REVIEW ARTICLE

Synthetic Approaches to Organoselenium Derivatives with Antimicrobial and Anti-Biofilm Activity

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Abstract: In the recent years, an increasing attention has been given to the biological activities exerted by organoselenium compounds. In 1984, Sies reported for the first time the ability of ebselen to mimic the activity of glutathione peroxidase. From this milestone, several studies reported the pharmacological properties of selenium-containing compounds including their exploitation as antimicrobials. In this context, this minireview presents the most recent examples of seleno derivatives endowed with antimicrobial activities while discussing the most interesting and recent synthetic procedures used to obtain these compounds.

Keywords: Biofilm, diselenides, gram-negative bacteria, gram-positive bacteria, selenium, benzoisoselenazolones.

1. INTRODUCTION

Multidrug resistance represents a major threat to human health in the 21st century currently defined as the Post-Antibiotic era. The difficulties in approaching the antimicrobial treatment have prompted researchers to develop new therapeutic strategies and to discover the next generation of safe and effective antimicrobial compounds. In parallel in these last 20 years, the researches have shown the essential role of Selenium in the human health. Indeed, a large number of studies reported the importance of this element in many biological processes and the potential applications of selenium compounds (both inorganic and organic forms) for the treatment of cancer, pain, inflammation, neurodegenerative, and infection diseases [1].

In this context, several works demonstrated the antimicrobial activity of organoselenium compounds against a large variety of microorganisms in both *in vitro* and *in vivo* settings, as recently described by Pietrella [2].

The object of this review is to detail the synthetic approaches to obtain organoselenium compounds endowed with antimicrobial activity and developed to overcome multidrug resistance. The present manuscript is organized in few paragraphs clustering the molecules according to their

structure. The last chapter has been focused on the analysis of the inhibitory effect of selenium in its inorganic form on microbial biofilm.

1.1. Diselenides and Selenocyanates

Pesarico *et al*, in 2013, described the 2,2-dithienyl diselenide (DTDS) **1a** (Fig. 1) as a compound with notable antimicrobial effect. This compound has bactericidal activity toward *Enterococcus faecalis* (MIC = 96.75 µg/ml) and *Staphylococcus saprophyticus* (MIC = 96.75 µg/ml), while it is bacteriostatic for *Bacillus cereus* (MIC = 24.18 µg/ml) and fungistatic for *Candida albicans* (MIC = 24.18 µg/ml). The authors also highlighted that the antimicrobial properties arose from a pro-oxidant activity as a result of the formation of radical species in cells upon treatment with DTDS [3].

Fig. (1). Chemical structures of 2,2-dithienyl diselenide **1a** and diphenyl diselenide **1b**.

Diphenyl diselenide **1b** (Fig. 1) is among the most studied compound of the diselenides class. It is a lipophilic and stable molecule largely used in synthetic organic chemistry. Biological studies demonstrated its potential use as antimicrobial agent. In particular, it was reported its antifun-

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gal effects against some mycetes [4]. Compound **1b** was tested *in vitro* and *in vivo* models, alone and in combination with antifungal drugs proving its inhibitory effect on the growth of *Candida glabrata* [5]. Taking inspiration from the structure of compound **1b**, Plano and co-workers reported the synthesis of a series of diselenides and selenocyanates endowed with antileishmanial activity (Scheme 1) [6]. Selenocyanates compounds **5** were obtained through the reaction of selenium dioxide with malonitrile, affording the exotic triselenide intermediate (compound **3**) then reacted with aromatics derivatives. At the same time, selenocyanate was formed through the reaction of haloarenes with potassium selenocyanate. The treatment of the obtained selenocyanates with sodium borohydride afforded the corresponding diselenides **6**.

Scheme 1. Synthesis of selenocyanates **5** and diselenides **6** derivatives proposed by Plano and co-workers.

Similarly, in 2015, Font and co-workers demonstrated that diselenide could be considered a molecular motif able to impart antileishmanial activity. In addition, authors structurally modified the diselenide scaffold checking the effects on the mechanism of action in order to extrapolate structural activity information for this class of compounds [7].

