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Synthesis and Structure-Activity Relationships of a Series of Novel Benzopyran-Containing Platelet Activating Factor Antagonists

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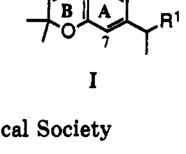
A class of N-substituted tetrahydrobenzopyrano[3,4-*c*]pyridines, I, have been identified as antagonists of platelet activating factor (PAF). The structural features essential for PAF binding were determined by systematic modification of three sites in the molecule. While *O*-alkyl analogues had little affect on binding potency, *N*-alkyl analogues exhibited a wide range of activity. Structural changes in the core ring system generally resulted in a loss of binding activity. Optimization of the N- and O-substituents resulted in the analogues **25-27** which exhibited K_i values ranging between 131 and 167 nM in a [^{3}H]PAF binding assay. Compound **23** was also active in a model of PAF-induced shock in the mouse following intravenous administration.

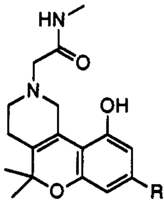
The endogenous phospholipid, platelet activating factor (PAF), has been implicated as a mediator in the pathophysiology of asthma, shock, psoriasis, gastric ulceration, and other disorders.[1] A number of structurally diverse PAF antagonists have been reported.[2]

As part of a program to identify novel and potent platelet activating factor antagonists, a screening effort was carried out in which compounds archived from past discovery programs at Abbott Laboratories were tested. Through this effort, a class of N-substituted tetrahydrobenzopyrano[3,4-*c*]pyridines, I, were discovered which exhibited PAF antagonist activity in a PAF receptor binding assay. These cannabinoid analogues were originally prepared at Abbott as analgesic, antihypertensive, and sedative hypnotic agents.[3-7] The tetrahydrobenzopyrano[3,4-*c*]pyridines are structurally distinct from any previously reported series of PAF receptor antagonists.[8]



I

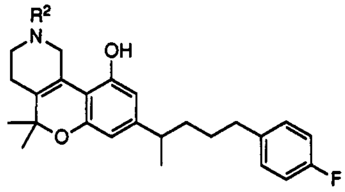
Table I. In Vitro Binding Activity of Selected C-8 Substituted Tetrahydrobenzopyrano[3,4-*c*]pyridines



compd	R^1	K_i, nM[a]
14[b]	$CH(CH_3)_2$	9000[c]
15[d]	$CH(CH_3)CH(CH_3)(CH_2)_4CH_3$	3680 ± 1430
16[d]	$CH(CH_3)(CH_2)_3$-*p*-FC_6H_4	331 ± 159
WEB 2086		98 ± 58

[a] The results represent the mean ± SD of $n \geq 2$ experiments unless otherwise noted. [b] See ref 3. [c] $n = 1$. [d] See ref 7.

Table II. In Vitro Binding Activity of Selected N-Substituted Tetrahydrobenzopyrano[3,4-*c*]pyridines



compd[a]	R^2	K_i, nM[b]
3[c]	H	11750 ± 1060
16[d]	$CH_2CONHCH_3$	331 ± 159
17	$CO_2C(CH_3)_3$	8% at 100 μM
18[e]	$COCH_2OH$	20500 ± 15,600
19[c]	$CH_2C{\equiv}CH$	3250 ± 1770
20[d]	$CH_2CON(CH_3)_2$	15770 ± 6960
21	$(CH_2)_3CO_2H$	656 ± 617
22	$(CH_2)_3CONHCH_3$	20700 ± 3110

[a] C, H, and N analyses for all compounds were within ±0.4% of the theoretical value. The theoretical values used for calculating C, H, and N for compounds **3** and **22** included $0.5H_2O$ and $1.25H_2O$, respectively. [b] The results represent the mean ± SD of $n \geq 2$ experiments. [c] See ref 4. [d] See ref 7. [e] See ref 6.

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(1) (a) Koltai, M.; Hosford, D.; Guinot, P.; Esanu, A.; Braquet, P. PAF A Review of its Effects, Antagonists and Possible Future clinical Implications (Part II). *Drugs* **1991**, *42*, 174-204. (b) Koltai, M.; Hosford, D.; Guinot, P.; Esanu, A.; Braquet, P. PAF A Review of its Effects, Antagonists and Possible Future clinical Implications (Part I). *Ibid.* **1991**, 9-29. (c) Braquet, P.; Mencia-Huerta, J. M.; Chabrier, P. E.; Tougui, L.; Vargaftig, B. B. The Promise of Platelet-Activating Factor. *ISI Atlas of Science: Pharmacology* **1987**, *1*, 187-198. (d) Braquet, P.; Touqui, L.; Shen, T. Y.; Vargaftig, V. V. Perspectives in Platelet-activating Factor Research. *Pharmacol. Rev.* **1987**, *39*, 97-145.

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(3) Razdan, R. K.; Terris, B. Z.; Pars, H. G.; Plotnikoff, N. P.; Dodge, P. W.; Dren, A. T.; Kyncl, J.: Somani, P. Drugs Derived from Cannabinoids. 2.^{1a} Basic Esters of Nitrogen and Carbocyclic Analogs. *J. Med. Chem.* **1976**, *19*, 454-460.

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(5) Lee, C.-M.; Michaels, R. J.; Zaugg, H. E.; Dren, A. T.; Plotnikoff, N. P.; Young, P. R. Cannabinoids. Synthesis and Central Nervous System Activity of 8-Substituted 10-Hydroxy-5,5-dimethyl-5*H*-[1]benzopyrano[4,3-*c*]pyridine and Derivatives. *J. Med. Chem.* **1977**, *20*, 1508-1511.

(6) Zaugg, H. E.; Kyncl, J. New Antihypertensive Cannabinoids. *J. Med. Chem.* **1983**, *26*, 214-217.

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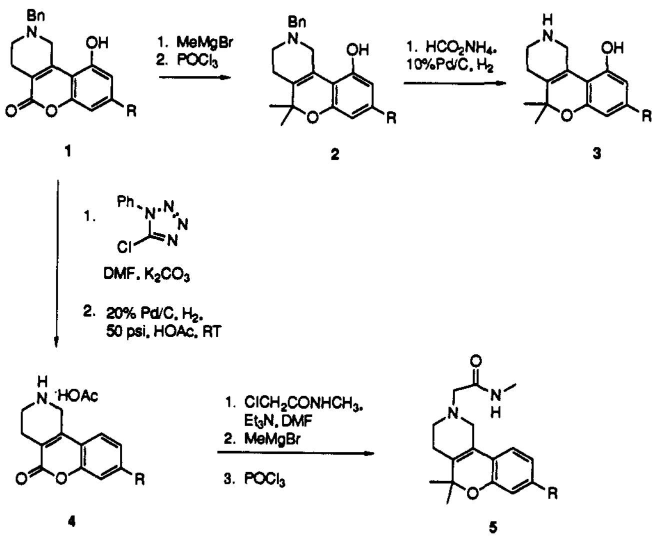
Scheme I



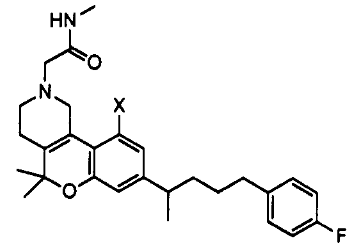
On the basis of these screening results, a systematic study was undertaken to examine the structural features essential for PAF antagonism by synthesizing several novel analogues. In this report both the synthesis and structure–activity relationships of a number of these novel PAF antagonists are described, many of which were potent inhibitors of PAF binding in vitro.

