ring carbon atoms remain constant, which allows the assignment of N-1 and N-2 isomers of carboxylic acid derivatives by ^{13}C-NMR spectroscopy.

These spectroscopic data are in agreement with the ^{13}C-NMR spectra of 1N- and 2N-substituted indazoles reported in the literature [1,2,8,11,12]. The structural assignments were ultimately confirmed by X-ray crystal structure analysis of compound **5b**.

Table 5. ^{13}C-NMR chemical shifts (δ in ppm) of 1*H*-indazole carboxylic acids **4b-i** and 2*H*-indazole carboxylic acids **5b-i.**

Nº	n	Solvent	C7	C4	C5	C6	C3	C3a	C7a	CO	NCH_2	CH_2
4b	1	MeOD	110.4	122.1	122.1	128.1	135.0	125.4	141.8	171.5	50.6	
4c	2	MeOD	110.6	122.0*	121.9*	127.8	134.5	125.2	141.0	174.6	45.2	35.1
4d	3	MeOD	110.3	122.2*	121.9*	127.8	134.1	125.2	141.0	174.6	48.6	26.2, 31.6
4d	3	$CDCl_3$	108.9	121.3*	120.7*	126.6	132.9	123.7	139.4	177.6	47.4	24.7, 30.8
4e	4	MeOD	110.3	122.1*	121.8*	127.7	133.8	125.2	140.9	177.0	49.2	23.3, 30.3, 34.3
4e	4	$CDCl_3$	108.8	121.2*	120.5*	126.4	132.7	123.7	139.3	178.3	48.2	21.9, 29.0, 33.4
4f	5	MeOD	110.4	122.2	121.8	127.7	133.8	125.1	140.9	177.4	49.3	25.6, 27.3, 30.6, 34.7
4f	5	$CDCl_3$	108.9	121.2	120.5	126.3	132.7	123.8	139.3	178.9	48.5	24.2, 26.2, 29.4, 33.8
4f	5	DMSO	109.6	120.8	120.3	125.9	132.4	123.4	139.2	174.4	47.9	24.1, 25.8, 29.2, 33.6
4g	6	MeOD	110.4	122.1*	121.8*	127.7	133.7	125.1	140.9	177.5	49.4	25.8, 27.4, 29.7, 30.7, 34.7
4h	9	MeOD	110.4	122.2*	121.8*	127.7	133.7	125.1	140.9	177.7	49.5	26.0, 27.7, 30.11, 30.18, 30.2, 30.3, 30.9, 34.9
4i	10	MeOD	110.4	122.1	121.8	127.7	133.7	125.1	140.9	177.7	49.5	26.0, 27.7, 30.1, 30.27, 30.34, 30.4, 30.9, 34.9
5b	1	DMSO	117.0	120.8	121.2	125.8	125.5	121.6	148.2	169.3	54.2	
5c	2	MeOD	117.4	121.6	122.7	127.6	125.9	122.9	150.1	174.0	49.9	35.6
5d	3	MeOD	117.4	121.6*	122.7*	127.5	125.5	123.1	150.1	176.2	53.4	27.0, 31.5
5e	4	MeOD	117.3	121.5*	122.6*	127.5	125.4	123.1	149.9	176.9	53.9	23.0, 31.0, 34.2
5f	5	MeOD	117.3	121.5	122.6	127.4	125.4	123.1	149.9	177.3	54.1	25.5, 27.1, 31.3, 34.6
5g	6	MeOD	117.3	121.5*	122.6*	127.4	125.3	123.0	149.9	177.5	54.2	25.8, 27.2, 29.6, 31.4, 34.7
5h	9	MeOD	117.3	121.5	122.6	127.4	125.3	123.1	149.9	177.7	54.3	26.0, 27.5, 30.0, 30.1, 30.2, 30.3, 31.6, 34.9
5i	10	MeOD	117.3	121.5*	122.6*	127.4	125.3	123.1	149.9	177.7	54.3	26.1, 27.5, 30.1, 30.2, 30.3, 30.38, 30.41, 31.6, 35.0

* These assignments may be reversed. The NMR assignment of the other compounds was done using two-dimensional NMR techniques.

The IR spectra of compounds **2** and **3** show $\nu_{(C=O)}$ stretching bands in the range of 1731-1748 cm^{-1} and $\nu_{(C-O)}$ stretching bands in the 1171-1212 cm^{-1}region. The $\nu_{(C=O)}$ stretching band frequencies are similar in both the N-1 and N-2 isomers. The absence of the NH stretching band confirmed the

substitution on the nitrogen atom. The IR spectra of indazole carboxylic acids **4** and **5** show broad bands in the 3500-2300 cm^{-1} region, corresponding to the hydrogen-bonded O-H characteristic of carboxylic acids. These bands overlap the C-H stretching region around 3000 cm^{-1}. The spectra also showed $\nu_{(C=O)}$ stretching bands at the usually lower frequency than the corresponding esters, in the 1689-1736 cm^{-1} region. In general, the $\nu_{(C=O)}$ stretching bands reveal a shift to lower wavenumber with an increasing alkyl side chain directly linked to the nitrogen atom of indazole.

The electron impact (EI) mass spectra of all compounds show the $[M]^+$ ions with relative abundances varying from 5 to 100% of the respective base peaks, with small molecular peaks for compounds with longer side chains. In most of the spectra, the ions with *m*/*z* values corresponding to $[IndzCH_2]^+$ and $[IndzH]^+$ (IndzH-Indazole) are either the base peaks or have high relative abundances. The mass spectra of 1*H*- and 2*H*-indazole ester derivatives **2** and **3** are similar and their fragmentation generally involves the formation of $[M\text{-}OR]^+$, $[M\text{-}COOR]^+$ and $[M\text{-}(CH_2)_nCOOR]^+$ ions. Mass spectra of the 1*H*- and 2*H*-indazole carboxylic acid derivatives **4** and **5** are also similar. Their fragmentation involves the formation of $[M\text{-}COOH]^+$ and $[M\text{-}(CH_2)_nCOOH]^+$ ions.

Molecular and crystal structure of 2-indazol-2-yl-acetic acid (**5b**)

2-Indazol-2-yl-acetic acid (**5b,** n = 1) was recrystallized from acetone/water solution to afford crystals suitable for X-ray diffraction studies. Compound **5b** crystallizes in the centrosymetric space group $P2_1/n$, with one molecule per asymmetric unit. The ORTEP [23] view of the molecule, with the atomic numbering scheme, is given in Figure 2. Detailed bond distances and angles and other structural parameters, are given in Table 6.

Figure 2. ORTEP [23] view of compound **5b** showing the atomic labelling scheme and the relative positioning of the indazole ring and the carboxylic moiety.

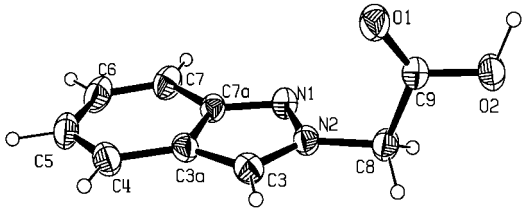


Table 6. Bond lengths [Å], angles [º] and other structural parameters for compound **5b.**

N1-C7a	1.349(2)	C3a-C4	1.421(2)
N1-N2	1.3526(19)	C8-C9	1.516(2)
N2-C3	1.334(2)	C5-C4	1.355(3)
N2-C8	1.446(2)	C5-C6	1.408(3)
C7a-C3a	1.413(2)	C7-C6	1.360(3)
C7a-C7	1.413(3)	C9-O1	1.200(2)
C3a-C3	1.384(3)	C9-O2	1.307(2)

Table 6. Cont.

C7a-N1-N2	104.08(12)	N2-C8-C9	112.22(14)
C3-N2-N1	113.32(14)	C4-C5-C6	121.66(18)
C3-N2-C8	127.88(16)	C5-C4-C3a	118.2(2)
N1-N2-C8	118.73(14)	C6-C7-C7a	117.5(2)
N1-C7a-C3a	111.07(15)	N2-C3-C3a	107.08(16)
N1-C7a-C7	128.05(17)	C7-C6-C5	122.1(2)
C3a-C7a-C7	120.86(16)	O1-C9-O2	125.35(16)
C3-C3a-C7a	104.44(14)	O1-C9-C8	124.33(15)
C3-C3a-C4	135.92(18)	O2-C9-C8	110.32(14)
C7a-C3a-C4	119.64(17)		

Angle between planes

C3a-C3-N1-N2-C7a and C9-O1-O2 87.2(1)

Torsion angles

N2-C8-C9-O1	10.0(3)	N1-N2-C8-C9	87.99(19)
N2-C8-C9-O2	-169.98(15)	C3-N2-C8-C9	-88.9(2)

