Accepted Manuscript

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PII: S0040-4020(16)30104-1

DOI: 10.1016/j.tet.2016.02.042

Reference: TET 27512

To appear in: *Tetrahedron*

Received Date: 14 December 2015

Revised Date: 17 February 2016

Accepted Date: 19 February 2016

Please cite this article as: Chen J-F, Liu Z-Q, Synthesis of Imidazo[1,2-*a*]quinoxalines by Double Groebke Reactions and Inhibitory Effects on Radicals and DNA Oxidation, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.02.042.

Synthesis of Imidazo[1,2-*a*]quinoxalines by Double Groebke Reactions and Inhibitory Effects on Radicals and DNA Oxidation

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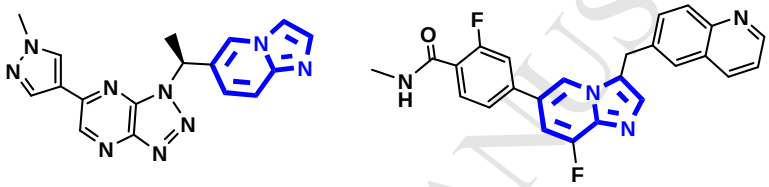
ABSTRACT

The *o*-phenylenediamine, aldehyde, and 2,4,4-trimethylpentan-2-yl isocyanide performed a Groebke 3CR to afford 2-aminoquinoxaline, which can react with an aldehyde and *t*-butyl isocyanide *via* another Groebke 3CR to give imidazo[1,2-*a*]quinoxaline. Exchanging two aldehydes in the sequential Groebke 3CR led to a couple of imidazo[1,2-*a*]quinoxaline isomer, in which the aldehyde moiety located at 2- or 4-position. The ferrocenyl group at 4-position in imidazo[1,2-*a*]quinoxaline was found to be active in trapping galvinoxyl radical, while the phenolic hydroxyl group at 2-position played a synergistic role with 4-ferrocenyl or 4-flavonyl group in scavenging 2,2'-diphenyl-1-picrylhydrazyl radical (DPPH). In addition, 4-ferrocenyl with *N*,*N*-dimethylaminophenyl group at 2-position was able to quench 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical ($ABTS^{+\cdot}$). Moreover, the combination of 4-ferrocenyl with 2-phenyl group (bearing *para*-*N*,*N*-dimethylamino or hydroxyl group) exhibited high inhibitory effect on DNA oxidation induced by 2,2'-azobis(2-amidinopropane hydrochloride) (AAPH).

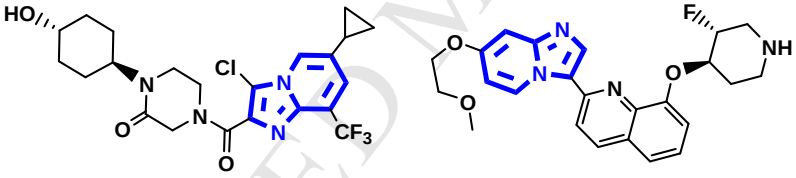
KEYWORDS Groebke 3CR, *N*-rich polyheterocycles, radical-scavenging property, DNA oxidation.

1. Introduction

Imidazoline-fused polyheterocycles are recently positioned at the convergence point in novel drug discovery. [1,2] As shown in Scheme 1, the scaffold of imidazo[1,2-*a*]pyridine was usually employed in the mesenchymal-epithelial transition factor (*c*-Met) inhibitor, [3,4] hepatitis C virus inhibitor, [5] and platelet-derived growth factor inhibitor [6]. In addition, an imidazoline linking with a thiadiazole was able to inhibit the receptor kinase of transforming growth factor-β, [7] and imidazo[1,2-*a*]pyrazine combining with coumarin can inhibit the growth of many kinds of tumor cells [8] because this structural moiety can be readily recognized by the active sites in the related enzymes. [9]



mesenchymal-epithelial transition (c-Met) inhibitor



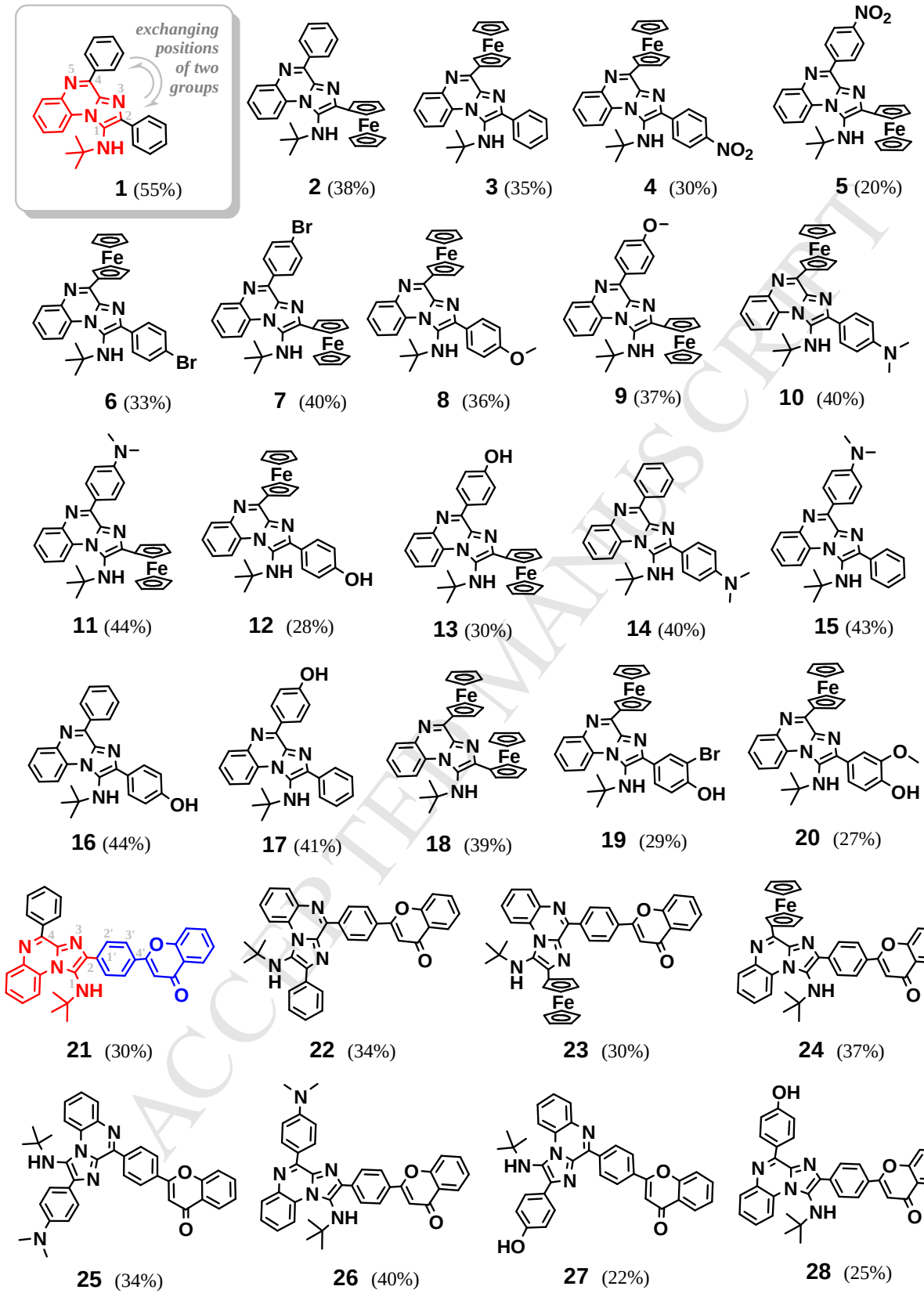
hepatitis C virus inhibitor **platelet-derived growth inhibitor**

Scheme 1 Recently found inhibitors containing imidazo[1,2-*a*]pyridine moiety.

Some methods have been applied to construct imidazo[1,2-*a*]-fused heterocycles. [10] For instance, palladium-catalyzed Suzuki reaction led to an arylation at C-3 position of imidazo[1,2-*a*]pyridine. [11] On the other hand, in the presence of *N*-iodosuccinimide, the reaction of 2-phenylacetaldehyde with 2-aminopyridine can also reach the same target. [12] The 3-phenylpropiolaldehyde can be converted into the imidazo moiety during the reaction with 2-aminopyridine in the case of CuI or $Pd(OAc)_2$ being the catalyst. [13] Some small molecules such as alcohol, thiol, and amine can form ether, thioether, and secondary amine as substituents in imidazo[1,2-*a*]pyridine. [14] Meanwhile, the nitrogen atom and C≡C in

N-propargylaminopyridine may take place an intramolecular nucleophilic addition to afford imidazo[1,2-*a*]pyridine scaffold.[15]

In addition to the aforementioned methods, Groebke-Blackburn-Bienaymé reaction (also called Groebke three-component-reaction, Groebke 3CR) offered a safety advantage for directly constructing the imidazo[1,2-*a*] moiety by using α-aminopyridine, aldehyde, and isocyanide as the starting materials.[16] Owing to successful utilization of Groebke 3CR, we have prepared the ferrocenyl-appended imidazo[1,2-*a*]pyridines and found that the introduction of ferrocenyl group into *N*-rich heterocycles enhanced the inhibitory effects on radicals and DNA oxidation.[17] In addition to some efforts applied to improve the reaction conditions of Groebke 3CR,[18,19,20] a previously reported method provided us with much safe way to obtain 2-aminoquinoxaline by the Groebke 3CR with 2,4,4-trimethylpentan-2-yl isocyanide being the precursor of amino group.[21] The produced 2-aminoquinoxaline performed another Groebke 3CR to generate imidazo[1,2-*a*]quinoxaline. The double Groebke 3CR procedure can be used to change the position of the aldehyde moiety in the Groebke 3CR adduct (see equation (1)). In our quest to discover novel inhibitors for DNA oxidation and radicals, as shown in Scheme 2, an imidazo[1,2-*a*]quinoxaline library with 28 members was built up to evaluate the inhibitory effects on 2,2'-azobis(2-amidinopropane hydrochloride) (AAPH, R-N=N-R, R=-$CMe_2C(=NH)NH_2$)-induced oxidation of DNA and on 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical ($ABTS^{+\cdot}$), 2,2'-diphenyl-1-picrylhydrazyl radical (DPPH), and galvinoxyl radicals, respectively.

