on different K channels? Do the K channel openers "activate" K channels or do they inhibit channel inactivation? Is phosphorylation/dephosphorylation a common means for regulation of K channel function? All of these questions represent important issues that will require exhaustive exploration.

The differences among existing K channel openers needs to be carefully explored in both animals and man. Just as the different structural classes of Ca channel blockers, exemplified by nifedipine, verapamil, and diltiazem, have certain pharmacological and therapeutic differences, the different structural classes of K channel openers may find distinct therapeutic niches. Diazoxide is much more potent than cromakalim or pinacidil in opening pancreatic ATP-dependent K channels, whereas cromakalim and pinacidil are more potent vasodilators, suggesting that not all K channel openers are alike.

Selectivity will likely be the key to future advances. There is a large diversity of K channel subtypes, and furthermore, there is a wide range of regulatory mechanisms for these subtypes. True tissue selectivity—if this goal is achievable—would represent a bona fide advance. In fact, the key to exploiting K channel openers for treatment of diseases other than hypertension will ultimately be determined by the issue of tissue selectivity. Selectivity can be electrophysiologic in that tissues may respond differently to a K channel opener on the basis of membrane potential differences. For example, in vitro studies reveal that cells with resting membrane potentials close to E_k (e.g., cardiac cells) are affected minimally by drugs such as pinacidil and cromakalim, whereas those with resting membrane potentials positive to the E_k are hyperpolarized (e.g., smooth muscle). Differences between normal and diseased tissues could also be exploited. In cardiac cells, chronic ischemia may result in partial membrane depolarization and action potential prolongation, rendering diseased tissues preferentially susceptible to K channel openers. Potential selectivity would also be obtained if K channel openers could be developed with selectivity for known subtypes of K channels that may be important in modulating physiological effects in different tissues. The discovery of suitable radioligands to label selectively K channel subtypes would also be an important advance. It is possible to label the high-conductance, Ca-activated K channel with radioiodinated charybdotoxin and the ATP-dependent K channel with [^{3}H]glyburide, but beyond this there is a dearth of radiolabeled K channel blockers. Moreover, no radioligands exist for the site of action of the K channel opening vasodilator drugs.

With the few exceptions noted in this Perspective, there are relatively few K channel openers or blockers available for widespread clinical application, and it will be some time before we know if the K channel modulators will become as pervasive in medicine as the Ca channel blockers. However, the field is poised for tremendous scientific advances through the diligent application of new experimental techniques and chemical probes and, at the very least, new vistas in ion channel science will be revealed.

Acknowledgment. Pamela J. Edmonds provided invaluable assistance in the preparation of the manuscript, Kathleen A. Cloutier performed exhaustive literature searching, and Joseph H. Krushinski assisted by preparing the artwork. We thank all of these co-workers, without whom this work would have been considerably more difficult.

Registry No. K, 7440-09-7.

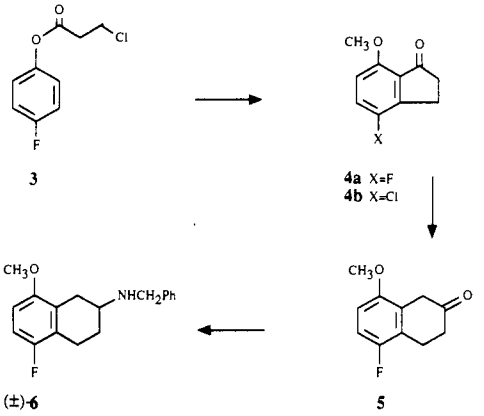
Communications to the Editor

(*S*)-5-Fluoro-8-hydroxy-2-(dipropylamino)tetralin: A Putative 5-HT$_{1A}$-Receptor Antagonist

Sir:

The 5-HT$_{1A}$ receptor[1,2] appears to be involved in a number of important brain functions such as regulation of mood, sleep, and sexual behavior. However, its functional role is not fully understood. This may be due to the lack of adequate pharmacological tools, that is, selective 5-HT$_{1A}$-receptor antagonists.[3,4] In this communication, we report that introduction of a C5-fluoro substituent into the potent 5-HT$_{1A}$-receptor agonist (*S*)-8-hydroxy-2-(di-

Scheme I



(1) Fargin, A.; Raymond, J. R.; Lohse, M. J.; Koblika, B. K.; Caron, M. G.; Lefkowitz, R. J. *Nature* **1988**, *335*, 358-360.