Hydrogen bond

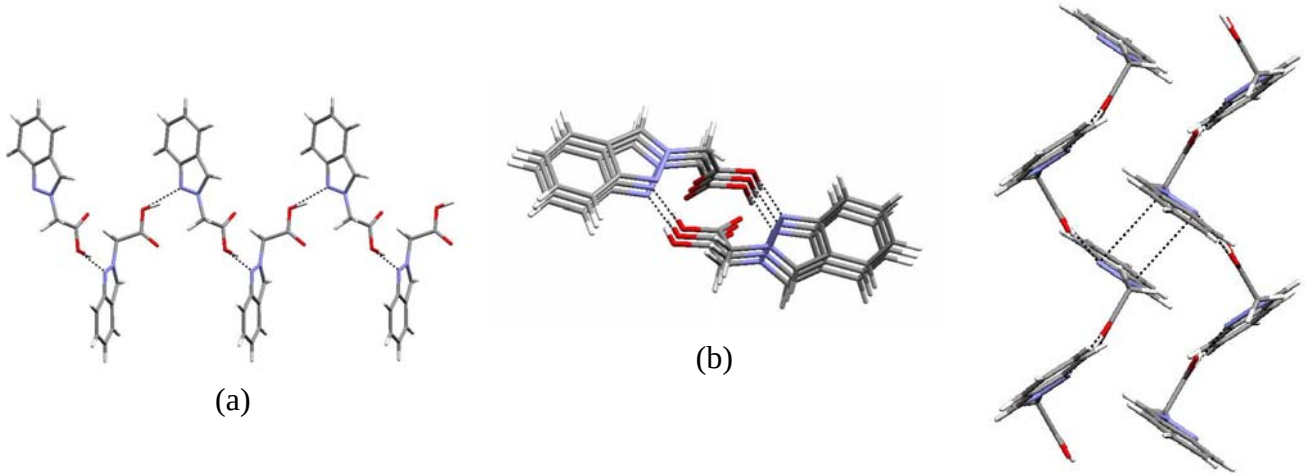
D-H…A	D-H	H...A	D...A	D-H..A
O2-H2...N1[a]	1.02(3) Å	1.68(3) Å	2.677(2) Å	164(3)°

[a]- symmetry operation 1/2-x,1/2+y,3/2-z

The molecular structure of the indazole is similar to that of related compounds reported in the literature [24]. As expected, the indazole moiety is planar, with maximum deviations of 0.0052(9) Å in the N1 atom. Atom C8 is still within the indazole least square plane, but the carboxyl group (COOH) is oriented perpendicularly, forming an angle of 87.2(1)° with the five membered pyrazole ring. The plane containing the COOH group bisects the indazole almost as a mirror plane, but no disorder was found in the molecule. The values of the torsion angles N2-C8-C9-O1 [10.0(3)º] and N2-C8-C9-O2 [-169.98(15)º], showing the planarity of the fragment, as well as N1-N2-C8-C9 [87.99(19)º] and C3-N2-C8-C9 [-88.9(2)º] support the relative orientation of the carboxy moiety described above.

The secondary structure of compound **5b** presents a one dimensional zigzag chain, due to the short O2-H...N1 intermolecular hydrogen bond [2.677(2) Å with an angle of 164(3)°], which is preferably observed, instead of the $R_2^2(8)$ main pattern found in carboxylic acid derivatives (C-O-H…O-C-O-H…O contacts) [25]. The one-dimensional zigzag chain along the **b** axis obtained with a C(6) synthon as well as the weak π…π contacts [~ 2.75(4) Å] within neighbouring chains are shown in the packing diagrams of Figure 3 (a, b and c, respectively). The supramolecular motif found in the crystal structure of compound **5b** agrees with the data in the literature, either for 1*H*-unsubstituted indazoles [26] where N-H…N hydrogen bonds are responsible for the supramolecular pattern, or with pyrazole [27] or even with pyrazole carboxylic acid derivatives [28] where the usual hydrogen bond ring pattern $R_2^2(8)$ [25] is not found, due to the strength of this heteromeric intermolecular interaction [29].

Figure 3. (a) and (b) View along axis **a** and **b** respectively, showing the C(6) hydrogen bond synthon, responsible for the zigzag chain. (c) Packing diagram along axis **c** shows the weak interaction between the zigzag neighbouring chains, due to the π…π contacts (drawings done with Mercury) [24b].



(a) (b) (c)

Conclusions

A series of seventeen esters and sixteen carboxylic acids with side chains with different length derived from indazole substituted at N-1 and N-2, is reported. General synthetic routes to these compounds have been described and their full spectroscopic characterization and structural features have been presented. Spectroscopic data were used to assign the substitution patterns and the major differences in these data are pointed out. Recrystallization of compound **5b** (n = 1) gave crystals suitable for X-ray crystal structure analysis. Application of these compounds to the synthesis of novel biologically active compounds will be described in a subsequent paper.

Acknowledgements

We thank Fundação para a Ciência e a Tecnologia (POCTI, POCI and FEDER programs) for provision of funding (Projects POCTI/QUI/39368/ 2001 and POCI/QUI/55508/2004).

Experimental

General

Reagents were used as purchased and were purified when necessary according to standard procedures [30]. 7-Bromoheptanoic acid ethyl ester was a gift from CU Chemie Uetikon GmbH (Germany). Column chromatography was performed on silica gel (230-400 Mesh) under a positive pressure of nitrogen. Melting points were determined on a Reichert Thermovar melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX 300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. The

assignment of ^{1}H- and ^{13}C- multiplicities was done using a DEPT sequence, two-dimensional NMR (HETCOR and COSY) and irradiations techniques (Tables 4 and 5). Infrared spectra were recorded on a Perkin Elmer FT-IR 1725xIR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic bands are quoted in cm^{-1}. Low-resolution mass spectra (MS) were recorded on a Kratos 25 RF or a Thermo Quest model GCQplus spectrometer. High-resolution mass spectra (HRMS) were obtained on a VG AutoSpect M instrument. Elemental analyses were performed on a CE instrument EA 1110CHNS-O or a Fisons EA-1108 elemental analyser (for compounds **4** and **5** see Table 2 and 3). Although compounds **2a-e** [19-21], **3b-e** [20,21], **4b-e** [20,21,31] and **5b-e** [20,21] have been noted previously in the literature, no full spectroscopic characterisation has been reported, therefore the full characterisation of these compounds is described herein.

General procedure 1 (using Kt-BuO as base). K*t*-BuO (1.6 eq.) was added to a solution of indazole **1** (1 eq.) in THF at 0 ^{o}C. The reaction mixture was warmed to r.t., stirred over 1 h. and then recooled to 0 ^{o}C. After 15 min., excess $X(CH_2)_nCO_2R$ was added and the reaction mixture was allowed to warm to r.t. and stirred for 0.5-4 h. The solvent was removed under reduced pressure and the residue was redissolved in EtOAc, washed successively with water and brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The resulting oil was purified by column chromatography (2:3 ether/petroleum ether).

General procedure 2 (using K_2CO_3 as base): A mixture of indazole **1** (1 eq.) and K_2CO_3 (3-10 eq.) in DMF was stirred at 80 ^{o}C. After 30 min., excess $X(CH_2)_nCO_2R$ was added and the reaction mixture was stirred for 4-24 h. at 80 ^{o}C. Upon cooling, the mixture was acidified with 10% aqueous HCl solution and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo* and the resulting oil was purified by column chromatography (2:3 ether/petroleum ether).

Indazole-1-carboxylic acid methyl ester (**2a**)

Following general procedure 1, reaction of indazole **1** (200 mg, 1.69 mmol) in THF (10 mL), K*t*-BuO (260 mg, 2.73 mmol) and $ClCO_2CH_3$ (0.13 mL, 1.69 mmol) for 30 min. gave compound **2a** (290 mg, 99%) as a white solid, mp 56-58 ºC (Lit. [19] 58-60 ºC); IR (KBr): 3013 (C-H)Ar, 2958 (C-H), 1736 (C=O), 1611, 1457 (C=C, C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.13 (s, 3 H, OCH_3), 7.36 (t, *J* = 7.8, 1 H, 5-H or 6-H), 7.58 (dt, *J* = 7.8 and 0.9, 1 H, 5-H or 6-H), 7.76 (d, *J* = 7.8, 1 H, 4-H), 8.20 (s, 1 H, 3-H), 8.26 (d, *J* = 8.4, 1 H, 7-H); MS (EI): *m/z* (%)= 176 (100) $[M]^+$, 145 (4) $[M\text{-}OMe]^+$, 118 (19) $[IndzH]^+$, 117 (9) $[M\text{-}CO_2Me]^+$; Anal. Calcd. for $C_9H_8N_2O_2$: C 61.36, H 4.58, N 15.90. Found: C 61.31, H 4.61, N 15.74.

Indazol-1-yl-acetic acid ethyl ester (**2b**) *and indazol-2-yl-acetic acid ethyl ester* (**3b**)

Following general procedure 1, reaction of indazole **1** (500 mg, 4.23 mmol) in THF (10 mL), K*t*-BuO (665 mg, 5.93 mmol) and $BrCH_2CO_2Et$ (0.56 mL, 5.08 mmol) for 2 h. gave compounds **2b** (474

mg, 55%) and **3b** (110 mg, 13%) as pale yellow oils. *Compound* **2b**: IR (film): 3064 (C-H)Ar, 2983, 2940 (C-H), 1748 (C=O), 1619, 1504, 1470, 1435 (C=C, C=N), 1210 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.21 (t, *J* = 7.2, 3 H, OCH_2CH_3), 4.18 (q, *J* = 7.2, 2 H, OCH_2CH_3), 5.13 (s, 2 H, NCH_2CO_2Et), 7.15 (m, 1 H, 5-H), 7.33 (m, 2 H, 6-H and 7-H), 7.72 (dd, *J* = 8.1 and 0.6, 1 H, 4-H), 8.04 (d, *J* = 0.9, 1 H, 3-H); MS (EI): *m/z* (%) = 204 (27) $[M]^+$, 131 (100) $[M\text{-}CO_2Et]^+$, 118 (2) $[IndzH]^+$; HRMS (EI): calcd. for $[M]^+$ ($C_{11}H_{12}N_2O_2$): 204.0899, found 204.0893. *Compound* **3b**: IR (film): 3121, 3065 (C-H)Ar, 2984, 2941 (C-H), 1746 (C=O), 1630, 1520, 1475, 1429 (C=C, C=N), 1212 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.28 (t, *J* = 7.2, 3 H, OCH_2CH_3), 4.25 (q, *J* = 7.2, 2 H, OCH_2CH_3), 5.19 (s, 2 H, NCH_2CO_2Et), 7.09 (t, *J* = 7.2, 1 H, 5-H), 7.29 (m, 1 H, 6-H), 7.66 (d, *J* = 8.4, 1 H, 4-H), 7.68 (dd, *J* = 8.7 and 0.6, 1 H, 7-H), 8.00 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 204 (64) $[M]^+$, 131 (100) $[M\text{-}CO_2Et]^+$, 118 (11) $[IndzH]^+$; HRMS (EI) calcd. for $[M]^+$ ($C_{11}H_{12}N_2O_2$): 204.0899, found 204.0903. Following general procedure 2, indazole **1** (3.00 g, 25.4 mmol) in DMF (10 mL), K_2CO_3 (10.53 g, 76.18 mmol) and $BrCH_2CO_2Et$ (4.2 mL, 38.1 mmol) gave compound **2b** (3.49 g, 67%) and compound **3b** (1.16 g, 22%) after reacting for 24 h.

