Articles

1,3-Diaryl-4,5,6,7-tetrahydro-2*H*-isoindole Derivatives: A New Series of Potent and Selective COX-2 Inhibitors in Which a Sulfonyl Group Is Not a Structural Requisite

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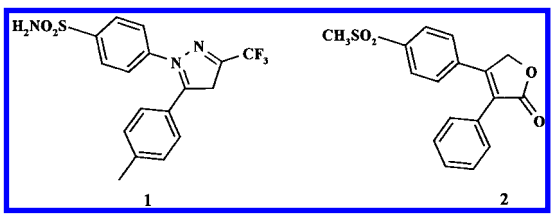
Novel tetrahydro-2*H*-isoindoles have been prepared and evaluated as inhibitors of the COX-2 isoenzyme. A 1,3-diaryl substitution on the central polycyclic ring system and absence of a sulfonyl moiety are the two structural features of this chemical series. A short and easy synthetic pathway produced several derivatives which were shown to be potent and selective COX-2 vs COX-1 inhibitors (IC_{50} = 0.6−100 nM for COX-2, 100−>1000 nM for COX-1). Structural modifications established that a bicyclic ring appended to the pyrrole nucleus and 4,4′-difluoro substitution on the phenyl rings were optimal for high inhibitory potency. Activity was confirmed in the human whole blood assay and subsequently in the murine air-pouch model in which in vivo PGE2 inhibitory activity was evaluated with respect to gastric tolerance (ED_{50} for inhibition of exudate PGE2 of 3 mg/kg and gastric PGE2 of 20 mg/kg). Gastric tolerance was further assessed after administration to mice of high doses (up to 400 mg/kg) of the inhibitors by measurement of gastric damage. This panel of studies allowed selection of a number of tetrahydro-2*H*-isoindoles which were compared in the adjuvant-induced arthritis model. Compounds **32** and **37** showed the most potent activity with ED_{50} values for edema inhibition in the noninjected paw of 0.35 and 0.15 mg/kg/day, respectively, after oral administration. In addition, this interesting antiinflammatory profile was accompanied by a protective effect against arthritis-induced osteopenia, the decrease being 50% with a dose of 0.25 mg/kg/day.

Introduction

It has been almost 10 years since Kujubu and Xie simultaneously but independently suggested that an inflammatory or mitogenic stimulus might result in gene expression responsible for the synthesis of a second, inducible cyclooxygenase isoenzyme, called COX-2.[1,2] Although very similar in structure (especially at the active site) to its constitutive counterpart (hence named COX-1), COX-2 rapidly emerged as an invaluable target for developing antiinflammatory agents with reduced gastrointestinal or renal secondary effects.

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used to treat pain, fever, and inflammatory conditions including osteoarthritis. Recently, it has been postulated that COX-2 inhibitors may effectively relieve symptoms in diseases, such as osteoarthritis, while exhibiting a considerably safer toxicity profile than classical NSAIDs, especially with respect to gastric complications.[3] It has recently been demonstrated that IL-1-stimulated chondrocytes from normal human cartilage expressed the COX-2 gene and produced the COX-2 protein, followed by PGE2 release.[4] Moreover, COX-2 protein overexpression has been detected in chondrocytes from osteoarthritic patients as compared with normal subjects, whereas COX-1 was not detected in either normal or osteoarthritic chondrocytes.[5] PGE2 overinduction in osteoarthritic cartilage has been shown to coincide with COX-2 upregulation, hence suggesting that PGE2 may be differentially regulated in normal and osteoarthritic cartilage.[6]

When we began our work in this field, only nimesulide,[7] its analogue NS 398,[8] and structural flosulide analogues[9,10] had been described as preferential COX-2 inhibitors. It soon became clear that the pyrazole derivatives reported by Searle were serious candidates for potent and selective COX-2 inhibition.[11] Soon after, Merck disclosed the structure of several potent and selective inhibitors, most of which were structurally related to the class of cyclopentenyl lactones.[12] Structural optimization work in both laboratories has culminated in the development of celecoxib (**1**)[13] and rofecoxib (Vioxx, **2**),[14] which have recently been marketed.



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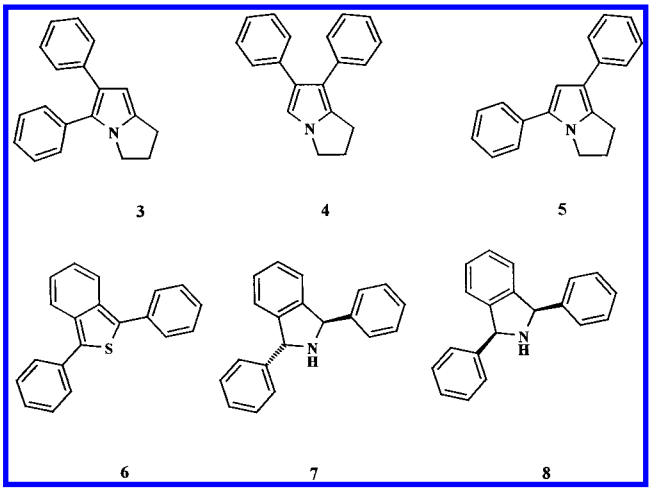
A 1,2-disubstitution by two aryl groups on a central core, usually a five- or six-membered heterocycle, seemed to be a common structural feature of the majority of the inhibitors. However, very recently, several structures have been reported in which the 1,2-substitution and/or the sulfonyl moiety on the aromatic ring were missing.[15] Thus, we reasoned that it would be worth investigating the inhibitory potential of compounds in which the central core constituted by a bicyclic ring system (exemplified below by a 2,3-dihydro-1*H*-pyrrolizine) was diversely substituted by two aryl or heteroaryl groups.

To our surprise, we found that 5,7-diphenyl-2,3-dihydro-1*H*-pyrrolizine (**5**) produced the same level of COX-2 inhibition as 5,6-diphenyl-2,3-dihydro-1*H*-pyrrolizine (**3**) in the mouse monocyte assay (Table 1).[16] This prompted us to extend our evaluation to derivatives **6**−**8**: these three compounds proved fairly potent and selective with at least 100-fold selectivity for COX-2. 1,3-Diphenyl-2,3-dihydro-1*H*-isoindole (**7**) was then evaluated in the adjuvant-induced arthritis assay in the rat where it gave a modest but significant 21% inhibition of the edema at the noninjected paw. Thus **7** was identified as our initial lead compound, suitable for further structural modifications.

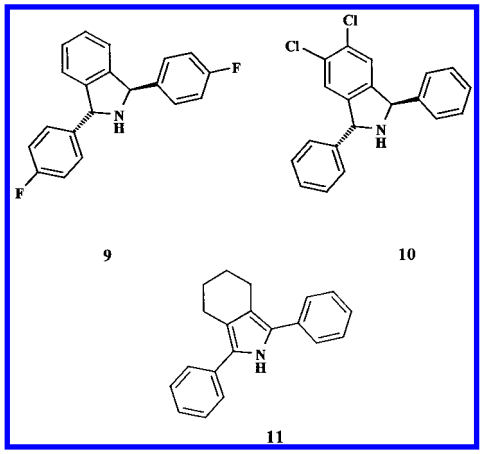


The first modifications performed in order to enhance the COX-2 inhibition potency of **7** were simple substitutions with halogen atoms on the phenyl rings: curiously, compounds **9** and **10** were found to exhibit weak activity, with an IC_{50} for COX-2 greater than 100 nM. We consequently decided to modify the structural core of compound **7** by replacing the 1,2-dihydroisoindole ring system by a cyclohexa[*c*]pyrrole moiety, and we observed that the resulting derivative **11** was a potent and selective COX-2 inhibitor with an IC_{50} of 1 nM vs 100−500 nM for COX-1.

At that time, **11** became our lead compound and was subjected to further modifications. In the present paper, we report our efforts to synthesize and evaluate structural analogues of compound **11** with the goal of identifying a potential candidate for preclinical development.

Chemistry

Most of the compounds described herein were prepared simply using two main synthetic routes. Symmetrically substituted phenyl ring-containing inhibitors



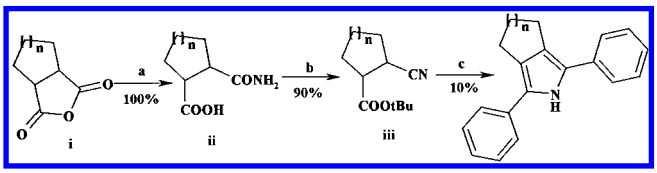
were obtained via route A as depicted in Scheme 1. The commercial cyclic anhydrides **i** were reacted with concentrated aqueous ammonia to yield the corresponding 2-carbamoylcycloalkylcarboxylic acids **ii**. Treatment with *tert*-butyl alcohol in a phenylsulfonyl chloride−pyridine mixture gave the 2-cyano *tert*-butyl esters **iii**, which were readily cyclized with 2 equiv of Grignard reagent in anhydrous ethyl ether to give the desired corresponding pyrroles.

Depending upon the substitution pattern, the other inhibitors described in this paper were prepared according to Schemes 2−4. In general, our synthetic strategy relied on preparation of suitably substituted 1,4-diketones which were subsequently condensed with appropriate amines (Paal−Knorr reaction) to produce the corresponding pyrroles.

The second synthetic pathway (route B, Scheme 2) allowed preparation of a broad array of compounds, including some already obtained via route A. The key step in this sequence involved a Diels−Alder reaction between a 2,3-unsaturated 1,4-diaryl diketone **vi** and butadiene or a cyclic diene. When not commercially available, the diketone was easily prepared by a Friedel−Craft reaction starting with the diacid chloride of fumaric acid **iv** and the suitably substituted aryl moiety **v**. The diketone **vii** resulting from the Diels−Alder reaction[17] was hydrogenated to give the saturated diketone **viii**, which was further reacted according to Paal−Knorr conditions to supply the desired inhibitors (path B1). Alternatively, diketone **vii** was condensed with ammonium formate or ammonium acetate in ethanol to produce the corresponding unsaturated diarylpyrrole derivatives **ix** (path B2).[18] Reduction of the double bond was efficiently accomplished using ammonium formate/palladium or cyclohexene/palladium (when halogen atoms were present on the aromatic rings) to give the same final compound as above.

