12, 93349-38-3; 12·$H_2C_2O_4$, 93349-47-4; 13, 93349-39-4; 13·$H_2C_2O_4$, 93349-48-5; 14, 93349-40-7; 14·$H_2C_2O_4$, 93349-49-6; 15, 93349-41-8; 15·$H_2C_2O_4$, 93349-50-9; 16, 36125-06-1; 17, 83495-51-6; 18, 3897-89-0; 19, 619-73-8; 20, 22114-98-3; 21, 13605-19-1; 3-pentanone oxime, 1188-11-0; cyclopentanone oxime, 1192-28-5; cyclohexanone oxime, 100-64-1; 4-heptanone oxime, 1188-63-2; 2,4-dimethyl-3-pentanone oxime, 1113-74-2; isopropylamine, 75-31-0; *tert*-butylamine, 75-64-9.

Syntheses and Complement Inhibitory Activities of 4-(2-Phenyl-1*H*-indol-3-yl)cyclohexane-1-carboxylic Acids

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The syntheses of 4-(2-phenyl-1*H*-indol-3-yl)cyclohexane-1-carboxylic acids are described. These compounds express potent in vitro inhibition of the human classical complement pathway, and qualitative SAR have been determined. Several of the in vitro active compounds also suppressed the complement dependent reverse passive Arthus reaction (RPAR) in guinea pigs.

The potential utility for drugs that inhibit complement dependent acute inflammatory events in diseases such as rheumatoid arthritis,[2] lupus erythematosus,[3] and glomerulonephritis[4] has been well documented. Although many chemicals, including several antiinflammatory agents, have been reported to be inhibitory of the complement cascade in vitro,[5] none has been shown to display clinical efficacy via this mechanism. Thus, with clear relevance to disease, an investigation was initiated to discover a complement inhibitory drug that would have utility in the treatment of acute inflammatory disease. It is the purpose of this paper to report on results of this effort by describing the syntheses and potent classical complement pathway inhibitory properties of a series of 4-(2-phenyl-1*H*-indol-3-yl)cyclohexane-1-carboxylic acids (**5–18**).

Chemistry. Scheme I depicts the several routes used to prepare the 4-(2-phenyl-1*H*-indol-3-yl)cyclohexanecarboxylic acids **5–18**. Central in this scheme is the $AcOH/Ac_2O/H_3PO_4$ condensation[6] of 2-phenyl-1*H*-indole (**1**) or 1-methyl-2-phenyl-1*H*-indole (**2**) with either 4-oxo-1,1-cyclohexanedicarboxylic acid (**3**) or 4-oxocyclohexanecarboxylic acid (**4**) that produced **5**, **6**, or **7**.

The reaction of **5** with $MeOH/MeSO_3H$ or $MeI/K_2CO_3/DMF$ gave the **5** Me ester. Similarly, **6** diMe ester or **7** diMe ester were formed upon treatment of **6** or **7** with $MeI/K_2CO_3/DMF$. N-Alkylation of **5** Me ester with $MeI/KOH/Me_2SO$[7] gave **8** Me ester, which was hydrolyzed with aqueous KOH to give **8**. N-Alkylation products **9** and **10** were prepared by alkylation of **5** with excess EtI or PrBr and NaH in DMF followed by KOH hydrolysis of the intermediate esters. The EtI alkylation procedure with NaH followed by alkaline hydrolysis was also used to prepare **11** from **6** diMe ester.

Hydrogenation of diacids **6** or **7** over Pd/C gave directly **12** and **13**, respectively. Hydrogenation products of monoacid **8** were prepared by a circuitous route which involved hydrogenation of **8** Me ester to give both cis (predominant) and trans (minor) products which were separated and hydrolyzed to the acids **14** and **15**. Stereochemical assignments of cis for **14** and **14** Me ester, and trans for **15** and **15** Me ester were based on the reported higher ^{13}C NMR cyclohexane methylene absorption frequencies for cis relative to trans of 1,4-dimethylcyclohexane[8] and 4-(1,1-dimethylethyl)-1-(methylsulfinyl)-

Table I. Effect of 4-(2-Phenyl-1*H*-indol-3-yl)cyclohexane-1-carboxylic Acids on the Classical Complement Pathway in Vitro and the Reverse Passive Arthus Reaction (RPAR) in Guinea Pigs[a]

compd	classical complement pathway inhibn, IC_{50}[b]	RPAR, inhibn (dose[c])
5	135 ± 2	64 ± 7[d] (80 iv)
6	485 ± 17	38 ± 8[e] (100 ip)
7	149 ± 25	
8	34 ± 3	78 ± 6[e] (300 ip)
9	65 ± 5	
10	93 ± 44	
11	130 ± 20	
12	425 ± 105	
13	231 ± 7	
14	>1000	66 ± 5[e] (100 ip)
15	42 ± 21	55 ± 8[d] (100 ip)
16	51 ± 15	76 ± 5[d] (100 ip)
17	105 ± 4	
18	51 ± 11	44 ± 14[f] (100 ip)
gold sodium thiomalate (GST)	1070 ± 90	
cobra venom factor (CVF)		ED_{50} = 7.9 units/kg ip

[a] See Experimental Section for details of assay systems. [b] IC_{50} in μM. [c] Dose in mg/kg. [d] $p < 0.001$. [e] $p < 0.01$. [f] $p < 0.025$.

