Synthesis of New Arylidencycloalkylpyrazoles of Potential Biological Interest

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Indazoles and pyrazoles are known to be pharmaceutically relevant molecules. In particular their application as both analgesic and antitumoral drugs has been reported. In order to investigate the properties of compounds belonging to these families, we have synthesised new cycloalkylpyrazoles bearing an arylidene group on the cycloalkyl ring, with the aim of modifying the biological profile of these molecules.

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Introduction.

Indazole-related molecules have been extensively studied both from the synthetic and the pharmacological point of view. Indeed, researchers from an important Italian pharmaceutical company dedicated a great effort to the study of indazole compounds over a period of 20 years. [1-5]. As a result of this work, they synthesised and introduced in therapy three interesting compounds: benzidamine (a non-steroidal and non-acidic anti-inflammatory), bendazac (a protein anti-denaturant) and lonidamine (an anticancer agent).

In a previous research on pyrazole derivatives as potential cyclooxygenase inhibitors, a new series of cycloalkylpyrazoles has been synthesised and studied [6].

Some of the newly synthesised compounds exhibited potent analgesic properties, comparable to those of the well-known drug fentanyl. Unfortunately, such good activity is associated with high toxicity.

In the present paper we wish to report on the synthesis of a new series of 3-substituted-1-aryl-cycloalkylpyrazoles, bearing an arylidene function on the cycloalkyl ring in order to act as a conjugated system with the heterocyclic ring. These products are structurally related to the anti-inflammatory benzidamine and to the anti-tumour derivative lonidamine.

Our research is also aimed at both optimising the potent analgesic power of the 3-dialkylcarbamoyl-derivatives, and removing or minimising their toxicity. Moreover, we wish to synthesize new anti-tumour compounds by means of suitable structural changes. In fact, the introduction of an arylidene group in the cycloalkyl ring gives both planarity and rigidity, leading to compounds structurally related to the recalled lonidamine.

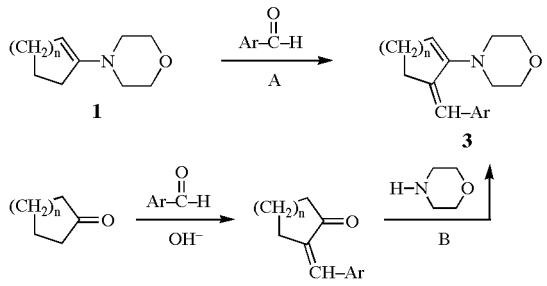
Results and Discussion.

The synthetic pathway to compounds **7-12** has been based on the well-known capability of nitrilimines (prepared "*in situ*" from the appropriate chlorophenylhydrazones) to easily undergo 1,3-dipolar cycloaddition reactions [7-14].

The arylidene enamines **3** (scheme 1) were obtained by treating aldehydes with 4-(1-cycloalkenyl)morpholine (method A), or by the reaction of the amine with arylidencycloketones **2**, which had been obtained by condensation of cycloalkanone with the appropriate aromatic aldehydes in diluted potassium hydroxide solution (method B), according to literature procedures [15-18]. Method A gives higher yields.

By using method B, the yields are lower even though the α,β-unsaturated ketone and the secondary amine are reacted at relatively low temperatures to minimise Michael-type addition [19].