The unsaturated diketone **vii-a** (R = H) was also condensed with methylamine to give intermediate **ix-a**, which was further hydrogenated to inhibitor **13**. **vii-a** was also condensed with carbobenzyloxyhydrazine to give the hydrazino derivative **ix-b**, which, upon hydrogenolysis, produced inhibitor **14**. This compound was further reacted with mesyl chloride to yield the monomethylsulfonyl derivative **15**. Condensation of **vii-a** with glycine *tert*-butyl ester followed by reduction of the double bond gave inhibitor **16**. Compounds **22** and **23** were obtained from diketone **vii-b**, whose fluorine atoms were substituted with 1 or 2 mol equiv of imidazole to

Scheme 1. Route A[a]



[a] Reagents: (a) concd NH_4OH; (b) tBuOH, pyridine, phenylsulfonyl chloride; (c) PhMgBr, Et_2O.

obtain the unsaturated diketones **vii-f** and **vii-g**, respectively. The monosubstituted intermediate **vii-f** was immediately hydrogenated to afford **viii-c**, while the bis-imidazole-containing **vii-g** was cyclized to give the unsaturated pyrrole intermediate **ix-f**. Finally, cyclization of **viii-c** and hydrogenation of **ix-f** gave the desired inhibitors **22** and **23**, respectively. Diketone **viii-a** (R = F) was used as a convenient starting intermediate for preparing inhibitors **34** and **35**: Mono- or disubstitution of the fluorine atoms on the phenyl rings of **viii-a** was performed with 1 or 2.5 mol equiv of sodium thiomethoxide in DMSO to give **viii-d** and **viii-f**, respectively. Oxidation with oxone ($2KHSO_5-KHSO_4-K_2SO_4$) in acetonitrile−water smoothly provided the corresponding mono- and disulfones **viii-e** and **viii-g**, which were cyclized under ammonium formate conditions as described above. **viii-a** was also used to prepare **39** and **40**: **viii-h** was obtained by nitration of **viii-a** in fuming nitric acid and was then reduced using the Fe/NH_4Cl system in dioxane−water to produce **viii-i**. Acetylation and final ring closure were achieved in a one-step process using ammonium acetate in acetic acid to give **39**. When ammonium formate was used instead of acetate, formylation and cyclization yielded the bis-formylamino derivative which was further reduced with LAH to the bis-methylamino-containing inhibitor **40** as the hydrochloride.

Two compounds were synthesized in which a pyrrolidine ring was appended on the pyrrole nucleus, using Scheme 3 (route C). According to the method developed by Padwa, the commercially available *N*-[(trimethylsilyl)methyl]benzylamine **x** was reacted with formaldehyde in methanol in the presence of potassium carbonate to provide the azomethine ylide equivalent *N*-[(trimethylsilyl)methyl]-*N*-methoxymethylbenzylamine **xi**;[19] lithium fluoride was used as a desilylating agent to generate the 1,3-dipole, which was subsequently cyclized with the dipolarophile **vi** (R = H) to pyrrolidine **xii**. The methodology reported in Scheme 2 was then successfully applied to the ring closure of **xii** (ammonium acetate, acetic acid, ethanol) to give **29**. Further debenzylation (ammonium formate, Pd/C) yielded inhibitor **30**, as the hydrochloride.

Compound **41** was conveniently prepared using the sequence outlined in Scheme 4 (route D). The bromomethyl ketone **xiv** as the hydrobromide was prepared from commercially available 4-acetylpyridine **xiii**, which was brominated using the reported methodology.[20] Phosphorane **xv** was then obtained by reacting **xiv** with triphenylphosphine and pyridine in acetonitrile and oxidative coupling with peracetic acid in dichloromethane smoothly afforded diketone **vi-a**.[21] As previously, this diketone was reacted with cyclopentadiene to give the unsaturated bicyclic diketone **vii-m**. Cyclization with ammonium acetate in acetic acid gave **ix-h**, and further reduction with ammonium formate and Pd/C produced inhibitor **41**.

Results and Discussion

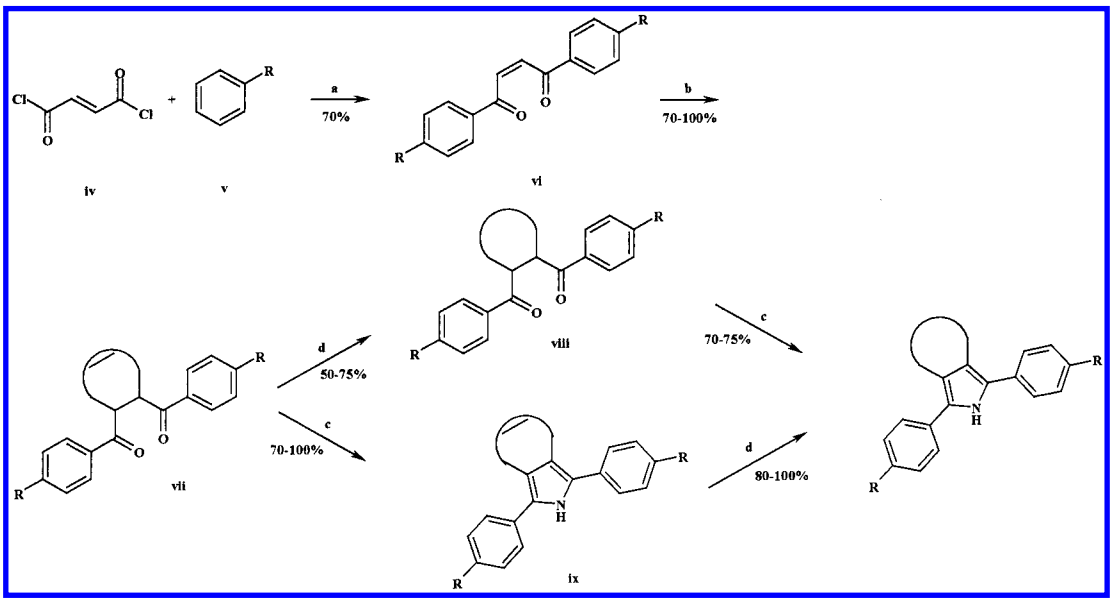
Biological evaluation of the compounds in this series initially involved measuring inhibitory potencies against both constitutive and inducible forms of cyclooxygenase, isolated from mouse resident peritoneal macrophages according to our previously published protocol.[16] The activity and selectivity of the most effective compounds were then confirmed using the human whole blood assay.[22] Assessment of in vivo efficacy with respect to local inflammation and gastric tolerance was performed by dosing the inhibitors orally in the murine air-pouch model.[23] Toxicity was evaluated by macroscopic examination of the gastric mucosa. Finally, the inhibitors with a good overall profile of efficacy and safety were evaluated in the adjuvant-induced arthritis model of chronic inflammation in the rat.[24]

Enzyme Inhibitory Activities. As expected, celecoxib (**1**) proved to be a potent and selective inhibitor in mouse macrophages giving an IC_{50} value of 4 nM against COX-2 (confidence limits, 95%: 1−15 nM), while it inhibited COX-1 with an IC_{50} of 3750 nM. The inhibitory activity of our lead compound **11** was within the same range of potency but was less selective, with IC_{50} values of 1.5 nM for COX-2 and 100 nM against COX-1.

Variations on the Pyrrole Nitrogen Atom. To explore the weakly acidic character of the pyrrole nucleus, the nitrogen atom was methylated or substituted with an amino group (Tables 2 and 3). *N*-Methylpyrrole derivative **13** was found to be completely devoid of inhibitory activity on COX-2, whereas compound **14** was a potent COX-2 inhibitor (IC_{50} = 1.8 nM); its affinity for COX-1 was much lower with an IC_{50} of 1000 nM. Another *N*-methyl derivative, **26**, was also completely devoid of activity on COX-2. Substitution of the nitrogen by larger groups bearing an acidic character, such as in **15** and **16**, also resulted in an significant drop in activity.

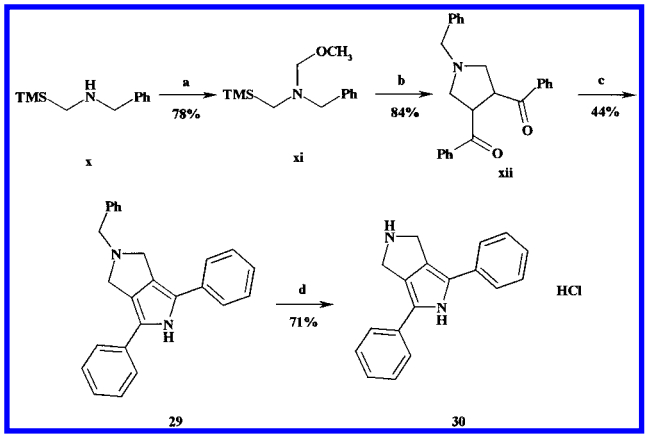
Variations on the Phenyl Rings. In contrast to the result obtained with **9** (IC_{50} COX-2 > 100 nM), introduction of a 4,4′-difluoro substitution (**17**) preserved a potent and selective activity with an IC_{50} for COX-2 of 1.7 nM (Tables 2 and 3). Furthermore, **17** was shown to be selective, with an IC_{50} for COX-1 of 100 nM. Increasing the size of the para substituents failed to improve efficacy: chlorine, methyl, methoxy, and thiomethoxy substitutions gave inhibitors **18**−**21**, with decreasing potencies from 5 to 500 nM. More complex variations with mono- (**22**) or disubstitution (**23**) incorporating an imidazole ring partly decreased or abolished enzyme inhibition. Thus the para position on the phenyl rings apparently exhibited limited tolerance to the size of the substituent, with the difluoro substitution being definitively the most promising one. Two compounds, **39** and **40**, structurally related to **32**, contain an acetamido or methylamino group at position 3; their COX-2 activity was very weak (>100 nM vs 1.1 nM for **32**), suggesting that the presence of a large substituent at the meta position is deleterious for activity. The preparation of 2,2′- and 3,3′-difluorophenyl-containing derivatives is currently under investigation to evaluate

