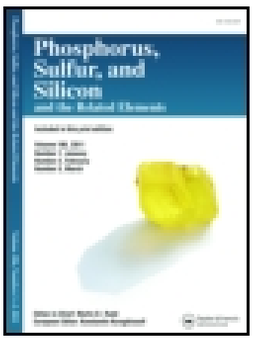

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External oxidant-free electrooxidative intramolecular S-N bond formation for one-pot synthesis for 3,5-disubstituted 1,2,4-thiadiazoles

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ABSTRACT

An electrochemical oxidative reaction protocol for the synthesis of 5-amino and 3,5-diamino substituted 1,2,4-thiadiazole derivatives has been developed under undivided electrolytic conditions. The newly developed one-pot methodology involves the reaction of isothiocyanates with amidines or guanidines to give the corresponding imidoyl thioureas, which are further cyclized in situ via electrooxidative intramolecular S-N bond formation to promote the final products. This protocol features a metal- and external oxidant-free approach, broad substrate scope, good functional group tolerance, excellent yields, and one-pot operation/reaction without the isolation of the intermediates.

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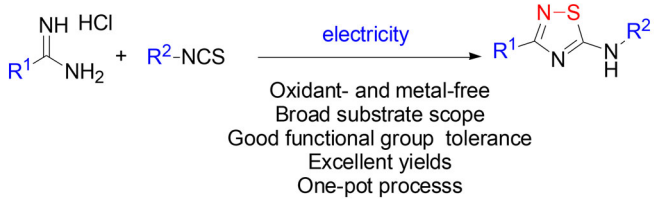
Metal-free; electrooxidative; intramolecular S-N bond formation; 3,5-disubstituted 1,2,4-thiadiazole

GRAPHICAL ABSTRACT



Introduction

The thiadiazole ring, a significant class of five-membered heterocyclic motifs, has attracted wide attention and plays important roles in drug discovery,[1] agriculture,[2] and functional materials.[3] In particular, 1,2,4-thiadiazoles are privileged structure class compounds that demonstrate widespread pharmacological activities, such as anticancer,[4] antimicrobial,[5] anticonvulsant,[6] fungicidal,[7] antihepatitis B virus,[8] and anti-HIV.[9] Owing to 1,2,4-thiadiazoles derivatives' possessing excellent performance in pharmaceutical science, a number of synthetic routes have been disclosed in the literatures, as summarized in Scheme 1. A common protocol for the synthesis of 1,2,4-thiadiazoles is oxidative dimerization of thioamides using various oxidants[10] and thermolysis of N^3-thiocarbamoylamidrazone ylide.[11] Cyclocondensation reaction of amidoximes with N-substituted thioureas in the presence of KF/Al_2O_3 was also reported.[12] In addition, palladium-catalyzed intermolecular Suzuki-Miyaura coupling reaction[13] and transition-metal-catalyzed intramolecular oxidative cyclization reaction[14] were reported for the synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles. Recently, various oxidants such as hypervalent iodine(III), I_2, and O_2 mediated synthesis of 3-substituted 5-amino-1,2,4-thiadiazoles through intramolecular oxidative S-N bond formation were reported.[15]

Despite these advances, the development of a green, practical and alternative method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles compounds is highly desired. Over the last decade, electrochemical synthesis has developed into a powerful tool; many significant advances have been achieved for construction carbon-carbon or carbon-heteroatom bonds in organic synthesis.[16] However, direct reports of the construction of heteroatom-heteroatom bond (such as N-N, S-S, N-S, P-O bonds) formation assisted by electrochemical-oxidation are scarce.[17] For example, Waldvogel developed a novel access to pyrazolidin-3,5-diones through anodic oxidation of 2,2-dimethylmalonic dianilides through intramolecular N-N bond formation.[17a] Very recently, Xu reported an oxidizing reagent- and transition-metal-free method for the synthesis of [1,2,3] triazolo[1,5-a]pyridines through electrochemical dehydrogenative N-N bond