Scheme 1

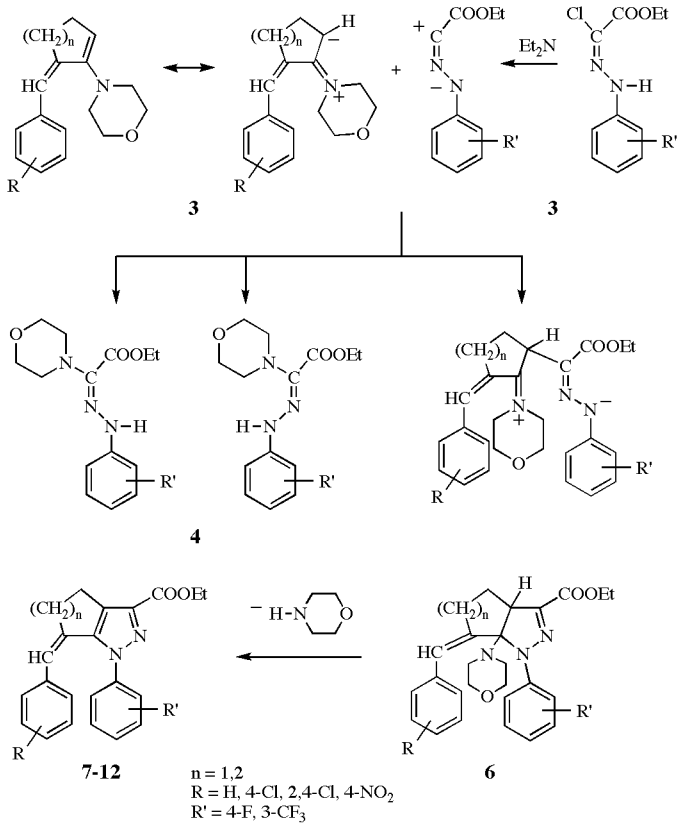


As generally happens in reactions between nitrilimines and dipolarophiles, we obtained both the 1,3-cycloaddition products **6-12**, and the 1,3-electrophilic addition products **4**. In the absence of a good polarophile, dimerisation of the nitrilimine and formation of the corresponding 1,4-dihydro-1,2,4,5-tetrazine could also occur [18-22].

The intermediate dihydropyrazole **6** could be isolated only when 4-(5-aryliden-1-cyclopenten-1-yl)-morpholine **3** (n = 1) is used. On strong acid treatment of these products, the pyrazoles **7-12** were formed. Probably, the relatively easy elimination of amine from the higher homologue **6** (n = 2) reflects the greater flexibility of the four-carbon bridge on the pyrazoles **11-12**, as compared to the more rigid three-carbon bridge, which imposes a steric strain on the pyrazole system [23].

Tlc (thin layer chromatography) revealed that compound **4** consists of two products with a very close Rf. Column chromatography, performed on silica gel, yielded two

Scheme 2



compounds that have been identified as the *E*- and *Z*–diastereoisomers.

The two diastereoisomers **4** were separated in the former fractions by column chromatography. These products were characterized either by analitical and spectroscopic methods or by comparison with samples obtained by direct reaction of the chlorophenylhydrazone with morpholine. In the latter fractions obtained from column chromatography, the pyrazolic compounds (**7-10**) were isolated and further purified by crystallization.

Their structures were assigned on the basis of analytical and spectroscopic data.

The ^{1}H nmr spectra agree with the assigned structures. For all the compounds, a peak related to the arylidenic proton, ranging between 6.60 and 7.50 ppm was observed, while the peaks related to the protons of the morpholine and the vinyl proton (5.30-5.54 ppm) of the starting enamine are absent. In other fractions obtained from column chromatography the mixture of the pyrazolinic derivatives **6** was present. All attempts to separate the two isomers with pyrazolinic structure **6**, both by crystallization, and by column chromatography, failed. The mixture of the two isomers, refluxed in hydrochloric acid, gives the corresponding pyrazolic derivative.

The diastereoisomers **4** could be well characterised by ^{1}H nmr spectroscopy, thanks to the different chemical shifts exhibited by the imine protons of the *E*- and *Z*-diastereoisomers (singlet between 9-9.12 ppm for *Z*-isomers and ranging between 10.55-10.65 ppm for *E*-isomers) [6].

The total amount of the two diastereoisomers is always lower than the amounts usually obtained for other enamines using ketones without α,β-insaturation. Probably, this is due to the strong polarophile character of the enamine **3**, deriving from the high conjugation between the arylidenic group and the enamine double bond.

In order to confirm the structure of the synthesised compounds further, the reaction has been carried out using dichloromethane as the solvent, and the temperature was kept in a range of 30-35 °C, stirring the reaction mixture over a period of four days. The reaction crude, which was obtained from the chlorophenylhydrazone and the enamine **3** (n = 1), was then analysed by thin layer chromatography. In these conditions, two products with very close Rf values are seen. Further purification and isolation allowed identification the two compounds as the two diastereoisomers of **4**.

Tlc revealed the formation of three additional products with very close Rf values, but easily distinguishable from the diastereoisomers **4**. An attempt to purify these three products was carried out by column chromatography

performed on silica gel (*n*-hexane/dichloromethane gradient). The pyrazolic compound (**7-12**) was separated, while it was not possible to purify the other two substances. The mixture of these two substances was analysed by both ^{1}H nmr spectroscopy and mass spectrometry, suggesting the pyrazoline structure **6** as the most probable one.