Scheme 2. Route B[a]



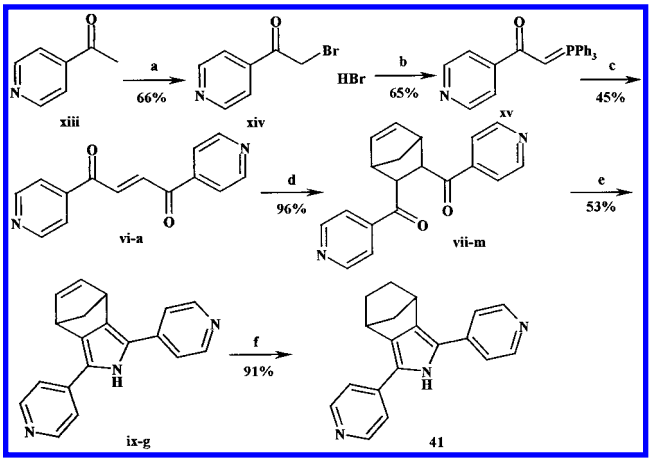
[a] Reagents: (a) $AlCl_3$, CS_2; (b) diene, toluene; (c) ammonium formate, ethanol or ammonium acetate, ethanol; (d) cyclohexene, 10% Pd/C, *N*-methylpyrrolidone or ammonium formate, 10% Pd/C, ethanol.

Scheme 3. Route C[a]



[a] Reagents: (a) 37% aq formaldehyde, K_2CO_3, methanol; (b) 1,2-dibenzoylethylene, LiF, acetonitrile; (c) ammonium acetate, acetic acid, ethanol; (d) ammonium formate, 10% Pd/C, ethanol, then aq HCl.

Scheme 4. Route D[a]



[a] Reagents: (a) Br_2, 48% HBr; (b) (i) PPh_3, acetonitrile, (ii) Et_3N, acetonitrile; (c) peracetic acid, dichloromethane; (d) freshly distilled cyclopentadiene, toluene; (e) ammonium acetate, acetic acid; (f) ammonium formate, 10% Pd/C, ethanol−dioxane.

the role of smaller substituents at ortho and meta positions. Finally, replacement of the two phenyl rings by a 4-substituted pyridine (**41**) resulted in loss of all activity against the COX-2 isoenzyme.

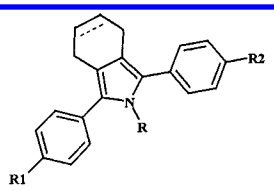
Variations on the Cycloalkyl Ring. At this point, we turned our attention to the nature of the cycloalkyl ring appended to the pyrrole nucleus (Tables 2 and 3). Introduction of a nonconjugated double bond at positions 6, 7 in the cyclohexyl ring gave compound **12**, which was slightly less active than its saturated analogue with an IC_{50} of 3.3 nM for COX-2. Introduction of two methyl groups on the cyclohexyl ring (cis/trans ratio: 85:15) in **24** had little effect on enzyme inhibitory activity but improved selectivity to a considerable extent (IC_{50} COX-2 = 3.1 nM and IC_{50} COX-1 = 1000 nM). Like its counterpart **12**, the unsaturated derivative **25** was less potent than **24** (IC_{50} COX-2 = 14.5 nM). The corresponding *N*-methyl derivative **26** was, as previously observed, completely inactive. Decreasing the size of the fused cycloalkyl ring produced encouraging results: the five-membered ring-containing compound **27** and its difluoro analogue **28** were found to be very potent and selective COX-2 inhibitors, with IC_{50} values of 0.7 and 2.9 nM, respectively. The selectivity vs COX-1 was in the same range for both analogues (IC_{50} = 250 and 100 nM, respectively) and similar to that of the six-membered ring-containing inhibitors. Insertion of a nitrogen atom into the five-membered ring gave the two pyrrolidinopyrrole derivatives **29** and **30**, which were essentially devoid of COX-2 inhibitory activity. Although less selective than their five-membered ring counter-

Table 1. IC_{50} Values for Various 1,2- and 1,3-Diaryl-Substituted Heterocycles

	IC_{50} (nM)			IC_{50} (nM)	
compd	COX-2	COX-1	compd	COX-2	COX-1
3	10	<1000	**8**	32.4	>2500
4	28.7	2500	**9**	>100	nd[a]
5	50.0	<1000	**10**	>100	nd
6	10.9	1000	**11**	1.5	250
7	10.0	>2500			

[a] nd, not determined.

Table 2. Modifications of the Pyrrole and Aryl Substituents



cpd	R	R_1	R_2	synth route	formula analysis[a]	mp (°C) recryst. solv.	IC_{50} COX-2[b] (nM)	IC_{50} COX-1[b] (nM)
11	H	H	H	A	$C_{20}H_{19}N$ C,H,N	146 CH[d]	1.5	100
12[c]	H	H	H	A	$C_{20}H_{17}N$ C,H,N	138 CH-EA[e]	3.3	100
13	CH_3	H	H	B2	$C_{20}H_{21}N$ C,H,N	143 ethanol	> 1000	nd[f]
14	NH_2	H	H	B2	$C_{20}H_{20}N_2$ C,H,N	161 ethanol	1.8	1000
15	$NHSO_2CH_3$	H	H	B2	$C_{21}H_{22}N_2O_2S$ C,H,N,S	196 MC[g]	500	> 1000
16	CH_2COOH	H	H	B2	$C_{20}H_{20}NO_2$ C,H,N	162 EA	> 100	nd
17	H	F	F	A	$C_{20}H_{17}F_2N$ C,H,N	139 pentane	1.7	100
18	H	CH_3S	CH_3S	A	$C_{22}H_{23}NS_2$ C,H,N,S	174 éthylether	500	500
19	H	CH_3	CH_3	B2	$C_{22}H_{23}N$ C,H,N	150 ethanol	16.7	500
20	H	OCH_3	OCH_3	B2	$C_{22}H_{23}NO_2$ C[h],H,N	146 ethanol	21.3	1000
21	H	Cl	Cl	B2	$C_{20}H_{17}Cl_2N$ C,H,N,Cl[i]	231 ethanol	5.0	> 5000
22	H	F	imidazol-1-yl	B1	$C_{23}H_{20}FN_3$ C[j],H,N	>250 CM-ethanol	42.0	500
23	H	imidazol-1-yl	imidazol-1-yl	B2	$C_{26}H_{23}N_5.2HCl$ C,H,N,Cl[k]	>260 water	> 100	1000

[a] Compounds gave satisfactory analyses (±0.4%) unless otherwise indicated. [b] IC_{50} values are concentrations of compounds required to achieve 50% inhibition against COX-1 and COX-2 from mouse resident macrophages. [c] Double bond present in positions 6, 7. [d] CH, cyclohexane. [e] EA, ethyl acetate. [f] nd, not determined. [g] MC, methylene chloride. [h] C: found, 78.65; calcd, 79.25. [i] Cl: found, 20.22; calcd, 20.72. [j] C: found, 76.76; calcd, 77.29. [k] Cl: found, 15.30; calcd, 14.82.

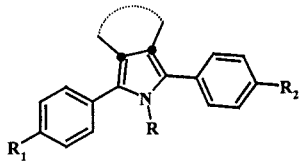
parts, the [2.2.1] bicyclic derivatives **31** and **32** exhibited nanomolar inhibitory activity against COX-2 [IC_{50} = 2.6 and 1.1 (0.05−17) nM, respectively] as well as good selectivity (IC_{50} for COX-1 = 100 nM). The corresponding unsaturated derivative **33** was almost as active, with an IC_{50} of 4.5 nM and comparable selectivity. Using this central 4-azatricyclo[5.2.1.$0^{2,6}$]deca-2, 5-diene system, we introduced one (**34**) or two (**35**) methylsulfonyl moieties in position 4 of the phenyl rings. This resulted in a major loss of activity, suggesting that the mechanism of interaction of our inhibitors with the active site of COX-2 is probably different from that of the reference inhibitors celecoxib or rofecoxib which contain a sulfonamide and a sulfone moiety, respectively. Results with the [2.2.2] bicyclic system-containing **36** and **37** paralleled those obtained with the bicycloheptane series, with COX-2 IC_{50} of 1.6 and 0.6 (0.1−3.3) nM, respectively. Selectivity of these inhibitors was also very encouraging: IC_{50} values against COX-1 were 250 and 230 nM, respectively. As expected, the unsaturated derivative **38** was 1 order of magnitude less potent than its saturated analogue **36**.

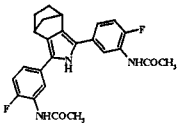
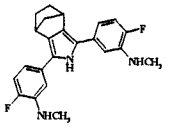
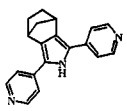
Human Whole Blood Assay. The potency and selectivity of celecoxib and of the most effective inhibitors were confirmed using the human whole blood assay according to Patrignani et al.[22] (Table 4). Compound **32** was found to be almost 1 order of magnitude more potent than **1** in terms of COX-1 and COX-2 inhibition, but its COX-1/COX-2 ratio was in the same range as that of celecoxib. More interestingly, compound **37**, which produced similar COX-2 inhibition as **1** and **32**, was less active on COX-1 with an IC_{50} of 30 μM and a COX-1/COX-2 ratio 20 times higher than that of the reference inhibitor.

Air-Pouch Model in the Mouse. The activity of our COX- 2 inhibitors given orally was assessed in an acute inflammation model, the air-pouch model.[23] This assay allowed the evaluation (Table 5) in the same animal of the PGE2 levels in the inflammatory exudate (mainly COX-2) and in the gastric mucosa (mainly COX-1).