(2) For reviews on the pharmacology and classification of 5-HT receptors, see: Hartig, P. R. *Trends Pharmacol. Sci.* **1989**, *10*, 64-69. Peroutka, S. J. *ISI Atlas Sci.* **1988**, *2*, 1-4. Leff, P.; Martin, G. R. *Med. Res. Rev.* **1988**, *8*, 187-202. Fozard, J. R. *Trends. Pharmacol. Sci.* **1987**, *8*, 501-506. Peroutka, S. J. In *Psychopharmacology: The Third Generation of Progress*; Meltzer, H. Y., Ed.; Raven Press: New York, 1987; pp 303-311. Göthert, M.; Schlicker, E. *J. Cardiovasc. Pharmacol.* **1987**, *10* (*Suppl. 3*), S3-S7. Conn, P. J.; Sanders-Bush, E. *Psychopharmacology* **1987**, *92*, 267-277. Bradley, P. B.; Engel, G.; Fenuik, W.; Fozard, J. R.; Humphrey, P. P. A.; Middlemiss, D. N.; Mylecharane, E. J.; Richarson, B. P.; Saxena, P. R. *Neuropharmacology* **1986**, *25*, 563-576.

(3) For reviews on 5-HT-receptor agonists and antagonists, see: Arvidsson, L.-E.; Hacksell, U.; Glennon, R. A. *Prog. Drug Res.* **1986**, *30*, 365-471. Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1-12. Fuller, R. W. *Adv. Drug. Res.* **1988**, *17*, 349-380. Kulkarni, S. K.; Aley, K. O. *Drugs Today* **1988**, *24*, 175-183.

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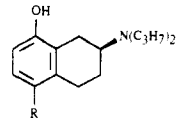
propylamino)tetralin [(*S*)-8-OH-DPAT; (*S*)-**1**][8-11] appears

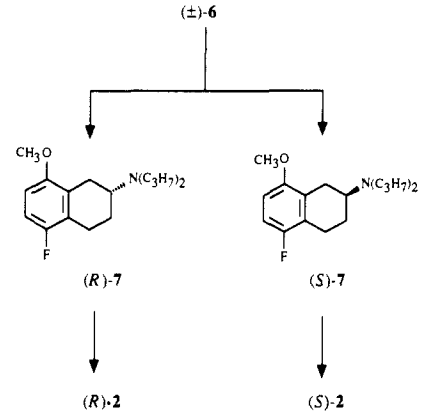


(*S*)-**1**: R=H
(*S*)-**2**: R=F

to abolish efficacy but not the affinity for 5-HT_{1A} receptors.[12] Thus, (*S*)-5-fluoro-8-hydroxy-2-(dipropylamino)-tetralin [(*S*)-**2**] behaves as a 5-HT_{1A}-receptor antagonist. This conclusion is corroborated by the ability of (*S*)-**2** to inhibit (*R*)-**1**-induced biochemical and behavioral changes in the rat in a dose-dependent manner. In contrast, racemic **2** is inactive in functional assays and (*R*)-**2**, although being of slightly lower potency than (*R*)- and (*S*)-**1**, exhibits pharmacological characteristics common to other tetralin-based 5-HT_{1A}-receptor agonists.[13]

The synthesis of (*R*)- and (*S*)-**2** were carried out as follows (Schemes I and II):[15] Esterification of 4-fluorophenol with 3-chloropropionyl chloride produced ester **3**, which was submitted to a Fries rearrangement[16] ($AlCl_3$, 25 → 180 °C) followed by methylation (CH_3I, K_2CO_3, acetone). Indanone **4a** was consistently contaminated with 5–10% of the 4-chloro-substituted **4b** (Scheme I). Apparently, the vigorous conditions used in the Fries rearrangement enable chlorine to partially displace the fluoro substituent. Although a variety of conditions were employed, it was not possible to decrease the amount of **4b** and at the same time obtain **4a** in a good yield. Crude **4a** was recrystallized to homogeneity from ethyl acetate.

