

In Vitro Activities of Iodonium Salts against Oral and Dental Anaerobes

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The comparative in vitro activities of 11 iodonium salt compounds, 0.12% chlorhexidine, and four antimicrobial agents against 322 anaerobic and fastidious potential dental and periodontal bacterial pathogens were studied. Iodonium salts 3, 4, 5, 9, and 10 had in vitro activities comparable to that of chlorhexidine against most isolates. These compounds may be suitable for incorporation into an oral mouthwash.

Biodiversity studies of subgingival plaque estimate that more than 400 different species may colonize the subgingival region (7, 8, 12), with approximately 20% of these species not being cultivable by current methods. These microbes occupy micro-biologically different ecological niches in the oral cavity. Subsets of these isolates, still not fully defined, are potentially pathogenic and cause a variety of orally related diseases. Periodontal diseases, including gingivitis and periodontitis, are chronic conditions that develop as a result of bacterial accumulations (plaque) on the teeth and gingivae. Their prevalence increases with increasing age, and approximately 50% of adults in the United States have gingivitis around three to four teeth at any given time. Moreover, 30% develop periodontitis and approximately 3% have advanced or aggressive periodontitis (1).

Gingivitis is of polymicrobial origin and can be reversed with good oral hygiene. Periodontitis is a major cause of tooth loss in humans. These diseases are associated with an alteration of the healthy oral flora and an increase in the isolation of periodontal pathogenic species, especially anaerobic bacteria such as *Bacteroides forsythus* (*Tannerella forsythensis*), *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Treponema denticola*, and a variety of uncultivable spirochetes (1, 8, 13). Therapies include adherence to good oral hygiene, dental procedures, and the administration of topical and oral antimicrobial agents.

Another adjunctive, popular approach is consumer self-administration of mouthwashes which contain a variety of ingredients to kill oral bacteria, including alcohol, cetylpyridinium chloride, zinc chloride, benzoic acid, benzalkonium chloride, eucalyptus oil, and thymol. Chlorhexidine gluconate-containing mouthwashes (e.g., Perio Rx) are available with medical or dental prescriptions. These have the ability to bind and penetrate plaque biofilm and prevent bacterial aggregation, slow multiplication, and extract endotoxins.

Iodonium salts are organic cations with profound and wide-

ranging physiological actions that are based on the inhibition of pyrroloquinoline quinone (or methoxatin 1), a bis(quinone) tricarboxylic acid that is an organic cofactor in the biological redox cycling process (2). These activities include mitochondrial toxicity causing blockage of gluconeogenesis, inhibition of the respiratory burst in stimulated neutrophils, and the inhibition of nitric oxide synthase (2) and broad-spectrum inhibitory activity against bacteria, fungi, yeasts, and small viruses (patent disclosure). Preliminary data (supplied by Charitable Leadership Foundation, Clifton, N.Y.) have suggested that iodonium salts have in vitro activity against a variety of anaerobic bacteria. In a series of experiments, we studied the comparative in vitro activity of several iodonium compounds, selected antimicrobials, and chlorhexidine gluconate against selected anaerobic oral and dental pathogens.

The NCCLS-approved reference agar dilution method was used (5, 6). Previously identified (3, 4) human oral flora isolates were taken from frozen stock cultures and streaked onto brucella agar plates to ensure purity and good growth. The isolates are identified in Tables 1 and 2. Iodonium compounds (Fig. 1) were manufactured according to previously published procedures (9–11, 14–16). Chlorhexidine gluconate (0.12%; Discus Dental, Culver City, Calif.) was donated by Sushma Nachnani. Reference standard powders of antimicrobial agents were obtained as follows: penicillin G, Sigma, St. Louis, Mo.; clindamycin, Pharmacia, Kalamazoo, Mich.; tetracycline, Bristol Meyer Squibb, Syracuse, N.Y.; and metronidazole, Searle Pharmaceuticals, Skokie, Ill. Powders were prepared according to the manufacturers' instructions and diluted by doubling dilutions to achieve test concentrations. Brucella agar plates supplemented with 5% laked sheep blood, hemin, and vitamin K1 and various concentrations of the study agents were prepared on the day of testing. Drug-free plates were included as growth controls. Using a Steers replicator, an inoculum of approximately 10⁵ CFU/spot was applied to the plates. Reference organisms (*Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, and *Eubacterium lentum* ATCC 43055) were included as controls. Inoculated plates were incubated in an anaerobic chamber at 37°C and examined after 48 h. The MIC was defined as the concentration of agent at