The most active compounds in vitro were evaluated in this model. The reference inhibitor celecoxib (**1**) showed potent antiinflammatory activity with an ED_{50} of 10 mg/kg, while a higher dose (ED_{50} > 40 mg/kg) was

Table 3. Modifications of the Ring Fused to the Pyrrole Nucleus



cpd	ring	R	R_1	R_2	synth route	formula analysis[a]	mp (°C)	IC_{50} COX-2[b]	IC_{50} COX-1[b] (nM)
24		H	H	H	B2	$C_{22}H_{23}N$ C,H,N	133 CH-EA[c]	3.1	1000
25		H	H	H	B2	$C_{22}H_{21}N$ C[d],H,N	212 ethanol	14.5	> 100
26		CH_3	H	H	B2	$C_{23}H_{23}N$ C,H,N	200-201 ethanol	> 1000	nd[e]
27		H	H	H	A	$C_{19}H_{17}N$ C,H,N	190 ethanol	0.7	250
28		H	F	F	A	$C_{19}H_{15}F_2N$ C,H,N	170 pentane	2.9	100
29		H	H	H	C	$C_{25}H_{22}N_2$ C,H,N	182 iPr_2O	> 100	nd
30		H	H	H	C	$C_{18}H_{16}N_2$. HCl ND[f]	> 260 water	> 100	1000
31		H	H	H	B2	$C_{21}H_{19}N$ C,H,N	162 dioxane	2.6	100
32		H	F	F	B1 or B2	$C_{21}H_{17}F_2N$ C,H,N	146 iPr_2O-pentane	1.1	100
33		H	F	F	B2	$C_{21}H_{15}F_2N$ C,H,N	189 ethanol	4.5	500
34		H	F	CH_3SO_2	B1	$C_{22}H_{20}FNO_2S$ C,H,N,S[g]	> 260 ethanol	700	> 5000
35		H	CH_3SO_2	CH_3SO_2	B1	$C_{23}H_{23}NO_4S_2$ C[h],H,N,S	> 260 CM-EA	> 10000	nd
36		H	H	H	B2	$C_{22}H_{21}N$ C,H,N	248 ethanol	1.6	250
37		H	F	F	B1	$C_{22}H_{19}F_2N$ C,H,N	202 ethanol	0.6	230
38		H	H	H	B2	$C_{22}H_{19}N$ C[i],H,N	224 ethanol	35.6	> 1000
39					B1	$C_{25}H_{23}F_2N_3O_2$ C[j],H,N	225 Et_2O	> 100	nd
40					B1	$C_{23}H_{23}F_2N_3$ 2 HCl C,H,N,Cl	196 diethyl ether	> 100	nd
41					D	$C_{19}H_{17}N_3$ 2 HCl C,H,N,Cl	264 methanol-dioxane	> 100	nd

[a] Compounds gave satisfactory analyses (±0.4%) unless otherwise indicated. [b] IC_{50} values are concentrations of compounds required to achieve 50% inhibition against COX-1 and COX-2 from mouse resident macrophages. [c] CH, cyclohexane; EA, ethyl acetate. [d] C: found, 87.81; calcd, 88.25. [e] nd, not determined. [f] ND, not determined but satisfactory results by high-resolution MS analysis were obtained. [g] S: found, 7.94; calcd, 8.41. [h] C: found, 61.93; calcd, 62.56. [i] C: found, 88.36; calcd, 88.85. [j] C: found, 68.45; calcd, 68.95.

Table 4. Inhibitory Potencies on Human Blood in Vitro

compd	IC_{50} (μM) COX-1	IC_{50} (μM) COX-2	COX-1/COX-2
1	9.3 (1.6−49.5)[a]	0.7 (0.1−6.6)	13.2
32	1 (0.4−2.2)	0.08 (0.01−1.04)	12.5
37	30	0.12 (0.04−0.32)	250

[a] Confidence limits, 95%.

Table 5. PGE2 Inhibitory Activities in the Air-Pouch Model

compd	ED_{50} (mg/kg)[a] inhib of gastric PGE2	ED_{50} (mg/kg)[a] inhib of exudate PGE2
1	>40	10
7	100	100
11	50	20
14	nd[b]	in[c]
17	50	20
19	nd	in
21	>80	20
27	10	20
28	>80	20
31	80	20
32	>40	6.8
36	>40	>40
37	>20	3.5

[a] ED_{50} values were evaluated using 3 or 4 dose points (at least 8 mice/group). [b] nd, not determined. [c] in, inactive.

needed to inhibit gastric PGE2. Although many of our inhibitors were equipotent to **1** in vitro, their potency did not always translate well in vivo: for example, dihydro-1*H*-isoindole **7** was found to be weakly active with an ED_{50} of 100 mg/kg for both PGE2 inhibitions. The initial lead compound **11** was fairly effective on exudate PGE2 inhibition, with an ED_{50} of 20 mg/kg, but this level of dose also resulted in significant gastric PGE2 inhibition (ED_{50} = 50 mg/kg). No improvement was obtained when the phenyl rings were 4-fluoro-disubstituted (**17**). Substitution of the pyrrole nitrogen (**14**) as well as introduction of a methyl group on the phenyl rings (**19**) produced low or erratic inhibition. Chlorine substitution (**21**) proved to be more effective on exudate PGE2 inhibition, with an ED_{50} of 20 mg/kg, and produced an interesting level of selectivity (ED_{50} for gastric PGE2 inhibition greater than 80 mg/kg). Five-membered ring-containing **27** gave strong inhibition of exudate PGE2 but was found to be half as selective as its six-membered ring counterpart. The difluoro analogue **28** was only as potent, but more selective. Similar levels of potency and selectivity were obtained with the [2.2.1] bicyclic system-containing inhibitor **31**, whereas remarkable improvements in activity and selectivity were obtained when a difluoro substitution was again introduced into this structure to yield **32**, which had an ED_{50} of 6.8 mg/kg for exudate PGE2 inhibition and >40 mg/kg for gastric PGE2 inhibition. The [2.2.2] bicyclic system-containing **36** was inactive on both PGE2 inhibitions, whereas its difluoro analogue **37** was the most potent PGE2 inhibitor, with an ED_{50} of 3.5 mg/kg for exudate PGE2. Selectivity was similar to that obtained with the [2.2.1] analogue **32**. In summary, these preliminary in vivo studies suggest that pharmacokinetics may play a crucial role in the general activity profile of the compounds described herein: A six-membered ring fused to the non-N-substituted pyrrole nucleus appears to be of prime importance for obtaining significant in vivo potency and selectivity, while a five-membered ring-containing derivative seems to produce inconsistent results; a one- or two-carbon bridge added to the six-membered ring improves activity, especially when a difluoro substitution is present on the phenyl rings appended to the pyrrole nucleus, giving the most interesting inhibitors **32** and **37**. Whether this is due to improved lipophilicity, acidic/basic character, or to other factors remains to be determined.

Table 6. Gastric Toxicity Studies

compd[a]	gastric score[b]	compd[a]	gastric score[b]
1	0.7 ± 0.2	**32**	0.3 ± 0.2
28	0.7 ± 0.4	**37**	0.3 ± 0.2
31	0.3 ± 0.3	indomethacin	2.4 ± 0.4

[a] Compounds were given orally at 400 mg/kg, except indomethacin at 2.5 mg/kg. [b] Gastric erosion was evaluated using a visual score ranging from 0 (normal) to 5 (perforation). Values shown are means ± SEM (8 animals/group); control values = 0.4 ± 0.2.

Table 7. Antiinflammatory Activity in the Adjuvant-Induced Arthritis Model: Noninjected Paw at Day 21

compd	inhib of edema ED_{50} (mg/kg/day) po[a]
1	0.32 (0.18−0.54)[b]
17	15%[c]
28	14%[d]
32	0.35 (0.16−0.69)
37	0.15 (0.05−0.36)

[a] 10 rats/group; edema volume of control = 1.18 mL. [b] ED_{50} values were estimated by linear regression. Confidence limits, 95%. [c] Inhibition at 2 mg/kg/day. [d] Inhibition at 2 mg/kg, twice daily.

Gastric Tolerance Assay in the Mouse. Evaluation of the gastrointestinal (GI) toxicity of our inhibitors was readily performed by assigning a visual individual score to the lesions observed 5 h after oral administration of the compounds in a high dosage (400 mg/kg) to fasted mice (Table 6). Briefly, a low incidence of gastric erosion was observed for the compounds reported hereafter. The score obtained with celecoxib was comparable to the value given by the five-membered ring-containing **28**. The gastric erosion score was slightly decreased after administation of the bicyclo [2.2.1]- and [2.2.2]-containing inhibitors **31**, **32**, and **37**. However, any of them was found to be significantly different from the control (0.4 ± 0.2).

Adjuvant-Induced Arthritis in the Rat. In this chronic model of inflammation, four compounds were evaluated and compared with celecoxib (**1**). As shown in Table 7, the results confirmed the strong antiinflammatory activity of celecoxib, with ED_{50} values for edema inhibition of the noninjected paw at day 21 of 0.32 mg/kg/day (lit. ED_{50} = 0.37 mg/kg/day).[11]

The four inhibitors reported in Table 7 differ only by the nature of the ring fused to the pyrrole nucleus; a remarkable finding is that the compounds containing a bicyclic structural core appended to the pyrrole ring were the only compounds that produced a potent and sustained antiinflammatory effect at doses similar to **1**. Dose−response curves obtained for **32** and **37** are given in Figure 1. While the activity of compound **32** was in the same range as that of celecoxib, **37** was 3.8 times more active (comparison of the regression lines). Moreover, another aspect of the protective effects of our inhibitors was shown on osteopenia (decrease in bone mineral content) induced by arthritis as assessed at the

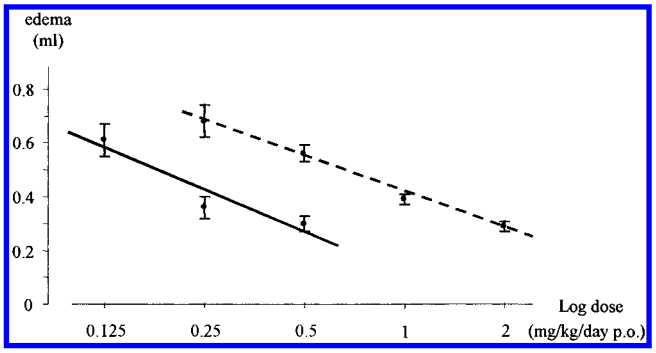


Figure 1. Antiinflammatory activity in the adjuvant-induced arthritis model (noninjected paw edema at day 21): dose−response curves for edema inhibition by compounds **32** (- -) and **37** (−); M ± SEM (8 rats/group); relative potency = 3.8.

proximal site of the femur. Compounds **32** and **37** induced a 50% decrease of osteopenia from a dose of 0.25 mg/kg/day, an effect closely similar to the result obtained with celecoxib (52%).

