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Efficient Two Steps Synthesis of Structurally Diverse Indolo[2,3-*b*]quinolines Derivatives

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A general and efficient synthesis of diverse tetracyclic indolo[2,3-*b*]quinolines derivatives was achieved through a palladium-catalyzed domino carboannulation/cross coupling and DDQ-mediated double cross-dehydrogenative C-N bond formations. This approach provides a straight forward, atom-economic and coincise route to easy access diverse range of tetracyclic indolo[2,3-*b*]quinolines and its analogues in excellent yields with good tolerance of functional groups.

Tetracyclic indoloquinolines are privileged structural motifs embedded in a wide variety of natural alkaloids and bioactive compounds (Fig 1).[1] In recent years, they drew much attention due to their striking biological activities, particularly as DNA intercalating and antimalarial properties and many other important pharmacological activities.[2] For example, 5-methylindolo[2,3-*b*]quinoline (neocryptolepine), is isolated from *Cryptolepissanguinolenta* and usually used in traditional West African medicine for the treatment of malaria.[3] Similarly, *6H*-indolo[2,3-*b*]quinoline (Norcryptotackieine) isolated from the leaves of *Justiciabetonica*,[4] and exhibits importantpharmacological properties such as potentantiplasmodial, antiproliferative, and antitumor activities.[5]

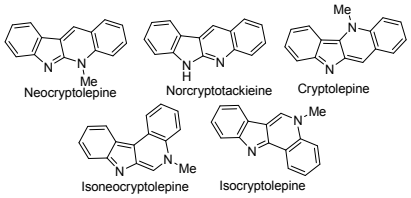

Figure 1. Examples of natural indoloquinoline derivatives

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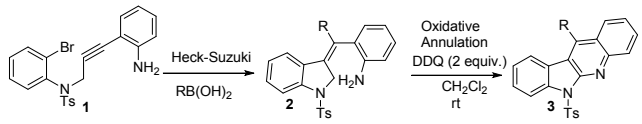
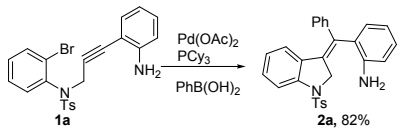
In addition, recently, these scaffolds have been the part of designing and synthesis of modern drugs.[6] Therefore, due to their significant applications in drug discovery research, several synthetic methods have been developed for the construction of indolo[2,3-*b*]quinolone ring structures since past decades.[7] Among the recent methods, some appear to be quite unique in the fabrication of their designs and, at the same time, usefulness of their strategies.[8] For example, Seidel's group achieved an easy access to the indolo[2,3-*b*]quinolines by the condensation between indoles and 2-aminobenzaldehydes in the presence of TFA or *p*-TsOH under refluxing condition in toluene.[8a] Liang *et al*. reported an iodine-mediated synthesis of indolo[2,3-*b*]quinolones via electrophilic substitution/amination reaction of indole with 1-(2-tosylaminophen-yl)ketones, in the presence of Cs_2CO_3 (2 equiv.) at 90 °C.[8b] Yin *et al*. developed a synthesis of indolo[2,3-*b*]quinolines from isoindigo derivatives in the presence of $SnCl_2$, in combination with AcOH/HCl under heating at 120 °C in moderate yields.[8e] Wang's group has published a Rh(III)-catalyzed synthesis of indoloquinoline by the reaction between indoles and isoxazoles in the presence of $AgSbF_5$/NaOAc at 100 °C.[8f] However, most of these methods usually have some limitations, such as, the use of prefunctionalized indole or quinoline derivatives as starting materials, low overall yield of the products and lack of flexibility. Considering the huge pharmaceutical applications of indolo[2,3-*b*]quinolines derivatives, the development of practical, straightforward, flexible and efficient synthetic methodologies is still in fancy.
The synthesis of pharmaceutically important molecules involving new strategies that are highly selective, atom- and energy-efficient, and environmentally benign is a primary challenge to synthetic chemist in this century. During our recent investigations towards the synthesis of polycyclic heterocycles and carbocycles through novel annulations reactions,[9] very recently, we have adopted a novel and efficient strategy for the synthesis of polycyclic heterocycles involving palladium-catalyzed intramolecular carbopalladation/Suzuki coupling and subsequent cycloisomerisation under mild conditions. In