Chemistry

With the exception of the B- and C-ring-modified analogues (Table V), all of the compounds described in this report could be synthesized from the common intermediate **3**, which was previously reported by Winn and Razdan.[4] A deviation from the procedure of Winn and Razden (Scheme I), **3** was prepared by treatment of benzopyrone **1** with 2 equiv of methylmagnesium bromide followed by dehydrative cyclization with phosphorus oxychloride to give *N*-benzyltetrahydrobenzopyrano[3,4-*c*]pyridine **2** in 95% yield (Scheme I). Catalytic transfer hydrogenolysis of the benzyl group then provided the free base **3**.

Compound **5**, lacking the phenolic OH function, was prepared (Scheme I) from intermediate **1** according to the protocol described by Conner.[10] Thus, alkylation of **1** with 5-chloro-1-phenyl-1*H*-tetrazole in the presence of potassium carbonate afforded the corresponding tetrazolyloxy compound, which underwent catalytic hydrogenolysis of both the tetrazolyloxy and benzyl groups to yield the deoxygenated amino compound, **4**. Alkylation with 2-chloro-*N*-methylacetamide, followed by Grignard addition to the lactone and subsequent cyclization with $POCl_3$, provided **5**.

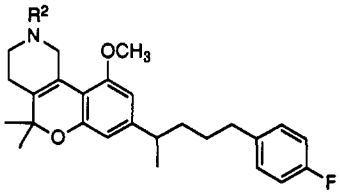
Table III. In Vitro Biological Activity of Representative O-Substituted *N*-Methyltetrahydrobenzopyrano[3,4-*c*]pyridineacetamides



compd[a]	X	K_i, nM[b]
16[c]	OH	331 ± 159
5[d]	H	345 ± 50
23	$OCH_2CO_2CH_2CH_3$	390 ± 127
24	OCH_2CO_2H	925 ± 35
25	$OCH_2CONHCH_3$	167 ± 117
26	$OCH_2CON(CH_3)_2$	157 ± 124
27	OCH_3	142 ± 45

[a] C, H, and N analyses for all compounds were within ±0.4% of the theoretical value. The theoretical values used for calculating compounds **23** and **24** included $0.5H_2O$, and for compounds **25** and **26** included $1.25H_2O$. [b] The results represent the mean ± SD of $n \geq 2$ experiments. [c] See ref 7. [d] See ref 10.

Table IV. Structure–Activity Relationships of Representative *N*-Alkyl-Substituted Methoxytetrahydrobenzopyrano[3,4-*c*]pyridines



compd[a]	R^2	K_i, nM[b]
28	H	16900 ± 6,930
29	CH_2-2-py	4205[c]
30[c]	CH_2CONH_2	945 ± 291
27	$CH_2CONHCH_3$	142 ± 45
31	$(CH_2)_2CONHCH_3$	5500 ± 710
32	$(CH_2)_2CO_2H$	4400 ± 2,970
33	$(CH_2)_3CO_2H$	690 ± 368
34	$(CH_2)_4CO_2H$	5500[c]
35	$(CH_2)_5CO_2H$	25000[c]

[a] C, H, and N analyses for all compounds were within ±0.4% of the theoretical value. Theoretical values used to calculate C, H, and N analyses included H_2O as follows: $1.25H_2O$ for **28**, **30**, and **33**; $0.75H_2O$ for **29** and **32**; $1.0H_2O$ for **34**; and $1.5H_2O$ for **35**. [b] The results represent the mean ± SD of $n \geq 2$ experiments unless otherwise noted. [c] $n = 1$.

The *tert*-butoxycarbonyl derivative **17** (Table II) was prepared in one step from **3** by acylation with 2-(((*tert*-butoxycarbonyl)oxy)imino)-2-phenylacetonitrile. Both the *N*-acyl analogue **18** and the *N*-alkyl analogues **16**, **19**, and **20** have been reported previously.[4,6–7] The *N*-alkyl analogues **21** and **22** were prepared from intermediate **3** by initial alkylation with ethyl 4-bromobutyrate. Saponification of the ester then yielded the acid **21** whereas transamination with trimethylaluminum and methylamine afforded the amide **22**.

The *N*,*O*-alkyl ethers in Tables III and IV were prepared from the *tert*-butoxycarbonyl (Boc) derivative **17** similar

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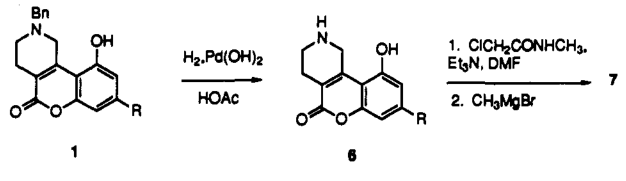
(8) Burstein recently reported that another cannabinoid analogue, tetrahydrocannabinol-7-oic acid, blocked the effects of PAF in various in vivo models. However, this compounds was not demonstrated to be a PAF receptor antagonist. (a) Burstein, S. H.; Audette, C. A.; Doyle, S. A.; Hull, K.; Hunter, S. A.; Latham, H. Antagonism to the Actions of Platelet Activating Factor by a Nonpsychoactive Cannabinoid. *J. Pharmacol. Exp. Ther.* 1989, *251*, 531–535. (b) Burstein, S. Tetrahydrocannabinol Derivatives as Platelet Activating Factor Antagonists. World Patent Application 8912 44 6, 1989, 2573–2597.

(9) Pars, H. G.; Granchelli, F. E.; Razdan, R. K.; Keller, J. K.; Teiger, D. G.; Rosenberg, F. J.; Harris, L. S. Drugs Derived from Cannabinoids. 1. Nitrogen Analogs, Benzopyranopyridines and Benzopyranopyrroles. *J. Med. Chem.* 1976, *19*, 445.