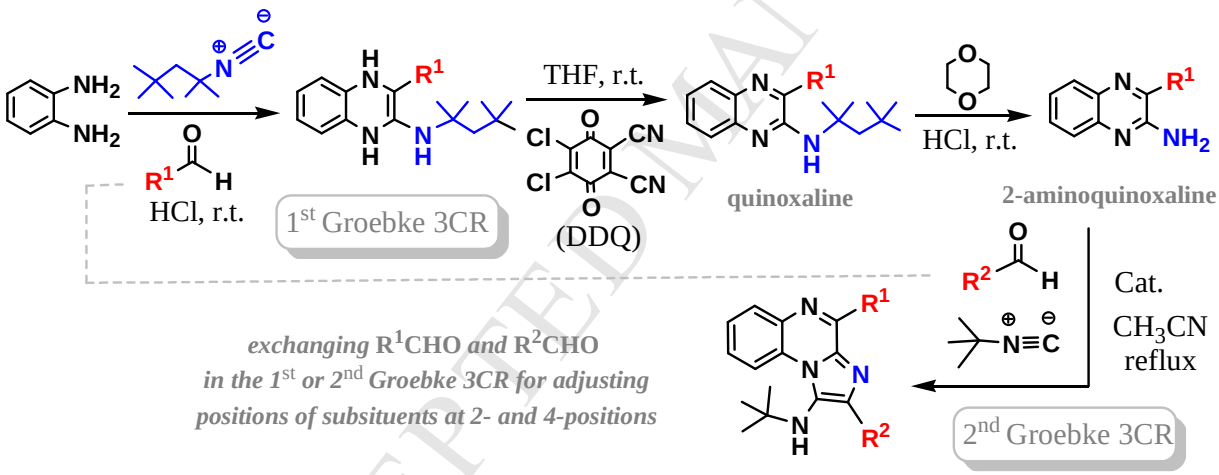


Scheme 2 Structures of imidazo[1,2-*a*]quinoxalines synthesized in this work.

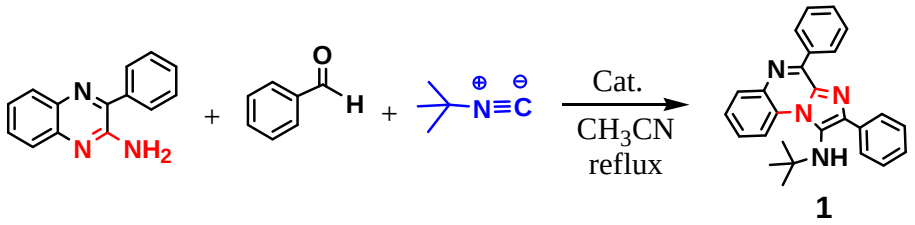
2. Results and Discussion

2.1. Synthesis.

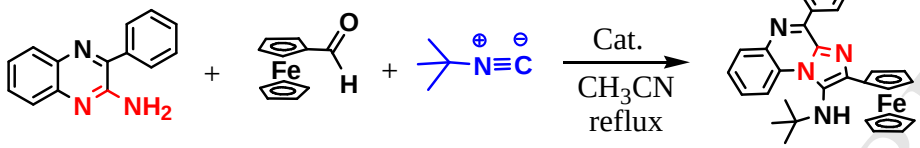
We herein applied a reported reaction condition to build up a series of imidazo[1,2-*a*]quinoxalines (see Scheme 2).[21] As shown in equation (1), a Groebke 3CR took place among *o*-phenylenediamine, aldehyde, and 2,4,4-trimethylpentan-2-yl isocyanide under concentrated HCl at room temperature. The produced 1,4-dihydroquinoxaline performed an aromatization by using 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) as the oxidant to afford quinoxaline. Subsequently, the amino group was generated by hydrolyzing 2,4,4-trimethylpentan-2-yl group with HCl, leading to the formation of 2-aminoquinoxaline as the reactant for the following Groebke 3CR. We still tested other catalysts for the second Groebke 3CR with equation (2), (3), and (4) being model reactions (see Table 1).



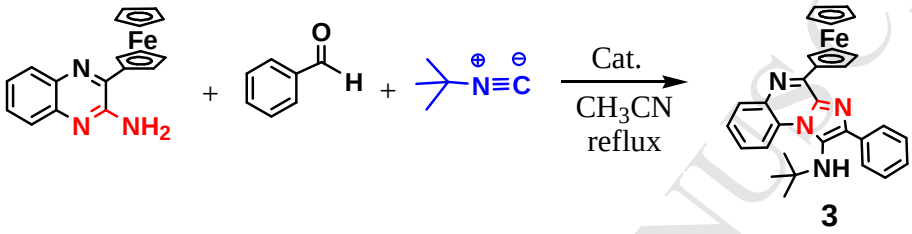
(1)



(2)



(3)



(4)

Table 1 Screening catalysts in the second Groebke 3CR.

Cat. [a]	Yield (%)		
	Reaction (2)	Reaction (3)	Reaction (4)
CH_3COOH	15	-	-
TsOH	40	35	-
AgOTf	12	-	10
$Ce(OTf)_3$	48	-	15
NH_4Cl	53	25	13
$SbCl_3$	44	20	5
$InCl_3$	65	30	20
$(CH_3)_3SiCl$	60	38	35
$LaCl_3$	78	33	40

[a] Equimolar amounts of both catalyst and all of the reactants.

Some Bronsted and Lewis acids were able to catalyze the reaction for producing **1** in the refluxing acetonitrile (see the column of reaction (2) in Table 1). Essentially, $(CH_3)_3SiCl$ and $LaCl_3$ were able to generate **1** with satisfactory yields.[22] In the case of ferrocenyl carboxaldehyde-involved Groebke 3CR (reaction (3)), no desired compound **2** was obtained when CH_3COOH,[23] AgOTf,[24] and $Ce(OTf)_3$[25] acted as catalysts, but other catalysts enabled the reaction (3) to afford **2** in yields of 20~38%. It appeared that ferrocenyl carboxaldehyde was so susceptible that can readily be decomposed during the reaction period even in the nitrogen atmosphere. It was reported that ferrocenyl carboxaldehyde was well-tolerated towards $LaCl_3$ in a solvent-free Groebke 3CR with 2-aminopyridine and cyclohexyl isocyanide being reactants.[22] We herein employed $LaCl_3$ to catalyze 2-aminoquinoxaline and *t*-butyl isocyanide in the Groebke 3CR, and low yield of compound **2** (33%) may be owing to the low reactivity of 2-aminoquinoxaline and low refluxing temperature. Attempts to perform the reaction (4) by using these catalysts led to the same results, in which only $(CH_3)_3SiCl$ and $LaCl_3$ can result in moderate yields (35% and 40%, respectively). Therefore, $(CH_3)_3SiCl$ and $LaCl_3$ were used in the following synthesis of imidazo[1,2-*a*]quinoxalines.

It was clear that $(CH_3)_3SiCl$ was not suitable for the hydroxyl-substituted aldehyde because it can react with hydroxyl group. Thus, **12**, **13**, **16**, **17**, **19**, **20**, **27**, and **28** were synthesized by utilizing $LaCl_3$ as the catalyst in the refluxing ethanol, while other imidazo[1,2-*a*]quinoxalines were prepared by using $(CH_3)_3SiCl$ as the catalyst in the refluxing acetonitrile. Exceptionally, **22**, **23**, and **25** were obtained in the media of chloroform, while **28** was obtained in the mixture of chloroform and ethanol (1:1, *v*:*v*) because 2-(4-formylphenyl)chromen-4-one as the reactant cannot be dissolved in ethanol or acetonitrile individually. In addition, low boiling point of these solvents cannot provide high temperature for the reaction but can avoid the decomposition of temperature-sensitive reactants. Under the optimized reaction condition (1 mmol $(CH_3)_3SiCl$ or $LaCl_3$, refluxing solvent), an aldehyde can be used in the first or the second Groebke 3CR to afford the final product with the aldehyde moiety at 2- or 4-position in imidazo[1,2-*a*]quinoxaline (see Scheme 2).

