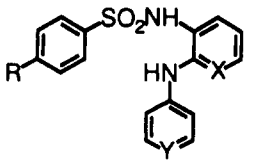
Table I. In Vitro Antiproliferative Activity of Compounds 1–6



compd	R	X	Y	IC_{50} (μg/mL)[a] colon 38	KB
1	CH_3	CH	CH	1.2	0.46
2	CH_3	N	CH	3.2	1.5
3	CH_3O	N	CH	0.45	0.27
4	CH_3O	N	$COCH_3$	3.6	1.9
5	CH_3O	N	COH	0.38	0.29
6	CH_3O	N	N	1.4	1.0

[a] Concentration to inhibit colon 38 and KB cell proliferation by 50% relative to untreated controls after 72 h of continuous drug exposure.

Table II. In Vitro Antitumor Activity of Compounds 2–6 against Colon 38[a]

compd	dose (mg/kg/day)	deaths/ total	T/C[b] (%)
2	100	0/6	20
	200	0/6	19
	400	0/6	1
3	50	0/6	27
	100	0/6	2
	200	0/6	1
4	50	0/6	30
	100	0/6	1
	200	2/6	0
5	12.5	0/6	59
	25	0/6	32
	50	0/6	3
	100	0/6	2
6	12.5	0/6	41
	25	0/6	35
	50	0/6	14

[a] The tumor was introduced by sc implantation of a 75-mg tumor fragment into the axillary region of female BDF_1 mice on day 0. Compounds 2–6 were administered orally on days 1–8. The tumors were excised and weighed on day 21. [b] (Tumor weight of treated mice/tumor weight of control mice) × 100.

of *p*-methyl or *p*-methoxybenzenesulfonyl chloride with 2-anilino-3-pyridinamine derivatives in pyridine at room temperature gave compounds 2–6 in good yields. The structures of these compounds were established by spectroscopic and analytical data.

Biological Activity and Discussion. A number of sulfanilamides, i.e., sulfadiazine, sulfapyridine, sulfamerazine, sulfamethazine, sulfisomidine, sulfadimethoxine, sulfathiazole, sulfamethoxazole, sulfamethizole, and sulfisoxazole, were tested for in vitro antiproliferative activity against colon 38 and KB cells. None of the sulfanilamides showed inhibitory activity against these cells (IC_{50} > 100 μg/mL).

Of the compounds tested, 1 was the first discovered sulfonamide with substantial in vitro antiproliferative activity (Table I). Although 1 showed only marginal in vivo antitumor activity against colon 38, further modification of the structure of 1 led to the discovery of analog 2 with good in vivo activity (Table II). Compound 2 showed antitumor activity against colon 38 in a dose-dependent manner after oral (po) administration on days 1–8. Replacement of the methyl group of 2 by a methoxy group (analog 3) increased both in vitro and in vivo activity. Substitution with a hydroxy group in position 4 of the anilino group of 3 (analog 5) did not affect in vitro activity but increased in vivo activity. No correlation between in vitro and in vivo antitumor activity was observed upon modification of the anilino group of 3 (3 vs 4–6). It is noteworthy that 2, 3, and 5 have a broad range of effective doses. Compound 5 has been selected for further evaluation. Compound 5 was found to inhibit mitosis of P388 cells at cytotoxic concentrations (IC_{50} = 0.32 μg/mL) as shown in Figure 1. Its excellent activity and wide range of effective doses in the colon 38 model and its structural novelty, unrelated to known antineoplasms, suggest that 5 may be a hopeful new antitumor agent for human solid tumors. Reports on the structure–activity relationships of this series of compounds, further data on the efficacy of 5 (E7010) in this and other tumor models, and the precise mechanism of action will be forthcoming.

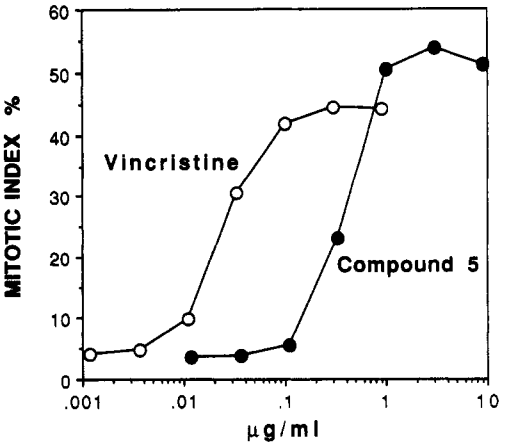


Figure 1. Effects of compound 5 and vincristine on the mitotic index of P388 cells in vitro. P388 cells were cultured with the drugs for 12 h. The cells were treated with 75 mM KCl, fixed with MeOH–AcOH, and stained with crystal violet. The mitotic index was determined by counting at least 300 cells (control 4.5%). Similar results were obtained in a second experiment.