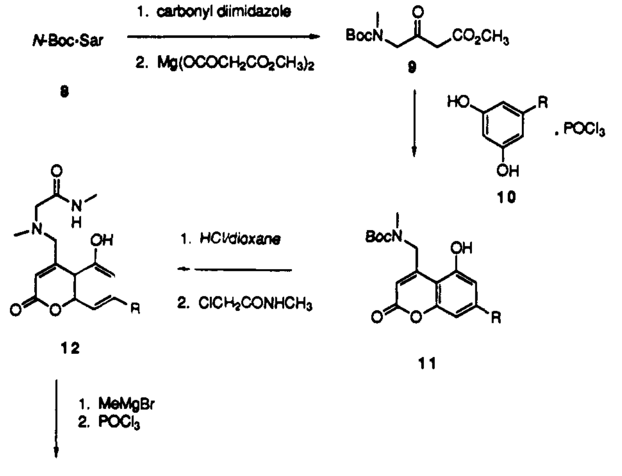
(10) (a) Connor, D. T.; Unangst, P. C.; Schwender, C. F.; Sorenson, R. J.; Carethers, M. E.; Puchalski, C.; Brown, R. E. Synthesis of 1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-ones. I. 3-Unsubstituted Compounds. *J. Heterocycl. Chem.* 1984, *21*, 1557–1559. (b) Musliner, W. J.; Gates, J. W., Jr. Dehydroxylation of Phenols; Hydrogenolysis of Phenolic Ethers: Biphenyl. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 150–152.

Scheme II



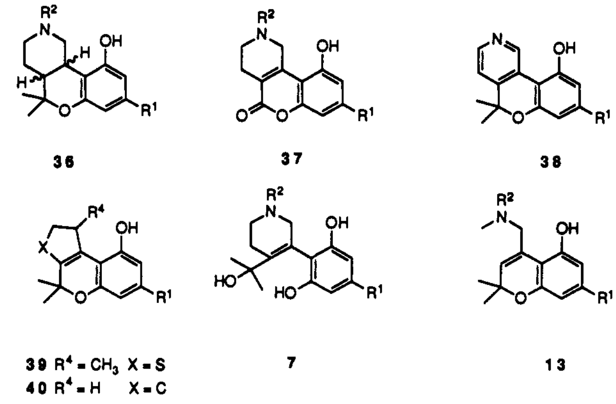
R = CH(CH$_3$)(CH$_2$)$_3$$p$-C$_6H_4$F

Scheme III



R = CH(CH$_3$)(CH$_2$)$_3$$p$-C$_6H_4$F

Table V. In Vitro Binding Activity of B- and C-Ring-Modified Benzopyrans



R^1 = CHCH$_3$(CH$_2$)$_3$C$_6$H$_4$F
R^2 = CH$_2$CONHMe

compd[a]	K_i, nM[b]
36	3300[c]
37	45% at 100 μM
38[d]	22% at 100 μM
39[e]	43750 ± 8840
40[e]	44% at 100 μM
7	23500 ± 707
13	1575 ± 460

[a] C, H, and N analyses for all compounds were within ±0.4% of the theoretical value. The theoretical values used to calculate C, H, and N analyses for compounds **36** and **37** included 0.5- 0.25H$_2$O, respectively. [b] The results represent the mean ± SD of $n \geq 2$ experiments unless otherwise noted. [c] $n = 1$. [d] See ref 5. [e] See ref 4.

to the procedure of Lee.[5] Thus, deprotonation of **17** with sodium hydride in DMF at 80 °C followed by O-alkylation with the appropriate alkyl halide in the presence of KI also at 80 °C gave the corresponding *N*-Boc ethers. Removal of the *tert*-butoxycarbonyl protecting group (4 N HCl/dioxane) followed by alkylation with 2-chloro-*N*-methylacetamide[11] in the presence of triethylamine afforded the expected ether analogues **23–26**. Similarly, the *N*-alkyl-*O*-methyl analogues in Table IV were prepared by alkylation of **16** with methyl iodide (NaH, THF, room temperature) followed by deprotection of the *tert*-butoxycarbonyl group and alkylation with the appropriate halo ester. Saponification of the corresponding ester then produced analogues **32–35** whereas transamination yielded the amides **27**, **30**, and **31**, respectively.

Compounds **38–40** (Table V) were prepared by literature methods: **38** was first reported by Lee[5] and **39–40** by Winn and Razden.[4] Triol **7** (Scheme II) was prepared from intermediate **1** by catalytic removal of the benzyl group followed by alkylation of the resulting amine with 2-chloro-*N*-methylacetamide and subsequent addition of methyl Grignard. Preparation of **13** was obtained through the synthesis illustrated in Scheme III. Homologation of *N*-Boc-Sar, **8**, afforded β-keto ester **9** which underwent a similar Pechmann reaction with resorcinol **10** to yield the bicyclic intermediate **11**. Removal of the *tert*-butoxycarbonyl protecting group followed by alkylation with 2-chloro-*N*-methylacetamide yielded the amide **12** which upon treatment with methyl Grignard followed by dehydrative cyclization afforded compound **13**.

Results and Discussion

The intrinsic binding affinity of compounds described in this report was determined through a [^{3}H]PAF binding assay using purified rabbit platelet membranes.[12] Measurement of the binding potencies of several reported PAF receptor antagonists was conducted routinely. For example, the reference antagonist WEB 2086 reported by Boehringer Ingelheim[13] and presently in phase II clinical trials exhibited a K_i value of 98 ± 58 nM in the aforementioned [^{3}H]PAF binding assay.

In order to evaluate the structure–activity relationships for PAF binding in these N-substituted tetrahydrobenzopyrano[3,4-*c*]pyridines, three sites on the molecule were systematically modified. Analogues with various nitrogen substituents, phenolic substituents, and compounds containing variations of the B- and C-ring nucleus were synthesized. A fourth site which could be modified was the substituent in position 8. However, since the synthesis of this series of tetrahydrobenzopyrano[3,4-*c*]pyridines required incorporation of the C-8 substituent at the beginning of a multistep sequence of reactions, we chose not to vary the nature of this substituent in our initial SAR studies. Hence, in this report we focus primarily on the 4-(4-fluorophenyl)-1-methylbutyl group, which on an initial brief survey of side chains incorporated in previously prepared compounds (Table I) imparted the best binding activity.

N-Alkyl Side Chain Modifications. The nature of the chain appended to the nitrogen atom was examined with regard to both chain length and the functional group at the chain terminus. In general *N*-acyl analogues, two of

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(11) Jacobs, W. A.; Heidelberger, M.; Rolf, I. P. On Certain Aromatic Amines and Chloroacetyl Derivatives. *J. Am. Chem. Soc.* **1919**, *41*, 458–474.

(12) Cheng, Y. C.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 percent inhibition (IC$_{50}$) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.

(13) Pharmacology of Hetrazepines as PAF Antagonists. Heuer, Hubert O. In *CRC Handbook of PAF and PAF Antagonists*; Braquet, P., Ed.; CRC Press: Boca Raton, FL, 1991; Chapter 8, pp 171–203.

which are represented in Table II (e.g. 17–18), were weak PAF antagonists; therefore, we focused our synthetic efforts on the preparation of *N*-alkyl analogues.