In summary, a 1,3-diaryl substitution on the central polycyclic ring system and absence of a sulfonyl moiety on the phenyl rings are the two distinctive structural features that distinguish the new chemical series described herein from the reference inhibitors **1** and **2**. COX-2 inhibition in the low-nanomolar range and COX-1/COX-2 selectivity ratios as high as 3 orders of magnitude were obtained. In the human whole blood assay, inhibitor **37** confirmed its interesting selectivity with a COX-1/COX-2 ratio of 250. Evaluation of GI toxicity (up to 400 mg/kg to normal mice) followed by the air-pouch assay allowed us to select a few candidates for evaluation in the adjuvant-induced arthritis model: after oral administration, inhibitors **32** and **37** showed strong antiinflammatory potential associated with a tissue-protective effect. On the basis of these findings, these two compounds have recently been proposed for further preclinical evaluation.

Experimental Section

Chemistry. Melting points were determined on a Tottoli apparatus and are not corrected. Elemental analyses (C, H, N, S, Cl) were carried out by the analytical department of the Institut de Recherches SERVIER; results obtained for specified elements are within ±0.4% of the theoretical values. Infrared spectra were recorded on a Bruker IFS 28 spectrophotometer in solution, in Nujol, or using KBr pellets; frequencies are expressed in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution (S.d.S. isotopes) in 5-mm tubes (Wilmad) at 27 °C and were collected on a Bruker AC 200 or AM 300 spectrometer. Chemical shifts (δ) are given in ppm with tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained on either a Nermag R 1010, a Finnigan MAT 95-Q, or a Finnigan MAT TSQ-7000.

Biology. In vitro cyclooxygenases assays were performed as reported in refs 15 and 21.

Air-Pouch in the Mouse. Air-pouches were induced in mice according to the method previously described.[23] After 18 h, compounds or vehicle were given orally, and 1 h later, 500 μL of a sterile solution of 1% carrageenan were injected into the air-pouch. Mice were sacrified by cervical dislocation 5 h after carrageenan injection. Pouches were lavaged with 2 mL of heparinized HBSS. The lavage fluid was immediatly cooled on ice, and PGE2 level was determined by EIA (Enzymo Immunoassay) after solid-phase extraction. In parrallel, the stomachs were excised, opened, rinsed in PBS, weighed and incubated in 5 mL of PBS for 15 min. After centrifugation, the supernatants were assayed for PGE2 by EIA.

Effect on Gastric Mucosa in the Mouse. Male Swiss mice, fasted overnight with free access to water, were dosed orally with compounds or vehicle 5 h before sacrifice by cervical dislocation. The stomach was removed, rised and opened for macroscopic assessment of mucosal damage by an observer unaware of the treatment according to a rating scale from 0 (normal) to 5 (perforation).

Adjuvant-Induced Arthritis in the Rat. Arthritis was induced and assessed in female Lewis rats according to the method previously described by Bonnet et al.[24]

Route A (Scheme 1). 2-Carbamoylcyclohexanecarboxylic Acid, i-a. To 66 mL of concentrated aqueous ammonia was added portionwise 46.25 g (0.3 mol) of *cis*-cyclohexane-1,2-dicarboxylic anhydride while maintaining the reaction temperature below 25 °C. The reaction mixture was stirred overnight, and acidified with 12 N HCl. The resulting precipitate was collected, washed with water and dried to give 51 g (100%) of the desired monoacid: mp 197 °C; IR (Nujol) 3435, 3217, 2600−2200, 1672, 1643 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.2−1.75 (6H, 3m), 1.9 (2H, m), 2.45−2.7 (2H, 2m), 6.70 and 7.15 (2H, br s), 11.85 (1H, br s).

6-Carbamoylcyclohex-3-enecarboxylic acid, i-b: mp 151 °C; IR (Nujol) 3600−2300, 1702−1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.1−2.55 (4H, m), 2.85 (2H, m), 5.6 (2H, br s), 6.85 (1H, br s), 7.2 (1H, br s), 11.5−12.5 (1H, br s).

2-Carbamoylcyclopentanecarboxylic acid, i-c: mp 140 °C; IR (Nujol) 3450−2300, 1706 cm^{-1}; ^1H NMR (D_2O) δ 1.7−2.3 (6H, m), 3.3 (2H, m).

2-Cyanocyclohexanecarboxylic acid *tert*-butyl ester, ii-a: bp 100−110 °C/0.01 mmHg; IR (KBr) 2238, 1729 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.2−1.75 (6H, 2m), 1.4 (9H, s), 1.9 (2H, m), 2.6 (1H,m), 3.35 (1H, q).

6-Cyanocyclohex-3-enecarboxylic acid *tert*-butyl ester, ii-b: IR (KBr) 2240, 1728, 1657−1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (9H, s), 2.45 (4H, m), 2.65 (1H, m), 3.35 (1H, m), 5.65 (1H, m), 5.85 (1H, m).

2-Cyanocyclopentanecarboxylic acid *tert*-butyl ester, ii-c: bp 80−82 °C/0.02 mmHg; IR (KBr) 2978−2879, 2241, 1728 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.48 (9H, s), 1.58−2.22 (6H, m), 2.91−3.37 (2H, m).

1,3-Diphenyl-4,5,6,7-tetrahydro-2*H*-isoindole, 11: mp 146 °C; IR (Nujol) 3437, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8 (4H, m), 2.8 (4H, m), 7.1−7.6 (10H, m), 8.25 (1H, br s).

1,3-Diphenyl-4,5-dihydro-2*H*-isoindole, 12: mp 138 °C; IR (Nujol) 3437,1604 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.40 (4H, s), 5.85 (2H, s), 7.20 (2H, t), 7.40 (4H, t), 7.65 (4H, d), 11.0 (1H, br s).

1,3-Di(4-fluorophenyl)-4,5,6,7-tetrahydro-2*H*-isoindole, 17: mp 139 °C IR (Nujol) 3469 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.70 (4H, m), 2.70 (4H, m), 7.25 (4H, m), 7.60 (4H, m), 10.80 (1H, br s).

1,3-Di(4-methylthiophenyl)-4,5,6,7-tetrahydro-2*H*-isoindole, 18: mp 174 °C; IR (Nujol) 3400, 1590, 823 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.74 (4H, m), 2.47 (6H, s), 2.71 (4H, m), 7.30 (4H, d), 7.54 (4H, d), 10.68 (1H, s).

1,3-Diphenyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole, 27: mp 190 °C; IR (Nujol) 3437, 3075−3056, 1610, 1591, 1490, 1163−1077 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (6H, m), 7.28−7.70 (10H, m), 8.32 (1H, br s).

1,3-Di(4-fluorophenyl)-2,4,5,6-tetrahydrocyclopenta[*c*]-pyrrole, 28: mp 170 °C; IR (Nujol) 3450 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.40 (2H, m), 2.80 (4H, m), 7.25 (4H, m), 7.70 (4H, m), 10.70 (1H, br s).

Route B (Scheme 2). (6-Benzoylcyclohex-3-enyl)(phenyl)methanone, vii-a. The preparation of this compound is reported in ref 16: mp 114 °C; IR (Nujol) 3037, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13−2.56 (4H, m), 4.15 (2H, m), 5.80 (2H, m), 7.50 (6H, m), 8.03 (4H, d).

[6-(4-Fluorobenzoyl)cyclohex-3-enyl](4-fluorophenyl)-methanone, vii-b: mp 125 °C; IR (Nujol) 3100, 3040, 1672, 1598, 1237, 852 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (2H, m), 2.55 (2H, m), 4.10 (2H, m), 5.80 (2H, m), 7.15 (4H, t), 8.05 (4H, dd).

[6-(4-Methylbenzoyl)cyclohex-3-enyl](*p*-tolyl)methanone, vii-c: mp 124 °C; IR (Nujol) 3466, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.35 (6H, s), 3.35 (4H, s), 5.90 (2H, s), 7.20 (4H, d), 7.55 (4H, d), 10.8 (1H, br s).

[6-(4-Methoxybenzoyl)cyclohex-3-enyl](4-methoxyphenyl)methanone, vii-d: mp 130 °C; IR (Nujol) 1661, 1539 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (2H, m), 2.5 (2H, m), 3.85 (6H, s), 4.07 (2H, m), 5.8 (2H, m), 6.93 (4H, d), 8.00 (4H, d).

[6-(4-Chlorobenzoyl)cyclohex-3-enyl](4-chlorophenyl)-methanone, vii-e: mp 125 °C; IR (Nujol) 1676, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.95−2.2 (2H, m), 2.45 (2H, m), 4.05 (2H, m), 5.80 (2H, d), 7.65 (4H, d), 8.05 (4H, d).

[6-(4-Fluorobenzoyl)cyclohex-3-enyl](4-imidazol-1-ylphenyl)methanone, vii-f: IR (Nujol) 1671, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (2H, m), 2.55 (2H, m), 4.1 (2H, m), 5.8 (2H, d), 7.15 (2H, t), 7.25 (1H, s), 7.35 (1H, s), 7.55 (2H, d), 7.95 (1H, s), 8.05 (2H, m), 8.15 (2H, d).

