Diaminoindanes as Microsomal Triglyceride Transfer Protein Inhibitors

Gary M. Ksander,* Reynalda deJesus, Andrew Yuan, Cynthia Fink, Michael Moskal, Eric Carlson, Paivi Kukkola, Natalie Bilci, Eli Wallace, Alan Neubert, David Feldman, Therese Mogelesky, Kevin Poirier, Michael Jeune, Ronald Steele, Jong Wasvery, Zouhair Stephan, Edna Cahill, Randy Webb, Aida Navarrete, Warren Lee, Joyce Gibson, Natalya Alexander, Haamid Sharif, and Ashok Hospattankar

Metabolic and Cardiovascular Diseases Research, Novartis Institute for Biomedical Reasearch, Summit, New Jersey 07901

Received June 27, 2001

The synthesis and biological activities of biarylamide-substituted diaminoindanes as microsomal triglyceride transfer protein (MTP) inhibitors are described. One of the more potent compounds, **8aR**, inhibited both the secretion of apoB from Hep G2 cells and the MTP-mediated transfer of triglycerides between synthetic acceptor and donor liposomes with IC_{50} values of 0.7 and 70 nM, respectively. In normolipidemic rats and dogs, oral administration of **8aR** dose-dependently reduced both plasma triglycerides and total cholesterol. Moreover, in rats and dogs, **8aR** also prevented the postprandial rise in plasma triglycerides following a bolus administration of a fat load. Because MTP inhibitors decrease very low density lipoprotein assembly in the liver, the potential for hepatic lipid accumulation was evaluated. In normolipidemic rats, hepatic cholesterol and triglyceride contents were dose-dependently increased by **8aR**. However, hepatic lipid accumulation resulted in negligible change in total liver weight and was reversible after withdrawal of the compound.

Introduction

Microsomal triglyceride transfer protein (MTP) is involved in the assembly of triglyceride-rich chylomicrons in enterocytes and very low density lipoproteins (VLDL) in hepatocytes. In the process of lipoprotein assembly, MTP accelerates the transfer of neutral lipids to apoB-containing lipoproteins.[1] The production of apoB is constitutive, but in the absence of triglycerides (TG), the apoB is readily degraded within the endoplasmic reticulum (ER) of enterocytes and hepatocytes. MTP accelerates the transfer of triglycerides, cholesterol esters, and phospholipids from the ER membranes of hepatocytes and enterocytes to apoB-containing lipoproteins in the lumen of the rough ER. Therefore, inhibition of the transfer of triglycerides and cholesterol ester by MTP is expected to stimulate apoB degradation, thus decreasing the intracellular pool of apoB available for the assembly of chylomicron and VLDL particles. A reduction in chylomicron particles should lead to decreased levels of postprandial plasma TG. Because plasma VLDL is a precursor for LDL particle formation, reduction in VLDL levels would lead to reduction in levels of triglycerides and LDL cholesterol. Therefore, an inhibitor of MTP and thus apoB secretion should reduce both plasma TG and cholesterol levels.[2]

The critical requirement of MTP for apoB secretion has been demonstrated by the human disease abetalipoproteinemia. In patients with this rare autosomal recessive genetic disorder, it has been demonstrated that mutations in the MTP gene are responsible for the absence of apoB-containing lipoproteins (chylomicrons, VLDL, IDL, and LDL) from the plasma.[3] Moreover, when nonhepatic, nonintestinal cells express certain recombinant truncated apoB variants, apoB is secreted only when MTP is coexpressed.[4] Similar genetic and cellular studies have indicated that MTP is integrally involved in the lipidation and assembly of intestinal chylomicrons and hepatic VLDL particles.[5]

Elevated levels of plasma TG and cholesterol are significant risk factors for myocardial infarction and the progression of coronary artery lesions.[6] There is a high prevalence of combined hyperlipidemia (elevated plasma cholesterol and triglycerides) among the hyperlipidemic population. Because MTP inhibitors have the potential to reduce both plasma cholesterol and TG, these agents could provide the maximum benefit for subjects with combined hyperlipidemia. In this paper we describe the synthesis and biological activities of MTP inhibitors.

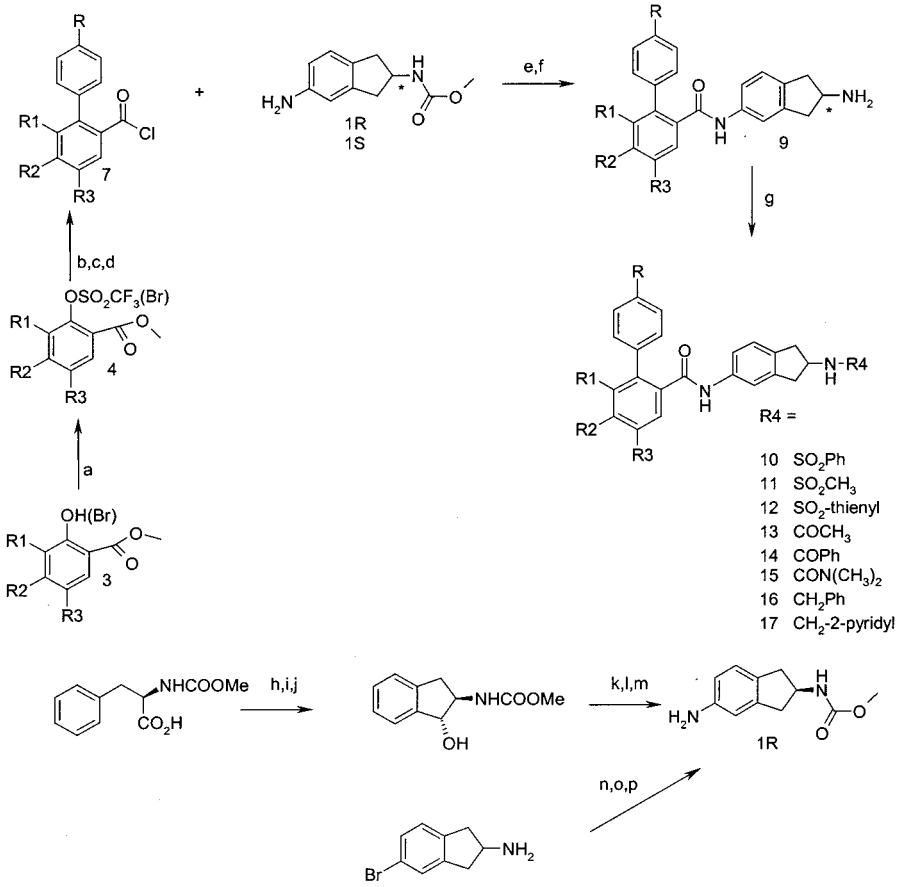
Chemistry

The preparation of diaminoindane derivatives is outlined in Scheme 1. Substituted *o*-bromo or -hydroxy benzoates were derivatized and coupled with aryl boronic acids under Suzuki coupling conditions to give the biaryl derivatives **5** in good yields. Hydrolysis of the aryl esters **5** to the carboxylic acid with 1 N NaOH followed by treatment with oxalyl chloride afforded the biaryl intermediates **7**. The chiral diaminoindane carbamates **1R** and **1S**, outlined in Scheme 1, were prepared using two routes from either *R* or *S* phenylalanine or via resolution of racemic 5-bromo-2-aminoindane followed by Buchwald amination. Synthetic details for the large-scale resolution process have been published.[7] The racemic diaminoindane (**1**) was prepared from 2-NHAc indane following a published procedure.[8] Amide formation by coupling the monosubstituted diamines **1** and acid chlorides **7** gave the biaryl-substituted diaminoamides **8**. Removal of the methyl carbamate with TMSI produced the biaryl 2-aminoindanes **9**. Reaction of **9** with the appropriate acylating agent gave the desired

* Address correspondence to this author at the Novartis Pharmaceuticals Corp., 556 Morris Ave., Summit, NJ 07901-1398 [telephone (908) 277-7529; fax (908) 277-2405; e-mail gary.ksander@pharma.novartis.com].

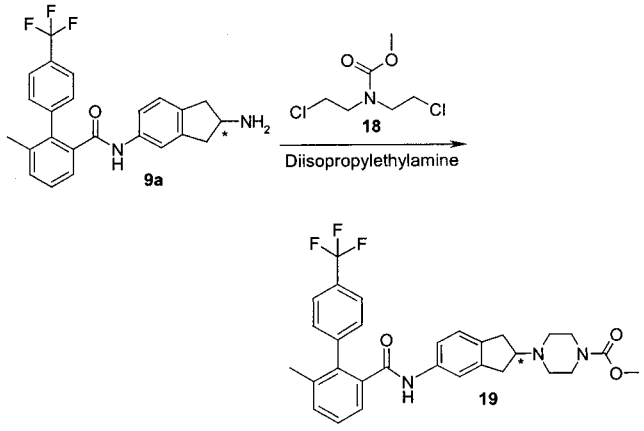
10.1021/jm010294e CCC: $20.00
Published on Web 11/21/2001

Scheme 1[a]



[a] Reagents and conditions: (a) mesyl chloride, diisopropyl amine; (b) trifluoromethylbenzyne boronic acid, $PdCl_2$ (dppf); (c) NaOH, EtOH; (d) oxalyl chloride; (e) pyridine, methylene chloride; (f) TMSI; (g) R^4X, base.

Scheme 2



N-substituted 2-aminoindanes **10**−**15**. The preparation of the *N*-alkyl derivatives **16** and **17** was accomplished by reductive amination of the free amines **9** with either benzaldehyde or 2-pyridine carboxaldehyde.

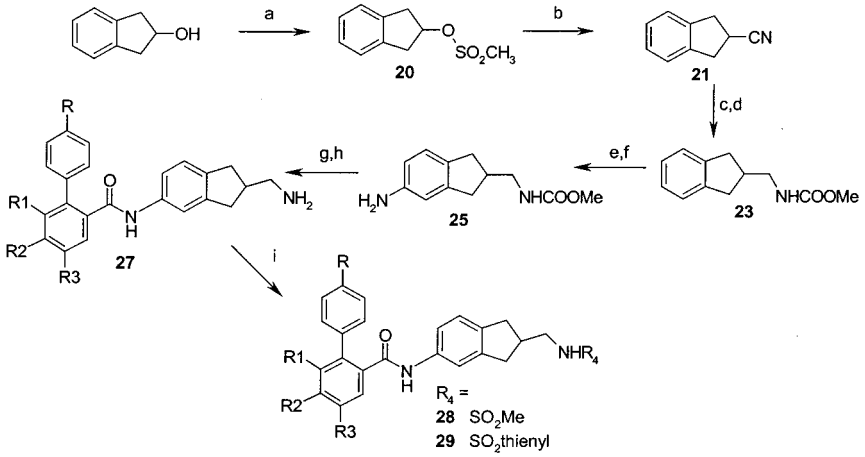
The piperazinoindane **19** was prepared in low yield by condensing *N*,*N*-bis(2-chloroethyl)carbamic acid methyl ester under basic conditions with **9a** (Scheme 2). The low yield was probably due to consumption of the alkylating agent under the reaction conditions.

The biaryl-substituted one-carbon-extended 2-indanes **26**−**29** were prepared by coupling the two intermediates **7** and **25** followed by deprotection and sulfonylation (Scheme 3). Treatment of 2-indanol with mesyl chloride followed by sodium cyanide in dimethylformamide (DMF) gave 2-cyanoindane, which was further reduced to the corresponding amine. At this point it was beneficial to prepare the methyl carbamate **23**, which met two objectives: a desired final substituent and a protecting group for further elaboration. Nitration of **23** gave a good yield of the desired racemic nitro derivative **24**. The regiochemistry in the nitration would be expected to give substitution para to the alkyl fused five-membered ring. Because of the symmetry of the molecule **23**, both para positions are equivalent, therefore producing the same racemic mixture. In the reaction mixture ~10% of the dinitration products were observed, which were separated from the desired product by flash chromatography. Hydrogenation of the nitro intermediate gave the mono-protected diamine **25**.