3-Indazol-1-yl-propionic acid ethyl ester (**2c**) *and 3-indazol-2-yl-propionic acid ethyl ester* (**3c**)

Following general procedure 2, reaction of indazole **1** (3.00 g, 25.4 mmol) in DMF (10 mL), K_2CO_3 (10.53 g, 76.18 mmol) and $Br(CH_2)_2CO_2Et$ (4.9 mL, 38.1 mmol) for 4 h. gave compounds **2c** (2.72g, 49%) and **3c** (2.53 g, 46%) as pale yellow oils. *Compound* **2c**: IR (film): 3062 (C-H)Ar, 2982, 2938 (C-H), 1734 (C=O), 1616, 1500, 1466, 1447 (C=C, C=N), 1192 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.16 (t, *J* = 7.2, 3 H, OCH_2CH_3), 2.96 (t, *J* = 6.9, 2 H, $CH_2CH_2CO_2Et$), 4.08 (q, *J* = 7.2, 2 H, OCH_2CH_3), 4.67 (t, *J* = 6.9, 2 H, NCH_2), 7.13 (t, *J* = 7.5, 1 H, 5-H), 7.38 (dt, *J* = 7.5 and 1.2, 1 H, 6-H), 7.48 (dd, *J* = 8.7 and 0.6, 1 H, 7-H), 7.70 (d, *J* = 8.1, 1 H, 4-H), 8.00 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 218 (90) $[M]^+$, 173 (58) $[M\text{-}OEt]^+$, 145 (31) $[M\text{-}CO_2Et]^+$, 131 (100) $[M\text{-}CH_2CO_2Et]^+$, 118 (45) $[IndzH]^+$; HRMS (EI) calcd. for $[M]^+$ ($C_{12}H_{14}N_2O_2$): 218.1055, found 218.1054. *Compound* **3c**: IR (film): 3121, 3062 (C-H)Ar, 2982, 2938 (C-H), 1733 (C=O), 1628, 1517, 1471, 1446 (C=C, C=N), 1201 (C-O) cm^{-1}; ^{1}H- NMR ($CDCl_3$): 1.21 (t, *J* = 7.2, 3 H, OCH_2CH_3), 3.03 (t, *J* = 6.6, 2 H, $CH_2CH_2CO_2Et$), 4.11 (q, *J* = 7.2, 2 H, OCH_2CH_3), 4.69 (t, *J* = 6.6, 2 H, NCH_2), 7.06 (t, *J* = 7.5, 1 H, 5-H), 7.27 (t, *J* = 8.7, 1 H, 6-H), 7.63 (d, *J* = 8.4, 1 H, 4-H), 7.68 (d, *J* = 8.7, 1 H, 7-H), 7.99 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 218 (75) $[M]^+$, 173 (24) $[M\text{-}OEt]^+$, 145 (45) $[M\text{-}CO_2Et]^+$, 131 (42) $[M\text{-}CH_2CO_2Et]^+$, 118 (100) $[IndzH]^+$; HRMS (EI) calcd. for $[M]^+$ ($C_{12}H_{14}N_2O_2$): 218.1055, found 218.1047. The reaction was also performed using general procedure 1. Analysis of the ^{1}H-NMR spectrum of the crude product indicated the presence of **2c**, **3c** and **1** in the ratio 15:15:70.

4-Indazol-1-yl-butyric acid ethyl ester (**2d**) *and 4-indazol-2-yl-butyric acid ethyl ester* (**3d**)

Following general procedure 2, reaction of indazole **1** (3.00 g, 25.4 mmol) in DMF (10 mL), K_2CO_3 (10.53 g, 76.18 mmol) and $Br(CH_2)_3CO_2Et$ (5.4 mL, 38.1 mmol) for 24 h. gave compounds **2d** (3.49 g, 59%) and **3b** (2.16 g, 37%) as pale yellow oils. *Compound* **2d**: IR (film): 3063 (C-H)Ar, 2981, 2939 (C-H), 1731 (C=O), 1616, 1500, 1466, 1447 (C=C, C=N), 1190 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.21 (t, *J* = 7.2, 3 H, OCH_2CH_3), 2.19-2.32 (m, 4 H, $CH_2CH_2CO_2Et$), 4.10 (q, *J* = 7.2, 2 H, OCH_2CH_3),

4.45 (t, *J* = 6.6, 2 H, NC*H*$_2$), 7.13 (dt, *J* = 7.5 and 0.9, 1 H, 5-H), 7.38 (m, 2 H, 6-H and 7-H), 7.71 (d, *J* = 8.1, 1 H, 4-H), 7.99 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 232 (75) [M]$^+$, 187 (100) [M-OEt]$^+$, 159 (9) [M-CO_2Et]$^+$, 145 (22) [M-CH_2CO_2Et]$^+$, 131 (76) [M-$(CH_2)_2CO_2$Et]$^+$, 118 (20) [IndzH]$^+$; HRMS (EI) calcd. for [M]$^+$ ($C_{13}H_{16}N_2O_2$): 232.1212, found 232.1212. *Compound* **3d**: IR (film): 3119, 3061 (C-H)Ar, 2982, 2980 (C-H), 1730 (C=O), 1628, 1515, 1469, 1445 (C=C, C=N), 1186 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.22 (t, *J* = 7.2, 3 H, OCH$_2$C*H*$_3$), 2,30 (m, 4 H, C*H*$_2$C*H*$_2$CO$_2$Et), 4.10 (q, *J* = 7.2, 2 H, OC*H*$_2$CH$_3$), 4.46 (t, *J* = 6.6, 2 H, NC*H*$_2$), 7.06 (dt, *J* = 7.5 and 0.6, 1 H, 5-H), 7.27 (m, 1 H, 6-H), 7.63 (d, *J* = 8.7, 1 H, 4-H), 7.70 (dd, *J* = 8.7 and 0.9, 1 H, 7-H), 7.88 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 232 (68) [M]$^+$, 187 (47) [M-OEt]$^+$, 159 (7) [M]$^+$, 145 (17) [M-CH_2CO_2Et]$^+$, 131 (100) [M-$(CH_2)_2CO_2$Et]$^+$, 118 (36) [IndzH]$^+$; HRMS (EI) calcd. for [M]$^+$ ($C_{13}H_{16}N_2O_2$): 232.1212, found 232.1218. The reaction was also performed using general procedure 1. Analysis of the ^{1}H-NMR spectrum of the crude product indicated the presence of **2d**, **3d** and **1** in the ratio 26:18:56.

5-Indazol-1-yl-pentanoic acid ethyl ester (**2e**) *and 5-indazol-2-yl-pentanoic acid ethyl ester* (**3e**)

Following general procedure 2, reaction of indazole **1** (3.00 g, 25.4 mmol) in DMF (10 mL), K_2CO_3 (10.53 g, 76.18 mmol) and Br$(CH_2)_4CO_2$Et (4.7 mL, 33.02 mmol) for 24 h. gave compounds **2e** (3.67 g, 59%) and **3e** (1.95 g, 31%) as pale yellow oils. *Compound* **2e**: IR (film): 3062 (C-H)Ar, 2982, 2939 (C-H), 1732 (C=O), 1616, 1500, 1466, 1447 (C=C, C=N), 1184 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.22 (t, *J* = 7.2, 3 H, OCH$_2$C*H*$_3$), 1.60-1.70 (m, 2 H, C*H*$_2$CH$_2$CO$_2$Et), 1.93-2.03 (m, 2 H, NCH$_2$C*H*$_2$), 2.32 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$Et), 4.10 (q, *J* = 7.2, 2 H, OC*H*$_2$CH$_3$), 4.40 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.13 (dt, *J* = 7.2 and 1.8, 1 H, 5-H), 7.39 (m, 2 H, 6-H and 7-H), 7.73 (td, *J* = 8.1 and 0.9, 1 H, 4-H), 7.99 (d, *J* = 0.9, 1 H, 3-H); MS (EI): *m/z* (%) = 246 (27) [M]$^+$, 201 (56) [M-OEt]$^+$, 173 (10) [M-CO_2Et]$^+$, 131 (100) [M-$(CH_2)_3CO_2$Et]$^+$, 118 (30) [IndzH]$^+$; HRMS (EI) calcd. for [M]$^+$ ($C_{14}H_{18}N_2O_2$): 246.1368, found 246.1362. *Compound* **3e**: IR (film): 3119, 3061 (C-H)Ar, 2980, 2942 (C-H), 1731 (C=O), 1630, 1516, 1469, 1446 (C=C, C=N), 1186 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.22 (t, *J* = 7.2, 3 H, OCH$_2$C*H*$_3$), 1.59-1.69 (m, 2 H, C*H*$_2$CH$_2$CO$_2$Et), 2.00-2.10 (m, 2 H, NCH$_2$C*H*$_2$), 2.32 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$Et), 4.10 (q, *J* = 7.2, 2 H, OC*H*$_2$CH$_3$), 4.41 (t, *J* = 6.9, 2 H, NC*H*$_2$), 7.06 (dt, *J* = 7.5 and 0.9, 1 H, 5-H), 7.27 (m, 1 H, 6-H), 7.63 (td, *J* = 8.4 and 0.9, 1 H, 4-H), 7.70 (dd, *J* = 8.7 and 0.9, 1 H, 7-H), 7.89 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 246 (62) [M]$^+$, 201 (63) [M-OEt]$^+$, 173 (35) [M-CO_2Et]$^+$, 159 (4) [M-CH_2CO_2Et]$^+$, 145 (11) [M-$(CH_2)_2CO_2$Et]$^+$, 131 (100) [M-$(CH_2)_3CO_2$Et]$^+$, 118 (62) [IndzH]$^+$; HRMS (EI) calcd. for [M]$^+$ ($C_{14}H_{18}N_2O_2$): 246.1368, found 246.1367.