N-Alkyl analogues (e.g. 16, 19–22) typically displayed a wide range of activity including analogues which were potent receptor antagonists. From Table II it is evident that both the chain length and the nature of the functional group at the chain terminus have a significant influence on the potency of these *N*-alkyl analogues. The free base 3 itself displayed weak binding activity (11 750 nM). The two analogues, 16 and 21, which exhibited binding activities of 331 and 656 nM, respectively, were among some of the more potent benzopyran containing PAF antagonists to emerge from this study.

***O*-Alkyl Modifications.** Three types of phenolic modifications were considered: ester analogues, ether analogues, and the deoxygenated analogue, 5 (Scheme I). Additional ester analogues were not synthesized, since in the cannabinoid literature there is ample evidence that esters or this type are metabolized to their phenolic congeners in vivo.[14] Therefore, the majority of analogues prepared were ethers such as those shown in Tables III and IV. In order to assess the importance of the phenol function for PAF binding, the deoxygenated analogue 5 was also prepared.

Examination of the data in Table III indicates that structural variations at the phenolic position were generally well tolerated and resulted in compounds with K_i values generally less than 400 nM. In fact, many of the ether analogues synthesized were of equal potency to or greater potency than the reference phenol 16 (R = H). In fact, the deoxygenated analogue 5 was equipotent to the reference phenol 16 with a K_i value of 345 nM. The optimal combination of nitrogen and oxygen substituents to be evaluated was the *N*-methylacetamide function on nitrogen with either a methyl or an *N*-methylacetamide substituent on oxygen. This substitution pattern is present in compounds 25–27 which were the most potent benzopyrans synthesized in this study, exhibiting K_i values ranging from 142 to 167 nM.

In an attempt to further optimize the binding activity of 27, one of the most potent analogues from Table III, the various N-substituted methoxy analogues shown in Table IV were prepared. The data in Table IV demonstrate again that the length of the chain and nature of the terminal functional group on the nitrogen atom exerts a significant influence on binding potency. As with the hydroxy analogues in Table II, the $CH_2CONHCH_3$ group present in 27 provided the greatest potency.

B-/C-Ring Modifications. The importance of the tricyclic ring system to the activity of these compounds was evaluated by synthesizing selected analogues in which one or both core rings were modified. Catalytic hydrogenation of the double bond in 16 over 10% Pd/C provided the saturated analogue 36 as an undetermined mixture of diastereomers, which was 10-fold less active than the parent compound (K_i = 3300 nM). Another close analogue of 16, the lactone 37, was found to be inactive. Likewise, the aromatized compound, 38, was inactive.

Consistent with these results was the fact that the more drastically altered analogues, 39 and 40, in which the C ring was replaced by another ring system, and 7, in which the B ring was disconnected, also resulted in inactive compounds. In contrast, the C-ring-disconnected analogue 13 retained modest binding activity with a K_i value of 1575 nM. From the binding data generated from these analogues it appears that the central B ring is essential for PAF binding activity and that an intact C ring is required for optimal binding potency.

Antagonism of PAF-Induced Platelet Degranulation. Selected compounds were characterized in an assay of a cellular response to PAF. The functional assay was based on PAF-induced degranulation of rabbit platelets. Platelet degranulation was measured by determining the amount of radioactivity released into the media from washed rabbit platelets prelabeled with [^{14}C]-5-hydroxytryptamine. The analysis of potencies obtained in the platelet functional and [^{3}H]PAF binding assays shows a significant correlation (r = 0.97, slope = 0.94, $p < 0.01$) between binding (K_i) and functional (IC_{50}) antagonism. For example: 16 had a K_i of 331 ± 159 nM and a K_b of 46 nM. In the absence of PAF, concentrations of up to 100 μM failed to stimulate the release of [^{14}C]5-HT. The data suggest the compounds are antagonists of a biologically relevant PAF receptor.

The specificity of the selected compounds tested in this study was assessed by utilizing non-PAF agonists as secretagogues in the functional assays described above. The potent tetrahydrobenzopyrano[3,4-*c*]pyridines 16 and 21 showed no inhibition of calcium ionophore, thrombin, and collagen-induced rabbit platelet release at concentrations at least 100-fold greater than their IC_{50} value against PAF.

In Vivo Evaluation. PAF has been shown to produce increased vascular permeability resulting in hemoconcentration leading to hypovolemia, severe hypotension, and often death.[15] For this reason it has been implicated as one of the mediators involved in various shock syndromes. A model of PAF-induced lethal shock in mice was used to evaluate the ability of selected benzopyrans to protect mice from PAF-induced shock. Compounds were evaluated by intravenous administration along with 100 μg/kg of PAF. The activity of compounds is reflected in the percentage of survivors at a given dose. Compound 23 was the most potent member of the series to be evaluated under these conditions. It exhibited an ED_{50} of 0.6 mg/kg iv. Unfortunately, members of this series were extremely short lived in vivo. For example compound 23 showed a pharmacokinetic half-life, as determined by HPLC, in the rat of 13 min after iv dosing. Therefore the in vivo activities of these compounds were dramatically reduced or absent unless they were coadministered with PAF.

Conclusions

This is the first report of a series of PAF antagonists containing the tetrahydrobenzopyrano[3,4-*c*]pyridine nucleus. Through screening efforts and evaluation of subsequent structure–activity relationships of key leads, the important structural elements for PAF binding were determined. Substitution on the nitrogen position, while sensitive to modifications, could be optimized to produce potent compounds such as 16 and 27 with 331 and 142 nM binding activities, respectively. Provided the *N*-methylacetamide function was present at the nitrogen position, all *O*-alkyl modifications evaluated were well tolerated, producing binding K_i values ranging from 140 to 390 nM. In fact, even the deoxygenated analogue 5 exhibited a binding activity in this range. The core B/C ring system was also found to be important for PAF binding activity,

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(14) Structure–activity relationships of cannabinoids. Razdan, R. K. In *National Institute on Drug Abuse Research Monograph Series*; Rapaka, R. S., Makriyannis, A., Eds.; NIDA: Rockville, MD, 1987; Vol. 79, pp 3–14.

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and modifications of any kind resulted in modest to severe reductions in binding potency. The in vivo antagonism of PAF was demonstrated by **23**, which produced protection against PAF-induced shock in the mouse.

Experimental Section

[^{3}H]PAF Receptor Binding Method. Citrated whole rabbit blood was obtained from Pel-Freez (Rogers, AR). Rabbit platelets were prepared by centrifugation and washing. The platelets were lysed by freeze–thawing and sonication; platelet membranes were prepared by centrifugation and washing. Final membrane preparations were stored frozen in 10 mM Tris/5 mM $MgCl_2$/2 mM EDTA (TME buffer, pH 7.0) with 0.25 M sucrose added for membrane stabilization.

