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Il Farmaco 53 (1998) 698–708

IL FARMACO

New cycloalkylpyrazoles as potential cyclooxygenase inhibitors☆

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Abstract

In this study some cycloalkyl-3-(*N*-substituted carbamoyl)-1-phenylpyrazoles have been synthesized in order to screen their capability to inhibit human cyclooxygenase. The synthetic pathway is based on the well known property of nitrilimines to undergo 1,3-dipolar cycloaddition reactions. The structures of all the synthesized compounds have been elucidated by means of both analytical and spectroscopic methods. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Cycloalkyl-3-(*N*-substituted carbamoyl)-1-phenylpyrazoles; Analgesic and antipyretic activity

Several derivatives of pyrazole are of pharmaceutical interest due to their analgesic power. Among them, derivatives of 5-isopyrazolone and pyrazolidine-3,5-dione are worth noting due to their clinical interest. Moreover, the synthesis and biological activity of some 3-substituted-1-phenylpyrazoles have been reported. It was also observed that pyrazoles bearing an electron donating group in the 5-position of the heterocycle ring showed the highest analgesic and anti-inflammatory activity. This was particularly evident when the substituent in the 3-position were either *N*-substituted-aminomethyl or -carbamoyl groups [1]. Other substituents, both on the benzene and on the heterocyclic ring, can severely modify the biological properties of such molecules [2,3].

In the present paper, we report on the synthesis of some 3-(*N*-substituted)-carbamoyl-1-phenylpyrazoles. The synthesized compounds are shown in Fig. 1. The synthetic pathway to compounds **8–22** is depicted in Schemes 1 and 2.

Chlorophenylhydrazones (**1**) were synthesized slightly modifying literature methods [4], i.e. by reacting the diazonium salt of the appropriate amine with 2-chloroacetoacetate.

The synthesis of 1-phenyl-3-carbethoxycycloalkyl-pyrazoles (**4**) (Scheme 1) has been based on the well known capability of nitrilimines (**1**) to undergo 1,3-dipolar cycloadditions in the presence of dipolarophiles [4–10].

As expected, nitrilimines show two different reacting pathways: 1,3-dipolar cycloaddition and 1,3-electrophilic addition.

Two different products can be obtained and their formation and ratio depend on several factors, mainly on the kind of the dipolarophile and the experimental conditions. Significative amounts of the 1,3-addition products **5** are formed in the presence of weak dipolarophiles.

Even if the enamine acts as a good polarophile, two distinct reaction pathways have been observed using dry chloroform as the solvent. When employing dry benzene a moderate increase of the cycloaddition product was observed.

The electrophilic attack of the chlorophenylhydrazone undergo both on the cycloalkane carbon and on the heterocyclic nitrogen atom, leading to the formation of either the cycloaddition product **4** or the 1,3-electrophilic addition product **5**, respectively.

As shown by TLC, compound **5** consists of two very similar products which were characterized by ^{1}H NMR as the *E*- and *Z*-diastereoisomers (Fig. 2).

^{1}H NMR showed a small chemical shift (1.5 ppm) between the imine protons of the *E*- and *Z*-diastereoisomers. This behavior is in contrast to what has been observed for analogous compounds where the chemical shift is in the range of 4–5 ppm [11–13]. This is probably due to the fact that both the *E*- and *Z*-diastereoisomers undergo the formation of intramolecular hydrogen bonds, that leads to the formation of a six- and five-membered ring, respectively.

☆ Dedicated to Professor Antonio Maccioni.