2.2. Scavenging radicals.

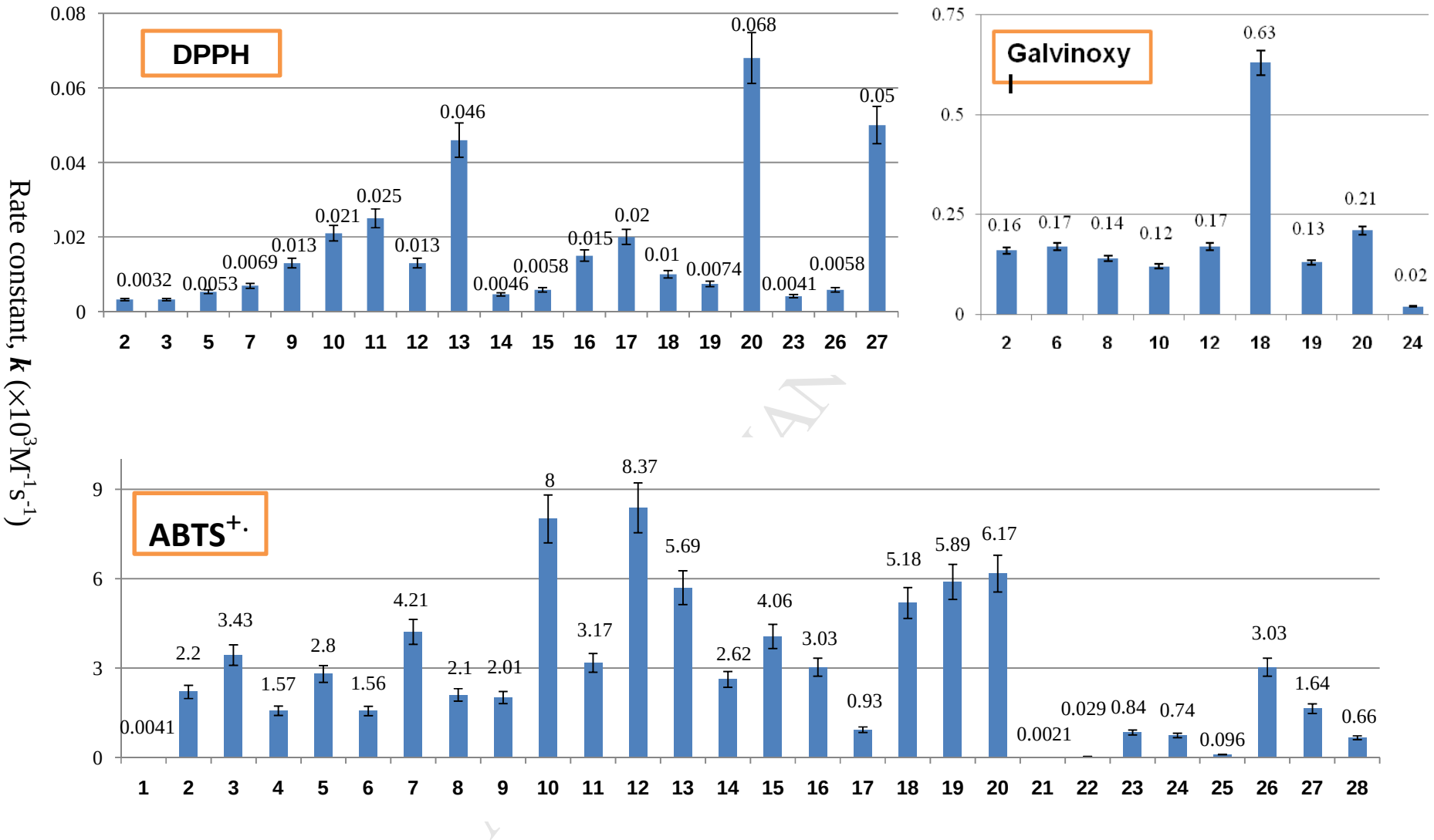
The reaction of an antioxidant with 2,2'-diphenyl-1-picrylhydrazyl radical (DPPH, a nitrogen-centered radical) followed the bimolecular kinetics as shown as equation (5). [26]

$$-\frac{d[\mathrm{DPPH}]}{dt} = \boldsymbol{r} = \boldsymbol{k}\,[\mathrm{DPPH}]\,[\mathrm{antioxidant}] \qquad (5)$$

The rate constant (***k***) can be calculated by the equation (5) when the reaction rate (***r***) along with the concentrations of DPPH and the antioxidant were measured at a certain time-point. But the concentrations of DPPH and the antioxidant at the beginning of the reaction (t = 0) were known, the equation (5) can be transformed into equation (6), in which $[\mathrm{DPPH}]_{t=0}$ and $[\mathrm{antioxidant}]_{t=0}$ referred to the concentrations of DPPH and the antioxidant at t = 0, and $\boldsymbol{r_0}$ was the reaction rate at the beginning of the reaction.

$$\boldsymbol{r_0} = \boldsymbol{k}\,[\mathrm{DPPH}]_{t=0}\,[\mathrm{antioxidant}]_{t=0} \qquad (6)$$

As we have reported a method for measuring $\boldsymbol{r_0}$, [27] the rate constants (***k***) of the reactions of imidazo[1,2-*a*]quinoxalines with DPPH were achieved and shown in Scheme 3.



Scheme 3 The rate constant (***k***) of imidazo[1,2-*a*]quinoxalines in quenching radicals.

We have measured the ***k*** of Trolox in trapping DPPH ($0.353\times10^{3}M^{-1}s^{-1}$). [27] The imidazo[1,2-*a*]quinoxalines used herein were not as active as Trolox in quenching *N*-centered radical of DPPH, and **1**, **4**, **6**, **8**, **21**, **22**, **24**, **25**, and **28** did not show any activities. It was worth pointing out that the relatively high ***k*** values of **13** ($0.046\times10^{3}M^{-1}s^{-1}$), **20** ($0.068\times10^{3}M^{-1}s^{-1}$), and **27** ($0.050\times10^{3}M^{-1}s^{-1}$) indicated that the phenolic hydroxyl group can provide hydrogen atom to be abstracted by *N*-centered radical, and the ferrocenyl group in **13** and **20** can also provide electrons to quench DPPH. In addition, the ferrocenyl group allowed **2** and **3** to exhibit lower activities towards DPPH (***k*** of **2** and **3** were both $0.0032\times10^{3}M^{-1}s^{-1}$) than **1** (no reaction with DPPH). Furthermore, the double ferrocenyl groups increased ***k*** value for **18** to $0.01\times10^{3}M^{-1}s^{-1}$, ~3-fold higher than that of **2** and **3**. This is in agreement with our previous observation on the benefit of ferrocenyl group for radical-scavenging property. [27] To be the isomer of **13**, **12** did not exhibit higher ***k*** value ($0.013\times10^{3}M^{-1}s^{-1}$) than that of **13**, indicating 2-ferrocenyl and 4-phenolic hydroxyl formed a powerful coordination for trapping *N*-centered radical, while diverse positions (4-ferrocenyl and 2-phenolic hydroxyl) cannot play the same role. Recently, we found that *N*,*N*-dimethylamino group in coumarin was active for trapping radicals, [28] and herein, high values of ***k*** of **10** ($0.021\times10^{3}M^{-1}s^{-1}$) and **11** ($0.025\times10^{3}M^{-1}s^{-1}$) also indicated that *N*,*N*-dimethylamino group in imidazo[1,2-*a*]quinoxaline was still effective towards DPPH. Similar ***k*** values of **2** and **3** implied that the ferrocenyl group at 2- or 4-positon cannot markedly influence the property of imidazo[1,2-*a*]quinoxaline in trapping DPPH, but **23** and **24** also consisting of ferrocenyl group exhibited quite different behaviors in this case. The ***k*** value of **23** ($0.0041\times10^{3}M^{-1}s^{-1}$) and no reaction of **24** with DPPH revealed that 4-flavonyl group was able to improve the radical-scavenging property of 2-ferrocenyl group. The comparison of ***k*** values of **27** (bearing 2-phenolic hydroxyl and 4-flavonyl group with $0.05\times10^{3}M^{-1}s^{-1}$ of ***k***) and **28** (bearing 2-flavonyl group and 4-phenolic hydroxyl, and no reaction with DPPH) demonstrated the aforementioned rules. Moreover, exchanging positions of *N*,*N*-dimethylaminophenyl and flavonyl groups generated **25** (bearing flavonyl group at 4-postion, and no reaction with DPPH) and **26** (bearing flavonyl group at 2-postion with $0.0058\times10^{3}M^{-1}s^{-1}$ of ***k***), in which

4-flavonyl group was inactive for *N*,*N*-dimethylamino in trapping DPPH.

The galvinoxyl radical was employed to determine the ability of an antioxidant to trap *O*-centered radical. As shown in Scheme 3, **2**, **6**, **8**, **10**, **12**, **18**, **19**, **20**, and **24** were able to react with galvinoxyl radical, and the ***k*** values were lower than that of Trolox ($1.70\times10^3 M^{-1}s^{-1}$). We herein found that **3**, **5**, **7**, **9**, **11**, **13**, **23** cannot react with galvinoxyl radical although both of them consisted of ferrocenyl group. Thus, only 4-ferrocenyl group was active to quench *O*-centered radical. The double ferrocenyl groups increased the ***k*** value of **18** ($0.63\times10^3 M^{-1}s^{-1}$) ~2 fold higher than that of **2** ($0.16\times10^3 M^{-1}s^{-1}$). Thus, the influence of the position of ferrocenyl group on trapping radicals can be identified by the reaction with galvinoxyl radical.