More recently, Shaaban and co-workers reported a rapid synthesis to obtain selenocyanates and symmetrical diselenides starting from 4-(2-(4-aminophenyl) diselanyl) benzenamine **7a** and 4-aminophenylselenocyanate **7b**, respectively [8]. The latter compounds were reacted with different cyclic anhydrides (maleic, succinic or glutaric anhydride) through dehydrative condensation, to obtain N-(4-amino-phenyl)-substituted amido-acids **9** and cyclic imides **10**, as shown in Scheme 2.

Once obtained, the compounds were tested for their antimicrobial properties against *Staphylococcus aureus*, *Escherichia coli* and *C. albicans*. As illustrated in Table 1, the best activities were observed against *S. aureus*, in addition, the N-substituted maleanilic acids **11** and the cyclic imide **12** showed a similar antifungal activity to that displayed by the marketed drug clotrimazole (Fig. 2).

Fig. (2). Selenocyanate derivatives with antifungal activity.

Table 1. Antibacterial and antifungal activities of compounds **11** and **12** expressed as the diameters (in mm) of inhibition zones of agar diffusion.

Compd. No.	Diameter Inhibition Zone in mm (% Activity Index)	
	<i>S. aureus</i>	<i>C. albicans</i>
11	16 (73)	27 (96)
12	21 (95)	28 (100)
Ampicillin	22 (100)	-
Clotrimazole	-	28 (100)

1.2. 1,3-Selenazoles and Benzoisoselenazolones Derivatives

The selenoamide functional group, especially when tethered into heterocyclic moieties, equips the molecules with important biological properties. One of the most studied compound in this class is ebselen **13** (2-phenyl-1,2-benzoselenazol-3-one) (Fig. 3). Ebselen and its analogs have been largely tested in several disease models and showed several effects on different biological systems. The most studied is the GPx-like activity that sometimes overlaps with the antioxidant effect [9]. In the context of antimicrobial drug development, ebselen and its derivatives have been reported to:

- inhibit UDP-NAG enolpyruvyl transferase (MurA), an important enzyme in the peptidoglycan biosynthesis [10a];
- inhibit the bacterial TrxR of *Bacillus anthracis* [10b];
- have bactericidal action against *Bacillus subtilis* (MIC = 0.5 µg/ml), *S. aureus* (MIC = 4 µg/ml), *Mycobacterium tuberculosis* (MIC = 10 µg/ml) and *Helicobacter pylori* (MIC = 3.13 - 12.5 µg/ml) [10b, 10c];
- inhibit mycobacterial growth through the interaction with antigen 85 (Ag85) complex [10d];
- inhibit New Delhi metallo-β-lactamase [10e];
- have a synergistic antibacterial effect with silver against multidrug-resistant Gram-negative bacteria [10f];
- inhibit hepatitis C virus (HCV) replication by inhibiting viral helicase [10g].

The plausible molecular mechanism behind the multiple activities of ebselen might derive from its ability to covalently

Scheme 2. Synthesis of selenocyanates and diselenides with antimicrobial activity.

Scheme 3. Synthesis of ferrocenyl selenazoles **18** and selenadiazoles **21**.

modify thiol groups of key cysteine residues at the active site of microbial enzymes or sensing proteins. The reactive site of the molecule is the Se-N bond that can be cleaved upon nucleophilic attack by thiol groups with formation of a new Se-S bond [10h, 10f].

Furthermore, ebselen has an inhibitory effect on H^+/K^+ ATPase. This suggests a potential application in the treatment of *H. pylori* infection, as reported by Macegoniuk and co-workers [11]. Ebselen and its derivatives have also the ability to inhibit bacterial urease [11].

Wójtowicz and co-workers synthesized aza-analogs of ebselen and tested their antibacterial, antiviral and antifungal activities. An improved antimicrobial activity has been observed with the substitution of the external benzene ring with a pyridine bearing small, non-polar alkyl groups preferentially in the C-2 position (compounds **14**, Fig. 3) [12].

Fig. (3). Chemical structure of ebselen and aza-analogs with antimicrobial properties.