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PII: S0014-827X(98)00090-1

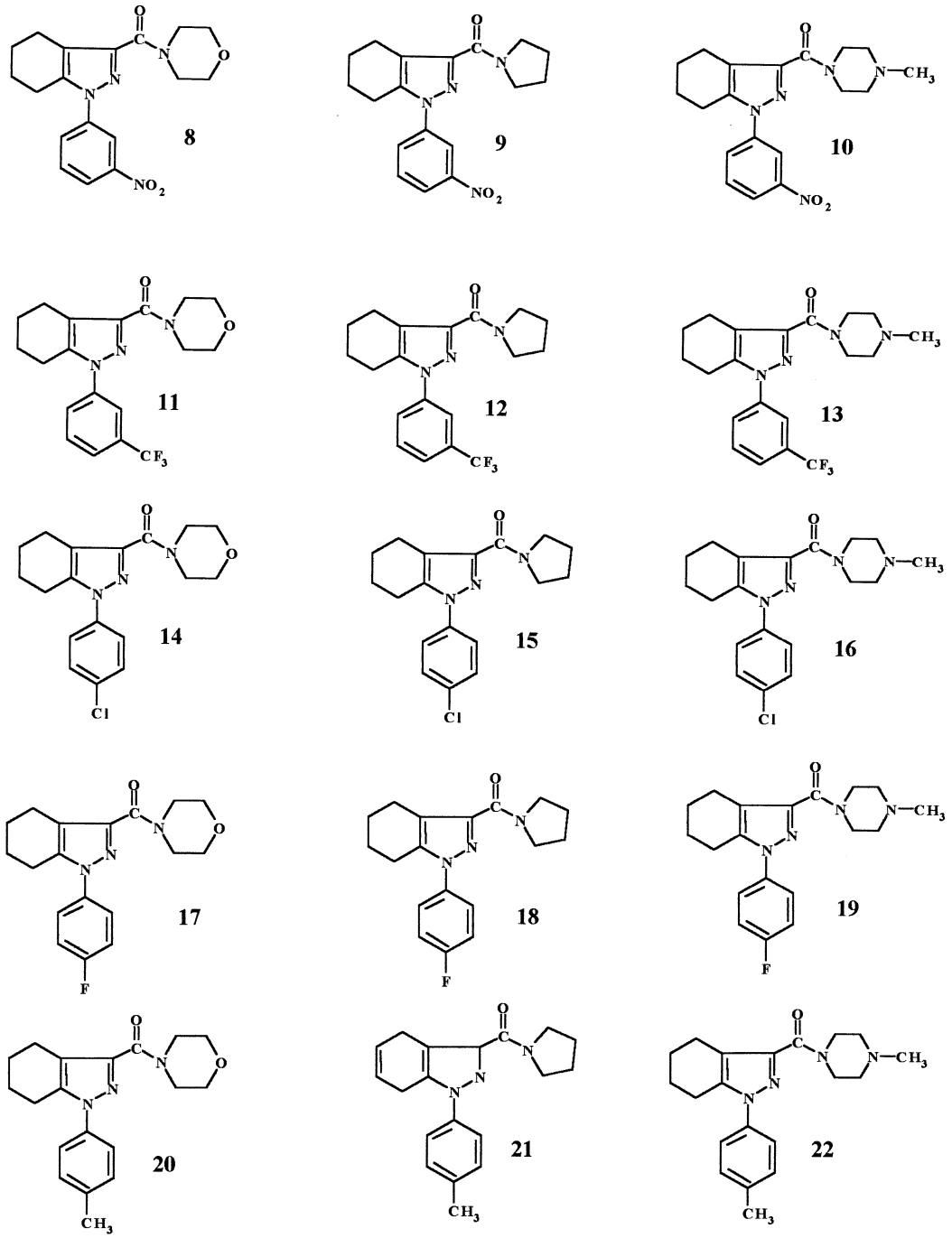
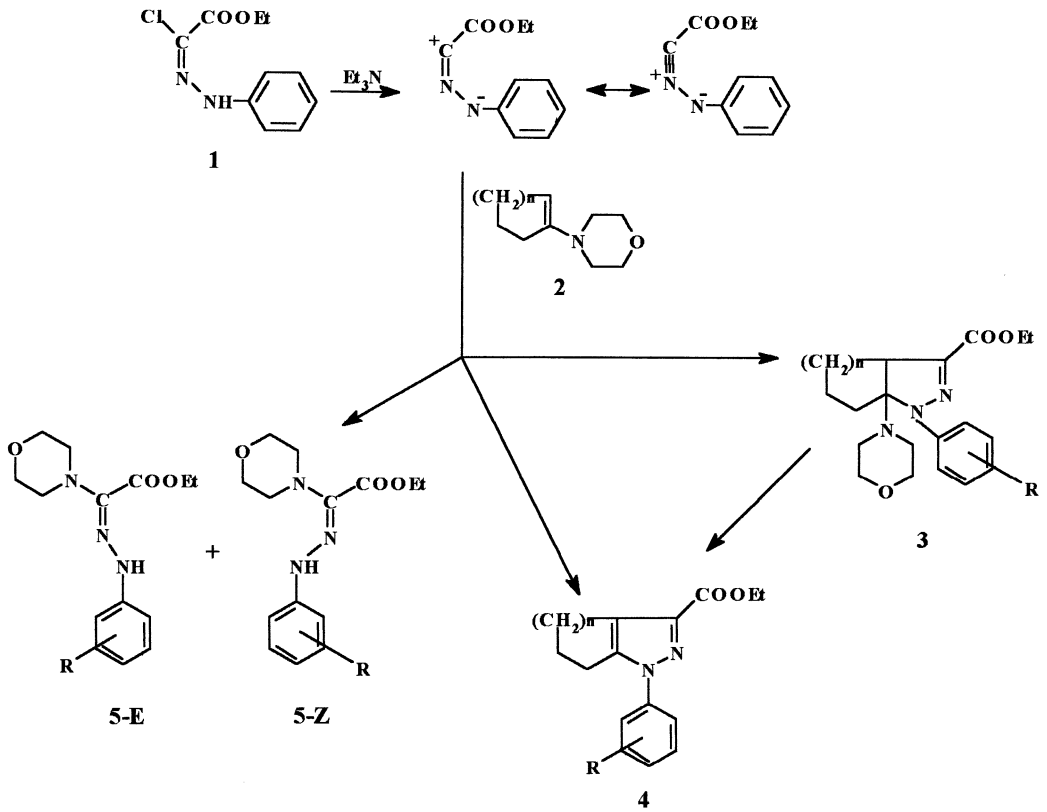
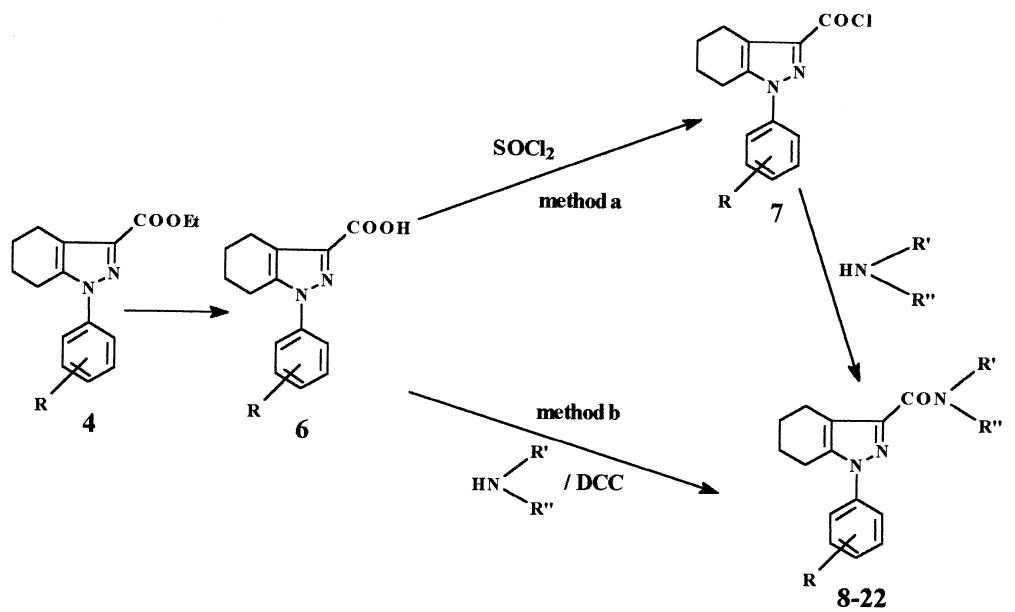


Fig. 1. Structures of the compounds under investigation.

Evidence of this is also given by differences in the physical properties of the two compounds. It is well known that the formation of intramolecular hydrogen bonds, rather than intermolecular, can dramatically affect the physical properties of compounds. In the case of the *E*-diastereoisomer, the hydrogen bond is formed between the imine hydrogen and the carbonyl oxygen, giving rise to a six-membered ring, while for the *Z*-isomer it is formed between the imine hydrogen and a nitrogen atom, leading to the formation of a less stable five-membered ring (Fig. 3). This is probably due to the lower stability of the intramolecular hydrogen bond and, in the case of the *Z*-diastereoisomer, a higher number of intermolecular bonds are formed, enhancing the cohesion between the molecules. All the *Z*-derivatives showed melting points about 20–40°C higher than the corresponding *E*-diastereoisomers.



Scheme 1. Synthetic pathway to compound **4**. a, R = 3-NO_2, $n = 2$; a′, R = 3-NO_2, $n = 1$; b, R = 3-CF_3, $n = 2$; c, R = 4-Cl, $n = 2$; d, R = 4-F, $n = 2$; e, R = 4-CH_3, $n = 2$.



Scheme 2. Synthetic pathway to compounds **8–22**. **8**: R = 3-NO_2, NR′R″ = morpholino; **9**: R = 3-NO_2, NR′R″ = pyrrolidino; **10**: R = 3-NO_2, NR′R″ = *N*-methylpiperazine; **11**: R = 3-CF_3, NR′R″ = morpholino; **12**: R = 3-CF_3, NR′R″ = pyrrolidino; **13**: R = 3-CF_3, NR′R″ = *N*-methylpiperazino; **14**: R = 4-F, NR′R″ = morpholino; **15**: R = 4-F, NR′R″ = pyrrolidino; **16**: R = 4-F, NR′R″ = *N*-methylpiperazine; **17**: R = 4-Cl, NR′R″ = morpholino; **18**: R = 4-Cl, NR′R″ = pyrrolidino; **19**: R = 4-Cl, NR′R″ = *N*-methylpiperazine; **20**: R = 4-CH_3, NR′R″ = morpholino; **21**: R = 4-CH_3, NR′R″ = pyrrolidino; **22**: R = 4-CH_3, NR′R″ = *N*-methylpiperazine.