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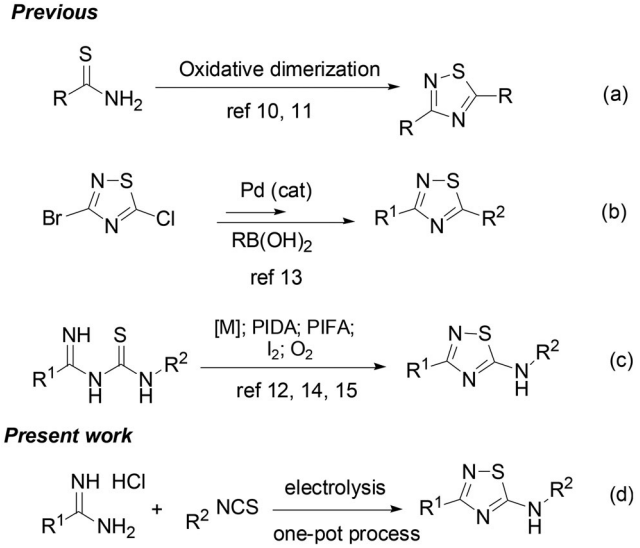


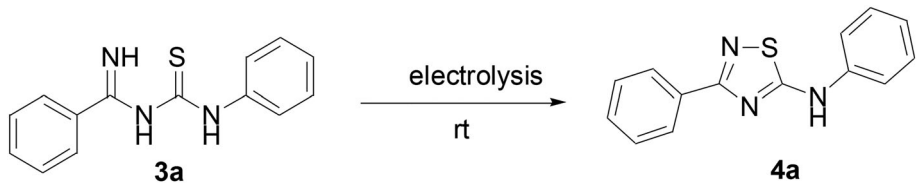
Scheme 1. Some conventional approaches to 3,5-disubstituted 1,2,4-thiadiazoles and our novel approach.

cyclization of pyridyl hydrazones.[17b] Nevertheless, electrochemical oxidative N-S bonds formation is still underexplored.[17] Herein we developed a versatile and efficient N-S bond formation reaction to access both 5-amino- and 3,5-diamino-substituted 1,2,4-thiadiazole derivatives through electrooxidative intramolecular S-N bond formation. Overall, the notable features of this reaction include the following: (1) neither a metal catalyst nor an exogenous-oxidant/additive is required; (2) the nucleophilic addition and the subsequent intramolecular S-N bond formation is performed in one-pot protocol without the isolation of the intermediates and (3) this protocol features a broad substrate scope, good functional group tolerance and excellent yields.

Results and discussion

Initially, we prepared the imidoyl thiourea **3a** by the reaction of amidine **1a** and phenyl isothiocyanate **2a**,[12] Then, we took **3a** as the model substrate to screen optimal reaction conditions for the synthesis of 5-amino-1,2,4-thiadiazole **4a** and the results are summarized in Table 1. When the

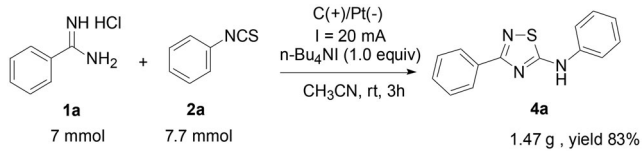
Table 1. Optimization of the reaction conditions[a].