Scheme II



Indanone **4a** was readily converted into tetralone **5** by a Wittig reaction ($Ph_3P{=}CH_2$, DMSO) followed by ring expansion[17] [$Tl(NO_3)_3$, $HC(OMe)_3$, MeOH] and hydrolysis of the resulting dimethyl ketal of **5** (aqueous HCl, Et_2O). The benzylamino derivative **6** was obtained from **5** by reductive amination [(i) $C_6H_5CH_2NH_2$, benzene; (ii) $NaCNBH_3$, MeOH, HCl]. Fractional crystallization of the diastereomeric tartrates of **6** from EtOH afforded the enantiomers in high stereochemical purities[18] (≥99% ee as determined by GLC analysis of the diastereomeric *O*-methylmandelic amides). The enantiomers of **6** were converted into (*R*)- and (*S*)-**2**,[19] respectively, by the following synthetic sequence (Scheme II): (i) debenzylation (H_2, Pd/C, MeOH) and (ii) *N*,*N*-dialkylation to produce (*R*)- and (*S*)-**7**, respectively (C_3H_7I, K_2CO_3, CH_3CN), and (iii) demethylation (48% HBr, 120 °C). The absolute configuration of (+)-**2**·HBr was determined by X-ray crystallography to be *R*.[20]

Racemic **2** was produced from **5** in three synthetic steps: (a) reductive amination [(i) $C_3H_7NH_2$, benzene; (ii) H_2, Pd/C, MeOH], (b) alkylation (C_3H_7I, K_2CO_3, CH_3CN), and (c) demethylation (48% HBr, 120 °C).

In preliminary experiments, racemic **2**·HBr was given to rats before administration of the aromatic L-amino acid decarboxylase inhibitor (3-hydroxybenzyl)hydrazine (NSD 1015)[21] and the brain levels of 5-HTP and DOPA were measured (by HPLC with electrochemical detection).[22]