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Isopropyl and Phenyl Esters of 3β-(4-Substituted phenyl)tropan-2β-carboxylic Acids. Potent and Selective Compounds for the Dopamine Transporter

Since (−)-cocaine (1) is a popular drug of abuse, much effort has been devoted to elucidating its neurochemical mode of action. Ritz et al.[1] correlated the potencies of cocaine and cocaine analogs in self-administration studies with their potencies in inhibiting [^{3}H]mazindol binding to the dopamine (DA) transporter in rat striatum and con-

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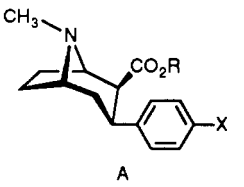
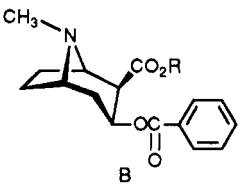
(1) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine Receptors on Dopamine Transporters Are Related to Self-administration of Cocaine. *Science* 1987, *237*, 1219–1223.

0022-2623/92/1835-2497$03.00/0

Table I. Receptor Binding Data for Cocaine Analogs[a,b]



A



B

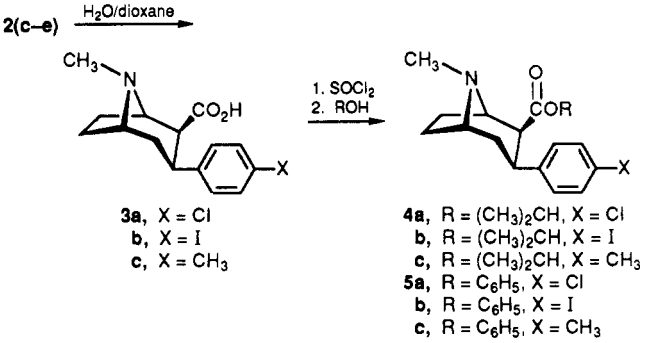
compd	structure type	X	R	DA [^{3}H]WIN 35,428 IC_{50} (nM)[c]	NE [^{3}H]mazindol IC_{50} (nM)[c]	5-HT [^{3}H]paroxetine IC_{50} (nM)[c]	NE/DA ratio	5-HT/DA ratio
2a	A	H	CH_3	23.0 ± 5.0[d]	2085 ± 69	1999 ± 64	91	87
2b	A	F	CH_3	15.7 ± 1.4[d]	1237 + 103	759 ± 47	79	48
2c	A	Cl	CH_3	1.17 ± 0.1[d]	45.1 ± 7.7	44.5 ± 1.3	39	38
2d	A	I	CH_3	1.26 ± 0.1[d]	34.6 ± 3.7	4.2 ± 0.3	28	3.3
2e	A	CH_3	CH_3	1.71 ± 0.3[d]	43.6 ± 6.8	240 ± 27	24	140
4a	A	Cl	$CH(CH_3)_2$	1.41 ± 0.13	2154 ± 176	1404 ± 7	1530	996
4b	A	I	$CH(CH_3)_2$	0.43 ± 0.05	864 ± 240	310 ± 77	2000	721
4c	A	CH_3	$CH(CH_3)_2$	5.29 ± 0.40	4295 ± 261	6406 ± 538	811	1210
5a	A	Cl	C_6H_5	1.99 ± 0.05	4574 ± 115	2335 ± 176	2300	1170
5b	A	I	C_6H_5	1.51 ± 0.34	18277 ± 2852	326 ± 84	12100	216
5c	A	CH_3	C_6H_5	3.27 ± 0.06	10845 ± 2159	29666 ± 4989	3320	9070
1	B		CH_3	102[e]	3825 ± 114	1059 ± 41	38	10
6	B		$CH(CH_3)_2$	211 ± 59[e]	23547 ± 1631	25733 ± 1212	112	122
7	B		C_6H_5	112 ± 36[e]	37435 ± 8659	57368 ± 5162	334	512
8	B		C_2H_5	130 ± 40[e]	26808 ± 16513	9057 ± 1029	206	70
9	B		C_3H_7	191 ± 46[e]	15756 ± 2708	4129 ± 357	83	22
10	B		$(CH_2)_3C_6H_5$	139 ± 24[e]	25107 ± 6075	374 ± 15	181	2.7