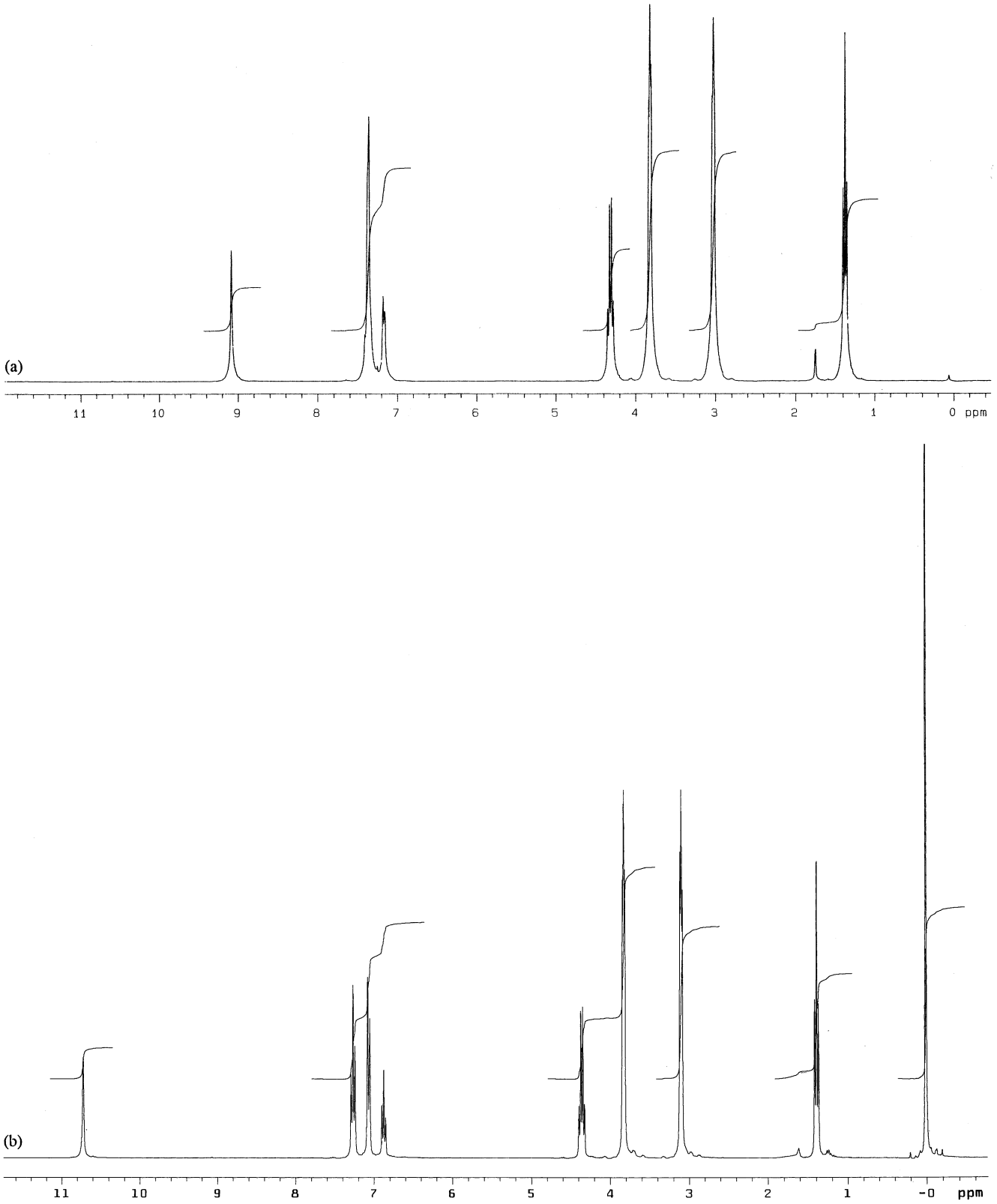
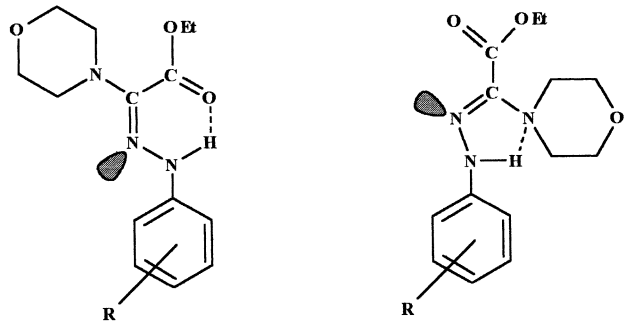


Fig. 2. ^{1}H NMR spectra for (a) *Z*- and (b) *E*-diastereoisomers of compounds **5**.

Only in the reaction between the cyclopentanone enamine (compound **2**; $n = 1$) and the chlorophenylhydrazones (**1**) four compounds were isolated. The pyrazolidinic derivative **3** was separated as a pure compound, which can be converted into the pyrazole derivative **4**, through the loss of a morpholine molecule, by simple heating in acetic acid for a few minutes.



5 E 5Z

Fig. 3. *E*- and *Z*-diastereoisomers of compounds **5**.

The reaction pathway is likely the same when the cyclohexanone enamines are used; four compounds are obtained as shown by TLC. Unfortunately, although the pyrazolidinic derivative is likely evidenced by chromatography, any attempt to isolate it failed. However, TLC of the reaction crude, as well as in the case of cyclopentanone enamines, showed the presence of a compound which can be easily converted into the pyrazolic derivative by simple heating in acetic acid.

Carboxylic acids (**6**) were obtained by hydrolysis of the corresponding esters and were then converted into acid chlorides (**7**) by treatment with thionyl chloride.

Condensation of acid chlorides (**7**) with the appropriate amines yielded the amides (**8–22**). These products were also obtained by direct coupling of carboxylic acids (**6**) with the appropriate amines in the presence of dicyclohexyl carbodiimide (DCC).

1. Experimental

All melting points were determined using an electrothermal melting point apparatus and are uncorrected. The IR spectra were obtained in Nujol with a Perkin–Elmer 398 spectrophotometer; ^{1}H NMR spectra were measured on a Varian EM 360 L using deuterochloroform as solvent and TMS as internal standard. Chemical shifts were reported as δ (ppm). Microanalysis for CHN were carried out on a Carlo Erba 1106 analyser. Electron ionization (EI) mass spectra were obtained by a Fisons QMD 1000 mass spectrometer (70 eV, 200 μA, ion source temperature 200°C). The samples were introduced directly into the ion source. Found molecular ions were in agreement with theoretical values. TLC was performed on silica gel plates (Merck F 254). Chromatography was accomplished with Merck silica gel (70–230 mesh).

