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Synthesis and Structure−Activity Relationships of Novel Histamine H_1 Antagonists: Indolylpiperidinyl Benzoic Acid Derivatives

Silvia Fonquerna,*,† Montse Miralpeix,*,‡ Lluís Pagès,† Carles Puig,† Arantxa Cardús,† Francisca Antón,‡ Álvaro Cárdenas,‡ Dolors Vilella,‡ Mónica Aparici,‡ Elena Calaf,‡ José Prieto,† Jordi Gras,‡ Josep M. Huerta,§ Graham Warrellow,† Jorge Beleta,‡ and Hamish Ryder†,‡

Almirall Prodesfarma S.A., Research Center, Cardener 68-74, 08024-Barcelona, Spain

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A series of indolylpiperidinyl derivatives were prepared and evaluated for their activity as histamine H_1 antagonists. Structure−activity relationship studies were directed toward improving in vivo activity and pharmacokinetic profile of our first lead (**1**). Substitution of fluorine in position 6 on the indolyl ring led to higher in vivo activity in the inhibition of histamine-induced cutaneous vascular permeability assay but lower selectivity toward $5HT_2$ receptor. Extensive optimization was carried out within this series and a number of histamine H_1 antagonists showing potency and long duration of action in vivo and low brain penetration or cardiotoxic potential were identified. Within this novel series, indolylpiperidines **15**, **20**, **48**, **51** and **52** exhibited a long half-life in rat and have been selected for further preclinical evaluation.

Introduction

Histamine is one of the most important chemical mediators and through its interaction with H_1 receptors, present in most tissues, is involved in the pathophysiology of allergic rhinoconjuntivitis, urticaria and atopic dermatitis. Among the broad range of allergic diseases, allergic rhinitis is the most prevalent condition, affecting 10 to 30% of adults and up to 40% of children, with increasing prevalence over the past decade.[1] The economic burden of this disease is enormous, as is the impact on the quality of life.[2]

Allergic rhinitis is an IgE-mediated disease that is provoked by either seasonal or perennial inhaled allergens. The symptoms of allergic rhinitis result from inflammation of the nasal mucosa, which is initiated by the interaction of aeroallergens with specific IgE antibodies attached primarily to mast cells, which accumulate in nasal epithelium in response to repeated exposure to allergen.[3] The interaction between mast cell-released mediators of inflammation, including histamine, leukotrienes, prostaglandins, tryptase and kinins, and neural and vascular structures within the nose, cause the allergic rhinitis symptoms of itch, sneeze, rhinorrhea and obstruction.[4]

The histamine H_1 antagonists are used as the first-line treatment for patients with allergic rhinitis.[5] They prevent symptoms associated with histamine release such as sneezing, rhinorrhea, nasal and conjunctival itching and lacrimation, although they do not control symptoms of nasal congestion.[6] Additional antiinflammatory effects of antihistamines have been described, although the specific mechanisms underlying these effects are not understood, it is not clear whether this is a class effect or is confined to certain members of the second-generation of these drugs. Nevertheless, it must be emphasized that most of the available data result from in vitro experiments performed at very high and irrelevant concentrations.[7]

First-generation antihistamines are effective and relatively inexpensive; however, they also cause sedation and dry mouth at therapeutic doses, due to their blood−brain barrier penetration and lack of receptor specificity. Somnolence is experienced by a significant percentage (10 to 40%) of patients using these drugs, and may impair driving and other types of performance.[8] In contrast, most second-generation histamine H_1-receptor antagonists have a greatly improved benefit-to-risk ratio compared to their predecessors, mainly because their reduced potential to cross the blood−brain barrier and higher receptor specificity.[9] Unfortunately, some of the second-generation antihistamines can produce fatal arrhythmogenic events, through impairing cardiac muscle repolarization. This results in the prolongation of the QT interval and the possible provocation of the specific polymorphic ventricular tachyarrhythmia, *torsades de pointes*.[10] Such toxic events may occur under the following conditions: overdosage, hepatic failure, concomitant use of CYP450 inhibitors and/or cardiotoxic drugs and finally preexistence of rhythm disturbances and more especially congenital long Q−T syndrome. Indeed, several second-generation histamine H_1-antihistamines are substrates and modulators of CYP450, in particular the subtype CYP3A4. Thus, their plasma and tissue levels may be increased and become toxic in the case of polymedication as well as the plasma and tissue levels of concomitantly administered drugs.[11]

This paper describes the synthesis and structure−activity relationships of new indolylpiperidinyl benzoic acid derivatives, a family of histamine H_1 antagonists with potent and long lasting activity in vivo, low liability

Corresponding authors. For S. Fonquerna: Treball 2, 08960 St Just Desvern, Spain. Phone: +34-93-291-3999. Fax: +34-93-312-8635. E-mail: sfonquerna@almirall.es. For M. Miralpeix: Cardener 68-74, 08024 Barcelona, Spain. Phone: +34-93-291-3468. Fax: +34-93-2827. E-mail: mmiralpe@almirall.es.

† Department of Medicinal Chemistry.

‡ Department of Biology.

§ Department of Structural Analysis of Drug Discovery Division.

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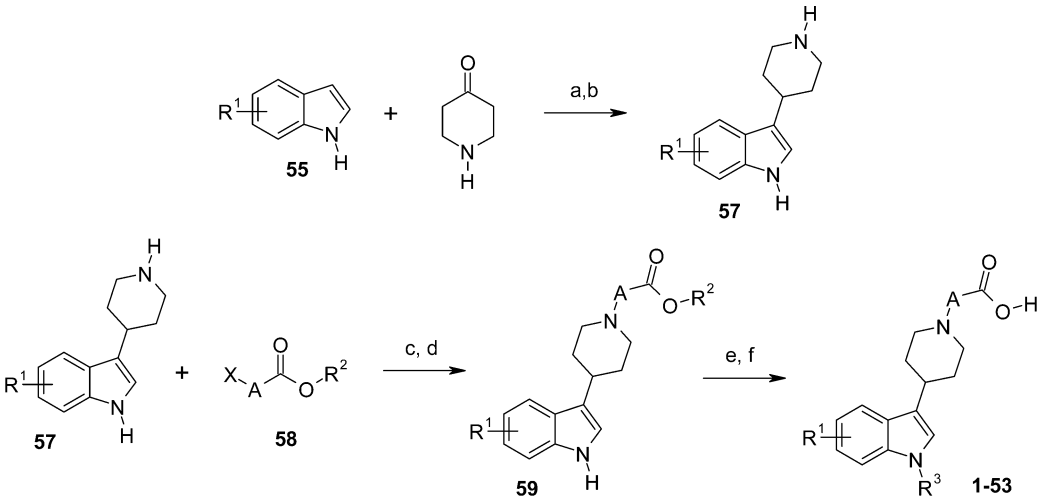
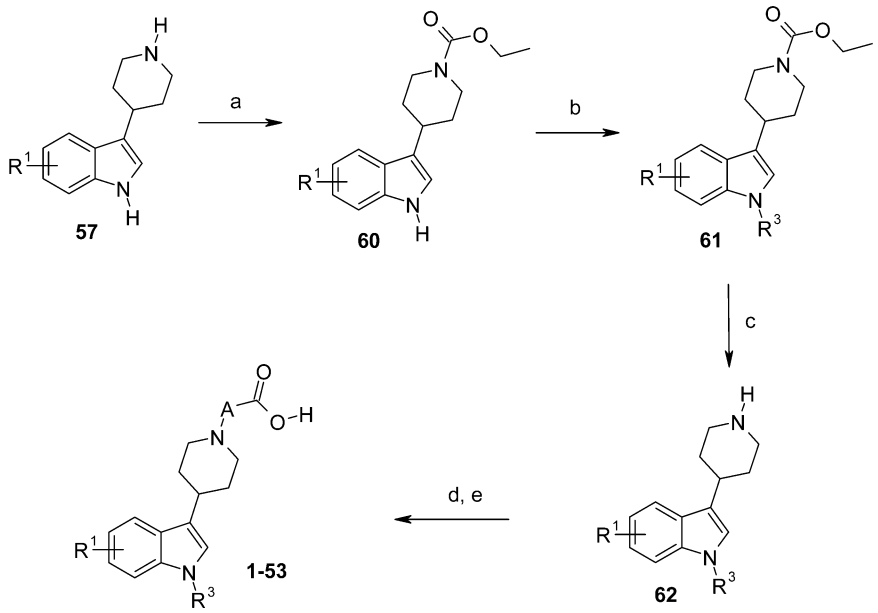
Scheme 1[a]



[a] Reagents and conditions: (a) KOH, MeOH, 70 °C, 5 h; (b) H_2, Pd−C (10%), 1 h; (c) K_2CO_3, methylisobutyl ketone, 100 °C, 18 h; (d) polymer-supported-NCO, Cl_2CH_2, rt, 3 h; (e) NaH, R^2X, rt, 15 h; (f) NaOH, EtOH, rt, 16 h.

Scheme 2[a]



[a] Reagents and conditions: (a) Et_3N, $ClCO_2Et$, DCM, 0 °C 1 h; (b) NaH, R^3X, 60 °C 1 h; (c) KOH, ^{i}PrOH, rfx 18 h; (d) $XACO_2R^2$, K_2CO_3, MIK, 90 °C, 15 h; (e) NaOH, EtOH, rt, 24 h.

to enter into the brain and lacking cardiotoxic potential. In addition, the compounds described in this paper show low metabolic clearance and absence of CYP450 inhibition that suggests a low potential for drug−drug interactions and intersubject variability in drug response. Overall, these characteristics may distinguish the antihistamines described in this paper from the second-generation antihistamines.

Chemistry. Two different strategies were designed in order to synthesize indolylpiperidine derivatives **1**−**53**. At the beginning of the optimization process, libraries of compounds were prepared to achieve a higher throughput. Combinatorial techniques,[12] such as the use of polymer-supported scavengers and automated purification in parallel, were applied. Scheme 1 shows the general synthetic approach used in a parallel fashion. Sequential condensation of a substituted indole with piperidone and further hydrogenation of the corresponding adducts gave indolylpiperidines **57**. Alkylation of indolylpiperidines **57** with appropriate halides **58** provided intermediates **59**. The unreacted excess of indolylpiperidines **57** was removed by incubation with a polymer-supported isocyanate, and the crude was purified in parallel by anionic exchange chromatography.[13] Further alkylation of indolic nitrogen with R^2X using sodium hydride as base and saponification of intermediates **59** followed by acidification provided indolylpiperidines **1**−**53**. Purification of final library members was achieved by semipreparative C-18 HPLC-MS.

Alternatively, when highly characterized compounds were required for advanced SAR studies, the sequential synthetic approach described in Scheme 2 was followed. Protection of indolylpiperidine **57** with ethyl chloroformate followed by alkylation of the indole ring with the appropriate alkyl or arylalkyl halide provided intermediates **61**. Further treatment with potassium hydroxide at 80 °C led to key derivatives **62**. Alkylation of

indolylpiperidines **62** with appropriately substituted halides **58** and further saponification afforded indolylpiperidines **1**−**53**.