The standard PAF receptor binding assay contained 10 μg of platelet membrane protein, 0.6 nM [^{3}H]C_{18}-PAF (from Amersham or New England Nuclear; specific activity 120–180 Ci/mmol), with and without test compound, in "binding buffer" consisting of TME with 0.25% bovine serum albumin added (Sigma, RIA grade). The final volume of the assay was 100 μL. The assay was conducted in Millititre-GV (Millipore Corp.) filtration plates; incubation time was for 60 min at room temperature (22–23 °C). "Specific binding" was operationally defined as the arithmetic difference between "total binding" of 0.6 nM [^{3}H]C_{18}-PAF (in the absence of added PAF) and "nonspecific binding" (in the presence of 1 μM PAF). After the prescribed incubation, platelet membranes were filtered under vacuum and washed with 1 mL of "binding buffer". The filters were dried and removed. The bound radioactivity was quantitated with a Berthold TLC-Linear Analyzer Model LB2842.

Dose–response curves of inhibition of specific [^{3}H]C_{18}-PAF binding by test compounds were conducted in triplicate, with at least four doses covering the active range. Experiments were repeated at least once. IC_{50} values (concentration producing 50% inhibition) were determined by point-to-point evaluation. K_i values of inhibitory binding constants were calculated according to the method of Cheng and Prusoff [*Biochem. Pharmacol.* **1973**, *22*, 3099–3108] whereby

$$K_i = \frac{IC_{50}}{1 + ([^3H]PAF/K_d[^3H]PAF)}$$

PAF-Induced Mouse Shock. Intravenous administration of C-16 PAF (Sigma; 100 μg/kg) in Dulbecco's phosphate-buffered saline containing 1% bovine serum albumin (Sigma RIA grade) (DPBS-BSA) results in a shock-like state characterized by hypovolemia, hypotension, and death within 30 min; 100 μg/kg of PAF administered to male Sasco mice (30–35 g) represents an approximate LD_{90} dose. Groups of 10 mice were pretreated (0–5 min) with test compound (0.1–30 mg per kg, iv) or vehicle (50% ethanol/50% DPBS-BSA) followed by PAF injection via a tail vein. Protection from PAF-induced lethality was determined 24 h later and generally corresponds to 7-day survival times (when determined). Statistics were performed by comparison to vehicle control groups by χ^2 analysis. Probability of <0.05 was considered significant. Protective effects diminished with lower dose and increased time between drug and PAF challenge.

PAF-Induced Cellular [^{14}C]-5-Hydroxytryptamine Release Assay. Blood was collected via an ear vein from NZW rabbits, diluted with 0.38% sodium citrate, and centrifuged (450*g*, 15 min) to obtain the platelet-rich plasma (PRP) supernatant. The PRP was then incubated with [^{14}C]serotonin (55 mCi/mmol, 0.16 μCi/mL) for 30 min at 37 °C and centrifuged (850 *g*, 15 min). The pellet was washed with calcium-free Tyrodes buffer and then resuspended with buffer to original PRP volume. Immediately prior to testing, the platelet suspension was diluted with one volume of 2 mM calcium Tyrodes buffer. The testing protocol was as follows: aliquots of the platelet suspension were incubated with antagonist for 5 min (final DMSO concentration 1%), agonist was added with orbital shaking at 37 °C for 6 min, and the release reaction was terminated by cooling and the addition of EDTA in saline (4 °C, final concentration 3 mM). The platelet suspension was then centrifuged (1200*g*, 15 min, 4 °C), and the supernatant was collected for measurement of radioactivity with a liquid scintillation counter. Mean sample counts, corrected for background serotonin release, were expressed as percent inhibition of release induced by PAF at its approximate EC_{50} (4 nM).

Synthesis. Melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet 5SXC FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). ^{1}H NMR spectra were recorded on a GE QE300 spectrometer, and chemical shifts are reported in parts per million (ppm, δ) relative to Me_4Si as an internal standard. Mass spectra were obtained on a Kratos MS-50 instrument with EI ion source (70 eV). Elemental analyses were performed by Robertson Laboratory, Inc., Madison, NJ. Analytical data indicated by elemental symbols were within 0.4% of theoretical values unless otherwise noted. Flash column chromatography was conducted using silica gel 60 (Merck, 230–400 mesh) obtained from VWR Scientific. THF was distilled from sodium and benzophenone. All other solvents were HPLC grade and used without further purification.

8-[4-(4-Fluorophenyl)-1-methylbutyl]-1,2,3,4-tetrahydro-10-hydroxy-5,5-dimethyl-5*H*-[1]benzopyrano[4,3-*c*]-pyridine-2-carboxylic Acid *tert*-Butyl Ester (17). To a solution of **3**[4] (10 g, 25 mmol) in CH_2Cl_2 (100 mL) at ambient temperature was added triethylamine (5.25 mL, 38 mmol, 1.5 equiv) followed by 2-(((*tert*-butoxycarbonyl)oxy)imino)-2-phenylacetonitrile (6.8 g, 27 mmol, 1.1 equiv). The reaction was stirred for 5 h or until the starting material was consumed as determined by TLC. The reaction mixture was partitioned between CH_2Cl_2 (250 mL) and saturated aqueous citric acid (200 mL). The organic extracts were washed with aqueous saturated NaCl (250 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a brown oil. Recrystallization from hot acetonitrile afforded 8.76 g (71%) of a granular off-white solid: mp 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 7.05 (m, 2 H), 6.9 (m, 2 H), 6.38 (br s, 1 H), 6.18 (br s, 1 H), 4.6 (br s, 2 H), 3.5 (m, 2 H), 2.5 (br m, 3 H), 2.18 (br m, 2 H), 1.5 (br s, 13 H), 1.35 (s, 6 H), 1.15 (d, 3 H, J = 7 Hz). Anal. ($C_{30}H_{38}FNO_4$) C, H, N.

Compound **21** was prepared in analogy to the procedure described by Pars.[9] Anal. ($C_{29}H_{36}FNO_4$) C, H, N.

8-[4-(4-Fluorophenyl)-1-methylbutyl]-1,2,3,4-tetrahydro-10-hydroxy-*N*,5,5-trimethyl-5*H*-[1]benzopyrano[4,3-*c*]-pyridine-2-butyramide (22). A suspension of **21** (340 mg, 0.7 mmol) in anhydrous THF (20 mL) was cooled to −5 °C, and triethylamine (0.22 mL, 1.55 mmol, 2 equiv) was added, followed by dropwise addition of isobutyl chloroformate (0.18 mL, 1.4 mmol, 2 equiv). The reaction mixture was stirred at −5 °C for 30 min and at ambient temperature for 15 min. Anhydrous methylamine was then bubbled into the solution for 10 min. The reaction was concentrated in vacuo and the residue partitioned between CH_2Cl_2 (30 mL) and 10% aqueous HCl (30 mL). The organic extract was washed with saturated aqueous bicarbonate (50 mL) and saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and filtered. The residue after solvent evaporation was purified by chromatography on silica gel with 10% MeOH/$CHCl_3$ to afford 55 mg (16%) of a light yellow solid: mp 86–88 °C; ^{1}H NMR ($CDCl_3$) δ 7.05 (m, 2 H), 6.9 (m, 2 H), 6.3 (s, 1 H), 6.2 (s, 1 H), 3.8 (br s, 2 H), 2.6–2.8 (cm, 4 H), 2.7 (d, 3 H, J = 5 Hz), 2.5 (m, 3 H), 2.3 (m, 4 H), 1.9 (m, 3 H), 1.5 (m, 4 H), 1.25 (s, 7 H), 1.1 (d, 3 H, J = 8 Hz); IR (KBr) ν 3200–3600 br, 2900 s, 1640, 1620, 1570, 1510, 1430 cm^{-1}. Anal. ($C_{30}H_{39}FN_2O_3 \cdot 1.25H_2O$) C, H, N.