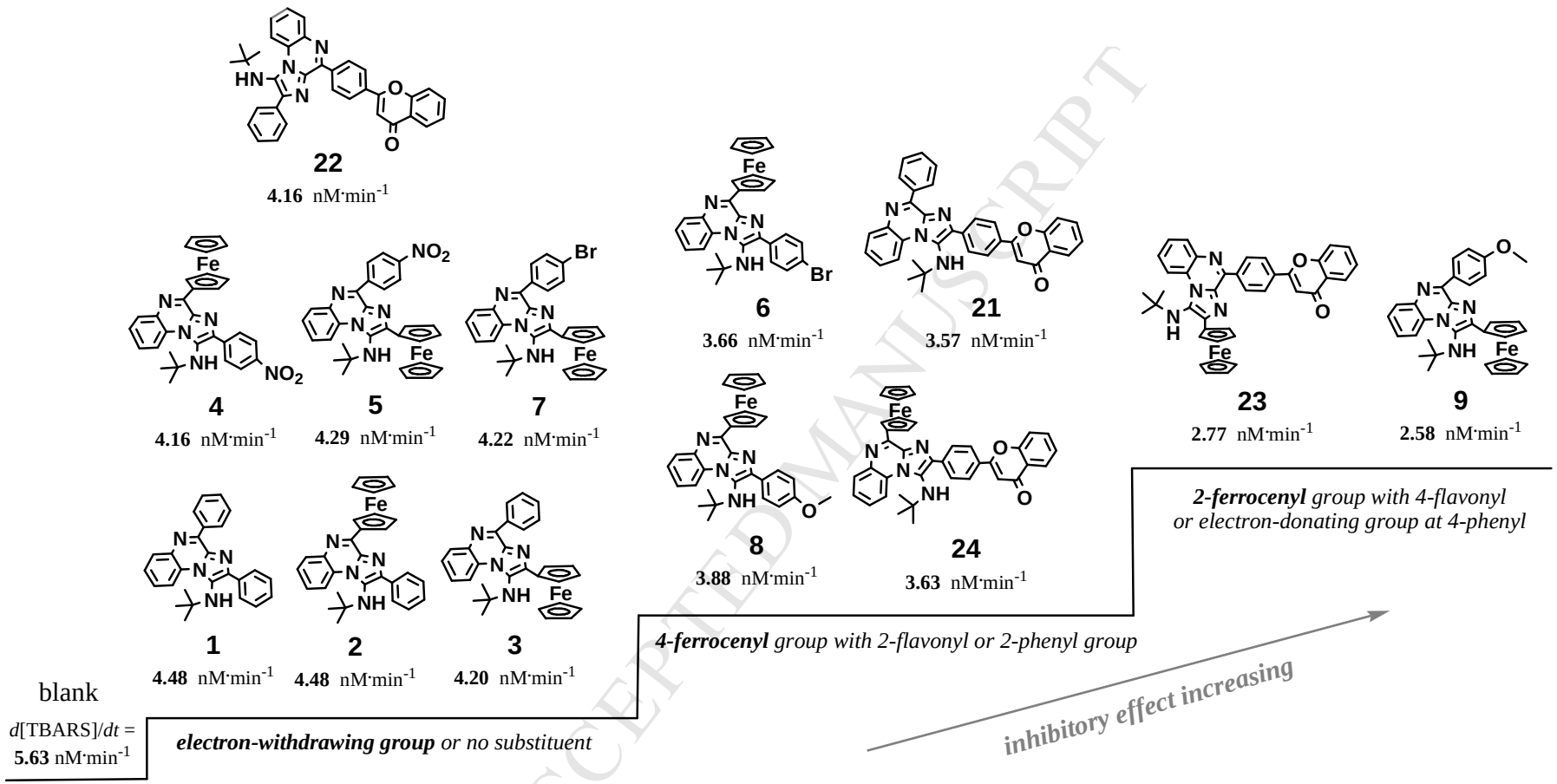
The oxidation of ABTS salt generated $ABTS^{+\cdot}$, which can be used to test the ability of an antioxidant to reduce radical.[29] Low ***k*** values of **1** ($0.0041\times10^3 M^{-1}s^{-1}$), **21** ($0.0021\times10^3 M^{-1}s^{-1}$), and **22** ($0.029\times10^3\ M^{-1}s^{-1}$) indicated that the skeleton of imidazo[1,2-*a*]quinoxaline emerged weak ability to reduce $ABTS^{+\cdot}$. Despite of **14**, **15**, **16**, **17**, **25**, **26**, **27**, and **28**, the ***k*** values of other imidazo[1,2-*a*]quinoxalines were all increased by the ferrocenyl group. We further compared ***k*** values of isomer couples, *i.e.*, **2** *vs* **3**, **4** *vs* **5**, **6** *vs* **7**, **12** *vs* **13**, **23** *vs* **24**, and found that 2-ferrocenyl group was more beneficial for the imidazo[1,2-*a*]quinoxaline to trap $ABTS^{+\cdot}$ than 4-ferrocenyl group. An electron-donating group such as $-OCH_3$ (in **8** *vs* **9**) and $-N(CH_3)_2$ (in **10** *vs* **11**, **14** *vs* **15**, **25** *vs* **26**) at 4-phenyl group played more active role for imidazo[1,2-*a*]quinoxaline in trapping $ABTS^{+\cdot}$ than that at 2-position. The comparison of ***k*** values of **16** *vs* **17**, **27** *vs* **28**, indicated that the phenolic hydroxyl group at 2-position was benefit to trap $ABTS^{+\cdot}$. The 4-ferrocenyl group in conjunction with -OH or $-N(CH_3)_2$ in 2-phenyl group increased the ***k*** of **12** and **10** to the highest values ($8.37\times10^3 M^{-1}s^{-1}$ and $8.00\times10^3 M^{-1}s^{-1}$, respectively).

2.3. Inhibiting DNA oxidation.

We attempted to use peroxyl radical ($^{\cdot}OOCMe_2C(=NH)NH_2$, deriving from the decomposition of AAPH) to initiate the oxidation of DNA, [30] during which the formed carbonyl species can be spectroscopically detected at 535 nm after reacting with thiobarbituric acid (TBA). Thus, the oxidation of DNA can be followed by determining the thiobarbituric acid reactive species (TBARS). [31] In the blank experiment (see Figure 4S), the concentration of TBARS linearly increased with the reaction period. The equation (7) indicated the relationship between the concentration of TBARS and the reaction period (*t*), and the coefficient (d[TBARS]/dt = 5.63 nM·min^{-1}) implied the rate of DNA oxidation. [32]

[TBARS (nM)] = 5.63 (± 0.28) *t* (min) + 3242.7 (± 162) (7)

As shown in Figure 4S (in the supporting formation), the addition of 100 μM **1**~**9**, and **21**~**24** actually changed the slope of lines of [TBARS]~*t*, and the equations of [TBARS]~*t* were involved in Table 4S. The d[TBARS]/dt was listed in Scheme 4. A low value of d[TBARS]/dt implied that the imidazo[1,2-*a*]quinoxaline possessed high ability to decrease the oxidative rate of DNA. It can be found from Scheme 4 that 2-ferrocenyl group together with 4-flavonyl (as **23**) or 4-phenyl with electron-donating group (as **9**) exhibited relatively higher inhibitory effect on DNA oxidation than other compounds contained in Scheme 4.

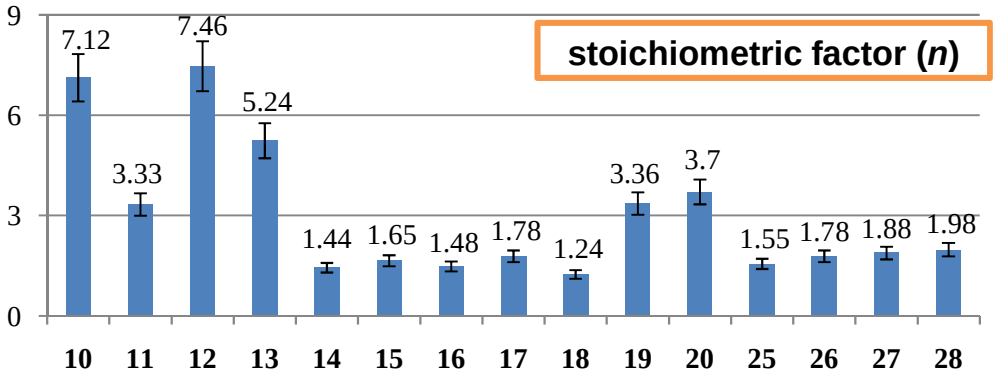


Scheme 4 The inhibitory effects of imidazo[1,2-*a*]quinoxalines without t_{inh} generated.

In addition to the aforementioned imidazo[1,2-*a*]quinoxalines, the addition of other compounds can inhibit the DNA oxidation for a period as shown in Figure 5S (in the supporting formation). The *inhibition period* (t_{inh}) started from t = 0 min and finished at the cross-point of tangents for inhibitory and oxidative periods. As shown in Figure 6S (in the supporting formation), t_{inh} correlated linearly with the concentration of imidazo[1,2-*a*]quinoxalines, and the equations of t_{inh}~[imidazo[1,2-*a*]quinoxaline] were collected in Table 5S. It has been proved that t_{inh} was related proportionally to the concentration of an antioxidant as shown as equation (8).[33]

$$t_{inh} = (n/R_i)\,[\text{antioxidant}] \qquad (8)$$

R_i referred to the initiation rate of the radical-induced oxidation, while the *stoichiometric factor* (n) stood for the number of the radical-propagation terminated by one molecule of the antioxidant. The coefficient in equations of t_{inh}~[imidazo[1,2-*a*]quinoxaline] (see Table 5S in the supporting formation) was equivalent to n/R_i, in which the initiation rate (R_i) of DNA oxidation was assumed to be equal to the radical-generation rate ($R_g = (1.4 \pm 0.2) \times 10^{-6}$ [AAPH] s^{-1}, *viz.*, $R_i = R_g = 1.4 \times 10^{-6} \times 40$ mM·s^{-1} = 3.36 μM·min^{-1}) since both DNA sodium salt and AAPH were water-soluble compounds, and the radical attacked DNA at the same phase.[34] Therefore, the n was the product of the coefficient in t_{inh}~[imidazo[1,2-*a*]quinoxaline] and R_i and outlined in Scheme 5.