6-Indazol-1-yl-hexanoic acid ethyl ester (**2f**) *and 6-indazol-2-yl-hexanoic acid ethyl ester* (**3f**)

Following general procedure 2, reaction of indazole **1** (200 mg, 1.69 mmol) in DMF (2 mL), K_2CO_3 (2.34 g, 16.93 mmol) and Br$(CH_2)_5CO_2$Et (0.6 mL, 3.39 mmol) for 5 h. gave compounds **2f** (276 g, 62%) and **3f** (150 mg, 34%) as pale yellow oils. *Compound* **2f**: IR (film): 3061 (C-H)Ar, 2979, 2938, 2865 (C-H), 1731 (C=O), 1616, 1499, 1465, 1446 (C=C, C=N), 1181 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.22 (t, *J* = 7,2, 3 H, OCH$_2$C*H*$_3$), 1.34 (m, 2 H, C*H*$_2$), 1.65 (m, 2 H, C*H*$_2$CH$_2$CO$_2$Et), 1.94 (m, 2 H, NCH$_2$C*H*$_2$), 2.27 (t, *J* = 7.5, 2 H, C*H*$_2$CO$_2$Et), 4.09 (q, *J* = 7.2, 2 H, OC*H*$_2$CH$_3$), 4.38 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.13 (dt, *J* = 7.2 and 1.8, 1 H, 5-H), 7.37 (m, 2 H, 6-H and 7-H), 7.73 (dd, *J* = 8.4 and

0.9, 1 H, 4-H), 7.98 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 260 (11) $[M]^+$, 215 (20) $[M\text{-}OEt]^+$, 187 (4) $[M\text{-}CO_2Et]^+$, 173 (14) $[M\text{-}CH_2CO_2Et]^+$, 131 (100) $[M\text{-}(CH_2)_4CO_2Et]^+$, 118 (14) $[IndzH]^+$; HRMS (EI) calcd. for $[M]^+$ ($C_{15}H_{20}N_2O_2$): 260.1525, found 260.1526. *Compound* **3f**: IR (film): 3119, 3062 (C-H)Ar, 2980, 2938 (C-H), 1732 (C=O), 1628, 1516, 1465 (C=C, C=N), 1186 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.29 (t, *J* = 7.2, 3 H, OCH_2CH_3), 1.35 (m, 2 H, CH_2), 1.67 (m, 2 H, $CH_2CH_2CO_2Et$), 2.03 (m, 2 H, NCH_2CH_2), 2.28 (t, *J* = 7.5, 2 H, CH_2CO_2Et), 4.10 (q, *J* = 7.2, 2 H, OCH_2CH_3), 4.40 (t, *J* = 7.2, 2 H, NCH_2), 7.07 (t, *J* = 7.8, 1 H, 5-H), 7.27 (t, *J* = 7.8, 1 H, 6-H), 7.64 (d, *J* = 8.4, 1 H, 4-H), 7.70 (d, *J* = 8.7, 1 H, 7-H), 7.89 (s, 1H, 3-H); MS (EI): *m/z* (%) = 260 (67) $[M]^+$, 215 (61) $[M\text{-}OEt]^+$, 187 (28) $[M\text{-}CO_2Et]^+$, 173 (78) $[M\text{-}CH_2CO_2Et]^+$, 131 (100) $[M\text{-}(CH_2)_4CO_2Et]^+$, 118 (61) $[IndzH]^+$; HRMS (EI) calcd. for $[M]^+$ ($C_{15}H_{20}N_2O_2$): 260.1525, found 260.1525. The reaction was also performed using general procedure 1. Analysis of the ^{1}H-NMR spectrum of the crude product indicated the presence of **2f**, **3f** and **1** in the ratio 39:39:22.

7-Indazol-1-yl-heptanoic acid ethyl ester (**2g**) *and 7-indazol-2-yl-heptanoic acid ethyl ester* (**3g**)

Following general procedure 2, reaction of indazole **1** (500 mg, 4.23 mmol) in DMF (5 mL), K_2CO_3 (2.92 g, 21.20 mmol) and $Br(CH_2)_6CO_2Et$ (1.64 mL, 8.46 mmol) for 5 h. gave compounds **2g** (714 mg, 61%) and **3g** (422 mg, 36%) as pale yellow oils. *Compound* **2g**: IR (film): 3061 (C-H)Ar, 2979, 2936, 2859 (C-H), 1731 (C=O), 1615, 1499, 1465, 1424 (C=C, C=N), 1180 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, *J* = 7.2, 3 H, OCH_2CH_3), 1.33 (m, 4 H, 2×(CH_2)), 1.57 (m, 2 H, CH_2), 1.93 (m, 2 H, CH_2), 2.25 (t, *J* = 7.5, 2 H, CH_2CO_2Et), 4.10 (q, *J* = 7.2, 2 H, OCH_2CH_3), 4.37 (t, *J* = 6.9, 2 H, NCH_2), 7.13 (dt, *J* = 7.2 and 1.5, 1 H, 5-H), 7.39 (m, 2 H, 6-H and 7-H), 7.72 (d, *J* = 8.1, 1 H, 4-H), 7.98 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 274 (7) $[M]^+$, 229 (11) $[M\text{-}OEt]^+$, 187 (17) $[M\text{-}CH_2CO_2Et]^+$, 173 (6) $[M\text{-}(CH_2)_2CO_2Et]^+$, 131 (100) $[M\text{-}(CH_2)_5CO_2Et]^+$, 118 (22) $[IndzH]^+$; HRMS (EI) calcd. for $[M]^+$ ($C_{16}H_{22}N_2O_2$): 274.1681, found 274.1680. *Compound* **3g**: IR (film): 3061 (C-H)Ar, 2979, 2933, 2859 (C-H), 1731 (C=O), 1628, 1515, 1466, 1446 (C=C, C=N), 1185 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, *J* = 7.2, 3 H, OCH_2CH_3), 1.35 (m, 4 H, 2×(CH_2)), 1.61 (m, 2 H, $CH_2CH_2CO_2Et$), 2.02 (m, 2 H, NCH_2CH_2), 2.27 (t, *J* = 7.2, 2 H, CH_2CO_2Et), 4.11 (q, *J* = 7.2, 2 H, OCH_2CH_3), 4.40 (t, *J* = 7.2, 2 H, NCH_2), 7.07 (t, *J* = 7.2, 1 H, 5-H), 7.27 (m, 1 H, 6-H), 7.64 (d, *J* = 8.4, 1 H, 4-H), 7.64 (dd, *J* = 8.4 and 0.9, 1 H, 7-H), 7.89 (d, *J* = 0.9, 1 H, 3-H); MS (EI): *m/z* (%) = 274 (15) $[M]^+$, 229 (21) $[M\text{-}OEt]^+$, 187 (27) $[M\text{-}CH_2CO_2Et]^+$, 173 (5) $[M\text{-}(CH_2)_2CO_2Et]^+$, 131 (100) $[M\text{-}(CH_2)_5CO_2Et]^+$, 118 (21) $[IndzH]^+$; HRMS (EI) calcd. for $[M]^+$ ($C_{16}H_{22}N_2O_2$): 274.1681, found 274.1679.

10-Indazol-1-yl-decanoic acid methyl ester (**2h**) *and 10-indazol-2-yl-decanoic acid methyl ester* (**3h**)

Following general procedure 2, reaction of indazole **1** (1.00 g, 8.46 mmol) in DMF (10 mL), K_2CO_3 (5.85 g, 42.30 mmol) and $Br(CH_2)_9CO_2Me$ (2.96 mL, 12.69 mmol) for 12 h. gave compounds **2h** (1.53 g, 63%) and **3h** (825 mg, 34%) as pale yellow oils. *Compound* **2h**: IR (film): 3061 (C-H)Ar, 2928, 2855 (C-H), 1739 (C=O), 1616, 1499, 1465, 1435 (C=C, C=N), 1196 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.26 (m, 10 H, 5×(CH_2)), 1.56 (m, 2 H, CH_2), 1.94 (m, 2 H, CH_2), 2.28 (t, *J* = 7.2, 2 H, $CH_2CO_2CH_3$), 3.65 (s, 3 H, OCH_3), 4.36 (t, *J* = 6.9, 2 H, NCH_2), 7.12 (dt, *J* = 7.2 and 1.5, 1 H, 5-H), 7.39 (m, 2 H, 6-H and 7-H), 7.72 (d, *J* = 8.1, 1 H, 4-H), 7.98 (d, *J* = 0.3, 1 H, 3-H); MS (EI): *m/z* (%) = 302 (20) $[M]^+$,