The mixture of the two substances was then refluxed in concentrated hydrochloric acid and the pyrazolic compounds (**7-12**) were obtained.

Very probably, the two substances are two pyrazoline isomers, differing in their junction of the cycloalkane to the pyrazoline ring. This hypothesis is strengthened by the easy elimination of a mole of morpholine to give the corresponding pyrazole derivative.

Interestingly, the formation of the pyrazoline derivative **6** was never observed when cyclohexanone enamines were employed.

Only formation of the tetrahydroindazole derivative, together with small amounts of 1,3-electrophilic addition products **4**, was observed. Formation of the pyrazolinic derivatives **6** was never observed, not even when the reaction was carried out at room temperature and/or in other solvents (benzene or chloroform).

The analytical and chemical-physical data for the tetrahydroindazoles are reported in table 2.

For the preparation of the corresponding amides **15-21** the usual methods (scheme 3) have been followed.

All the synthesised amides showed a well detectable C=O band ranging between 1675 and 1635 cm^{-1} on the ir spectra. ^{1}H-nmr and mass spectra agree with the assigned structures. The chemical-physical and analytical data are reported in table 3.

Table 1

Compounds **3a-g**

Compd	n	R	Formula	m.p. (°C)	Yield (%)	m/z	C (%)*	H (%)*	N (%)*
3a	1	H	$C_{16}H_{19}NO$	85-86	78	241	79.63 (79.30)	7.93 (7.88)	5.80 (5.77)
3b	1	4-Cl	$C_{16}H_{18}NClO$	89-90	81	275	69.69 (69.95)	6.58 (6.61)	5.08 (5.10)
3c	1	2,4-Cl	$C_{16}H_{17}NCl_2O$	147-48	75	310	61.94 (62.15)	5.52 (5.48)	4.52 (4.49)
3d	1	4-NO_2	$C_{16}H_{18}N_2O_3$	137-38	71	286	67.12 (66.87)	6.34 (6.37)	9.79 (9.84)
3e	1	3-NO_2	$C_{16}H_{18}N_2O_3$	124-26	60	286	67.12 (67.39)	6.34 (6.31)	9.79 (9.82)
3f	2	H	$C_{17}H_{21}NO$	108-09	66	255	79.95 (80.30)	8.29 (8.33)	5.49 (5.51)
3g	2	4-Cl	$C_{17}H_{20}NClO$	124-25	73	289	70.46 (70.21)	6.96 (6.93)	4.83 (4.85)

* Found values are in parentheses.

Table 2

Compounds **7-12**

Compd	n	R	R'	Formula	m.p. (°C)	Yield (%)	m/z	C (%)*	H (%)*	N (%)*
7	1	H	4-F	$C_{22}H_{19}FN_2O_2$	135-36	33	362	72.91 (73.18)	5.28 (5.31)	7.73 (7.69)
8	1	4-Cl	4-F	$C_{22}H_{18}ClFN_2O_2$	169-70	37	396	66.59 (66.73)	4.57 (4.54)	7.06 (7.10)
9	1	4-NO_2	4-F	$C_{22}H_{18}FN_3O_4$	189-90	20	407	64.86 (64.59)	4.45 (4.41)	10.31 (10.27)
10	1	2,4-Cl	3-CF_3	$C_{23}H_{17}N_2Cl_2F_3O_2$	192-95	27	481	57.40 (57.29)	3.56 (3.57)	5.82 (5.79)
11	2	H	4-F	$C_{23}H_{21}N_2FO_2$	147-48	31	376	73.39 (73.62)	5.62 (5.59)	7.44 (7.48)
12	2	4-Cl	3-CF_3	$C_{24}H_{20}N_2F_3ClO_2$	200-01	34	460	62.55 (62.29)	4.37 (4.40)	6.08 (6.11)