1.1. Starting materials

1-*N*-Morpholinocyclohex-1-ene (**2**), 1-*N*-morpholinocyclopent-1-ene (**2**) ($n = 1$) [14,15], and 2-chloroacetoacetate [16] were prepared according to established procedures. The chlorophenylhydrazones (**1**) were prepared as described in literature [2,4,17,18]: 0.2 mol of the diazonium salt of the corresponding amide were added to a cool mixture of 0.2 mol of sodium acetate and 0.2 mol of 2-chloroacetoacetate in 300 ml of ethanol. The mixture was then stirred for 3 h and left overnight at 0°C. The precipitated product was filtered off, washed with water and recrystallized from the suitable solvent.

*1.2. Synthesis of 1-(3-nitrophenyl)-3-carbethoxy-4,5,6,7-tetrahydroindazole (**4a**) (general method)*

In a three necked flask 6.7 g (0.04 mol) of freshly distilled enamine (**2**) and 4.1 g (0.04 mol) of dry triethylamine were dissolved in 50 ml of dry chloroform. A solution of phenylhydrazone (**1**), 10.84 g (0.04 mol), dissolved in 100 ml of dry chloroform was added dropwise at room temperature (r.t.). The reaction mixture was stirred at r.t. for 12 h and then washed three times with water. The organic layer was dried on dry sodium sulfate. Evaporation of the solvent under reduced pressure yielded a thick oil which was purified by column chromatography, with a chloroform–hexane (1:1) mixture used as the eluent.

Column chromatography yielded two products. The former is the expected 1-(3-nitrophenyl)-3-carbethoxy-4,5,6,7-tetrahydroindazole, which was friabilized with isopropyl ether–hexane and then crystallized from ethanol. Pale yellow crystals; m.p. 120–121°C. Yield 37%.

IR spectra of compounds **4**: all the synthesized compounds **4** show a well detectable C=O adsorption band between 1710 and 1720 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3H, CH_3); 1.78 (t, 4H, CH_2); 2.79 (t, 2H, CH_2); 2.85 (t, 2H, CH_2); 4.40 (q, 2H, O–CH_2); 7.60–8.40 (m, 4H, Ar).

TLC analysis of the latter revealed the presence of two products with very similar R_f values that were isolated by crystallization.

Analytical and spectral data are in agreement with structure **5** (Scheme 1).

IR spectra of compounds **5**: all the synthesized compounds **5** show a well-detectable C=O adsorption band ranging between 1710 and 1720 cm^{-1} and a clear stretching N–H band at 3300–3450 cm^{-1}.

^{1}H NMR spectra (Fig. 2) show the presence of the two diastereoisomers **5a-***E* and **5a-***Z*; m.p.: 79.5–80.5 and 124–126°C, respectively.

*1.2.1. 2-(N-Morpholino)-2-(3-nitrophenyl)-hydrazidoyl-oxalic ethyl ester (**5a**-E)*

^{1}H NMR ($CDCl_3$): δ 1.39 (t, 3H, CH_3); 3.05 (t, 4H, CH_2–N); 3.85 (t, 4H, O–CH_2); 4.34 (q, 2H, O–CH_2); 7.41–7.96 (m, 4H, Ar); 10.56 (s, 1H, NH).

Table 1
1-Aryl-3-carbethoxy-cycloalkylpyrazole (**4**)

Comp.	R	*n*	Formula	M^+	M.p. (°C)	Crystal/solvent	Yield (%)	C (%)[a]	H (%)[a]	N (%)[a]
4a	*m*-NO_2	2	$C_{16}H_{17}N_3O_4$	315	120–121	Ethanol	37	60.95 (61.25)	5.43 (5.47)	13.32 (13.28)
4a′	*m*-NO_2	1	$C_{15}H_{15}N_3O_4$	301	127–128	Ethyl/ac.	32	59.79 (60.05)	5.02 (5.05)	13.95 (14.00)
4b	*m*-CF_3	2	$C_{17}H_{17}N_2O_2F_3$	338	118–119	Ethanol	35	60.35 (60.21)	5.07 (5.05)	8.28 (8.33)
4c	*p*-Cl	2	$C_{16}H_{17}N_2O_2Cl$	304	143	Ethanol	64	63.06 (62.92)	5.62 (5.65)	9.19 (9.12)
4d	*p*-F	2	$C_{16}H_{17}N_2O_2F$	288	132–133	Ethanol	53	66.66 (66.87)	5.94 (5.91)	9.71 (9.67)
4e	*p*-CH_3	2	$C_{17}H_{20}N_2O_2$	284	110–111	Ethanol	67	71.80 (72.04)	7.09 (7.11)	9.85 (9.81)

[a] Found values in parentheses.

*1.2.2. 2-(N-Morpholino)-2-(3-nitrophenyl)-hydrazidoyl-oxalic ethylester (**5a**-Z)*

^{1}H NMR ($CDCl_3$): δ 1.39 (t, 3H, CH_3); 3.05 (t, 4H, CH_2–N); 3.85 (t, 4H, O–CH_2); 4.34 (q, 2H, O–CH_2); 7.41–7.96 (m, 4H, Ar); 9.12 (s, 1H, NH).

The same method has been employed for the synthesis of the following products listed in Table 1.

*1.2.3. 1-(3-Nitrophenyl)-3-carbethoxy-6H-4,5-dihydroindazole (**4a′**) (n = 1)*

Column chromatography of the reaction crude yielded three products:

1. pale yellow crystals, compound **4a′** ($n = 1$), m.p. 127–128°C. Yield 32%. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3H, CH_3); 1.78–1.83 (m, 2H, CH_2); 2.79 (t, 2H, CH_2); 2.85 (t, 2H, CH_2); 4.40 (q, 2H, CH_2); 7.60–8.40 (m, 4H, Ar);
2. **5-***E* and **5-***Z* diastereoisomers;
3. the third product is the 1-(3-nitrophenyl)-4aH-3-carbethoxy-8a-morpholino-5,6,7,8a-tetrahydroindazole (**3a**) ($n = 1$).

^{1}H NMR ($CDCl_3$): δ 1.36 (s, 3H, CH_3); 1.50–1.57 (m, 2H, CH_2); 1.76 (q, 2H, CH_2); 1.81 (t, 2H, CH_2); 1.89 (t, 1H, CH); 2.70 (t, 4H, N–CH_2); 3.69 (t, 4H, O–CH_2); 4.40 (q, 2H, O–CH_2); 7.60–8.40 (m, 4H, Ar).

These compounds **3** have only been isolated when the cyclopentanone enamines are employed. Their structure was determined by means of ^{1}H NMR and mass spectroscopy. By heating, during the crystallization process, compound **3** is converted into **4a′** ($n = 1$). The reaction is highly favored by acids. As an example, the conversion is completed in a few minutes in the presence of acetic acid.