{**6-[4-(Imidazol-1-yl)benzoyl]cyclohex-3-enyl**}**(4-imidazol-1-ylphenyl)methanone, vii-g:** mp 268 °C; IR (Nujol) 1662, 1605−1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (2H, m), 2.60 (2H, m), 4.1 (2H, m), 5.8 (2H, d), 7.25 (2H, s), 7.35 (2H, s), 7.55 (4H, d), 7.95 (2H, s), 8.15 (4H, d).

(6-Benzoyl-3,4-dimethylcyclohex-3-enyl)(phenyl)methanone, vii-h: mp 113 °C; IR (Nujol) 1675 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.65 (6H, s), 2.1−2.4 (4H, m), 4.1 (2H, m), 7.6 (6H, m), 8.05 (4H, d).

(3-Benzoylbicyclo[2.2.1]hept-5-en-2-yl)(phenyl)methanone, vii-i: mp 80 °C; IR (Nujol) 1666, 1579−1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (1H, d), 1.91 (1H, d), 3.16 (1H, s), 3.36 (1H, s), 3.98 (1H, dd), 4.51 (1H, dd), 5.84 (1H, m), 6.43 (1H, m), 7.50 (6H, m), 8.01 (4H, t).

[3-(4-Fluorobenzoyl)bicyclo[2.2.1]hept-5-en-2-yl](4-fluorophenyl)methanone, vii-j: mp 104 °C; IR (Nujol) 1666, 1620, 1598 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.4 and 1.8 (2H, 2dd), 3.1 and 3.3 (2H, 2 br s), 3.8 and 4.4 (2H, 2d), 5.85 and 6.4 (2H, 2dd), 7.3 (4H, m), 8.1 (4H, m).

(3-Benzoylbicyclo[2.2.2]oct-5-en-2-yl)(phenyl)methanone, vii-k: mp 131 °C; IR (Nujol) 3100, 1673, 1596−1579, 778−688 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.9−2.0 (4H, m), 2.90 (2H, m), 4.10−4.30 (2H, dd), 6.10−6.45 (2H, tt), 7.55 (6H, m), 7.90−7.98 (4H, dd).

[3-(4-Fluorobenzoyl)bicyclo[2.2.2]oct-5-en-2-yl](4-fluorophenyl)methanone, vii-l: mp 144 °C; IR (Nujol) 1669, 1597−1506, 1228−1208 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0−2.0 (4H, m), 3.0 (2H, m), 4.1−4.4 (2H, 2dd), 6.2−6.5 (2H, 2t), 7.2 (4H, m), 8.1 (4H, m).

Path B1 (Scheme 2). [3-(4-Fluorobenzoyl)bicyclo[2.2.1]-hept-2-yl](4-fluorophenyl)methanone, viii-a. The ethylenic intermediate **vii-j** (3.82 g, 0.011 mol) was heated overnight at 80 °C in 100 mL of *N*-methylpyrrolidone in the presence of 20 mL of cyclohexene and 0.6 g of 10% Pd/C. After evaporation of the solvent, the residue was taken up with ethyl acetate, washed with water, and dried over calcium sulfate. Filtration and evaporation gave a solid which was washed with ethanol and pentane to give 2.7 g (71%) of the desired hydrogenated compound: mp 108 °C; IR (Nujol) 3100, 1671, 1597 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.9−1.8 (6H, m), 2.5 and 2.75 (2H, m), 3.98 and 4.35 (2H, m), 7.4 (4H, t), 8.1 (4H, m).

[3-(4-Fluorobenzoyl)bicyclo[2.2.2]oct-2-yl](4-fluorophenyl)methanone, viii-b: from **vii-l**; mp 128 °C; IR (Nujol) 1668, 1600−1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4−1.7 (6H, m), 1.9−2.1 (4H, m), 4.4 (2H, s), 7.1 (4H, m), 8.05 (4H, m).

[6-(4-Fluorobenzoyl)cyclohex-3-anyl](4-imidazol-1-ylphenyl)methanone viii-c: from **vii-f**; IR (Nujol) 3300−2400, 1620, 1580 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.75−2.7 (8H, 2m), 7.15 (1H, s), 7.25 (2H, m), 7.6−7.85 (7H, m), 8.3 (1H, br s).

[3-(4-Fluorobenzoyl)bicyclo[2.2.1]hept-2-yl](4-methylthiophenyl)methanone, viii-d. 2.5 g (0.0073 mol) of difluoro derivative **viii-a** was reacted in 50 mL of DMSO with 1 mol equiv of sodium thiomethoxyde (0.47 g, 0.0073 mol). The reaction was heated at 80 °C for 2 h, then at room temperature overnight. The reaction mixture was poured into 150 mL of water and extracted with ethyl acetate. The organic layer was decanted and washed with water, then dried over calcium sulfate. Filtration and evaporation gave a crude solid that was chromatographed (silica gel, cyclohexanes−ethyl acetate 95:5) to give 0.3 g (11%) of the desired compound: mp 107 °C; IR (Nujol) 1665 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.95−1.75 (6H, m), 2.5 (3H, s), 2.5 (1H, m), 2.7 (1H, m), 3.95 (1H, m), 4.3 (1H, m), 7.35 (4H, m), 7.85−8.2 (4H, m).

[3-(4-Fluorobenzoyl)bicyclo[2.2.1]hept-2-yl](4-methylsulfonylphenyl)methanone, viii-e. The methylmercaptan derivative **viii-d** (1.1 g, 0.003 mol) was dissolved in 60 mL of a 1:1 mixture of acetonitrile and dioxane. 30 mL of water was added, followed by addition of 5.5 g of oxone (potassium peroxomonosulfate). The reaction mixture was stirred at room temperature for 24 h, filtered and evaporated. The residue was taken up with methylene chloride, washed with water, and dried over calcium sulfate. Evaporation of the solvent afforded a solid which was washed with pentane to give 1 g (84%) of the desired sulfone: mp 142 °C; IR (Nujol) 1669, 1740, 1330, 1151 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.0−1.8 (6H, 3m), 2.75 (2H, m), 3.35 (3H, s), 4.0 (1H, m), 4.4 (1H, m), 7.35 (2H, m), 8.1−8.3 (6H, m).

[3-(4-Methylthiobenzoyl)bicyclo[2.2.1]hept-2-yl](4-methylthiophenyl)methanone, viii-f. 7.3 g (0.0215 mol) of difluoro derivative **viii-a** was reacted in 120 mL of DMSO with sodium thiomethoxide (2.74 g, 0.043 mol). The reaction was heated at 80 °C for 7 h, then at 50 °C for 20 h. After evaporation of the solvent, the crude residue was chromatographed (silica gel, cyclohexanes−ethyl acetate 95:5) to give 2.7 g (32%) of the desired compound: mp 112 °C; IR (Nujol) 1661, 1590 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.9−1.8 (6H, 3m), 2.55 (6H, s), 2.4 and 2.7 (2H, 2 br s), 3.95 and 4.3 (2H, 2 br s), 7.35 (4H, d), 7.8−8.15 (4H, 2d).

[3-(4-Methylsulfonylbenzoyl)bicyclo[2.2.1]hept-2-yl](4-methylsulfonylphenyl)methanone, viii-g: obtained as the monosulfone **viii-e**; mp 148−150 °C; IR (Nujol) 1682, 1315−1292, 1154 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.9−1.8 (6H, m), 2.5 and 2.75 (2H, m), 3.3 (6H, 2s), 4.05 and 4.45 (2H, m), 8.1 (4H, d), 8.15−8.3 (4H, m).

[3-(4-Fluoro-3-nitrobenzoyl)bicyclo[2.2.1]hept-2-yl](4-fluoro-3-nitrophenyl)methanone, viii-h. 40 mL of fuming nitric acid was cooled at 0 °C, and 15 g (0.044 mol) of the difluoro derivative **viii-a** was added portionwise. After 15 min at 0 °C, the reaction was stirred at room temperature for 1 h, then poured on 100 g of crushed ice. The gummy solid was taken up with ethyl acetate. The organic layer was washed with water and dried over calcium sulfate. After evaporation of the solvent, the resulting solid was washed with ethanol to give 8.1 g (43%) of a white solid: mp 161 °C; IR (Nujol) 1688, 1613, 1539−1348 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0−1.9 (6H, m), 2.55 (1H, br s), 2.8 (1H, br s), 4.05 (1H, d), 4.45 (1H, m), 7.45 (2H, td), 8.3 (2H, m), 8.75 (2H, m).

[3-(4-Fluoro-3-aminobenzoyl)bicyclo[2.2.1]hept-2-yl](4-fluoro-3-aminophenyl)methanone, viii-i. 8 g (0.019 mol) of the dinitro intermediate **viii-h** was reacted with 24 g of Fe and 4 g of ammonium chloride in a mixture of 200 mL of dioxane, 200 mL of ethanol and 150 mL of water. After 1.5 h at reflux, the reaction was filtered and evaporated. The residue was dissolved in ethyl acetate, the organic solution was washed with water, and dried over calcium sulfate. Evaporation of the solvent gave a crude solid which was chromatographed (silica gel, CH_2Cl_2−ethanol 95:5) to give the diamino compound (5.6 g, 81%): mp 167 °C; IR (Nujol) 3417, 3347, 1661, 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1−1.8 (6H, m), 2.5 (1H, br s), 2.70 (1H, br s), 3.9 (4H, br s), 4.0 (1H, d), 4.3 (1H, m), 7.0 (2H, td), 7.4 (4H, m).