The two-carbon-extended analogue **34** was prepared starting with 2-indanone. The two-carbon extension was introduced by reacting 2-indanone with trimethylphosphonoacetate and sodium hydride (Scheme 4). Hydrogenation of the double bond, amide formation from the ester with ammonium hydroxide and ammonium hydrochloride, followed by lithium aluminum hydride reduction gave the desired amine **33**. Following the same synthetic sequence of nitration, reduction, and coupling as described in Scheme 3 produced the desired target **34**.

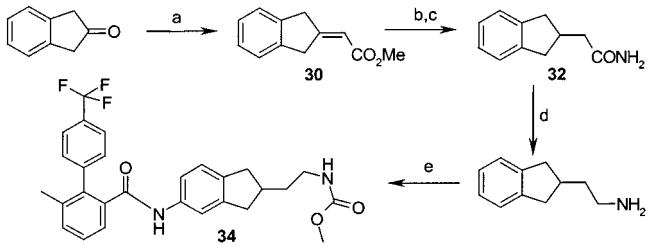
The preparation of the seven-membered ring analogues **37**−**9** is shown in Scheme 5. Condensation of hydroxylamine hydrochloride with 5,6,8,9-tetrahydro-7*H*-cycloheptabenen-7-one followed by reduction with

Scheme 3[a]



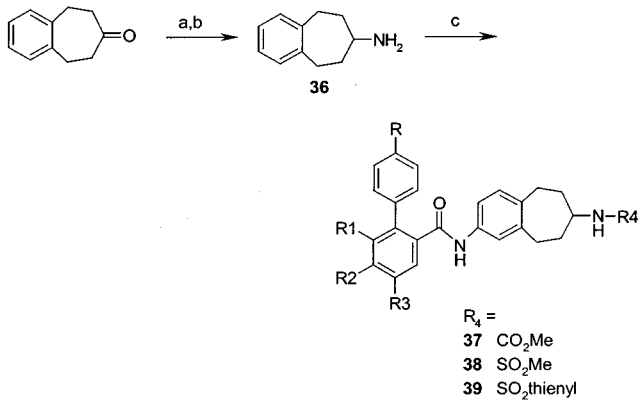
[a] (a) Mesyl chloride, diisopropylethylamine; (b) NaCN, DMF; (c) lithium aluminum hydride; (d) methyl chloroformate; (e) HNO_3/TFA; (f) H_2/Pd−C; (g) **7**, pyridine; (h) TMSI; (i) R^4-X.

Scheme 4[a]



[a] (a) Trimethylphosphonoacetate, NaH; (b) H_2/Pd−C; (c) NH_4OH, NH_4Cl; (d) lithium aluminum hydride; (e) sequence as described in Scheme 3.

Scheme 5[a]



[a] (a) Hydroxylamine hydrochloride; (b) $NaBH_4$; (c) sequence as described in Scheme 3.

sodium borohydride gave the desired amine **36**. Elaboration of the monoamine **36** as described in Scheme 3 gave the desired seven-membered ring analogues **37**−**39**.

In Vitro Results and Discussion

Presently there are no structural data available to produce a molecular model for MTP. Therefore, we profiled compounds by first using random screening for inhibitors of apoB secretion[5c,9] (primary screen) followed by an assay that measured MTP-mediated transfer of labeled triglycerides[10] between synthetic vesicles (secondary screen).

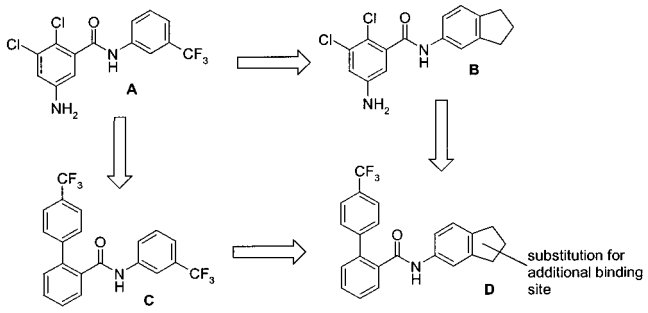


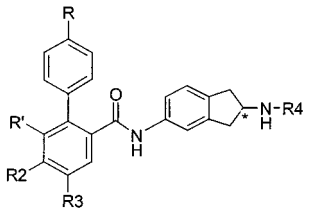
Figure 1. Random screening hit.

Apolipoprotein B is synthesized and secreted by human hepatoma cells (Hep G2). The secreted apoB is associated with lipids, and the rate of apoB secretion from cells is dependent on the MTP-mediated lipidation of apoB. The secondary screen (MTP-mediated transfer activity) was designed to test the ability of compounds to interfere with MTP-mediated transfer of triglycerides from synthetic phospholipid donor vesicles to the synthetic acceptor vesicles. The use of synthetic liposomes in the MTP transfer assay creates a nonphysiological condition that affects the assay sensitivity. Therefore, the apoB secretion assay in Hep G2 cells provided data under more physiological conditions. The structure−activity relationship discussion will be based on the cellular apoB secretion data.

The simple amide, compound **A (**Figure 1), was identified in the high-throughput apoB secretion assay. The general strategy was to keep either the acid or the amine constant and vary the other component. This approach led to compounds **B** and **C** with improved in vitro potency. Mixing and matching acids and amines led to the biarylindane structure **D**. An additional binding site, needed for low nanomolar potency, was accessed by substituting heteroatoms around the five-membered ring, which led to the diaminoindanes (Table 1).

By keeping the trifluoromethyl substituent (R) constant on the distal biaryl ring and modifying R^1−R^4, some general conclusions can be made concerning the in vitro apoB secretion inhibitory activity of these compounds (Table 1). Both *R* and *S* carbamates are potent inhibitors of apoB secretion. However, the *R*

Table 1. In Vitro ApoB and MTP Inhibition of Substituted Diaminoindanes

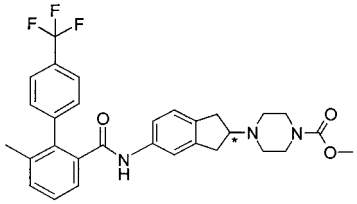


compd	chirality	R	R^1	R^2	R^3	R^4	apoB IC_{50} (nM)	MTP IC_{50} (nM)
8aR	R	CF_3	CH_3	H	H	CO_2Me	0.7	70
8aS	S	CF_3	CH_3	H	H	CO_2Me	6.4	70
8bR	R	CF_3	H	H	H	CO_2Me	1.9	68
8bS	S	CF_3	H	H	H	CO_2Me	5.2	110
10bS	S	CF_3	H	H	H	SO_2Ph	1.3	105
10bR	R	CF_3	H	H	H	SO_2Ph	42	650
11aR	R	CF_3	CH_3	H	H	SO_2CH_3	8.8	204
11aS	S	CF_3	CH_3	H	H	SO_2CH_3	1.8	34
11b	racemic	CF_3	H	H	H	SO_2CH_3	60	120
8dR	R	CF_3	H	H	CH_3	CO_2Me	2.2	170
8eR	R	CF_3	CF_3	H	H	CO_2Me	1.8	50
8fR	R	CF_3	H	H	CF_3	CO_2Me	7.5	410
12aS	S	CF_3	CH_3	H	H	SO_2-thienyl	0.9	50
12gS	S	CF_3	CH_3	H	CH_3	SO_2-thienyl	1.0	20
12gR	R	CF_3	CH_3	H	CH_3	SO_2-thienyl	2.6	180
8gS	S	CF_3	CH_3	H	CH_3	CO_2CH_3	2.5	90
8gR	R	CF_3	CH_3	H	CH_3	CO_2CH_3	1.1	70
13b	racemic	CF3	H	H	H	$COCH_3$	120	80
14b	racemic	CF3	H	H	H	COPh	270	>1000
15b	racemic	CF3	H	H	H	$CON(CH_3)_2$	120	80
16b	racemic	CF3	H	H	H	CH_2Ph	340	4800
17aR	R	CF3	CH_3	H	H	CH_2-2−pyr	1.7	100
17aS	S	CF3	CH_3	H	H	CH_2-2−pyr	30% at 100 nM	410
10h	racemic	F	CH_3	H	H	SO_2Ph	1.2	240
12h	racemic	F	CH_3	H	H	SO_2-thienyl	1.4	50
11h	racemic	F	CH_3	H	H	SO_2CH_3	8.3	170
10i	racemic	CH_3	CH_3	H	H	SO_2Ph	2.5	93
10j	racemic	CN	CH_3	H	H	SO_2Ph	5.5	120
10k	racemic	Cl	CH_3	H	H	SO_2Ph	2.4	100
11k	racemic	Cl	CH3	H	H	SO_2CH_3	6.6	100
12k	racemic	Cl	CH_3	H	H	SO_2-thienyl	3.0	120
8lR	R	Cl	CH_3	H	CH_3	CO_2Me	3.4	120
10m	racemic	Cl	OCH_3	H	H	SO_2Ph	2	110
11m	racemic	Cl	OCH_3	H	H	SO_2CH_3	15	70
10n	racemic	H	H	H	H	SO_2Ph	12	710

enantiomer is 3−6-fold more active. In the sulfonamide series the reverse appears to be the rule. The (*S*) methyl and thienyl sulfonamides are ∼3−4-fold more potent than the corresponding *R* enantiomer. A difference of 30-fold in potency of enantiomers was observed between the phenyl sulfonamides **10b(S)** and **10b(R)**. However, the greatest difference in activity between enantiomers was observed in the methylene 2-pyridyl compounds **17a(R)** and **17a(S)**.

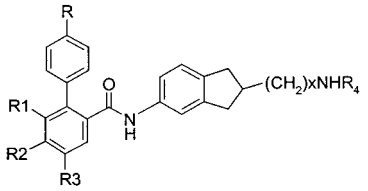
In general, compounds with a methyl group on the proximal phenyl ring, R^1 position, were more potent than those with hydrogen in the R^1 position. Methyl substitution in the R^3 position and in combination with R^1 methyl substitution resulted in compounds with similar activities. Substitution on the 2-aminoindane, R^4, included carbamate, sulfonamide, amide, urea, and alkylamine. The carbamates, phenyl, thienyl, methyl sulfonamides, and methylene 2-pyridyl derivatives are all potent inhibitors of apoB secretion. A significant decrease in activity was observed with amides (**13b** and **14b**), the urea **15b**, and the benzylamine **16b**. The trifluoromethyl substituent (R) on the distal aromatic biphenyl ring can be replaced by a fluoro, methyl, cyano, or chloro substituent while maintaining or producing a slight 2−3-fold reduction of inhibitory activity. In the absence of a para substituent (R = H) a 10-fold reduction of apoB inhibitory activity was observed. It was found that the 2-aminoindane nitrogen could be incorporated in a piperazine ring (Table 2) and maintain good in vitro activity. The *R*-enantiomer was ∼20 times more potent than the corresponding *S*-enantiomer. Although only a limited number of racemic methylene- or ethylene-extended derivatives were prepared, good in vitro

Table 2. In Vitro ApoB and MTP Inhibition of Substituted Piperazinoindanes



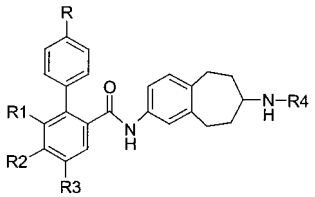
compd	R	R^1	R^2	R^3	chirality	apoB IC_{50} (nM)	MTP IC_{50} (nM)
19aR	CF_3	CH_3	H	H	R	1.8	40
19aS	CF_3	CH_3	H	H	S	43	1000