continuation to these investigations,[9e,f,g,h] we first synthesied 3-indoline derivative **2** bearing *ortho*-amino group on the aryl ring of methylene unit using palladium-catalyzed intramolecular domino carbopalladation-Suzuki coupling of 2-halo-*N*-propargylanilide derivatives **1** with arylboronic acids. We anticipated that compound could undergo oxidative cross-dehydrogenative coupling (CDC) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) between allylic Csp^3–H of indoline ring with free $–NH_2$ group. Very recently, DDQ has been proven as an efficient metal free oxidant for CDC reactions of carbon-carbon bond formation reactions,[10] but the formation of C–N bond via DDQ-mediated cross-dehydrogenative couplings (CDC) are relatively rare until recently.[11] Therefore, the present strategy for the synthesis of indolo[2,3-*b*]quinolines should be very practical, challenging and attractive in the modern context of organic chemistry research. In this communication, we report a new, efficient and general approach for the synthesis of diversely substituted indolo[2,3-*b*]quinolines derivatives through two stages domino reaction.



Scheme 1 Our Strategy for the Construction of Indolo[2,3-*b*]quinolines

Our approach commenced with the synthesis of 3-indoline derivative **2a** by palladium-catalyzed domino Heck-Suzuki coupling of 2-bromo-*N*-propargylanilide **1a** with phenylboronic acid according to our recently developed method.[9e,f] The reaction of compound **1a** and phenylboronic acid was carried out using 5 mol% of $Pd(OAc)_2$, 10 mol% of tricyclohexylphosphine (PCy_3) at 75 °C in the presence of 2.5 M K_2CO_3, to afford the desired 3-substituted indoline derivative **2a** in 82% yield (Scheme 2). The carbopalladation reaction proceeds through an intramolecular *syn*-carbopalladation via a 5-*exo-dig* cyclisation process in preference to 6-*endo-dig* cyclisation with the alkyne unit to give a σ-alkylpalladium(II) intermediate, and a subsequent intermolecular Suzuki coupling with phenylboronic acid derivatives gave the desired product **2a** in a stereoselective fashion. The preference of 5-*exo-dig* cyclisation over 6-*endo-dig* cyclisation could be rationalized on the basis of lower energy transition state for 5-*exo-dig* cyclisation as bulky palladium complex ends up at the less hindered side of the product, and the length of tether is also play an important role for this mode of cyclisation.



[a]***Reaction conditions:*** **1a** (0.3 mmol), phenylboronic acid (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), PCy_3 (0.03 mmol), 2.5 M K_2CO_3 (1mL), 2 mL ethanol-toluene (1:1) at 75 °C.

Scheme 2 Preparation of Substrate 2a by Heck-Suzuki coupling.[a]

After preparing the desired substrate **2a**, we attempted to develop a suitable reaction condition for the oxidative cross-dehydrogenative coupling (CDC) of allylic Csp^3–H of indoline ring with $–NH_2$ group to achieve the synthesis of indolo[2,3-*b*]quinoline **3a** with respect to various oxidizing agents, solvents, and temperature. Considering the efficiency of DDQ for metal free oxidant in CDC reactions, we first carried out the intramolecular oxidative C–H amination of **2a** in the presence of DDQ (1 equiv). It was observed that the substrates **2a** rapidly converted into the mixture of compounds at room temperature. We inferred that due to the insufficient amount of DDQ, a mixture of compounds was formed including some unreacted starting materials. Next we attempted the said reaction with 2 equiv. of DDQ, we were pleased to observe that the starting compound **2a** was completely converted to **3a** at room temperature in quantitative yield within 1 h (Table 1, entry 1). Other solvents such as 1,2-dichloroethane and nitromethane also worked well, but furnished slightly lower yields of **3a**, in 90% and 93%, respectively (Table 1, entries 3 and 4). Next, other oxidizing agents, such as TBHP, CAN, PIDA and TEMPO, were evaluated for this process using **2a** in DCM at room temperature. It was found that TBHP, PIDA and TEMPO (Table 1, entries 4, 6 and 7) did not work under these reaction conditions, while CAN afforded 85% yield (Table 1, entry 5). However, the cycloammination reaction with DDQ in combination with TEMPO (Tetramethyl morphline *N*-Oxide) as a co-oxidant (Table 1, entry 8) also worked efficeintly and gave the desired product quntitatively. Thus, DDQ (2 equiv) in DCM at room temperature was adopted as the standard reaction condition for the additional study.