Entry	Electrode	Electrolyte	Solvent	Yield[b] (%)
1	C(+)/Pt(-)	n-Bu_4NPF_6	DMSO	89
2	C(+)/Pt(-)	n-Bu_4NPF_6	CH_3OH	87
3	C(+)/Pt(-)	n-Bu_4NPF_6	CH_3CN	92
4	C(+)/Pt(-)	n-Bu_4NPF_6	DCM	90
5	C(+)/Pt(-)	n-Bu_4NPF_6	1,4-dioxane	trace
6	C(+)/Pt(-)	n-Bu_4NPF_6	H_2O	trace
7	C(+)/Pt(-)	n-Bu_4NPF_6	THF	trace
8	C(+)/Pt(-)	$LiClO_4$	CH_3CN	86
9	C(+)/Pt(-)	n-Bu_4NClO_4	CH_3CN	72
10	C(+)/Pt(-)	n-Bu_4NI	CH_3CN	98
11	C(+)/Pt(-)	Et_4NPF_6	CH_3CN	91
12	C(+)/Pt(-)	Et_4NOTs	CH_3CN	92
13	C(+)/Pt(-)	n-Bu_4NBF_4	CH_3CN	87
14	C(+)/Pt(-)	n-Bu_4NBr	CH_3CN	88
15	C(+)/Pt(-)	KI	CH3CN	91
16	C(+)/C(-)	n-Bu_4NI	CH_3CN	92
17	Pt(+)/Pt(-)	n-Bu_4NI	CH_3CN	93
18	Pt(+)/C(-)	n-Bu_4NI	CH_3CN	87
19[c]	C(+)/Pt(-)	n-Bu_4NI	CH_3CN	89
20[d]	C(+)/Pt(-)	n-Bu_4NI	CH_3CN	74
21[e]	C(+)/Pt(-)	n-Bu_4NI	CH_3CN	93
22[f]	C(+)/Pt(-)	n-Bu_4NI	CH_3CN	68
23[g]	C(+)/Pt(-)	n-Bu_4NI	CH_3CN	trace
24[h]	C(+)/Pt(-)	n-Bu_4NI	CH_3CN	92
25[i]	C(+)/Pt(-)	n-Bu_4NI	CH_3CN	98

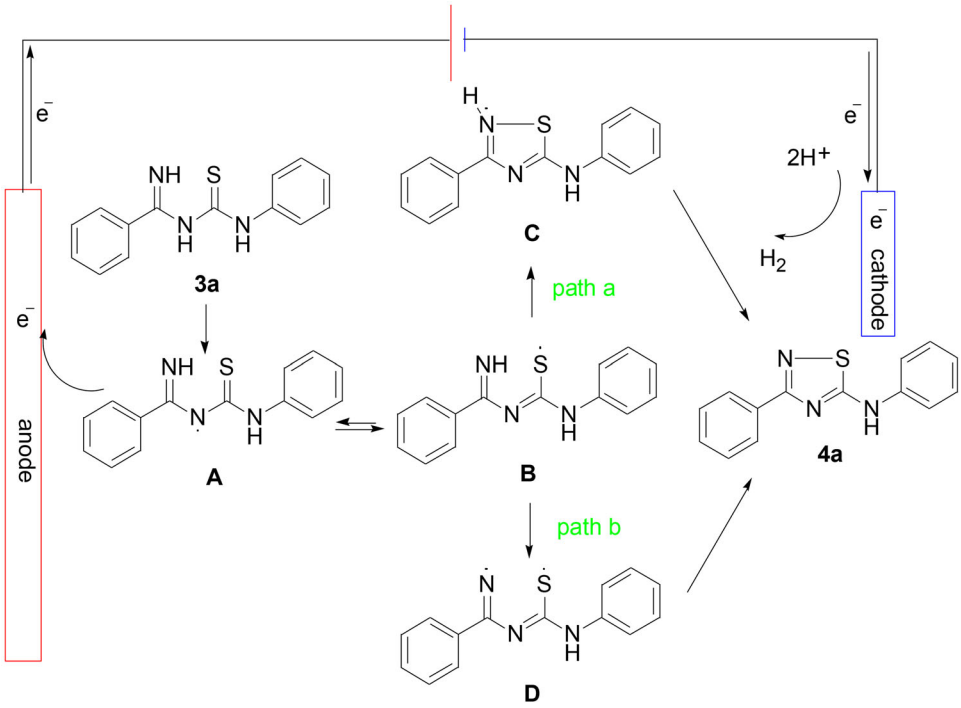
[a]Reaction conditions: Graphite rod anode (ϕ 6 mm), platinum plate cathode(10 mm × 10 mm), **3a** (0.3 mmol), electrolyte (0.05 M), solvent (6 ml), the electrolysis was conducted at a constant current (20 mA) for 3 h in an undivided cell under air.
[b]Yields of the isolated products.
[c]n-Bu_4NI = 0.03 M.
[d]n-Bu_4NI = 0.02 M.
[e]I = 15 mA.
[f]I = 10 mA.
[g]No current.
[h]Under N_2.
[i]one-pot protocol.