Table 3. In Vitro ApoB and MTP Inhibition of Substituted Aminoindanes



compd	X	R	R^1	R^2	R^3	R^4	apoB IC_{50} (nM)	MTP IC_{50} (nM)
28a	1	CF_3	CH_3	H	H	SO_2CH_3	6.5	150
26a	1	CF_3	CH_3	H	H	CO_2CH_3	4.1	24
29a	1	CF_3	CH_3	H	H	SO_2-thienyl	1.9	14
26g	1	CF_3	CH_3	H	CH_3	CO_2CH_3	2.2	40
26k	1	Cl	CH_3	H	H	CO_2CH_3	8.7	100
28k	1	Cl	CH_3	H	H	SO_2CH_3	16.0	500
34a	2	CF_3	CH_3	H	H	CO_2CH_3	10	70

Table 4. In Vitro ApoB and MTP Inhibition of Substituted Diaminocycloheptabenzenes



compd	R	R^1	R^2	R^3	R^4	apoB IC_{50} (nM)	MTP IC_{50} (nM)
37a	CF_3	CH_3	H	H	CO_2Me	1.6	20
38a	CF_3	CH_3	H	H	SO_2CH_3	2.3	80
39a	CF_3	CH_3	H	H	SO_2-thienyl	1.6	140
37g	CF_3	CH_3	H	CH_3	CO_2Me	2.4	20
38k	Cl	CH_3	H	H	SO_2CH_3	5.0	90
37k	Cl	CH_3	H	H	CO_2CH_3	2.0	80

activity was observed (Table 3). The in vitro potency of the benzofused seven-membered ring compounds again demonstrates the overall flexibility of the SAR in this region of the molecule (Table 4).

In Vivo Results and Discussion

Inhibition of Plasma Triglycerides and Total Cholesterol in Normolipidemic Rats. Overnight-fasted normolipidemic rats were administered a single oral dose of inhibitor in a cornstarch vehicle (Table 5). Blood samples were collected 2, 6, and 24 h postdosing and assayed for triglycerides and total cholesterol. After the 6 h time point the rats were given free access to food. Therefore, the 2 and 6 h triglycerides and total cholesterol blood levels are assumed to be a result of MTP inhibition in the liver, whereas lipid reduction at the 24 h time point results from MTP inhibition in both gut and liver.

Both carbamate enantiomers **8aR** and **8aS** reduce plasma TG and total cholesterol (CH) in rats. Effective reduction of plasma lipids (60−80%) was observed after oral administration of 5 mg/kg at the 2 and 6 h time points after dosing. The difference in efficacy between these enantiomers was observed 24 h postdosing, when the *R*-enantiomer at 50 mg/kg reduced TG and CH for >24 h but the *S*-enantiomer was ineffective. The desmethyl derivative **8bR** reduced plasma TG and CH at 6 h after dosing; however, no reduction was observed

Table 5. Time Course for Inhibition of Plasma Triglycerides and Total Cholesterol in Normolipidemic Rats after Oral Administration

compd	dose	TG % reduction[a] 2, 6, and 24 h post oral dosing	CH % reduction[a] 2, 6, and 24 h post oral dosing
8aR	50	81, 71, 63	33, 52, 60
8aR	10	84, 68, NS	41, 58, 16
8aR	5	78, 59, NS	30, 47, NS
8aS	50	78, 74, NS	27, 43, NS
8aS	5	85, 71, NS	33, 45, NS
8bR	50	69, 74, NS	20, 39, NS
10bR	50	NS, NS, NS	NS, NS, NS
10bS	50	57, 30, NS	21, NS, NS
11aR	50	33, 33, NS	12, 15, NS
11aS	50	74, 68, NS	27, 42, NS
8dR	50	NS, NS, NS	NS, NS, NS
12aS	50	88, 83, 76	25, 50, 67
12aS	10	83, 56, NS	26, 39, NS
12aS	5	74, 37, NS	23, 34, NS
12gS	50	77, 48, 46	21, 34, 47
12gR	50	79, 68, NS	33, 46, NS
17aR	50	91, 88, NS	40, 57, 29
17aR	10	86, 47, NS	34, 35, NS
19aR	50	80, 56, 44	35, 50, 18
19aR	10	70, NS, 29	40, 29, 15
19aS	50	58, NS, NS	23, 20, NS
26a	50	49, NS, NS	NS, NS, NS
34a	50	NS, NS, NS	NS, NS, NS
37a	50	39, NS, NS	20, 20, NS
38a	50	81, 53, NS	29, 41, 17
37g	50	73, 44, 36	17, 21, 22

[a] Values represent mean percent inhibition for drug-treated rats versus a separate group of vehicle-treated animals. All values are significant where $p < 0.05$ using an unpaired t test. $N = 6$. NS, no significant change.

at the 24 h time point. The presence of a methyl substituent (R^1) apparently increases the duration of action.

As mentioned earlier, the *S*-enantiomers in the sulfonamide series inhibited apoB secretion and MTP-mediated transfer of triglycerides in vitro to a greater extent as compared to their respective *R*-enantiomers. The in vivo effects of the phenylsulfonamide enantiomers **10bS** and **10bR** correlate with their respective in vitro activity. The phenylsulfonamide **10bS**, although weaker than the methyl carbamates **8aR** and **8aS**, did reduce plasma TG and CH ,whereas the less in vitro active **10bR** enantiomer failed to reduce plasma lipids even at a relatively high dose of 50 mg/kg. This trend was also observed with the methyl sulfonamides **11aS** and **11aR** and the thienyl sulfonamides **12gS** and **12gR**. The most potent sulfonamide, equivalent to the carbamate **8aR**, is **12aS**. This inhibitor significantly reduced triglycerides and total cholesterol over the entire 24 h testing period.

The methyl carbamate **8dR**, where R^1 is hydrogen and R^3 is methyl, did not reduce plasma TG or CH at any time point. Interestingly, the corresponding methyl carbamate **8gR**, where R^1 and R^3 are methyl substituents, effectively reduced lipids for up to 6 h. Differences in the metabolism of these two compounds could explain these results.

The basic inhibitor *N*-methyl-2-pyridyl derivative, **17aR**, reduced triglycerides and total cholesterol very effectively over a 6 h period. Another basic inhibitor, the pipirazine derivative **19aR**, showed a slightly different profile from that of the previously mentioned compounds. This compound appeared to lose efficacy from 2 to 6 h after dosing at 50 mg/kg; however, activity

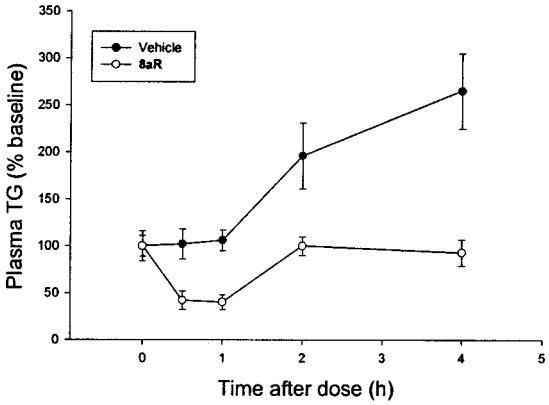


Figure 2. Reduction of postprandial plasma TG by **8aR** in rats. Each point represents the mean ± SEM of baseline; n = 6 for each treatment group. Baseline TG values for rats were 46 ± 14 mg/dL.

was maintained over the next 6−24 h. After administration of 10 mg/kg **19aR**, there was no reduction of plasma TG at 6 h. However, there was a modest but significant reduction at 24 h. It should be noted again that the rats were given free access to food after the blood sample at 6 h. Therefore, the 24 h data point reflects inhibition of MTP in both the gut and liver. The vehicle control animals showed significant increased levels of plasma TG due to a prandial response from food intake. Blocking of the prandial rise in triglycerides could explain the overall reduction of triglycerides noted at the 24 h time point.

Postprandial Effects in Normolipidemic Rats. Delayed clearance of postprandial lipemia has long been proposed as a risk factor for atherosclerosis. Agents that attenuate postprandial lipemia can act either by inhibiting the production of or accelerating the clearance of intestinal triglyceride-rich particles. Inhibitors of MTP are expected to interfere with the assembly of both gut-derived (chylomicrons) and liver-derived (VLDL) particles. The effect of **8aR** was tested on postprandial lipemia after the consumption of a well-defined oral fat load consisting of 320 mg of corn oil mixed with 430 mg of sucrose in a total volume of 1 mL.

Male Sprague−Dawley rats were orally treated with a single dose of 1 mg/kg of either **8aR** or vehicle followed immediately by an oral fat load. Blood samples were collected at 0, 0.5, 1, 2, and 4 h, and plasma was assayed for triglycerides. As shown in Figure 2, **8aR** effectively prevented the elevation of plasma TG after a bolus fat load.

Inhibition of Plasma Triglycerides and Total Cholesterol in Normolipidemic Dogs. The time course for inhibition of plasma TG and CH in normolipidemic dogs after daily oral administration for 4 days is shown in Table 6. The MTP inhibitors were suspended in cornstarch vehicle and administered by oral gavage. Plasma samples were taken 24 h after dosing. Compounds **8aR**, **19aR**, **17aR**, and **12aS** effectively reduced plasma levels of triglycerides and total cholesterol after daily oral doses of <10 mg/kg/day. Greater than 50% reduction of lipids was observed with **8aR** and **19aR** at 2.5 mg/kg, and marginal activity was observed at a dose of 1 mg/kg.

Postprandial Effects in Normolipidemic Dogs. In male normolipidemic dogs both compounds, **8aR** and **19aR**, at 1 mg/kg p.o. completely blocked the prandial increase in plasma TG induced by the administration of 100 mL of cream. This effect persisted over 4 h (Figure 3). This result is consistent with the hypothesis that MTP inhibition in the gut decreases the synthesis of gut-derived chylomicrons and thus atherogenic remnant lipoproteins.

Hepatic Lipid Accumulation in Normolipidemic Rats. Because MTP inhibitors are known to suppress apoB production and interfere with VLDL assembly in liver without reducing hepatic triglyceride synthesis, lipid accumulation in the liver is expected in animals treated with MTP inhibitors. Accordingly, the effect of **8aR** on hepatic triglyceride and cholesterol concentrations was studied in normolipidemic rats.

In normolipidemic rats, hepatic lipid content was dose-dependently increased by **8aR** and was inversely correlated with plasma lipid lowering (Table 7). In this model, hepatic cholesterol and triglyceride content started at about 0.1 and 0.4% of total liver weight, respectively, in vehicle-treated rats. At an oral dose of 5 mg/kg/day with **8aR** hepatic cholesterol and triglyceride content never exceeded 0.3 and 1.8% of total liver weight, respectively. Because lipids represent only a minor fraction of total liver weight, it was not surprising that these changes in hepatic lipid content had no significant impact on total liver weight. The reversibility of hepatic lipid accumulation was studied in the same rat model. Both liver cholesterol and TG were increased after 5 days of dosing of **8aR** at 5 mg/kg (Table 8). Six days after treatment withdrawal, hepatic lipid concentrations were fully returned too normal.

In summary, the series of substituted diaminoindanes and the seven-membered ring homologues are novel inhibitors of MTP that prevented the secretion of apoB-containing lipoproteins from liver-derived Hep G2 cells. The inhibitors **8aR** and **19aR** effectively reduced plasma TG and CH levels in normolipidemic rats and dogs. In addition, these compounds blocked the postprandial rise in triglycerides after an oral fat load. Therefore, these studies suggest that **8aR** and **19aR** reduce the formation of gut-derived chylomicrons and liver-derived VLDL/LDL. Because MTP inhibitors have the potential to reduce both plasma TG and CH, MTP inhibitors that meet safety criteria could provide maximum benefit for subjects with elevated lipids. Thus, MTP inhibitors could provide an opportunity to treat combined hyperlipidemia and atherosclerosis.