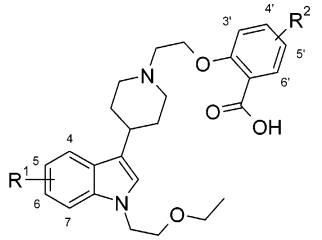
Biology. Biological Evaluation. To determine structure−activity relationships, all compounds described were evaluated for their affinity for the guinea-pig cerebellum histamine H_1 receptor in a radioligand binding assay.[14] Selectivity was assessed by testing their binding affinity against the human 5-HT_2 and the rat alpha-1 receptors.[15,16] High affinity compounds for the histamine H_1 receptor, with at least 10 times selectivity versus the other two receptors, were evaluated for their antihistamine activity in the rat histamine-induced cutaneous vascular permeability model.[17] Compounds showing potent and stable oral antihistamine activity after 8 h postadministration in this model were then tested for their capacity to cross the blood−brain barrier in the H_1 ex vivo binding assay in mice.[18] Finally, for selected compounds, pharmacokinetics studies were performed in rats in order to determine the half-life of elimination. For the most promising compounds, the effect on QT interval prolongation in anaesthetised guinea-pigs[19] and the inhibitory effect on CYP3A4 isoform were measured.

Results and Discussion

One of our lead structures when we initiated a histamine H_1 antagonist program was compound **1** which was related to some previously known mixed 5-lipoxygenase inhibitor/H_1 antagonist.[20] Compound **1** was a selective histamine H_1 antagonist able to inhibit histamine induced cutaneous vascular permeability increase in rats after 1 h of oral administration with higher potency than some standard compounds (Table 6). However, oral activity suffered from a 10-fold decrease after 8 h. This was in accordance with its pharmacokinetic profile showing a fast onset but a short half-life in vivo (Table 5). In terms of safety, compound **1** showed a lack of adverse side effects commonly related to antihistamines such as sedation and cardiovascular toxicity (Table 6). The aim of our work was to modify the structure in order to improve the duration of action and pharmacokinetic profile while maintaining the nonsedative properties and absence of potential cardiac toxicity.

Our initial synthetic efforts were directed toward determining the effect of substitution on the aromatic rings of compound **1** (Table 1) on antihistaminic activity. The presence of a methoxy group in 5-position of the indolyl ring (**2**) enhanced in vivo activity with respect to unsubstituted analogue **1** while keeping a similar pattern of in vitro antihistaminic affinity and selectivity. Halogen derivatives in position 5 and 6 of the indolyl ring (**3**, **4** and **5**) were less selective than compound **1** whereas the 7-bromo derivative (**6**), although showing similar potency in vitro, was 30-fold less active in vivo. The methyl (**7**) and trifluoromethyl (**8**) derivatives had lower potency. On the other hand, substitution on the benzoic acid ring (**9**, **10**, **11** and **12**) generally led to derivatives with lower selectivity. However, compound **13**, with a methoxy group in position 4, met our selectivity criteria and showed similar potency in vivo to analogue **1** although selectivity toward the 5-HT_2 receptor was slightly reduced.

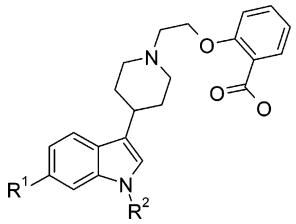
Table 1. Effect of Aromatic Substitution on in Vitro and in Vivo Activity



compd	R^1	R^2	H_1[a]	5HT_2[a]	α_1[b]	HICVP[c] (4 h)[d]
1	H	H	86	3272	10	0.1
2	5-OMe	H	155	6700	>10	0.035
3	5-F	H	100	500	10	−
4	6-F	H	76	260	10	−
5	5-Br	H	150	1500	3.6	−
6	7-Br	H	80	1397	10	>3
7	7-Me	H	500	3100	7.6	−
8	6-CF_3	H	>500	2900	6.9	−
9	H	6′-F	500	850	10	−
10	H	3′-5′-diBr	225	500	6.9	−
11	H	5′-Me	221	225	8.6	−
12	H	5′-acetyl	219	950	>10	−
13	H	4′-OMe	34	779	>10	0.17

[a] Data are indicated as IC_{50} (nM). [b] Data are indicated as IC_{50} (μM). [c] Histamine-induced cutaneous vascular permeability model. [d] Data are indicated as ED_{50} (mg/kg).

Table 2. Effect of the Indole Substitution on in Vitro and in Vivo Activity



compd	R^1	R^2	H_1[a]	5HT_2[a]	α_1[b]	HICVP[c] (4 h)[d]
1	H	2-ethoxyethyl	86	3272	10	0.1
14	H	2-methoxyethyl	83	>10000	>10	1.1
15	F	2-methoxyethyl	140	1185	>10	0.29
16	H	butyl	127	9105	>10	0.74
17	H	cyclopropylmethyl	140	>10000	>10	0.6
18	F	cyclopropylmethyl	121	10000	>10	0.11
19	H	allyl	97	>10000	>10	3
20	H	[1,3]-dioxolanethyl	354	4517	6.5	0.46
21	H	1-furan-2-ylmethyl	98	10000	>10	3
22	F	1-furan-2-ylmethyl	37	870	>10	0.32
23	H	1-thiophen-2-ylmethyl	98	500	3.7	- -
24	H	5-chlorothiophen-2-ylmethyl	120	1858	>10	3
25	F	5-chlorothiophen-2-ylmethyl	28	1025	>10	1
26	H	2-[1,4]-dioxan-2-ylethyl	390	2100	6.2	3
27	H	2-pyridin-2-ylethyl	570	2900	>10	- -

[a] Data are indicated as IC_{50} (nM). [b] Data are indicated as IC_{50} (μM). [c] Histamine-induced cutaneous vascular permeability model. [d] Data are indicated as ED_{50} (mg/kg).

We then focused on modifications to the of *N*-alkyl chain on the indole (Table 2). As general trends, we observed that derivatives with alkyl, alkoxyalkyl, cyclolalkyl, heterocyclolalkyl and heterocycloaryl chains showed a range of affinity and selectivity similar to analogue **1** whereas activity in vivo was slightly reduced. However, entries **20**, **26** and **27** with dioxolanylethyl, dioxanylethyl and pyridinylethyl groups led to derivatives with low antihistaminic activity and less selectivity than compound **1**. The presence of a fluorine

atom in position 6 of the indolyl ring turned out to be decisive in order to improve oral activity (**15**, **18**, **22** and **25**). We observed that comparing a different set of compounds with the same substitution pattern, in vivo activity was at least 3-fold higher in 6-fluoro-substituted derivatives.

The next area of exploration was the alkoxybenzoic acid moiety (Table 3). Initial changes were directed toward differences in relative regiochemistry (**28** and **29**) and the length of the alkoxy chain (**30**, **31** and **32**). The most promising compound was **31**, which showed a 9-fold improvement of in vivo activity compared to **1**, although with reduced selectivity versus 5-HT_2. Other variations such as elongating the distance between the carboxylic acid and the phenyl group (**33**, **34** and **35**) led to derivatives with a good profile of affinity and selectivity but with low in vivo potency. On the other hand, substitution of the phenyl group by an heterocycle afforded either low affinity (**39**) or low selectivity (**40**). Since 3-methylenebenzoic acid (**31**) had been identified as a good substitution pattern we decided to study in more detail the effect of adding various functional groups. Compound **36** with a methoxy group ortho to the carboxylic acid showed a 5-fold enhanced in vivo potency compared to compound **1** together with similar selectivity.

Having established the best substitution around three different areas of the indolylpiperidine scaffold in terms of activity and selectivity, we then proceeded to synthesize a combinatorial library using the optimized fragments (Table 4). As a general trend, we observed that they all were selective antihistamines in vitro vs $5HT_2$ and alpha-1 receptors with the main differences based on their behavior in vivo depending on the nature of benzoic acid chain. Derivatives containing 2-ethoxybenzoic acid showed high in vivo activity with some loss of action after 8 h and low brain penetration, whereas compounds with 3-methylbenzoic acid showed low oral activity. Derivatives containing 2-methoxy-5-methylbenzoic acid showed high in vivo activity and longer duration of action although some of them had low ED_{50} values (<5 mg/kg) in the H1 ex vivo model suggesting that they may cross the blood−brain barrier. Cetirizine, a second-generation antihistamine that has been shown to cause some degree of somnolence[21] and reduced motivation to perform workday activities,[22] had an ED_{50} of 5 mg/kg in this model.

At this point of the study, we were interested in identifying potent in vivo antihistamines with a stable and long duration of action as well as low capacity to cross the blood−brain barrier (with ED_{50} higher than cetirizine). Pharmacokinetic profiles of compounds with an ED_{50} greater than 8 mg/kg in the H_1 ex vivo assay and consistent oral potency after 8 h were evaluated in rats (Table 5). In accordance with the longer duration of oral activity observed in selected compounds, the half-lives of **15**, **20**, **48**, **51** and **52** compounds were longer than that for compound **1**. Moreover, the small volumes of distribution suggest low affinity of all these compounds for tissues components and reduced potential for toxicity.

Finally, the potential to cause adverse cardiac effects was also assessed for compounds **1**, **15**, **48** and **51**. The effect on QT prolongation interval was measured in anaesthetised guinea-pigs at different prefixed doses (3, 10 and 30 mg/kg, iv). The data shown in Table 6 indicated that at 10 mg/kg (iv) compounds **1** and **51** and even at 30 mg/kg (iv) compounds **15** and **48** did not produce any significant increase in the QT interval. For cetirizine and loratadine, the two most prescribed second-generation antihistamines, the maximal dose without effect were 3 and 10 mg/kg (iv), respectively. It is noteworthy that none of these compounds were inhibitors of CYP3A4 (Table 6), indicating low drug−drug interaction potential.

Conclusions

We have identified a novel series of indolylpiperidinyl benzoic acid derivatives as potent in vivo histamine H_1 antagonists with long lasting activity, low brain penetration and lacking cardiotoxic potential. In addition, our compounds have absence of CYP3A4 inhibition indicating low drug−drug interaction potential.

Relative to our initial lead compound (**1**), we have improved in vivo activity and pharmacokinetic profile. We have demonstrated that a 6-fluoro substituent on the indolyl ring enhances in vivo activity albeit with a slight loss of selectivity. We have also discovered that derivatives containing the 2-methoxy-5-methylbenzoic acid fragment have high in vivo activity and a longer duration of action. A selected group of histamine H_1 antagonists showing potent activity and long duration of action in vivo with low capacity to cross the blood−brain barrier has also been identified. Their overall pharmacological profile suggests that these novel compounds constitute a promising series of potent and safe antihistamines with an improved therapeutic window compared with some marketed antihistamines (Table 6). Compounds **15**, **48** and **51** have been selected for further preclinical profiling, based on their duration of action in vivo, pharmacokinetic profile, low brain penetration and lack of cardiotoxic potential. Results of these studies will be reported in due course.

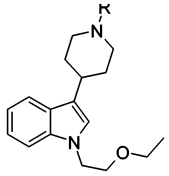
Experimental Section

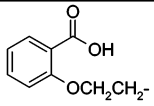
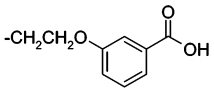
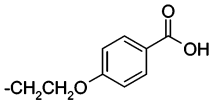
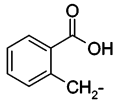
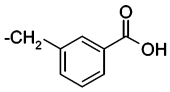
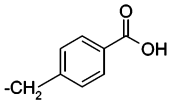
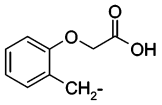
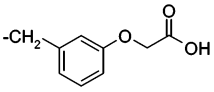
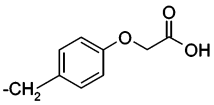
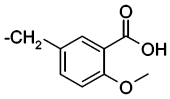
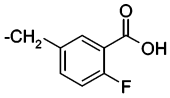
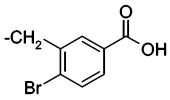
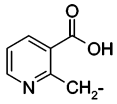
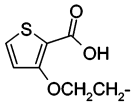
Chemistry. General. Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received. All organic solutions were dried over sodium sulfate. Concentration refers to evaporation under vacuum using a Büchi rotatory evaporator. Reaction products were purified, when necessary, by flash chromatography on silica gel (40−63 μm) with the solvent system indicated. Spectroscopic data were recorded on a Varian Gemini 300 or a Varian Gemini 200 spectrometer. Melting points were recorded on a Büchi 535 apparatus. Where analyses are indicated only by symbols of the elements, results obtained were within 0.4% of the theoretical values.