(4) 5-HT_{1A} receptor antagonists such as (−)-pindolol and methiothepin are nonselective and the arylpiperazine derivatives BMY 7378 and NAN 190, which have been claimed to be antagonists,[5,6] appear to be mixed agonists/antagonists.[7]
(5) Chaput, Y.; De Montigny, C. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 359–370.
(6) Glennon, R. A.; Naiman, N. A.; Pierson, M. E.; Titeler, M.; Lyon, R. A.; Herndon, J. L.; Miesenheimer, B. *Drug. Dev. Res.* **1989**, *16*, 335–343.
(7) Sharp, T.; Backus, L. I.; Hjorth, S.; Bramwell, S. R.; Grahame-Smith, D. G. *Eur. J. Pharmacol.* **1990**, *176*, 331–340. Hjorth, S.; Sharp, T. *Life Sci.* **1990**, *46*, 955–963.
(8) Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. *J. Med. Chem.* **1981**, *24*, 921–923. Arvidsson, L.-E.; Hacksell, U.; Johansson, A. M.; Nilsson, J. L. G.; Lindberg, P.; Sanchez, D.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 45–51.
(9) Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G. *J. Neural Transm.* **1982**, *55*, 169–188.
(10) For reviews on the pharmacology of **1**, see: Arvidsson, L.-E. *Drugs Future* **1985**, *10*, 916–919. Brain 5-HT_{1A} Receptors; Dourish, C. T., Ahlenius, S., Hutson, P. H., Eds.; Ellis Horwood: Chichester, England, 1987.
(11) Both enantiomers of **1** are 5-HT_{1A}-receptor agonists, the *R* enantiomer being about twice as potent as the antipode.[8]
(12) Introduction of fluoro substituents in the aromatic ring also has dramatic effects on the biological activity in other drugs: Kirk, K. L.; Creveling, C. R. *Med. Res. Rev.* **1984**, *4*, 189–220.
(13) Typically, such compounds induce a behavioral syndrome in rats (5-HT motor syndrome)[14] and inhibit the synthesis and release of 5-HT. See, for example, refs 3 and 8.
(14) Jacobs, B. L. *Life Sci.* **1976**, *19*, 777–786. Ortmann, R. *Pharmacopsychiatria* **1985**, *18*, 198–201.
(15) All new compounds reported herein exhibit ^1H, ^{13}C NMR, IR, mass spectra, and elemental analysis (within 0.4% of the calculated value) in agreement with the assigned structures.
(16) Compare: Wagatsuma, S.; Higuchi, S.; Ito, H.; Nakano, T.; Naoi, Y.; Sakai, K.; Matsui, T.; Takahashi, Y.; Nishi, A.; Sano, S. *Org. Prep. Proced. Int.* **1973**, *5*, 65–70.
(17) Taylor, E. C.; Chiang, C.-S.; McKillop, A. *Tetrahedron Lett.* **1977**, 1827–1830.
(18) The addition of (+)-L-tartaric acid to an EtOH solution of (±)-**6** led to preferential precipitation of the tartrate salt of (+)-(*R*)-**6**. Three recrystallizations from EtOH produced the pure diastereomeric salt: $[\alpha]^{22}_D$ +76.8° (*c* 0.25, MeOH), mp 207–208.5 °C. The pure *S* enantiomer of **6** was obtained similarly from the combined mother liquors by treatment with (−)-D-tartaric acid.
(19) (*R*)-**2**·HCl: mp 215–216.5 °C; $[\alpha]^{22}_D$ = +82.4° (*c* 1.0, MeOH); ^1H NMR (CD_3OD) δ 6.76 (dd, $J^1 = J^2$ = 8.8 Hz, C6-H), 6.59 (dd, J^1 = 8.8 Hz, J^2 = 5 Hz, C7-H), 1.58–3.95 (m, 15 H), 1.05 (t, 6 H); ^{13}C NMR (CD_3OD) δ 155.3 (C5, $J_{C,F}$ = 234 Hz), 152.3 (C8, $J_{C,F}$ = 2 Hz), 124.2 (C4a, $J_{C,F}$ = 20 Hz), 122.4 (C8a, $J_{C,F}$ = 4 Hz), 113.8 (C6, $J_{C,F}$ = 23 Hz), 113.3 (C7, $J_{C,F}$ = 9 Hz), 61.5 (C2), 54.0 (Cα's), 25.4 (C1, $J_{C,F}$ = 1.5 Hz), 23.9 (C3), 22.9 (C4, $J_{C,F}$ = 4 Hz), 19.8 (Cβ's'), 11.4 (Cγ's); ^{19}F NMR (CD_3OD, $CFCl_3$ as internal standard) δ −130.5. (*S*)-**2**·HCl gave identical spectra, mp 215.5–217 °C; $[\alpha]^{22}_D$ −83.7° (*c* 1.0, MeOH).
(20) Dr. Ingeborg Csöregh, Department of Structural Chemistry, Arrhenius Laboratory, University of Stockholm, Sweden, unpublished.
(21) Carlsson, A.; Davis, J. N.; Kehr, W.; Lindqvist, M.; Atack, C. V. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1972**, *275*, 153–168.
(22) For experimental detail, see: Björk, L.; Mellin, C.; Hacksell, U.; Andēn, N.-E. *Eur. J. Pharmacol.* **1987**, *143*, 55–63.

Table I. Effects of the Enantiomers of **2** on the Accumulation of 5-HTP and DOPA in Rat Brain[a]

compd	dose, μmol/kg sc	5-HTP,[b] ng/g		DOPA,[b] ng/g	
		striatum	limbic	striatum	limbic
(*R*)-**2**	10	59.7 ± 6.9**	86.5 ± 7.9**	1187 ± 45	398 ± 22
(*S*)-**2**	32	91.4 ± 8.9	152 ± 12	682 ± 64**	324 ± 19
(*S*)-**2** + (*R*)-**1**	32 + 0.32	101 ± 8.6	146 ± 9.0	895 ± 6.1*	355 ± 24
(*R*)-**1**	0.32	53.3 ± 5.5**	103 ± 4.7**	909 ± 52	371 ± 23
control		114 ± 5.4	186 ± 8.4	1206 ± 56	420 ± 22

[a] Nonpretreated rats received (*R*)-**1**, (*R*)-**2**, or (*S*)-**2** subcutaneously 60 min before death and NSD 1015 (287 μmol/kg sc) 30 min before death. (*S*)-**2** was given 70 min before death to rats receiving both (*R*)-**1** and (*S*)-**2**. [b] Shown are the means ± SEM, n = 9 and 5–7 in the control and experimental groups, respectively. Statistics: one-way analysis of variance followed by Tukey's post hoc test; $^{**}p < 0.01$, $^{*}p < 0.05$ vs controls.