Experimental Section

^{1}H NMR spectra were recorded on VarianXL 400 MHz, Varian 300 MHz, and/or Bruker AC 250 MHz spectometers with trimethylsilane as internal standard. Optical rotations were measured with a Perkin-Elmer model 241 polarimeter. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All reactions were carried out under an atmosphere of nitrogen unless otherwise noted. Chiral purity was determined using a Dynamax SD-200 HPLC system.

[1,1′-Biphenyl]-2-carboxylic Acid, 6-Methyl-4′-(trifluoromethyl)-, Methyl Ester (5a). A mixture of methyl 2-bromo-3-methylbenzoate (8.81 g, 38.5 mmol), 4-(trifluoromethyl)-benzeneboronic acid (8.04 g, 42.3 mmol), $PdCl_2$(dppf) (1.57 g, 1.92 mmol), K_3PO_4 (32.6 g, 153 mmol), and 150 mL of DME was refluxed for 16 h under an atmosphere of nitrogen. The reaction mixture was poured into water and extracted twice

Table 6. Time Course for Inhibition of Plasma Total Cholesterol and Triglycerides in the Normolipidemic Dog after Daily Oral Administration for 4 Days

compd	dose (mg/kg/day)	plasma TG[a] (mg/dL) day 0	day 2	day 3	day 4	plasma CH[a] (mg/dL) day 0	day 2	day 3	day 4
8aR	5	48 ± 3	22 ± 3*	16 ± 3*	12 ± 2* (−75%)	124 ± 9	87 ± 11*	68 ± 9*	54 ± 7* (−56%)
	2.5	59 ± 9	32 ± 5*	25 ± 4*	23 ± 5* (−61%)	113 ± 4	90 ± 10*	76 ± 12*	57 ± 8* (−50%)
	1	46 ± 4	42 ± 3	48 ± 6	45 ± 4	110 ± 6	103 ± 9	101 ± 9	89 ± 6* (−19%)
19aR	10	62 ± 8	24 ± 6*	18 ± 3*	19 ± 3* (−70%)	143 ± 7	79 ± 15*	50 ± 12*	31 ± 10* (−78%)
	5	37 ± 3	20 ± 2*	17 ± 1*	14 ± 2* (−61%)	127 ± 9	79 ± 10*	53 ± 8*	38 ± 7* (−70%)
	2.5	58 ± 9	28 ± 5*	20 ± 2*	25 ± 5* (−57%)	109 ± 5	67 ± 6	53 ± 5*	42 ± 4* (−61%)
	1	38 ± 3	28 ± 4	26 ± 4	28 ± 4 (−27%)	120 ± 8	91 ± 16	83 ± 14	73 ± 14* (−39%)
17aR	10	46 ± 9	26 ± 4*	27 ± 4*	23 ± 3* (−51%)	125 ± 8	69 ± 7*	54 ± 6*	36 ± 4* (−71%)
	5	36 ± 2	38 ± 3	41 ± 2	32 ± 2	130 ± 8	110 ± 10*	99 ± 11*	94 ± 9* (−28%)
12aS	5	31 ± 2	24 ± 2*	24 ± 2*	20 ± 3* (−34%)	120 ± 3	81 ± 12*	72 ± 12*	70 ± 14 (−42%)

[a] Lipid levels were measured 24 h postdosing. Values in parentheses represent mean percent inhibition for drug-treated dogs. $n = 6$. *, $p < 0.05$ (one-way ANOVA).

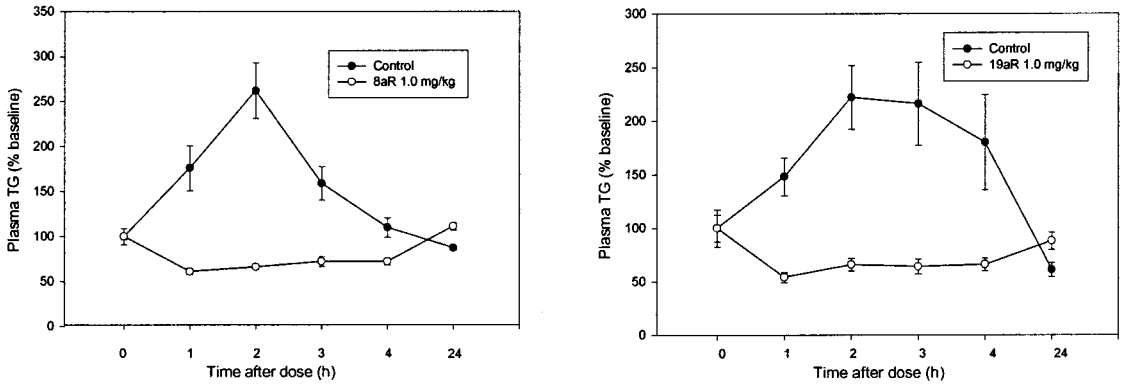


Figure 3. Reduction of postprandial TG in normolipidemic dogs. Dogs were dosed with **8aR** and **19aR** at 1 mg/kg. The fat challenge (100 mL of cream) was administered 2 h after dosing. Each point represents the mean ± SEM of baseline, $n = 6$ for each treatment group.

Table 7. Effect of **8aR** on Lipid Accumulation in Normolipidemic Rat Livers

dose (mg/kg)	cholesterol[a] (mg/g of liver)	triglyceride[a] (mg/g of liver)	liver wt[a] (g)
vehicle	1.29 ± 0.04	4.12 ± 0.24	8.94 ± 0.27
0.5	1.40 ± 0.08	4.61 ± 0.51	9.13 ± 0.44
1	2.01 ± 0.13*	8.16 ± 0.81*	9.60 ± 0.28
5	3.09 ± 0.28*	17.7 ± 1.25*	9.79 ± 0.51

[a] Data represent mean ± SEM ($n = 8$ per group). *Statistically different from vehicle by Student's t test ($p < 0.05$)

Table 8. Effect of Treatment Withdrawal of **8aR** on the Reversal of Hepatic Lipid Accumulation in Normolipidemic Rat Livers

time of analysis	cholesterol[a] (mg/g of liver)	triglyceride[a] (mg/g of liver)
after treatment		
vehicle	1.33 ± 0.10	2. 81 ± 0.24
8aR	2.76 ± 0.15*	13.6 ± 1.78*
after washout		
vehicle	1.13 ± 0.08	2.54 ± 0.26
8aR	1.12 ± 0.13	2.38 ± 0.42

[a] Data represent mean ± SEM ($n = 8$ per group). *Statistically different from vehicle by Student's t test ($p < 0.05$). Treatment with 5 mg/kg and washout periods lasted 5 and 6 days, respectively.

with EtOAc. The organic layer was washed with sodium bicarbonate and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on silica gel eluting first with hexanes followed by EtOAc/hexanes (1:9) to give 10.75 g (95%) of **5a** as an oil.

[1,1′-Biphenyl]-2-carboxylic Acid, 6-Methyl-4′-(trifluoromethyl)- (6a). A mixture of ester **5a** (10.75 g, 36.56 mmol) in 250 mL of ethanol and 1 N NaOH (73.1 mmol) was refluxed for 5 h, cooled, and stirred overnight. The reaction mixture was concentrated, diluted with water, and washed with ether. The aqueous layer was acidified with 1 N HCl, extracted with EtOAc, washed with brine, dried ($MgSO_4$), filtered, and concentrated to give 9.59 g of **6a** as a white solid.

[1,1′-Biphenyl]-2-carbonyl Chloride, 6-Methyl-4′-(trifluoromethyl)- (7a). To a 0 °C solution of **6a** (9.59 g, 34.25 mmol) in 200 mL of CH_2Cl_2 was added oxalyl chloride (11.95 mL, 137 mmol) followed by 3 drops of DMF. The reaction mixture was stirred at room temperature for 16 h and concentrated to give 8.9 g of **7a** as a yellow viscous oil.

Carbamic Acid, [(2*R*)-2,3-Dihydro-5-[[[6-methyl-4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-1*H*-inden-2-yl]-, Methyl Ester (8aR). To a 0 °C solution of **1R** (9.5 g, 46.12 mmol) in 200 mL of CH_2Cl_2 and pyridine (4.47 mL, 55.34 mmol) was added 0.63 M **7a** (80.5 mL, 50.73 mmol in CH_2Cl_2), and the reaction mixture was stirred for 15 min. The organic layer was washed with 1 N HCl, $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was triturated with 25 mL of warm EtOAc and 50 mL of hexanes to give 12.8 g of **8aR** as a white solid. The mother liquor was chromatographed on silica gel eluting with EtOAc/hexanes (1:1), which afforded another 6.93 g of **8aR** (91%) melting at 156−157 °C; $[\alpha]_D$ −12.85 (c 11.36 DMSO); ^{1}H NMR (DMSO-d_6) δ 10.03 (s, 1H), 7.74 (s, 1H), 7.72 (s, 1H), 7.48−7.38 (m, 5H), 7.27 (s, 1H), 7.12 (d, 1H, $J = 9.5$ Hz), 7.03 (d, 1H, $J = 8$ Hz), 4.19 (m, 1H), 3.52 (s, 3H), 3.33 (brs, 1H), 4.19 (q, 2H, $J = 7.1$ Hz), 2.70 (m, 1H), 2.66 (m, 1H), 2.08 (s, 3H); chiral purity >99% (retention time = 13.03 min using a Daicel chirapak AD 0.46 cm × 25 cm eluting with 1:3 isopropyl alcohol/hexanes). Anal. ($C_{26}H_{23}F_3N_2O_3$) C, H, N.

Prepared similarly was **8aS**: $[\alpha]_D$ +11.78 (c 10.466, DMSO); chiral purity >99%. Anal. ($C_{26}H_{23}F_3N_2O_3$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[(2*R*)-2-Amino-2,3-dihydro-1*H*-inden-5-yl]-6-methyl-4′-(trifluoromethyl)- (9aR). A mixture of **8aR** (1.53 g, 3.27 mmol), 75 mL of acetonitrile,

and trimethylsilyliodide (1.86 mL, 13 mmol) was stirred overnight at room temperature. Methanol was added, and the mixture was concentrated, cold 1 N NaOH added, and the mixture was extracted with EtOAc. The organic layer was washed with aqueous $Na_2S_2O_3$ and brine, dried, filtered, concentrated and recrystallized from ether to give 1.19 g (89%) of **9aR** as a white solid melting at 109−112 °C: ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.70 (s, 1H), 7.4 (m, 5H), 7.05 (m, 2H), 6.86 (s, 1H), 6.74 (d, 1H), 3.81 (m, 1H), 3.09 (dd, 2H), 2.60 (dd, 2H), 2.18 (s, 3H), 1.6 (bs, 2H). Prepared similarly were **9bR**, **9bS**, **9gR**, and **9gS**.