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TABLE 1. Comparative in vitro activities of IS-5 and -6 against anaerobic and fastidious dental and oral pathogens

Organism and agent	No. of isolates	MIC ($\mu\text{g/ml}$) ^b		
		Range	50%	90%
<i>Actinomyces</i> spp. ^a	18			
IS-5		8->64	64	64
IS-6		64->256	>256	>256
Clindamycin		≤ 0.03 ->32	0.125	>32
Penicillin G		≤ 0.03 -0.25	0.06	0.25
Tetracycline		0.125-16	0.5	1
Metronidazole		≤ 0.03 ->32	4	>32
<i>Eubacterium saburreum</i>	10			
IS-5		0.25->64	>64	>64
IS-6		128-256	256	256
Clindamycin		≤ 0.03 -0.25	0.25	0.25
Penicillin G		≤ 0.03 -0.125	0.06	0.125
Tetracycline		0.125-16	0.5	16
Metronidazole		0.06-0.5	0.125	0.25
<i>Eubacterium</i> spp. ^b	25			
IS-5		0.06->64	>64	>64
IS-6		64->256	128	256
Clindamycin		≤ 0.03 ->32	0.25	0.25
Penicillin G		≤ 0.03 -0.5	≤ 0.03	0.125
Tetracycline		0.06-8	0.25	2
Metronidazole		≤ 0.03 ->32	0.125	2
<i>Peptostreptococcus micros</i>	21			
IS-5		0.125-1	0.5	1
IS-6		8-128	64	128
Clindamycin		0.06-0.25	0.125	0.125
Penicillin G		≤ 0.03 -0.25	≤ 0.03	≤ 0.03
Tetracycline		0.0-4	0.125	2
Metronidazole		0.06-0.25	0.25	0.25
<i>Peptostreptococcus</i> spp. ^c	16			
IS-5		0.25-2	1	1
IS-6		64->512	256	>512
Clindamycin		≤ 0.03 ->32	≤ 0.03	0.5
Penicillin G		≤ 0.03 -0.25	0.06	0.25
Tetracycline		0.125-32	0.5	4
Metronidazole		0.06-2	0.25	1
NSF GPB ^d	19			
IS-5		0.125->64	64	>64
IS-6		128->256	>256	>256
Clindamycin		≤ 0.03 ->32	≤ 0.03	0.5
Penicillin G		≤ 0.03 -1	0.125	1
Tetracycline		0.125-32	1	16
Metronidazole		0.125->32	32	>32
<i>Campylobacter</i> spp. ^e	18			
IS-5		0.125-1	0.5	1
IS-6		128->512	256	512
Clindamycin		0.06-4	0.25	2
Penicillin G		≤ 0.03 -2	0.5	>32
Tetracycline		0.125-4	0.5	2
Metronidazole		0.25-4	1	4
<i>Fusobacterium nucleatum</i>	26			
IS-5		0.25-16	4	16
IS-6		64->256	256	>256
Clindamycin		≤ 0.03	≤ 0.03	≤ 0.03
Penicillin G		≤ 0.03 -0.125	≤ 0.03	≤ 0.03
Tetracycline		0.25-1	0.5	1
Metronidazole		≤ 0.03 -0.125	≤ 0.03	0.125
<i>Fusobacterium</i> spp. ^f	9			
IS-5		0.06-1	0.25	-
IS-6		64-512	128	-
Clindamycin		≤ 0.03 -0.06	≤ 0.03	-