Table 1. Optimization of Reaction Conditions for the Synthesis of 3a[a]

Entry	Reagent	Solvent	Temp	Time	Yield(%)
1	DDQ	DCM	rt	1	quant
2	DDQ	DCE	rt	1.5	90
3	DDQ	CH_3NO_2	rt	1	93
4	CAN	DCM	rt	1.5	85
5	TBHP	DCM	rt	3	NR
6	PIDA	DCM	rt	3	NR
7	TEMPO	DCM	rt	3	NR
8	DDQ+TEMPO	DCM	rt	1	quant

[a]*Reaction conditions:* **2a** (0.3 mmol), reagents (0.6 mmol), solvent (2 mL).

To demonstrate the generality of this strategy, we intended to synthesize a series of indolo[2,3-*b*]quinolines following the aforementioned two steps reactions. The preparations of intermediate substrates **2b**–**2f** were carried out by domino Heck-Suzuki coupling in high yields (79% to 90%) (Table 2). Substrates containing various groups, such as electron-donating –Me and weakly electron-withdrawing –Cl on the 2-bromo-N-propargylanilide ring, underwent smooth reaction in very good yields, 83% and 79%, respectively (Table 2, entries 2b–2c). Similarly, phenylboronic acids bearing –OMe and –Cl were well tolerated under the reaction conditions, (Scheme 2, entries **2e**–

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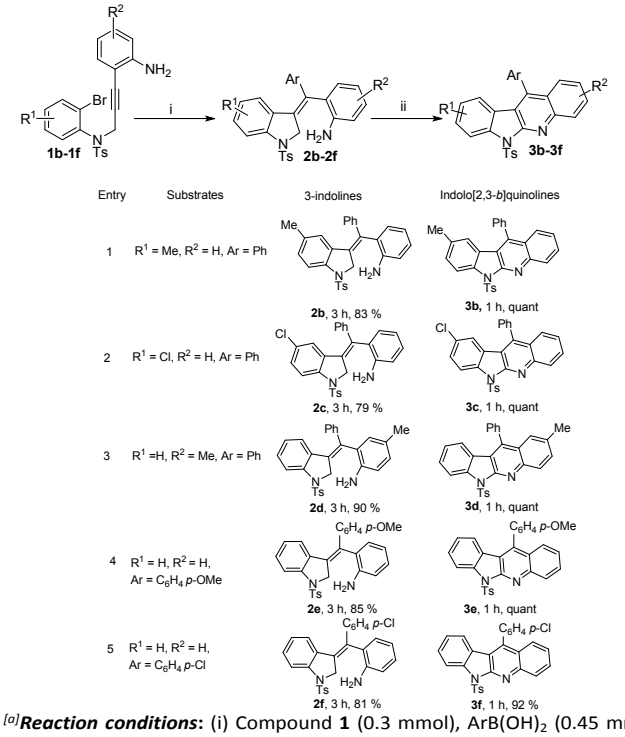
2f) and gave the desired products in good yields, 85% and 81%, respectively. Substrate **2d**, in which –Me group is present on the aryl ring of 2-alkynyl aniline moiety, afforded **2d** in 90% yield (Table 2). Next, the 3-indoline derivatives **2b**–**2f** were subjected to DDQ-mediated oxidative cycloamination process as described for the synthesis of **3a**. Gratifyingly, it was found that the substrates **2b**–**2e** rapidly converted into the desired products **3b**–**3e** at the room temperature in quantitative yield, and the substrate **2f** afforded 92% yield of the desired product **3f** (Table 2). Therefore, it appears that there was no significant electronic effect of the substituent on the aryl ring onto the olefinic motif during the C–N bond formation.