reaction was carried out under 20 mA constant current in an undivided cell, the desired product (**4a**) could be obtained in 89% yield with n-Bu_4NPF_6 as the electrolyte in DMSO at room temperature for 3 h (Table 1, entry 1). Inspired by this result, different solvents were investigated. It was found that the solvent had an important influence on the reaction. For instance, changing the solvent to MeOH, CH_3CN or DCM had little effect on the yield whereas CH_3CN was the best choice (Table 1, entries 2–4). Other solvents such as 1,4-dioxane, H_2O and THF could hardly promote the reaction (Table 1, entries 5–7). Various electrolytes were also investigated. $LiClO_4$, n-Bu_4NClO_4, n-Bu_4NI, Et_4NPF_6, Et_4NOTs, n-Bu_4NBF_4 and n-Bu_4NBr, were screened (Table 1, entries 8–14), and it was found that n-Bu_4NI was the most efficient electrolyte for this electrochemical reaction (Table 1, entry 10). Interestingly, the inorganic salt KI, as an electrolyte, can also promote the reaction with excellent yield (Table 1, entry 15). Next, it was found that the electrode materials had slight influence on the yields and graphite as the working electrode and Pt plate as the counter electrode is the best efficiency to provide the S-N bond formation product **1a** (Table 1, entries 16–18). Subsequently, the amount of the electrolyte were also investigated, a slightly reduced yield was obtained when the amount of n-Bu_4NI was decreased to 0.03 M (Table 1, entry 19). However, a sharply reduced yield was obtained when further decreasing the amount of n-Bu_4NI to 0.02 M (Table 1, entry 20). Moreover, we investigated the current intensity; it was found that 20 mA/cm^2 was the optimal value (Table 1, entries 21 and 22). Finally, the control experiment indicated no reaction occurred, with starting materials recovered, when the reaction was conducted without electricity (Table 1, entry 23). Furthermore, a comparable yield was obtained under argon atmosphere, which means that the passage of electricity was essential for this efficient transformation (Table 1, entry 24). In order to simplify the reaction, we attempted to carry out the nucleophilic addition and oxidative cyclization in a one-pot fashion. The desired product **4a** was obtained in similar yield when the resulted intermediate compound imidoyl thiourea **3a** was conducted for the directly usage of next step in the same reaction vessel under the optimal reaction conditions (Table 1, entry 25).



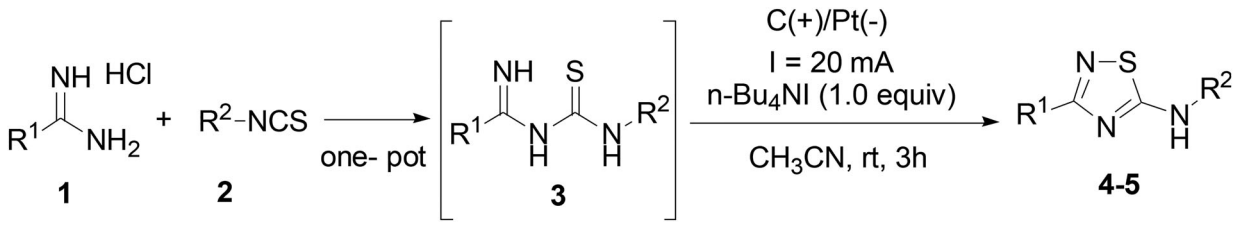
Scheme 2. Large-scale synthesis.

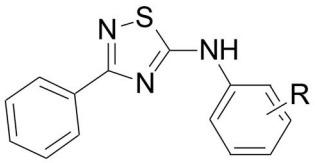
With the optimized reaction conditions in hand, the scope and generality of the reaction was subsequently investigated in a one-pot fashion and the results are summarized in Table 2. Aryl isothiocyanates **2** bearing an electron withdrawing or electron donating group on the phenyl ring smoothly reacted with phenyl amidine **1a** to afford the desired 5-amino- 1,2,4-thiadiazoles **4b–4i** in excellent yields. Various functional groups, including *p*-Me, *p*-OMe, *p*-F, *p*-Cl, *p*-Br, *p*-I, *m*-Me, and *m*-Cl, were tolerated. In addition, no obvious steric effect of substituents on the aromatic isothiocyanates **1** was found. For instance, the *ortho*-methyl substituted isothiocyanates **1j** afforded the desired product **4j** in 89% yield. On the other hand, various substituted amidines were readily treated with phenyl isothiocyanate **2a**, the corresponding products **4k-o** could still be obtained in high to excellent yields. Moreover, both various substituted amidines and isothiocyanates could provide the desired products in 98% and 96% yield (**4p** and **4q**), respectively. Furthermore, heterocycle substituted isothiocyanates **2k**,