Continued on following page

TABLE 1—Continued

Organism and agent	No. of isolates	MIC ($\mu\text{g/ml}$) ^b		
		Range	50%	90%
Penicillin G		≤ 0.03 –0.25	≤ 0.03	—
Tetracycline		≤ 0.03 –1	0.25	—
Metronidazole		≤ 0.03 –0.25	0.125	—
<i>Porphyromonas</i> spp. ^g	6			
IS-5		0.25–1	0.25	—
IS-6		256–>512	256	—
Clindamycin		≤ 0.03 –2	≤ 0.03	—
Penicillin G		≤ 0.03 –0.5	≤ 0.03	—
Tetracycline		0.06–1	0.25	—
Metronidazole		≤ 0.03 –4	0.125	—
Nonpigmented <i>Prevotella</i> spp. ^h	29			
IS-5		≤ 0.03 –0.25	0.125	0.25
IS-6		ND		
Clindamycin		≤ 0.03 –>32	≤ 0.03	≤ 0.03
Penicillin G		≤ 0.03 –>32	0.125	>32
Tetracycline		0.125–>32	8	32
Metronidazole		0.06–2	0.5	1
Indole-positive pigmented <i>Prevotella</i> spp. ⁱ	23			
IS-5		≤ 0.03 –0.125	0.125	0.125
IS-6		ND		
Clindamycin		≤ 0.03	≤ 0.03	≤ 0.03
Penicillin G		≤ 0.03 –16	1	16
Tetracycline		≤ 0.03 –8	0.5	8
Metronidazole		≤ 0.03 –1	0.25	0.5
Indole-negative pigmented <i>Prevotella</i> spp. ^j	23			
IS-5		0.06–0.5	0.125	0.25
IS-6		ND		
Clindamycin		≤ 0.03 –>32	≤ 0.03	0.25
Penicillin G		≤ 0.03 –8	0.5	8
Tetracycline		0.06–32	4	32
Metronidazole		≤ 0.03 –2	0.25	1
<i>Veillonella</i> spp.	36			
IS-5		0.06–4	1	2
IS-6		512–>512	512	>512
Clindamycin		≤ 0.03 –>32	0.06	0.125
Penicillin G		0.06–8	1	8
Tetracycline		0.5–32	2	16
Metronidazole		0.125–4	2	4
Miscellaneous GNRs ^k	17			
IS-5		0.06–4	0.25	2
IS-6		32–>512	256	>512
Clindamycin		≤ 0.03 –2	≤ 0.03	0.25
Penicillin G		≤ 0.03 –1	0.125	0.5
Tetracycline		0.125–4	0.5	2
Metronidazole		≤ 0.03 –4	0.5	4
<i>Eikenella corrodens</i>	31			
IS-5		0.5–1	0.5	1
IS-6		ND	—	—
Clindamycin		8–>32	>32	>32
Penicillin G		0.25–2	1	2
Tetracycline		1–4	2	2
Metronidazole		8–>32	>32	>32

^a *Actinomyces gerencseriae* (one isolate), *A. israelii* (four), *A. meyeri* (one), *A. naeslundii* (two), *A. odontolyticus* (two), *A. radingae* (one), *A. turicensis* (four), *A. viscosus* (one), unidentified *Actinomyces* species (two).

^b *Collinsella aerofaciens* (seven isolates), *Pseudoramibacter alactolyticus* (one), *Eubacterium lentum* (one), *E. timidum* (four), *E. yurii* (five), unidentified *Eubacterium* species (seven).

^c *Peptostreptococcus anaerobius* (six isolates), *P. magnus* (five), *P. prevotii* (three), unidentified *Peptostreptococcus* species (two).