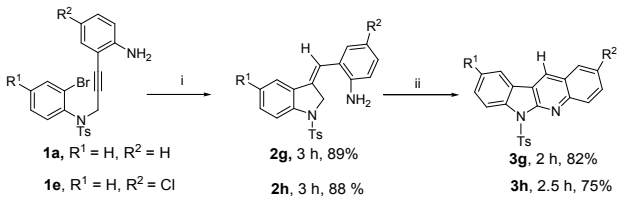
Table 2. Synthesis of Indolo[2,3-*b*]quinolines via Heck-Suzuki and DDQ-Mediated C-H Amination.[a]



[a]***Reaction conditions***: (i) Compound **1** (0.3 mmol), $ArB(OH)_2$ (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), PCy_3 (0.03 mmol), 2.5 M K_2CO_3 (1 mL), 2 mL ethanol-toluene (1:1), 75 °C. (ii) Compound **2** (0.2 mmol), DDQ (0.4 mmol), CH_2Cl_2 (2 mL), rt.

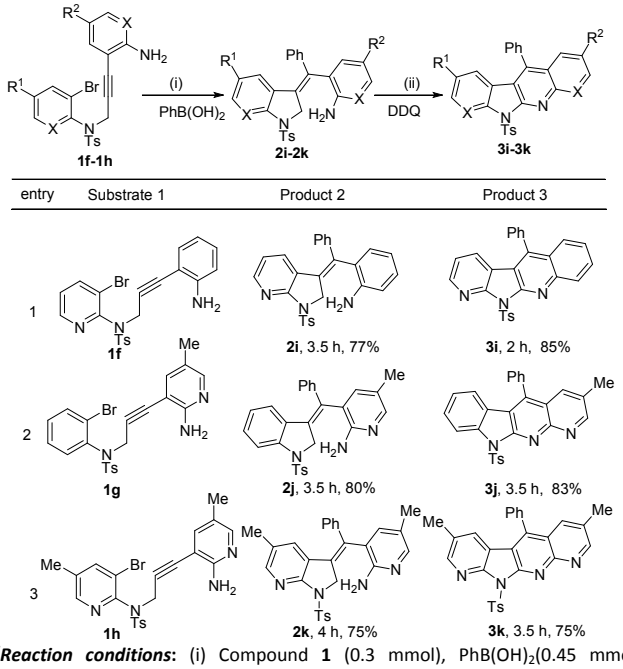
To demonstrate the generality of this strategy, we intended to synthesize a series of indolo[2,3-*b*]quinolines following the aforementioned two steps reaction conditions. The preparations of substrates **2b**–**2f** were carried out by domino Heck-Suzuki coupling in high yields (79% to 90%) (Table 2). Substrates containing various groups, such as electron-donating –Me and weakly electron-withdrawing –Cl on the 2-bromo-N-propargylanilide ring, underwent smooth reaction in very good yields, 83% and 79%, respectively (Table 2, entries 2b–2c). Similarly, phenylboronic acids bearing –OMe and –Cl were well tolerated under the reaction conditions, (Scheme 2, entries **2e**–**2f**) and gave the desired products in good yields, 85% and 81%, respectively. Substrate **2d**, in which –Me group is present on the aryl ring of 2-alkynyl aniline moiety, afforded **2d** in 90% yield (Table 2). Next, the 3-indoline derivatives **2b**–**2f** were subjected to DDQ-mediated oxidative amination process as described for the synthesis of **3a**. Gratifyingly, it was found that the substrates **2b**–**2e** rapidly converted into the desired products **3b**–**3e** at the room temperature in quantitative yield, and the substrate **2f** afforded 92% yield of the desired product **3f** (Table 2). Therefore, it appears that there was no significant electronic effect of the substituent on the aryl ring onto the olefinic motif during the C–N bond formation.

Next, to expand the synthetic utility of this strategy, we prepared the substrates **2g** and **2h** by Pd-catalyzed reductive carobopalladation of 2-bromo-N-propergylanilide derivatives using $Pd(OAC)_2/PCy_3$, in the presence of 2.5 M K_2CO_3 in toluene-ethanol mixture according to our previous method.[9c] The desired 3-indoline derivatives **2g** and **2h** were obtained in 89% and 88%, respectively. Next, when these compounds were treated with 2 equiv of DDQ in DCM at room temperature and afforded desired products **3g** and **3h** in 82% and 75% yields, respectively (Scheme 3).