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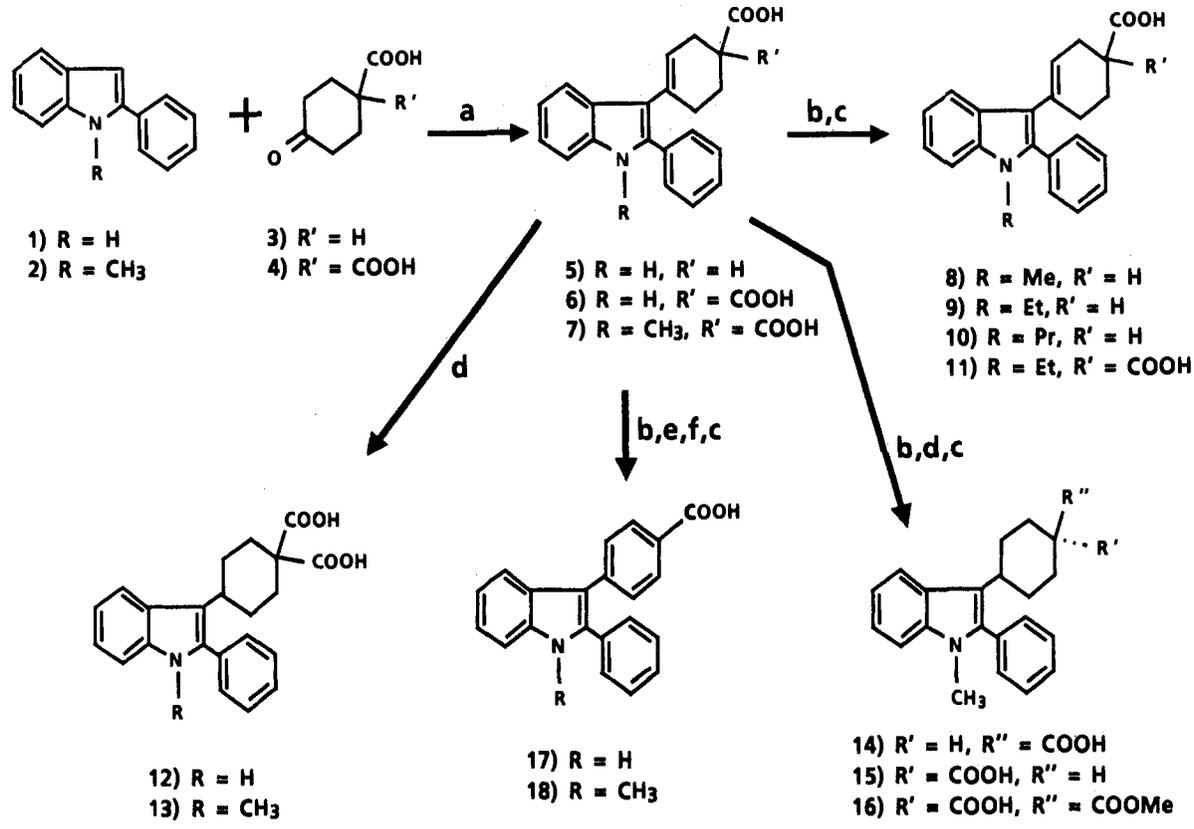
Scheme I[a]



[a] (a) H_3PO_4, AcOH, Ac_2O. (b) Base, RX. (c) KOH. (d) H_2, Pd/C. (e) K_2CO_3, MeI. (f) DDQ.

cyclohexane[9]. Thus, *cis*-14 and *cis*-14 Me ester have $C_{2,6}$ absorptions at δ 27.3 and 27.8 and $C_{3,5}$ absorptions at δ 28.6 and 29.1, respectively, while *trans*-15 and *trans*-15 Me ester have $C_{2,6}$ absorptions at δ 31.6 and 32.3 and $C_{3,5}$ absorptions at δ 29.1 and 29.4, respectively. Hydrogenation of 7 diMe ester followed by mild basic hydrolysis gave a single monoacid–monoester 16 which was assigned trans acid stereochemistry because equatorial cyclohexanecarboxylic acid esters are known to be more rapidly hydrolyzed than their axial isomers.[10]

Aromatization of 5 Me ester or 8 Me ester with DDQ followed by alkaline hydrolysis gave benzoic acids 17 and 18, respectively.