Procedure for the Preparation of Intermediates 57. 3-(1,2,3,6-Tetrahydropyridin-4-yl)-1*H*-indole (56a). Indole (30.0 g, 0.26 mol) was dissolved in a solution of potassium hydroxide (77.6 g, 1.38 mol) in methanol (690 mL). 4-Piperidone monohydrate hydrochloride (102.3 g, 0.66 mol) was added in one portion, and the mixture was heated to reflux for 5 h. Potassium chloride precipitated upon cooling to room temperature, and it was filtered off. The liquid phase was concentrated until only one-third of the liquid remained in the round-bottom flask. Water was added, and a solid precipitated, which was filtered and washed with ethyl ether. 31.9 g (63% yield) of the final product was obtained. Melting point:183−185 °C (lit.[23]: 178−181 °C).

3-Piperidin-4-yl-1*H*-indole (57a). Compound **56a** (3.08 g, 14.0 mmol) was hydrogenated in a Parr apparatus during 1 h

Table 3. Effect of Piperidine Substitution on in Vitro and in Vivo Activity

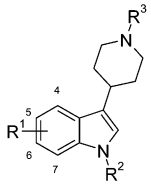


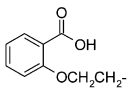
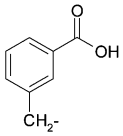
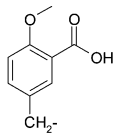
compd	R	H_1[a]	$5HT_2$[a]	α_1[b]	HICVP[c] (4h)[d],
1		86	3272	10	0.1
28		145	123	2	--
29		150	691	3	--
30		330	3050	>10	3
31		218	1774	>10	0.011
32		7%@500mM	0%@500mM	8%@10μM	--
33		196	2095	>10	>3
34		130	1915	>10	3
35		322	3982	>10	>3
36		145	5350	>10	0.02
37		300	500	10	--
38		345	5600	>10	3
39		11%@500mM	28%@500mM	4%@10μM	--
40		100	<100	<10	--

[a] Data are indicated as IC_{50} (nM). [b] Data are indicated as IC_{50} (μM).). [c] Histamine-induced cutaneous vascular permeability model. [d] Data are indicated as ED_{50} (mg/kg).

at 3 bar with Pd/C 10% (0.31 g) in 60 mL of methanol and 60 mL of a saturated solution of hydrogen chloride in methanol. The catalyst was filtered under inert atmosphere, and the solvent was removed at reduced pressure. A solution of sodium hydroxide (0.56 g; 14.0 mmol)) in methanol (45 mL) was added, and after 2.5 h at room temperature, the solvent was removed

Table 4. Pharmacological Profile of Indolylpiperidinyl Benzoic Acid Derivatives



compd	R^1	R^2	R^3	H_1[a]	$5HT_2$	α_1[b]	HICVP[c] (4h)[d]	HICVP[c] (8h)[d]	H_1 *ex vivo*[d]
1	H	2-ethoxyethyl		86	3272	10	0.1	0.22	8
2	5-OMe	2-ethoxyethyl		155	6700	>10	0.035	0.08	>100
15	6-F	2-methoxyethyl		140	1185	>10	0.29	0.13	40
16	H	butyl		127	>10000	>10	0.74	0.8	100
41	6-F	butyl		47	2150	>10	0.07	0.14	10
17	H	cyclopropylmethyl		140	>10000	>10	0.6	1.3	>100
18	6-F	cyclopropylmethyl		121	>10000	>10	0.11	0.5	--
20	H	[1,3]-dioxolan-2-ethyl		354	4517	6.5	0.45	0.9	>100
22	6-F	1-furan-2-ylmethyl		37	870	>10	0.32	2.2	--
42	6-F	1-furan-3-ylmethyl		42	880	>10	0.12	0.17	19
32	H	2-ethoxyethyl		218	1774	>10	0.011	0.15	4.5
43	6-F	2-methoxyethyl		150	3850	>10	1	--	--
44	5-OMe	2-ethoxyethyl		500	>10000	>10	>3	--	--
45	H	1-furan-2-ylmethyl		87	630	>10	1	--	--
46	H	1-thienyl-2-ylmethyl		90	1334	>10	3	--	--
47	H	5-chlorothiophen-2-ylmethyl		103	10000	>10	>3	--	--
37	H	2-ethoxyethyl		145	5350	>10	0.02	0.01	0.5
48	H	2-methoxyethyl		470	>10000	>10	0.05	0.14	9.5
49	6-F	2-methoxyethyl		245	>10000	>10	0.06	0.02	4
50	6-F	1-furan-3-ylmethyl		96	1500	>10	0.02	0.037	7
51	H	1-thienyl-2-ylmethyl		125	3200	>10	0.24	0.56	11.5
52	6-F	1-thienyl-2-ylmethyl		91	3000	>10	0.20	0.66	29
53	6-F	5-chlorothiophen-2-ylmethyl		150	3059	>10	0.19	0.09	5.5

[a] Data are indicated as IC_{50} (nM). [b] Data are indicated as IC_{50} (μM). [c] Histamine-induced cutaneous vascular permeability model. [d] Data are indicated as ED_{50} (mg/kg).

under reduced pressure. Sodium chloride was removed from the crude mixture by precipitation with ethanol (18 mL) and dichloromethane (18 mL). After filtration and removal of the solvent under reduced pressure, 3.10 g (100% yield) of **57a** was obtained. ^{1}H NMR (DMSO-d_6, 200 MHz, δ[ppm]) 1.46−1.64 (m, 2H), 1.83−1.89 (m, 2H), 2.57−2.69 (dt, ^2J = 12.1 Hz, ^3J = 2.3 Hz, 2H), 2.76−2.82 (tt, J = 11.70, 3.51 Hz, 1H), 2.98−3.04 (d, J = 12.1 Hz, 2H), 6.90−7.07 (m, 3H), 7.31−7.34 (d, J = 7.8 Hz, 1H), 7.53−7.57 (d, J = 7.4 Hz, 1H), 10.79 (s, 1H).

The following analogues were prepared using the procedure outlined for **57a** above.

5-Methoxy-3-piperidin-4-yl-1*H*-indole (57b). ^{1}H NMR (DMSO-d_6, 200 MHz, δ[ppm]) 1.49−1.62 (m, 2H), 1.83−1.95 (m, 2H), 2.62 (s, 1H), 2.60−2.85 (m, 3H), 2.95−3.08 (m, 2H), 3.78 (s, 3H), 6.70−6.76 (m, 1H), 7.05 (m, 2H), 7.20−7.23 (m, 1H), 10.64 (s, 1H).

5-Fluoro-3-piperidin-4-yl-1*H*-indole (57c). ^{1}H NMR (DMSO-d_6, 200 MHz, δ[ppm]) 1.42−1.63 (m, 2H), 1.81−1.87 (m, 2H), 2.56−2.69 (td, J = 12.1, 2.3 Hz, 1H), 2.78 (tt, J = 11.7, J = 3.5 Hz, 2H), 2.98−3.04 (m, 2H), 6.83−6.94 (td, J = 8.9, J = 2.3 Hz, 1H), 7.14−7.15 (m, 1H), 7.26−7.35 (m, 2H), 10.90 (s, 1H).

6-Fluoro-3-piperidin-4-yl-1*H*-indole (57d). ^{1}H NMR (DMSO-d_6, 200 MHz, δ[ppm]) 1.44−1.64 (m, 2H), 1.83−1.89 (d, J = 12.5 Hz, 2H), 2.59−2.70 (m, 2H), 2.74−2.89 (m, 1H), 2.99−3.05 (d, J = 12.1 Hz, 2H), 6.75−6.86 (m, 1H), 7.07−7.13 (m, 2H), 7.50−7.57 (dd, J = 8.6, J = 5.5 Hz, 1H), 10.88 (s, 1H).

Table 5. Pharmacological and ADME Profile of Indolylpiperidinyl Benzoic Acid Derivatives

compd	H_1[a]	HICVP[b] (4 h)[c]	HICVP[b] (8 h)[c]	H_1 ex vivo[c]	$t_{1/2}$ (h)	V_{ss} (L/kg)	Cl (L/kg·h)
1	86	0.1	0.22	8	1.1	0.7	0.6
2	155	0.035	0.08	>100	0.9	0.5	0.8
15	140	0.29	0.13	40	3.4	0.3	0.1
16	127	0.74	0.8	100	1.6	0.4	0.4
20	354	0.45	0.9	>100	2.9	0.5	0.3
48	470	0.05	0.14	9.5	3.9	0.6	0.2
51	125	0.24	0.56	11.5	3.1	1.8	0.6
52	81	0.20	0.66	29	3.8	1.1	0.3

[a] Data are indicated as IC_{50} (nM). [b] Histamine-induced cutaneous vascular permeability model. [c] Data are indicated as ED_{50} (mg/kg). V_{ss}: Volume of distribution at the steady state. Cl: Clearance.

Table 6. Efficacy and Safety Data for Selected Compounds and Standards

compd	HICVP[a] (1 h)[b]	H_1 ex vivo[b]	QTc[c,d] (iv)	CYP3A4 inhibition,[e] %
1	0.02	8	10	0
15	0.16	40	30	15
48	0.03	9.5	30	−9
51	0.32	11.5	10	−5
cetirizine	0.51	5	3	13
loratadine	0.75	12.9	10	30

[a] Histamine-induced cutaneous vascular permeability model. [b] Data are indicated as ED_{50} (mg/kg, po). [c] Data are indicated as maximal dose without effect (mg/kg, iv). [d] Doses tested: 3, 10, and 30 mg/kg (iv). [e] Data correspond to the incubation performed with 25 μM compound concentration and without 15 min of preincubation.

5-Bromo-3-piperidin-4-yl-1*H*-indole (57e). ^{1}H NMR (DMSO-d_6, 200 MHz, δ[ppm]) 1.80−2.10 (m, 4H), 2.90−3.20 (m, 5H), 7.15−7.21 (m, 2H), 7.27−7.30 (m, 1H), 7.85 (s, 1H), 11.18 (s, 1H).

7-Bromo-3-piperidin-4-yl-1*H*-indole (57f). ^{1}H NMR (DMSO-d_6, 200 MHz, δ[ppm]) 1.55−1.61 (m, 2H) 1.82−1.95 (m, 2H), 2.55−2.67 (m, 2H), 2.78−2.90 (m, 2H), 2.92−3.15 (m, 2H), 6.88−6.95 (m, 2H), 7.10 (s, 1H), 7.30−7.35 (m, 1H), 7.56−7.64 (m, 1H).

7-Methyl-3-piperidin-4-yl-1*H*-indole (57g). ^{1}H NMR (DMSO-d_6, 200 MHz, δ[ppm]) 1.52−1.66 (m, 2H), 1.83−1.90 (m, 2H), 2.42 (s, 3H), 2.52−2.71 (m, 2H), 2.74−2.89 (m, 1H), 2.99−3.95 (m, 2H), 6.84−6.87 (m, 2H), 7.03−7.04 (m, 1H), 7.35−7.40 (m, 1H), 10.72 (s, 1H).

3-Piperidin-4-yl-6-trifluoromethyl-1*H*-indole (57h). ^{1}H NMR (DMSO-d_6, 200 MHz, δ[ppm]) 1.60−1.72 (m, 2H), 1.87−1.90 (m, 2H), 2.58−3.15 (m, 5H), 7.22−7.26 (d, J = 7.8 Hz, 1H), 7.35 (s, 1H), 7.68 (s, 1H), 7.75−7.80 (d, J = 8.2 Hz, 1H), 11.30 (s, 1 H).