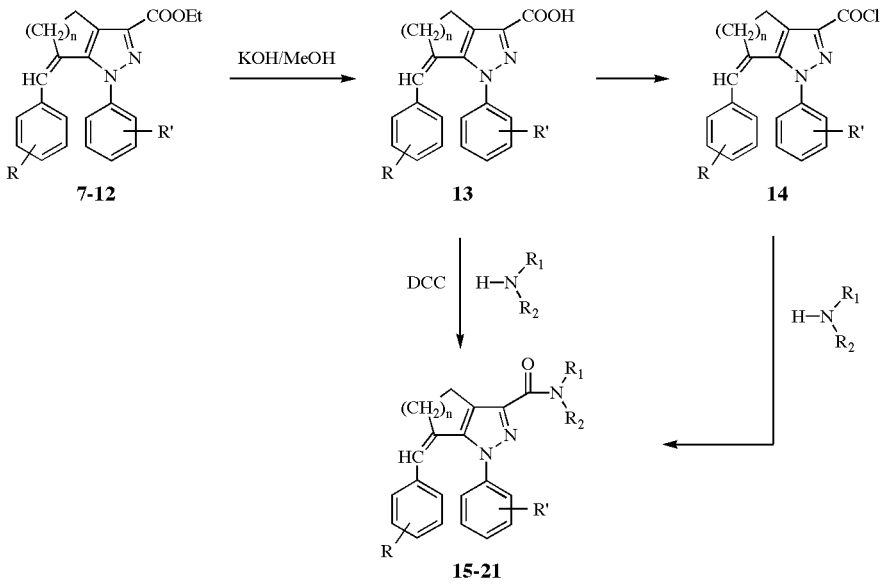
* Found values are in parentheses.

Table 3
Compounds **15-21**

Compd	N	R	R'	N-R_2R_3	Formula	m.p. (°C)	m/z	C(%)*	H(%)*	N(%)*
15	1	H	4-F	$N(CH_2)_2O$	$C_{24}H_{22}FN_3O_2$	168-69	403	71.45	5.50	10.41
								(71.17)	(5.47)	(10.35)
16	1	4-Cl	4-F	$N(CH_2)_2N\text{-}CH_3$	$C_{25}H_{24}ClFN_4O$	174-75	450	66.59	5.36	12.42
								(66.82)	(5.32)	(12.37)
17	1	2,4-Cl	3-CF_3	$N(CH_2)_2O$	$C_{25}H_{20}Cl_2F_3N_3O_2$	178-80	522	57.48	3.86	8.04
								(57.70)	(3.83)	(8.00)
18	1	4-NO_2	4-F	$N(CH_2)_2O$	$C_{24}H_{21}N_4Cl_2FO_4$	196-97	448	64.28	4.72	12.50
								(64.53)	(4.69)	(12.46)
19	1	4-Cl	3-CF_3	NC_4H_8	$C_{25}H_{21}N_3ClF_3O$	164-66	471	63.63	4.49	8.90
								(63.80)	(4.52)	(8.87)
20	2	H	4-F	$N(CH_2)_2N\text{-}CH_3$	$C_{26}H_{27}N_4FO$	170-72	430	72.53	6.32	13.01
								(72.77)	(6.29)	(12.95)
21	2	4-Cl	3-CF_3	$N(CH_2)_2O$	$C_{26}H_{23}N_3F_3ClO_2$	194-96	501	62.22	4.62	8.37
								(61.98)	(4.59)	(8.35)

* Found values are in parentheses.

Scheme 3



EXPERIMENTAL

Melting points are uncorrected and were determined on a Reichert Kofler thermopan apparatus. Infrared (ir) spectra were recorded on a Perkin-Elmer 1640 FT spectrometer (KBr discs or nujol, in cm^{-1}). ^1H nmr spectra were recorded on a Bruker AMX (300 MHz) using tetramethylsilane (TMS) as internal standard (chemical shifts in δ values). Electron ionisation (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. Elemental analyses were obtained on a Perkin-Elmer 240 B microanalyser. The structures of all compounds were assigned on the basis of ir, nmr, mass spectra, and elemental analysis.

Starting Materials.

1-Morpholinocyclopent-1-ene and 1-Morpholinocyclohex-1-ene [15], arylidencycloalkylketones [16-17], 2-chloroacetoacetate [24], and chlorophenylhydrazones [6] were prepared according to established procedures.

General Method for the Synthesis of Compounds **3**.

Method A.

In a flask, equipped with a Dean-Stark apparatus, 0.15 mol of freshly distilled enamine **1** and 0.1 mol of aldehyde were dissolved in 150-200 mL of dry benzene, together with a catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred at room temperature for 5-10 minutes and then under reflux, since

the amount of water formed during the reaction remains constant (6-12 h). Evaporation of the solvent under vacuum yielded a thick oil, which was pulverized by a mixture of isopropyl ether/ethanol, and then crystallized with the same solvents.