[a]***Reaction conditions***: (i) Compound **1** (0.3 mmol), $Pd(OAc)_2$ (0.015 mmol), PCy_3 (0.03 mmol), 2.5 M K_2CO_3 (1 mL), 2 mL ethanol-toluene (1:1 mixture), 75 °C. (ii) Compound **2** (0.2 mmol), DDQ (0.4 mmol), CH_2Cl_2 (2 mL), rt.

Scheme 3 Substrates Scope for Carbopalladation and Cycloamination.

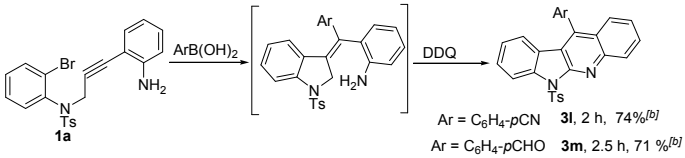


[a]***Reaction conditions***: (i) Compound **1** (0.3 mmol), $PhB(OH)_2$(0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), PCy_3 (0.03 mmol), 2.5 MK_2CO_3 (1 mL), 2 mL 75 °C. (ii) Compound **2** (0.2 mmol), DDQ (0.4 mmol), CH_2Cl_2 (2 mL), rt.

Scheme 4 Synthesis of *aza*-indolo[2,3-*b*]quinolines[a]

Finally, to make this strategy even more general and flexible, we incorporated additional nitrogen atoms into both of the rings at two ends of the tetracyclic system; the results are described in Scheme 4. Similarly, 3-indoline derivative containing 2-amino pyridine ring for the discovery of new pharmaceutically a(Scheme 4, **2j**) furnished indolo[2,3-*b*]naphthyridine **3j** in 83% yield. Finally, we were pleased to find that *aza*-indoline tethered 2-amino pyridine derivative **2k** furnished the hitherto unknown tetracyclic *aza*-indolo[2,3-*b*]naphthyridine **3k** in 75% yield. Along this line, it is important to note that, as indolo[2,3-*b*]quinolines acted as DNA-intercalator, in this context the synthesis of these *aza*-heterocyclic ring systems would be highly attractive in order to assemble a library of new tetracyclic framework ctive compounds.

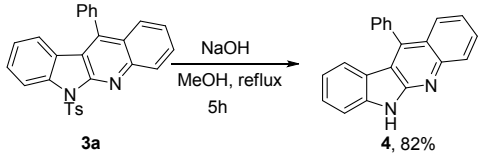
Although, the Heck Suzuki reaction in most of the cases gave a clean reaction product, but we noticed that the Heck-Suzuki coupling reaction of aryllboronic acid bearing strong electron-withdrawing groups such as –CHO and –CN, furnished a nonseparable mixture. To avoid the cumbersome purification of these compounds, the crude products were directly reacted with DDQ, as depicted in Scheme 5. To our delight, the desired products were also obtained in high yields in the two steps, such as **3l** and **3m**, in 74% and 71%, respectively.



[a]Reaction Conditions: i) **1a** (0.3 mmol), $PhB(OH)_2$ (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), PCy_3 (0.03 mmol), K_2CO_3 (2.5 M, 1mL), 75 °C, 3h. Ii) DDQ (0.6 mmol), CH_2Cl_2 (2 mL), rt. [b]Two step yields.

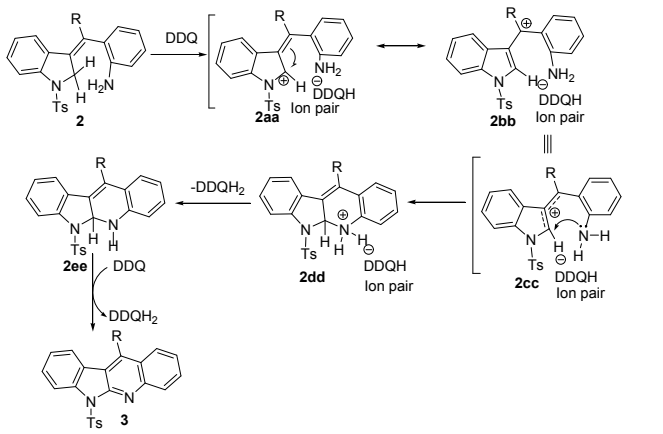
Scheme 5 Synthesis of indoloquinolines without isolation of intermidate.[a]

Furthermore, as the natural products do not contain any protecting groups, and hence, we also attempted detosylation of **3a** in the presence of dil NaOH solution and methanol under reflux. Pleasantly, the detosylated product **4** was obtained in 82% yield (Scheme 6).