Table II. Affinities of the Enantiomers of **2** at [^{3}H]-8-OH-DPAT Labeled 5-HT_{1A}-Receptor Sites and [^{3}H]Sandoz 205-501 Labeled DA D_2-Receptor Sites

compd	5-HT_{1A} sites[a]		DA D_2 sites[b]	
	K_i,	n_H	K_i, nM	n_H
(*R*)-**2**	6.1	0.89	730	0.85
(*S*)-**2**	52	0.49	400	1.09
(±)-**1**	1.0	0.92	975	0.98

[a] The method has been described previously (see ref 31). [b] The binding of [^{3}H]sandoz 205-501 (103 Ci/mmol, Amersham international plc) to washed membrane fragments of the rat striatum was preformed according to the method described by Creese et al.[32] The K_D value for [^{3}H]sandoz 205-501 was 4.5 nM and the B_{max} value was 25.6 pmol/g of tissue in the experiments in which the test compounds were examined. The K_i values were calculated from IC_{50} values of inhibitor curves using 10 nM of the radioligand. n_H was obtained from Hill plots.

This assay is based on the observation that 5-HT_{1A}-receptor agonists (as well as DA D_2 receptor agonists) inhibit the biosynthesis of the corresponding monoamine.[23] Consequently, the monoamine synthesis can be used as an indicator of receptor activation. In contrast to (±)-**1**, which powerfully decreases 5-HTP levels in the limbic and striatal brain regions at 0.1 μmol/kg sc,[9] (±)-**2** (41 μmol/kg sc, n = 3) did not induce any clear-cut biochemical changes in the rat brain. Similarly, whereas the racemate and both enantiomers of **1** (0.5–1 μmol/kg sc) induced flat body posture and foreleg movements (5-HT syndrome)[14] in rats in which the presynaptic monoamine stores had been depleted by reserpine pretreatment, (±)-**2** (41 μmol/kg, sc) did not change the behavior of the reserpine-pretreated rats.

Also each enantiomer of **2** was tested in the biochemical and behavioral assays:[24] (*R*)-**2** (10 μmol/kg sc) induced a considerable decrease in 5-HTP levels in nonpretreated rats (Table I) and elicited a full-blown 5-HT syndrome in reserpinized rats. In addition, (*R*)-**2** potently displaced racemic [^{3}H]-8-OH-DPAT from cortical 5-HT_{1A}-binding sites in vitro (Table II). Thus, (*R*)-**2** seems to be a 5-HT_{1A}-receptor agonist, similar in profile to **1** but less potent. In contrast, (*S*)-**2** (32 μmol/kg sc) did not significantly affect the 5-HTP levels in nonpretreated rats (Table I) or the behavior of reserpine-pretreated rats. It did, however, displace [^{3}H]-8-OH-DPAT from 5-HT_{1A} receptors although with less potency than the *R* enantiomer (Table II). In addition, (*S*)-**2** but not (*R*)-**2** induced a decrease in striatal DOPA levels. Therefore, the abilities of (±)-**1**, (*R*)-, and (*S*)-**2** to displace the DA D_2 ligand [^{3}H]sandoz 205-501[25] from rat striatal tissue was investigated (Table II). Indeed, (*S*)-**2** was about twice as potent as (±)-**1** and (*R*)-**2** in this respect. It should be noted, however, that the affinity of (*S*)-**2** for 5-HT_{1A} receptors is 8-fold higher than that for DA D_2-receptors.

The results described above indicate that (*S*)-**2** is a 5-HT_{1A} receptor antagonist. To verify this hypothesis we investigated if (*S*)-**2** was able to antagonize the actions of (*R*)-**1**: (*S*)-**2** (32 μmol/kg sc) did counteract the (*R*)-**1** (0.32 μmol/kg sc) induced decrease of 5-HTP levels in the striatal and limbic rat brain parts (Table I). A weak inhibition of the (*R*)-**1**-induced effect was observed also at a dose of 3.2 μmol/kg of (*S*)-**2**. In addition, the behavioral effects of (*R*)-**1** (1 μmol/kg sc) in reserpinized rats were completely blocked by pretreatment with (*S*)-**2** (10 μmol/kg sc, 10 min before). Pretreatment with (*S*)-**2**, 2 h before, attenuated the (*R*)-**1**-induced behavior but no blockade was observed when (*S*)-**2** was given 4 h before (*R*)-**1**. This antagonism was equally effective after pretreatment with the DA D_2-receptor antagonist haloperidol (2 mg/kg ip). Thus, the mechanism by which (*S*)-**2** antagonizes (*R*)-**1**-induced effects does not appear to involve a dopaminergic component. Fluorine differs only little in size from hydrogen[26] and its effect on the acidity of the phenol group of **2** should be minimal.[27] Preliminary NMR experiments and molecular mechanics calculations indicate that the fluorine substituent does not induce any conformational change.[28] Thus, the major difference between **2** and **1** may be related to their electronic distribution.[29] Consequently, the present results indicate that the efficacy of (*S*)-**1** may be further modified by changing the electronic properties of the aromatic ring.[30]

