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Venting-while-Heating Microwave-Assisted Synthesis of 3-Arylthioindoles

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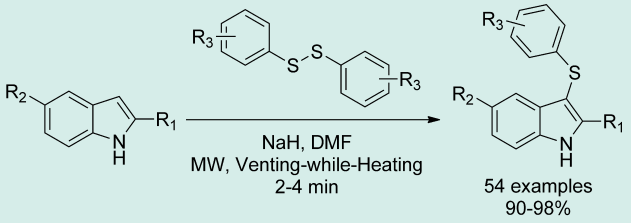
Supporting Information

ABSTRACT: We report the first example of venting-while-heating microwave-assisted synthesis of a small library of 3-arylthioindoles. Compounds were prepared in excellent isolated yields (90−98%) within 4 min in a closed vessel by treating indoles with disulfides in the presence of sodium hydride in anhydrous *N*,*N*-dimethylformamide. The method was not affected by electron-donating and -withdrawing substituents both on 3-arylthio moiety and at 2- and 5-positions of the indole nucleus.



R_1 = H, Me, Ph, COOH, COOEt; R_2 = H, Cl, OMe; R_3 = H, Cl, OMe, 2,4-Cl_2, 2,5-OMe_2, 3,4,5-OMe_3

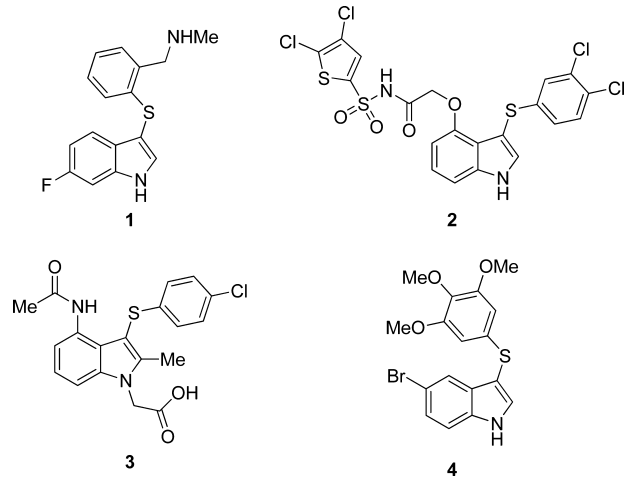
KEYWORDS: *microwave-assisted organic synthesis, dielectric heating, venting while heating, sulfenylation, 3-arylthioindoles, indole*

3-Arylthioindoles are endowed with a large spectrum of biological activities, being potentially useful for the treatment of some diseases, such as affective (e.g., **1**),[1] vascular (e.g., **2**),[2] and respiratory disorders (e.g., **3**)[3] (Chart 1). Among these, we reported the strong antitumor activity of 3-((3,4,5-trimethoxyphenyl)thio)-1*H*-indoles (e.g., **4**) and some related bioisosteres at the sulfur bridge as potent inhibitors of both tubulin polymerization and of cancer cell, by binding the colchicine site of tubulin.[4]

The synthesis of 3-arylthioindoles included the direct sulfenylation of the indole ring by disulfides,[5−7] quinone mono-*O*,*S*-acetals,[8,9] sulfenyl halides,[10,11] *N*-(arylthio)-succinimides,[12] *N*-(arylthio)phthalimides,[13] and activated thiols.[14−20] 3-Sulfenylindoles were also prepared by palladium-catalyzed annulation of 2-(1-alkynyl)benzenamines with disulfides[21] and by tetrabutylammonium iodide-induced electrophilic cyclization of the same starting materials with arylsulfenyl chlorides.[22,23]

Our interest in new anticancer agents required a general, simple, high-yielding and very fast method to synthesize 3-arylthioindoles. First, our attention was focused on 3-((3,4,5-trimethoxyphenyl)thio)-1*H*-indoles, being the 3,4,5-trimethoxyphenyl portion crucial for small molecules that bind the colchicine site of tubulin.[24] Our experiments showed that 2-carboxylate derivatives can be synthesized in very low yields by reacting the appropriate indole with 3,4,5-trimethoxythiophenol in the presence of *N*-chlorosuccinimide.[4a,b] Furthermore, treatment of 2*H*- or 2-methylindole with 3,4,5-trimethoxythiophenol in the presence of iodine/potassium iodide gave the corresponding 3-arylthioindoles in moderate yields.[4c] Our experience suggested that these results could be explained mainly by taking into account the high instability of the 3,4,5-trimethoxybenzenethiol, even at very low temperatures, leading us to explore the use of the more stable and easy to handle corresponding disulfide.