Path B2 (Scheme 2). 2-Methyl-1,3-diphenyl-4,7-dihydro-2*H*-isoindole, ix-a. To 2.9 g (0.01 mol) of **vii-a** in 50 mL of ethanol as added 7.75 mL (0.1 mol) of a 40% aqueous methylamine solution, followed by 2.9 mL (0.05 mol) of acetic acid. The reaction mixture was refluxed overnight. A white solid precipitated on cooling, which was washed with ethanol and pentane. After drying at 50 °C under 0.01 mmHg overnight, 2.1 g (74%) of the desired compound was obtained: mp 129 °C; IR (Nujol) 3075, 3057, 3025, 1602, 1491, 1075 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 3.39 (4H, s), 3.49 (3H, s), 5.91 (2H, s), 7.26−7.48 (10H, m).

2-Benzyloxycarbonylamino-1,3-diphenyl-4,7-dihydro-2*H*-isoindole, ix-b: from **vii-a**; mp 184 °C; IR (Nujol) 3202, 1708, 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.26 (4H, s), 5.05 (2H, s), 5.90 (2H, s), 7.02−7.45 (15H, m).

1,3-Di-*p*-tolyl-4,7-dihydro-2*H*-isoindole, ix-c: from **vii-c**; mp 142 °C; IR (Nujol) 3466, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.35 (6H, s), 3.35 (4H, s), 5.9 (2H, s), 7.2 (4H, d), 7.55 (4H, d), 10.8 (1H, s).

1,3-Bis(4-methoxyphenyl)-4,7-dihydro-2*H*-isoindole, ix-d: from **vii-d**; mp 155 °C; IR (Nujol) 3438, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.3 (4H, m), 3.75 (6H, s), 5.9 (2H, s), 6.95 (4H, d), 7.55 (4H, d), 10.7 (1H, br s).

1,3-Bis(4-chlorophenyl)-4,7-dihydro-2*H*-isoindole, ix-e: from **vii-e**; IR (Nujol) 3460, 1594 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.4 (4H, s), 5.9 (2H, s), 7.45 (4H, d), 7.7 (4H, d), 11.1 (1H, br s).

1,3-Bis[4-(imidazol-1-yl)phenyl]-4,7-dihydro-2*H*-isoindole, ix-f: from **vii-g**; mp > 260 °C; IR (Nujol) 1510 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.45 (4H, d), 5.94 (2H, m), 7.12 (2H, s), 7.70 (4H, d), 7.78 (6H, d), 8.29 (2H, s), 11.15 (2H, s).

3,5-Diphenyl-4-azatricyclo[5.2.1.0^{2,6}]deca-2,5,8-triene, ix-g. This compound is described in ref 17.

1,3-Diphenyl-5,6-dimethyl-4,7-dihydro-2*H*-isoindole, 25: from **vii-a**; mp 212 °C; IR (Nujol) 3459, 1601 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.8 (6H, s), 3.3 (4H, s), 7.2 (2H, t), 7.45 (4H, m), 7.65 (4H, m), 10.9 (1H, br s).

1,3-Diphenyl-2,5,6-trimethyl-4,7-dihydro-2*H*-isoindole, 26. 3.18 g (0.01 mol) of **vii-h** was dissolved in 25 mL of THF and 0.6 g of acetic acid was added, followed by 8 mL of a 40% aqueous methylamine solution. The reaction was heated at 60 °C for 18 h. The solvents were evaporated and the residue was taken up with ethanol. Filtration of the resulting solid and washing with ethanol and pentane gave 2.95 g (94%) of the desired compound: mp 200−201 °C; IR (Nujol) 1601, 1576, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.74 (6H, s), 3.21 (4H, s), 3.50 (3H, s), 7.25−7.5 (10H, m).

3,5-Bis(4-fluorophenyl)-4-azatricyclo[5.2.1.0^{2,6}]deca-2,5,8-triene, 33. 28 g (0.08 mol) of intermediate **vii-j** was refluxed for 24 h with 25 g of ammonium acetate in 400 mL of 2-propanol. The solvent was evaporated, and the residue was taken up with ethyl acetate. The organic layers were washed with a 10% solution of sodium bicarbonate, brine, dried over calcium sulfate, and evaporated. The crude solid was recrystallized from anhydrous ethanol to give 19.3 g (73%) of the desired compound: mp 189 °C; IR (Nujol) 3442 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.30−2.40 (2H, 2d), 4.05 (2H, s), 6.75 (2H, s), 7.20 (4H, t), 7.70 (4H, dd), 10.0 (1H, s).

3,5-Diphenyl-4-azatricyclo[5.2.2.0^{2,6}]undeca-2,5,8-triene, 38: from **vii-l**; mp 224 °C; IR (Nujol) 3413, 1616, 1593 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.6 (4H, m), 4.2 (2H, m), 6.55 (2H, m), 7.2 (2H, m), 7.45 (4H, t), 7.7 (4H, d), 10.4 (1H, br s).

1,3-Diphenyl-2-methyl-4,5,6,7-tetrahydro-2*H*-isoindole, 13. 1.4 g (0.0049 mol) of ethylenic compound **ix-a** was hydrogenated in 100 mL of ethanol for 3 h at reflux in the presence of 0.5 g of 10% Pd/C and 1.85 g of ammonium formate. After cooling, the reaction mixture was filtered, and the filtrate was evaporated. The residue was taken up in ethyl acetate, washed with a 10% aqueous sodium hydrogenocarbonate solution, and water. Drying over calcium sulfate was followed by filtration and evaporation to give a solid that was recrystallized from ethanol to give 1 g (71%) of the saturated compound: mp 143 °C; IR (Nujol) 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (4H, m), 2.65 (4H, m), 3.45 (3H, s), 7.2−7.5 (10H, m).

1,3-Diphenyl-2-amino-4,5,6,7-tetrahydro-2*H*-isoindole, 14: from **ix-b**; mp 161 °C; IR (Nujol) 3357−3224, 3041, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (4H, m), 2.63 (4H, m), 4.42 (2H, br s), 7.25−7.49 (10H, m).

1,3-Diphenyl-4,5,6,7-tetrahydroisoindole-2-methylsulfonylamine, 15. Compound **14** (1.3 g, 0.0045 mol) was dissolved in 30 mL pyridine and mesyl chloride (0.35 mL, 0.0045 mol) was added dropwise in 5 mL of dichloromethane. After 2 h, 0.35 mL of mesyl chloride was added, and the reaction was stirred overnight; the solvents were evaporated, and the residue was taken up with ethyl acetate. The organic layers were washed with water, 10% citric acid and brine. The solution was dried over calcium sulfate, and evaporated to give 1.6 g of a compound. Purification on silica gel (CH_2Cl_2−hexane 2:1) gave 340 mg (20%) of the desired compound: mp 196 °C; IR (Nujol) 3251, 1326, 1146 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6−2.0 (4H, m), 2.2 (3H, s), 2.35−3.0 (4H, 2m), 7.2−7.5 (10H, m).

(1,3-Diphenyl-4,5,6,7-tetrahydroisoindol-2-yl)acetic acid, 16: from **vii-a**; mp 162 °C; IR (Nujol) 2700−2300, 1679, 1602 cm^{-1}; ^{1}H NMR (CH_3OH-d_4) δ 1.75 (4H, m), 2.55 (4H, m), 4.3 (2H, s), 7.2−7.4 (10H, m).

1,3-Di-*p*-tolyl-4,5,6,7-tetrahydro-2*H*-isoindole, 19: from **ix-c**; mp 150 °C; IR (Nujol) 3475, 1611 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.70 (4H, m), 2.32 (6H, s), 2.70 (4H, m), 7.18 (4H, d), 7.48 (4H, d), 10.70 (1H, br s).

1,3-Di(4-methoxyphenyl)-4,5,6,7-tetrahydro-2*H*-isoindole, 20: from **ix-d**; mp 146 °C; IR (Nujol) 3421−3396, 1600−1587 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.70 (4H, m), 2.65 (4H, m), 3.8 (6H, s), 6.95 (4H, d), 7.5 (4H, d), 10.55 (1H, br s).

1,3-Di(4-chlorophenyl)-4,5,6,7-tetrahydro-2*H*-isoindole, 21: from **ix-e**; mp 231 °C; IR (Nujol) 3462, 1593, 830 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.75 (4H, m), 2.70 (4H, m), 7.46 (4H, d), 7.62 (4H, d), 10.95 (1H, br s).

1-(4-Fluorophenyl)-3-[4-(imidazol-1-yl)phenyl]-4,5,6,7-tetrahydro-2*H*-isoindole, 22: from **viii-c**; mp > 250 °C; IR (Nujol) 3300−2400, 1620−1580 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.75−2.7 (8H, 2m), 3.4 (4H, m), 5.95 (2H, s), 7.15 (1H, s), 7.25 (2H, m), 7.6−7.85 (7H, m), 8.3 (1H, s), 11.0 (1H, s).

1,3-Di[4-(imidazol-1-yl)phenyl]-4,5,6,7-tetrahydro-2*H*-isoindole hydrochloride, 23: from **ix-f**; mp > 260 °C; IR (Nujol) 3700−2000, 1604 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.70 (4H, m), 2.75 (4H, m), 7.05 (2H, s), 7.4 (4H, d), 7.65 (2H, s), 7.75 (4H, d), 8.15 (2H, s).

1,3-Diphenyl-5,6-dimethyl-4,5,6,7-tetrahydro-2*H*-isoindole, 24: from **25**; mp 133 °C; IR (Nujol) 3438, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85−1.2 (6H, 2d), 2.0 (2H, m), 2.5 (2H, dd), 2.85 (2H, dd), 7.2 (2H, m), 7.4 (4H, m), 7.65 (4H,d), 10.8 (1H, br s).

3, 5-Diphenyl-4-azatricyclo[5.2.1.0^{2,6}]deca-2, 5-diene, 31: from **ix-g**; mp 162 °C; IR (Nujol) 3328, 1616−1594 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (2H, m), 1.72 (1H, d), 2.0 (3H, m), 3.60 (2H, m), 7.20 (1H, t), 7.40 (2H, t), 7.55 (2H,d), 7.90 (1H, br s).