Biology. Compounds 5–18 were evaluated in vitro for their inhibition of human complement (C1–C9) using hemolytic molecular titrations[11] (Table I), and comparative IC_{50}s were calculated from the resulting dose responses. The IC_{50} calculated for gold sodium thiomalate (GST), a known complement inhibitor,[12] was 1070 μM and has been included in Table I for reference purposes. Thirteen of the 14 carboxylic acids testes by this method exhibited potent inhibition of the classical complement pathway (Table I) with a range in IC_{50} from 34 (8) to 485 μM (6). Correlation of the IC_{50}s with structure has led to the identification of several structural features that enhance potency. The most important feature is the trans stereochemistry of the carboxylic acid relative to the indole on the cyclohexane ring which allows the indole and carboxylic acid moieties to be fully extended and maximally separated from each other. Compound 15 has this trans stereochemistry and has an IC_{50} = 42 μM, while 14, which has the cis stereochemistry, has an IC_{50} > 1000 μM. The trans carboxylic acid stereochemistry is also present in inhibitors 12, 13, and 16. Complement inhibitory, quasi-equatorial cyclohexenecarboxylic acids 5–11 and benzoic acids 17 and 18 have carboxylic acids that are positioned relative to the indole ring in an orientation similar to the trans cyclohexanes. The distance between the 3-indole carbon and the carboxylic acid for trans cyclohexane, cyclohexene, and benzene compounds is 5.8 Å as measured on Dreiding models, and the distance between these same carbons of the cis cyclohexane 14 is 4.8 Å. It should also be noted that rotation of the ring bearing the carboxylic acid about the 3-indole bond confers little change in the relative orientation of the carboxylic acid in the trans cyclohexane, cyclohexene, and benzene compounds, whereas the corresponding change is much greater in the cis cyclohexane compound 14. Of less importance, but contributing to enhanced potency, are the effects of N-alkylation of the indole and mono- or dicarboxylic acid functionality on the cyclohexanes. In six of seven cases tested, *N*-alkyl substituted compounds were significantly better inhibitors than the unsubstituted parents. Thus, 8, and 9 were more potent than 5. Similarly, 7 and 11 were more potent than 6, and 13 and 18 were more potent than 12 and 17, respectively. Only in the case of 10 was there a numerical but not statistically significant enhancement of activity over the unsubstituted 5. In the monocarboxylic acid series, *N*-Me substitution gave the most potent compound 8, while in the dicarboxylic acid series, activity of the *N*-Me compound 7 was not significantly different from the *N*-Et compound 11. The monocarboxylic acids 5, 8, 9, and 15 proved to be consistently more potent inhibitors than their

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dicarboxylic acid counterparts, **6**, **7**, **11**, and **13**, respectively. A parameter that did not seem to influence activity was the degree of saturation of the cyclohexane ring. Thus, **5** and **17** appeared to be equipotent, as were **15**, **8**, and **18**.

Prior to developing the structural requirements of complement inhibitory activity in this series, a specific inhibitory site within the complement cascade was determined for compound **6** and this will be the subject of a separate publication. The relatively selective inhibitory activity of **6** (unpublished data) suggests that the "qualitative" SAR reported here may be the result of a specific reaction step. Alternately, it is possible that more than a single complement site has been altered, making the interpretation of these data more difficult.

The effects of these compounds (**5**–**18**) on the alternative complement pathway activity was also determined by hemolytic molecular titrations. None expressed significant activity (data not shown).

The reverse passive Arthus reaction (RPAR) in guinea pigs was chosen as a complement mediated model of acute inflammation to be used to identify compounds with in vivo complement inhibitory activity. Cobra venom factor (CVF) is known to suppress the RPAR by depleting complement levels in animals and it was used as reference material.[13]

The suppressive effects on the RPAR displayed by several of the in vitro complement inhibitors, when administered iv or ip, are reported in Table I. No test compound was active via the oral route (data not shown). Although in vivo suppression of the RPAR was established for this series of compounds, this activity was not consistent with the structural requirements that were determined in vitro. Not only were the in vitro active compounds **5**, **6**, **8**, **15**, **16**, and **18** active in the RPAR but the inactive compound **14** also showed efficacy. Metabolism of **14** to a complement inhibitor is a possible explanation for this unexpected result. Alternatively, suppression of the RPAR might be via an unknown complement independent mechanism. Further investigations will be necessary to clarify this issue.

In summary, evidence has been presented supporting the contention that 4-(2-phenyl-1*H*-indol-3-yl)cyclohexane-1-carboxylic acids possess unique structural features related to classical complement pathway inhibitory activity. These unique structural features include (a) orientation of the carboxylic acid in a trans stereochemistry rather than cis relative to the indole, (b) having the indole nitrogen substituted, and (c) placing one carboxylic acid function rather than two at the 1-position of the cyclohexane.