Scheme 6. Detosylation of indolo[2,3-*b*]quinoline3a

The mechanism of domino Heck-Suzuki/reductive carbopalladtion has already been described in our previous reports.[9b,c] On the basis of our experimental results and following the previous literature,[12] a tentative mechanism for the DDQ mediated oxidative C–H amination is delineated in Scheme 6. Different mechanistic pathways have been postulated in the literatures for the DDQ mediated oxidation depending on subtrates and reaction conditions. The most common and direct mechanism is initial one step hydride transfer from the substrate to DDQ and a carbocation intermediated is generated. The other mechanistic pathways are initial electron transfer from the substrates to DDQ to form the radical cation of the substartes. DDQ mediated radical pathway is generally eastablished by the inhibition of reaction in the presence of radical scavenger.[13] We noticed that the radical scavanger, TEMPO (2 equiv) did not affect the DDQ mediated dehydrogenative cycloamination process in the present reaction system (Table 1, entry 8). Therefore, we assumed that the activation of allylic Sp^3C–H bond might be initiated through an hydride ion transfer mechanism from the substrate **2** to DDQ resulting generation of an allylic carbocation **2aa**/$DDQH^-$ ion pair. The allylic carbocation intermediate **2aa** is stabilized by resonance and furnished a benzylic cation **2bb**. Then cycloamination took place by intramolecular nucleohilic attack of $–NH_2$ group to the allylic cationic centre resulting dihydropyridinium ion intermediate **2dd**. Finally, deprotonation of the substrate **2dd** by $DDQH^-$ produced dihyropyridine intermediate **2ee** with concomitant formation of $DDQH_2$. In the next step, hydride transfer from **2ee** to DDQ and subsequent deprotonation leading to the desired indolo[2,3-*b*]quinoline derivative **3**.



Scheme 7 Proposed Mechanism for DDQ-mediated Cycloamination

This work not only represented a new strategy to provide a conceptually alternative route, but also due to easy availability of starting materials and efficiency of the double annulations processes, this method could offer a practical and arguably an ideal strategy for the rapid access to diversified indolo[2,3-*b*]quinoline derivatives with high atom economy and step economy. Moreover, the products obtained in our strategy could easily be converted to natural occurring indolo[2,3-*b*]quinolines such as Norcryptotackieine, by simple detosylation of **3g**. To the best of our knowledge this is the first report of preparation of indolo[2,3-*b*]quinoline derivatives through carbopalladation/cross-coupling and subsequent DDQ mediated allylic Csp^3–H amination reaction from 2-bromo-N-[3-(2-aminophenyl)prop-2-ynyl]-N-tosylanilide.

All the structures were characterized by ^1H, ^{13}C NMR and HRMS spectra and one of the structure **3e** confirmed by X-ray diffraction (See supporting information).

Conclusions

In summary, we have developed a novel and efficient two steps strategies involving Pd-catalyzed carbocyclisation/cross-coupling and subsequent DDQ-mediated intramolecular double oxidative amination reaction to construct medicinally useful indolo[2,3-*b*]quinoline derivatives in an atom efficetnt maner. This method was found to be general and displays a wide substrate scopes, good functional groups tolerance, and provides excellent yields of the desired products. Importantly, this strategy has also been utilized for the synthesis of tetracyclic *aza*-indolo[2,3-*b*]quinolines, indolo[2,3-*b*]napthyridine and *aza*-inolo[2,3-*b*]napthyridine derivatives for the first time. Further studies toward applications of these concise protocol to access other bioactive scaffolds are currently underway in our laboratory.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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