[a] All new compounds exhibit ^{1}H NMR spectral data in agreement with assigned structures. The compounds were characterized and tested as their hydrochloride salts. Elemental analyses were within ±0.4% of theoretical values for C, H, N, and Cl. [b] The binding studies and data analyses were carried out as described in ref 9. [c] Mean ± standard error of four experiments performed in triplicate. [d] Taken from ref 7. [e] Taken from ref 8.

cluded that the cocaine receptor related to drug abuse was associated with DA-uptake inhibition. Bergman and coworkers[2] reached a similar conclusion. Several biochemical and pharmacological studies have also supported this DA hypothesis.[3]

(−)-Cocaine (1) inhibits the uptake of serotonin (5-HT) and norepinephrine (NE) as well as DA into presynaptic terminals;[4,5] the highly potent cocaine analogs 3β-phenyl- and 3β-(4′-fluorophenyl)tropan-2β-carboxylic acid methyl esters (**2a** and **2b**, respectively) act similarly.[4-6] In fact, even though transporter-selective compounds are needed to study the neurochemical mode of action of cocaine, we are not aware of any cocaine analogs that are potent and highly selective for the DA transporter. Such analogs would be valuable compounds for studying the pharmacological and behavioral effects associated with binding to the dopamine transporter and could lead to therapeutic agents useful in the treatment of cocaine abuse.

Scheme I



During the course of our investigation to determine the structural features of (−)-cocaine (1) needed for potent binding to the DA transporter, we found that the 3β-(4′-substituted phenyl)tropan-2β-carboxylic acid methyl esters (**2c–e**) possessed low nanomolar potency for the cocaine binding site on the DA transporter.[7] In addition, we discovered that replacement of the methyl group in the 2-carbomethoxy functionality of cocaine with other groups had only small effect on potency at the DA transporter.[8] In this communication, we report the binding potency of these cocaine analogs at the norepinephrine (NE) and serotonin (5-HT) transporters and present the syntheses and receptor binding data of some new ester analogs of

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(5) Reith, M. E. A.; Meisler, B. E.; Sershen, H.; Lajtha, A. Structural Requirements for Cocaine Congeners to Interact with Dopamine and Serotonin Uptake Sites in Mouse Brain and to Induce Stereotyped Behavior. *Biochem. Pharmacol.* **1986**, *35*, 1123–1129.

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(7) Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, Ligand Binding, QSAR, and CoMFA Study of 3β-(p-Substituted phenyl)tropan-2β-carboxylic Acid Methyl Esters. *J. Med. Chem.* **1991**, *34*, 2719–2927.

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several 3β-(4′-substituted phenyl)tropan-2β-carboxylic acid methyl esters (2).

Chemistry

Scheme I outlines the general synthesis used to prepare the isopropyl (4) and phenyl (5) esters of 3β-(4′-chlorophenyl)-, 3β-(4′-iodophenyl)-, and 3β-(4′-methylphenyl)-tropan-2β-carboxylic acids (3a–c). Hydrolysis of 2c–e in aqueous dioxane gives the corresponding acids 3a–c. Treatment of 3a–c with thionyl chloride gives the acid chlorides which were converted to the isopropyl esters of 3β-(4′-chlorophenyl)-, 3β-(4′-iodophenyl)-, and 3β-(4′-methylphenyl)tropan-2β-carboxylic esters [4a (CTC-iPr), 4b (ITC-iPr), and 4c (MTC-iPr), respectively] by treatment with isopropyl alcohol. Analogous treatment with phenol afforded the phenyl esters of 3β-(4′-chlorophenyl)-, 3β-(4′-iodophenyl)-, and 3β-(4′-methylphenyl)tropan-2β-carboxylic esters [5a (CTC-Ph), 5b (ITC-Ph), and 5c (MTC-Ph), respectively].