Experimental Section

Biology. C1–C9 Molecular Titrations. Hemolytic molecular titrations of classical complement activity were performed according to Rapp and Borsos[11] and complement inhibition assessed according to Hong et al.[14] Operationally, drug was maintained in the presence of complement during the lytic reaction of sensitized erythrocytes. Equal volumes (0.2 mL) of normal human serum (NHS), diluted in GVB^{2+}[15] to effect lysis at $Z = 1$, and drug at various concentrations were mixed at 0 °C. The dilution of NHS effecting 63% lysis of optimally sensitized sheep erythrocyte (EA) was previously determined (1:100 to 1:200). EA (0.2 mL of 1.5×10^8 cells/mL) and 1.8 mL of GVB^{2+} were added to the reaction mixture followed by incubating at 37 °C for 60 min. The extent of lysis was determined spectrophotometrically at 412 nm. The ratio of drug treated to untreated (Z/Z_0) reaction mixtures was determined as a function of drug concentration. The concentration of drug effecting 50% suppression ($Z/Z_0 = 0.5$ or IC_{50}) was determined.

Reverse Passive Arthus Reaction (RPAR). Male guinea pigs (250–300 g) were administered chicken egg albumin (CEA) intravenously (20 mg/kg) immediately before intradermal injection of 0.2 mL of goat anti-CEA containing 2.4 mg of Ab protein/mL. The hemorrhagic response was allowed to develop for 4 h, and the animals were sacrificed and skin lesions excised. The skin sections were homogenized, water extracted, and cleared, and the optical density at 541 or 412 nm was determined. A paired Student t test was used to estimate significant inhibition of drug-treated groups. P values less than 0.025 were considered significant. Drug was administered ip 2 h before eliciting the Arthus response and iv administration was effected 20 min before elicitation.

Chemistry. Microanalytical determinations were obtained on all new compounds reported and were carried out by Instranal Laboratories, Inc., Rensselaer, NY, and Galbraith Laboratories Inc., Knoxville, TN. Analyses for the indicated elements were within ±0.4% of the theoretical values. Melting points are uncorrected. ^{13}C NMR spectra were determined on either a JEOL FX-60 60-MHz or JEOL FX-270 270-MHz instrument. Chemical shifts (δ) are reported in ppm relative to Me_4Si (δ 0.00, internal standard).

4-(2-Phenyl-1*H*-indol-3-yl)-3-cyclohexene-1-carboxylic Acid (5). A mixture of 100 g (0.52 mol) of 2-phenylindole, 80.8 g (0.57 mol) of 4-oxocyclohexanecarboxylic acid,[16] 518 mL of AcOH, 103.6 mL of Ac_2O, and 25.9 mL of 85% H_3PO_4 was stirred at room temperature for 3 days and chilled in an ice bath to 20 °C. The precipitate that resulted was collected, washed with H_2O, pressed dry, and taken up in ether. This solution was washed with H_2O three times and with brine one time, dried ($MgSO_4$), charcoaled, evaporated to 200 mL, and let stand for 2 days to give a precipitate. The precipitate was collected and combined with a second crop to give 72.7 g (44%) of **5**: mp 178–179 °C. A small portion was recrystallized from MeCN: mp 180–183 °C. Anal. ($C_{21}H_{19}NO_2$) C, H, N.

4-(2-Phenyl-1*H*-indol-3-yl)-3-cyclohexene-1,1-dicarboxylic Acid (6). By use of the method described for the preparation of **5**, 105.9 g (0.57 mol) of 4-oxo-1,1-cyclohexanedicarboxylic acid[16] was transformed into crude **6**, which was slurried with 250 mL of boiling MeCN and collected to give 78 g (42%) of **6**: mp 216 °C dec. A small portion was recrystallized from Et_2O:$CHCl_2$:hexane: mp 207–209 °C. Anal. ($C_{22}H_{19}NO_4$) C, H, N.

4-(1-Methyl-2-phenyl-1*H*-indol-3-yl)-3-cyclohexene-1,1-dicarboxylic Acid (7). A mixture of 9.0 g (0.043 mol) of 1-methyl-2-phenylindole, 9.3 g (0.05 mol) of 4-oxo-1,1-cyclohexanedicarboxylic acid, 100 mL of AcOH, 4.7 mL of Ac_2O, and 1 mL of 85% H_3PO_4 was stirred at room temperature for 17 h, and then 100 mL of H_2O was added dropwise to give a white solid which was collected and washed with H_2O. The solid was taken up in Et_2O, washed with H_2O three times and with brine two times, dried ($MgSO_4$), concentrated in vacuo, and crystallized from MeCN to give 8.4 g (52%) of **7**: mp 210–211 °C. Anal. ($C_{23}H_{21}NO_4$) C, H, N.