Chart 1. 3-Arylthioindoles Exhibiting Biological Activities



Pursuing our recent interest in microwave-assisted organic synthesis of heterocyclic compounds of biological interest,[25] we wish to report the preparation of a small library of 3-arylthioindoles under venting-while-heating. Compounds **5**−**58** were quickly prepared in high yields by reacting indoles **59**−**69** with disulfide **70**−**79** in a closed vessel (Scheme 1). To the best of our knowledge, methods involving the use of microwave heating for the synthesis of 3-arylthioindoles have not been reported. Furthermore, potential advantages of the

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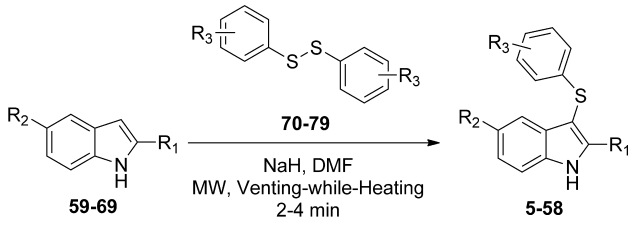
Scheme 1. Venting-while-Heating Microwave-Assisted Synthesis of 3-Arylthioindoles 5-58

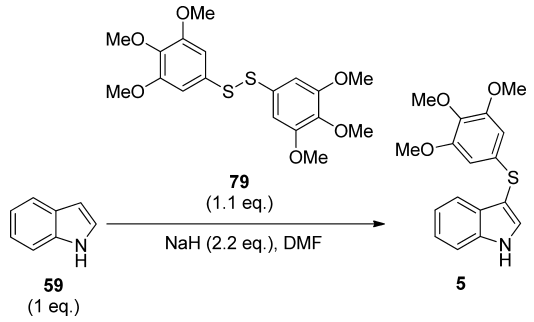


R_1 = H, Me, Ph, COOH, COOEt; R_2 = H, Cl, OMe; R_3 = H, Cl, OMe, 2,4-Cl_2, 2,5-OMe_2, 3,4,5-OMe_3

technology of venting-while-heating (ActiVent)[26] in microwave-assisted organic synthesis have never been explored.

As a model study, we investigated the reaction of 1*H*-indole (**59**) with 1,2-bis(3,4,5-trimethoxyphenyl)disulfide[4a] (**79**) in the presence of sodium hydride (NaH) in anhydrous *N*,*N*-dimethylformamide (DMF) to furnish 3-((3,4,5-trimethoxyphenyl)thio)-1*H*-indole (**5**) (Table 1). The best molar ratio

Table 1. Optimization of Reaction Conditions for Compound 5



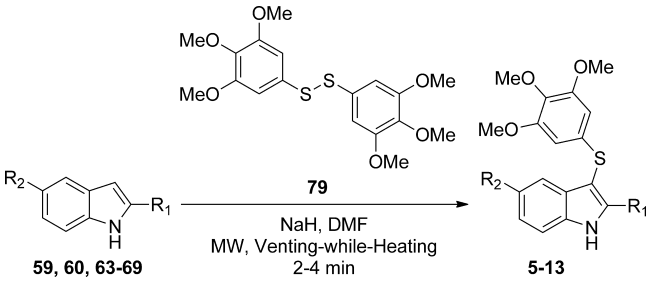
entry	heating	temp (°C)	time	power (W)	ActiVent[a]	yield[b] (%)
1	oil bath	60	12 h			90
2	oil bath	130	10 min			2
3	MW[c]	100	2 min	70	off	35
4	MW	130	2 min	100	off	45
5	MW	160	2 min	130	off	40
6	MW	130	4 min	100	off	25
7	MW	130	8 min	100	off	15
8	MW	100	2 min	90	on	65
9	MW	130	2 min	120	on	98