[1,1′-Biphenyl]-2-carboxamide, *N*-[(2*R*)-2,3-Dihydro-2-[(phenylsulfonyl)amino]-1*H*-inden-5-yl]-6-methyl-4′-(trifluoromethyl)- (10bR). To a 0 °C solution of **9bR** (0.868 g, 2.19 mmol) in 20 mL of CH_2Cl_2 and diisopropylethylamine (0.454 mL, 2.63 mmol) was added benzenesulfonyl chloride (0.308 g, 2.41 mmol), and the mixture was stirred for 30 min. An additional aliquot of diisopropylethylamine (0.045 mL) and benzenesulfonyl chloride (0.031 mL) was added and the reaction was stirred for 30 min. The organics were washed with 1 N HCl, $NaHCO_3$, and brine, dried, filtered, concentrated, chromatographed on silica gel eluting with EtOAc/hexanes (1:1), and triturated with ether to give 765 mg (65%) of **10bR** as a white solid melting at 152−153 °C; $[\alpha]_D$ +8.48 (*c* 10.79, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 10.2 (s, 1H), 8.02 (d, 1H, J = 7 Hz), 7.83 (s, 1H), 7.82 (s, 1H), 7.75 (s, 1H), 7.72 (s, 1H), 7.6−7.4 (m, 10H), 7.32 (s, 1H), 7.2 (d, 1H, J = 9 Hz), 7.01 (d, 1H, J = 8), 3.85 (m, 1H), 2.8 (m, 2H), 2.62 (m, 2H). Anal. ($C_{29}H_{23}F_3N_2O_3S$) C, H, N.

Prepared similiarly was **10bS** melting at 152−153 °C: $[\alpha]_D$ −7.3 (*c* 10.15 CH_3OH); Anal. ($C_{29}H_{23}F_3N_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[(2*R*)-2,3-Dihydro-2-[(2-pyridinylmethyl)amino]-1*H*-inden-5-yl]-6-methyl-4′-(trifluoromethyl)- (17aR). A mixture of **9bR** (2.46 g, 6.0 mmol) and 2-pyridinecarboxaldehyde (0.67 g, 6.3 mmol) in 60 mL of methanol was stirred for 5 h. The polymer-supported borohydride resin (2.5 mmol/g, 2.6 g, 6.5 mmol) was added and the mixture stirred overnight. The resin was removed by filtration and the solution concentrated. The residue was dissolved in 50 mL of ethyl acetate, and excess ether previously saturated with HCl gas was added. The dihydrochloride salt of **17aR** crystallized (2.32 g, 67%) as a light yellow solid melting at 281−283 °C: $[\alpha]_D$ −23.2 (*c* 1.13 DMSO); ^{1}H NMR (DMSO-d_6) δ 10.15 (s, 1H), 8.68 (d, 1H; J = 4.9 Hz), 7.97 (t, 1H, J = 6.2 Hz), 7.70 (m, 3H), 7.5 (m, 7H), 7.16 (d, 1H, J = 9.4 Hz), 7.10 (d, 1H, J = 7.2 Hz), 4.4 (brs, 2H), 4.04 (m, 1H), 3.13 (m, 4H), 2.09 (s, 3H); chiral purity >99%. Anal. ($C_{30}Cl_2H_{28}F_3N_3O$) C, H, N. Prepared similarly was **17aS** as the non-HCl salt melting at 161−162 °C: $[\alpha]_D$ +13.5 (*c* 0.915 DMSO). Anal. ($C_{30}H_{26}F_3N_3O$) C, H, N.

Prepared similarly as described above were the following:

Carbamic Acid, [(2*S*)-2,3-Dihydro-5-[[[4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-1*H*-inden-2-yl]-, Methyl Ester 8bS: melting at 172−174 °C; $[\alpha]_D$ +5.506 (*c* 10.27 CH_3OH); ^{1}H NMR (DMSO-d_6) δ 10.25 (s, 1H), 7.78 (s, 1H), 7.73 (s, 1H), 7.65−7.35 (m, 8H), 7.20 (d, 1H), 7.07 (d, 1H), 4.20 (m, 1H), 3.53 (s, 1H), 3.08 (d, 1H), 3.00 (d, 1H), 2.7 (m, 2H). Anal. ($C_{25}H_{21}F_3N_2O_3$) C, H, N.

Carbamic Acid, [(2*R*)-2,3-Dihydro-5-[[[4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-1*H*-inden-2-yl]-, Methyl Ester 8bR: melting at 169−173 °C; $[\alpha]_D$ −5.29 (*c* 8.88 CH_3OH). Anal. ($C_{25}H_{21}F_3N_2O_3$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[(2*S*)-2,3-Dihydro-2-[(methylsulfonyl)amino]-1*H*-inden-5-yl]-6-methyl-4′-(trifluoromethyl) 11aS: melting at 191−194 °C; $[\alpha]_D$ +12.54 (*c* 1.052 CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 10.05 (s, 1H), 7.77 (s, 1H), 7.73 (s, 1H), 7.5−7.3 (m, 6H), 7.29 (s, 1H), 7.11 (d, 1H), 7.02 (d, 1H), 4.05 (m, 1H), 3.10 (m, 2H), 2.96 (s, 3H), 2.75 (m, 2H), 2.08 (s, 3H); chiral purity >97%. Anal. ($C_{25}H_{23}F_3N_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[(2*R*)-2,3-Dihydro-2-[(methylsulfonyl)amino]-1*H*-inden-5-yl]-6-methyl-4′-(trifluoromethyl) 11aR: melting at 95−100 °C; $[\alpha]_D$ −10.94 (*c* 9.056 CH_2Cl_2). Anal. ($C_{25}H_{23}F_3N_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[2,3-Dihydro-2-[(methylsulfonyl)amino]-1*H*-inden-5-yl]-4′-(trifluoromethyl)-11b: melting at 195−197 °C; ^{1}H NMR (DMSO-d_6) δ 10.25 (s, 1H), 7.77 (s, 1H), 7.74 (s, 1H), 7.65−7.47 (m, 6H), 7.39 (s, 1H), 7.36 (d, 1H), 7.21 (d, 1H), 7.07 (d, 1H), 4.39 (m, 1H), 3.12 (m, 2H), 2.95 (s, 3H), 2.78 (m, 2H). Anal. ($C_{24}H_{21}F_3N_2O_3S$) C, H, N.

Carbamic Acid, [(2*R*)-2,3-Dihydro-5-[[[4-methyl-4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-1*H*-inden-2-yl]-, Methyl Ester 8dR: 218−221 °C; $[\alpha]_D$ −8.51 (*c* 9.088 DMSO); ^{1}H NMR ($CDCl_3$) δ 7.69−7.53 (m, 5H), 7.36 (m, 3H), 7.17 (s, 1H), 7.09 (d, 1H), 6.86 (d, 1H), 5.40 (br, 1H), 4.46 (m, 1H), 3.66 (s, 3H), 3.23 (d, 1H), 3.18 (d, 1H), 2.48 (s, 3H). Anal. ($C_{26}H_{23}F_3N_2O_3$) C, H, N.

Carbamic Acid, [(2*R*)-5-[[[4′,6-Bis(trifluoromethyl)-[1,1′-biphenyl]-2-yl]carbonyl]amino]-2,3-dihydro-1*H*-inden-2-yl]-, Methyl Ester 8eR: melting at 203−205 °C; $[\alpha]_D$ −11.38 (*c* 9.74 in CH_3OH); ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1H, J = 7 Hz), 7.92 (d, 1H, J = 7 Hz), 7.7−7.6 (m, 3H), 7.54 (s, 1H), 7.51 (s, 1H), 7.05 (d, 1H, J = 8 Hz), 6.98 (s, 1H), 6.72 (m, 2H), 4.81 (m, 1H), 4.45 (m, 1H), 3.65 (s, 3H), 3.21 (d, 1H, J = 6 Hz), 3.16 (d, 1H, J = 6 Hz), 2.73 (d, 1H, J = 4 Hz), 2.69 (d, 1H, J = 4 Hz). Anal. ($C_{26}F_6H_{20}N_2O_3$) C, H, N.

Carbamic Acid, [(2*R*)-5-[[[4,4′-Bis(trifluoromethyl)-[1,1′-biphenyl]-2-yl]carbonyl]amino]-2,3-dihydro-1*H*-inden-2-yl]-, Methyl Ester 8fR: melting at 199−200 °C; $[\alpha]_D$ −9.75 (*c* 5.49 in DMSO); ^{1}H NMR ($CDCl_3$) δ 8.07 (s, 1H), 7.82 (d, 1H, J = 8 Hz), 7.74 (s, 1H), 7.71 (s, 1H), 7.6 (m, 3H), 7.16 (s, 1H), 7.09 (d, 1H, J = 8 Hz), 6.89 (s, 1H), 6.81 (d, 1H, J = 9 Hz), 4.80 (m, 1H), 4.48 (m, 1H), 3.23 (d, 1H, J = 7 Hz), 3.19 (d, 1H, J = 7 Hz), 2.77 (m, 1H), 2.71 (m, 1H). Anal. ($C_{26}F_6H_{20}N_2O_3$) C, H, N.

Carbamic Acid, [(2*R*)-5-[[[4,4′-Bis(trifluoromethyl)-[1,1′-biphenyl]-2-yl]carbonyl]amino]-2,3-dihydro-1*H*-inden-2-yl]-, Methyl Ester 12aS: melting at 95−99 °C; $[\alpha]_D$ −4.82 (*c* 1.00, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 10.0 (s, 1H), 8.20 (d, 1H), 7.95 (d, 1H), 7.77 (s, 1H), 7.74 (s, 1H), 7.62 (d, 1H), 7.5−7.35 (m, 5H), 7.20 (m, 2H), 7.09 (d, 1H), 6.98 (d, 1H), 3.95 (m, 1H), 2.90 (m, 2H), 2.65 (m, 2H), 2.09 (s, 3H); chiral purity >98%. Anal. ($C_{28}F_3H_{23}N_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[(2*S*)-2,3-Dihydro-2-[(2-thienylsulfonyl)amino]-1*H*-inden-5-yl]-4,6-dimethyl-4′-(trifluoromethyl)- 12gS: melting at 153−155 °C; $[\alpha]_D$ −2.53 (*c* 8.4, DMSO); ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.67 (s, 1H), 7.63 (s, 1H), 7.62 (s, 1H), 7.44 (s, 1H), 7.41 (d, 1H), 7.24 (s, 1H), 7.12 (m, 1H), 7.00 (s, 1H), 6.96 (d, 1H), 6.75 (s, 1H), 6.67 (d, 1H), 4.97 (d, 1H), 4.18 (m, 1H), 3.1 (m, 2H), 2.68 (m, 2H), 2.40 (s, 3H), 2.15 (s, 3H); chiral purity >98%. Anal. ($C_{29}H_{25}F_3N_2O_3S_2$).

[1,1′-Biphenyl]-2-carboxamide, *N*-[(2*R*)-2,3-Dihydro-2-[(2-thienylsulfonyl)amino]-1*H*-inden-5-yl]-4,6-dimethyl-4′-(trifluoromethyl)- 12gR: melting at 161−162 °C; $[\alpha]_D$ +5.89 (*c* 1.21, CH_3OH). Anal. ($C_{29}H_{25}F_3N_2O_3S_2$).

Carbamic Acid, [(2*R*)-5-[[[4,6-Dimethyl-4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-2,3-dihydro-1H-inden-2-yl]-, Methyl Ester 8gR: melting at 144−145 °C; $[\alpha]_D$ −12.82 (*c* 8.35, DMSO); ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 7.66 (s, 1H), 7.45 (s, 2H), 7.42 (s, 1H), 7.24 (s, 1H), 7.05 (s, 1H), 7.02 (s, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 6.69 (d, 1H), 4.81 (d, 1H), 4.47 (m, 1H), 3.65 (s, 3H), 3.21 (d, 1H), 3.15 (d, 1H), 2.73 (d, 1H), 2.67 (d, 1H), 2.42 (s, 3H), 2.13 (s, 3H). Anal. ($C_{27}H_{25}F_3N_2O_3$) C, H, N.