^d NSF GPB, non-spore-forming gram-positive bacillus. *Bifidobacterium* sp. (one isolate), *Lactobacillus catenaforme* (two), *L. delbrueckii* (one), *L. fermentum* (one), *L. minutus* (one), *L. oris* (two), *L. plantarum* (three), unidentified *Lactobacillus* species (one), *Propionibacterium acnes* (five), *P. avidum* (two).

^e *Campylobacter consisus* (one isolate), *C. gracilis* (six), *C. mucosalis* (two), *C. rectus* (five), *C. sputorum* (three), unidentified *Campylobacter* species (one).

^f *Fusobacterium naviforme* (two isolates), *F. necrophorum* (seven).

^g *Porphyromonas catoniae* (one isolate), *P. endodontalis* (one isolate), *P. gingivalis* (three), unidentified *Porphyromonas* species (one).

^h *P. buccae* (14 isolates), *P. buccalis* (one), *P. dentalis* (one), *P. disiens* (one), *P. oralis* (two), *P. oris* (seven), *P. oulorum* (one), *P. zoogloformans* (one), unidentified *Prevotella* species (one).

ⁱ *P. intermedia-nigrescens* group (three isolates), *P. intermedia* (14), *P. pallens* (six).

^j *P. denticola* (two isolates), *P. loescheii* (two), *P. melaninogenica* (18), *P. tanneriae* (two).

^k GNRs, gram-negative rods. *Bacteroides capillosus* (one isolate), *B. ureolyticus* (one), *Capnocytophaga ochracea* (two), *Dialister pneumosintes* (two), *Leptotrichia buccalis* (four), *Selenomonas flueggei* (five), *S. infelix* (two).

^l 50% and 90%, MICs at which 50 and 90% of isolates are inhibited, respectively. ND, not done; —, not reported.