*1.2.4. 1-(3-Trifluoromethylphenyl)-3-carbethoxy-4,5,6,7-tetrahydroindazole (**4b**)*

The pyrazole derivative **4b** was obtained as pale yellow crystals, m.p. 118–119°C. Yield 35%.

^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, CH_3); 1.79 (t, 4H, CH_2); 2.78 (t, 2H, CH_2); 2.85 (t, 2H, CH_2), 4.32 (q, 2H, O–CH_2); 7.80–8.40 (m, 4H, Ar).

Along with the expected cycloaddition product **4b**, the electrophilic addition product **5b** (*E* and *Z*) was also obtained, m.p. 83–85 and 110–111°C, respectively.

*1.2.5. 2-(N-Morpholino)-2-(3-trifluoromethylphenyl)-hydrazidoyl-oxalic ethyl ester (**5b**-E)*

^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, CH_3); 3.04 (t, 4H, CH_2–N); 3.83 (t, 4H, O–CH_2); 4.30 (q, 2H, O–CH_2); 7.25–7.41 (m, 4H, Ar); 10.60 (s, 1H, NH).

*1.2.6. 2-(N-Morpholino)-2-(3-trifluoromethylphenyl)-hydrazidoyl-oxalic ethyl ester (**5b**-Z)*

^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, CH_3); 3.04 (t, 4H, CH_2–N); 3.83 (t, 4H, O–CH_2); 4.30 (q, 2H, O–CH_2); 7.25–7.41 (m, 4H, Ar); 9.08 (s, 1H, NH).

*1.2.7. 1-(4-Chlorophenyl)-3-carbethoxy-4,5,6,7-tetrahydroindazole (**4c**)*

Column chromatography of the reaction crude, obtained as described above, yielded two products. Compound **5** (*E* and *Z*) was obtained in lower yield than in the previously described reactions, while the yield of compound **4c** was enhanced. Crystallization from ethanol yielded compound **4c** as white crystals, m.p. 143°C. Yield 64%.

^{1}H NMR ($CDCl_3$): δ 1.42 (t, 3H, CH_3); 1.80 (t, 4H, CH_2); 2.66 (t, 2H, CH_2); 2.81 (t, 2H, CH_2), 4.42 (q, 2H, O–CH_2); 7.20–7.50 (m, 4H, Ar).

*1.2.8. 2-(N-Morpholino)-2-(4-chlorophenyl)-hydrazidoyl-oxalic ethyl ester (**5c**-E)*

M.p. 86–87°C. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3H, CH_3); 3.08 (t, 4H, CH_2–N); 3.81 (t, 4H, O–CH_2); 4.34 (q, 2H, O–CH_2); 7.10–7.27 (m, 4H, Ar); 10.62 (s, 1H, NH).

*1.2.9. 2-(N-Morpholino)-2-(4-chlorophenyl)-hydrazidoyl-oxalic ethylester (**5c**-Z)*

M.p. 112–113°C. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3H, CH_3); 3.08 (t, 4H, CH_2–N); 3.81 (t, 4H, O–CH_2); 4.34 (q, 2H, O–CH_2); 7.10–7.27 (m, 4H, Ar); 9.01 (s, 1H, NH).

*1.2.10. 1-(4-Fluorophenyl)-3-carbethoxy-4,5,6,7-tetrahydroindazole (**4d**)*

Compound **4d** was obtained as previously described. White crystals, m.p. 132–133°C. Yield 53%.

Table 2
1-Aryl-4,5,6,7-tetrahydroindazole-3-carboxylic acid (**6**)

Comp.	R	*n*	Formula	M^+	M.p. (°C)	Crystal/solvent	Yield (%)	C (%)[a]	H (%)[a]	N (%)[a]
6a	*m*-NO_2	2	$C_{14}H_{13}N_3O_4$	287	203	AcOH/AcOEt	68	58.53 (58.72)	4.56 (4.59)	14.63 (14.55)
6a′	*m*-NO_2	1	$C_{13}H_{11}N_30_4$	273	206–207	AcOH/acetonitrile	65	57.14 (56.95)	4.06 (4.08)	15.38 (15.29)
6b	*m*-CF_3	2	$C_{15}H_{13}N_2O_2F_3$	310	209–210	AcOH dil.	66	58.07 (57.86)	4.22 (4.19)	9.02 (8.97)
6c	*p*-Cl	2	$C_{14}H_{13}N_2O_2Cl$	276	217	AcOH dil.	85	60.77 (60.90)	4.73 (4.70)	10.12 (10.08)
6d	*p*-F	2	$C_{14}H_{13}N_2O_2F$	260	213–214	AcOH dil.	78	64.61 (64.51)	5.03 (4.99)	10.76 (10.70)
6e	*p*-CH_3	2	$C_{15}H_{16}N_2O_2$	256	199–200	AcOH dil.	90	70.29 (70.51)	6.29 (6.31)	10.93 (10.89)

[a] Found values in parentheses.

^{1}H NMR ($CDCl_3$): δ 1.43 (t, 3H, CH_3); 1.81 (t, 4H, CH_2); 2.67 (t, 2H, CH_2); 2.82 (t, 2H, CH_2), 4.42 (q, 2H, O–CH_2); 7.30–7.60 (m, 4H, Ar).

Also in this case the electrophilic cycloaddition products **5d** (*E* and *Z*) diastereoisomers were obtained, m.p. 78–79 and 108–110°C, respectively.

*1.2.11. 2-(N-Morpholino)-2-(4-fluorophenyl)-hydrazidoyl-oxalic ethyl ester (**5d**-E)*

^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, CH_3); 3.05 (t, 4H, CH_2–N); 3.81 (t, 4H, O–CH_2); 4.35 (q, 2H, O–CH_2); 6.95–6.97 (m, 4H, Ar); 10.64 (s, 1H, NH).

*1.2.12. 2-(N-Morpholino)-2-(4-fluorophenyl)-hydrazidoyl-oxalic ethyl ester (**5d**-Z)*

^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, CH_3); 3.05 (t, 4H, CH_2–N); 3.81 (t, 4H, O–CH_2); 4.35 (q, 2H, O–CH_2); 6.95–6.97 (m, 4H, Ar); 9.02 (s, 1H, NH).

*1.2.13. 1-(4-Methylphenyl)-3-carbethoxy-4,5,6,7-tetrahydroindazole (**4e**)*

The previously reported procedure was employed for the synthesis of compound **4e**.

^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3H, CH_3); 1.80 (t, 4H, CH_2); 2.28 (s, 3H, CH_3); 2.63 (t, 2H, CH_2); 2.70 (t, 2H, CH_2), 4.39 (q, 2H, O–CH_2); 7.40–7.70 (m, 4H, Ar).

Together with the expected compound **4e** the corresponding electrophilic addition compounds **5e** (*E* and *Z*) have been obtained, m.p. 73–74 and 98–99°C, respectively.