Carbamic Acid, [(2*S*)-5-[[[4,6-Dimethyl-4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-2,3-dihydro-1H-inden-2-yl]-, Methyl Ester 8gS: melting at 147−148 °C; $[\alpha]_D$ +10.20 (*c* 8.56, DMSO). Anal. ($C_{27}H_{25}F_3N_2O_3$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[2-(Acetylamino)-2,3-dihydro-1*H*-inden-5-yl]-4′-(trifluoromethyl)- 13b: melting at 210−212 °C; ^{1}H NMR (DMSO-d_6) δ 10.2 (s, 1H), 8.10 (d, 1H), 7.77 (s, 1H), 7.74 (s, 1H), 7.50−7.65 (m, 6H), 7.42 (s, 1H), 7.22 (d, 1H), 7.10 (d, 1H), 4.40 (m, 1H), 3.09 (m, 2H), 3.04 (m, 2H), 1.77 (s, 3H).

Benzamide, *N*-[2,3-Dihydro-5-[[[4′-(trifluoromethyl)-[1,1′-biphenyl]-2-yl]carbonyl]amino]-1*H*-inden-2-yl]- 14b:

melting at 253−255 °C; ^{1}H NMR (DMSO-d_6) δ 10.2 (s, 1H), 8.63 (d, 1H), 7.86 (s, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 7.65−7.40 (m, 10H), 7.22 (d, 1H), 7.10 (d, 1H), 4.69 (m, 1H), 3.18 (m, 2H), 2.90 (m, 2H); *m*/*z* 518.0 (M + NH_4).

[1,1′-Biphenyl]-2-carboxamide, *N*-[2-[[(Dimethylamino)carbonyl]amino]-2,3-dihydro-1*H*-inden-5-yl]-4′-(trifluoromethyl)- 15b: melting at 231−233 °C; ^{1}H NMR (DMSO-d_6) δ 10.20 (s, 1H), 7.76 (s 1H), 7.70 (s, 1H), 7.65−7.45 (m, 8H), 7.37 (s, 1H), 7.19 (d, 1H), 7.04 (d, 1H), 6.31 (d, 1H), 4.32 (m, 1H), 3.04 (d, 1H), 2.97 (d, 1H), 2.76 (s, 6h), 2.72 (m, 2H). Anal. ($C_{26}H_{24}F_3N_3O_2$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[2,3-Dihydro-2-[(phenylmethyl)amino]-1*H*-inden-5-yl]-4′-(trifluoromethyl)- 16b: melting at 179−183 °C; ^{1}H NMR (DMSO-d_6) δ 10.2 (s, 1H), 7.78 (s, 1H), 7.74 (s, 1H), 7.67−7.50 (m, 7H), 7.40−7.18 (m, 6H), 7.05 (d, 1H), 3.74 (s, 2H), 3.49 (m, 1H), 3.01 (m, 1H), 2.66 (m, 2H). Anal. ($C_{30}H_{25}F_3N_2O$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[2,3-Dihydro-2-[(phenylsulfonyl)amino]-1*H*-inden-5-yl]-4′-fluoro-6-methyl- 10h: melting at 192−195 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.90 (s, 1H), 7.7−7.5 (m, 3H), 7.4−6.6 (m, 11H), 4.69 (d, 1H), 4.12 (m, 1H), 3.05 (m, 2H), 2.70 (m, 2H), 2.12 (s, 3H). Anal. ($C_{29}H_{25}FN_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[2,3-Dihydro-2-[(2-thienylsulfonyl)amino]-1*H*-inden-5-yl]-4′-fluoro-6-methyl- 12h: melting at 114−115 °C; ^{1}H NMR (DMSO-d_6) δ 9.95 (s, 1H), 8.20 (d, 1H), 7.95 (d, 1H), 7.61 (d, 1H), 7.4−7.1 (m, 7H), 6.98 (d, 1H), 3.93 (m, 1H), 2.9 (m, 2H), 2.55 (m, 2H), 2.18 (s, 3H). Anal. ($C_{27}H_{23}FN_2O_3S_2$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[2,3-Dihydro-2-[(methylsulfonyl)amino]-1*H*-inden-5-yl]-4′-fluoro-6-methyl- 11h: melting at 208−210 °C; ^{1}H NMR (DMSO-d_6) δ 9.95 (s, 1H), 7.45−7.1 (m, 10H), 7.02 (d, 1H), 4.06 (m, 1H), 3.12 (d, 1H), 3.08 (d, 1H), 2.94 (s, 3H), 2.75 (m, 2H), 2.10 (s, 3H). Anal. ($C_{24}H_{23}FN_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[2,3-Dihydro-2-[(phenylsulfonyl)amino]-1*H*-inden-5-yl]-4′,6-dimethyl- 10i: melting at 104−107 °C; ^{1}H NMR (CDCl) δ 7.90 (s, 1H), 7.88 (s, 1H), 7.76 (d, 1H), 7.65−7.50 (m, 3H), 7.4−7.2 (m, 6H), 7.07 (s, 1H), 6.93 (d, 1H), 6.86 (s, 1H), 6.52 (d, 1H), 4.68 (d, 1H), 4.11 (m, 1H), 3.05 (m, 2H), 2.64 (m, 2H), 2.41 (s, 3H), 2.16 (s, 3H). Anal. ($C_{30}H_{28}N_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, 4′-Cyano-*N*-[2,3-dihydro-2-[(phenylsulfonyl)amino]-1*H*-inden-5-yl]-6-methyl- 10j: melting at 133−136 °C; ^{1}H NMR (DMSO-d_6) δ 10.1 (s, 1H), 8.0 (m, 2H), 7.90−7.77 (m, 4H), 7.70−7.55 (m, 4H), 7.46−7.0 (m, 6H), 3.86 (m, 1H), 2.82 (m, 2H), 2.60 (m, 2H), 2.50 (s, 3H); *m*/*z* 508.6 (M + 1).

[1,1′-Biphenyl]-2-carboxamide, 4′-Chloro-*N*-[2,3-dihydro-2-[(phenylsulfonyl)amino]-1*H*-inden-5-yl]-6-methyl- 10k: melting at 224−226 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (s, 1H), 7.89 (s, 1H), 7.65−7.5 (m, 4H), 7.4 (m, 4H), 7.25 (s, 1H), 7.23 (s, 1H), 7.12 (s, 1H), 6.98 (d, 1H), 6.87 (s, 1H), 6.70 (d, 1H), 4.68 (d, 1H), 4.10 (m, 1H), 3.0 (m, 2H), 2.68 (m, 2H), 2.14 (s, 3H). Anal. ($C_{29}H_{25}ClN_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, 4′-Chloro-*N*-[2,3-dihydro-2-[(methylsulfonyl)amino]-1*H*-inden-5-yl]-6-methyl- 11k: melting at 160−163 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (m, 2H), 7.45−7.0 (m, 7H), 6.86 (s, 1H), 6.75 (d, 1H), 4.48 (d, 1H), 4.35 (m, 1H), 3.30 (d, 1H), 3.23 (d, 1H), 3.01 (s, 3H), 2.86 (m, 2H), 2.12 (s, 3H). Anal. ($C_{24}H_{23}ClN_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, 4′-Chloro-*N*-[2,3-dihydro-2-[(2-thienylsulfonyl)amino]-1*H*-inden-5-yl]-6-methyl- 12k: melting at 217−219 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (m, 2H), 7.45−7.10 (m, 9H), 7.03 (d, 1H), 6.86 (s, 1H), 6.70 (d, 1H), 4.76 (d, 1H), 4.21 (m, 1H), 3.10 (m, 2H), 2.7 (m, 2H), 2.18 (s, 3H). Anal. ($C_{27}H_{23}ClN_2O_3S_2$) C, H, N.

Carbamic Acid, [(2*R*)-5-[[(4′-Chloro-4,6-dimethyl[1,1′-biphenyl]-2-yl)carbonyl]amino]-2,3-dihydro-1*H*-inden-2-yl]-, Methyl Ester 8lR: melting at 140−141 °C; $[\chi]_D$ −10.06 (*c* 9.21 DMSO); ^{1}H NMR ($CDCl_3$) δ 7.48 (s, 1H), 7.43 (s, 1H), 7.40 (s, 1H), 7.3−7.2 (m, 3H), 7.26 (s, 1H), 7.05 (d, 1H), 6.83 (s, 1H), 6.72 (d, 1H), 4.87 (br, 1H), 4.48 (m, 1H), 3.66 (s, 3H), 3.23 (m, 2H), 2.73 (m, 2H), 2.40 (s, 3H), 2.12 (s, 3H). Anal. ($C_{26}H_{25}ClN_2O_3$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, 4′-Chloro-*N*-[2,3-dihydro-2-[(phenylsulfonyl)amino]-1*H*-inden-5-yl]-6-methoxy- 10m: melting at 148−150 °C; ^{1}H NMR (CDCl) δ 7.91 (s, 1H), 7.86 (s, 1H), 7.65−7.30 (m, 9H), 7.07 (m, 2H), 6.96 (d, 2H), 6.75 (s, 1H), 6.65 (d, 1H), 4.67 (d, 1H), 4.12 (m, 1H), 3.75 (s, 3H), 3.05 (m, 2H), 2.65 (m, 2H). Anal. ($C_{29}H_{25}ClN_2O_4S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, 4′-Chloro-*N*-[2,3-dihydro-2-[(methylsulfonyl)amino]-1*H*-inden-5-yl]-6-methoxy- 11m: melting at 99−102 °C; ^{1}H NMR (DMSO-d_6) δ 10.01 (s, 1H), 7.5−7.0 (m, 11H), 4.08 (m, 1H), 3.70 (s, 3H), 3.15 (d, 1H), 3.08 (d, 1H), 2.94 (s, 3H), 2.77 (m, 2H). Anal. ($C_{24}H_{23}ClN_2O_4S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[2,3-Dihydro-2-[(phenylsulfonyl)amino]-1*H*-inden-5-yl]- 10n: melting at 100−103 °C; ^{1}H NMR (DMSO-d_6) δ 10.10 (s, 1H), 8.03 (d, 1H), 7.85 (s, 1H), 7.82 (s, 1H), 7.7−7.25 (m, 13H), 7.17 (d, 1H), 6.98 (d, 1H), 3.87 (m, 1H), 2.75 (m, 2H), 2.62 (m, 2H). Anal. ($C_{28}H_{24}N_2O_3S$) C, H, N.

1-Piperazinecarboxylic Acid, 4-[(2*R*)-2,3-Dihydro-5-[[[6-methyl-4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-1*H*-inden-2-yl]-, Methyl Ester (19aR). To a solution of **18** (0.339, 1.705 mmol) in 3 mL of diisopropylethylamine was added **9a** (0.70 g, 1.705 mmol). The mixture was heated to reflux for 3 h, cooled, and concentrated, and the residue was taken up in aqueous $NaHCO_3$ and EtOAc. The organic layer was dried, filtered, concentrated, and chromatographed on silica gel eluting with EtOAc to give 130 mg (14%) of **19aR** as a solid melting at 177−178 °C: $[\alpha]_D$ −2.9 (*c* 10.26, DMSO); ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.70 (s, 1H), 7.60 (m, 1H), 7.4 (m, 4H), 7.03 (m, 2H), 6.91 (s, 1H), 6.72 (d, 1H), 3.70 (s, 3H), 3.54 (m, 4H), 3.19 (m, 1H), 3.0 (m, 2H), 2.71 (m, 2H), 2.52 (m, 2H); chiral purity >99%. Anal. ($C_{30}H_{30}F_3N_3O_3$) C, H, N. Prepared similarly was **19aS**: melting at 94−97 °C; $[\alpha]_D$ +3.5 (*c* 5.00, DMSO); chiral purity >99%. Anal. ($C_{30}H_{30}F_3N_3O_3$) C, H, N.