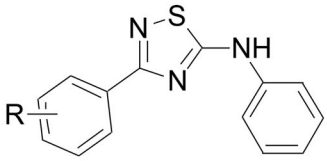
Scheme 3. Proposed reaction mechanism.

Table 2. Synthesis of 3-substituted 5-amino-1,2,4- thiadiazoles[a,b].

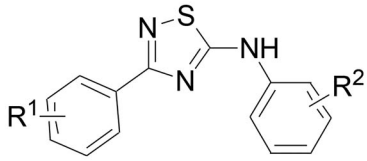




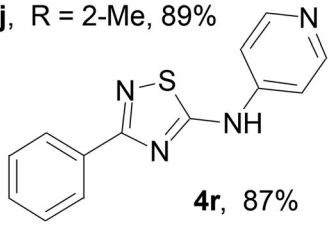
4a, R = 4-H, 98%
4b, R = 4-Me, 96%
4c, R = 4-OMe, 97%
4d, R = 4-F, 96%
4e, R = 4-Cl, 97%
4f, R = 4-Br, 92%
4g, R = 4-I, 94%
4h, R = 3-Me, 95%
4i, R = 3-Cl, 92%
4j, R = 2-Me, 89%



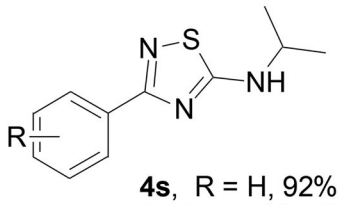
4k, R = 4-Me, 97%
4l, R = 4-OMe, 91%
4m, R = 4-F, 88%
4n, R = 4-Cl, 91%
4o, R = 4-Br, 89%



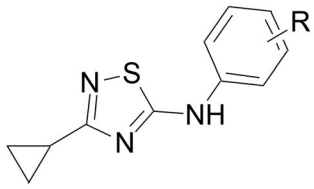
4p, R^1 = Me; R^2 = Me, 98%
4q, R^1 = OMe; R^2 = Me, 96%



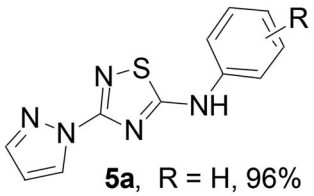
4r, 87%



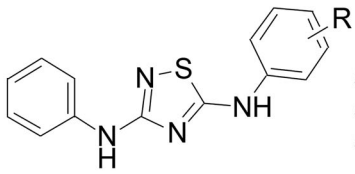
4s, R = H, 92%
4t, R = 4-Me, 93%
4u, R = 4-Br, 88%



4v, R = H, 87%
4w, R = 3-Me, 91%
4x, R = 3-Cl, 87%



5a, R = H, 96%
5b, R = 4-Me, 92%
5c, R = 4-OMe, 94%



5d, R = H, 95%
5e, R = 4-Me, 97%
5f, R = 4-Cl, 96%

[a]Reaction conditions: Graphite rod anode (ϕ 6 mm), platinum plate cathode (10 mm × 10 mm), constant current = 20 mA, **1** (0.30 mmol), **2** (1.1 equiv., 0.33 mmol), n-Bu_4NI (1.0 equiv., 0.3 mmol), CH_3CN (6.0 mL), rt, under air, 3 h. [b]Yields of the isolated products.

such as 3-pyridyl, were reacted with **1a**, and the desired products **4k** were obtained in 87% yield. Gratifyingly, alkyl isothiocyanates like isopropyl isothiocyanate was compatible with the optimized conditions as well, affording the desired products **4s**-**u** in excellent yields. However, alkyl amidine such as methyl and ethyl amidines were not compatible under the reaction conditions and no desired products were detected. Interestingly, alkyl amidines such as cyclopropyl amidine reacted smoothly to afford the desired products **4v**-**x** in very high yields. In addition, the present protocol is suitable for phenylguanidines as substrates and afforded a series of N_3,N_5-symmetrically and N_3,N_5-asymmetrically substituted 3,5-diamino-1,2,4-thiadiazoles (**5a**-**f**) in excellent yields.