Methyl 4-(2-Phenyl-1*H*-indol-3-yl)-3-cyclohexene-1-carboxylate (5 Me Ester). A solution of 70.0 g (0.22 mol) of **5**, 35.2 g (1.1 mol) of MeOH, 350 mL of CH_2Cl_2, and 0.5 mL of methanesulfonic acid was heated under reflux for 21 h. The reaction mixture was cooled, washed with H_2O, dried (Na_2SO_4), concentrated in vacuo, and crystallized from EtOAc:hexane to give 51.8 g (71%) of **5** Me ester in two crops: mp 175–177 °C. Anal. ($C_{22}H_{21}NO_2$) C, H, N.

Alternatively, **5** Me ester (mp 166-175 °C) was prepared in 81% yield from 31 g (0.098 mol) of **5**, 47 g (0.34 mol) of powdered K_2CO_3, 47 mL (0.75 mol) of MeI, and 117 mL of DMF by using the method described for the preparation of dimethyl 4-(2-

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phenyl-1*H*-indol-3-yl)-3-cyclohexene-1,1-dicarboxylate (**6** diMe ester).

Methyl 4-(1-Methyl-2-phenyl-1*H*-indol-3-yl)-3-cyclohexene-1-carboxylate (8 Me Ester). A partial solution of 8.06 g (0.122 mol) of crushed KOH pellets in 100 of mL Me_2SO was prepared by stirring the mixture for 45 min. **5** Me ester (12.0 g, 0.036 mol) was added in portions with stirring during 15 min to the partial solution. The resulting dark-red solution was stirred for 45 min, cooled in an ice bath, and treated dropwise with 10.2 g (0.072 mol) of MeI in 50 mL Me_2SO. Stirring was continued at room temperature for 3 h. The reaction mixture was cooled again in an ice bath and 250 mL of H_2O was added followed by Et_2O. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O two times. The combined Et_2O solutions were washed with H_2O and brine, dried ($MgSO_4$), concentrated in vacuo, and crystallized from Et_2O:hexane to give 10.4 g of a solid (mp 122–125 °C). This solid was dissolved in $CHCl_3$ and the solution was charcoaled, concentrated in vacuo, and crystallized from $CHCl_3$:Et_2O:hexane two times to give 4.67 g (38%) of 8 Me ester: mp 135–136 °C. Anal. ($C_{23}H_{23}NO_2$) C, H, N.

4-(1-Methyl-2-phenyl-1*H*-indol-3-yl)-3-cyclohexene-1-carboxylic Acid (8). To a solution of 5.6 g (0.085 mol) of KOH in 150 mL of EtOH was added 6.9 g (0.020 mol) of 8 Me ester. This mixture was heated under reflux until solution resulted. Heating was continued 4 h and then the solution was cooled, concentrated in vacuo, dissolved in H_2O, and made acidic with 2 N HCl to give a precipitate. The solid was collected, washed with H_2O, dissolved in Et_2O, washed with H_2O, dried (Na_2SO_4), charcoaled, concentrated in vacuo, and recrystallized twice from Et_2O:hexane to give 5.6 g (85%) of **8**: mp 171–172 °C. Anal. ($C_{22}H_{21}NO_2$) C, H, N.

4-(1-Ethyl-2-phenyl-1*H*-indol-3-yl)-3-cyclohexene-1-carboxylic Acid (9). To 40 g (0.85 mol) of NaH (50% in oil) that was washed with pentane three times and stirred in 60 mL of DMF was added 12.2 g (0.38 mol) of **5** in portions. After the addition was complete, the mixture was heated at 50 °C for 2 h and then cooled in an ice bath, and 8 mL (0.10 mol) of EtI was added dropwise. The mixture was stirred at room temperature overnight and at 40 °C for 3 h. The reaction mixture was cooled, quenched with 250 mL of cold H_2O, and extracted with 500 mL of Et_2O. The Et_2O extract was washed with H_2O two times and brine one time, dried ($MgSO_4$), charcoaled, and concentrated in vacuo to give 13.5 g of an oil. This oil was combined with a solution of 2.6 g (0.04 mol) of KOH in 160 mL of EtOH and stirred at room temperature overnight. The reaction mixture was poured into 400 mL of cold H_2O, and the resulting mixture was washed with CH_2Cl_2 three times and Et_2O one time, filtered through filter cell, and made acidic with AcOH to give a precipitate. This precipitate was collected, washed with H_2O, and dried at 85 °C (0.1 mm) overnight to give 10.7 g (80%) of **9**: mp 147–150 °C. Anal. ($C_{23}H_{23}NO_2$) C, H, N.

4-(2-Phenyl-1-propyl-1*H*-indol-3-yl)-3-cyclohexene-1-carboxylic Acid (10). By use of the method described for the preparation of **9**, 15.0 g (0.047 mol) of **5** was transformed into 8.9 g (53%) of **10**: mp 126–127 °C. Anal. ($C_{24}H_{25}NO_2$) C, H, N.