271 (15) [M-OMe]$^+$, 243 (2) [M-CO_2Me]$^+$, 229 (23) [M-CH_2CO_2Me]$^+$, 187 (12) [M-$(CH_2)_4CO_2$Me]$^+$, 173 (16) [M-$(CH_2)_5CO_2$Me]$^+$, 131 (100) [M-$(CH_2)_8CO_2$Me]$^+$, 118 (34) [IndzH]$^+$; HRMS (EI) calcd. for [M]$^+$ ($C_{18}H_{26}N_2O_2$): 302.1994, found 302.1985. *Compound* **3h**: IR (film): 3060 (C-H)Ar, 2928, 2855 (C-H), 1739 (C=O), 1628, 1515, 1466, 1436 (C=C, C=N), 1196 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.27 (m, 10 H, 5×(C*H*$_2$)), 1.59 (m, 2 H, C*H*$_2$), 2.00 (m, 2 H, C*H*$_2$), 2.28 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$C*H*$_3$), 3.65 (s, 3 H, OC*H*$_3$), 4.39 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.06 (m, 1 H, 5-H), 7.26 (m, 1 H, 6-H), 7.64 (d, *J* = 8.4, 1 H, 4-H), 7.70 (dd, *J* = 8.7 and 0.9, 1 H, 7-H), 7.89 (s, 1 H, 3-H); MS (EI): *m/z* = 302 (68) [M]$^+$, 271 (35) [M-OMe]$^+$, 229 (54) [M-CH_2CO_2Me]$^+$, 187 (42) [M-$(CH_2)_4CO_2$Me]$^+$, 173 (37) [M-$(CH_2)_5CO_2$Me]$^+$, 131 (100) [M-$(CH_2)_8CO_2$Me]$^+$, 118 (91) [IndzH]$^+$; HRMS (EI) calcd. for [M]$^+$ ($C_{18}H_{26}N_2O_2$): 302.1994, found 302.1992.

11-Indazol-1-yl-undecanoic acid methyl ester (**2i**) *and 11-indazol-2-yl-undecanoic acid methyl ester* (**3i**)

Following general procedure 2, reaction of indazole **1** (1.02 g, 8.61 mmol) in DMF (10 mL), K_2CO_3 (5.85 g, 42.33 mmol) and Br$(CH_2)_{10}CO_2$Et (3.06 mL, 12.68 mmol) for 7 h. gave compounds **2i** (1.64 g, 60%) as a white solid and **3i** (1.04 g, 38%) as a pale yellow oil. *Compound* **2i**: mp 52-54 °C; IR (KBr): 3058 (C-H)Ar, 2914, 2847 (C-H), 1741 (C=O), 1617, 1495, 1466, 1438 (C=C, C=N), 1176 (C-O) cm^{-1}; ^{1}H-MR ($CDCl_3$): δ 1.28 (m, 12 H, 6×(C*H*$_2$)), 1.60 (m, 2 H, C*H*$_2$), 1.92 (m, 2 H, C*H*$_2$), 2.29 (t, *J* = 7.5, 2 H, C*H*$_2$CO$_2$C*H*$_3$), 3.66 (s, 3 H, OC*H*$_3$), 4.37 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.13 (t, *J* = 7.2, 1 H, 5-H), 7.38 (m, 2 H, 6-H and H-7), 7.72 (d, *J* = 8.1, 1 H, 4-H), 7.98 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 316 (6) [M]$^+$, 243 (11) [M-$(CH_2)CO_2$Me]$^+$, 187 (7) [M-$(CH_2)_5CO_2$Me]$^+$, 173 (11) [M-$(CH_2)_6CO_2$Me]$^+$, 131 (100) [M-$(CH_2)_9CO_2$Me]$^+$, 118 (41) [IndzH]$^+$. Anal. Calcd. for $C_{19}H_{28}N_2O_2$: C 72.12, H 8.92, N 8.85. Found: C 72.15, H 8.87, N 8.79. *Compound* **3i**: IR (film): 3060 (C-H)Ar, 2922, 2855 (C-H), 1732 (C=O), 1628, 1515, 1465, 1435 (C=C, C=N), 1771 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.25 (m, 12 H, 6×(C*H*$_2$)), 1.60 (m, 2 H, C*H*$_2$), 2.00 (m, 2 H, C*H*$_2$), 2.29 (t, *J* = 7.5, 2 H, C*H*$_2$CO$_2$C*H*$_3$), 3.65 (s, 3 H, OC*H*$_3$), 4.40 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.06 (m, 1 H, 5-H), 7.26 (m, 1 H, 6-H), 7.64 (td, *J* = 8.7 and 0.9, 1 H, 4-H), 7.70 (dd, *J* = 8.7 and 0.6, 1 H, 7-H), 7.90 (d, *J* = 0.6, 1 H, 3-H); MS (EI): *m/z* = 316 (78) [M]$^+$, 285 (40) [M-OMe]$^+$, 243 (72) [M-CH_2CO_2Me]$^+$, 187 (42) [M-$(CH_2)_5CO_2$Me]$^+$, 173 (39) [M-$(CH_2)_6CO_2$Me]$^+$, 131 (100) [M-$(CH_2)_9CO_2$Me]$^+$, 118 (90) [IndzH]$^+$; HRMS (EI) calcd. for [M]$^+$ ($C_{19}H_{28}N_2O_2$): 316.2151, found 316.2154.

General procedure 3: Indazole ester derivative (**2** or **3**) (1 eq.) and excess aqueous NaOH solution (10 M) was stirred at reflux for 1-5 h. After cooling, the mixture was acidified with 10% aqueous HCl solution and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting solid was purified by recrystallisation from ethyl acetate/petroleum ether. The following compounds were prepared following this procedure:

Indazol-1-yl-acetic acid (**4b**)

Reaction of compound **2b** (2.42 g, 11.86 mmol) in aqueous NaOH solution (10 M, 10 mL) for 5 h. gave compound **4b** (2.02 g, 97%) as white crystals, mp 186-188 ºC (Lit. [20] 185-186 ºC (H_2O)); IR (KBr): 3300-2300 (COO-H), 3112 (C-H)Ar, 2943 (C-H) 1736 (C=O), 1618, 1507, 1464 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 5.22 (s, 2 H, NCH_2), 7.17 (dt, *J* = 7.5 and 0.9, 1 H, 5-H), 7.42 (dt, *J* = 7.2 and 0.9, 1 H, 6-H), 7.51 (dd, *J* = 8.4 and 0.9, 1 H, 7-H), 7.76 (d, *J* = 7.5, 1 H, 4-H), 8.04 (d, *J* = 0.6, 1 H, 3-H); MS (EI): *m/z* (%) = 176 (33) $[M]^+$, 131 (100) $[M\text{-}CO_2H]^+$.

3-Indazol-1-yl-propionic acid (**4c**)

Reaction of compound **2c** (2.72 g, 12.45 mmol) in aqueous NaOH solution (10 M, 10 mL) for 3 h. gave compound **4c** (2.32 g, 98%) as white crystals, mp 106-107 ºC (Lit. [20] 105.5-106.5 ºC (C_6H_6/petroleum ether)); IR (KBr): 3300-2300 (COO-H), 2932 (C-H), 1718 (C=O), 1655, 1618, 1502, 1466 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 2.91 (t, *J* = 6.9, 2 H, C$H_2$$CO_2$H), 4.65 (t, *J* = 6.6, 2 H, NCH_2), 7.13 (t, *J* = 7.8, 1 H, 5-H), 7.39 (t, *J* = 7.8, 1 H, 6-H), 7.59 (d, *J* = 8.1, 1 H, 7-H), 7.71 (d, *J* = 8.1, 1 H, 4-H), 8.00 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 190 (20) $[M]^+$, 131 (100) $[M\text{-}CH_2CO_2H]^+$, 118 (9) $[IndzH]^+$.

4-Indazol-1-yl-butyric acid (**4d**)

Reaction of compound **2d** (3.49 g, 15.02 mmol) in aqueous NaOH solution (10 M, 15 mL) for 3 h. gave compound **4d** (2.85 g, 93%) as white crystals, mp 60-62 ºC; IR (KBr): 3300-2400 (COO-H), 3057 (C-H)Ar, 2948 (C-H), 1690 (C=O), 1616, 1497, 1463 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 2.10-2.27 (m, 4 H, CH_2CH_2), 4.45 (t, *J* = 6.9, 2 H, NCH_2), 7.13 (t, *J* = 7.8, 1 H, 5-H), 7.39 (m, 1 H, 6-H), 7.54 (d, *J* = 8.4, 1 H, 7-H), 7.73 (dd, *J* = 8.1 and 0.9, 1 H, 4-H), 8.00 (s, 1 H, 3-H); ^{1}H NMR ($CDCl_3$): δ 2.23 (m, 2 H, NCH_2CH_2), 2.35 (t, *J* = 7.2, 2 H, C$H_2$$CO_2$H), 4.49 (t, *J* = 6.6, 2 H, NCH_2), 7.13 (dt, *J* = 7.2 and 0.9, 1 H, 5-H), 7.39 (m, 2 H, 6-H and 7-H), 7.72 (d, *J* = 8.1, 1 H, 4-H), 8.02 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 204 (14) $[M]^+$, 131 (100) $[M\text{-}(CH_2)_2CO_2H]^+$, 118 (9) $[IndzH]^+$.