The 1,3-selenazole structure has been recently employed as a template to obtain ferrocenyl analogs endowed with antibacterial activity (Scheme 3). The synthetic methods

involve the reaction between primary aryl selenocarboxamides **17** with (2-bromoacetyl) ferrocene **16** to give the corresponding 2-diaryl-4-ferrocenyl-1,3 selenazoles **18**. At the same time, the reaction of 1-cyanoferrocene **19** with sodiumhydroselenide, and subsequent treatment with $Na_2[PdCl_4]$, gave 3,5-diferrocenyl-1,2,4-selenadiazole **21**. From a pharmacological point of view, interesting results were obtained against the Gram-negative Bacteria *E. coli* and *Pseudomonas aeruginosa* [13] (Table 2).

Table 2. Antibacterial activities of compounds **18a**, **18b** and **21**.

Compd. No.	MIC $\mu\text{g/ml}$		
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
18a	10	5	5
18b	5	0.5	5
21	10	5	5
Chloramphenicol	0.1	0.1	0.1

The expression of efflux systems by bacteria is a key issue that the researchers should take into account when they try to tackle multidrug resistance, especially of Gram-negative ones. Several compounds have been developed to block efflux pumps and restore the activity of antibacterials [14]. In this context, hydrazinoselenazoles **22-24** (Fig. 4) were recently reported. They proved antibacterial activity

Fig. (4). Hydrazinoselenazoles with antibacterial activity.

against several strains of *P. aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter aerogenes* and *E. coli* with MICs ranging from 0.5 to 8 $\mu\text{g/ml}$ in the presence of an efflux pump inhibitor, phenylalanine arginine β -naphthylamide. Study of structure activity relationship showed that in the hydrazinoselenazoles molecules, the presence of the selenoamide group is pivotal for the antibacterial effect while the presence of the chlorine substituent in the aromatic ring *para* position improves the affinity for bacteria efflux pumps [15].

1.3. Selenoquinoline

Quinoline-based drugs are known to possess several biological effects, including antimicrobial activity. Thus, in the last 15 years, various quinoline derivatives endowed with antimalarial, antileishmanial, antifungal, antiviral and antibacterial activities have been synthesized [16]. In order to join the quinoline feature of privileged scaffold with selenium activities, some selenoquinolines have been developed. In this context, a synthetic approach to obtain these compounds was reported by Zhang and co-workers. As shown in Scheme 4 the preparation of compound 27 entails the electrophilic cyclization of C-C triple bond containing anilines [17].

Scheme 4. Synthesis of selenoquinolines by electrophilic cyclization of substituted anilines.

Abdel-Hafez and co-workers investigated the annulation reaction of sodium hydroselenide (NaSeH) with 2-chloro-3-cyano-4-methylquinoline to synthesized several seleno[2,3-*b*]quinolines (Scheme 5). All of the compounds were then screened for their pharmacological properties. In particular, 4-methylquinoline-2(1*H*)selenone derivatives showed an interesting activity against *Aspergillus flavus*, *Aspergillus niger*, *C. albicans* and *Fusarium oxysporum*, which is however lower if compared to that of the commercially available antifungal drugs [18a].

More recently, the same research group reported a series of seleno[2,3-*b*]quinolines, which were synthesized through the treatment of N-ethoxymethylene-aminoselenoquinoline derivatives with 1-amino-N-substituted sulfamides, as described in Scheme 6. The products obtained were tested

against both Gram-positive and Gram-negative bacteria, evidencing more activity toward the first, especially against *Serratia marcescens* [18b].

A new class of 2-selenolbenzo[*h*]quinoline 3-carbaldehydes showed a potent bactericidal activity due to their ability to intercalate and bind to DNA. The synthetic approach involves two steps: an initial reaction of N-arylacetylamide in presence of phosphorus oxychloride (POCl_3) in DMF, subsequently, the chloride portion was replaced using NaHSe to obtain the final compound 40 (Scheme 7). Compound 40 showed MICs between 8 and 16.25 $\mu\text{g/ml}$ against a panel of clinical isolate microorganisms [19].

Hayat and co-workers studied the antiamoebic activity of 2-(quinolin-8-yloxy)acetohydrazones 44 and their cyclized products, 1,2,3-selenodiazole 45 (Scheme 8). The cyclization was conducted using selenium dioxide and acetic acid on compound 44, which in turn, obtained through a multistep approach. The study of antiamoebic activity showed that the cyclized products were weaker if compared to the 2-(quinolin-8-yloxy)acetohydrazones. The best in class among compounds 45 showed an IC_{50} of 0.46 μM , though. The authors proposed that the presence of both the quinoline ring and the hydrazone linkage with N-H free group are pivotal for the antiamoebic activity [20].