4-(1-Ethyl-2-phenyl-1*H*-indol-3-yl)-3-cyclohexene-1,1-dicarboxylic Acid (11). A mixture of 56 g (0.15 mol) of **6**, 136 g (0.99 mol) of powdered K_2CO_3, and 369 mL of DMF was stirred at room temperature 2 h. MeI (146.8 mL, 2.08 mol) was added and the mixture was heated under reflux in a hot H_2O bath for 4 h. After stirring overnight at room temperature, the excess MeI was removed by concentrating the reaction mixture in vacuo at 30 °C. The mixture was then poured into 1200 mL of H_2O and extracted with EtOAc three times. The combined EtOAc extracts were washed with H_2O two times and brine one time, dried ($MgSO_4$), and concentrated in vacuo to give 63.1 g of the crude **6** diMe ester that was used in subsequent reactions without further purification.

To 1.8 g (0.37 mol) of NaH (50% in oil) that was washed three times with pentane and slurried and stirred in 50 mL of DMF was added 12 g (0.031 mol) of the crude **6** diMe ester in poritions. After addition was complete, the mixture was heated at 50 °C for 2 h and then cooled in an ice bath, and 3.0 mL (0.048 mol) of EtI was added dropwise. The mixture was stirred at room temperature overnight and at 40 °C for 3 h. The reaction mixture was cooled, quenched with 300 mL of cold H_2O, and extracted with Et_2O. The Et_2O extract was washed with H_2O two times and brine one time, dried ($MgSO_4$), and concentrated in vacuo to give 11.8 g of an oil which was combined with 4.3 g (0.065 mol) of KOH, 11.8 mL of H_2O, and 217 mL of EtOH, and heated under reflux for 5 h. The precipitate was collected (7.1 g), taken up in H_2O, filtered, and made acidic with 10% HCl to give a precipitate. This precipiate was collected, washed with H_2O, and dried at 70 °C (0.1 mm) overnight to give 5.7 g (49%) of **11**: mp 160–165 °C. Anal. ($C_{24}H_{23}NO_4$) C, H, N.

4-(2-Phenyl-1*H*-indol-3-yl)cyclohexane-1,1-dicarboxylic Acid (12). A solution of 5.3 g (0.015 mol) of **6** in 100 mL of EtOH was combined with 1.2 g of 10% Pd/C and hydrogenated on a Parr apparatus at room temperature for 3 h. After the catalyst was removed, the solution was concentrated in vacuo to a gum. This gum was crystallized from Et_2O:hexane and then recrystallized three times from Et_2O:hexane to give 4.0 g (74%) of **12**: mp 196–197 °C. Anal. ($C_{22}H_{21}NO_4$) C, H, N.

4-(1-Methyl-2-phenyl-1*H*-indol-3-yl)cyclohexane-1,1-dicarboxylic Acid (13). By use of the method described for the preparation of **12**, except that dioxane replaced EtOH as solvent, 7.5 g (0.020 mol) of **7** was hydrogenated to give 3.8 g (51%) of **13**: mp 230 °C dec (after one crystallization from acetone:hexane). Anal. ($C_{23}H_{23}NO_4$) C, H, N.

***cis*-4-(1-Methyl-2-phenyl-1*H*-indol-3-yl)cyclohexane-1-carboxylic Acid (14) and *trans*-4-(1-Methyl-2-phenyl-1*H*-indol-3-yl)cyclohexane-1-carboxylic Acid (15).** By use of the method described for the preparation of **13**, 35 g (0.10 mol) of **8** Me ester was hydrogenated to give 35 g of a gum that was a mixture of two products (SiO_2 TLC, toluene eluate, R_f 0.3 and 0.4). The gum was triturated with Et_2O and the solid that formed was collected, washed with Et_2O, and dried to give 18.8 g of solid that was recrystallized from heptane to give 14.4 g (41%) of **14** Me ester with TLC R_f 0.4: mp 125–126 °C; ^{13}C NMR ($CDCl_3$) δ 175.6 (COO), 137.2, 136.6, 132.4, 130.7, 128.1, 127.8, 126.2, 121.2, 120.3, 118.7, 118.1, 109.2, (indole and phenyl), 51.3 (CH_3O), 38.3 (*C*HCOO), 35.8 (indole CH), 30.4 (CH_3N), 29.1 (C_2 and C_6), 27.8 (C_3 and C_5). Anal. ($C_{23}H_{25}NO_2$) C, H, N.