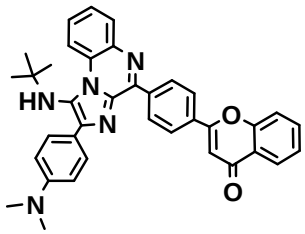


Scheme 5 The stoichiometric factor (***n***) of imidazo[1,2-*a*]quinoxalines in inhibiting DNA oxidation.

The inhibitory effects of **10**~**20** and **25**~**28** on AAPH-induced oxidation of DNA can also be discussed based on ***n*** values. Among all of the tested compounds, **12** and **10** stood out as the most efficacious compounds with 7.46 and 7.12 of *n* values, respectively. This is in line with the observation in scavenging $ABTS^{+\cdot}$ test, in which 4-ferrocenyl group in conjunction with -OH or $(CH_3)_2N$- in 2-phenyl group were active to quench $ABTS^{+\cdot}$. Exchanging the order of the aforementioned functional groups generated isomers **13** and **11** with high *n* values (5.24 and 3.33, respectively). The similar *n* values of **19** and **20** (3.36 and 3.70, respectively) also implied that 4-ferrocenyl group was not as active as that at 2-position. However, the double ferrocenyl groups did not allow **18** to exhibit strongly inhibitory effect on AAPH-induced oxidation of DNA, and introducing phenyl or flavonyl group did not enhance the *n* values of **14**~**17** and **25**~**28** (just ranging from 1.44 to 1.98, lower than that of ferrocenyl-appended compounds). Trolox also cannot generate inhibitory period (t_{inh}) and thus, the stoichiometric factor (***n***) cannot be obtained to be the reference for the comparison with other compounds. [27]

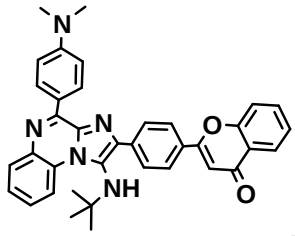
With the oxidative potentials ($E_{1/2}$) of **1** (1.13 V), **21** (1.12 V), and **22** (1.11 V) as the reference, the introduction of ferrocenyl group into 4- or 2-position markedly decreased $E_{1/2}$ of **2** and **3** (0.69 and 0.67 V, respectively) and of **23** and **24** (0.66 and 0.72 V, respectively). Thus, the benefit of ferrocenyl group for increasing antioxidative effect was owing to decrease the oxidative potential for imidazo[1,2-*a*]quinoxaline. The installation of phenolic hydroxyl group for ferrocenyl-appended imidazo[1,2-*a*]quinoxalines did not further decrease $E_{1/2}$ of **12** and **13** (0.60 and 0.65 V, respectively). However, lower $E_{1/2}$ of **27** and **28** (0.93 and 1.01 V, respectively) than that of the corresponding hydroxyl-free compounds (**21** and **22**) still revealed the antioxidative role of phenolic hydroxyl group. Upon structures of **27** and **28**, replacing hydroxyl group by $(CH_3)_2N$- generated **25** and **26**. The $E_{1/2}$ to 0.69 V (**25**) and 0.91 V (**26**) revealed that $(CH_3)_2N$- decreased the oxidative potential more efficiently than hydroxyl group. Finally, comparing the ***k*** and ***n*** values of **25** and **26** with those of a previously reported compound, ethyl 2-(2-(4-hydroxyphenyl)*H*-imidazo[1,2-a]pyridin-3-ylamino)acetate, [17] one can find

that the antioxidative effects of the compounds in the present work were generally lower than that in our previous report. The $E_{1/2}$ of ethyl 2-(2-phenyl)H-imidazo[1,2-*a*]pyridin-3-ylamino)acetate (a compound without phenolic hydroxyl group) was 0.50 V, [17] lower than that of **25** and **26** (0.69 and 0.91 V, respectively), indicating that the compounds in the present work were more difficult to be oxidized than those in our previous report. But the flavonyl group made *N*,*N*-dimethylaminophenyl group exhibit antioxidative effect in the imidazo[1,2-*a*]quinoxaline scaffold, which may be a novel candidate for the screening of antioxidative drugs.



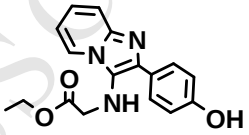
25

k (ABTS$^{+\cdot}$) = 0.096 mM^{-1}s^{-1}
k (DPPH) = 0.00 mM^{-1}s^{-1}
k (galvinoxyl) = 0.00 mM^{-1}s^{-1}
n = 1.55



26

k (ABTS$^{+\cdot}$) = 3.03 mM^{-1}s^{-1}
k (DPPH) = 0.0058 mM^{-1}s^{-1}
k (galvinoxyl) = 0.00 mM^{-1}s^{-1}
n = 1.78



Ethyl 2-(2-(4-hydroxyphenyl)H-imidazo[1,2-a]pyridin-3-ylamino)acetate

k (ABTS$^{+\cdot}$) = 13.58 mM^{-1}s^{-1}
k (DPPH) = 1.05 mM^{-1}s^{-1}
k (galvinoxyl) = 0.31 mM^{-1}s^{-1}
n = 5.70

3. Conclusion

We applied a Groebke 3CR to prepare 2-aminoquinoxaline, which was the reactant for the following Groebke 3CR to afford imidazo[1,2-*a*]quinoxaline. Some substituted benzaldehydes along with ferrocenyl carboxaldehyde and 2-(4-formylphenyl)chromen-4-one took part in the aforementioned sequential Groebke 3CR to give isomers with the aldehyde allocating 2- or 4-position in imidazo[1,2-*a*]quinoxaline. The installation of a flavonyl group into imidazo[1,2-*a*]quinoxaline did not exhibit additional activity towards either radicals or DNA oxidation, but 4-ferrocenyl group emerged as an active feature for inhibiting DNA oxidation and radicals. The combination of 2-phenolic hydroxyl with 4-ferrocenyl increased antioxidative effectiveness of imidazo[1,2-*a*]quinoxaline. In the continued quest for novel antioxidative drugs, ferrocenyl-appended imidazo[1,2-*a*]quinoxaline will offer a valuable choice and thus be worth exploring in due course.

4. Materials and Methods

4.1. Materials and Instrumentation.

AAPH and naked DNA sodium salt were products of ACROS Organics, Geel, Belgium, and diammonium salt of 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate) (ABTS salt), DPPH, and galvinoxyl radical were products of Fluka Chemie GmbH, Buchs, Switzerland. Solvents and reagents used in the synthesis were obtained commercially and used as such unless noted otherwise. All of the products were identified by ^{1}H and ^{13}C NMR spectroscopy (Bruker Avance III 400 MHz spectrometer) and HRMS spectrometry (ESI as the ionization mode) equipped with HPLC (Agilent 1290-micrOTOF Q II). The NMR spectra were provided in Supporting Information.

4.2. Preparation of 2-(4-formylphenyl)chromen-4-one and 2-aminoquinoxalines.

A mixture of 2-hydroxyacetophenone (0.01 mol) and *p*-phthalaldehyde (0.012 mol) was stirred in 50 mL of ethanol, and 0.5 mL of piperidine was added and refluxed under stirring for overnight. The cooled mixture was purified on a silica gel column with CH_2Cl_2 being the eluent to afford chalcone. Then, the chalcone was dissolved in dimethyl sulfoxide (DMSO), followed by adding I_2 (0.01 equiv.). The mixture was stirred at 110°C in N_2 atmosphere for overnight and then poured into ice water to collect solid product, which was further purified on a silica gel column with CH_2Cl_2 / ethyl acetate being the eluent to afford 2-(4-formylphenyl)chromen-4-one.

To a 50 mL of methanolic solution of *o*-phenylenediamine (0.01 mol) was added the equimolar aldehyde, 2,4,4-trimethylpentan-2-yl isocyanide, and concentrated HCl. The solution was stirred at room temperature in N_2 atmosphere for overnight. After methanol was evaporated, 50 mL of the saturated aqueous solution of $NaHCO_3$ was added to the mixture, and the aqueous layer was extracted with $CHCl_3$ and dried over anhydrous $MgSO_4$. The combined organic solvent were removed under vacuum, and the residue was dissolved in 50 mL of anhydrous tetrahydrofuran (THF), to which 1 equiv.

of 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ, dissolved in 10 mL of THF) was added. The above mixture was stirred at room temperature for overnight, and the solvent was removed under vacuum. The residue was purified on a silica gel column with CH_2Cl_2 being the eluent to give quinoxalines.

The quinoxaline (5 mmol) was dissolved in 4N HCl in dioxane (50 mL) and stirred at room temperature for overnight. Then, the mixture was poured into ice water, and $NaHCO_3$ was added until pH > 7. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were dried over anhydrous $MgSO_4$. Then, the organic solvent was removed under vacuum, and the residue was purified on a silica gel column with CH_2Cl_2/ethyl acetate being the eluent to give 2-aminoquinoxaline.