Regarding the quinoline class of compounds, Savegnago and co-workers synthesized a series of novel 4-arylchalcogenyl-7-chloroquinolines 48 starting from 4,7-dichloroquinoline 46 with diaryl dichalcogenides in presence of KOH , as a base, and DMSO as solvent at 100°C (Scheme 9) [21]. These products were recently also reported to exhibit anti-inflammatory and antinociceptive properties [22].

1.4. Selenopyridazine and Selenopyridine Derivatives

The selenopyridazine containing compounds is less investigated than other classes of organoselenium molecules reported in literature. Nevertheless, pyridazines are interesting as insecticide, herbicide and antifungal agents. A series of seleno[2,3-*c*]pyridazine and pyrimido[4',5':4,5]seleno[2,3-*c*]pyridazine derivatives was prepared by Abdel-Hafez and co-workers and tested for their anti-inflammatory, analgesic and antimicrobial activities. Selenopyridazine derivatives 49 and 54, obtained from 4-cyano-5,6-diphenylpyridazine-3(2) selenone 51 as reported in Scheme 10, were tested *in vitro* against Gram-positive bacteria (*B. cereus*), Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *S. marcescens*) and fungal species (*A. flavus*, *A. niger*, *F. oxysporum* and *C. albicans*). The best results were obtained with the antifungal activity studies. In particular -CN and -CONH₂-substituted derivatives were the best in class [23].

Scheme 5. Synthesis of seleno[2,3-*b*]quinolines **32** and **33**. Scheme 6. Synthesis of sulfanylamido selenolo[2,3-*b*]quinolines **37**. Scheme 7. Synthesis of 2-selenolbenzo[*h*]quinoline 3-carbaldehyde.

Scheme 8. Synthesis of 2-(quinolin-8-yloxy)acetohydrazones and their cyclized products, 1,2,3-selenodiazole.

Scheme 9. Synthesis of 4-phenylseleno-7-chloroquinoline.

Scheme 10. Synthesis of selenopyridazines.

Scheme 11. Synthesis of seleno[2,3-*b*]pyridine derivatives.

Fig. (5). Chemical structure of selenolo pyridine derivatives.

The same research group also reported that the seleno[2,3-*c*]pyridazines and selenopyridines proved active in a series of experiments meant to discover new antibacterials. In the case of selenopyridazines derivatives, the results showed that these compounds are inactive against Gram-negative bacteria (*S. marcescens*, *E. coli*, *P. aeruginosa*), as well as Gram-positive ones (*B. cereus*, *S. aureus*). The selenopyridine derivatives 55, reported in Fig. (5), were the most active with the analogue bearing the $-\text{COCH}_3$ group showing most potent inhibitory activity against Gram-positive and Gram-negative bacteria [18b].

Abdel-Hafez and co-workers synthesized a series of seleno[2,3-*b*]pyridine derivatives starting from 4-chloro-2,7,9-trimethylpyrido[3',2':4,5]seleno[2,3-*b*]pyrimidine 56 to obtain a new class of fused tri- and tetracyclic systems through nucleophilic substitution reaction with ethanolamine, morpholine and thiourea, as showed in Scheme 11 [24].

1.5. Selenonucleoside Analogs and Other Organoselenium Compounds as Antivirals

In the last years, a widely used approach to reduce the drug resistance is the development of nucleoside analogs to be employed as antimetabolite agents. A possible strategy to obtain chalcogen-containing nucleosides consisted in the isosteric replacement of oxygen with Se or S, in different positions of the sugar moiety, most likely through the Pummer reaction [25]. Past studies reported that oxaselenolane nucleosides, containing a selenium atom in

the 3' position, exhibited anti-HIV and anti-HBV activities [26].

Other synthetic studies started from a chiral moiety, such as *D*-ribose or *D*-glutamic acid, as reported by Jeong, Jayakathan and co-workers to yield selenonucleosides. These products are interesting for their antiviral activities since they operate as competitive inhibitors of the reverse transcriptase of HIV or as DNA chain terminators [27].