5-Indazol-1-yl-pentanoic acid (**4e**)

Reaction of compound **2e** (216 mg, 0.879 mmol) in aqueous NaOH solution (10 M, 1 mL) for 2 h. gave compound **4e** (189 mg, 99%) as white crystals, mp 82-83 ºC; IR (KBr): 3500-2400 (COO-H), 3108 (C-H)Ar, 2931 (C-H), 1712 (C=O), 1617, 1501, 1454 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.55 (m, 2 H, C$H_2$$CH_2CO_2$H), 1.92 (m, 2 H, NCH$_2CH_2$), 2.27 (t, *J* = 7.2, 2 H, C$H_2$$CO_2$H), 4.40 (t, *J* = 6.9, 2 H, NCH_2), 7.12 (t, *J* = 7.5, 1 H, 5-H), 7.38 (t, *J* = 8.1, 1 H, 6-H), 7.53 (d, *J* = 8.7, 1 H, 7-H), 7.72 (d, *J* = 8.1, 1 H, 4-H), 7.98 (s, 1 H, 3-H); ^{1}H-NMR ($CDCl_3$): δ 1.66 (m, 2 H, CH_2), 1.99 (m, 2 H, CH_2), 2.37 (t, *J* = 7.2, 2 H, C$H_2$$CO_2$H), 4.41 (t, *J* = 6.9, 2 H, NCH_2), 7.14 (dt, *J* = 7.2 and 2.1, 1 H, 5-H), 7.40 (m, 2 H, 6-H and 7-H), 7.73 (d, *J* = 8.1, 1 H, 4-H), 8.02 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 218 (16) $[M]^+$, 131 (100) $[M\text{-}(CH_2)_3CO_2H]^+$, 118 (19) $[IndzH]^+$.

6-Indazol-1-yl-hexanoic acid (**4f**)

Reaction of compound **2f** (1.35 g, 5.19 mmol) in aqueous NaOH solution (10 M, 5 mL) for 2 h. gave compound **4f** (1.20 g, 100%) as white crystals, mp 69-70 °C; IR (KBr): 3500-2350 (COO-H), 3058, 3042 (C-H)Ar, 2969, 2936, 2871 (C-H), 1691 (C=O), 1638, 1617, 1498, 1438 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.30 (m, 2 H, C*H*$_2$), 1.60 (m, 2 H, C*H*$_2$CH$_2$CO$_2$H), 1.92 (m, 2 H, NCH$_2$C*H*$_2$), 2.22 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$H), 4.40 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.13 (t, *J* = 7.1, 1 H, 5-H), 7.39 (dt, *J* = 7.8 and 0.9, 1 H, 6-H), 7.53 (d, *J* = 8.7, 1 H, 7-H), 7.73 (d, *J* = 8.1, 1 H, 4-H), 7.98 (s, 1 H, 3-H); ^{1}H-NMR ($CDCl_3$): δ 1.38 (m, 2 H, C*H*$_2$), 1.67 (m, 2 H, C*H*$_2$CH$_2$CO$_2$H), 1.95 (m, 2 H, NCH$_2$C*H*$_2$), 2.33 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$H), 4.40 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.14 (dt, *J* = 6.9 and 2.1, 1 H, 5-H), 7.40 (m, 2 H, 6-H and 7-H), 7.72 (d, *J* = 8.1, 1 H, 4-H), 8.00 (s, 1 H, 3-H); ^{1}H-NMR (DMSO): δ 1.22 (m, 2 H, C*H*$_2$), 1.49 (m, 2 H, C*H*$_2$CH$_2$CO$_2$H), 1.80 (m, 2 H, NCH$_2$C*H*$_2$), 2.14 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$H), 4.37 (t, *J* = 6.9, 2 H, NC*H*$_2$), 7.10 (dt, *J* = 6.9 and 0.9, 1 H, 5-H), 7.35 (dt, *J* = 7.8 and 0.9, 1 H, 6-H), 7.63 (dd, *J* = 8.4 and 0.9, 1 H, 7-H), 7.73 (d, *J* = 8.1, 1 H, 4-H), 8.03 (d, *J* = 0.9, 1 H, 3-H); MS (EI): *m/z* (%) = 232 (13) $[M]^+$, 173 (19) $[M\text{-}CH_2CO_2H]^+$, 131 (100) $[M\text{-}(CH_2)_4CO_2H]^+$, 118 (25) $[IndzH]^+$.

7-Indazol-1-yl-heptanoic acid (**4g**)

Reaction of compound **2g** (720 mg, 2.61 mmol) in aqueous NaOH solution (10 M, 2.5 mL) for 2 h. gave compound **4g** (474 mg, 74%) as white crystals, mp 54-58 °C; IR (KBr): 3350-2400 (COO-H), 3041 (C-H)Ar, 2929, 2908, 2855 (C-H), 1701 (C=O), 1614, 1561, 1462 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.30 (m, 4 H, 2×(C*H*$_2$)), 1.51 (m, 2 H, C*H*$_2$), 1.90 (m, 2 H, C*H*$_2$), 2.22 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$H), 4.39 (t, *J* = 6.9, 2 H, NC*H*$_2$), 7.13 (dt, *J* = 7.8 and 0.9, 1 H, 5-H), 7.39 (dt, *J* = 7.8 and 0.9, 1 H, 6-H), 7.53 (dd, *J* = 8.4 and 0.9, 1 H, 7-H), 7.73 (d, *J* = 8.1, 1 H, 4-H), 7.98 (d, *J* = 0.6, 1 H, 3-H); MS (EI): *m/z* (%) = 246 (12) $[M]^+$, 187 (21) $[M\text{-}CH_2CO_2H]^+$, 131 (100) $[M\text{-}(CH_2)_5CO_2H]^+$, 118 (31) $[IndzH]^+$.

10-Indazol-1-yl-decanoic acid (**4h**)

Reaction of compound **2h** (1.02 g, 3.36 mmol) in aqueous NaOH solution (10 M, 3.0 mL) for 2 h. gave compound **4h** (913 mg, 93%) as white crystals, mp 78-81 °C; IR (KBr): 3360-2400 (COO-H), 3041 (C-H)Ar, 2932, 2915, 2845 (C-H), 1689 (C=O), 1615, 1497, 1467, 1428 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.24 (m, 10 H, 5×(C*H*$_2$)), 1.54 (m, 2 H, C*H*$_2$), 1.87 (m, 2 H, C*H*$_2$), 2.23 (t, *J* = 7.5, 2 H, C*H*$_2$CO$_2$H), 4.39 (t, *J* = 6.9, 2 H, NC*H*$_2$), 7.13 (t, *J* = 7.5, 1 H, 5-H), 7.38 (t, *J* = 7.5, 1 H, 6-H), 7.52 (d, *J* = 8.4, 1 H, 7-H), 7.73 (dd, *J* = 8.4 and 0.9, 1 H, 4-H), 7.98 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 288 (13) $[M]^+$, 229 (11) $[M\text{-}CH_2CO_2H]^+$, 187 (9) $[M\text{-}(CH_2)_4CO_2H]^+$, 173 (14) $[M\text{-}(CH_2)_5CO_2H]^+$, 131 (100) $[M\text{-}(CH_2)_8CO_2H]^+$, 118 (51) $[IndzH]^+$.

11-Indazol-1-yl-undecanoic acid (**4i**)

Reaction of compound **2i** (755 mg, 2.39 mmol) in aqueous NaOH solution (10 M, 3 mL) for 2 h. gave compound **4i** (686 mg, 95%) as white crystals, mp 73-74 °C; IR (KBr): 3350-2400 (COO-H),

3041 (C-H)Ar, 2921, 2849 (C-H), 1691 (C=O), 1615, 1497, 1464, 1428 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.23 (m, 12 H, 6×(C*H*$_2$)), 1.54 (m, 2 H, C*H*$_2$CH$_2$CO$_2$H), 1.86 (m, 2 H, NCH$_2$C*H*$_2$), 2.24 (t, *J* = 7.5, 2 H, C*H*$_2$CO$_2$H), 4.38 (t, *J* = 6.9, 2 H, NC*H*$_2$), 7.12 (dt, *J* = 7.8 and 0.9, 1 H, 5-H), 7.38 (dt, *J* = 7.8 and 1.2, 1 H, 6-H), 7.51 (dd, *J* = 8.4 and 0.6, 1 H, 7-H), 7.72 (dd, *J* = 8.1 and 0.9, 1 H, 4-H), 7.98 (d, *J* = 0.9, 1 H, 3-H); MS (EI): *m/z* (%) = 302 (6) $[M]^+$, 243 (7) $[M\text{-}CH_2CO_2H]^+$, 187 (6) $[M\text{-}(CH_2)_5CO_2H]^+$, 173 (10) $[M\text{-}(CH_2)_6CO_2H]^+$, 131 (100) $[M\text{-}(CH_2)_9CO_2H]^+$, 118 (59) $[IndzH]^+$.

Indazol-2-yl-acetic acid (**5b**)

Reaction of compound **3b** (100 mg, 0.49 mmol) in aqueous NaOH solution (10 M, 1 mL) for 2 h. gave compound **5b** (83 mg, 96%) as white crystals, mp 254-256 ºC (Lit. [20] 257 ºC (dec.)); IR (KBr): 3300-2300 (COO-H), 3130 (C-H)Ar, 2986, 2944 (C-H), 1719 (C=O), 1628, 1517, 1481 (C=C, C=N) cm^{-1}; ^{1}H-NMR (DMSO): δ 5.29 (s, 2 H, NC*H*$_2$), 7.03 (t, *J* = 7.5, 1 H, 5-H), 7.24 (t, *J* = 8.7, 1 H, 6-H), 7.58 (d, *J* = 8.7, 1 H, 7-H), 7.71 (d, *J* = 8.4, 1 H, 4-H), 8.36 (d, *J* = 0.9, 1 H, 3-H); MS (EI): *m/z* (%) = 176 (5) $[M]^+$, 131 (100) $[M\text{-}CO_2H]^+$, 118 (34) $[IndzH]^+$.