Method B.

Cycloketones (0.1 mol) were allowed to react with the appropriate aldehyde (0.05 mol) in water solution of potassium hydroxide (50 ml 0.4%). The reaction mixture was stirred overnight and then extracted with chloroform. The organic layer was then dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. A thick oil is obtained which is friabilised from isopropyl ether and used for the next step of the reaction without further purification. A benzene solution of the obtained 2-arylidencycloketone is reacted under reflux, in a flask, equipped with a Dean-Stark apparatus, with an equimolar amount of the appropriate amine in the presence of *p*-toluensulfonic acid as catalyst. The mixture is refluxed until the calculated amount of water is distilled off. Evaporation of the solvent under vacuum yielded a thick oil, which was pulverized by a mixture of isopropyl ether/ethanol, and then crystallized with the same solvents.

Chemical-physical and analytical data are reported in table 1. All enamines were characterized by mass spectra and ir, where a strong band in the 1630-1590 cm^{-1} region and absence of the carbonyl band is observed.

4-(5-Benzyliden-1-cyclopenten-1-yl)morpholine (**3a**).

This compound has ^{1}H nmr ($CDCl_3$): δ 2.30-2.38 (m, 2H, CH_2); 2.64-2.70 (t, 2H, CH_2); 2.85-2.88 (t, 4H, N-CH_2); 3.74-3.78 (t, 4H, O-CH_2); 5.30-5.35 (t, 1H, CH_2-*CH*=); 6.40 (s, 1H, ph-CH=); 7.30-7.50 (m, 5H, phenyl protons).

4-[5-(4-Chlorobenzyliden)-1-cyclopenten-1-yl] morpholine (**3b**).

This compound has ^{1}H nmr ($CDCl_3$): δ 2.38-2.42 (m, 2H, CH_2); 2.65-2.70 (t, 2H**,** CH_2); 2.85-2.90 (t, 4H, N-CH_2); 3.75-3.80 (t, 4H, O-CH_2); 5.37-5.40 (t, 1H, CH_2-*CH*=); 6.50 (s, 1H, ph-CH=); 7.10-7.33 (m, 4H, phenyl protons).

4-[5-(2,4-Dichlorobenzyliden)-1-cyclopenten-1-yl]morpholine (**3c**).

This compound has ^{1}H nmr ($CDCl_3$): δ 2.38-2.43 (m, 2H, CH_2); 2.68-2.73 (t, 2H, CH_2); 2.88-2.90 (t, 4H, N-CH_2); 3.77-3.80 (t, 4H, O-CH_2); 5.38-5.40 (t, 1H, CH_2-*CH*=); 6.56 (s, 1H, ph-CH=); 7.14-7.33 (m, 3H, phenyl protons).

4-[5-(4-Nitrobenzyliden)-1-cyclopenten-1-yl]morpholine (**3d**).

This compound has ^{1}H nmr ($CDCl_3$): δ 2.47-2.50 (m, 2H, CH_2); 2.87-2.95 (m, 6H, CH_2 and N-CH_2); 3.80-3.84 (t, 4H, O-CH_2); 5.50-5.54 (t, 1H, CH_2-*CH*=); 6.50 (s, 1H, ph-CH=); 7.40-8.22 (m, 4H, phenyl protons).

4-[5-(3-Nitrobenzyliden)-1-cyclopenten-1-yl] morpholine(**3e**).

This compound has ^{1}H nmr ($CDCl_3$): δ 2.45-2.49 (m, 2H, CH_2); 2.84-2.90 (m, 6H, CH_2 and N-CH_2); 3.79-3.82 (t, 4H, O-CH_2); 5.47-5.49 (t, 1H, CH_2-*CH*=); 6.40 (s, 1H, ph-CH=); 7.40-8.18 (m, 4H, phenyl protons).

4-(6-Benzyliden-1-cyclohexen-1-yl)morpholine (**3f**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.30-1.40 (m, 2H, CH_2); 1.80-2.00 (t, 2H, CH_2); 2.25-2.44 (m, 2H, CH_2); 2.48-2.75 (t, 4H, N-CH_2); 3.47-3.71 (t, 4H, O-CH_2); 4.90-5.00 (t, 1H, CH_2-*CH*=); 6.60 (s, 1H, ph-CH=); 6.85-7.40 (m, 5H, phenyl protons).