The Et_2O filtrate was concentrated to a gum (16 g). This gum was dissolved in a minimum of toluene and subjected to HPLC chromatography on SiO_2 with toluene:hexane (9:1) as eluate to give a pure fraction as determined by TLC of the R_f 0.3 compound which was recrystallized from heptane to give 0.8 g of **15** Me ester: mp 141–142 °C; ^{13}C NMR ($CDCl_3$) δ 176.4 (COO), 137.2, 137.0, 132.3, 130.6, 128.1, 127.9, 126.1, 121.2, 120.1, 118.6, 117.4, 109.4 (indole and phenyl), 51.3 (CH_3O), 42.9 (*C*HCOO), 35.7 (indole CH), 32.2 (C_2 and C_6), 30.4 (CH_3N), 29.4 (C_3 and C_5). Anal. ($C_{23}H_{25}NO_2$) C, H, N.

By use of the method described for the preparation of **8**, 7 g (0.02 mol) of 14 Me ester was transformed into 5.1 g (77%) of **14**: mp 270–271 °C (recrystallized from dioxane:H_2O); ^{13}C NMR (Me_2SO-d_6) δ 175.7 (COO), 136.9 136.2, 131.6, 130.2, 128.0, 127.8, 125.7, 120.7, 119.4, 118.1, 117.3, 109.6 (indole and phenyl), 37.5 (*C*HCOO), 35.3 (indole CH), 30.1 (CH_3N), 28.6 (C_2 and C_6), 27.3 (C_3 and C_5). Anal. ($C_{22}H_{23}NO_2$) C, H, N.

By use of the method described for the preparation of **8**, 5.0 g (0.014 mol) of **15** Me ester was transformed into 2.8 g (60%) of **15**: mp 178–180 °C (crystallized from Et_2O); ^{13}C NMR (Me_2SO-d_6) δ 176.2 (COO), 136.8 136.4, 131.7, 130.2, 128.0, 127.8, 125.7, 120.7, 119.6, 118.2, 116.7, 109.5 (indole and phenyl), 42.0 (*C*HCOO), 35.4 (indole CH), 31.6 (C_2 and C_6), 30.0 (CH_3N), 29.1 (C_3 and C_5). Anal. ($C_{22}H_{23}N_2$) C, H, N.

***cis*-4-(1-Methyl-2-phenyl-1*H*-indol-3-yl)-1,1-cyclohexanedicarboxylic Acid Monomethyl Ester (16).** To 1.8 g (0.037 mol) of NaH (50% in oil) that was washed with pentane three times and stirred in 50 mL of DMF was added dropwise 11.8 g (0.030 mol) of crude **6** diMe ester in 30 mL of DMF. After the addition was complete, the mixture was heated at 50 °C for 2 h and then cooled in an ice bath, and 3.0 mL (0.048 mol) of MeI was added dropwise. The mixture was stired at room temperature overnight and at 50 °C for 3 h. The reaction mixture was poured into 300 mL of H_2O and extracted with Et_2O two times. The combined Et_2O extracts were washed with H_2O two times and brine one time, dried ($MgSO_4$), and concentrated in vacuo to give 10.6 g of resinous residue. By use of the method described for the preparation of **13**, 10 g (0.025 mol) of the above resinous residue was hydrogenated to give 5.0 g (44% overall) of dimethyl

4-(1-methyl-2-phenyl-1*H*-indol-3-yl)-1,1-cyclohexanedicarboxylate (16 Me ester): mp 134–135 °C (crystallized from EtOH). Anal. ($C_{25}H_{27}NO_4$) C, H, N.

To a solution of 3.2 g (0.049 mol) of KOH in 50 mL of MeOH and 5 drops of H_2O was added 2.0 g (0.0049 mol) of 16 Me ester. This solution was heated under reflux for 1 h and then concentrated in vacuo at room temperature. The residue was suspended in H_2O, made acidic with 3 N HCl, and extracted with Et_2O. The Et_2O extract was washed with brine two times, dried ($MgSO_4$), concentrated in vacuo, and crystallized from Et_2O:hexane to give 0.8 g (42%) of 16: mp 192–193 °C. Anal. ($C_{24}H_{25}NO_4$) C, H, N.

4-(2-Phenyl-1*H*-indol-3-yl)benzoic Acid (17). To a solution of 43.4 g (0.13 mol) of 5 Me ester in 400 mL of dioxane was added 63.6 g (0.28 mol) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) followed by 50 mL of dioxane. The resulting pea-green suspension was stirred and heated under reflux for 19 h. The reaction mixture was coooled in an ice bath and the insoluble 2,3-dichloro-5,6-dicyanohydroquinone was collected, washed with hot dioxane:hexane, and dried to give 51.3 g (80%): mp 302-305 °C. The reaction mixture filtrate was concentrated and partitioned between EtOAc:toluene and ice H_2O. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to give 40 g of a semisolid. This semisolid was subjected to column chromatography on 1000 g of SiO_2 with toluene and toluene:EtOAc (9:1) as eluting solvents and gave 27.0 g of a red-orange solid: mp 163-165 °C. Purification of this material by HPLC on SiO_2 using hexane:toluene (1:4) as eluting solvent, followed by crystallization from EtOAc:hexane, gave 25.2 g (59%) of 17 Me ester: mp 165–166 °C. Anal. ($C_{22}H_{17}NO_2$) C, H, N.