[a]Venting-while-heating. [b]Isolated yield. [c]Microwave.

indole/disulfide/NaH was found to be 1/1.1/2.2 (data not shown). Despite a non optimal loss tangent value (tan δ = 0.161),[27] DMF was chosen as solvent mainly because of the very low solubility of the starting disulfide. By comparison, the same reaction needed an oil bath heating time of 12 h to furnish compound **5** in high yield (entry 1, Table 1). Alternatively, derivative **5** was prepared in fair yield (47%) by reacting 1*H*-indole with 3,4,5-trimethoxybenzenethiol in the presence of iodine/potassium iodide for 1 h at 25 °C.[4d]

When we heated the reaction mixture at 100 °C for 2 min by applying a microwave irradiation of 70 W, derivative **5** was isolated in low yield (entry 3, Table 1). The latter did not significantly improve when the temperature was raised to 130 and 160 °C, using a power of 100 and 130 W, respectively (entries 4 and 5, Table 1). Furthermore, extending the time up

Table 2. Venting-while-Heating Microwave-Assisted Synthesis of 3-((3,4,5-trimethoxyphenyl)thio)-1*H*-indoles 5−13



entry	indole	product	R_1	R_2	yield[a] (%)	lit. yield/time[b] (%/min)	method
1	**59**	**5**	H	H	97	47/60[4d]	A[c]
2	**60**	**6**	Me	H	96	53/60[4d]	A
3	**63**	**7**	COOEt	H	88	1/75[4c]	B[d]
4	**64**	**8**	H	Cl	98	59/60[4d]	A
5	**65**	**9**	H	OMe	94	30/60[4d]	A
6	**66**	**10**	Me	Cl	96	54/60[4d]	A
7	**67**	**11**	Me	OMe	93	29/60[4d]	A
8	**68**	**12**	COOEt	Cl	92	6/75[4c]	B
9	**69**	**13**	COOEt	OMe	90	4/75[4c]	B

[a]Isolated yield. [b]Yield and time from indicated reference. [c]Indole (1 equiv), disulfide (1.1 equiv), NaH (2.2 equiv), closed vessel, 130 °C, 120 W, 2 min, ActiVent. [d]Indole (1 equiv), disulfide (1.1 equiv), NaH (2.2 equiv), closed vessel, 130 °C, 120 W, 4 min, ActiVent.

to 4 and 8 min caused a decrease of the yield as a probable consequence of the dielectric overheating (entries 6 and 7, Table 1). On the contrary, compound **5** was isolated in 65% yield when the reaction mixture was vented while heating at 100 °C for 2 min with a power of 90 W (entry 8, Table 1). Thus, the optimal yield (98%) was reached when the reaction mixture was irradiated with a power of 120 W at 130 °C for 2 min in the same conditions (entry 9, Table 1). At the same temperature and in a comparable short time period, derivative **5** was obtained in very low yield when we heated the reaction mixture in an oil bath (entry 2, Table 1).

The result could be explained by taking into account that the venting of the reaction mixture allows the release of the internal pressure of the vial during the experiment and maintain a high power of microwave irradiation for all reaction time. In fact, when we performed the sulfenylation without venting the mixture (Figure 1A), the hydrogen pressure (resulted from the reaction of NaH with indole) limited the microwave irradiation because the instrument automatically reduces the irradiation power to a lower level to not exceed the operational limits of the system. On the contrary, venting of the hydrogen gas during the microwave heating allowed a higher level of microwave power to be directly transferred to the reaction mixture, driving the reaction to proceed to completion (Figure 1B).