General Procedure for the Parallel Preparation of Compounds 1−40. 2-(2-{4-[1-(2-Ethoxyethyl)-1*H*-indol-3-yl]piperidin-1-yl}ethoxy)benzoic Acid (1). 2-(2-Chloroethoxy)benzoic acid methyl ester (0.22 g, 0.50 mmol) was added to a mixture of **57a** (0.10 g, 0.50 mmol), potassium carbonate (0.08 g, 0.60 mmol) and potassium iodide (0.04 g, 0.20 mmol) in isobutylmethyl ketone (1.5 mL) under nitrogen atmosphere. The mixture was heated at 90 °C for 18 h. After cooling to room temperature, dichloromethane (1.5 mL) and polystyrene methylisocyanate (0.08 g, 0.10 mmol) were added, and the mixture was stirred at room temperature for 3 h. After filtration, the solution was placed directly on a 500 mg Varian SCX ion exchange column. The column was washed with methanol (5 mL), and the product was eluted with 20:1 methanol/ammonia mixture (5 mL). The solvent was removed under reduced pressure affording 0.11 g (60% yield) of **59a**.

A 60% dispersion of NaH in mineral oil (0.016 g, 0.36 mmol) was added to a solution of **59a** (0.080 g, 0.2 mmol) in anhydrous dimethylformamide (1 mL) under nitrogen atmosphere. After stirring at room temperature for 30 min, ethoxyethyl bromide (0.060 g, 0.320 mmol) was added. The crude mixture was stirred at room temperature for 15 h. The solvent was removed under reduced pressure, and ethanol (1 mL) was added. Aqueous NaOH (2 M, 0.20 mL) was added, and the crude mixture was stirred at room temperature for 16 h. The crude mixture was neutralized with a aqueous HCl (2 N, 0.2 mL) and the solvent was removed at reduced pressure. The mixture was purified using a 500 mg Varian C18 chromatography column affording 0.041 g (45% yield) of compound **1**.

General Procedure for Preparation of Intermediates 60. 4-(1*H*-Indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (60a). 57a (10.0 g, 50.0 mmol) was dissolved in dichloromethane (100 mL), and triethylamine (7.7 mL, 55.0 mmol) was added. Once cooled in an ice-bath, a solution of ethyl chloroformate (5.5 mL, 55.0 mmol) in dichloromethane (3 mL) was added dropwise. After 1 h of stirring at 0 °C, the reaction mixture was washed with water. The organic phase was dried over magnesium sulfate and filtered and the solvent removed under reduced pressure. The final product (12.7 g, 93% yield) was precipitated with a mixture of hexane/ethyl ether 5:1. Melting point: 101−104 °C. ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.3 (t, 3H), 1.7 (qd, 2H), 2.1 (m, 2H), 2.8−3.1 (m, 3H), 4.2 (q, 2H), 4.3 (m, 2H), 6.9 (s, 1H), 7.0−7.3 (m, 2H), 7.4 (d, 1H), 7.7 (d, 1H), 8.1 (bs, 1H).

4-(5-Methoxy-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (60b). Compound **60b** was synthesized in a fashion analogous to that of compound **60a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.20−1.24 (t, 3H), 1.56−1.72 (m, 2H), 1.98−2.12 (m, 2H), 2.80−3.08 (m, 3H), 3.80 (s, 3H), 4.15−4.40 (m, 4H), 6.80−6.95 (m, 2H), 7.05 (s, 1H), 7.20−7.28 (m, 1H), 8.17 (s, 1H).

4-(6-Fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (60c). Compound **60c** was synthesized in a fashion analogous to that of compound **60a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 0.95 (t, 3H), 1.3 (m, 6H), 1.5−1.8 (m, 4H), 1.9 (m, 1H), 2.0 (s, 1H), 2.9 (t, 2H), 3.9 (t, 2H), 4.1 (q, 2H), 4.2 (m, 2H), 6.7 (s, 1H), 6.7−6.9 (m, 2H), 7.5 (m, 1H).

General Procedure for Preparation of Intermediates 61. 4-[1-(2-Ethoxyethyl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid Ethyl Ester (61a). 60a (4.9 g, 18.0 mmol) was dissolved in dimethylformamide (60 mL), and a dispersion of 60% NaH in mineral oil (0.9 g, 23.0 mmol) was added in portions at room temperature. After 30 min of stirring, 1-bromo-2-ethoxyethane (2.48 mL, 20.0 mmol) was added dropwise. The reaction mixture was heated at 60 °C for 1 h. The solvent was removed under reduced pressure and the residue suspended in water and extracted with ethyl acetate. The organic phase was washed successively with water and brine, dried over magnesium sulfate, filtered and evaporated to dryness to provide 6.2 g (100% yield) of the final product as a semisolid, pure enough to perform the next synthetic step. ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.1 (t, 3H), 1.3 (t, 3H), 1.7 (qd, 2H), 2.1 (m, 2H), 2.8−3.1 (m, 3H), 3.4 (q, 2H), 3.7 (t, 2H), 4.2 (q, 2H), 4.3 (m, 4H), 6.9 (s, 1H), 7.0−7.3 (m, 2H), 7.35 (d, 1H), 7.6 (d, 1H).

4-[1-(2-Methoxyethyl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid Ethyl Ester (61b). Compound **61b** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.20−1.40 (m, 5H), 1.50−1.80 (m, 2H), 2.80−3.10 (m, 3H), 3.35 (s, 3H), 3.65 (t, 2H), 4.05−4.38 (m, 6H), 6.89 (s, 1H), 7.00−7.38 (m, 3H), 7.57−7.63 (m, 1H).

4-(1-Butyl-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (61c). Compound **61c** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 0.95 (t, 3H), 1.3 (m, 6H), 1.5−1.8 (m, 4H), 1.9 (m, 1H), 2.0 (s, 1H), 2.9 (t, 2H), 3.9 (t, 2H), 4.1 (q, 2H), 4.2 (m, 2H), 6.9 (s, 1H), 7.0−7.3 (m, 2H), 7.4 (d, 1H), 7.7 (d, 1H).

4-(1-Cyclopropylmethyl-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (61d). Compound **61d** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 0.30−0.40 (m, 2H), 0.55−0.75 (m, 2H), 0.80−0.95 (m, 1H), 1.25 (t, 3H), 1.60−1.78 (m, 2H),

2.00−2.10 (m, 2H), 2.85−3.09 (m, 3H), 3.90 (d, 2H), 4.19 (q, 2H), 4.20−4.30 (m, 2H), 6.90 (s, 1H), 7.10−7.39 (m, 3H), 7.63 (d, 1H).

4-(1-Furan-2-ylmethyl-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (61e). Compound **61e** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.20−1.24 (t, 3H), 1.55−1.74 (m, 2H), 1.98−2.14 (m, 2H), 2.80−3.06 (m, 3H), 4.10−4.37 (m, 4H), 5.20 (s, 2H), 6.20−6.38 (m, 2H), 6.89 (s, 1H), 7.14−7.43 (m, 2H), 7.36−7.42 (m, 2H), 7.60−7.72 (m, 1H).

4-(1-Thiophen-2-ylmethyl-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (61f). Compound **61f** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.20−1.23 (t, 3H), 1.56−1.78 (m, 2H), 1.96−2.10 (m, 2H), 2.80−3.05 (m, 3H), 4.06−4.40 (m, 4H), 5.40 (s, 2H), 6.83−6.94 (m, 3H), 7.10−7.20 (m, 3H), 7.35−7.39 (m, 1H), 7.58−7.64 (m, 1H).

4-[1-(5-Chlorothiophen-2-ylmethyl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid Ethyl Ester (61g). Compound **61g** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.20−1.25 (t, 3H), 1.56−1.72 (m, 2H), 1.98−2.14 (m, 2H), 2.80−3.16 (m, 3H), 4.03−4.39 (m, 4H), 5.30 (s, 2H), 6.60−6.78 (m, 2H), 7.14−7.30 (m, 3H), 7.60−7.72 (m, 1H).

4-[1-(2-Ethoxyethyl)-5-methoxy-1*H*-indol-3-yl]piperidine-1-carboxylic Acid Ethyl Ester (61h). Compound **61h** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.02−1.25 (m, 6H), 1.55−1.74 (m, 2H), 1.95−2.07 (m, 2H), 2.80−3.04 (m, 3H), 3.38−3.43 (m, 2H), 3.60−3.68 (m, 2H), 3.80 (s, 3H), 4.10−4.40 (m, 6H), 6.80−6.96 (m, 2H), 7.10 (s, 1H), 7.22−7.30 (m, 1H).

4-[6-Fluoro-1-(2-methoxyethyl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid Ethyl Ester (61i). Compound **61i** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.20−1.40 (m, 5H), 1.50−1.80 (m, 2H), 2.80−3.10 (m, 3H), 3.35 (s, 3H), 3.65 (t, 2H), 4.05−4.38 (m, 6H), 6.77−6.83 (m, 2H), 6.90−7.07 (m, 1H), 7.43−7.55 (m, 1H).

4-(1-Butyl-6-fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (61j). Compound **61j** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 0.95 (t, 3H), 1.3 (m, 6H), 1.5−1.8 (m, 4H), 1.9 (m, 1H), 2.0 (s, 1H), 2.9 (t, 2H), 3.9 (t, 2H), 4.1 (q, 2H), 4.2 (m, 2H), 6.7 (s, 1H), 6.7−6.9 (m, 2H), 7.5 (m, 1H).

4-(1-Cyclopropylmethyl-6-fluoro-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (61k). Compound **61k** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 0.30−0.40 (m, 2H), 0.55−0.75 (m, 2H), 0.80−0.95 (m, 1H), 1.25 (t, 3H), 1.60−1.78 (m, 2H), 2.00−2.10 (m, 2H), 2.85−3.09 (m, 3H), 3.90 (d, 2H), 4.19 (q, 2H), 4.20−4.30 (m, 2H), 6.70 (s, 1H), 6.70−6.90 (m, 2H), 7.5 (m, 1H).

4-(6-Fluoro-1-furan-2-ylmethyl-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (61l). Compound **61l** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.20 (t, 3H), 1.52−1.66 (m, 2H), 1.90−2.05 (m, 2H), 2.89−3.06 (m, 3H), 4.12−4.37 (m, 4H), 5.10 (s, 2H), 6.18−6.25 (m, 2H), 6.90−7.00 (m, 2H), 7.05−7.12 (m, 1H), 7.35 (s, 1H), 7.45−7.58 (m, 1H).

4-(6-Fluoro-1-thiophen-2-ylmethyl-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (61m). Compound **61m** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.20−1.32 (t, 3H), 1.56−1.78 (m, 2H), 1.96−2.12 (d, 2H), 2.78−3.06 (m, 3H), 4.12−4.39 (m, 4H), 5.30 (s, 2H), 6.73−7.03 (m, 5H), 7.20−7.24 (m, 1H), 7.40−7.46 (m, 1H).

4-[1-(5-Chlorothiophen-2-ylmethyl)-6-fluoro-1*H*-indol-3-yl]piperidine-1-carboxylic Acid Ethyl Ester (61n). Compound **61n** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.18−1.24 (t, 3H), 1.40−1.56 (m, 2H), 1.95−2.08 (m, 2H), 2.76−3.05 (m, 3H), 4.12−4.38 (m, 4H), 5.20 (s, 2H), 6.60−6.97 (m, 5H), 7.43−7.56 (m, 1H).