3-Indazol-2-yl-propionic acid (**5c**)

Reaction of compound **3c** (2.53 g, 11.61 mmol) in aqueous NaOH solution (10 M, 10 mL) for 2.5 h. gave compound **5c** (2.16 g, 98%) as white crystals, mp 147-149 ºC (Lit. [20] 148-149 ºC (H_2O)); IR (KBr): 3300-2300 (COO-H), 3128 (C-H)Ar, 2927 (C-H), 1708 (C=O), 1626, 1516, 1476 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 3.00 (t, *J* = 6.6, 2 H, C*H*$_2$CO$_2$H), 4.68 (t, *J* = 6.6, 2 H, NC*H*$_2$), 7.04 (t, *J* =7.5, 1 H, 5-H), 7.26 (m, 1 H, 6-H), 7.57 (dd, *J* = 8.9 and 0.9, 1 H, 7-H), 7.64 (d, *J* = 8.4, 1 H, 4-H), 8.18 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 190 (29) $[M]^+$, 145 (7) $[M\text{-}CO_2H]^+$, 131 (13) $[M\text{-}CH_2CO_2H]^+$, 118 (100) $[IndzH]^+$.

4-Indazol-2-yl-butyric acid (**5d**)

Reaction of compound **3d** (143 mg, 0.62 mmol) in aqueous NaOH solution (10 M, 1 mL) for 2 h. gave compound **5d** (122 mg, 97%) as white crystals, mp 132-134 ºC; IR (KBr): 3450-2300 (COO-H), 3119 (C-H)Ar, 2937 (C-H), 1698 (C=O), 1626, 1508, 1474, (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 2.26 (m, 4 H, C*H*$_2$C*H*$_2$CO$_2$H), 4.49 (t, *J* = 6.6, 2 H, NC*H*$_2$), 7.06 (t, *J* = 7.8, 1 H, 5-H), 7.28 (t, *J* = 8.1, 1H, 6-H), 7.58 (d, *J* = 8.7, 1 H, 7-H), 7.67 (d, *J* = 8.4, 1 H, 4-H), 8.19 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 204 (28) $[M]^+$, 131 (100) $[M\text{-}(CH_2)_2CO_2H]^+$, 118 (55) $[IndzH]^+$.

5-Indazol-2-yl-pentanoic acid (**5e**)

Reaction of compound **3e** (168 mg, 0.68 mmol) in aqueous NaOH solution (10 M, 2 mL) for 2 h. gave compound **5e** (134 mg, 90%) as white crystals, mp 112-114 ºC; IR (KBr): 3450-2300 (COO-H), 3129 (C-H)Ar, 2944 (C-H), 1701 (C=O), 1636, 1508, 1458 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.55 (m, 2 H, C*H*$_2$CH$_2$CO$_2$H), 2.00 (m, 2 H, NCH$_2$C*H*$_2$), 2.30 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$H), 4.41 (t, *J* = 6.9, 2 H, NC*H*$_2$), 7.05 (t, *J* = 8.1, 1 H, 5-H), 7.26 (t, *J* = 8.7, 1 H, 6-H), 7.58 (d, *J* = 8.7, 1 H, 7-H), 7.66

(d, *J* = 8.4, 1 H, 4-H), 8.16 (d, *J* = 1.5, 1 H, 3-H); MS (EI): *m/z* (%) = 218 (5) $[M]^+$, 173 (3) $[M-CO_2H]^+$, 131 (24) $[M-(CH_2)_3CO_2H]^+$, 118 (11) $[IndzH]^+$, 61 (100).

6-Indazol-2-yl-hexanoic acid (**5f**)

Reaction of compound **3f** (1.05 mg, 4.04 mmol) in aqueous NaOH solution (10 M, 3 mL) for 2 h. gave compound **5f** (553 mg, 59%) as white crystals, mp 86-87 °C; IR (KBr): 3330-2400 (COO-H), 3131 (C-H)Ar, 2948, 2867 (C-H), 1717 (C=O), 1626, 1517, 1466, 1451 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.31 (m, 2 H, C*H*$_2$), 1.62 (m, 2 H, C*H*$_2$CH$_2$CO$_2$H), 1.98 (m, 2 H, NCH$_2$C*H*$_2$), 2.25 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$H), 4.41 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.04 (t, *J* = 7.2, 1 H, 5-H), 7.26 (t, *J* = 7.2, 1 H, 6-H), 7.57 (d, *J* = 8.7, 1 H, 7-H), 7.66 (d, *J* = 8.4, 1 H, 4-H), 8.16 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 232 (23) $[M]^+$, 173 (50) $[M-CH_2CO_2H]^+$, 131 (100) $[M-(CH_2)_4CO_2H]^+$, 118 (82) $[IndzH]^+$.

7-Indazol-2-yl-heptanoic acid (**5g**)

Reaction of compound **3g** (251 mg, 1.28 mmol) in aqueous NaOH solution (10 M, 1.5 mL) for 30 min. gave compound **5g** (195 mg, 62%) as white crystals, mp 77-78 °C; IR (KBr): 3350-2400 (COO-H), 3127 (C-H)Ar, 2934, 2857 (C-H), 1707 (C=O), 1629, 1515, 1465, 1433 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.32 (m, 4 H, 2×(C*H*$_2$)), 1.56 (m, 2 H, C*H*$_2$), 1.96 (m, 2 H, C*H*$_2$), 2.24 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$H), 4.40 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.05 (t, *J* = 7.5, 1 H, 5-H), 7.27 (t, *J* = 7.5, 1 H, 6-H), 7.58 (d, *J* = 8.7, 1 H, 7-H), 7.66 (d, *J* = 8.4, 1 H, 4-H), 8.16 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 246 (26) $[M]^+$, 187 (51) $[M-CH_2CO_2H]^+$, 173 (18) $[M-(CH_2)_2CO_2H]^+$, 131 (100) $[M-(CH_2)_5CO_2H]^+$, 118 (78) $[IndzH]^+$.

10-Indazol-2-yl-decanoic acid (**5h**)

Reaction of compound **3h** (710 mg, 2.35 mmol) in aqueous NaOH solution (10 M, 2.5 mL) for 2 h. gave compound **5h** (611 mg, 90%) as white crystals, mp 68 °C; IR (KBr): 3350-2400 (COO-H), 3128 (C-H)Ar, 2922, 2850, (C-H), 1711 (C=O), 1627, 1515, 1469, 1432 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.27 (m, 10 H, 5×(C*H*$_2$)), 1.55 (m, 2 H, C*H*$_2$), 1.97 (m, 2 H, C*H*$_2$), 2.24 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$H), 4.41 (t, *J* = 6,9, 2 H, NC*H*$_2$), 7.05 (t, *J* = 7.5, 1 H, 5-H), 7.27 (t, *J* = 7.2, 1 H, 6-H), 7.58 (d, *J* = 8.7, 1 H, 7-H), 7.67 (d, *J* = 8.4, 1 H, 4-H), 8.18 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 288 (33) $[M]^+$, 229 (20) $[M-CH_2CO_2H]^+$, 187 (20) $[M-(CH_2)_4CO_2H]^+$, 173 (21) $[M-(CH_2)_5CO_2H]^+$, 131 (97) $[M-(CH_2)_8CO_2H]^+$, 118 (100) $[IndzH]^+$.

11-Indazol-1-yl-undecanoic acid (**5i**)

Reaction of compound **3i** (311 mg, 0.98 mmol) in aqueous NaOH solution (10 M, 1.5 mL) for 2 h. gave compound **5i** (276 mg, 93%) as white crystals, mp 82 °C; IR (KBr): 3500-2390 (COO-H), 3127 (C-H)Ar, 2935, 2916, 2848 (C-H), 1708 (C=O), 1629, 1515, 1462, 1434 (C=C, C=N) cm^{-1}; ^{1}H-NMR (MeOD): δ 1.27 (m, 12 H, 6×(C*H*$_2$)), 1.56 (m, 2 H, C*H*$_2$), 1.98 (m, 2 H, C*H*$_2$), 2.25 (t, *J* = 7.5, 2 H, C*H*$_2$CO$_2$H), 4.42 (t, *J* = 7.2, 2 H, NC*H*$_2$), 7.05 (t, *J* = 7.2, 1 H, 5-H), 7.27 (t, *J* = 7.5, 1 H, 6-H), 7.57 (d,

J = 8.7, 1 H, 7-H), 7.67 (dd, *J* = 8.1 and 0.6, 1 H, 4-H), 8.19 (s, 1 H, 3-H); MS (EI): *m/z* (%) = 302 (18) $[M]^+$, 243 (16) $[M\text{-}CH_2CO_2H]^+$, 187 (17) $[M\text{-}(CH_2)_5CO_2H]^+$, 173 (18) $[M\text{-}(CH_2)_6CO_2H]^+$, 131 (98) $[M\text{-}(CH_2)_9CO_2H]^+$, 118 (100) $[IndzH]^+$.

X-ray data analysis of compound **5b**

Data were collected in a CAD-4, equipped with a rotating anode, using Cu radiation (λ=1.5418 Å). Cell dimensions were determined from the setting angles of 25 reflections. Data were corrected for Lorentz and polarization effects. The structure was solved by direct methods using SIR97 [32] and refined using SHELXL [33] within the WinGX suite of programs [34]. Non-hydrogen atoms were refined anysotropically and H atoms were identified from the Fourier difference map and allowed to refine freely. The crystal data and refinement parameters are summarized in Table 7.

CCDC 279230 contains the supplementary crystallographic data on this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; E-mail: deposit@ccdc.cam.ac.uk.

Table 7. Crystal data and structure refinement for compound **5b**.