Optimized reaction conditions were further validated by reacting 1,2-bis(3,4,5-trimethoxyphenyl)disulfide (**79**) with 2- (**60** and **63**), 5- (**64** and **65**), and 2,5-(di)substituted indoles (**66**−**69**) to furnish the corresponding 3-arylthioindoles **6** and **7** (entries 2 and 3, Table 2), **8** and **9** (entries 4 and 5, Table 2), and **10**−**13** (entries 6−9, Table 2), respectively. By comparing with our previously reported results, it should be noted that the new method not only considerably reduced the

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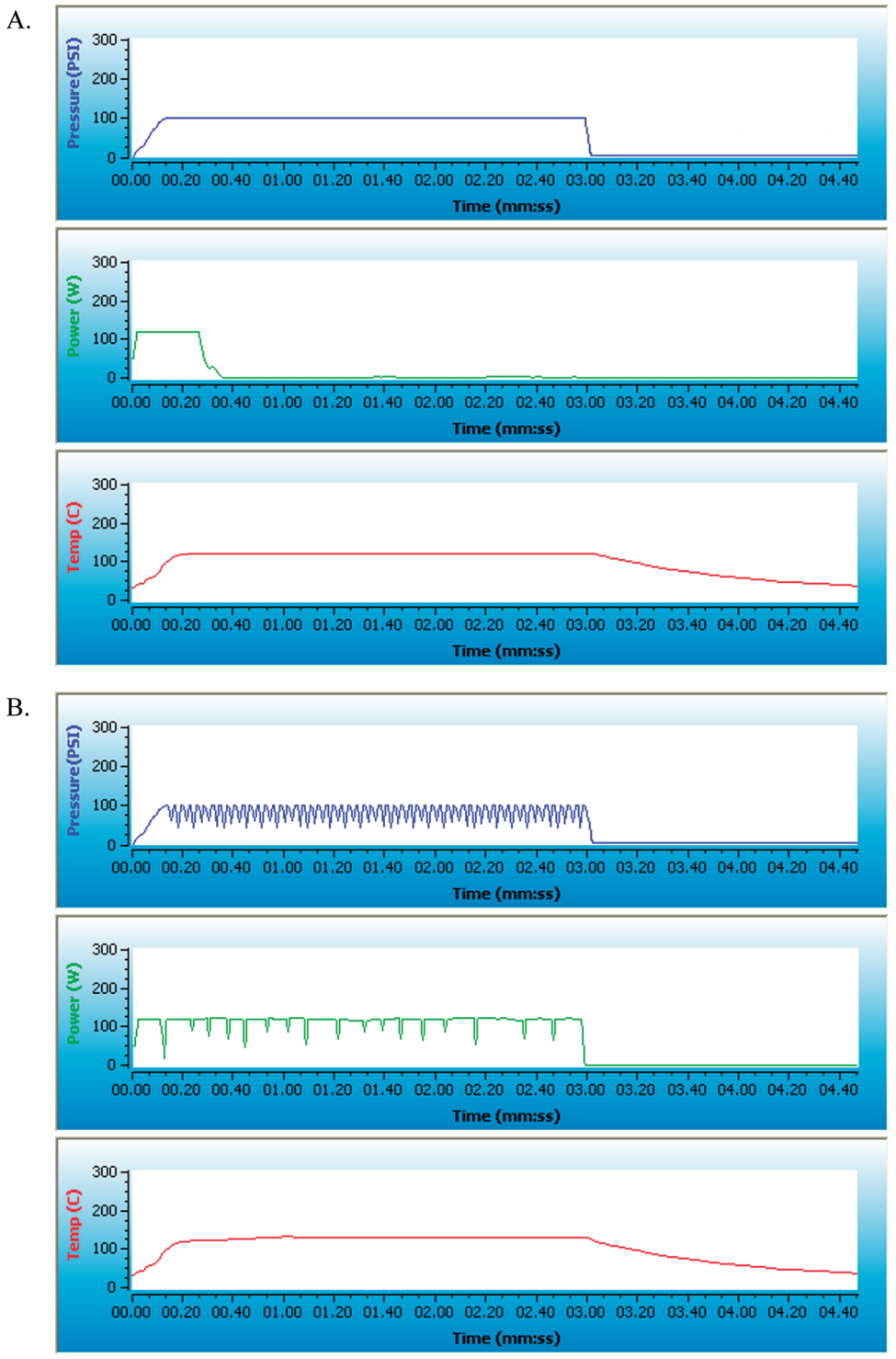