4-(6-Fluoro-1-furan-3-ylmethyl-1*H*-indol-3-yl)piperidine-1-carboxylic Acid Ethyl Ester (61o). Compound **61o** was synthesized in a fashion analogous to that of compound **61a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.20−1.23 (t, 3H), 1.51−1.76 (m, 2H), 1.95−2.08 (m, 2H), 2.79−3.08 (m, 3H), 4.07−4.38 (m, 4H), 5.00 (s, 2H), 6.20 (s, 1H), 6.79−7.00 (m, 3H), 7.23−7.39 (m, 2H), 7.54−7.59 (m, 2H).

General Procedure for Preparation of Intermediates 62. 1-(2-Ethoxyethyl)-3-piperidin-4-yl-1*H*-indole (62a). **61a** (6.2 g, 18.0 mmol) was dissolved in a 2-propanol (120 mL), and potassium hydroxide (12.0 g, 0.18 mol) was added. The reaction mixture was refluxed for18 h. The solvent was removed under reduced pressure, and ice−water was added to the residue. Concentrated hydrochloric acid was added dropwise with stirring until acidic pH value. Then sodium hydroxide (8 N) was added dropwise until basic pH value. After 30 min of stirring under these conditions, the mixture was extracted with dichloromethane, washed successively with water and brine, dried over magnesium sulfate, filtered and evaporated to dryness. 4.8 g (97%) of the desired final product was obtained as a yellowish oil. ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.2 (t, 3H), 1.7 (qd, 2H), 2.1 (m, 4H), 2.9 (t, 2H), 3.0 (tt, 1H), 3.2 (m, 2H), 3.4 (q, 2H), 3.7 (t, 2H), 4.3 (t, 2H) 6.9 (s, 1H), 7.0−7.4 (m, 3H), 7.7 (d, 1H).

1-(2-Methoxyethyl)-3-piperidin-4-yl-1*H*-indole (62b). Compound **62b** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.55−2.15 (m, 5H), 2.78−3.05 (m, 3H), 3.10−3.24 (m, 2H), 3.30 (s, 3H), 3.64−3.78 (m, 2H), 4.19−4.33 (m, 2H), 6.89 (s, 1H), 7.00−7.38 (m, 3H), 7.57−7.63 (m, 1H).

1-Butyl-3-piperidin-4-yl-1*H*-indole (62c). Compound **62c** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 0.9 (t, 3H), 1.2−1.4 (m, 2H), 1.5−1.9 (m, 3H), 1.9 (m, 1H), 2.0 (s, 1H), 2.6−2.9 (m, 3H), 3.1−3.2 (m, 2H), 3.9 (t, 2H), 4.1 (q, 2H), 6.9 (s, 1H), 7.0−7.3 (m, 2H), 7.4 (d, 1H), 7.7 (d, 1H).

1-Cyclopropylmethyl-3-piperidin-4-yl-1*H*-indole (62d). Compound **62d** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 0.30−0.40 (m, 2H), 0.55−0.65 (m, 2H), 0.80−0.93 (m, 1H), 1.60−1.75 (m, 2H), 2.00−2.13 (m, 2H), 2.78−2.88 (t, 2H), 2.90−3.12 (m, 1H), 3.16−3.24 (m, 2H), 3.86−3.98 (d, 2H), 6.99 (s, 1H), 7.11−7.39 (m, 3H), 7.65 (d, 1H).

1-Furan-2-ylmethyl-3-piperidin-4-yl-1*H*-indole (62e). Compound **62e** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.60−1.81 (m, 2H), 1.92−2.10 (m, 3H), 2.76−2.98 (m, 3H), 3.20 (d, 2H), 5.20 (s, 2H), 6.20−6.38 (m, 2H), 6.89 (s, 1H), 7.14−7.43 (m, 2H), 7.36−7.42 (m, 2H), 7.60−7.72 (m, 1H).

3-Piperidin-4-yl-1-thiophen-2-ylmethyl-1*H*-indole (62f). Compound **62f** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.60−1.81 (m, 2H), 1.92−2.10 (m, 3H), 2.76−2.98 (m, 3H), 3.20 (d, 2H), 5.40 (s, 2H), 6.83−6.94 (m, 3H), 7.10−7.20 (m, 3H), 7.35−7.39 (m, 1H), 7.58−7.64 (m, 1H).

1-(5-Chlorothiophen-2-ylmethyl)-3-piperidin-4-yl-1*H*-indole (62 g). Compound **62g** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.56−1.78 (m, 2H), 1.98−2.15 (m, 2H), 2.76−3.02 (m, 3H), 3.14−3.26 (d, 2H), 5.30 (s, 2H), 6.60−6.78 (m, 2H), 7.14−7.30 (m, 3H), 7.60−7.72 (m, 1H).

1-(2-Ethoxyethyl)-5-methoxy-3-piperidin-4-yl-1*H*-indole (62h). Compound **62h** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.05−1.20 (t, 3H), 1.57−2.05 (m, 5H), 2.75−2.88 (m, 3H), 3.17−3.22 (m, 2H), 3.38−3.50 (m, 2H), 3.62−3.72 (m, 2H), 3.80 (s, 3H), 4.16−4.25 (m, 2H), 6.80−6.96 (m, 2H), 7.10 (s, 1H), 7.22−7.30 (m, 1H).

6-Fluoro-1-(2-methoxyethyl)-3-piperidin-4-yl-1*H*-indole (62i). Compound **62i** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.55−1.78 (m, 2H), 1.92−2.16 (m, 1H), 2.70−2.96 (m,

3H), 3.10−3.30 (m, 2H), 3.31 (s, 3H), 3.60−3.74 (t, 2H), 4.15−4.21 (t, 1H), 6.79−7.05 (m, 2H), 7.10−7.28 (m, 1H), 7.44−7.58 (m, 1H).

1-Butyl-6-fluoro-3-piperidin-4-yl-1*H*-indole (62j). Compound **62j** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 0.9 (t, 3H), 1.2−1.4 (m, 2H), 1.5−1.9 (m, 4H), 1.9 (m, 1H), 2.0 (s, 1H), 2.6−2.9 (m, 3H), 3.1−3.2 (m, 2H), 3.9 (t, 2H), 4.1 (q, 2H), 6.7−6.9 (m, 2H), 7.5 (m, 1H).

1-Cyclopropylmethyl-6-fluoro-3-piperidin-4-yl-1*H*-indole (62k). Compound **62k** was synthesized in a fashion analogous to that of compound **62a.** ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 0.30−0.40 (m, 2H), 0.55−0.65 (m, 2H), 0.80−0.93 (m, 1H), 1.60−1.75 (m, 2H), 2.00−2.13 (m, 2H), 2.78−2.88 (t, 2H), 2.90−3.12 (m, 1H), 3.16−3.24 (m, 2H), 3.86−3.98 (d, 2H), 6.70 (s, 1H), 6.70−6.90 (m, 2H), 7.5 (m, 1H).

6-Fluoro-1-furan-2-ylmethyl-3-piperidin-4-yl-1*H*-indole (62l). Compound **62l** was synthesized in a fashion analogous to that of compound **62a**. ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.57−1.64 (m, 2H), 1.92−2.17 (m, 3H), 2.62−2.85 (m, 3H), 3.06−3.20 (m, 2H), 5.10 (s, 2H), 6.18−6.25 (m, 2H), 6.90−7.00 (m, 2H), 7.05−7.12 (m, 1H), 7.35 (s, 1H), 7.45−7.58 (m, 1H).

6-Fluoro-3-piperidin-4-yl-1-thiophen-2-ylmethyl-1*H*-indole (62m). Compound **62m** was synthesized in a fashion analogous to that of compound **62a**. ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.56−1.78 (m, 2H), 1.98−2.10 (m, 2H), 2.72−3.02 (m, 4H), 3.18−3.29 (m, 2H), 5.30 (s, 2H), 6.78−7.08 (m, 5H), 7.20−7.28 (m, 1H), 7.51−7.60 (m, 1H).

1-(5-Chlorothiophen-2-ylmethyl)-6-fluoro-3-piperidin-4-yl-1*H*-indole (62n). Compound **62n** was synthesized in a fashion analogous to that of compound **62a**. ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.56−1.78 (m, 2H), 1.98−2.10 (m, 2H), 2.72−3.02 (m, 4H), 3.18−3.29 (m, 2H), 5.20 (s, 2H), 6.60−6.97 (m, 5H), 7.43−7.56 (m, 1H).

6-Fluoro-1-furan-3-ylmethyl-3-piperidin-4-yl-1*H*-indole (62o). Compound **62o** was synthesized in a fashion analogous to that of compound **62a**. ^{1}H NMR ($CDCl_3$, 200 MHz, δ[ppm]) 1.55−1.72 (m, 2H), 1.93−2.10 (m, 2H), 2.62−2.90 (m, 3H), 3.15−3.22 (m, 2H), 5.00 (s, 2H), 6.20 (s, 1H), 6.79−7.00 (m, 3H), 7.23−7.39 (m, 2H), 7.54−7.59 (m, 2H).

General Procedure for Preparation of Compounds 1−53 for Confirmation of Structure. 2-(2-{4-[1-(2-Ethoxyethyl)-1*H*-indol-3-yl]piperidin-1-yl}ethoxy)-4-methoxybenzoic Acid (13). To a solution of **62a** (1.94 g, 7.13 mmol) in methylisobutyl ketone (35 mL) were added triethylamine (2.10 mL, 12.12 mmol), 2-(2-chloroethoxy)-4-methoxybenzoic acid methyl ester (2.26 g, 9.72 mmol) and potassium iodide (0.12 g, 0.7 mmol). The crude mixture was heated at 90 °C for 15 h. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic phase was dried over sodium sulfate and filtered and the solvent evaporated to afford 4 g of a crude mixture which was used without further purification in the next synthetic step. The crude material was dissolved in ethanol (20 mL) and aqueous NaOH (2 N, 7.13 mL) was added. After stirring for 24 h at room temperature, the solvent was removed at reduced temperature, and water (20 mL) was added. The solution was neutralized with aqueous hydrochloric acid (6 N) and extracted with chloroform. The organic phase was dried over sodium sulfate and filtered and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography over silica gel affording 1.4 g (42%) of **13**. Melting point: 66.6−67.9 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, δ[ppm]) 1.14−1.18 (t, J = 7.0 Hz, 3H), 1.88−2.09 (m, 4H), 2.31−2.39 (m, 2H), 2.82−2.86 (m, 3H), 3.09−3.13 (d, J = 11.3 Hz, 2H), 3.42−3.49 (q, J = 7.0, 2H), 3.71−3.75 (t, J = 6.1 Hz, 2H), 3.84 (s, 3H), 4.22−4.26 (t, J = 6.1 Hz, 2H), 4.35−4.39 (t, J = 5.2 Hz, 2H), 6.54−6.55 (m, 1H), 6.61−6.65 (dd, J = 8.9 Hz, J = 2.1 Hz, 1H), 6.97 (s, 1H), 7.05−7.10 (t, J = 7.5 Hz, 1H), 7.16−7.21 (t, J = 7.6 Hz, 1H), 7.33−7.35 (d, J = 8.2 Hz, 1H), 7.57−7.60 (d, J = 8.0 Hz, 1H), 7.93−7.96 (d, J = 8.6 Hz, 1H). Anal. ($C_{27}H_{34}N_2O_5$) C, H, N.