10-[(Ethoxycarbonyl)methoxy]-8-[4-(4-fluorophenyl)-1-methylbutyl]-1,2,3,4-tetrahydro-*N*,5,5-trimethyl-5*H*-[1]-benzopyrano[4,3-*c*]pyridine-2-acetamide (23). To a suspension of NaH (60% dispersion in mineral oil, 51 mg, 1.3 mmol, 1.4 equiv) in DMF (4 mL) was added **17** (450 mg, 0.91 mmol) in DMF (2 mL), and the suspension was heated to 80 °C for 2 h. The reaction mixture was allowed to cool to ambient temperature, and KI (30 mg, 0.18 mmol, 0.2 equiv) was added followed by ethyl bromoacetate (0.14 mL, 1.3 mmol, 1.4 equiv). The reaction mixture was again heated to 80 °C for 2 h and then allowed to cool to ambient temperature. The mixture was poured into hexane (15 mL) and H_2O (15 mL), and the layers were separated. The aqueous phase was extracted with hexanes (4 × 10 mL), and the combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with 8% ethyl acetate/hexane to afford 347 mg (66%) of a yellow oil.

The *tert*-butoxycarbamoyl ether (347 mg, 0.6 mmol) prepared above was stirred with a solution of 4 N HCl in dioxane (2 mL) for 2 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in DMF (3 mL), and 2-chloro-*N*-methylacetamide (83 mg, 0.8 mmol, 1.3 equiv) was added in one portion followed by triethylamine (0.33 mL, 2.4 mmol, 4 equiv). The reaction mixture was stirred for 24 h and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), and the layers were separated. The aqueous phase was washed with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were washed with saturated NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified on silica gel with 10% hexane/ethyl acetate to afford 150 mg (45%) of a white foam: ^1H NMR ($CDCl_3$) δ 7.3 (br m, 1 H), 7.05 (m, 2 H), 6.9 (m, 2 H), 6.4 (s, 1 H, J = 1.5 Hz), 6.1 (d, 1 H, J = 1.5 Hz), 4.55 (s, 2 H), 4.23 (q, 2 H, J = 8 Hz), 3.65 (br s, 2 H), 3.17 (s, 2 H), 2.83 (d, 3 H, J = 6 Hz), 2.7 (t, 2 H, J = 6 Hz), 2.45–2.55 (cm, 3 H), 2.25 (br m, 2 H), 1.5 (br m, 4 H), 1.35 (s, 6 H), 1.3 (t, 3 H, J = 8 Hz), 1.15 (d, 3 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 171.3, 168.4, 162.7, 159.5, 153.9, 153.5, 148.5, 138.0, 130.9, 129.7, 122.6, 115.0, 114.7, 110.5, 109.3, 103.7, 65.6, 61.3, 61.2, 55.3, 50.3, 39.9, 37.5, 35.0, 29.5, 26.2, 25.7, 24.5, 22.0, 14.3; IR ($CDCl_3$) ν 3000, 1750, 1670, 1510 cm^{-1}. Anal. ($C_{32}H_{41}FN_2O_5{\cdot}0.5H_2O$) C, H, N.

10-(Carboxymethoxy)-8-[4-(4-fluorophenyl)-1-methylbutyl]-1,2,3,4-tetrahydro-*N*,5,5-trimethyl-5*H*-[1]benzopyrano[4,4-*c*]pyridine-2-acetamide (24). To a solution of **23** (150 mg, 0.27 mmol) in a 3:1 (v:v) mixture of THF and H_2O (5 mL) was added $LiOH{\cdot}H_2O$ (50 mg, 1.3 mmol, 4.5 equiv). The reaction mixture was stirred at ambient temperature for 16 h and then concentrated in vacuo. The residue was dissolved in H_2O (5 mL), and 10% aqueous HCl was added until a pH of 4 was reached. The aqueous solution was extracted with 10% isopropyl alcohol/$CHCl_3$ (4 × 10 mL), and the combined organic extracts were concentrated in vacuo to afford 130 mg (92%) of an amorphous yellow solid: ^1H NMR ($CDCl_3$) δ 8.4 (br m, 1 H), 7.05 (m, 2 H), 6.9 (m, 2 H), 6.35 (s, 1 H), 6.2 (s, 1 H), 4.5 (s, 2 H), 4.2 (br s, 2 H), 3.55 (br s, 2 H), 3.1 (t, 2 H, J = 6 Hz), 2.75 (d, 3 H, J = 5 Hz), 2.55 (m, 4 H), 2.4 (br m, 2 H), 1.5 (m, 4 H), 1.35 (s, 6 H), 1.2 (m, 3 H). Anal. ($C_{30}H_{37}FN_2O_5{\cdot}0.5H_2O$) C, H, N.

Compounds **25** and **26** were prepared in an analogous fashion to the procedure described for **23** but substituting the appropriate N-substituted 2-chloroacetamide for ethyl bromoacetate. **25**: Anal. ($C_{31}H_{40}FN_3O_4{\cdot}1.25H_2O$) C, H, N. **26**: Anal. ($C_{32}H_{42}FN_3O_4{\cdot}1.25H_2O$) C, H, N.

8-[4-(4-Fluorophenyl)-1-methylbutyl]-1,2,3,4-tetrahydro-10-methoxy-5,5-dimethyl-5*H*-[1]benzopyrano[4,3-*c*]pyridine (28). To a suspension of NaH (95%; 29.4 mmol, 2 equiv) in THF (100 mL) was added a solution of **17** (6.97 g, 14.1 mmol) in THF (5 mL). The reaction was stirred for 45 min at ambient temperature, whereupon methyl iodide (3.5 mL, 56 mmol, 4 equiv) was added to the reaction mixture, and the resultant mixture was stirred an additional 3 h at ambient temperature. The solution was poured into aqueous ammonium chloride (150 mL), and the aqueous layer was extracted with EtOAc (3 × 100 mL), washed with saturated aqueous NaCl (300 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a pale yellow foam.