4-[6-(4-chlorobenzyliden)-1-cyclohexen-1-yl]morpholine (**3g**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.40-1.80 (m, 2H, CH_2); 2.02-2.28 (t, 2H, CH_2); 2.30-2.50 (m, 2H, CH_2); 2.52-2.80 (t, 4H, N-CH_2); 3.50-3.75 (t, 4H, O-CH_2); 4.98-5.22 (t, 1H, CH_2-*CH*=); 6.66 (s, 1H, ph-CH=); 6.88-7.45 (m, 4H, phenyl protons).

General Method for the Synthesis of Ethyl-l-aryl-6-aryliden-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxylate (**7-10**).

Method A.

In a three-necked flask 4-(5-aryliden-1-cyclopenten-1-yl) morpholine (0.1 mol) and triethylamine (0.1 mol) were dissolved in 100 mL of dry dichloromethane. The appropriate ethyl ester of chloroglyoxylic acid phenylhydrazone (0.1 mol), dissolved in 200-250 mL of the same solvent, was added dropwise to this solution at low temperature (0-5 °C) and under vigorous stirring. The solution was stirred at 30-35 °C for four days, and then washed several times with water and finally dried over sodium sulfate. Evaporation of the solvent yielded a thick oil, which was purified by silica gel column chromatography, using a hexane/dichloromethane mixture as eluent (1:1 gradient).

Ethyl-1-(4-fluorophenyl)-6-benzyliden-6a-morpholine-1,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrazole-3-carboxylate (**6**) (n = 1; R = H; R' = 4-F).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.35-1.39 (t, 3H, CH_3); 1.63-1.82 (m, 2H, CH_2); 1.85-1.92 (t, 2H, CH_2); 2.15-2.26 (t, 1H, CH); 2.68-2.75 (t, 4H, N-CH_2); 3.70-3.75 (t, 4H, O-CH_2); 4.38-4.45 (q, 2H, O-CH_2); 6.60 (br, 1H, ph-CH=); 6.85-7.53 (m, 9H, phenyl protons).

Method B.

The enamine, the triethylamine, and the ethyl arylazochloroacetate were reacted in equimolar amounts, in anhydrous benzene and refluxed for 10-12 hours. After elimination of the solvent, a dense oily mass is obtained. The residue is extracted with ether and then dried. The residue is purified on silica gel column chromatography, with hexane-dichloromethane (1:1 gradient) as eluent. With this procedure the pyrazolic derivative is obtained almost exclusively. Analytical data and m/z values are reported in Table 2. With this procedure compounds **7-10** were synthesised.

Ethyl-1-(4-fluorophenyl)-6-benzyliden-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxylate (**7**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.33-1.38 (t, 3H, CH_3); 1.60-1.83 (t, 2H, CH_2); 2.01-2.12 (t, 2H, CH_2); 4.29-4.34 (q, 2H, O-CH_2); 6.49 (s, 1H, ph-CH=); 6.88-7.50 (m, 9H, phenyl protons).

Ethyl-1-(4-fluorophenyl)-6-(4-chlorobenzyliden)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxylate (**8**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.36-1.41 (t, 3H, CH_3); 1.75-1.81 (t, 2H, CH_2); 2.09-2.19 (t, 2H, CH_2); 4.32-4.39 (q, 2H, O-CH_2); 6.45 (s, 1H, ph-CH=); 6.88-7.52 (m, 8H, phenyl protons).

Ethyl-1-(4-fluorophenyl)-6-(4-nitrobenzyliden)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxylate (**9**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.40-1.45 (t, 3H, CH_3); 1.77-1.82 (t, 2H, CH_2); 2.21-2.25 (t, 2H, CH_2); 4.34-4.40 (q, 2H,

O-CH_2); 6.80 (s, 1H, ph-CH=); 7.11-8.00 (m, 8H, phenyl protons).

Ethyl-1-(3-trifluoromethylphenyl)-6-(2,4-dichlorobenzyliden)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxylate (**10**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.38-1.43 (t, 3H, CH_3); 1.78-1.81 (t, 2H, CH_2); 2.19-2.23 (t, 2H, CH_2); 4.33-4.40 (q, 2H, O-CH_2); 6.78 (s, 1H, ph-CH=); 7.08-7.95 (m, 7H, phenyl protons).