4.3. Synthesis of imidazo[1,2-a]quinoxalines.

The acetonitrile solution (25 mL) of 2-aminoquinoxaline (1 mmol) and aldehyde (1 mmol) was refluxed for 3 h and then cooled to room temperature. The catalyst (1 mmol $(CH_3)_3SiCl$ or $LaCl_3$) was added and stirred at room temperature for 1 h. Then, *tert*-butyl isocyanide (1 mmol) was added, and the mixture was refluxed for 36 h. After completion of the reaction as indicated by TLC, the mixture was poured into $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over anhydrous $MgSO_4$ and then removed under vacuum. The residue was purified on a silica gel column to give imidazo[1,2-*a*]quinoxalines **1**-**28**.

tert-Butyl-(2,4-diphenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**1**). A white solid, yield: 215 mg (55%). R_f = 0.37 (ethyl acetate : petroleum ether = 1 : 8, *v:v*), m.p.: 180-182°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.68 (m, 1H), 8.77 (d, *J* = 7.2 Hz, 2H), 8.15 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.58-7.52 (m, 5H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.38(t, *J* = 7.2 Hz, 1H), 3.56 (s, 1H), 1.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.2, 141.8, 137.0, 136.4, 135.1, 134.5, 130.5, 130.4, 130.3, 129.4, 128.7, 128.4, 128.0, 126.7, 126.0, 117.3, 57.8, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{26}H_{24}N_4$ 393.2080, found: 393.2066.

tert-Butyl-(2-phenyl-4-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**2**). A red solid, yield: 175 mg (35%). R_f = 0.38 (ethyl acetate : petroleum ether = 1 : 8, *v:v*), m.p.: 192-194°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.58 (m, 1H), 8.05 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.54-7.49 (m, 4H), 7.40 (m, 1H), 5.89 (s, 2H), 4.59 (s, 2H), 4.10 (s, 5H), 3.52 (s, 1H), 0.99 (s ,9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.2, 141.1, 135.4, 134.1, 130.1, 129.3, 128.8, 128.7, 128.6, 127.8, 125.9, 125.5, 117.4, 71.2, 71.0, 69.9, 57.8, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{30}H_{28}FeN_4$ 501.2055, found: 501.1701.

tert-Butyl-(2-ferrocenyl-4-phenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**3**). A yellow solid, yield: 190 mg (38%). R_f = 0.47 (ethyl acetate : petroleum ether = 1 : 8, *v:v*). m.p.: 215-217°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.69 (d, *J* = 4.8 Hz, 1H), 8.90 (d, *J* = 4.4 Hz, 2H), 8.07 (d, *J* = 0.8 Hz, 1H), 7.70-7.59 (m, 5H), 5.08 (s, 2H), 4.77 (s, 1H), 4.36 (s, 2H), 4.14 (s, 5H), 0.96 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 149.2, 136.6, 136.4, 134.2, 130.3, 130.2, 130.0, 129.0, 128.1, 126.4, 125.7, 121.8, 117.2, 80.5, 69.7, 68.8, 68.5, 57.4, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{30}H_{28}FeN_4$ 501.2055, found: 501.1717.

tert-Butyl-(2-(*p*-nitrophenyl)-4-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**4**). A red solid, yield: 164 mg (30%). R_f = 0.17 (ethyl acetate : petroleum ether = 1 : 8, *v :v*). m.p.: 254-256°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.44 (m, 1H), 8.37 (d, *J* = 7.6 Hz, 2H), 8.17 (d, *J* = 7.6 Hz, 2H), 8.02 (m, 1H), 7.52 (m, 2H), 5.82 (s, 2H), 4.60 (s, 2H), 4.09 (s, 5H), 3.40 (s, 1H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 153.5, 146.9, 142.0, 138.5, 137.4, 134.7, 130.8, 129.7, 128.8, 128.6, 126.3, 125.8, 123.9, 117.1, 79.9, 71.2, 70.8, 69.9, 58.1, 29.9. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{30}H_{27}FeN_5O_2$ 546.1906, found: 546.1543.

tert-Butyl-(4-(*p*-nitrophenyl)-2-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**5**). A red solid, yield: 109 mg, 20 %. R_f = 0.34 (ethyl acetate : petroleum ether = 1 : 8, *v:v*). m.p.: 223-225°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.61 (m, 1H), 9.17 (d, *J* = 8.8 Hz, 2H), 8.42 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 1H), 7.61-7.55 (m, 2H), 4.90 (s, 2H), 4.50 (s, 2H), 4.27 (s, 5H), 3.19 (s, 1H), 1.07 (s, 9H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ: 148.6, 146.3, 142.5, 140.8, 136.5, 134.0, 131.1, 130.5, 130.3, 129.2, 127.4, 126.2, 123.2, 117.4, 70.0, 69.0, 57.6, 29.9. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{30}H_{27}FeN_5O_2$ 546.1906, found: 546.1550.

tert-Butyl-(2-(*p*-bromophenyl)-4-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**6**). A red solid, yield: 191 mg (33%). R_f = 0.34 (ethyl acetate : petroleum ether = 1 : 8, *v:v*). m.p.: 215-217°C. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.52 (m, 1H), 8.01 (m, 1H), 7.82 (m, 2H), 7.50 (m, 2H), 5.82 (s, 2H), 4.58 (s, 2H), 4.09 (s, 5H), 3.40 (s, 1H), 1.01(s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.2, 139.7, 137.3, 134.4, 134.2, 131.7, 130.0, 129.7, 129.5, 128.6, 125.9, 125.5, 121.7, 117.1, 80.1, 71.0, 70.7, 69.8, 57.7, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{30}H_{27}FeBrN_4$ 579.0757, found: 579.0783.

tert-Butyl-(4-(*p*-bromophenyl)-2-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**7**). A yellow solid, yield: 231 mg (40%). R_f = 0.45 (ethyl acetate : petroleum ether = 1 : 8, *v:v*). m.p.: 237-239°C. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59-8.57 (m, 1H), 8.87 (d, *J* = 8.4 Hz, 2H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.55-7.52 (m, 2H), 4.76 (s, 2H), 4.36 (s, 2H), 4.18 (s, 5H), 3.20 (s, 1H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.8, 140.3, 136.6, 135.4, 134.0, 131.9, 131.3, 130.1, 129.0, 126.6, 125.8, 124.9, 117.3, 80.4, 69.7, 68.8, 68.6, 57.5, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{30}H_{27}FeBrN_4$ 579.0757, found: 579.0780.

tert-Butyl-(2-(*p*-methoxyphenyl)-4-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**8**). A red solid, yield: 208 mg (36%). R_f = 0.20 (ethyl acetate : petroleum ether = 1 : 8, *v:v*). m.p.: 200-202°C. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.54 (s, 1H), 8.04 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.47 (s, 2H), 7.05-7.03 (m, 2H), 6.88 (s, 2H), 4.57 (s, 2H), 4.09 (s, 5H), 3.87 (s, 3H), 3.43 (s, 1H), 0.98 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 152.9, 140.9, 137.0, 133.9, 129.7, 129.4, 129.2, 128.8, 127.9, 125.7, 125.4, 117.2, 114.0, 80.1, 71.0, 70.9, 69.9, 57.5, 55.4, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{31}H_{30}FeON_4$ 531.1875, found: 531.1825.

tert-Butyl-(4-(*p*-methoxyphenyl)-2-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**9**). A yellow solid, yield: 196 mg (37%). R_f = 0.31 (ethyl acetate : petroleum ether = 1 : 8, *v:v*). m.p.: 230-232°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.57-9.55 (m, 1H), 8.96 (d, *J* = 8.8 Hz, 2H), 8.08 (s, 1H), 7.51-7.49 (m, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 4.82 (s, 2H), 4.40 (s, 2H), 4.23 (s, 5H), 3.93 (s, 3H), 3.18 (s, 1H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.5, 148.7, 140.1, 136.9, 134.3, 132.0, 123.0, 129.4, 128.9, 126.0, 125.7, 117.3, 113.6, 70.0, 69.0, 68.7, 57.4, 55.5, 29.9. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{31}H_{30}FeON_4$ 531.1875, found: 531.1821.

tert-Butyl-(2-(*p*-dimethylaminophenyl)-4-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**10**). A red solid, yield: 217 mg (40%). R_f = 0.19 (ethyl acetate : petroleum ether = 1 : 8, *v:v*). m.p.: 207-209°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.58-9.56 (m, 1H), 8.03 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.48-7.45 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.89 (s, 2H), 4.56 (s, 2H), 4.09 (s, 5H), 3.47 (s, 1H), 3.05 (s, 6H), 1.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.7, 150.0, 141.4, 137.1, 133.8, 129.2, 129.1, 129.0, 128.9, 125.5, 125.2, 123.3, 117.3, 112.3, 80.3, 70.9, 70.8, 69.8, 57.4, 40.5, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{32}H_{33}FeN_5$ 544.2164, found: 544.2128.

tert-Butyl-(4-(*p*-dimethylaminophenyl)-2-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**11**). A yellow solid, yield: 239 mg (44%). R_f = 0.26 (ethyl acetate : petroleum ether = 1 : 8, *v:v*). m.p.: 235-237°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.54-9.52 (m, 1H), 9.00-8.99 (m, 2H), 8.07 (s, 1H), 7.48-7.42 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 4.79 (s, 2H), 4.35 (s, 2H), 4.21 (s, 5H), 3.17 (s, 1H), 3.10 (s, 6H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 139.5, 137.3, 131.7, 129.7, 129.6, 128.8, 127.9, 125.5, 125.3, 121.9, 117.2, 111.6, 69.8, 68.9, 68.4, 57.4, 40.4, 29.9. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{32}H_{33}FeN_5$ 544.2164, found: 544.2129.