In the anti-HIV research field, the aminoacid containing aromatic diselenide, known as DiSeBAs, developed by Sancineto in 2015 are worth mentioning [28]. They exerted a potent antiviral activity at low micromolar concentration by plausibly inhibiting the key viral protein NCp7 (Table 3) [29]. The synthetic procedure first entails the preparation of the key diselenobenzoic acid 62 obtained by introducing the diselenide moiety as a nucleophile in the reaction where the electrophile is the diazonium salt of anthranilic acid. Once obtained, the acid was coupled with the aminoacids protected at the carboxyl terminal as esters. The ester intermediates were finally converted into the target acids through mild basic hydrolysis (Scheme 12).

Table 3. Antiviral activities of compounds 64.

Compd. No.	MIC $\mu\text{g/ml}$		
	HIV-1(HIB) EC ₅₀ (μM) ^a	CC ₅₀ (μM) ^b	SI ^c
64a	13.83	165	12
64b	13.91	136	10
64c	10.2710	138	13
64d	3.15	117	37
64e	3.31	107	32
DIBA-1	3	11	6

^aEC₅₀: concentration of compound required to achieve 50% protection of MT-4 cells from HIV induced cytopathogenicity, as determined by the MTT method; ^bCC₅₀: concentration of compound that reduces the viability of mock-infected cells by 50%, as determined by the MTT method; ^cSI: ratio of CC₅₀/EC₅₀

Scheme 12. Synthesis of DiSeBAs.

Scheme 13. Synthesis of 4'-selenonucleosides analogues.

Scheme 14. Synthesis of selenopyrimidines analogues.

The major difficulties to generate 4'-selenonucleosides involved the glycosylation of purine. This reaction is unusually regioselective but not stereoselective thus yielding, beside the natural isomer, also the unnatural one [27]. The synthesis of 4'-selenoadenosine and 4'-selenoguanosine started from the conversion of *D*-ribose in 2,3-*O*-isopropylidene-1-lyxono-1,4-lactone **65**, in which the primary hydroxyl group is protected with *tert*-butyldiphenylsilyl (TBDPS) group and subsequently reduced to give the diol **67**. The mesylation and selenylation of these products gave the 4'-selenosugar [27a, c]. The selenosugar **71** is then converted into selenonucleoside through the condensation with the purine moiety (Scheme 13). This can be realized with different strategies: by a Pummer-type reaction [27a], or under Vorburgger conditions using silylated 6-chloro purine in the presence of

trimethylsilyl trifluoromethanesulfonate (TMSOTf), obtaining the natural isomers [27c].

Furthermore, the synthesis of 4'-selenopyrimidine **74** can be conducted using hypervalent iodine species. In particular, the selenosugar **73** is treated with iodosylbenzene, TMSOTf, 2,6-lutidine and silylated uracile, as reported in Scheme 14 [30]. A similar approach has been recently extended for the synthesis of 4'-selenopurine [31].

Most of synthesized 4'-selenonucleosides are endowed with weak antiviral properties. Specific studies demonstrated that the inactivity of these products derives from the absence of phosphorylation by cellular kinases [32]. This happens probably because of the bulky selenium in 4'-selenonucleosides that hampers the kinase activity. To overcome this problem, Sahu and co-workers have designed a novel series of selenonucleoside based on one-carbon homologation strategy. The compounds were obtained starting from homoseleno sugar **75** through the synthetic sequence shown in Scheme 15. Final products, 5'-homo-4'-selenouridine **80** and 5'-homo-4'-selenoadenosine **82**, exhibited antiviral activity against herpes simplex virus (HSV-1) ($\text{EC}_{50} = 2.3$ and 2.9 μM , respectively) [32b].

The selenoanalogues of the anti-HSV and anti-human cytomegalovirus (HCMV) acyclovir (compound **83**) and ganciclovir (compound **84** Fig. 6) were synthesized [33].

Scheme 15. Synthesis of 5'-homo-4'-selenonucleosides by Seleno-Michael reaction.

Fig. (6). Chemical structures of Selenoacyclovir and Selenoganciclovir.