Figure 1. Reaction pressure, power, and temperature profiles using standard (A) and venting-while-heating (B) microwave-assisted synthesis.

time, but above all significantly increases the yield of the reactions. In particular, 2-carboxylate derivatives (**63**, **68**, and **69**) benefited from the new method, jumping yields from 1−6% to 85−88%. Furthermore, the same compounds required a longer microwave irradiation time, because of the strong electron-withdrawing effect of the ester group (method B). Nevertheless, in contrast to that observed by Atkinson and co-workers,[5] prolonged microwave irradiation did not lead to competing ester cleavage with formation of thioanisole. Likely, the venting of the mixture removed at the same time hydrogen and thiol, allowing the reaction to proceed.

These encouraging results prompted us to investigate the reaction of indoles **59**−**63** with disulfides **70**−**78** (Table 3). The latter were quickly prepared by oxidation of the appropriate thiol with 1,3-dibromo-5,5-dimethylhydatoin according to Alam and co-workers.[28]

Thus, 3-arylthioindoles **14**−**40** (entries 1−27, Table 3) were prepared in only 2 min by treating 2-H (**59**), 2-Me (**60**), and 2-Ph (**61**) indoles with diphenyl- (**70**), bis(2-chlorophenyl)-

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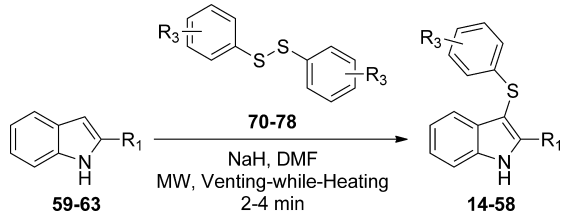
Table 3. Venting-while-Heating Microwave-Assisted Synthesis of 3-Arylthioindoles 14−58



59-63 14-58

entry	indole	disulfide	product	R_1	R_3	yield[a] (%)	method
1	**59**	**70**	**14**	H	H	98	A[b]
2	**59**	**71**	**15**	H	2-Cl	95	A
3	**59**	**72**	**16**	H	3-Cl	96	A
4	**59**	**73**	**17**	H	4-Cl	98	A
5	**59**	**74**	**18**	H	2-OMe	95	A
6	**59**	**75**	**19**	H	3-OMe	96	A
7	**59**	**76**	**20**	H	4-OMe	95	A
8	**59**	**77**	**21**	H	2,4-Cl_2	98	A
9	**59**	**78**	**22**	H	2,5-OMe_2	95	A
10	**60**	**70**	**23**	Me	H	94	A
11	**60**	**71**	**24**	Me	2-Cl	96	A
12	**60**	**72**	**25**	Me	3-Cl	98	A
13	**60**	**73**	**26**	Me	4-Cl	96	A
14	**60**	**74**	**27**	Me	2-OMe	94	A
15	**60**	**75**	**28**	Me	3-OMe	93	A
16	**60**	**76**	**29**	Me	4-OMe	95	A
17	**60**	**77**	**30**	Me	2,4-Cl_2	98	A
18	**60**	**78**	**31**	Me	2,5-OMe_2	92	A
19	**61**	**70**	**32**	Ph	H	96	A
20	**61**	**71**	**33**	Ph	2-Cl	97	A
21	**61**	**72**	**34**	Ph	3-Cl	95	A
22	**61**	**73**	**35**	Ph	4-Cl	96	A
23	**61**	**74**	**36**	Ph	2-OMe	94	A
24	**61**	**75**	**37**	Ph	3-OMe	92	A
25	**61**	**76**	**38**	Ph	4-OMe	90	A
26	**61**	**77**	**39**	Ph	2,4-Cl_2	96	A
27	**61**	**78**	**40**	Ph	2,5-OMe_2	93	A
28	**62**	**70**	**41**	COOH	H	92	C[c]
29	**62**	**71**	**42**	COOH	2-Cl	93	C
30	**62**	**72**	**43**	COOH	3-Cl	94	C
31	**62**	**73**	**44**	COOH	4-Cl	96	C
32	**62**	**74**	**45**	COOH	2-OMe	91	C
33	**62**	**75**	**46**	COOH	3-OMe	89	C
34	**62**	**76**	**47**	COOH	4-OMe	90	C
35	**62**	**77**	**48**	COOH	2,4-Cl_2	95	C
36	**62**	**78**	**49**	COOH	2,5-OMe_2	90	C
37	**63**	**70**	**50**	COOEt	H	93	B[d]
38	**63**	**71**	**51**	COOEt	2-Cl	89	B
39	**63**	**72**	**52**	COOEt	3-Cl	94	B
40	**63**	**73**	**53**	COOEt	4-Cl	95	B
41	**63**	**74**	**54**	COOEt	2-OMe	91	B
42	**63**	**75**	**55**	COOEt	3-OMe	90	B
43	**63**	**76**	**56**	COOEt	4-OMe	91	B
44	**63**	**77**	**57**	COOEt	2,4-Cl_2	93	B
45	**63**	**78**	**58**	COOEt	2,5-OMe_2	89	B