(23) Andén, N.-E.; Carlsson, A.; Häggendal, J. *Annu. Rev. Pharmacol.* **1969**, *9*, 119–134.
(24) In all experiments with the enantiomers of **2**, the number of rats in each group was ≥5.
(25) Closse, A.; Frick, W.; Markstein, R.; Mauter, R.; Nordmann, R. *J. Neural Transm.* **1985**, *62*, 231–248.
(26) The van der Waals radius of fluorine is 1.35 Å and that of hydrogen is 1.2 Å: *Handbook of Chemistry and Physics*, 68th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1987–1988.
(27) The pK_a values in water of phenol and 4-fluorophenol are 10.00 and 9.81, respectively: Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall Ltd.: London, 1971; p 87.
(28) The conformational preferences of **1** have been studied: Arvidsson, L.-E.; Karlén, A.; Norinder, U.; Sundell, S.; Kenne, L.; Hacksell, U. *J. Med. Chem.* **1988**, *31*, 212–221.
(29) We have, however, not excluded the possibilities, suggested by one of the reviewers, that the hydroxy group may act as a hydrogen acceptor and that the fluoro substituent may influence the basicity of the oxygen or that the fluoro substituent may form a hydrogen bond with the receptor.
(30) Partial 5-HT_{1A}-receptor agonists appear to be of therapeutic value in the treatment of anxiety: Traber, J.; Glaser, T. *Trends Pharmacol. Sci.* **1987**, *8*, 432–437.
(31) Liu, Y.; Mellin, C.; Björk, L.; Svensson, B.; Csöregh, I.; Helander, A.; Kenne, L.; Andén, N.-E.; Hacksell, U. *J. Med. Chem.* **1989**, *32*, 2311–3218.
(32) Creese, I.; Padgett, L.; Fayzcini, E.; Lopez, F. *Eur. J. Pharmacol.* **1979**, *56*, 411–412.

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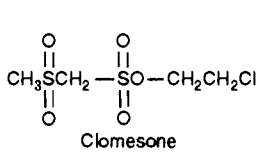
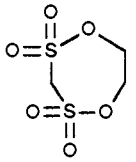
Phenyl Selenones: Alkyl Transfer by Selenium-Carbon Bond Cleavage[1]

Sir:

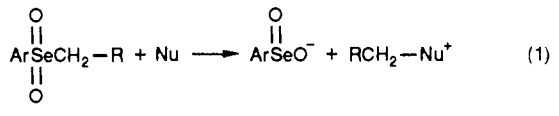
Systematic chemical modifications of nitrosoureas and triazenes led to the discovery of 2-chloroethylating antitumor agents. This class of cross-linking agents includes BCNU (carmustine), CCNU (lomustine), MeCCNU (semustine), PCNU, BIC, and MCIC.[2] They are highly active in vivo against a broad range of murine neoplasms, but have demonstrated relatively narrow clinical activity. Clomesone and Cyclodisone, derivatives of sulfonates, are examples of bifunctional 2-chloroethyl derivatives currently under active development.[3] Both have shown broad-spectrum anticancer activities and unique biological activities.[3,4]



Clomesone


Cyclodisone

Organoselenones (Se:VI) are known to undergo nucleophilic displacements, yielding seleninates and alkyl–nucleophile adducts as shown in eq 1.[5] The characteristically



(1)

high nucleophilic selectivities of organoselenones that we describe in the present report was implicit in the observations that methyl phenyl selenone is about 3 times as reactive as methyl iodide toward dimethyl sulfide,[5b] and that decyl phenyl sulfide is isolated as the sole reaction product in the treatment of decyl phenyl selenone and nonyl bromide or iodide with sodium thiophenolate in ethanolic solution.[6] These findings indicated a potential of organoselenones as biological alkylating agents. By contrast, organosulfones, analogues of selenones, generally exhibit high chemical and thermal stability,[7] and the bond cleavage between sulfur and carbon in a sulfone takes place only under exceptional circumstances.