2-(2-{4-[1-(2-Ethoxyethyl)-5-methoxy-1*H*-indol-3-yl]piperidin-1-yl}ethoxy)benzoic Acid (2). Compound **2** was synthesized in a fashion analogous to that of compound **13**. Melting point: 156.1−159.2 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.02−1.07 (t, J = 7.0 Hz, 3H), 1.86−2.09 (m, 4H), 2.62−2.71 (m, 2H), 2.82−2.94 (m, 1H), 2.96−2.99 (m, 2H), 3.22−3.26 (m, 2H), 3.34−3.41 (q, J = 7.0 Hz, 2H), 3.62−3.65 (t, J = 5.34 Hz, 2H), 3.80 (s, 3H), 4.19−4.23 (t, J = 6.6 Hz, 2H), 4.44−4.47 (m, 2H), 6.73−6.76 (dd, J = 8.9 Hz, 2.1 Hz, 1H), 6.99−7.04 (t, J = 7.5 HZ, 1H), 7.09 (s, 1H), 7.14−7.15 (m, 1H), 7.22−7.25 (m, 1H), 7.32−7.41 (m, 2H), 7.50−7.53 (dd, J = 7.5 Hz, J = 1.4 Hz, 1H). Anal. ($C_{27}H_{34}N_2O_5$) C, H, N.

2-(2-{4-[6-Fluoro-1-(2-methoxyethyl)-1*H*-indol-3-yl]piperidin-1-yl}ethoxy)benzoic Acid (15). Compound **15** was synthesized in a fashion analogous to that of compound **13.** Melting point: 119.6.-120.1 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.89−1.96 (m, 4H), 2.60−2.66 (m, 3H), 2.87−3.10 (m, 4H), 3.22 (s, 3H), 3.60−3.64 (t, J = 5.2 Hz, 2H), 4.23−4.26 (t, J = 5.1 Hz, 2H), 4.39−4.46 (m, 2H), 6.81−6.88 (m, 1H), 6.99−7.04 (t, J = 7.3 Hz, 1H), 7.13 (s, 1H), 7.20−7.40 (m, 3H), 7.5−7.54 (m, 1H), 7.62−7.67 (dd, J = 8.6 Hz, J = 5.5 Hz, 1H). Anal. ($C_{25}H_{29}FN_2O_4$) C, H, N.

2-{2-[4-(1-Butyl-1*H*-indol-3-yl)piperidin-1-yl]ethoxy}benzoic Acid (16). Compound **16** was synthesized in a fashion analogous to that of compound **13.** Melting point: 158.7−159.9 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 0.87−0.90 (t, J = 7.2 Hz, 3H), 1.21−1.31 (m, 2H), 1.67−1.76 (m, 2H), 1.87−2.02 (m, 4H), 2.60−2.67 (m, 2H), 2.85−2.97 (m, 3H), 3.20−3.23 (d, J = 12.1 Hz, 2H), 4.09−4.13 (t, J = 7.0 Hz, 2H), 4.42−4.45 (t, J = 5.3 Hz, 2H), 6.96−7.03 (m, 2H), 7.09−7.13 (m, 1H), 7.22−7.24 (d, J = 8.2 Hz, 1H), 7.37−7.42 (m, 2H), 7.52−7.55 (m, 1H), 7.63−7.65 (d, J = 7.8 Hz, 1H). Anal. ($C_{26}H_{32}N_2O_3$) C, H, N.

2-{2-[4-(1-Cyclopropylmethyl-1*H*-indol-3-yl)piperidin-1-yl]ethoxy}benzoic Acid (17). Compound **17** was synthesized in a fashion analogous to that of compound **13.** Melting point: 158.6−160.3 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 0.32−0.39 (m, 2H), 0.47−0.53 (m, 2H), 1.10−1.31 (m, 1H), 1.85−2.05 (m, 4H), 2.60−2.69 (m, 2H), 2.85−2.98 (3H), 3.20−3.24 (d, J = 11.6 Hz, 2H), 3.97−4.00 (d, J = 7.0 Hz, 2H), 4.42−4.45 (t, J = 4.9 Hz, 2H), 6.97−7.04 (m, 2H), 7.09−7.14 (m, 1H), 7.20−7.24 (m, 2H), 7.36−7.41 (m, 1H), 7.44−7.47 (d, J = 7.9 Hz, 1H), 7.52−7.55 (dd, J = 7.6 Hz, J = 1.8 Hz, 1H), 7.64−7.67 (d, J = 7.9 Hz, 1H). Anal. ($C_{26}H_{30}N_2O_3$) C, H, N

2-{2-[4-(1-Cyclopropylmethyl-6-fluoro-1*H*-indol-3-yl)piperidin-1-yl]ethoxy}benzoic Acid (18). Compound **18** was synthesized in a fashion analogous to that of compound **13.** Melting point: 97 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 0.33−0.35 (m, 2H), 0.54−0.67 (m, 2H), 1.20−1.25 (m, 1H), 1.98−2.01 (m, 4H), 2.32−2.41 (m, 2H), 2.82−2.85 (m, 3H), 3.13−3.17 (d, 2H), 3.84−3.86 (m, 2H), 4.41−4.45 (m, 2H), 6.80−6.87 (m, 2H), 6.99−7.12 (m, 4H), 7.41−7.50 (m, 2H), 7.89−7.93 (dd, 1H).

2-{2-[4-(1-Allyl-1*H*-indol-3-yl)piperidin-1-yl]ethoxy}benzoic Acid (19). Compound **19** was synthesized in a fashion analogous to that of compound **13**. Melting point: 123.1−125.3 °C. ^{1}H NMR (Cl_3CD, 300 MHz, δ[ppm]) 1.96−2.03 (m, 4H), 2.33−2.41 (m, 2H), 2.82−2.91 (m, 3H), 3.13 (d, 2H), 4.40−4.44 (m, 2H), 4.66−4.68 (m,2H), 5.08−5.22 (m, 2H), 5.91−6.04 (m, 1H); 6.10 (bs, 1H), 6.92 (s, 1H), 7.04−7.11 (m. 3H), 7.18 (t, 1H), 7.21−7.31 (m, 1H), 7.41 (t, 1H), 7.57 (d, 1H), 7.89 (d, 1H).

2-(2-{4-[1-(2-[1,3]Dioxolan-2-yl-ethyl)-1*H*-indol-3-yl]piperidin-1-yl}ethoxy)benzoic Acid (20). ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.85−2.10 (m, 6H), 2.59−2.72 (m, 2H), 2.84−3.01 (m, 3H), 3.20−3.24 (m, 2H), 3.76−3.81 (m, 2H), 3.91−3.96 (m, 2H), 4.18−4,23 (t, J = 7.2 Hz, 2H), 4.39−4.49 (m, 2H), 4.77−4.80 (t, J = 4.6 Hz, 2H), 6.97−7.04 (m, 2H), 7.10−7.15 (m, 2H), 7.21−7.24 (d, J = 8.2 Hz, 1H), 7.26−7.40 (m, 2H), 7.52−7.54 (m, 1H), 7.64−7.67 (d, J = 7.9 Hz, 1H). Anal. ($C_{27}H_{32}N_2O_5$) C, H, N

2-{2-[4-(6-Fluoro-1-furan-2-ylmethyl-1*H*-indol-3-yl)piperidin-1-yl]ethoxy}benzoic Acid (22). Compound **22** was synthesized in a fashion analogous to that of compound **13.** Melting point: 173.5−174.5 °C. ^{1}H NMR (DMSO-d_6, 300 MHz,

δ[ppm]) 1.82−2.01 (m, 4H), 2.56−2.70 (m, 2H), 2.82−2.97 (m, 3H), 3.19−3.23 (d, 11.9 Hz, 2H), 4.41−4.45 (t, J = 5.2 Hz, 1H), 5.34 (s, 2H), 6.39−6.41 (dd, J = 3.4 Hz, J = 1.8 HZ, 1H), 6.49−6.50 (m, 1H), 6.83−6.90 (m, 1H), 6.99−7.04 (m, 1H), 7.18−7.24 (m, 2H), 7.36−7.42 (m, 2H), 7.52−7.55 (dd, J = 7.63 Hz, J = 1.83 Hz, 1H), 7.58−7.59 (m, 1H), 7.64−7.69 (dd, J = 8.70 Hz, J = 5.34 Hz, 1H). Anal. ($C_{27}H_{27}FN_2O_4$) C, H, N.

4-{4-[1-(2-Ethoxyethyl)-1*H*-indol-3-yl]piperidin-1-ylmethyl}benzoic Acid (31). Compound **31** was synthesized in a fashion analogous to that of compound **13.** Melting point: 143.9−145.4 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.01−1.06 (m, 3H), 1.61−1.77 (m, 2H), 1.91−1.95 (m, 2H), 2.14−2.21 (t, J = 11 Hz, 2H), 2.73−2.81 (m, 1H), 2.91−2.94 (m, 2H), 3.34−3.41 (q, J = 7.0 Hz, 2H), 3.60−3.67 (m, 4H), 4.22−4.26 (t, J = 5.3 Hz, 2H), 6.95−7.00 (t, J = 7.0 Hz, 1H), 7.07−7.13 (m, 2H), 7.40−7.48 (m, 2H), 7.53−7.59 (m, 2H), 7.83−7.86 (d, J = 7.6 Hz, 1H), 7.94 (s, 1H).

3-{4-[1-(2-Ethoxyethyl)-1*H*-indol-3-yl]piperidin-1-ylmethyl}benzoic Acid (32). Compound **32** was synthesized in a fashion analogous to that of compound **13.** Melting point: °C.143.9−145.4 ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.01−1.06 (t, J = 7 Hz, 3H), 1.60−1.78 (m, 2H), 1.91−1.95 (m, 2H), 2.14−2.21 (t, J = 11 Hz, 2H), 2.70−2.83 (m, 1H), 2.91−2.94 (d, J = 11.3 Hz, 2H), 3.34−3.41 (q, J = 7 Hz, 2H), 3.60 (s, 2H), 3.63−3.67 (t, J = 5.5 Hz, 2H), 4.22−4.26 (m, 2H), 6.95−7.00 (t, J = 7.3 Hz, 1H), 7.07−7.13 (m, 2H), 7.40−7.48 (m, 2H), 7.53−7.59 (m, 2H), 7.83−7.86 (d, 7.6 Hz, 1H), 7.94 (s, 1H). Anal. ($C_{25}H_{30}N_2O_3$) C, H, N.

5-{4-[1-(2-Ethoxyethyl)-1*H*-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic Acid (36). Compound **36** was synthesized in a fashion analogous to that of compound **13.** Melting point: 232.7−233.7 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.01−1.06 (t, J = 6.9 Hz, 3H), 1.55−1.71 (m, 2H), 1.88−1.96 (m, 2H), 2.07−2.14 (m, 2H), 2.64−2.79 (m, 1H), 2.87−2.91 (m, 2H). 3.37−3.41 (m, 2H), 3.47 (s, 2H), 3.62−3.65 (t, J = 5.3 Hz, 2H), 3.80 (s, 3H), 4.19−4.23 (t, J = 5.5 Hz, 2H), 6.78−6.85 (m, 2H), 7.06−7.12 (m, 2H), 7.27−7.31 (dd, J = 10.1, J = 2.3 Hz, 1H), 7.41−7.45 (dd, J = 8.4 Hz, J = 2.3 Hz, 1H), 7.50−7.57 (m, 2H). Anal. ($C_{26}H_{32}N_2O_4$) C, H, N.

5-{4-[1-(2-Ethoxyethyl)-1*H*-indol-3-yl]piperidin-1-ylmethyl}-2-fluorobenzoic Acid (37). Compound **37** was synthesized in a fashion analogous to that of compound **13.** Melting point: 225.8−226.5 °C.^{1}H NMR (DMSO-d_6, 200 MHz, δ[ppm]) 1.0 (t, J = 7.0 Hz, 3 H) 1.7 (m, 2 H) 1.9 (m, 2 H) 2.1 (m, 2 H) 2.7 (m, 1 H) 2.9 (d, J = 10.1 Hz, 2 H) 3.3 (m, 2H) 3.4 (s, 2H) 3.7 (m, 2 H) 4.2 (m, 2 H) 7.0 (m, 1 H) 7.1 (m, 2 H) 7.4 (m, 2 H) 7.5 (m, 3 H).