Results and Discussion

Table I lists the IC_{50} values for several previously reported cocaine analogs,[7,8] as well as the new analogs prepared in this study, at the DA, NE, and 5-HT transporters. The binding studies and data analyses were carried out as previously reported[9] using [^{3}H]WIN 35,428, [^{3}H]mazindol, and [^{3}H]paroxetine as ligands for the DA, NE, and 5-HT transporters, respectively. Relative to cocaine, 3β-phenyltropan-2β-carboxylic acid methyl ester (2a) showed enhanced potency at both the DA and NE transporters with slightly decreased potency at the 5-HT transporter. The 4′-chloro (2c), 4′-iodo (2d), and 4′-methyl (2e) analogs of 2a showed enhanced potency relative to cocaine (1) for all three transporters. In contrast, the 4′-fluoro analog 2b showed enhanced potency at DA and NE with little change at the 5-HT transporters. Compounds 2a–e, which showed NE/DA and 5-HT/DA ratios of 24–91 and 3.3–140, respectively, were not very selective for the DA transporter.

We had previously reported that the replacement of the methyl group in the 2-position ester of cocaine with an ethyl, propyl, isopropyl, phenyl, or phenylpropyl (compounds 6–10 in Table I) resulted in no more than a 2-fold decrease in potency at the dopamine transporter.[7] However, a 24- and 54-fold decrease in potency at the 5-HT transporter and a 6- and 10-fold decrease at the NE transporter was observed for the isopropyl and phenyl analogs 6 and 7, respectively. Moreover, analogs 6 and 7 with NE/DA ratios of 112 and 334, respectively, and 5-HT/DA ratios of 122 and 512, respectively, are reasonably selective for the DA transporter. Surprisingly, the phenylpropyl ester 10 showed a threefold higher potency for the 5-HT transporter relative to cocaine.

Within the new series of isopropyl, 4a–c, and phenyl, 5a–c, esters, only small effects on potency, relative to the parent methyl esters 2c–e, were observed at the DA transporter. However, it should be noted that 3β-(4′-iodophenyl)tropan-2β-carboxylic acid isopropyl ester (4b) with an IC_{50} of 0.43 nM is the most potent cocaine analog at the dopamine transporter thus far reported.[10] Compounds 4a–c and 5a–c showed large decreases in potency for the NE (25–528-fold) and 5-HT (27–124-fold) transporters relative to the analogous methyl esters 2c–d. Compounds 4c, 5a, and 5c are also highly selective for the DA transporter. 3β-(4′-Methylphenyl)tropan-2β-carboxylic acid phenyl ester (5c) with an IC_{50} of 3.27 nM for the DA transporter and NE/DA and 5-HT/DA ratios of 3320 and 9070, respectively, is one of the most selective cocaine analogs for the DA transporter reported to date.

Recently, we reported that [^{125}I]-3β-(4′-iodophenyl)tropan-2β-carboxylic acid methyl ester ([^{125}I]RTI-55), which is the iodine-125 analog of 2d ([^{125}I]-2d), was a useful ligand for examining the DA and 5-HT transporter in vitro and in vivo.[11–13] In addition, we and others have shown that the iodine-123 analog [^{123}I]-2d is a promising single photon emission computed tomography (SPECT) ligand for the DA and 5-HT transporters.[14–18] However, 2d is not very selective for the DA transporter, showing NE/DA and 5-HT/DA ratios of 28 and 3.3, respectively (Table I). In contrast, 4b, the isopropyl ester analog of 2d, shows high selectivity for the DA transporter with NE/DA and 5-HT/DA ratios of 2000 and 721. Similarly, the analogous phenyl ester 5b is also highly selective with NE/DA and 5-HT/DA ratios of 12 100 and 216, respectively. Thus, the iodine-125 and iodine-123 analogs of 4b and 5b might prove to be more useful radioligands for the DA transporter.

The results from this study point to the significance of substitution of the phenyl ring of 2a and of changes in the ester function of cocaine and of 2a and its analogs on affinities for the DA, NE, and 5-HT transporters. To our knowledge, the iodinated analog 4b is the most potent

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(18) Melting point, ^{1}H NMR, specific rotation, and analysis data for 4a–c and 5a–c are available from the authors upon request.

cocaine analog for the DA transporter, and analog **5c** is the most selective analog thus far reported. In addition, analog **4b** is also the most selective of known iodinated ligands for the DA transporter and may be useful for the study of the DA transporter. These results suggest that further studies will lead to even more selective, highly potent cocaine analogs for the DA transporter.

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Book Reviews

Progress in Drug Research. Volume 36. Edited by Ernst Jucker. Birkhäuser Verlag, Basel, Boston, Berlin. 1991. 475 pp. 16.5 × 24.5 cm. ISBN 0-8176-2582-8. $249.00.