p-(1-*tert*-Butylamino-4-ferrocenyl-imidazo[1,2-*a*]quinoxalin-2-yl)phenol (**12**). A red solid, yield: 144 mg (28%). R_f = 0.39 (ethyl acetate : petroleum ether = 1 : 2, *v:v*). m.p.: 195-197°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.59-9.56 (m, 1H), 8.01-7.99 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.49-7.47 (m, 2H),

7.11 (d, *J* = 8.0 Hz, 2H), 5.84 (s, 2H), 5.54 (s, 1H), 4.55 (s, 2H), 4.08 (s, 5H), 3.46 (s, 1H), 1.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4, 152.7, 141.2, 137.0, 133.7, 129.6, 129.2, 129.0, 128.8, 126.3, 125.6, 125.4, 117.3, 116.0, 80.2, 77.2, 70.8, 70.7, 69.8, 52.8, 29.7. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{30}H_{28}FeON_4$ 517.1710, found: 517.1673.

p-(1-*tert*-Butylamino-2-ferrocenyl-imidazo[1,2-*a*]quinoxalin-4-yl)phenol (**13**). A red solid, yield: 155 mg (30%). R_f = 0.48 (ethyl acetate : petroleum ether = 1 : 2, *v:v*). m.p.: 244-246°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.00 (s, 1H), 9.67-9.65 (m, 1H), 8.89 (d, *J* = 8.8 Hz, 2H), 8.01-7.97 (m, 1H), 7.65-7.54 (m, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 5.07 (s, 2H), 4.72 (s, 1H), 4.35 (s, 2H), 4.12 (s, 5H), 0.95 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.7, 147.3, 139.8, 136.1, 133.3, 131.7, 129.7, 129.3, 128.3, 127.1, 126.0, 125.6, 116.9, 114.9, 80.2, 69.2, 68.7, 68.0, 56.1, 29.4. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{30}H_{28}FeON_4$ 517.1710, found: 517.1666.

tert-Butyl-[2-(*p*-dimethylaminophenyl)-4-phenyl-imidazo[1,2-*a*]quinoxalin-1-yl]-amine (**14**). A yellow solid, yield: 174 mg (40%). R_f = 0.26 (ethyl acetate : petroleum ether = 1 : 6, *v:v*). m.p.: 210-212°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.63-9.60 (m, 1H), 8.89 (d, *J* = 7.2 Hz, 2H), 8.10-8.06 (m, 1H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.53-7.45 (m, 4H), 7.39-7.35 (m, 1H) 6.87 (d, *J* = 8.8 Hz, 2H), 3.54 (s, 1H), 3.08 (s, 6H), 0.99 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.2, 149.7, 142.3, 136.9, 136.6, 134.2, 130.3, 130.2, 130.1, 129.6, 129.4, 128.3, 126.4, 125.7, 123.0, 117.3, 112.4, 57.6, 40.6, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{28}H_{29}N_5$ 436.2502, found: 436.2418.

tert-Butyl-[4-(*p*-dimethylaminophenyl)-2-phenyl-imidazo[1,2-*a*]quinoxalin-1-yl]-amine (**15**). A yellow solid, yield: 187 mg (43%). R_f = 0.29 (ethyl acetate : petroleum ether = 1 : 6, *v:v*). m.p.: 271-273°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.67-9.65 (m, 1H), 8.81-8.79 (m, 2H), 8.14-8.11 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.57-7.50 (m, 5H), 6.85 (s, 2H), 3.53 (s, 1H), 3.02 (s, 6H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 149.7, 141.3, 135.3, 134.6, 131.6, 130.2, 129.7, 129.0, 128.7, 128.6,

127.8, 125.8, 125.5, 117.2, 111.7, 57.7, 40.4, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{28}H_{29}N_5$ 436.2502, found: 436.2486.

p-(1-*tert*-Butylamino-4-phenyl-imidazo[1,2-*a*]quinoxalin-2-yl)phenol (**16**). A white solid, yield: 122 mg (44%). R_f = 0.30 (ethyl acetate : petroleum ether = 1 : 2, *v:v*). m.p.: 283-285°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.77 (t, *J* = 8.0 Hz, 1H), 9.57 (s, 1H), 8.79-8.77 (m, 2H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.72-7.68 (m, 1H), 7.64-7.58 (m, 4H), 6.87 (d, *J* = 7.6 Hz, 2H), 4.98 (s, 1H), 0.95 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.8, 157.7, 148.6, 142.2, 136.5, 133.6, 132.6, 130.7, 130.3, 129.3, 128.5, 127.4, 126.4, 125.9, 117.5, 116.3, 115.5, 56.8, 30.0. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{26}H_{24}N_4O$ 409.2029, found: 409.2004.

p-(1-*tert*-Butylamino-2-phenyl-imidazo[1,2-*a*]quinoxalin-4-yl)phenol (**17**). A white solid, yield: 167 mg (41%). R_f = 0.40 (ethyl acetate : petroleum ether = 1 : 2, *v:v*). m.p.: 250-252°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.01 (s, 1H), 9.76-9.73 (m, 1H), 8.79 (d, *J* = 8.8 Hz, 2H), 8.12-8.10 (m, 2H), 8.04-8.01 (m, 1H), 7.66-7.04 (m, 1H), 7.62-7.58 (m, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.41-7.37 (m, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 1H), 0.94 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.3, 148.5, 141.4, 136.6, 135.2, 133.9, 132.2, 131.0, 129.9, 129.0, 128.6, 128.1, 127.3, 126.7, 126.5, 117.5, 115.4, 56.9, 29.9. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{26}H_{24}N_4O$ 409.2029, found: 409.2011.

tert-Butyl-[2,4-diferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl]-amine (**18**). A red solid, yield: 237 mg (39%). R_f = 0.43 (ethyl acetate : petroleum ether = 1 : 8, *v:v*). m.p.: 244-246°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53-9.50 (m, 1H), 8.00-7.98 (m, 1H), 7.48-7.44 (m, 2H), 5.93 (s, 2H), 4.82 (s, 2H), 4.60 (s, 2H), 4.37 (s, 2H), 4.24 (s, 5H), 4.13 (s, 5H), 3.17 (s, 1H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.5, 139.2, 137.2, 134.0, 129.2, 128.6, 125.4, 125.1, 117.2, 80.7, 80.4, 70.8, 70.5, 69.7, 69.6, 68.5, 68.3, 57.3, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{34}H_{32}Fe_2N_4$ 609.1405, found: 609.1348.

p-(1-*tert*-Butylamino-4-ferrocenyl-imidazo[1,2-*a*]quinoxalin-2-yl)-*o*-methoxyphenol (**19**). A red solid, yield: 173 mg (29%). R_f = 0.64 (ethyl acetate : dichloromethane = 1 : 20, *v:v*). m.p.: 226-228°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53-9.50 (m, 1H), 8.09 (s, 1H), 8.02-8.00 (m, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.51-7.48 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 5.83 (s, 2H), 4.85 (s, 2H), 4.09 (s, 5H), 3.36 (s, 1H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.9, 137.3, 134.1, 131.9, 129.5, 129.4, 129.3, 129.2, 125.8, 125.5, 117.1, 116.1, 110.5, 80.1, 71.0, 70.7, 69.6, 57.6, 29.9. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{30}H_{27}BrFeN_4O$ 596.0953, found: 596.0780.

p-(1-*tert*-Butylamino-4-ferrocenyl-imidazo[1,2-*a*]quinoxalin-2-yl)-*o*-bromophenol (**20**). A red solid, yield: 148 mg (27%). R_f = 0.59 (ethyl acetate : dichloromethane = 1 : 20, *v:v*). m.p.: 207-209°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.57-9.54 (m, 1H), 8.04 (s, 1H), 7.50-7.48 (m, 3H), 7.33-7.31 (m, 1H), 7.06-7.03 (m, 1H), 5.86 (s, 2H), 5,78 (s, 1H), 4.58 (s, 2H), 4.10 (s, 5H), 4.05 (s, 3H), 3.46 (s, 1H), 1.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.9, 145.6, 141.0, 137.3, 133.9, 129.4, 128.8, 127.7, 125.7, 125.4, 121.5, 117.2, 114.4, 111.4, 80.3, 70.8, 70.7, 69.8, 57.6, 56.2, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{31}H_{30}FeN_4O_2$ 547.1797, found: 547.1829.

tert-Butyl-(2-phenyl-4-flavonyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**21**). A white solid, yield: 166 mg (25%). R_f = 0.31 (ethyl acetate : dichloromethane = 1 : 20, *v:v*). m.p.: 275-277°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.71-9.69 (m, 1H), 9.03 (d, *J* = 8.4 Hz, 2H), 8.34 (s, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.76-7.72 (m, 1H), 7.64-7.61 (m, 3H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.47-7.40 (m, 2H), 6.96 (s, 1H), 3.63 (s, 1H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5, 163.1, 156.3, 148.2, 142.1, 139.2, 136.6, 134.8, 134.2, 133.8, 133.0, 130.8, 130.4, 129.4, 128.7, 128.6, 128.1, 127.1, 126.2, 126.1, 125.7, 125.2, 124.1, 118.2, 117.3, 108.0, 57.8, 29.7. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{35}H_{28}N_4O_2$ 537.2291, found: 537.2283.