The retrosynthetic approach to obtain selenoacyclovir **83** and selenoganciclovir **84** consists in the condensation of the glycosyl donor selenomethyl bromide, prepared by the reaction of the diselenide with NaBH_4 and CH_2Br_2 , with 2-amino-6-chloropurine (route I) or by the reaction of selenium anion with bromomethyl purine (route II) (Scheme 16). From a pharmacological point of view, while selenoacyclovir showed a potent activity against the herpes virus HSV-1 and HSV-2, selenoganciclovir was moderately active against HCMV.

1.6. Organoselenium Compounds and Se-Nanoparticles as Antibiofilm Agents

Bacteria can grow and proliferate in planktonic or sessile forms, depending if they exist as independent, single, cells or constitute aggregates called biofilms [34a]. In the latter case, the bacteria produce several types of polymeric substances, such as proteins, polysaccharides and DNA, which form the

extracellular matrix. An important characteristic of the biofilm is that it allows bacteria aggregates to resist at higher doses of antibiotic than single cells [34]. In addition, the bacterial aggregates embedded in biofilm are less susceptible to immune system action, decreasing the migratory capacity of phagocytes [34b]. Biofilm is also important because it allows bacteria to survive in disadvantageous conditions, thus representing an environmental reservoir [35]. Biofilms exert the ability of adhesion on sterile surfaces, included medical devices and implants, such as catheters, artificial limbs, and heart valves [34a, c]. Not only bacteria but also fungi are able to organize themselves in biofilms, for example *Candida* strains [36]. For these reasons, the development of biofilm-inhibitors and antibiofilm agents attracted the interest of the scientific community.

Regarding the organoselenium compounds, few studies are reported in the literature. In 2014, Bueno and co-workers have observed a decrease of biofilm formation in *C. albicans* following the administration of 4,4-dichloro diphenyl diselenide **89** (Fig. 7) [37].

Fig. (7). Chemical structure of 4,4-dichloro diphenyl diselenide.

Scheme 16. Retrosynthesis of selenoacyclovir and selenoganciclovir.

Fig. (8). Structures of diselenides endowed with antibiofilm activity.

Some of us tested a series of diselenides **90**, reported in Fig. (8), for their anti-biofilm activity. The diselenides assayed showed antibiofilm activity at a concentration lower than the minimum inhibitory concentration (MIC)s. The best results were observed for antibiofilm activity against Gram-positive bacteria (*S. aureus* and *Staphylococcus epidermidis*) than against *P. aeruginosa*. Some of the diselenides also exhibited activity against biofilm formation of *C. albicans* among these bis[ethyl-*N*-(2'-selenobenzoyl)glycinate] is worth to be mentioned [38].

Besides the synthesis of organoselenium compounds, other approaches have also been followed to develop selenium containing constructs. Some of them include the coating of medical devices with selenium polymers [39] and the development of selenonanoparticles (Se_{nps}) [40]. Exploiting the ability of these materials to catalyze the formation of superoxide radicals, Tran and co-workers evaluated the antibiofilm activity of novel organoselenium-methacrylate polymers (SeMAP) against *S. aureus* and *P. aeruginosa* [39a]. Similarly, it has been demonstrated the antibiofilm action of selenocyanatodiacetic acid (SCAA), which can coat hemodialysis catheters, thus representing a valid inhibitor system of *S. aureus* biofilm *in vivo* [39b].

Furthermore, the synthesis of Se_{nps} can be conducted using a large variety of approaches, which can be classified in physicochemical techniques [39a] or those using biological systems, such as bacteria, fungi and other natural extracts [40].

CONCLUSION

Microbial resistance and biofilm formation are serious, global health threats researchers have to deal with for the development of a next generation antimicrobial therapy. In this context, not only organoselenium compounds but also selenium-based materials, could represent a source of inspiration because of their easy chemical accessibility and valuable pharmaceutical properties. In addition, being relatively poorly explored from a medicinal chemistry perspective selenium containing molecules can be easily patented thus intellectually protected. Being not yet commercialized, they are supposed to be active against microorganisms resistant to marketed drugs. Taken together, these issues clearly highlight how important is the development of synthetic approaches aimed to prepare organoselenium compounds and selenium-containing materials, and the present minireview embodies an attempt to collect the most recent examples.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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