[a]Isolated yield. [b]Indole (1 equiv), disulfide (1.1 equiv), NaH (2.2 equiv), closed vessel, 130 °C, 120 W, 2 min, ActiVent. [c]Indole (1 equiv), disulfide (1.1 equiv), NaH (3.3 equiv), closed vessel, 130 °C, 120 W, 4 min, ActiVent. [d]Indole (1 equiv), disulfide (1.1 equiv), NaH (2.2 equiv), closed vessel, 130 °C, 120 W, 4 min, ActiVent.

(**71**), bis(3-chlorophenyl)- (**72**), bis(4-chlorophenyl)- (**73**), bis(2-methoxyphenyl) (**74**), bis(3-methoxyphenyl) (**75**), bis(4-methoxyphenyl) (**76**), bis(2,4-dichlorophenyl) (**77**), and bis(2,5-dimethoxyphenyl) (**78**) disulfides in the presence of NaH (2.2 equiv) (method A). Reaction products were isolated in excellent yields ranging from 90% to 98%. The method was not affected both by electron-donating and -withdrawing substituents on 3-arylthio moiety and by methyl and phenyl groups at 2-position of the indole nucleus.

However, the presence of a withdrawing group at 2-position of the indole ring, such as carboxylic acid or ethyl carboxylate functions, did not allow to have in high yields 3-arylthioindoles **41**−**49** (entries 28−36, Table 3) and **50**−**58** (entries 37−45, Table 3), respectively. On the contrary, they were successfully prepared by treating 1*H*-indole-2-carboxylic acid (**62**) or ethyl 1*H*-indole-2-carboxylate (**63**) with disulfides **70**−**78** in the presence of 3.3 equiv (method C) or 2.2 equiv (method B) of NaH at 130 °C for 4 min with a power of 120 W.

In conclusion, we report the first example of venting-while-heating microwave-assisted synthesis of 3-arylthioindoles. Compounds were prepared in excellent isolated yields (90−98%) within 4 min, by treating indoles with disulfides in the presence of NaH in a closed vessel. Electron-donating and -withdrawing substituents on 3-arylthio moiety as well as at 2- and 5-positions of the indole nucleus were well tolerated. The time of the reaction was significantly shortened by microwave heating. At the same time, the venting of the reaction mixture permitted the use of a higher level of microwave irradiation, allowing the reaction to proceed. Finally, the method could provide a rapid, simple, and efficient access to a wide range of 3-sulfenylindoles of biological interest by a combinatorial approach.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data of all synthesized compounds, example of microwave output graphics, and copies of ^{1}H NMR spectra of compounds **15**, **16**, **18**, **21**, **22**, **24**, **25**, **27**, **28**, **30**, **31**, **33**, **34**, **36**, **37**, **39**, **40**, **42**−**49**, **51**−**53**, **57**, **58**, **72**, **77**, and **78**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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