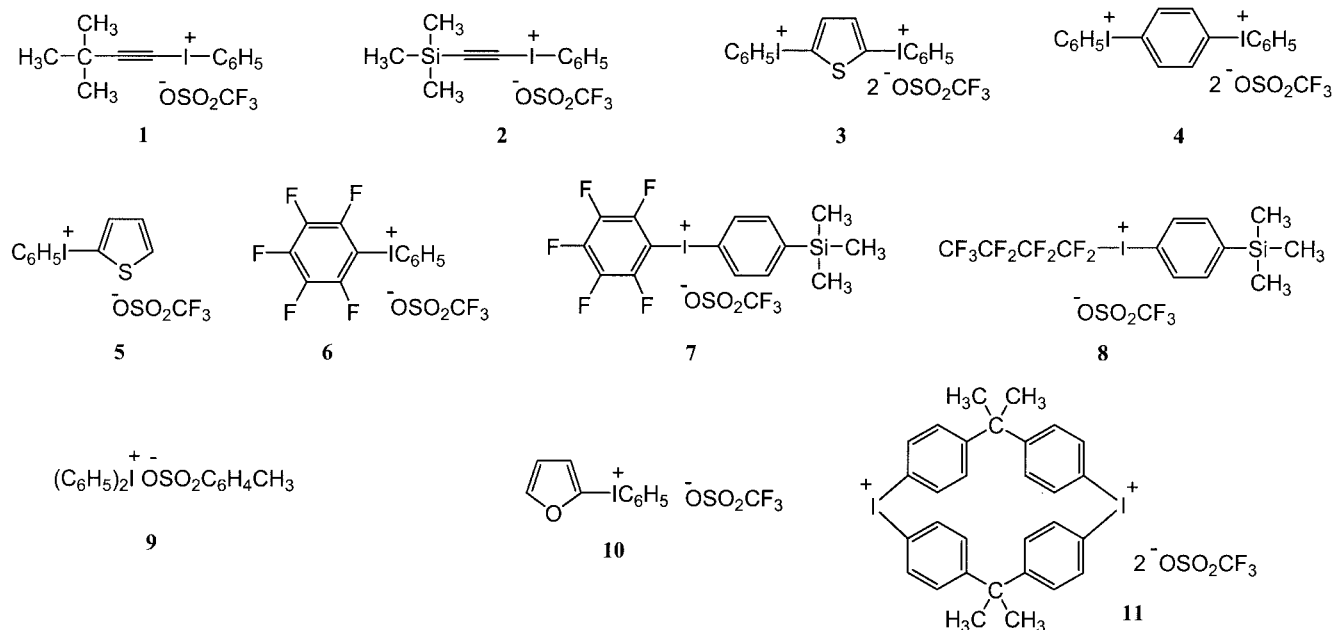


FIG. 1. Chemical structures of IS-1 to -11.

which a marked reduction occurred in the appearance of growth compared to growth on a drug-free plate.

Of note were initial problems of solubilizing iodonium salt compound 5 (IS-5) and IS-6 to prepare stock solutions. IS-6

was initially found to have a milky appearance in dimethyl sulfoxide, did not dissolve in phosphate buffer or water, and became particulate with the addition of NaOH. Ultimately, IS-5 and -6 were solubilized in methanol with subsequent serial

TABLE 2. Comparative in vitro activities of IS-1 to IS-11 and chlorhexidine against representative unique strains of dental and oral pathogens

Organism	Activity ($\mu\text{g/ml}$) of ^a :											
	Chlorhexidine	IS-1	IS-2	IS-3	IS-4	IS-5	IS-6	IS-7	IS-8	IS-9	IS-10	IS-11
<i>Porphyromonas gingivalis</i>	4	32	>64	0.5	0.5	0.25	>64	>64	16	0.125	0.25	32
<i>P. gingivalis</i>	4	>64	>64	1	2	0.5	>64	>64	64	0.125	0.5	>64
<i>Prevotella melaninogenica</i>	4	>64	>64	1	1	0.125	>64	>64	16	0.5	0.5	>64
<i>P. melaninogenica</i>	7.5	>64	>64	1	1	0.125	>64	>64	16	0.5	0.25	>64
<i>P. oris</i>	30	64	>64	0.5	1	0.06	>64	>64	16	0.25	0.25	>64
<i>P. oris</i>	7.5	>64	>64	1	2	0.06	>64	>64	32	0.25	0.5	>64
<i>P. buccae</i>	15	64	>64	1	1	0.125	>64	>64	16	0.5	0.25	>64
<i>P. buccae</i>	15	64	>64	1	1	0.125	>64	>64	16	0.5	0.25	>64
<i>P. intermedia</i>	7.5	32	>64	1	2	0.06	>64	>64	32	0.06	0.5	>64
<i>P. intermedia</i>	4	16	>64	1	2	0.06	>64	>64	32	0.125	0.5	>64
<i>Selenomonas infelix</i>	30	>64	>64	2	2	0.125	>64	>64	>64	0.25	0.5	>64
<i>S. flueggei</i>	7.5	32	>64	1	1	0.25	>64	>64	64	0.125	0.5	>64
<i>Fusobacterium nucleatum</i>	15	16	64	0.25	0.5	1	>64	32	8	0.125	0.25	>64
<i>Veillonella</i> sp.	4	>64	>64	8	2	1	>64	>64	>64	2	4	>64
<i>Veillonella</i> sp.	4	>64	>64	8	2	0.5	>64	>64	64	1	4	>64
<i>Eikenella corrodens</i>	30	>64	>64	32	32	0.5	>64	>64	>64	16	8	>64
<i>E. corrodens</i>	30	>64	>64	16	16	0.5	>64	>64	>64	8	4	>64
<i>Campylobacter rectus</i>	15	>64	>64	2	2	0.5	>64	>64	64	0.25	1	>64
<i>C. rectus</i>	15	>64	>64	1	2	0.5	>64	>64	64	0.25	1	>64
<i>C. gracilis</i>	4	>64	>64	8	4	1	>64	>64	>64	2	4	>64
<i>Collinsella aerofaciens</i>	30	>64	>64	8	8	NT	>64	>64	>64	1	8	>64
<i>C. aerofaciens</i>	30	>64	>64	2	4	0.25	>64	>64	>64	4	4	>64
<i>Eubacterium yurii</i>	60	>64	>64	2	8	NT	>64	>64	64	0.25	4	>64
<i>E. yurii</i>	30	>64	>64	1	4	NT	>64	>64	64	0.25	1	>64
<i>E. saburreum</i>	7.5	>64	>64	1	4	NT	>64	>64	64	0.5	0.5	>64
<i>E. saburreum</i>	4	>64	>64	2	2	NT	>64	>64	64	1	0.5	>64
<i>Actinomyces israeli</i>	2	>64	>64	16	8	NT	>64	>64	64	2	8	>64
<i>A. turicensis</i>	7.5	>64	>64	32	32	NT	>64	>64	>64	32	16	>64
<i>B. fragilis</i> ATCC 25285	60	>64	>64	8	8	1	>64	>64	64	1	4	>64