1*H*-Inden-2-ol, 2,3-Dihydro-, Methanesulfonate (20). To a 0 °C solution of 2-indanol (20 g, 149 mmol) in 300 mL of CH_2Cl_2 and diisopropylethylamine (28.6 mL, 164 mmol) was added methylsulfonyl chloride (11.5 mL, 149 mmol) and (dimethylamino)pyridine (1.82 g, 14.9 mmol). The mixture was stirred for 30 min without cooling. An additional 0.2 equiv of diisopropylamine and methylsulfonyl chloride was added and the mixture stirred for 16 h. The organic layer was washed with 1 N HCl, $NaHCO_3$, and brine, dried, filtered, concentrated, and recrystallized from ethanol to give 28.4 g (90%) of **20** as a solid.

1*H*-Indene-2-carbonitrile, 2,3-Dihydro- (21). A mixture of **20** (10 g, 47.17 mmol) and sodium cyanide (3.10 g, 63.7 mmol) in 100 mL of DMF was heated to 90 °C for 3 h. The mixture was poured into ice water and extracted with ether. The ether layer was washed with brine and aqueous lithium chloride, dried, filtered, concentrated, and chromatographed on silica gel eluting with EtOAc/hexanes (1:4) to give 3.3 g (49%) of **21** as a yellow oil.

1*H*-Indene-2-methanamine, 2,3-Dihydro- (22). To a 0 °C solution of **21** (3.5 g, 24.47 mmol) in 100 mL of ether was added lithium alluminum hydride (0.929 g, 24.27 mmol). The mixture was stirred for 3 h, and 1.8 mL of water, 0.93 mL of 15% NaOH, another 4.5 mL of water, and 100 mL of EtOAc were added. To this mixture was added $MgSO_4$, and the solids were removed by filtration. The filtrate was concentrated to give 2.65 g (93%) of **22**. This material was used as is in the next step.

Carbamic Acid, [(2,3-Dihydro-1*H*-inden-2-yl)methyl], Methyl Ester (23). To a 0 °C solution of **22** (2.2 g, 14.9 mmol) and diisopropylethylamine (3.31 mL, 17.9 mmol) in 50 mL of CH_2Cl_2 was added methyl chloroformate. The mixture was stirred for 1 h, and the organics were washed with 1 N HCl, $NaHCO_3$, and brine, dried, filtered, concentrated, and chromatographed on silica gel eluting with EtOAc/hexanes (1:4) to give 2.18 g (71%) of **23**.

Carbamic Acid, [(2,3-Dihydro-5-nitro-1*H*-inden-2-yl)-methyl]-, Methyl Ester (24). To a 0 °C solution of **23** (2.18 g, 10.6 mmol) in 13.2 mL of trifluoroacetic acid was added fuming nitric acid (2.71 mL, 66.5 mmol). The mixture was stirred for 3 h, and CH_2Cl_2 and ice water were added. The organic layer was washed with water, $NaHCO_3$, and brine, dried, filtered, concentrated, and chromatographed on silica gel eluting with EtOAc/hexanes (1:3) to give 2.6 g (98%) of **24**.

Carbamic Acid, [(5-Amino-2,3-dihydro-1*H*-inden-2-yl)-methyl]-, Methyl Ester (25). A mixture of **24** (2.6 g, 10.4 mmol) and 0.3 g of 10% palladium on carbon in 50 mL of EtOAc at room temperature was hydrogenated at 50 psi of 16 h. The mixture was filtered and concentrated to give 2.05 g (82%) of **25**.

Carbamic Acid, [[2,3-Dihydro-5-[[[6-methyl-4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-1*H*-inden-2-yl]methyl]-, Methyl Ester (26a). To a 0 °C solution of **25** (183 mg, 0.832 mmol) in 10 mL of CH_2Cl_2 was added pyridine (0.081 mL, 0.998 mmol) followed by **7a** (1.93 mL, 0.998 mmol, 0.516 M in CH_2Cl_2). The mixture was stirred for 30 min, washed with 1 N HCl, $NaHCO_3$, and brine, dried, filtered, concentrated, and chromatographed on silica gel eluting with EtOAc/hexanes (2:3) to give 360 mg (90%) of **26a** as a foam. Crystallization from EtOAc/hexanes/Et_2O gave a sample melting at 137−139 °C: ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.67 (s, 1H), 7.57 (m, 1H), 7.5−7.3 (m, 4H), 7.1−6.9 (m, 3H), 6.72 (d, 1H), 4.87 (bs, 1H), 3.64 (s, 3H), 3.20 (m, 2H), 2.9 (m, 2H), 2.7−2.5 (m, 3H), 2.15 (s, 3H). Anal. ($C_{27}H_{25}F_3N_2O_3$) C, H, N.

Prepared similarly as previously described are the following:

[1,1′-Biphenyl]-2-carboxamide, *N*-[2,3-Dihydro-2-[[(methylsulfonyl)amino]methyl]-1*H*-inden-5-yl]-6-methyl-4′-(trifluoromethyl)- 28a: melting at 178−180 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.70 (s, 1H), 7.63 (m, 1H), 7.5−7.4 (m, 4H), 7.03 (m, 2H), 6.80 (s, 1H), 6.72 (d, 1H), 4.22 (t, 1H), 3.16 (t, 2H), 3.02 (m, 2H), 2.96 (s, 3H), 2.63 (m, 3H), 2.18 (s, 3H). Anal. ($C_{26}H_{25}F_3N_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, *N*-[2,3-Dihydro-2-[[(2-thienylsulfonyl)amino]methyl]-1*H*-inden-5-yl]-6-methyl-4′-(trifluoromethyl)- 29a: melting at 107−108 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1H), 7.70 (s, 1H), 7.65−7.57 (m, 3H), 7.5−7.4 (m, 4H), 7.09 (t, 1H), 7.0 (m, 2H), 6.81 (s, 1H), 6.70 (d, 1H), 4.53 (t, 1H), 3.08 (t, 2H), 2.97 (m, 2H), 2.6 (m, 3H), 2.16 (s, 3H). Anal. ($C_{29}H_{25}F_3N_2O_3S_2$) C, H, N.

Carbamic Acid, [[5-[[[4,6-Dimethyl-4′-(trifluoromethyl)-[1,1′-biphenyl]-2-yl]carbonyl]amino]-2,3-dihydro-1*H*-inden-2-yl]methyl]-, Methyl Ester 26g: melting at 108−110 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.70 (s, 1H), 7.47 (s, 2H), 7.43 (s, 1H), 7.25 (s, 1H), 7.01 (d, 1H), 6.97 (s, 1H), 6.78 (s, 1H), 6.71 (d, 1H), 4.75 (br, 1H), 3.70 (s, 3H), 3.24 (t, 2H), 3.01 (d, 1H), 2.96 (d, 1H), 2.7−2.5 (m, 3H), 2.41 (s, 3H). Anal. ($C_{28}H_{27}F_3N_2O_3$) C, H, N.

Carbamic Acid, [[5-[[(4′-Chloro-6-methyl[1,1′-biphenyl]-2-yl)carbonyl]amino]-2,3-dihydro-1*H*-inden-2-yl]-methyl]-, Methyl Ester 26k: melting at 133−135 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (m, 1H), 7.48−7.35 (m, 4H), 7.36 (m, 2H), 7.11 (s, 1H), 7.03 (d, 1H), 6.86 (s, 1H), 6.74 (d, 1H), 4.79 (br, 1H), 3.67 (s, 3H), 3.23 (t, 2H), 2.97 (m, 2H), 2.61 (m, 3H), 2.16 (s, 3H). Anal. ($C_{26}H_{25}ClN_2O_3$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, 4′-Chloro-*N*-[2,3-dihydro-2-[[(methylsulfonyl)amino]methyl]-1*H*-inden-5-yl]-6-methyl- 28k: melting at 65−66 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 1H), 7.4−7.2 (m, 4H), 7.27 (m, 2H), 7.25 (s, 1H), 7.05 (d, 1H), 6.86 (s, 1H), 6.74 (d, 1H), 4.30 (br, 1H), 3.17 (t, 2H), 3.05 (m, 2H), 2.95 (s, 3H), 2.65 (m, 3H), 2.16 (s, 3H). Anal. ($C_{25}H_{25}ClN_2O_3S$) C, H, N.

Acetic Acid, (1,3-Dihydro-2*H*-inden-2-ylidene)-, Methyl Ester (30). To an ice bath cooled suspension of sodium hydride (4.74 g, 118 mmol) in 100 mL of THF was added trimethylphosphonoacetate (21.6 g, 118 mmol). The mixture was stirred at room temperature for 30 min and cooled with an ice bath, and 2-indanone (6.5 g, 49.4 mmol) in 100 mL of THF was added dropwise. The mixture was stirred overnight, poured into saturated sodium chloride, and extracted with EtOAc. The organic extracts were dried over magnesium sulfate, filtered, concentrated under reduced pressure, and purified by silica gel chromatography eluting first with hexanes followed with CH_2Cl_2 to give 5.8 g (76%) of **30** as a yellow oil.

1*H*-Indene-2-acetic Acid, 2,3-Dihydro-, Methyl Ester (31). A solution of **30** (5.5 g, 29.2 mmol) in 100 mL of EtOAc was degassed, and 10% palladium on carbon (1.5 g) was added. The mixture was shaken under 50 psi of H_2 gas for 1 h. The mixture was filtered and concentrated under reduced pressure to give 5.6 g (100%) of **31** a white solid.

1*H*-Indene-2-acetamide, 2,3-Dihydro- (32). A mixture of **31** (2.85 g, 15 mmol), concentrated ammonium hydroxide (60 mL), and ammonium chloride (2.4 g, 45 mmol) was stirred in a pressure bottle at 100 °C for 16 h. The mixture was cooled to room temperature and then placed in an ice bath. The solid was collected, washed with water, and dried under reduced pressure to give 1.85 g (71%) of **32**.

1*H*-Indene-2-ethanamine, 2,3-Dihydro- (33). To a room temperature solution of **32** (3.5 g, 20 mmol) in 200 mL of THF was added in portions lithium aluminum hydride (1.14 g, 30 mmol). The mixture was stirred for 30 min, refluxed for 4 h, and stirred at room temperature overnight. The reaction was quenched with the sequential addition of water (4.2 mL), 15% NaOH (4.2 mL), and water (12.6 mL), diluted with EtOAc, dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give 3.6 g of **33** as a brown oil. The crude material was used as is and purified as the methyl carbamate.

Prepared similarly as previously described was **carbamic acid, [2-[2,3-dihydro-5-[[[6-methyl-4′-(trifluoromethyl), [1,1′-biphenyl]-2-yl]carbonyl]amino]-1*H*-inden-2-yl]ethyl], methyl ester (34a)**: melting at 162−165 °C; ^{1}H NMR ($CDCl_3$) δ 7.81 (d, 1H), 7.7−7.4 (m, 6H), 7.09 (s, 1H), 7.04 (d, 1H), 6.86 (s, 1H), 6.79 (d, 1H), 4.65 (br, 1H), 3.66 (s, 3H), 3.24 (m, 2H), 3.00 (dd, 2H), 2.50 (m, 3H), 1.68 (t, 2H), 1.57 (s, 3H). Anal. ($C_{28}H_{27}F_3N_2O_3$) C, H, N.

Hydroxylamine, *N*-(6,7,8,9-Tetrahydro-5*H*-benzo[*a*]cyclohepten-7-yl)- (35). To 5,6,8,9-tetrahydro-7*H*-cycloheptabenzen-7-one (3.33 g, 20.7 mmol) and hydroxylamine hydrochloride (2.17 g, 31.2 mmol) in 40 mL of water was slowly added a solution of sodium carbonate (1.65 g, 15.59 mmol) in 20 mL of water. The mixture was stirred overnight. The solid was filtered off, washed with water, and dried at 50 °C under reduced pressure to give 2.04 g (56%) of **35** as a white solid.