A mixture of 13.2 g (0.040 mol) of 17 Me ester and 11.2 g (0.17 mol) of KOH in 250 mL of EtOH was stirred and heated under gentle reflux for 4 h to give a solution. The cooled solution was concentrated in vacuo and partitioned between cold H_2O and Et_2O, and the aqueous layer was separated, made acidic with 6 N HCl, and extracted with EtOAc. The EtOAc extract was dried (Na_2SO_4), concentrated in vacuo, and triturated with hexane to give a solid which was collected and recrystallized three times from acetone:EtOAc:hexane to give 8.9 g (71%) of 17: mp 252–253 °C. Anal. ($C_{21}H_{15}NO_2$) C, H, N.

4-(1-Methyl-2-phenyl-1*H*-indol-3-yl)benzoic Acid (18). By use of the method described for the preparation of 17, except that 18 was recrystallized from dioxane:H_2O, 10.2 g (0.030 mol) of 8 Me ester was transformed into 7.3 g (74%) of 18: mp 232–235 °C. Anal. ($C_{22}H_{17}NO_2$) C, H, N.

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Registry No. 1, 948-65-2; 2, 3558-24-5; 3, 874-61-3; 4, 58230-12-9; 5, 93503-50-5; 5 Me ester, 93503-51-6; 6, 93503-52-7; 6 diMe ester, 93503-53-8; 7, 93503-54-9; 7 diMe ester, 93503-55-0; 8, 93503-56-1; 8 Me ester, 93503-57-2; 8·K, 93503-58-3; 9, 93503-59-4; 9 Me ester, 93503-60-7; 10, 93503-61-8; 11, 93503-62-9; 11 diMe ester, 93503-63-0; 12, 93503-64-1; 13, 93503-65-2; 14, 93503-66-3; 14 Me ester, 93503-67-4; 15, 93503-68-5; 15 Me ester, 93503-69-6; 16, 93503-70-9; 16 Me ester, 93503-71-0; 16 Me ester didehydro, 93503-55-0; 16·K, 93503-72-1; 17, 93503-73-2; 17 Me ester, 93503-74-3; 18, 93503-75-4; 2,3-dichloro-5,6-dicyanohydroquinone, 4640-41-9; EtI, 75-03-6; PrBr, 106-94-5; DDQ, 84-58-2.

Imidazo[1,5-*a*]pyridines: A New Class of Thromboxane A_2 Synthetase Inhibitors

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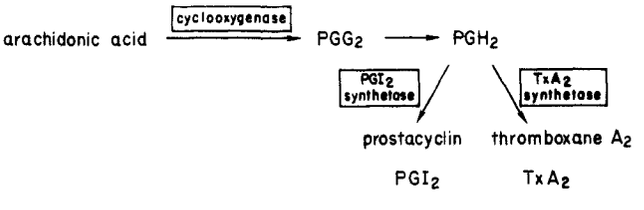
The synthesis and structure–activity profile of a new class of potent and highly specific thromboxane A_2 synthetase inhibitors is described. The most potent member of this series in vitro is determined to be imidazo[1,5-*a*]-pyridine-5-hexanoic acid (9).

Thromboxane A_2 (TxA_2) is an extremely unstable natural product with potent vasoconstricting, bronchoconstricting, and platelet aggregating activities.[2] It has been implicated in the etiology of a variety of disorders including vasospasm, stroke, ischemia, and myocardial infarction.[3] The biosynthesis of TxA_2 from arachidonic acid is blocked by classical nonsteroidal antiinflammatory drugs which prevent the formation of its precursors prostaglandin G_2 and prostaglandin H_2 by inhibiting cyclooxygenase (Scheme I).

Since TxA_2 and prostacyclin (PGI_2) share PGG_2 as a common precursor, inhibition of cyclooxygenase necessarily blocks the formation of the antiaggregatory vasodilator, PGI_2. A selective inhibitor of TxA_2 synthetase, which has no inhibitory effect on prostacyclin synthetase, would appear to have therapeutic potential especially in the treatment of platelet-mediated disorders.[4] Thromboxane synthetase inhibitors may have therapeutic utility in several conditions where platelets are believed to play a role in the disease process, e.g., thromboembolic disorders,[5] pulmonary hypertension,[6] cardiac ischemia,[7] endotoxin shock,[8] and tumor metastasis.[9]

Scheme I. Biosynthesis of Prostacyclin and Thromboxane A_2



Imidazole and pyridine, and especially their N- and 3-substituted derivatives, respectively, are the only re-

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