Recently, we reported[8] the synthesis, kinetic behavior, and cytotoxicity of alkylating organoselenides, isosteres of classical nitrogen and sulfur mustards. Despite the high polarizability of the selenium atom, however, and the expectation of increased nucleophilic selectivities,[9] this class showed generally low Swain–Scott s constants (with some exceptions), perhaps resulting from overly high reactivities of the ethyleneselenonium ion intermediates resulting in excessive hydrolysis. In addition, the aqueous solubility of this series was low. To date, however, there has been no reported application of organoselenone chemistry to any drug design including cross-linking antitumor agents.

The anticipation of high nucleophilic selectivity among organoselenones was particularly attractive, in view of the fact of broad antitumor activities of ethylenimines and platinating agents, which are highly selective, in contrast to nitrosoureas, which are not[9a] and have a narrow spectrum of clinical activity. We now describe alkylating organoselenones, in which the selenone moiety acts as a leaving group via Se–C breakage, that have desirable properties of slowed reactivity (compared to selenides), high selectivity (AA), and short cross-linking distance (similar to cisplatin).

Table I presents the results of chemical kinetic parameters and antiproliferative activities of a sulfone and aryl haloalkyl selenones 1–6 and closely related nitrogen, sulfur, and selenium compounds. In the alkylation reactions of 1–6, 4-(4-nitrobenzyl)pyridine (NBP) was used as a model biologic nucleophile that somewhat resembles the N7 site of guanine.[9a] The reactions were carried out at 37 °C in aqueous acetone in the presence of Tris-HCl buffer at pH 7.4 as described in the previous report.[7] Experimental first-order rate constants, k'_{nbp}, were obtained from the plots of log (percent remaining alkylating species) vs time, where NBP was present in pseudo-first-order excess. AA is a parameter of nucleophilic selectivity, which is the

(1) Part of this work was presented at the 12th Annual National Organometallic Chemistry Workshop, Potoshi, Missouri, May 20–23, 1988.
(2) Montgomery, J. A. *Acc. Chem. Res.* **1986**, *19*, 293.
(3) Narayanan, V. L. In *New Avenues in Developmental Cancer Chemotherapy*; Harrap, K. R., Connors, T. A., Eds.; Academic Press: New York, 1987; Chapter 20.
(4) (a) Gibson, N. W. *Cancer Res.* **1989**, *49*, 154. (b) Alexander, J. A.; Bowdon, B. J.; Wheeler, G. P. *Cancer Res.* **1986**, *46*, 6024. (c) Hartley, J. A.; Gibson, N. W.; Kohn, K. W.; Mattes, W. B. *Cancer Res.* **1986**, *46*, 1943. (d) Gibson, N. W.; Hartley, J. A.; Kohn, K. W. *Cancer Res.* **1986**, *46*, 1679. (e) Shealy, Y. F.; Krauth, C. A.; Laster, W. R., Jr. *J. Med. Chem.* **1984**, *27*, 664.
(5) (a) Uemura, S.; Fukuzawa, S.; Toshimitsu, A. *J. Chem. Soc., Chem. Commun.* **1983**, 1501. (b) Reich, H. J. In *Proceedings of the Fourth International Conference on the Organic Chemistry of Selenium and Tellurium*; Berry, F. J., McWhinnie, W. R., Eds.; The University of Aston: Birmingham, 1983; pp 258–272.
(6) Krief, A.; Dumont, W.; Denis, J.-N. *J. Chem. Soc., Chem. Commun.* **1985**, 571.
(7) Durst, T. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: New York, 1979; Vol. 3, pp 171–195.
(8) Kang, S.-I.; Spears, C. P. *J. Med. Chem.* **1987**, *30*, 597.
(9) (a) Spears, C. P. *Mol. Pharmacol.* **1982**, *19*, 496. (b) Edwards, J. O. *J. Am. Chem. Soc.* **1954**, *76*, 1547. (c) Edwards, J. O. *J. Am. Chem. Soc.* **1956**, *78*, 1819. (d) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16.

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