The crude material prepared above was dissolved in a solution of 4 N HCl in dioxane (40 mL) and stirred for 2 h. The reaction mixture was then concentrated in vacuo and partitioned between saturated aqueous $NaHCO_3$ (100 mL) and EtOAc (100 mL). The organic extract was washed with saturated aqueous NaCl (100 mL), and the organic extract was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography with 5% MeOH/$CHCl_3$ to afford 4.36 g (77%) of a yellow oil: ^1H NMR ($CDCl_3$) δ 7.1 (m, 2 H), 6.9 (m, 2 H), 6.35 (s, 1 H), 6.2 (s, 1 H), 4.2 (br s, 2 H), 3.75 (s, 3 H), 3.3 (br s, 2 H), 2.5 (m, 6 H), 1.45–1.6 (cm, 4 H), 1.35 (s, 6 H), 1.18 (d, 3 H), J = 8 Hz); IR ($CDCl_3$) ν 2950, 2600–3000, 1610, 1570, 1510 cm^{-1}. Anal. ($C_{26}H_{32}FNO_2{\cdot}1.25H_2O$) C, H, N.

Compound **26** was prepared from **25** by alkylation with 2-picolyl chloride. Anal. ($C_{32}H_{37}FN_2O_2{\cdot}0.75H_2O$) C, H, N.

8-[4-(4-Fluorophenyl)-1-methylbutyl]-1,2,3,4-tetrahydro-10-methoxy-*N*,5,5-trimethyl-5*H*-[1]benzopyrano[4,3-*c*]pyridine-2-acetamide (27). To a 0 °C solution of **25** (2.45 g, 6 mmol) in DMF (24 mL) was added triethylamine (2.36 mL, 17 mmol, 3 equiv) followed by ethyl bromoacetate (0.85 mL, 7.6 mmol, 1.3 equiv). The reaction mixture was stirred at ambient temperature for 18 h and then concentrated in vacuo. The residue was partitioned between $CHCl_3$ (50 mL) and H_2O (50 mL), and the aqueous phase was extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The ester was purified by silica gel chromatography with 30% hexanes/ethyl acetate to afford 2.8 g (95%) of a yellow oil.

Methylamine (ca. 5 mL) was condensed into a graduated addition funnel equipped with a dry ice condensor, toluene (45 mL) was added, and ca. 1 mL of the freshly prepared methylamine in toluene solution (>2.5 equiv) was added to a solution of trimethylaluminum in toluene (2 M, 1.3 mL, 2.5 mmol, 2.5 equiv) at −10 °C. The complex was stirred for 20 min at −10 °C and at ambient temperature for another 45 min. A solution of the ester prepared above (500 mg, 1 mmol, 1 equiv) in toluene (1 mL) was added to the complex at ambient temperature. After 10 min the reaction mixture was heated to 40 °C overnight. The solution was allowed to cool to ambient temperature and then poured into a mixture of $CHCl_3$ (10 mL) and H_2O (10 mL). The resulting emulsion was suction filtered through a pad of Celite (5 g), and the layers were separated. The aqueous phase was extracted with $CHCl_3$ (2 × 15 mL), and the combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried over Na_2SO_4, and filtered. After solvent evaporation the residue was purified by flash chromatography on silica gel with 5% hexane/ethyl acetate to afford 450 mg (93%) of a yellow oil: ^1H NMR ($CDCl_3$) δ 7.25 (br s, 1 H), 7.05 (m, 2 H), 6.9 (m, 2 H), 6.35 (s, 1 H), 6.25 (s, 1 H), 3.75 (s, 3 H), 3.5 (t, 2 H, J = 1 Hz), 3.15 (s, 2 H), 2.83 (d, 3 H, J = 6 Hz), 2.7 (t, 2 H, J = 6 Hz), 2.5–2.6 (cm, 3 H), 2.25 (m, 2 H), 1.5 (cm, 4 H), 1.35 (s, 6 H), 1.2 (d, 3 H, J = 7 Hz); IR ($CDCl_3$) ν 3400, 2800–3000, 1670, 1610, 1570, 1510 cm^{-1}. Anal. ($C_{29}H_{37}FN_2O_3$) C, H, N.

Compound **30** was prepared in analogous fashion to **27** using ammonia in place of methylamine.

8-[4-(4-Fluorophenyl)-1-methylbutyl]-1,2,3,4-tetrahydro-10-methoxy-5,5-dimethyl-5*H*-[1]benzopyrano[4,3-*c*]pyridine-2-propionic Acid (32). To a solution of **28** (0.7 g, 1.7 mmol) in DMF (20 mL) was added triethylamine (0.71 mL, 5.13 mmol, 3 equiv) followed by methyl 3-bromopropionate (0.37 mL, 3.4 mmol, 2 equiv). The reaction mixture was stirred under N_2 for 16 h and then diluted with H_2O (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic extracts were washed with saturated aqueous NaCl (300 mL), dried over $MgSO_4$, and filtered. After solvent removal, flash chromatography on silica gel with 2% MeOH/$CHCl_3$ afforded 690 mg (82%) of a light yellow oil.

The ester prepared above (0.69, 1.39 mmol) was dissolved in a 5:1 solution (v:v) of THF and H_2O (24 mL), and 292 mg (7 mmol, 5 equiv) of lithium hydroxide monohydrate was added in one portion. The reaction was stirred at ambient temperature overnight. The reaction was concentrated in vacuo, the aqueous solution was acidified to a pH of 4–4.5 with aqueous 10% citric acid (10 mL) and extracted with $CHCl_3$ (3 × 15 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 650 mg (97%) of a colorless foam: ^1H NMR ($CDCl_3$) δ 7.05 (m, 2 H), 6.95 (m, 2 H), 6.35 (d, 1 H, J = 1 Hz), 6.25 (d, 1 H, J = 1 Hz), 3.85 (br s, 2 H), 3.75 (s, 3 H), 3.0 (m, 4 H), 2.5–2.65 (cm, 5 H), 2.35 (m, 2 H), 1.5–1.6 (m, 4 H), 1.35 (s, 6 H), 1.2 (d, 3 H, J = 7 Hz); IR ($CDCl_3$) ν 2900–3000, 1720 br, 1610, 1560, 1510 cm^{-1}. Anal. ($C_{29}H_{36}FNO_4{\cdot}0.75H_2O$) C, H, N.

Compound **31** was prepared from **32** in analogous fashion to the preparation of **27**. Anal. ($C_{30}H_{39}FN_2O_3$) C, H, N.

Compounds **33**–**35** were prepared from **28** by alkylation with the appropriate halo ester according to the method for preparation of **32**. **33**: Anal. ($C_{30}H_{38}FNO_4{\cdot}H_2O$) C, H, N. **34**: Anal. ($C_{31}H_{40}FNO_4{\cdot}1.0H_2O$) C, H, N. **35**: Anal. ($C_{32}H_{42}FNO_4{\cdot}1.25H_2O$) C, H, N.