Empirical formula	$C_9\ H_8\ N_2O_2$
Formula weight	176.17
Temperature	293(2) K
Wavelength	1.54184 A
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a = 9.615(2) Å
	b = 8.524(2) Å β = 92.420(10)º
	c = 10.109(6) Å
Volume	827.8(6) A^3
Z, Calculated density	4, 1.414 Mg/m^3
Absorption coefficient	0.855 mm^{-1}
F(000)	368
Crystal size	0.5 x 0.4 x 0.2 mm
Theta range for data collection	6.80 to 59.39 deg.
Limiting indices	-10<=h<=0, -9<=k<=0, -11<=l<=11
Reflections collected / unique	1281 / 1201 [R(int) = 0.0134]
Completeness to theta = 59.39	99.2%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1201 / 0 / 151
Goodness-of-fit on F^2	1.134
Final R indices [I>2sigma(I)]	R_1 = 0.0411, wR_2 = 0.0980
R indices (all data)	R_1 = 0.0571, wR_2 = 0.1054
Extinction coefficient	0.017(2)
Largest diff. peak and hole	0.210 and -0.223 e. $Å^{-3}$

References

1. (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry: Pyrazoles and their benzo derivatives*; Katritzky, A. R.; Rees, C. W., Ed.; Pergamon Press: Oxford, **1984**; Vol. 5, pp. 167-303; (b) Elguero, J. In *Comprehensive Heterocyclic Chemistry II: Pyrazoles*, Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, **1996**; Vol. *3*, pp. 1-75.
2. (a) Stadlbauer, W. In *Houben-Weyl, Methoden der Organischen Chemie: Indazole (Benzopyrazole)*; Schaumann, E.; Ed.; Georg-Thieme-Verlag Stuttgart: New York, **1994**; Vol. *E8b*, Hetarenes III/2, pp. 764-864; (b) Stadlbauer W. In *Science of Synthesis: Indazoles*, Neier, R., Ed.; Georg-Thieme-Verlag Stuttgart: New York, **2002**; Vol. *2.12.4* (Hetarenes), pp. 227-324.
3. Ikeda, Y.; Takano, N.; Matsushita, H.; Shiraki, Y.; Koide, T.; Nagashima, R.; Fujimura, Y.; Shindo, M.; Suzuki, S.; Iwasaki, T. *Arzneim.-Forsch.* **1979**, *29*, 511-520.
4. Picciola, G.; Ravenna, F.; Carenini, G.; Gentili, P.; Riva, M. *Farmaco Ed. Sci.* **1981**, *36*, 1037-1056.
5. *The Merck Index*, 12th edition; Budavari, S., Ed,; Merck & Co.: Rahway, New Jersey, **1996**.
6. Mosti, L.; Menozzi, G.; Fossa, P.; Schenone, P.; Lampa, E.; Parrillo, C.; D'Amisco, M.; Rossi, F. *Farmaco* **1992**, *47*, 567-584.
7. Andronati, S.; Sava, V.; Makan, S.; Kolodeev, G. *Pharmazie* **1999**, *54*, 99-101.
8. Kharitonov, V. G.; Sharma, V. S.; Magde, D.; Koesling, D. *Biochemistry* **1999**, *38*, 10699-10706.
9. (a) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenberg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Rayner, M. M.; Lam, G. N.; Chang, C.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2919-2924; (b) Sun, J.-H.; Teleha, C. A.; Yan, J.-S.; Rodgers; J. D.; Nugiel, D. A. *J. Org. Chem.* **1997**, *62*, 5627-5629.
10. (a) Morie, T.; Harada, H.; Kato, S. *Synth. Commun.* **1997**, *27*, 559-566; (b) Bermudez, J.; Fake, C. S.; Joiner, G. F.; Joiner, K. A.; King, F. D.; Miner, W. D.; Sanger, G. J. *J. Med. Chem.* **1990**, *33*, 1924-1929.
11. Nofre, C.; Tinti, J. M.; Quar, F. *FR Patent 26099603*, **1988**.
12. Catalán, J.; Valle, J. C.; Claramunt, R. M.; Boyer, G.; Laynez, J.; Gómez, J.; Jiménez, P.; Tomás, F.; Elguero, J. *J. Phys. Chem.* **1994**, *41*, 10606-10612.
13. (a) Escande, A.; Lapasset, J.; Faure, R.; Vicenta, E.-J.; Elguero, J. *Tetrahedron* **1974**, *30*, 2903-2909; (b) Faure, R.; Vicent, E. J.; Elguero, J. *Heterocycles* **1983**, *20*, 1713-1716; (c) Catalán, J.; Paz, J. L. G.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 57-60; (d) Foces-Foces, C.; Hager, O.; Jagerovic, N.; Jimeno, M. L.; Elguero, J. *Chem. Eur. J.* **1997**, *3*, 121-126.
14. (a) Black, P. J.; Heffernan, M. L. *Aust. J. Chem.* **1963**, *14*, 1051-1055; (b) Jaffari, G. A.; Nunn, A. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2371-2374; (c) Palmer, M. H.; Findlay, R. H.; Kennedy, S. M. F.; McIntyre, P. S. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1695-1700; (d) Brown, F. J.; Yee, Y. K.; Cronk, L. A.; Hebbel, K. C.; Krell, R. D.; Snyder, D. W. *J. Med. Chem.* **1990**, *33*, 1771-1781.
15. Yamazaki, T.; Baum, G.; Shechter, H. *Tetrahedon Lett.* **1974**, *49-50*, 4421-4424.
16. Begtrup, M.; Claramunt, R. M.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 99-104.
17. Cheung, M.; Boloor, A.; Stafford, J. A. *J. Org. Chem.* **2003**, *68*, 4093-4095.
18. (a) Elguero, J.; Fruchier, A.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1966**, 2075-2084; (b) Buu-Hoï, N. P.; Hoeffinger, J.-P.; Jacquignon, P. *Bull. Soc. Chim. Fr.* **1967**, 2019-2020; (c) Elguero, J.;

Fruchier, A.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1969**, 2064-2076; (d) Elguero, J.; Fruchier, A.; Jacquier, R.; Scheidegger, U. *J. Chim. Phys. Phys.-Chim. Biol* **1971**., *68*, 1113-1121; (e) Palmer, M. H.; Findlay, R. H.; Kennedy, S. M. F.; McIntyre, P. S. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1695-1700; (f) Bouchet, P.; Fruchier, A.; Joncheray, G.; Elguero, J. *Org. Magn. Reson.* **1977**, *9*, 716-718; (g) Stefaniak, L. *Org. Magn. Reson.* **1978**, *11*, 385-389; (h) Elguero, J.; Fruchier, A.; Tjiou, E. M.; Trofimenko, S. *Khim. Geterotsikl. Soedin.* **1995**, *9*, 1159-1179.

19. Kingsbury, W. D.; Gyurik, R. J.; Theodorides, V. J.; Parish, R. C.; Gallagher, Jr., G. *J. Med. Chem.* **1976**, *19*, 839-840.
20. Auwers, K. V.; Allardt, H. G. *Ber.* **1926**, *59*, 95-100.
21. Levy, D. E.; Smyth M. S.; Scarborough, R. M. *WO Patent 03/022214*, **2003**.
22. Costa, M. R. G.; Curto, M. J. M.; Davies, S. G.; Duarte, M. T.; Resende, C.; Teixeira, F. C. *J. Organomet. Chem.* **2000**, *604*, 157-169.
23. Farrugia, L. J. *J. Appl. Cryst.* **1997**, *30*, 565 (based on ORTEP-III (v.1.0.3.) by Johnson C. K.; Burnett, M. N.).
24. (a) Allen, F. H. *Acta Cryst.* **2002**, *B58*, 380-388; (b) Bruno, I. J.; Cole, J. C.; Edginton, P. R.; Kessler, M.; Macrae, C. F.; MacCabe, P. M.; Pearson, J.; Taylor, R. *Acta Cryst.* **2002**, *B58*, 389-397.
25. (a) Ferguson, G.; Gallagher; J. F.; McAlees, A. J. *Acta Cryst.* **1995**, *C51*, 454-458; (b) Bernstein, J.; Davies, R. E.; Shimoni, L.; Chang, N.-L. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1555-1573; (c) Allen, F. H.; Motherwell, W. D. S.; Raithby, P. R.; Shields, G. P.; Taylor, R. *New J. Chem.* **1999**, 25-34.
26. (a) Foces-Foces, C. *Acta Cryst.* **2005**, *E61*, o337-o339; (b) Hager, O.; Foces-Foces, C.; Jagerovic, N.; Elguero, J.; Trofimenko, S. *Acta Cryst*. **1996**, *C52*, 2894-2896.
27. (a) Foces-Foces, C.; Echevarría, A.; Jagerovic, N.; Alkorta, I.; Elguero, J.; Langer, U.; Klein, O.; Minguet-Bomvehí, M.; Limbach, H.-H. *J. Am. Chem. Soc.* **2001,** *123*, 7898-7906; (b) Foces-Foces, C.; Alkorta, I.; Elguero, J. *Acta Cryst.* **2000**, *B56*, 1018-1028; (c) Ching, N.; Pan, L.; Huang, X.; Li, J. *Acta Cryst.* **2000**, *C56*, 1124-1125.
28. Boa, A. N.; Crane, J. D. *Acta Cryst.* **2004**, *E60*, o966-o967.
29. Aakeröy, C. B.; Salmon, D. J. *Cryst. Eng. Comm.* **2005**, *7*, 439-448.
30. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd Edition; Pergamon Press: Oxford, **1980**.
31. Konoike, T.; Araki, Y.; Hayashi, T.; Sakurai, K.; Tozyo, T. *EP Patent 628569*, **1994**.
32. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115-119.
33. Sheldrick, G. M. SHELXL, *A Program for Refining Crystal Structures*; University of Göttingen: Göttingen, Germany, **1997**.
34. Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837-837.

Sample Availability: Available from authors.