*1.2.14. 2-(N-Morpholino)-2-(4-methylphenyl)-hydrazidoyl-oxalic ethyl ester (**5e**-E)*

^{1}H NMR ($CDCl_3$): δ 1.39 (t, 3H, CH_3); 2.88 (s, 3H, Ar–CH_3); 3.07 (t, 4H, CH_2–N); 3.83 (t, 4H, O–CH_2); 4.31 (q, 2H, O–CH_2); 6.95–7.26 (m, 4H, Ar); 10.70 (s, 1H, NH).

*1.2.15. 2-(N-Morpholino)-2-(4-methylphenyl)-hydrazidoyl-oxalic ethyl ester (**5e**-Z)*

^{1}H NMR ($CDCl_3$): δ 1.39 (t, 3H, CH_3); 2.88 (s, 3H, Ar–CH_3); 3.07 (t, 4H, CH_2–N); 3.83 (t, 4H, O–CH_2); 4.31 (q, 2H, O–CH_2); 6.95–7.26 (m, 4H, Ar); 9.04 (s, 1H, NH).

*1.3. Synthesis of 1-aryl-4,5,6,7-tetrahydroindazole-3-carboxylic acid (**6**) (general method)*

The carboxylic acids **6** (Table 2) were obtained by hydrolysis of the corresponding esters **4**.

The hydrolysis was accomplished following two different methods:

*1.3.1. 1-(3-Nitrophenyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (**6a**) (method a)*

To a solution of KOH (14 g) in H_2O (70 ml) and methanol (70 ml) the ester **4a** (31.5 g, 0.1 mol) was added and the mixture was refluxed for 4 h, then allowed to cool down to r.t., diluted with water (200 ml) and finally neutralized with 10% HCl water solution. The obtained solid was filtered and crystallized from acetic acid–ethyl acetate.

*1.3.2. 1-(3-Nitrophenyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (**6a**) (method b)*

The ester **4a** (0.014 mol) was dissolved in 25 ml of boiling ethanol and 25 ml of water and then 5 ml of a water solution of 30% NaOH was added.

The reaction mixture was refluxed and the ethanol was distilled off, during which time the volume was kept constant by adding water.

The mixture was then cooled and neutralized with 10% HCl water solution. The solution was then refluxed for a few minutes in the presence of charcoal and rapidly filtered. To the boiling solution HCl was added and the acid **6a** precipitated out of this solution.

The carboxylic acid **6a** was obtained as white crystals that were further purified by crystallization from acetic acid–ethyl acetate. Yield is generally higher following method b.

Pale yellow crystals, m.p. 203°C. Yield 68%.

IR spectra: all the synthesized acids **6** show the C=O adsorption band ranging between 1700 and 1710 cm^{-1} and a large band corresponding to the OH group from 3000 to 2800 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.84 (t, 4H, CH_2); 2.80 (t, 2H, CH_2); 2.86 (t, 2H, CH_2); 5.30 (s, 1H, COOH); 7.60–8.40 (m, 4H, Ar).

The carboxylic acids listed in Table 2 were prepared according to method b.

*1.3.3. 1-(3-Nitrophenyl)-4,5-dihydro-6H-cyclopenta-[b]-pyrazole-3-carboxylic acid (**6a′**) (n = 1).*

Compound **6a′** was synthesized as described above. Pale yellow crystals were obtained, m.p. 206–207°C. Yield 65%.

^{1}H NMR ($CDCl_3$): δ 1.78–1.83 (m, 2H, CH_2); 2.80 (t, 2H, CH_2); 2.86 (t, 2H, CH_2); 5.30 (s, 1H, COOH); 7.60–8.40 (m, 4H, Ar).

*1.3.4. 1-(3-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-indazole-3-carboxylic acid (**6b**)*

White crystals, m.p. 209–210°C. Yield 66%.

^{1}H NMR ($CDCl_3$): δ 1.85 (t, 4H, CH_2); 2.76 (t, 2H, CH_2); 2.80 (t, 2H, CH_2); 5.29 (s, 1H, COOH); 7.50–8.30 (m, 4H, Ar).

*1.3.5. 1-(4-Chlorophenyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (**6c**)*

White crystals, m.p. 217°C. Yield 85%.

^{1}H NMR ($CDCl_3$): δ 2.44 (t, 4H, CH_2); 3.23 (t, 2H, CH_2); 3.44 (t, 2H, CH_2); 5.25 (s, 1H, COOH); 7.40–7.80 (m, 4H, Ar).

*1.3.6. 1-(4-Fluorophenyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (**6d**)*

White crystals, m.p. 213–214°C. Yield 78%.

^{1}H NMR ($CDCl_3$): δ 2.42 (t, 4H, CH_2); 3.25 (t, 2H, CH_2); 3.47 (t, 2H, CH_2); 5.26 (s, 1H, COOH); 7.40–7.90 (m, 4H, Ar).

*1.3.7. 1-(4-Methylphenyl)-4,5,6,7-tetrahydroindazole-3-carboxylic acid (**6e**)*

White crystals, m.p. 199–200°C. Yield 90%.

^{1}H NMR ($CDCl_3$): δ 2.18 (t, 4H, CH_2); 2.37 (s, 3H, CH_3); 2.45 (t, 2H, CH_2); 2.50 (t, 2H, CH_2); 5.00 (s, 1H, COOH); 7.40–8.60 (m, 4H, Ar).

*1.4. Synthesis of 1-aryl-3-chlorocarbonyl-4,5,6,7-tetrahydroindazole (**7**) (general method)*

*1.4.1. 1-(3-Nitrophenyl)-3-chlorocarbonyl-4,5,6,7-tetrahydroindazole (**7a**)*

To a solution of the carboxylic acid (**6a**) 2.87 g (0.01 mol) in dry benzene (30 ml), thionyl chloride 1.5 ml (0.02 mol) was added dropwise under vigorous stirring. The mixture was refluxed for 1 h and then the solvent was removed under reduced pressure. The acid was obtained as white powder that was crystallized from ethanol. Yield 52%, m.p. 107–108°C.

IR spectra: all the prepared acid chlorides show a clear C=O stretching band at 1780–1800 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.80 (t, 4H, CH_2); 3.68 (t, 2H, CH_2); 3.94 (t, 2H, CH_2); 7.58–8.32 (m, 4H, Ar).

The acid chlorides (Table 3) were obtained according to this method.

*1.4.2. 1-(3-Nitrophenyl)-3-chlorocarbonyl-6H-4,5-dihydroindazole (**7a′**) (n = 1)*

^{1}H NMR ($CDCl_3$): δ 1.79–1.81 (m, 2H, CH_2); 3.68 (t, 2H, CH_2); 3.94 (t, 2H, CH_2); 7.58–8.32 (m, 4H, Ar).

*1.4.3. 1-(3-Trifluoromethylphenyl)-3-chlorocarbonyl-4,5,6,7-tetrahydroindazole (**7b**)*

^{1}H NMR ($CDCl_3$): δ 1.79 (t, 4H, CH_2); 3.62 (t, 2H, CH_2); 3.88 (t, 2H, CH_2); 7.56–8.29 (m, 4H, Ar).