^a NT, not tested.

dilution in water to achieve the test concentrations. However, these attempts led to a shortage of IS-6, and all isolates could not be tested with this compound. The results of the study of IS-5 and IS-6 are shown in Table 1. IS-5 was generally very active against most isolates tested, while IS-6 was generally poorly active. Clindamycin had overall good activity except against *Eikenella corrodens* isolates, as expected. Tetracycline was active against a broad spectrum of isolates with the exception of some strain of *Prevotella* spp. and *Veillonella* spp. Penicillin had limited activity against some strains of *Veillonella* and *Campylobacter* spp.; 40 of 76 (52.6%) *Prevotella* strains and 2 of 6 *Porphyromonas* strains produced beta-lactamase and were resistant to penicillin. All gram-negative strains were susceptible to metronidazole, although most strains of *Actinomyces*, *Propionibacterium*, and *Lactobacillus* spp. were resistant, as expected.

Because of the disparity in activity of IS-5 and -6, we screened 28 individual representative isolates (Table 2) to determine the overall activity and relative value for future studies of the other iodonium salt compounds. Iodonium salt compounds fell into two groups: group 1 (IS-1, -2, -6, -7, -8, and -11) showed poor activity and group 2 (IS-3, -4, -5, -9, and -10) had moderate to good activity against the oral and dental anaerobic and fastidious oral pathogens tested. However, this activity was also variable between the various compounds within the group and the different isolates. The activity of chlorhexidine, an active ingredient in some mouthwashes, is also shown in Table 2. The activity of the iodonium salt compounds of group 2 was generally superior to or at least equivalent to that of chlorhexidine.

Several compounds, IS-3, IS-4, IS-5, IS-9, and IS-10, had good in vitro activity against the oral and dental pathogens tested. Upon review of the structures of the various iodonium compounds tested, no obvious trend in structure-activity function emerged. These results are therefore empirical. Since the original concept of their development is for use as potential topical agents or incorporation into a mouthwash, it was noted that their activities were generally equivalent to that of chlorhexidine. Oral antimicrobial agents tested such as tetracycline, which is also used in solutions and topically, showed good in vitro activity. However, antibiotics should be reserved for therapeutic intervention and are not to be used for chemical control or elimination of plaque, e.g., in elderly and/or handicapped patients. Disinfecting solutions without antibiotics, like formulations with iodonium salts, would help topical dental care.

Nevertheless, it seems important to determine the structure-activity relationship between the different iodonium compounds against individual isolates or, even more importantly,

against combinations of isolates that are encountered in periodontal and other diseases to allow the design and synthesis of a new generation of more active iodonium compounds for potential use as oral decontaminants and mouthwashes. It might be possible to make new analogs based on the active structures with di- ions and/or heterocyclic rings to determine any trends or structure-activity relationships. As demonstrated by the results of this study, some iodonium compounds may have potential for topical dental use.

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