To further probe the practical utility of the electrochemical oxidative N-S bond formation, a gram-scale experiment was conducted. 1.1 g (7.0 mmol) scale of **1a** could be converted to **4a** in 83% yield under the optimized reaction (Scheme 2).

On the basis of the above-mentioned results and the previous reports,[17e,f] a possible mechanism for this dehydrogenative N-S bond formation was proposed as shown in Scheme 3. Firstly, benzamidine hydrochloride **1a** reacts with isothiocyanate **2a** to afford the intermediate **3a** in the

presence of base. Then intermediate **3a** could begin with the anodic oxidation to form the amidinate radical intermediate **A**, which isomerizes to the sulfur radical intermediate **B**. then, there are two possible pathways leading to product **4a**. The first reaction pathway is an intramolecular radical-cascade cyclization of **B** to generate the intermediate **C**; Then, further anodic oxidative deprotonation of the intermediate **C** would afford the final product **4a**. The other pathway (path b) is the further anodic oxidation of **B** to afford the formation of a di-radical species **D**, which forms the final product **4a** through intramolecular cyclization.

Experimental

General information

Unless otherwise noted, all reagents, and solvents were purchased from commercial suppliers and used without further purification. The reactions were carried out under air. The instrument for electrolysis is a dual display potentiostat (DJS-292B) (made in China). The anodic electrode was graphite rod (ϕ 6 mm) and cathodic electrode was platinum plate (15 mm × 15 mm × 0.3 mm). Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200–300 mesh silica gel in petroleum (bp. 60–90 °C). 1H and 13 C NMR data were recorded with Bruker Advance III (400 MHz) spectrometers with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. and DMSO (2.50 ppm for 1 H NMR, 39.50 ppm for 13 C NMR). Melting point was determined using X-4 made by Peking Taike Apparatus Co. Ltd. High resolution mass spectra (HRMS) were measured with a Waters Micromass GCT instrument.

General procedure for one-pot synthesis for 3,5-disubstituted 1,2,4-thiadiazoles

In an oven-dried undivided three-necked bottle (25 mL) equipped with a stir bar, amidine or guanidines hydrochloride **1** (0.3 mmol), isothiocyanate **2** (0.33 mmol), NEt_3 (0.6 mmol), and CH_3CN (6 mL) were added and stirred at room temperature until the reaction was complete. The resulting imidoyl thiourea **3** was obtained without isolation. Subsequently, the three-necked bottle was equipped with graphite rod (6 ϕ mm, about 15 mm immersion depth in solution) as the anode and platinum plate (15 mm × 15 mm × 0.3 mm) as the cathode, n-Bu_4NI (0.3 mmol, 0.05 M) was added. Then the electrolysis system was stirred at a constant current of 20 mA at room temperature for 3 h. When the reaction finished, the reaction mixture was washed with water and extracted with ethyl acetate (10 mL x 3). The organic layers were combined, dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel to give pure products **4** and **5**. The Supplemental Materials contains full characterization for products 4 and 5 and sample ^1H and ^{13}C NMR spectra (Supplementary material, Figures S1–S58).

Conclusion

In summary, we disclosed an environmentally friendly method for the synthesis of 1,2,4-thiadiazole synthesis via a electrochemical oxidative N-S bond formation. Under exogenous-oxidant-free and metal catalyst-free electrochemical oxidation conditions, the present approach works well with a wide range of amidines and thioureas substrates to afford a variety of 5-amino-1,2,4-thiadiazoles in excellent yields in an undivided cell. Furthermore, this method provides a facile access to both N3,N^5-symmetrically and N^3,N^5-asymmetrically substituted 3,5-diamino-1,2,4- thiadiazole derivatives. Additionally, the proposed mechanism was provided and further work needs to be done to elucidate the mechanism.

Funding

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