*1.4.4. 1-(4-Chlorophenyl)-3-chlorocarbonyl-4,5,6,7-tetrahydroindazole (**7c**)*

^{1}H NMR ($CDCl_3$): δ 1.80 (t, 4H, CH_2); 2.67 (t, 2H, CH_2); 2.76 (t, 2H, CH_2); 7.33–7.50 (m, 4H, Ar).

*1.4.5. 1-(4-Fluorophenyl)-3-chlorocarbonyl-4,5,6,7-tetrahydroindazole (**7d**)*

^{1}H NMR ($CDCl_3$): δ 1.82 (t, 4H, CH_2); 2.55 (t, 2H, CH_2); 2.64 (t, 2H, CH_2); 7.50–8.31 (m, 4H, Ar).

Table 3
1-Aryl-3-chlorocarbonyl-4,5,6,7-tetrahydroindazole (**7**)

Comp.	R	*n*	Formula	M^+	M.p. (°C)	Crystal/solvent	Yield (%)	C (%)[a]	H (%)[a]	N (%)[a]
7a	*m*-NO_2	2	$C_{14}H_{12}N_3O_3Cl$	305	107–108	Ethanol	52	55.00 (55.28)	3.96 (4.00)	13.74 (13.66)
7a′	*m*-NO_2	1	$C_{13}H_{10}N_3O_3Cl$	291	110–111	Ethanol	50	53.53 (53.70)	3.46 (3.49)	14.40 (14.29)
7b	*m*-CF_3	2	$C_{15}H_{12}N_2OF_3Cl$	328	105–106	Ethanol	47	54.81 (55.00)	3.68 (3.71)	8.52 (8.47)
7c	*p*-Cl	2	$C_{14}H_{12}N_2OCl_2$	295	111–112	Ethanol/ *n*-hexane	80	56.97 (56.80)	4.10 (3.98)	9.49 (9.54)
7d	*p*-F	2	$C_{14}H_{12}N_2OFCl$	278	103–104	Ethanol/ *n*-hexane	75	60.33 (60.55)	4.34 (4.37)	10.05 (9.98)
7e	*p*-CH_3	2	$C_{15}H_{15}N_2OCl$	274	97–98	Ethanol	96	65.57 (65.38)	5.50 (5.47)	10.20 (10.16)

[a] Found values in parentheses.

*1.4.6. 1-(4-Methylphenyl)-3-chlorocarbonyl-4,5,6,7-tetrahydroindazole (**7e**)*

^{1}H NMR ($CDCl_3$): δ 1.81 (t, 4H, CH_2); 2.20 (s, 3H, CH_3); 2.25 (t, 2H, CH_2); 2.45 (t, 2H, CH_2); 7.60–8.40 (m, 4H, Ar).

*1.5. Synthesis of 1-aryl-3-(carbamoyl-N-substituted)-tetrahydroindazoles (**8–22**) (general method)*

Two different methods have been employed for the synthesis of these compounds.

*1.5.1. 1-(3-Nitrophenyl)-3-(morpholinocarbamoyl)-4,5,6,7-tetrahydroindazole (**8**) (method a)*

To a solution of morpholine 1.2 ml (10 mmol) and pyridine 0.6 ml (5 mmol) in dry benzene (10 ml) a solution of the acid chloride **7a** (5 mmol) in dry benzene (40 ml) was added dropwise under vigorous stirring. The reaction was stirred for 6 h at r.t., then water (0.5 ml) was added and the mixture was stirred for another 15 min. The mixture was extracted with chloroform and the organic layer washed with 10% HCl water solution, in order to remove the excess of pyridine, then with water and finally dried with sodium sulfate.

Evaporation of the solvent under reduced pressure yielded an oil that can be easily friabilized with either *n*-hexane or isopropyl ether. Yield 80%.

*1.5.2. 1-(3-Nitrophenyl)-3-(morpholinocarbamoyl)-4,5,6,7-tetrahydroindazole (**8**) (method b)*

A mixture of the carboxylic acid (**6a**) 2.87 g (0.01 mol) and dicyclohexylcarbodiimide (**4**), 12 g (0.02 mol) in 30 ml dichloromethane and 20 ml of dimethylformamide was stirred for 15 min at r.t. The formation of a precipitate of dicyclohexylurea was observed. An excess of morpholine, 3 ml (0.03 mol), was then added. The reaction was stirred at r.t. for 30 min then heated up to 60°C and stirred for a further 8 h.

Filtration of the reaction mixture yielded a white solid (m.p. 232–233°C), that was identified as dicyclohexylurea. The solution was washed twice with acidic water (2 × 10 ml), then with a 10% water solution of sodium hydrogen carbonate (2 × 10 ml) and finally with water.

The organic layer was dried on anhydrous sodium sulfate and then evaporated under reduced pressure. An oil was obtained that can be friabilized from isopropyl ether and crystallized from ethanol. Yield 65%.

IR spectra: all the synthesized amides show a well detectable C=O band between 1670 and 1640 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.80 (t, 4H, CH_2); 2.75 (t, 4H, N–CH_2); 3.68 (t, 2H, CH_2); 3.75 (t, 4H, O–CH_2); 3.94 (t, 2H, CH_2); 7.60–8.32 (m, 4H, Ar).

Table 4
1-Aryl-3-(carbamoyl-*N*-substituted)-tetrahydroindazoles (**8–22**)