General Method for the Synthesis of Ethyl-1-aryl-7-aryliden-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylate (**11-12**).

Equimolar amounts of 4-(6-aryliden-1-cyclohexen-1-yl)morpholine, ethyl ester of chloroglyoxylic acid phenylhydrazone **5**, and triethylamine were dissolved in dry dichloromethane and allowed to react according to the procedure described for the preparation of ethyl-l-aryl-6-aryliden-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxylate (**7**-**10**).

Ethyl-1-(4-fluorophenyl)-7-benzyliden-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylate (**11**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.30-1.35 (t, 3H, CH_3); 1.72-1.77 (m, 2H, CH_2); 2.22-2.34 (t, 2H, CH_2); 2.43-2.55 (t, 2H, CH_2); 4.30-4.42 (q, 2H, O-CH_2); 6.56 (s, 1H, ph-CH=); 6.85-7.50 (m, 9H, phenyl protons).

Ethyl-1-(3-trifluoromethylphenyl)-7-(4-chlorobenzyliden-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylate (**12**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.33-1.37 (t, 3H, CH_3); 1.70-1.77 (m, 2H, CH_2); 2.23-2.35 (t, 2H, CH_2); 2.43-2.56 (t, 2H, CH_2); 4.29-4.43 (q, 2H, O-CH_2); 6.63 (s, 1H, ph-CH=); 6.90-7.82 (m, 8H, phenyl protons).

General Method for the Synthesis of 1-Aryl-6-aryliden-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxylic Acid (**13**).

The ester (0.01 mol) is dissolved in a boiling mixture of 40 mL of ethanol and water. An aqueous solution (5 mL) of NaOH (30%) is then added dropwise. The reaction mixture is refluxed for 1 hour and the ethanol is distilled off keeping the volume constant by adding water. The reaction is allowed to cool down and neutralized with 10% hydrochloric acid. The solution is treated with charcoal, boiled for a few minutes, and filtered while still warm. By adding HCl the carboxylic acids are obtained as white or yellowish crystals which were used to prepare the acyl chlorides **14** without further purification. With the same procedure 1-aryl-7-aryliden-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylic acids were prepared.

General Method for the Synthesis of 1-Aryl-3-chlorocarbonyl-7-aryliden-4,5,6,7-tetrahydro-1*H*-indazole (**14**).

Thionyl chloride (0.02 mol) was added dropwise under vigorous stirring to a solution of carboxylic acid **13** (n = 2) (0.01 mol) in dry benzene (50 mL). The mixture was refluxed for 1 hour and then the solvent removed under reduced pressure. A white-greyish dust was obtained, which was used directly for the preparation of compounds **15-19**. With the same procedure 1-aryl-3-chlorocarbonyl-6-aryliden-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazoles were also prepared.

General Method for the Synthesis of 1-Aryl-6-aryliden-3-(carbamoyl-substituted)-1,4,5,6-tetrahydrocyclopenta[c]pyrazole (**15-19**).

Method A.

A solution of acid chloride **14** (n = 1) (5 mmol) in dry benzene was added dropwise under vigorous stirring to a solution of the opportune amine (10 mmol) and pyridine (5 mmol) in dry benzene (15 mL). The reaction was stirred for 10 hours at r.t. at which time water (1 mL) was added and the mixture was stirred for further 20 minutes. 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 over sodium sulfate. Evaporation of the solvent under reduced pressure yielded an oil that could easily be pulverised by isopropyl ether and crystallized from an appropriate solvent. Analytical and chemical-physical data are reported in table 3.

Method B.

A mixture of the appropriate carboxylic acid **13** (n = 1) (10 mmol), dicyclohexylcarbodiimide (10 mmol) in 30 mL of dichloromethane, and 15 mL of dimethylformamide was stirred for 25 minutes at r.t. An excess of amine (15 mmol) was then added. The reaction was stirred at r.t. for 30-40 minutes then heated up to 60 °C and stirred for further 10 minutes. The formed dicyclohexylurea was filtered off and the solution was washed twice with acid water, then with a 10% water solution of sodium carbonate, and finally with water. The organic layer was dried over anhydrous sodium sulfate and then evaporated under reduced pressure. A thick oil was obtained, which was pulverised by isopropyl ether/methanol, and crystallized from an appropriate solvent. The analytical, chemical-physical and spectrometric data are reported in table 3. Using this procedure compounds **15-21** were obtained.