3,5-Bis(4-fluorophenyl)-4-azatricyclo[5.2.1.0^{2,6}]deca-2,5-diene, 32: from **viii-a or 33**; mp 146 °C; IR (Nujol) 3436, 1223, 833 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2 (2H, d),1.70 (1H, d), 1.90 (1H, d), 1.95 (2H, d), 3.55 (2H, s), 7.20 (4H, t), 7.70 (4H, dd), 10.35 (1H, br s).

3-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-4-azatricyclo[5.2.1.0^{2,6}]deca-2,5-diene, 34: from **viii-d**; mp > 260 °C; IR (Nujol) 3360, 1141 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2 and 1.65−2.05 (6H, m), 3.2 (3H, s), 3.65 (2H, m), 7.3 (2H, m), 7.7−8.0 (6H, m), 10.65 (1H, br s).

3,5-Bis(4-methylsulfonylphenyl)-4-azatricyclo[5.2.1.0^{2,6}]-deca-2,5-diene, 35: from **viii-g**; mp > 260 °C; IR (Nujol) 3342, 1588, 1313−1144 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2−1.75−2.0 (6H, m), 3.35 (6H, s), 3.75 (2H, m), 7.98 (8H, m), 10.88 (1H, br s).

3,5-Diphenyl-4-azatricyclo[5.2.2.0^{2,6}]undeca-2,5-diene, 36: from **38**; mp 248 °C; IR (Nujol) 3420, 1616−1595 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.4 (4H, m), 1.8 (4H, m), 3.35 (2H, m), 7.15 (2H, m), 7.4 (4H, m), 7.65 (4H, d), 10.6 (1H, br s).

3,5-Bis(4-fluorophenyl)-4-azatricyclo[5.2.2.0^{2,6}]undeca-2,5-diene, 37: from **viii-b**; mp 202 °C; IR (Nujol) 3457, 1508 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.4 (4H, m), 1.8 (4H, m), 3.3 (2H, s), 7.2 (4H, dd), 7.65 (4H, dd), 10.6 (1H, br s).

3,5-Bis(3-acetamido-4-fluorophenyl)-4-azatricyclo-[5.2.1.0^{2,6}]deca-2,5-diene, 39: obtained from **viii-i** by cyclization and acetylation with ammonium acetate in acetic acid as described above for compound **33**; mp 225 °C; IR (Nujol) 3290, 1673, 1608−1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2 (2H, m), 1.65 (1H, d), 1.75−2.0 (3H, m), 2.1 (6H, s), 3.6 (2H, s), 7.2 (2H, dd), 7.45 (2H, m), 8.2 (2H, d), 9.7 (2H, br s), 10.3 (1H, br s).

3,5-Bis(3-formamido-4-fluorophenyl)-4-azatricyclo-[5.2.1.0^{2,6}]deca-2,5-diene: IR (Nujol) 3284, 1691, 1609, 1528 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.0−2.0 (4H, m), 3.55 (2H, s), 7.2−7.4 (4H, m), 8.4 (4H, m), 10.1 (3H, br s).

3,5-Bis(3-methylamino-4-fluorophenyl)-4-azatricyclo-[5.2.1.0^{2,6}]deca-2,5-diene Hydrochloride, 40. 8.14 g (0.02 mol) of the diformylated intermediate obtained above was dissolved in 150 mL of THF and added dropwise to a suspension of 1.52 g (0.04 mol) of LAH in 150 mL of THF. The reaction was refluxed for 1.5 h and after cooling was hydrolyzed with 10 mL of 2-propanol and 6 mL of brine. Filtration and evaporation of the filtrate gave a crude residue that was chromatographed (silica gel, CH_2Cl_2). To the purified solid dissolved in 10 mL of diethyl ether was added 10 mL of 4 M HCl in dioxane. The resulting solid was filtered, washed with diethyl ether and dried to give 2.9 g (37%) of the title compound: mp 196 °C; IR (Nujol) 3254, 2700−2300, 1619, 1581, 1519 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2 (2H, m), 1.7 (1H, d), 1.8−1.95 (3H, m), 2.9 (6H, s), 3.6 (2H, s), 7.1−7.4 (6H, m), 7.6 (2H, br s), 10.5 (1H, br s).

Route C (Scheme 3). (4-Benzoyl-1-benzylpyrrolidin-3-yl)(phenyl)methanone, xii. 4.75 g (0.02 mol) of *N*-benzyl-*N*-methoxymethyl-*N*-[(trimethylsilyl)methyl]amine (**xi**; Aldrich) was reacted with 4.72 g (0.02 mol) of dibenzoylethylene and 0.65 g (0.025 mol) of lithium fluoride in 50 mL of acetonitrile. The temperature was maintained at 40 °C for 6 h, then the reaction was stirred at room temperature for 18 h. The reaction mixture was then poured into 200 mL of water. Extraction with ethyl acetate was followed by washing with water and brine. Drying over calcium sulfate and evaporation gave 7.4 g of an oil which was chromatographed (silica gel, CH_2Cl_2−AcOEt 1:1) to give 6.2 g (84%) of compound **xii** as a colorless oily residue: IR (Nujol) 1680, 1581, 1620−1579 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.8−3.12 (2H, dd) 3.7 (2H, s), 4.65 (2H, m), 7.15−7.3 (5H, m), 7.4 (4H, m), 7.5 (2H, m), 7.92 (4H, d).

2-Benzyl-4,6-diphenyl-1,2,3,5-tetrahydropyrrolo[3,4-*c*]-pyrrole, 29: cyclization performed according to the method used for compound **33**; mp 182 °C; IR (Nujol) 3429, 1673, 1610−1595 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.9 (4H, s), 4.05 (2H, s), 7.15 (2H, m), 7.2−7.5 (9H, m), 7.6 (4H, d).

4,6-Diphenyl-1,2,3,5-tetrahydropyrrolo[3,4-*c*]pyrrole, 30: prepared according to the method used for compound **13;** mp >260 °C; IR (Nujol) 3303, 2750−2400, 1595 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.55 (4H, s), 7.25 (2H, m), 7.45 (4H, m), 7.7 (4H, d), 10.25 (1H, br s), 11.45 (1H, br s).

Route D (Scheme 4). 1-Pyridin-4-yl-2-(triphenyl-λ^5-phosphanylidene)ethanone, xv. Triphenylphosphine (3.25 g, 0.0125 mol) was dissolved in 40 mL of toluene. 4-Bromoacetylpyridine **xiv** (3.5 g, 0.0125 mol) was then added, followed by triethylamine (1.73 mL, 0.0125 mol) dropwise. After stirring for 2 h, the reaction mixture was filtered; the solid was washed with ethyl acetate and ethanol to give 3.1 g (65%) of a pale brown solid: mp 224 °C; IR (Nujol) 1577, 1515 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.6 (1H, d), 7.5−7.8 (17H, m), 8.6 (2H, d).

1,4-Dipyridin-4-ylbut-2-ene-1,4-dione, vi-a. 30 g (0.079 mol) of phosphorane **xv** was dissolved in 200 mL of dichloromethane, and 30 g of 4A molecular sieves was added. A solution of 37% peracetic acid in acetic acid was diluted with 100 mL of dichloromethane and added dropwise at 5 °C within 45 min. After stirring 15 more min, the solution was filtered and evaporated. The residue was taken up with dichloromethane and a 10% solution of sodium hydrogenocarbonate. The organic layer was washed with water, dried over calcium sulfate and evaporated. The solid was taken up with ethanol, filtered and washed with pentane to give 4.2 g (45%) of a brown solid: mp 222 °C; IR (Nujol) 3086, 3048, 1659, 1556 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.9 (2H, s), 7.95 (4H, d), 8.9 (4H, d).

[3-(Pyridin-4-ylcarbonyl)bicyclo[2.2.1]hept-5-en-2-yl]-pyridin-4-ylmethanone, vii-m. 4.4 g (0.018 mol) of diketone obtained above was dissolved in 80 mL of toluene and 4 g (0.061 mol) of freshly distilled cyclopentadiene was added. The reaction mixture was heated at 120 °C for 2.5 h in a sealed vessel. After cooling, the reaction was filtered and evaporated. The residue was washed with diisopropyl ether to give a yellow solid (5.4 g, 96%): mp 171 °C; IR (Nujol) 3062−3047, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) presence of endo/exo isomers δ 1.55 (m) and 1.85 (d) (2H), 3.15 (m) and 3.40 (m) (2H), 3.9 (d) and 4.48 (t) (2H), 5.94 (m) and 6.45 (m) (2H), 7.80 (4H, 2d), 8.83 (4H, d).

3,5-Dipyridin-4-yl-4-azatricyclo[5.2.1.0^{2,6}]deca-2,5,8-triene, ix-h. 4.8 g (0.016 mol) of compound **xvii** and 12.2 g (0.016 mol) of ammonium acetate were refluxed in 50 mL of acetic acid. After 3 h, the solvent was evaporated, water was added, and the reaction mixture was alkalinized with potassium carbonate. The resulting solid was filtered and washed with water. Chromatography (silica gel, CH_2Cl_2−CH_3OH 1:1) gave a yellow solid (2.4 g, 53%) which was identified as the desired compound: mp > 250 °C; IR (Nujol) 3136, 1607−1592 cm^{-1}; ^{1}H NMR (DMSO-d_6) 2.4 (2H, dd), 4.3 (2H, s), 6.8 (2H, s), 7.7 (4H, d), 8.5 (4H, d), 10.5 (1H, br s).

3,5-Dipyridin-4-yl-4-azatricyclo[5.2.1.0^{2,6}]deca-2,5-diene Dihydrochloride, 41. This compound was prepared according to the method used for compound **13**. The dihydrochloride was obtained after dissolving the pure base in dioxane−methanol 1:1 and adding dropwise a solution of 4 M HCl in dioxane: mp 264 °C; IR (Nujol) 3400−2500, 1624, 1602−1586 cm^{-1}; ^{1}H NMR (DMSO-d_6) 1.2 (2H, m), 1.8 (1H, m), 2.1 (3H, m), 3.9 (2H, s), 8.5 (4H, d), 8.8 (4H, d), 12.5 (1H, br s).

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