2-{2-[4-(1-Butyl-6-fluoro-1*H*-indol-3-yl)piperidin-1-yl]-ethoxy}benzoic Acid (41). Compound **41** was synthesized in a fashion analogous to that of compound **13.** Melting point: 149.4−150.9 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 0.86−0.91 (t, J = 7.3 Hz, 3H), 1.18−1.32 (m, 2H), 1.62−1.75 (m, 2H), 1.83−2.03 (m, 4H), 2.61−2.69 (m, 2H), 2.83−2.99 (m, 3H), 3.20−3.24 (m, 2H), 4.05−4.10 (t, J = 6.9 Hz, 2H), 4.42−4.46 (m, 2H), 6.80−6.87 (m, 1H), 6.99−7.04 (t, J = 7.5 Hz, 1H), 7.15 (s, 1H), 7.21−7.41 (m, 3H), 7.52−7.55 (m, 1H), 7.62−7.67 (dd, J = 8.9, 5.5 Hz, 1H).

2-{2-[4-(6-Fluoro-1-furan-3-ylmethyl-1*H*-indol-3-yl)piperidin-1-yl]ethoxy}benzoic Acid (42). Compound **42** was synthesized in a fashion analogous to that of compound **13.** Melting point: 153.3−154.5 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.82−2.02 (m, 4H), 2.56−2.71 (m, 2H), 2.81−3.01 (m, 3H), 3.19−3.23 (d, J = 11.9 Hz, 2H), 4.42−4.44 (m, 2H), 5.14 (s, 2H), 6.82−6.88 (m, 1H), 6.99−7.04 (t, J = 7.5 Hz, 1H), 7.21−7.24 (m, 2H), 7.35−7.42 (m, 2H), 7.52−7.57 (m, 2H), 7.63−7.68 (dd, J = 8.7 Hz, J = 5.3 Hz, 1H), 7.75 (s, 1H).

3-{4-[6-Fluoro-1-(2-methoxyethyl)-1*H*-indol-3-yl]piperidin-1-ylmethyl}benzoic Acid (43). Compound **43** was synthesized in a fashion analogous to that of compound **13.** Melting point: 184.3−184.9 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.58−1.75 (m, 2H), 1.90−1.93 (d, J = 11 Hz, 2H), 2.13−2.20 (t, J = 11 Hz, 2H), 2.68−2.81 (m, 1H), 2.80−2.93 (d, J = 10.7 Hz, 2H), 3.21 (s, 3H), 3.60 (s, 2H), 3.61−3.63 (m, 2H), 4.20−4.24 (t, J = 5.2 Hz, 2H), 6.79−6.86 (m, 1H), 7.12 (s, 1H), 7.27−7.32 (m, 1H), 7.44−7.59 (m, 3H). 7.83−7.86 (d, J = 7.6 Hz, 1H), 7.94 (s, 1H).

3-{4-[1-(2-Ethoxyethyl)-5-methoxy-1*H*-indol-3-yl]piperidin-1-ylmethyl}benzoic Acid (44). Compound **44** was synthesized in a fashion analogous to that of compound **13.** Melting point: 139.8−141.6 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.01−1.06 (t, J = 7.0 Hz, 3H). 1.59−1.76 (m, 2H), 1.91−1.95 (m, 2H), 2.16−2.23 (t, J = 10.8 Hz, 2H), 2.66−2.81 (m, 1H), 2.92−2.95 (d, J = 11.0 Hz, 2H), 3.33−3.40 (q, J = 7.9 Hz, 2H), 3.60−3.64 (m, 4H), 3.75 (s, 3H), 4.17−4.21 (t, J = 5.5 Hz, 2H), 6.72−6.75 (dd, J = 8.7 Hz, J = 2.3 Hz, 1H), 7.00−7.01 (m, 1H), 7.08 (s, 1H), 7.30−7.33 (d, J = 8.9 Hz, 1H), 7.43−7.48 (t, J = 7.6 Hz, 1H), 7.56−7.58 (d, J = 7.6 Hz, 1H), 7.84−7.86 (d, J = 7.6 Hz, 1H), 7.95 (s, 1H).

3-[4-(1-Furan-2-ylmethyl-1*H*-indol-3-yl)piperidin-1-ylmethyl]benzoic Acid (45). Compound **45** was synthesized in a fashion analogous to that of compound **13.** Melting point: 153.9−155.1 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.57−1.76 (m, 2H), 1.87−1.98 (m, 2H), 2.12−2.19 (t, J = 10.7 Hz, 2H), 2.69−2.82 (m, 1H), 2.89−2.93 (m, 2H), 3.59 (s, 2H), 6.37−6.44 (m, 2H), 6.96−7.01 (t, J = 7.3 Hz, 1H). 7.08−7.13 (t, J = 7.3 Hz, 1H), 7.17 (s, 1H), 7.44−7.60 (m, 4H), 7.83−7.85 (m, 1H), 7.92 (s, 1H).

3-[4-(1-Thiophen-2-ylmethyl-1*H*-indol-3-yl)piperidin-1-ylmethyl]benzoic Acid (46). Compound **46** was synthesized in a fashion analogous to that of compound **13.** Melting point: 228.7−229.2 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.60−1.78 (m, 2H), 1.91−1.95 (d, J = 11.6 Hz, 2H), 2.2 (t, J = 11.0 Hz, 2H), 2.69−2.83 (m, 1H), 2.90−2.94 (d, J = 11.0 Hz, 2H), 3.60 (s, 2H), 5.52 (s, 2H), 6.93−7.01 (m, 2H), 7.08−7.13 (m, 2H), 7.24 (s, 1H), 7.36.7.38 (m, 1H), 7.42−7.57 (m, 4H), 7.84−7.86 (d, J = 7.6 Hz, 1H), 7.94 (s, 1H).

3-{4-[1-(5-Chlorothiophen-2-ylmethyl)-1*H*-indol-3-yl]-piperidin-1-ylmethyl}benzoic Acid (47). Compound **47** was synthesized in a fashion analogous to that of compound **13.** Melting point: 232.0−233.8 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.86−2.01 (m, 4H), 2.85−3.10 (m, 3H), 3.21−3.47 (m, 4H), 5.49 (s, 2H), 6.93−7.03 (m, 3H), 7.10−7.15 (t, J = 7.5 Hz, 1H), 7.25 (s, 1H), 7.50−7.66 (m, 2H), 7.84−7.87 (m, 1H), 7.99−8.01 (d, J = 7.6 Hz, 1H), 8.15 (s, 1H).

2-Methoxy-5-{4-[1-(2-methoxyethyl)-1*H*-indol-3-yl]piperidin-1-ylmethyl}benzoic Acid (48). Compound **48** was synthesized in a fashion analogous to that of compound **13.** Melting point: 241.9−242.2 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.59−1.77 (m, 2H), 1.90−1.94 (m, 2H), 2.11−2.19 (m, 2H), 2.68−2.81 (m, 1H), 2.90−2.93 (d, J = 11 Hz, 2H), 3.20 (s, 3H), 3.50 (s, 2H), 3.59−3.63 (t, J = 5.2 Hz, 2H), 3.79 (s, 3H), 4.22−4.25 (t, J = 5.3 Hz, 2H), 6.92−7.00 (m, 1H), 7.05−7.10 (m, 3H), 7.39−7.44 (m, 2H), 7.52−7.58 (m, 2H). Anal. ($C_{25}H_{30}N_2O_4$) C, H, N.

5-{4-[6-Fluoro-1-(2-methoxyethyl)-1*H*-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic Acid (49). Compound **49** was synthesized in a fashion analogous to that of compound **13**. Melting point: 244.1−245.2 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.52−1.70 (m, 2H), 1.87−1.92 (m, 2H), 2.05−2.14 (m, 2H), 2.65−2.77 (m, 1H), 2.86−2.90 (m, 2H), 3.19 (s, 3H), 3.46 (s, 2H), 3.58−3.61 (t, J = 5.2 Hz, 2H), 3.79 (s, 3H), 4.19−4.22 (t, J = 5.3 Hz, 2H), 6.77−6.84 (m, 1H), 7.05−7.10 (m, 2H), 7.25−7.30 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H), 7.40−7.44 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H), 7.49−7.53 (dd, J = 8.7 Hz, J = 5.3 Hz, 1H), 7.56−7.57 (d, J = 2.1 Hz, 1H). Anal. ($C_{25}H_{29}FN_2O_4$) C, H, N.

5-[4-(6-Fluoro-1-furan-3-ylmethyl-1*H*-indol-3-yl)piperidin-1-ylmethyl]-2-methoxybenzoic Acid (50). Compound **50** was synthesized in a fashion analogous to that of compound **13.** Melting point: 249.7−252.4 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.55−1.67 (m, 2H), 1.86−2.96 (m, 2H), 2.07−2.22 (m, 2H), 2.67−2.81 (m, 1H), 2.90−2.94 (m, 2H), 3.51 (s, 2H), 3.81 (s, 3H), 5.11 (s, 2H), 6.40 (s, 1H), 6.78−6.88 (m, 1H), 7.07−7.10 (d, J = 8.5 Hz, 1H), 7.21 (s, 1H), 7.36−7.46 (m, 3H), 7.50−7.59 (m, 3H), 7.72 (s, 1H).

2-Methoxy-5-[4-(1-thiophen-2-ylmethyl-1*H*-indol-3-yl)-piperidin-1-ylmethyl]benzoic Acid (51). Compound **51** was synthesized in a fashion analogous to that of compound **13.**

Melting point: 241.8−242.9 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.59−1.73 (m, 2H), 1.91−1.95 (m, 2H), 2.09−2.17 (t, J = 11.0 Hz, 2H), 2.72−2.80 (m, 1H), 2.89−2.92 (d, J = 11.0 Hz, 2H), 3.49 (s, 2H), 3.80 (s, 3H), 5.62 (s, 2H), 6.93−7.01 (m, 2H), 7.06−7.12 (m, 3H), 7.23 (s, 1H), 7.36−7.38 (dd, J = 5.2 Hz, J = 1.2 Hz, 1H), 7.42−7.46 (dd, J = 8.4 Hz, J = 2.3 Hz, 1H), 7.48−7.58 (m, 3H). Anal. ($C_{27}H_{28}N_2O_3S$) C, H, N, S.

5-[4-(6-Fluoro-1-thiophen-2-ylmethyl-1*H*-indol-3-yl)piperidin-1-ylmethyl]-2-methoxybenzoic Acid (52). Compound **52** was synthesized in a fashion analogous to that of compound **13.** Melting point: 244.8−246.4 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.59−1.70 (m, 2H), 1.89−1.93 (m, 2H), 2.10−2.18 (t, J = 11 Hz, 2H), 2.71−2.78 (m, 1H), 2.89−2.93 (d, J = 11.3 Hz, 2H), 3.50 (s, 2H), 3.80 (s, 3H), 5.50 (s, 2H), 6.80−6.87 (m, 1H), 6.94−6.96 (dd, J = 8.7 Hz, J = 5.0 Hz, 1H), 7.06−7.13 (m, 2H), 7.23 (s, 1H), 7.36−7.45 (m, 3H), 7.52−7.58 (m, 2H). Anal. ($C_{27}H_{27}FN_2O_3S$) C, H, N, S.