5*H*-Benzo[*a*]cyclohepten-7-amine, 6,7,8,9-Tetrahydro- (36). To a suspension of $NaBH_4$ (1.72 g, 45.5 mmol) in 40 mL of DMF cooled in an ice bath was added $TiCl_4$ (4.11 g, 21.7 mmol). To this mixture was added **35** (1.9 g, 10.8 mmol) in 40 mL of DMF dropwise. The mixture was stirred overnight, poured into ice water (150 mL), made basic with 28% ammonia (20 mL), and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 1.8 g of **36** as an oil. The crude material was used as is and purified as the methyl carbamate.

Prepared similarly as previously described are the following:

Carbamic Acid, [6,7,8,9-Tetrahydro-2-[[[6-methyl-4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-5*H*-benzo[*a*]cyclohepten-7-yl]-, Methyl Ester (37a): melting at 190−193 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.71 (s, 1H), 7.63 (m, 1H), 7.47−7.37 (m, 4H), 6.96 (d, 1H), 6.86 (d, 1H), 6.79 (s, 1H), 6.76 (s, 1H), 4.62 (br, 1H), 3.76 (m, 1H), 3.66 (s, 3H), 2.67 (m, 4H), 2.17 (s, 3H), 2.11 (m, 2H), 1.23 (m, 2H). Anal. ($C_{28}H_{27}F_3N_2O_3$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, 6-Methyl-*N*-[6,7,8,9-tetrahydro-7-[(methylsulfonyl)amino]-5H-benzo[*a*]cyclohepten-2-yl]-4′-(trifluoromethyl)- 38a: melting at 131−134 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1H), 7.72 (s, 1H), 7.64 (m, 1H), 7.5−7.4 (m, 4H), 6.97 (d, 1H), 6.86 (d, 1H), 6.81 (s, 2H), 4.19 (d, 1H), 3.62 (m, 1H), 2.98 (s, 3H), 2.68 (m, 4H), 2.18 (m, 2H), 2.15 (s, 3H), 1.41 (m, 2H). Anal. ($C_{27}H_{27}F_3N_2O_3S$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, 6-Methyl-*N*-[6,7,8,9-tetrahydro-7-[(2-thienylsulfonyl)amino]-5*H*-benzo[*a*]cyclohepten-2-yl]-4′-(trifluoromethyl)- 39a: melting at 209−212 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.69 (s, 1H), 7.63 (m, 3H), 7.43 (m, 4H), 7.10 (m, 1H), 6.93 (d, 1H), 6.82 (d, 1H), 6.78 (s,

2H), 4.53 (d, 1H), 3.54 (m, 1H), 2.7−2.5 (m, 4H), 2.16 (s, 3H), 2.0 (m, 2H), 1.45 (m, 2H). Anal. ($C_{30}H_{27}F_3N_2O_3S_2$) C, H, N.

Carbamic Acid, [2-[[[4,6-Dimethyl-4′-(trifluoromethyl)-[1,1′-biphenyl]-2-yl]carbonyl]amino]-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-7-yl]-, Methyl Ester 37g: melting at 158−161 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 7.69 (s, 1H), 7.45 (s, 2H), 7.43 (s, 1H), 7.24 (s, 1H), 6.95 (d, 1H), 6.84 (d, 1H), 6.73 (s, 1H), 6.72 (s, 1H), 4.6 (br, 1H), 3.7 (m, 1H), 3.66 (s, 3H), 2.70−2.62 (m, 4H), 2.42 (s, 3H), 2.13 (s, 3H), 2.10 (m, 2H), 1.24 (m, 2H). Anal. ($C_{29}H_{29}F_3N_2O_3$) C, H, N.

[1,1′-Biphenyl]-2-carboxamide, 4′-Chloro-6-methyl-*N*-[6,7,8,9-tetrahydro-7-[(methylsulfonyl)amino]-5*H*-benzo-[*a*]cyclohepten-2-yl]- 38k: melting at 138−141 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 1H), 7.45−7.38 (m, 4H), 7.27 (m, 2H), 6.98 (d, 1H), 6.9−6.8 (m, 3H), 4.21 (d, 1H), 3.62 (m, 1H), 3.00 (s, 3H), 2.68 (m, 4H), 2.21 (m, 2H), 2.16 (s, 3H), 1.21 (m, 2H). Anal. ($C_{26}H_{27}ClN_2O_3S$) C, H, N.

Carbamic Acid, [2-[[(4′-Chloro-6-methyl[1,1′-biphenyl]-2-yl)carbonyl]amino]-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-7-yl]-, Methyl Ester 37k: melting at 184−187 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 1H), 7.45−7.35 (m, 4H), 7.28 (m, 2H), 6.97 (d, 1H), 6.9−6.8 (m, 3H), 4.62 (m, 1H), 3.80 (m, 1H), 3.66 (s, 3H), 2.69 (m, 4H), 2.16 (s, 3H), 2.13 (m, 2H), 1.3 (m, 2H). Anal. ($C_{27}H_{27}ClN_2O_3$) C, H, N.

References

(1) (a) Wetterau, J. R.; Zilversmit, D. B. A triglyceride and cholesterol ester transfer protein associated with liver microsomes. *J. Biol.Chem.* **1984**, *259*, 10863−10866. (b) Boren, J.; Rustaeus, S.; Wettesten, M.; Andersson, M.; Wiklund, A.; Olofsson, S. O. Influence of triacylglycerol biosynthesis rate on the assembly of ApoB-100-containing lipoproteins in Hep G2 cells. *Arterioscler. Thromb.* **1993**, *13*, 1743−1754. (c) Leiper, J. M.; Bayliss, J. D.; Pease, R. J.; Brett, D. J.; Scott, J.; Shoulders, C. C. Microsomal triglyceride transfer protein, the abetalipoproteinemia gene product, mediates the secretion of apolipoprotein B containing lipoproteins from heterologous cells. *J. Biol. Chem.* **1994**, *269*, 21951−21954.

(2) (a) Wetterau, J. R.; Gregg, R. E.; Harrity, T. W.; Arbeeny, C.; Cap, M.; Jolibois, K. G.; Kunselman, L. K.; Lan, S.-J.; Maccagnan, T. J.; Ricci, B.; Yan, M.; Young, D.; Chen, Y.; Fryszman, O. M.; Logan, J. V. H.; Musial, C. L.; Poss, M. A.; Robl, J. A.; Simpkins. L. M.; Slusarchyk, W. A.; Sulsky, R.; Taunk, P.; Magin, D. R.; Tino, J. A.; Lawrence, R. M.; Dickson, Jr., J. K.; Biller, S. A. An MTP inhibitor that normalizes atherogenic lipoprotein levels in WHHL rabbits. *Science* **1998**, *282*, 751−754. (b) Robl, J. A.; Sulsky, R.; Sun, C.-Q.; Simpkins, L. M.; Wang, T.; Dickson, J. K., Jr.; Chen, Y.; Magnin, D. R.; Taunk, P.; Slusarchyk, W. A.; Biller, S. A.; Lan, S.-J.; Connolly, F.; Kunselman, L. K.; Sabrah, T.; Jamil, H.; Gargon, D.; Harrity, T. W.; Wetterau, J. R. A novel series of highly potent benzimidazole-based microsomal triglyceride transfer protein inhibitors. *J. Med. Chem.* **2001**, *44*, 815−856.

(3) (a) Wetterau, J. R.; Aggerbeck, L. P.; Bouma, M. E.; Eisenberg, C.; Munck M., et al. Absence of microsomal triglyceride transfer protein in individuals with abetalipoproteinemia. *Science* **1992**, *258*, 999−1001. (b) Rader, D. J.; Brewer, H. B. Abetalipoproteinemia: New insights into lipoprotein assembly and vitamin E metabolism from a rare genetic disease. *JAMA−J. Am. Med. Assoc.* **1993**, *270*, 865−869. (c) Shoulders, C. C.; Brett, D. J.; Bayliss, J. D.; Narcisi, T.; Jaruz, A.; Grantham, T. T., et al. Abetalipoproteinemia is caused by defects of the gene encoding the 97 kDa subunit of a microsomal triglyceride transfer protein. *Hum. Mol. Genet.* **1993**, *2*, 2109−2116.

(4) (a) Leiper, J. M.; Bayliss, J. D.; Pease, R. J.; Brett, D. J.; Scott, J.; Shoulders, C. C. Microsomal triglyceride transfer protein, the abetalipoproteinemia gene product, mediates the secretion of apolipoprotein B containing lipoproteins from heterologous cells. *J. Biol. Chem.* **1994**, *269*, 21951−21954. (b) Gordon, D. A.; Jamil, H.; Sharp, D.; Mullaney, D.; Yao, Z.; Gregg, R. E.; Wetterau, J. R. Secretion of apoB containing lipoproteins from HeLA cells dependent on expression of the microsomal triglyceride transfer protein and is regulated by lipid availability. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 7628−7632.

(5) (a) Lin, M. C.; Arbeeny, C.; Bergquist, K.; Kienzle, B.; Gordon, D. A.; Wetterau, J. R. Cloning and regulation of hamster microsomal triglyceride transfer protein. The regulation is independent from that of other hepatic and intestinal proteins which participates in the transport of fatty acids and triglycerides. *J. Biol. Chem.* **1994**, *269*, 29138−29145. (b) Patel, S. B.; Grundy, S. M. Heterologous expression of apolipoprotein B carboxy terminal truncates: a model for the study of lipoprotein biogenesis. *J. Lipid Res.* **1995**, *36*, 2090−2103. (c) Hahn, S. E.; Goldberg, D. M. Factors affecting the regulation of apoB secretion by liver cells. *J. Clin. Lab. Anal.* **1995**, *9*, 431−449. (d) Lamberg, A.; Jauhiainen, M.; Metso, J.; Ehnholm, C.; Shoulders, C.; Scott, J.; Pihlajaniemi, T.; Kivirikko, K. I. The role of protein disulfide isomerase in the microsomal triacylglycerol transfer protein does not reside in its isomerase activity. *Biochem. J.* **1996**, *315*, 533−536.

(6) Hodis, H. N.; Mack, W. J.; Azen, S. P.; Alaupovic, P.; Pogoda, J. M.; LaBree, L.; Hemphill, L. C.; Kramsch, D. M.; Blamkenhorn, D. H. Triglyceride and cholesterol rich lipoproteins have a differential effect on mild/moderate and severe progression as assessed by quantitative coronary angiography in a controlled trial with Lovastatin. *Circulation* **1994**, *90*, 42−49.

(7) (a) Prashad, M.; Hu, B.; Har, D.; Repic, O.; Blacklock, T. J.; Acemoglu, M. Efficient and practical syntheses of *R*-(5-amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester. *Adv. Synth. Catal.* **2001**, *343*, 461−472. (b) Manuscript for the preparation of (*R*)- and (*S*)-(5-amino-2,3-dihydro-1*H*-inden-2-yl)-carbamic acid methyl ester (**1R**, **1S**) from *R* and *S*-phenylalanine is in progress.

(8) For the preparation of racemic **1** see patent WO 0005201.

(9) ApoB secretion assay conditions were modified from literature procedures. (a) Ordovas, J. M.; Oeterson, J. P.; Santaniello, P.; Cohn, J.; Wilson, P.; Schaefer, E. *J. Lipid Res.* **1987**, *28*, 1216. (b) Calvo, C.; Bustos, P.; Giraudo, P.; Ulloa, N.; Sepulveda, J.; Verdugo, C.; Toledo, L. A. *J. Atheroscler Thromb.* **1997**, *4*, 45.

(10) MTP transfer assay conditions were modified from literature procedures. Haghpassand, M.; Wilder, D.; Moberly, J. B. *J. Lipid Res* **1996**, *37*, 1468.

JM010294E