Comp.	R_1	NR″	Formula	M^+	M.p. (°C)	Crystal/solvent	Yield (%)	C (%)[a]	H (%)[a]	N (%)[a]
8	*m*-NO_2	*c*-$N(C_4H_8)_2O$	$C_{18}H_{20}N_4O_4$	356	175–177	Ethanol/*n*-hexane	80	60.66 (60.96)	5.66 (5.63)	15.72 (15.63)
9	*m*-NO_2	*c*-NC_4H_8	$C_{18}H_{20}N_4O_3$	340	170–172	Ethanol/*n*-hexane	83	63.51 (63.70)	5.92 (5.96)	16.46 (16.41)
10	*m*-NO_2	*c*-$N(CH_2CH_2)NCH_3$	$C_{19}H_{23}N_5O_3$	369	164–165	Ethanol/isop. ether	77	61.78 (62.00)	6.27 (6.24)	18.96 (18.88)
11	*m*-CF_3	*c*-$N(CH_2CH_2)_2O$	$C_{19}H_{20}N_3O_2F_3$	379	165–166	Ethanol/isop. ether	75	60.15 (59.97)	5.31 (5.30)	11.07 (11.02)
12	*m*-CF_3	*c*-NC_4H_8	$C_{19}H_{20}N_3OF_3$	363	169–171	Ethanol/isop.ether	80	62.80 (63.00)	5.55 (5.58)	11.56 (11.50)
13	*m*-CF_3	*c*-$N(CH_2CH_2)NCH_3$	$C_{20}H_{23}N_4OF_3$	392	158–160	Ethanol/isop.ether	71	61.21 (61.42)	5.91 (5.89)	14.28 (14.33)
14	*p*-Cl	*c*-$N(CH_2CH_2)_2O$	$C_{18}H_{20}N_3O_2Cl$	345	174–176	Ethanol	81	62.52 (62.60)	5.83 (5.87)	12.15 (12.09)
15	*p*-Cl	*c*-NC_4H_8	$C_{18}H_{20}N_3OCl$	329	153	Ethanol	90	65.55 (65.63)	6.11 (6.15)	12.73 (12.69)
16	*p*-Cl	*c*-$N(CH_2CH_2)NCH_3$	$C_{19}H_{23}N_4OCl$	358	147–149	Ethanol	78	63.60 (63.47)	6.46 (6.49)	15.61 (15.55)
17	*p*-F	*c*-$N(CH_2CH_2)_2O$	$C_{18}H_{20}N_3O_2F$	329	168–169	Ethanol	76	65.64 (65.85)	6.12 (6.15)	12.75 (12.68)
18	*p*-F	*c*-NC_4H_8	$C_{18}H_{20}N_3OF$	313	162–163	Ethanol	79	68.99 (69.25)	6.43 (6.46)	13.40 (13.35)
19	*p*-F	*c*-$N(CH_2CH_2)NCH_3$	$C_{19}H_{23}N_4OF$	342	155–157	Ethanol/isop. ether	67	66.65 (66.49)	6.77 (6.80)	16.36 (16.41)
20	*p*-CH_3	*c*-$N(CH_2CH_2)_2O$	$C_{19}H_{23}N_3O_2$	325	142–144	Ethanol	85	70.13 (70.27)	7.12 (7.09)	12.91 (12.86)
21	*p*-CH_3	*c*-NC_4H_8	$C_{19}H_{23}N_3O$	309	146–148	Ethanol	93	73.76 (73.82)	7.49 (7.51)	13.58 (13.53)
22	*p*-CH_3	*c*-$N(CH_2CH_2)NCH_3$	$C_{20}H_{26}N_4O$	338	137–139	Ethanol	81	71.01 (71.27)	7.69 (7.71)	16.56 (16.48)

[a] Found values in parentheses.

According to this method the following products (Table 4) were prepared:

1.6. 1-(3-Nitrophenyl)-3-(pyrrolidinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(9)***

^{1}H NMR ($CDCl_3$): δ 1.78 (t, 4H, CH_2); 1.92 (t, 4H, CH_2); 2.69 (t, 2H, CH_2); 2.83 (t, 2H, CH_2); 3.64 (t, 4H, N–CH_2); 7.60–8.32 (m, 4H, Ar).

1.7. 1-(3-Nitrophenyl)-3-(4′-N-methylpiperazinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(10)***

^{1}H NMR ($CDCl_3$): δ 1.24 (s, 3H, CH_3); 1.79 (t, 4H, CH_2); 2.71 (t, 2H, CH_2); 2.84 (t, 2H, CH_2); 3.74 (t, 4H, CH_2–N–Me); 4.00 (t, 4H, N–CH_2); 7.60–8.32 (m, 4H, Ar).

1.8. 1-(3-Trifluoromethylphenyl)-3-(morpholinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(11)***

^{1}H NMR ($CDCl_3$): δ 1.81 (t, 4H, CH_2); 2.77 (t, 4H, N–CH_2); 3.70 (t, 2H, CH_2); 3.76 (t, 4H, O–CH_2); 3.95 (t, 2H, CH_2); 7.58–8.28 (m, 4H, Ar).

1.9. 1-(3-Trifluoromethylphenyl)-3-(pyrrolidinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(12)***

^{1}H NMR ($CDCl_3$): δ 1.80 (t, 4H, CH_2); 1.93 (t, 4H, CH_2); 2.70 (t, 2H, CH_2); 2.83 (t, 2H, CH_2); 3.64 (t, 4H, N–CH_2); 7.58–8.28 (m, 4H, Ar).

1.10. 1-(3-Trifluoromethylphenyl)-3-(4′-N-methylpiperazinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(13)***

^{1}H NMR ($CDCl_3$): δ 1.25 (s, 3H, CH_3); 1.80 (t, 4H, CH_2); 2.71 (t, 2H, CH_2); 2.85 (t, 2H, CH_2); 3.74 (t, 4H, CH_2–N–Me); 4.01 (t, 4H, N–CH_2); 7.58–8.30 (m, 4H, Ar).

1.11. 1-(4-Chlorophenyl)-3-(morpholinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(14)***

^{1}H NMR ($CDCl_3$): δ 1.78 (t, 4H, CH_2); 2.72 (t, 4H, N–CH_2); 3.69 (t, 2H, CH_2); 3.76 (t, 4H, O–CH_2); 3.99 (t, 2H, CH_2); 7.20–7.50 (m, 4H, Ar).

1.12. 1-(4-Chlorophenyl)-3-(pyrrolidinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(15)***

^{1}H NMR ($CDCl_3$): δ 1.78 (t, 4H, CH_2); 1.92 (t, 4H, CH_2); 2.70 (t, 2H, CH_2); 2.84 (t, 2H, CH_2); 3.65 (t, 4H, N–CH_2); 7.20–7.50 (m, 4H, Ar).

1.13. 1-(4-Chlorophenyl)-3-(4′-N-methylpiperazinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(16)***

^{1}H NMR ($CDCl_3$): δ 1.24 (s, 3H, CH_3); 1.79 (t, 4H, CH_2); 2.71 (t, 2H, CH_2); 2.84 (t, 2H, CH_2); 3.74 (t, 4H, CH_2–N–Me); 4.00 (t, 4H, N–CH_2); 7.20–7.50 (m, 4H, Ar).

1.14. 1-(4-Fluorophenyl)-3-(morpholinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(17)***

^{1}H NMR ($CDCl_3$): δ 1.77 (t, 4H, CH_2); 2.70 (t, 4H, N–CH_2); 3.67 (t, 2H, CH_2); 3.75 (t, 4H, O–CH_2); 3.97 (t, 2H, CH_2); 7.20–7.80 (m, 4H, Ar).

1.15. 1-(4-Fluorophenyl)-3-(pyrrolidinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(18)***

^{1}H NMR ($CDCl_3$): δ 1.77 (t, 4H, CH_2); 1.92 (t, 4H, CH_2); 2.70 (t, 4H, N–CH_2); 2.84 (t, 2H, CH_2); 3.67 (t, 2H, CH_2); 7.20–7.80 (m, 4H, Ar).

1.16. 1-(4-Fluorophenyl)-3-(4′-N-methylpiperazinocarbamoyl)-4,5,6,7-tetrahydroindazole ***(19)***

^{1}H NMR ($CDCl_3$): δ 1.24 (s, 3H, CH_3); 1.77 (t, 4H, CH_2); 2.70 (t, 2H, CH_2); 2.84 (t, 2H, CH_2); 3.74 (t, 4H, CH_2–N–Me); 4.00 (t, 4H, N–CH_2); 7.20–7.80 (m, 4H, Ar).

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