2-{7-[4-(4-Fluorophenyl)-1-methylbutyl]-5-hydroxy-10,10-dimethyl-2,3,4,4a,10,10a-hexahydro-1*H*-9-oxa-3-azaphenanthren-3-yl}-*N*-methylacetamide (36). Catalytic hydrogenation of a solution of **16**[7] (62 mg, 0.1 mmol) in MeOH (3 mL) over 10% Pd/C (30 mg) at 4 atm of H_2 pressure and ambient temperature afforded after filtration and purification by flash chromatography on silica gel with ethyl acetate 60 mg (99%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 7.23 (br s, 1 H), 7.05 (m, 2 H),

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6.93 (m, 2 H), 6.28 (d, 1 H, $J = 1$ Hz), 6.2 (d, 1 H, $J = 1$ Hz), 4.3 (br d, 1 H, $J = 12$ Hz), 3.13 (m, 1 H), 3.0 (d, 1 H, $J = 17$ Hz), 2.85 (d, 1 H, $J = 17$ Hz), 2.78 (br d, 1 H, $J = 11$ Hz), 2.55 (dd, 5 H, $J = 5, 9$ Hz), 2.48 (m, 1 H), 2.23 (br dd, 1 H, $J = 3, 12$ Hz), 1.5–1.8 (cm, 9 H), 1.35 (s, 3 H), 1.25 (s, 3 H), 1.18 (dd, 3 H, $J = 2, 7$ Hz); IR ($CDCl_3$) ν 2800–3300 br, 1660, 1620, 1570, 1510, 1430 cm^{-1}. Anal. ($C_{28}H_{37}FN_2O_3{\cdot}0.5H_2O$) C, H, N.

8-[4-(4-Fluorophenyl)-1-methylbutyl]-1,2,3,4-tetrahydro-10-hydroxy-*N*-methyl-5-oxo-5*H*-[1]benzopyrano[4,3-*c*]pyridine-2-acetamide (37). A solution of 1[4] (2.2 g, 4.67 mmol) in acetic acid (100 mL) over $Pd(OH)_2$ catalyst (2.1 g) was hydrogenated at 1 atm of H_2 pressure at ambient temperature for 16 h. The solution was then filtered through a pad of Celite (10 g), washed with glacial acetic acid (150 mL), and concentrated in vacuo. After azeotropic drying with toluene (2 × 25 mL) the residue was partitioned between $CHCl_3$ (250 mL) and saturated aqueous $NaHCO_3$(250 mL). The organic extract was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 2.1 g (98%) of an oil.

The material prepared above (2.1 g, 4.67 mmol) was dissolved in DMF (50 mL) and triethylamine (5 mL, 36 mmol, 7.7 equiv), and 2-chloro-*N*-methylacetamide (1.5 g, 14 mmol, 3 equiv) was added. The reaction mixture was stirred at ambient temperature for 48 h and then concentrated in vacuo. The residue was diluted with H_2O (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated NaCl (300 mL), dried over $MgSO_4$, and filtered. After solvent removal, purification by silica gel chromatography with ethyl acetate afforded a yellow solid which after recrystallization from ethyl acetate and hexanes afforded 1.1 g (52%) of an off-white solid: mp 165–168 °C; ^1H NMR ($CDCl_3$) δ 7.5 (br d, 1 H, $J = 5$ Hz), 7.05 (m, 2 H), 6.9 (m, 2 H), 6.63 (d, 2 H, $J = 10$ Hz), 4.1 (s, 2 H), 3.3 (s, 2 H), 2.8 (m, 3 H), 2.6–2.8 (cm, 5 H), 2.5 (m, 2 H), 1.45–1.6 (cm, 5 H), 1.2 (d, 3 H, $J = 7$ Hz). Anal. ($C_{26}H_{29}FN_2O_4{\cdot}0.25H_2O$) C, H, N.

2-{5-[4-[4-(4-Fluorophenyl)-1-methylbutyl]-2,6-dihydroxyphenyl]-4-(1-hydroxy-1-methylethyl)-3,6-dihydro-2*H*-pyridin-1-yl}-*N*-methylacetamide (7). To a solution of MeMgBr (3.0 M, 1.37 mL, 4.1 mmol, 10 equiv) in ether cooled to 0 °C was added a solution of **34** (179 mg, 0.4 mmol) in toluene (20 mL). The reaction mixture was stirred at ambient temperature under nitrogen for 16 h. The reaction was quenched with saturated aqueous ammonium chloride (25 mL), and the layers were separated. The organic extract was washed with saturated NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford after silica gel chromatography with 5% $MeOH/CHCl_3$ 190 mg (98%) of a white solid: mp 203–204 °C; ^1H NMR ($CDCl_3$–CD_3OD) δ 7.07 (m, 2 H), 6.9 (m, 2 H), 6.2 (s, 2 H), 3.08 (s, 2 H), 3.0 (br s, 2 H), 2.8 (s, 3 H), 2.75 (t, 2 H, $J = 6$ Hz), 2.43–2.55 (cm, 6 H), 1.3 (m, 4 H), 1.2 (s, 6 H), 1.18 (d, 3 H, $J = 6$ Hz); IR (KBr) ν 3000–3600 br, 2900, 1650, 1620, 1510, 1430 cm^{-1}. Anal. ($C_{28}H_{37}FN_2O_4$) C, H, N.

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Benzofuran Bioisosteres of Hallucinogenic Tryptamines

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The benzofuran analogues of the hallucinogens 5-methoxy-*N*,*N*-dimethyltryptamine and 5-methoxy-α-methyltryptamine were synthesized and evaluated for affinity at the serotonin $5\text{-}HT_2$ and $5\text{-}HT_{1A}$ receptors in rat brain homogenate, labeled with [^{125}I]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane ([^{125}I]DOI) and [^3H]-8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin ([^3H]-8-OH-DPAT), respectively. At the $5\text{-}HT_2$ receptor, the benzofurans had slightly decreased affinities, approximately one-third and one-sixth those of the indoles, for the primary amines and the tertiary amines, respectively. The benzofurans also had lower affinity at the $5\text{-}HT_{1A}$ receptor, but decreased only about 20–30% from that of the indole isosteres. Thus, the $5\text{-}HT_{1A}$ receptor is less discriminating with respect to preference for an indole versus a benzofuran, although all of the compounds did have higher affinities for the $5\text{-}HT_2$ receptor than for the $5\text{-}HT_{1A}$ receptor. It is suggested that benzofurans may be useful in the design of serotonin receptor ligands.

We recently reported on the biological activity of compounds **1a** and **1b**, which proved to possess high LSD-like potency in an animal behavioral model, as well as high affinity for the agonist-labeled state of the serotonin $5\text{-}HT_2$ receptor.[1] In view of the similar biological activity of the indole **2**,[2] one could speculate that the 2,3-dihydrofuran ring of **1** served as a bioisosteric replacement of the pyrrole ring of the indole.

A logical question which presented itself was whether a fully aromatic benzofuran might itself also be a bioisostere for an indole. Although benzo[*b*]thiophenes have been investigated as analogues of indoles,[3] only a few early reports seem to exist relevant to the use of benzofurans to replace indoles.[4–7] Furthermore, the chemical properties

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