5-{4-[1-(5-Chlorothiophen-2-ylmethyl)-6-fluoro-1*H*-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic Acid (53). Compound **53** was synthesized in a fashion analogous to that of compound **13.** Melting point: 232.5−233.4 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ[ppm]) 1.62−1.73 (m, 2H), 1.90−1.94 (m, 2H), 2.15−2.22 (t, J = 10.7 Hz, 2H), 2.72−2.80 (m, 1H), 2.92−2.95 (d, J = 10.7 Hz, 2H), 3.53 (s, 2H), 3.80 (s, 3H), 5.45 (s, 2H), 6.83−6.89 (m, 1H), 6.95−7.08 (m, 3H), 7.24 (s, 1H), 7.39−7.43 (m, 2H), 7.54−7.59 (m, 2H). Anal. ($C_{27}H_{26}ClFN_2O_3S$) C, H, N, S.

Biology. In Vitro Assays: Preparation of Compound Solutions. Stock solutions (10^{-2} M) of the tested compounds were prepared in 100% DMSO. Further dilutions were performed in 50% DMSO.

The specific radioligand binding to the receptors is defined as the difference between the total binding and nonspecific binding determined in the presence of an excess of unlabeled ligand.

Histamine H_1 Receptor Binding Assay. Binding to the histamine H_1 receptors was performed in guinea pig cerebellum membranes as described by Chang et al.[14] Briefly, the membrane suspensions (160 μg/mL) were incubated at 30 °C with 0.7 nM [^{3}H]-mepyramine and different concentrations of the test compounds in a final volume of 0.5 mL. Binding reactions were terminated by filtration after 30 min of incubation, and the bound radioactivity was determined. Nonspecific binding was measured in the presence of 10 μM of promethazine. The affinity of each compound to the receptor was determined by using at least six different concentrations run in duplicate. IC_{50} values were obtained by nonlinear regression by use of SAS on a DEC AXP computer.

5-HT_2 Receptor Binding Assay. Binding of [^{3}H]-ketanserine to 5-HT_2 receptors in human cortex membranes was measured according to Pazos et al.[15] Assays were carried out at 37 °C in tubes containing an aliquot of cortex membranes (170 μg of protein per mL) in incubation buffer (50 mM Tris-HCl, pH 7.7) with 1 nM [^{3}H]-ketanserine in a final volume of 1 mL. Nonspecific binding was defined in the presence of 10 μM mianserine. Binding reactions were terminated after 30 min of incubation by filtration, and the bound radioactivity was determined. The affinity of each compound to the receptor was determined by using at least six different concentrations run in duplicate. IC_{50} values were obtained by nonlinear regression by use of SAS on a DEC AXP computer.

Alpha-1 Receptor Binding Assay. Binding of [^{3}H]-prazosin to alpha-1 receptors in rat brain membranes was measured according to Greengrass et al.[16] Assays were carried out at room temperature in 96-well plates containing an aliquot of brain membranes (340 μg of protein per mL) in incubation buffer (50 mM Tris-HCl, pH 7.7) with 0.25 nM [^{3}H]-prazosin in a final volume of 0.25 mL. Nonspecific binding was defined in the presence of 100 μM prazosin. Binding reactions were terminated after 60 min of incubation by filtration, and the bound radioactivity was determined. The affinity of each compound to the receptor was determined by using at least six different concentrations run in duplicate. IC_{50} values were obtained by nonlinear regression by use of SAS on a DEC AXP computer.

In Vivo Assays: General Procedures. The animals were fasted from the 16 h prior to the experiments, with water ad libitum. Test compounds were dissolved in a solution containing 0.5% methylcellulose and 0.1% Tween 80 in distilled water and administered in a volume of 10 mL/kg. All the experimental protocols used in this paper have been approved by the appropriate animal ethics committees.

Histamine-Induced Cutaneous Vascular Permeability in Rats. Determination of Compound's Duration of Action. Overnight starved male Wistar rats weighing between 150 and 175 g were used. One, 4, 8 or 24 h after the oral administration of the test compounds, the animals (n = 5 per condition) were slightly anaesthetised with ethyl ether in order to shave the back and carry out four intradermal injections of 5 μg of histamine administered in a volume of 0.05 mL (100 μg/mL of histamine were dissolved in 0.9% saline solution). 0.5 mL of a solution of 0.5% Evans Blue dissolved in 0.9% saline solution was immediately inoculated via the caudal vein. All the animals were sacrificed by cervical dislocation 1 h after administration of histamine. The surface skin containing the four papules caused by the histamine was then sectioned. The papules were evaluated by taking two measurements corresponding to the maximum and minimum diameters of the papule and applying the formula for calculating the area of an ellipse. Results were calculated as the inhibitory effect of each drug on the area of the papule caused by intradermal injection of histamine.[17]

H_1 ex Vivo Binding Assay in Mice. The objective of this assay was to evaluate the capacity of the compounds to cross the blood−brain barrier. The assay was performed essentially as described by Leysen et al.[18] with the following modifications. Overnight starved male Swiss albino mice (20−25 g) were treated orally with different doses of the test compounds, 90 min later they were killed, and the whole brain was dissected out and homogenized in 10 mL of ice-cold 0.05 M Na^+/K^+ phosphate buffer (pH 7.4). One mL aliquot of the homogenate was incubated, per triplicate, with 0.1 mL [^{3}H]-mepyramine (2 nM final concentration, 27 Ci/mmol, Amersham) during 40 min at 30 °C. The [^{3}H]-mepyramine bound to the membranes was determined by immediately filtration of the homogenates under vacuum onto the glass fiber filters (Whatman GF/B), followed by three rapid rinses with 5 mL of cold buffer containing 10 μM cold mepyramine. The radioactivity bound in the filters was determined by liquid scintillation spectrometry. The nonspecific binding was determined by treating the animals with 30 mg/kg po D-chlorpheniramine maleate. Mice treated with vehicle (methylcellulose 0.5% and tween 0.1%) were used to determine the total binding. Three animals were used for each tested dose.

Measurement of Electrocardiographic (EGC; Especially QT Interval Prolongation) Effects in Guinea Pigs. Male Dunkin-Hartley guinea pigs weighing between 500 and 600 g were anesthetised with urethane at the dose of 1.5 g/kg. The trachea was cannulated and connected to a respiration pump (Ugo Basile model 7025, tidal volume 10 mL/kg, frecuency 60 cycles/min). The left jugular vein was cannulated to administer the drugs. Surface electrodes were implanted to pick up the ECG signal which was recorded in a Hewlett-Packard cardiograph. Readings of the ECG were taken every 15 min during the stabilization period, which was no less than 30 min. The drugs were administered by intravenous perfusion for 3 min. ECG records were taken on completion of perfusion and at 15, 30, 45 and 60 min after administration of three different doses: 3, 10 and 30 mg/kg (iv). The control animals received vehicle only. The increase in the QTc interval was corrected for the heart rate according to Bazett formula. Compound effects on the QTc interval were calculated as the change in ms from baseline values.

HPLC Analysis for Pharmacokinetic Studies. Compounds were administered intravenously (1 mg/kg) to male Wistar rats. Animals were fasted overnight before administra-

tion. Blood samples were collected at different time points from 0.1 to 24 h postadministration. Plasma was separated by centrifugation and stored at −20 °C until analysis. Plasma concentrations were determined by HPLC as described below. Pharmacokinetic parameters were determined by noncompartmental analysis using WinNonlin (Pharsight, Inc. Mountain, CA). Plasma levels (for compounds **1**, **2**, **15**, **16**, **20**, **51** and **52**) were determined by an isocratic HPLC (515 pump, Waters) and UV detection (λ = 225 nm, UV2487 Waters) method using an on-line solid-phase system (PROSPEKT, Spark-Holland) assisted by a sampling injector (ASPEC XL, Gilson). Briefly, 1 mL of acidic solution (20 mM, pH 4, sodium acetate buffer for compounds **2**, **15**, **51**, **52**; or 5 mM trifluoroacetic acid for compounds **1**, **16**, **20**) was added to 5 mL disposable conical tubes containing 100 μL of plasma (200 μL for compound **1**). The mixture was shaken for 15 s with a vortex and centrifuged at 4000 rpm for 10 min (Megafuge 1.0R, Heraeus). Samples were then loaded into a Gilson sample processor. The on-line solid-phase extraction was carried out by the PROSPEKT system connected to a Gilson sample injector, using C2 and C2-end capped (for compounds **51** and **52**) cartridges (Baker). The passage of the fluids through the cartridges was carried out by the ASPEC sampling injector, using the following sample preparation steps: (1) activate the cartridge with 1.5 mL of acetonitrile (methanol for compound **1**), (2) condition the cartridge with 1.5 mL of 0.2 M acetic acid (10 mM trifluoracetic for compound **1**), (3) load the sample, (4) wash out the sample with 2 mL of water and 1 mL of acetonitrile:water (30:70 v/v for compounds **1**, **2**, **51**, **52**; 40:60 v/v for compounds **15** and **16**, and 35:65 v/v for compound **20**). Finally the elution into the analytical column (C18, 150 × 4 mm, Kromasil 100, Teknokroma) was carried out by passing through the cartridge mobile phase during 1 min at a flow rate of 1 mL/min. The mobile phase was a mixture of acetonitrile (methanol for compound **2**) and 20 mM sodium phosphate containing 0.2% of triethylamine. The corresponding isocratic method were:28% of organic for compound **20**, 30% of organic for compounds **1**, **15**, **52**, 32% of organic for compound **51**, 35% of organic for compound **16** and 48% of organic for compound **2**. The column temperature was kept at 40 °C. With these conditions all compounds had a retention time in the range between 9 and 12 min. Plasma levels of compound **48** were determined by a HPLC-MS system (HPLC Alliance HT2790 and a ZMD mass spectrometer Micromass-Waters). Briefly 150 μl of acetonitrile containing 0.2% of trifluoroacetic acid were added to a 5 mL disposable conical tubes containing 50 μL of plasma. The mixture was shaken for 15 s with a vortex and centrifuged at 4000 rpm for 10 min (Megafuge 1.0R, Heraeus). 100 μL of supernatant were transferred to a vial and 10 μl were injected on the HPLC/MS system. Isocratic conditions at a flow of 250 μL/min were applied to the chromatographic system using a column of 100 × 2.1 mm, C18, 5 μM (Teknokroma) kept at 40 °C. The mobile phase was a mixture of acetonitrile and 10 mM formic acid contining 2.5 mM of NH_3 (75:25, v/v). The mass spectrometer was working in ESI $^+$ mode at *m/z* 423 (30 kV cone voltage, desolvation temperature 250° C).

In Vitro Inhibition of the Cytochrome P450 System (CYP3A4). Compounds at the concentration of 5 and 25 μM were incubated with pooled human microsomes (0.1 mg protein/mL) in a medium containing 50 mM potassium phosphate buffer (pH 7.4), 1 mM EDTA and 3 mM $MgCl_2$. Incubation was performed with and without 15 min. of preincubation. The reaction was initiated by the addition of the NADPH generating system (1 mM $NADP^+$, 5 mM glucose-6-phosphate and 1.5 UI/mL glucose-6-phosphate dehydrogenase). Incubations were done in a shaking bath at 37° C for 10 min. Sodium acetate buffer (20 mM, pH 4) was added to stop the reaction and samples were centrifugated at 4000 rpm and 20 °C for 10 min prior to HPLC analysis. Analysis was done with solid-phase extraction and UV detection. In all the assays, 50 μM testosterone and 0.05 μM ketoconazole were used as the specific substrate of CYP3A4 and positive control, respectively. All concentrations are expressed as the final concentration in the incubation mixture. Final acetonitrile concentration was 2%.

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Supporting Information Available: Table of elemental analyses data. This material is available free of charge via the Internet at http://pubs.acs.org.

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