1-(4-Fluorophenyl)-6-benzyliden-3-morpholinecarbamoyl-1,4,5,6-tetrahydrocyclopenta[c]pyrazole (**15**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.62-1.84 (t, 2H, CH_2); 2.00-2.10 (t, 2H, CH_2); 2.75-2.86 (t, 4H, N-CH_2) 3.80-3.95 (t, 4H, O-CH_2); 6.50 (s, 1H, ph-CH=); 6.82-7.53 (m, 9H, phenyl protons).

1-(4-Fluorophenyl)-6-(4-chlorobenzyliden)-3-(4-methylpiperazinylcarbamoyl)-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole (**16**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.74-1.82 (t, 2H, CH_2); 2.10-2.21 (t, 2H, CH_2); 2.75 (s, 3H, CH_3); 3.72-3.77 (t, 4H, N-CH_2); 3.97-4.02 (t, 4H, N-CH_2); 6.45 (s, 1H, ph-CH=); 6.88-7.52 (m, 8H, phenyl protons).

1-(3-Trifluoromethylphenyl)-6-(2,4-dichlorobenzyliden)-3-morpholinecarbamoyl-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole (**17**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.80-1.83 (t, 2H, CH_2); 2.20-2.25 (t, 2H, CH_2); 2.75-2.81 (t, 4H, N-CH_2); 3.82-3.98 (t, 4H, O-CH_2); 6.80 (s, 1H, ph-CH=); 7.10-7.95 (m, 7H, phenyl protons).

1-(4-Fluorophenyl)-6-(4-nitrobenzyliden)-3-morpholinecarbamoyl-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-(**18**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.75-1.81 (t, 2H, CH_2); 2.10-2.18 (t, 2H, CH_2); 2.77-2.85 (t, 4H, N-CH_2); 3.83-3.97 (t, 4H, O-CH_2); 6.80 (s, 1H, ph-CH=); 7.10-7.98 (m, 8H, phenyl protons).

1-(3-Trifluoromethylphenyl)-6-(4-chlorobenzyliden)-3-pyrrolidinecarbamoyl-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-(**19**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.69-1.78 (t, 2H, CH_2); 1.85-1.97 (m, 4H, N-CH_2); 2.12-2.22 (t, 2H, CH_2); 2.70-2.79 (t,

4H, N-CH_2); 6.52 (s, 1H, ph-CH=); 6.90-7.95 (m, 8H, phenyl protons).

General Method for the Synthesis of 1-Aryl-7-aryliden-3-(carbamoyl-substituted)-4,5,6,7-tetrahydro-1*H*-indazole (**20, 21**).

The same procedure used for the preparation of 1-aryl-6-aryliden-3-(carbamoyl-substituted)-1,4,5,6-tetrahydrocyclopenta-[*c*]pyrazole was followed.

1-(4-Fluorophenyl)-7-benzyliden-3-(4-methylpiperazinylcarbamoyl)-4,5,6,7-tetrahydro-1*H*-indazole (**20**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.45-1.60 (m, 2H, CH_2); 2.20-2.65 (m, 4H, CH_2); 2.70 (s, 3H, CH_3); 3.75-3.82 (t, 4H, N-CH_2); 3.98-4.02 (t, 4H, N-CH_2); 6.48 (s, 1H, ph-CH=); 6.79-7.54 (m, 9H, phenyl protons).

1-(3-Trifluoromethylphenyl)-7-(4-chlorobenzyliden)-3-morpholinecarbamoyl-4,5,6,7-tetrahydro-1*H*-indazole (**21**).

This compound has ^{1}H nmr ($CDCl_3$): δ 1.70-1.77 (m, 2H, CH_2); 2.22-2.35 (t, 2H, CH_2); 2.40-2.57 (t, 2H, CH_2); 2.77-2.85 (t, 4H, N-CH_2) 3.85-4.00 (t, 4H, O-CH_2); 6.70 (s, 1H, ph-CH=); 6.90-7.82 (m, 8H, phenyl protons).

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