The last review in this series published in the *Journal of Medicinal Chemistry* appeared in 1982 (pg 1267 of issue 10). In that review Carl Kaiser summarizes volume 25: "...in keeping with previous issues...consists of...subjects of general interest to those involved in drug research," and "in keeping with other volumes..., the topics are generally unrelated..., the book is of greater utility as a library reference source...an encyclopedic reference." Such a description characterizes volume 36 and the 10 intervening volumes published between 1982 and 1991. This volume is referenced generally into the late 1980s, contain a volume index, has an index of titles (unfortunately incomplete) found in volumes 1–36, an author (alphabetical and with addresses) and paper (article) index for volumes 1–36, and a price tag $89 more than in 1982.

Volume 36 contains five articles: (1) Pharmacology of synthetic organic selenium compounds, by M. J. Parnham and E. Graf, includes discussions on antineoplastic selenopurines and selenazoles; certain inorganics; coumarin relatives; selenium-dependent glutathione peroxidase and lipid peroxidation; antiarrhythmic and antihypertensive species; the mechanism of acute antihypertensive activity of phenyl-2-aminoethyl selenide; reactive oxygen species and antilipidemic, antiinflammatory, and CNS drugs; antimalarial and antiviral compounds; ebselen metabolism; radioimaging agents; compounds affecting liver damage; and a rather large list of patented selenium-containing structures whose biological properties have not been subjected to peer review. The redox properties of these drugs, and applicable drug design concepts should be incorporated into medicinal chemistry courses. (2) Opiate receptors: Search for new drugs, by V. M. Kolb, provides references to numerous reviews and key references, considers opioid receptor modeling by computer and NMR methods, interesting message-address and hybrid drug concepts, and their use in drug design. This chapter is of particular interest to medicinal chemists in search of a concise summary of important opiate receptor lecture material. (3) Chemistry and pharmacology of cannabis, by R. Seth and S. Sinha, reveals isolation and characterization methods; physical–chemical and spectroscopic properties of the cannabinoids; similar discussions of basic nitrogen-containing compounds found in cannabis including substances such as L-(+)-isoleucine betaine, the four cannabamines and anhydrocannabisativine, and certain cyclic and polycyclic phenols including spiro systems. Forensic methods of detection and identification are discussed in some detail. Pharmacological effects of cannabis on the reproductive, gastrointestinal, lung, cardiovascular and nerve systems, appetite, intraocular pressure, blood sugar, hormones, hypertension, analgesia, ulcer formation, tumors, inflammation, hypothermia, allergenicity, and cough reflex are covered. The work concludes with a discussion of pharmacokinetics and metabolism. Numerous disciplines encompassing medicinal and natural product chemistry through forensic toxicology will find useful information summarized in this section. (4) Drug receptors and control of the cardiovascular system: Recent advances, by R. R. Ruffolo, Jr., J. P. Hieble, D. P. Brooks, G. Z. Feuerstein, and A. J. Nichols, is a comprehensive article (pp 117–360) with individual current sections on (1) control of the cardiovascular system, (2) α-adenoceptors, (3) β-adenoceptors, (4) dopamine, (5) serotonin, (6) vasoactive lipid, (7) angiotensin II, (8) purinergic, (9) vasopressin, (10) peptide, and (11) histamine receptors wherein each section is individually referenced. Although deficient in chemical structures and SAR, the pharmacology and mechanism discussions are excellent. This well-written article represents an excellent starting point for medicinal chemists or pharmacologists who need to learn more about or be brought up-to-date on cardiovascular biology and applicable targets for drug development. (5) Molecular modeling and quantitative structure–activity analysis of antibacterial sulfanilamides and sulfones, by P. G. De Benedett, serves to orient the reader on the methods and approaches applicable to the title topic and is an excellent source of lecture material for academic medicinal chemists. Prototropic and conformational equilibria and molecular and submolecular descriptors (empirical, theoretical, interactive) are discussed. Subsequently, QSAR equations relating to different levels of biological complexity (bacterial and enzymic) are analyzed and rationalized in some detail. The role of sulfanilamide anionic, imidic, and amidic forms and QSAR involving both experimental and theoretical descriptors provide a basis for interesting discussions. A partial least squares analysis of enzymic inhibition data values of multisubstituted sulfones is presented, and the article concludes with a presentation on molecular superposition of inhibitors and receptor mapping.

Thus, volume 36 continues in the traditional thrust of the editor. All five chapters have information of considerable medicinal chemical and pharmacological interest and are recommended reading for either the generalist or the specialist.

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