tert-Butyl-(2-flavonyl-4-phenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**22**). A white solid, yield: 160 mg (30%). R_f = 0.35 (ethyl acetate : dichloromethane = 1 : 20, *v:v*). m.p.: 263-265°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.58-9.56 (m, 1H), 8.80-8.78 (m, 2H), 8.25-8.23 (m, 2H), 8.07-8.00 (m, 4H), 7.73-7.69 (m, 1H), 7.59-7.53 (m, 6H), 7.42 (t, *J* = 8.0 Hz, 1H), 6.88 (s, 1H), 3.59 (s, 1H), 1.02 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.4, 162.9, 156.2, 149.8, 140.7, 138.1, 134.4, 133.8, 131.2, 130.8, 130.7, 130.3, 130.0, 129.0, 128.9, 128.3, 126.9, 126.4, 126.3, 125.7, 125.3, 124.2, 118.1, 117.1, 107.5, 58.0, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{35}H_{28}N_4O_2$ 537.2291, found: 537.2252.

tert-Butyl-(2-ferrocenyl-4-flavonyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**23**). A yellow solid, yield: 193 mg (30%). R_f = 0.41 (ethyl acetate : dichloromethane = 1 : 20, *v:v*). m.p.: 233-235°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.62-9.60 (m, 1H), 9.14 (d, *J* = 7.6 Hz, 2H), 8.28 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 7.6 Hz, 2H), 7.76-7.73 (m, 1H), 7.67-7.65 (m, 1H), 7.59-7.58 (m, 1H), 7.47-7.44 (m, 1H), 6.99 (s, 1H), 4.83 (s, 2H), 4.42 (s, 2H), 4.23 (s, 5H), 3.26 (s, 1H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5, 163.2, 156.4, 147.5, 136.6, 134.2, 133.8, 132.9, 130.8, 130.3, 130.2, 129.1, 126.9, 126.0, 125.9, 125.8, 125.3, 124.1, 118.2, 117.3, 108.1, 100.0, 80.4, 69.8, 68.9, 68.7, 57.5, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{39}H_{32}N_4O_2$ 645.1954, found: 645.1705.

tert-Butyl-(2-flavonyl-4-ferrocenyl-imidazo[1,2-*a*]quinoxalin-1-yl)-amine (**24**). A red solid, yield: 238 mg (37%). R_f = 0.41 (ethyl acetate : dichloromethane = 1 : 15, *v:v*). m.p.: 213-215°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.55-9.53 (m, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 8.17-8.10 (m, 4H), 8.04-8.02 (m, 1H), 7.76-7.72 (m, 1H), 7.64-7.62 (m, 1H), 7.53-7.44 (m, 1H), 6.94 (s, 1H), 5.86 (s, 2H), 4.61 (s, 2H), 4.11 (s, 5H), 3.49 (s, 1H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5, 163.1, 156.3, 153.3, 139.5, 138.8, 137.3, 134.4, 133.8, 130.6, 130.4, 129.5, 128.8, 126.5, 126.0, 125.8, 125.6, 125.3, 124.1, 118.1, 117.2, 107.5, 80.1, 71.1, 70.8, 69.9, 57.9, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{39}H_{32}N_4O_2$ 645.1954, found: 645.1712.

tert-Butyl-[2-(*p*-dimethylaminophenyl)-4-flavonyl-imidazo[1,2-*a*]quinoxalin-1-yl]-amine (**25**). A yellow solid, yield: 197 mg (34%). R_f = 0.20 (ethyl acetate : dichloromethane = 1 : 15, *v:v*). m.p.: 280-282°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.70-9.67 (m, 1H), 9.05 (d, *J* = 8.8 Hz, 2H), 8.28-8.25 (m, 1H), 8.17-8.12 (m, 3H), 7.77-7.71 (m, 3H), 7.64-7.56 (m, 3H), 7.46-7.43 (m, 1H), 6.96-6.89 (m, 3H), 3.55 (s, 1H), 3.05 (s, 6H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5, 163.2, 156.3, 147.9, 142.4,

139.6, 136.7, 134.0, 133.8, 132.7, 130.8, 130.3, 129.8, 129.3, 126.8, 126.0, 125.9, 125.7, 125.2, 124.1, 118.2, 117.3, 112.5, 107.9, 57.6, 40.6, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{37}H_{33}N_5O_2$ 580.2713, found: 580.2510.

tert-Butyl-[4-(*p*-dimethylaminophenyl)-2-flavonyl-imidazo[1,2-*a*]quinoxalin-1-yl]-amine (**26**). A yellow solid, yield: 231 mg (40%). R_f = 0.25 (ethyl acetate : dichloromethane = 1 : 15, *v:v*). m.p.: 285-287°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.56 (d, *J* = 8.0 Hz, 1H), 8.89 (d, *J* = 7.6 Hz, 2H), 8.28-8.26 (m, 1H), 8.10-8.05 (m, 5H), 7.75-7.71 (m, 1H), 7.62-7.60 (m, 1H), 7.55-7.43 (m, 3H), 6.92-6.87 (m, 3H), 3.49 (s, 1H), 3.09 (s, 6H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5, 163.1, 156.3, 152.0, 149.6, 139.6, 138.6, 137.3, 134.9, 133.8, 131.5, 130.5, 129.8, 128.9, 126.3, 126.0, 125.7, 125.6, 125.2, 124.1, 124.0, 118.1, 117.0, 111.6, 107.4, 57.8, 40.3, 29.8. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{37}H_{33}N_5O_2$ 580.2713, found: 580.2662.

p-(1-*tert*-Butylamino-4-flavonyl-imidazo[1,2-*a*]quinoxalin-2-yl)phenol (**27**). A white solid, yield: 121 mg (22%). R_f = 0.25 (ethyl acetate : dichloromethane = 1 : 10, *v:v*). m.p.: 291-293°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.78 (d, *J* = 8.4 Hz, 1H), 9.60 (s, 1H), 9.04 (d, *J* = 8.8 Hz, 2H), 8.37 (d, *J* = 8.4 Hz, 2H), 8.14-8.09 (m, 2H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.89-7.86 (m, 2H), 7.76-7.74 (m, 3H), 7.56-7.54 (m, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.02 (s, 1H), 0.97 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 177.6, 162.5, 156.2, 147.2, 142.3, 139.3, 136.4, 134.9, 133.6, 132.9, 132.0, 130.8, 130.5, 130.4, 129.4, 129.1, 127.8, 126.6, 126.5, 126.1, 125.7, 125.3, 123.9, 119.1, 115.5, 108.0, 56.9, 30.0. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{35}H_{28}N_4O_3$ 553.2240, found: 553.2051.

p-(1-*tert*-Butylamino-2-flavonyl-imidazo[1,2-*a*]quinoxalin-4-yl)phenol (**28**). A white solid, yield: 138 mg (25%). R_f = 0.28 (ethyl acetate : dichloromethane = 1 : 10, *v:v*). m.p.: 301-303°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.15 (s, 1H), 9.75-9.73 (m, 1H), 8.81 (d, *J* = 8.8 Hz, 2H), 8.40-8.37 (m, 2H), 8.50 (d, *J* = 8.8 Hz, 2H), 8.10-8.09 (m, 1H), 8.06-8.03 (m, 1H), 7.88-7.85 (m, 2H), 7.68 (t, *J* = 8.4 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.56-7.52 (m, 1H), 7.17 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.24 (s, 1H),

0.99 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 177.6, 160.3, 156.2, 148.6, 140.1, 138.4, 136.7, 134.8, 134.2, 132.2, 131.8, 130.4, 130.0, 129.3, 129.1, 129.0, 127.2, 127.0, 126.7, 126.0, 125.3, 123.9, 119.1, 117.6, 115.5, 107.3, 57.2, 30.0. HRMS (ESI): *m/z* calcd for $[M+H]^+$ of $C_{35}H_{28}N_4O_3$ 553.2240, found: 553.2220.

4.4. Scavenging $ABTS^{+\cdot}$, DPPH, and galvinoxyl radicals.

Solutions of DPPH and galvinoxyl radicals were prepared by dissolving solids of DPPH and galvinoxyl radical in ethanol directly. The absorbance was around 1.00 at 517 nm (for DPPH, ε_{DPPH} = 4.09×10^3 $M^{-1}cm^{-1}$) and 428 nm (for galvinoxyl radical, $\varepsilon_{galvinoxyl}$ = 1.4×10^5 $M^{-1}cm^{-1}$), respectively. The $ABTS^{+\cdot}$ was generated in 2.0 mL of aqueous solution of 4.0 mM ABTS salt and 1.41 mM $K_2S_2O_8$ after 20 h, and then, was diluted with 100 mL of ethanol. The absorbance of $ABTS^{+\cdot}$ was also around 1.00 at 734 nm ($\varepsilon_{ABTS+\cdot}$ = 1.6×10^4 M^{-1} cm^{-1}). At the ambient temperature (25°C), a certain concentration of an imidazo[1,2-*a*]quinoxaline (dissolved in dimethyl sulfoxide (DMSO) as the stock solution, 0.1 mL) was mixed with 1.9 mL of a radical solution, and the absorbance of the mixture was immediately recorded and then measured with a certain time interval (see Supporting Information).

4.5 Inhibiting AAPH-induced oxidation of DNA.

AAPH and DNA sodium salt were dissolved in phosphate buffered solution (PBS: 8.1 mM Na_2HPO_4, 1.9 mM NaH_2PO_4, 10.0 μM EDTA, pH=7.4) at room temperature. An imidazo[1,2-*a*]quinoxaline was dissolved in DMSO as the stock solution. Then, DMSO solution of the imidazo[1,2-*a*]quinoxaline was added to the mixture of DNA and AAPH with a certain final concentration. Meanwhile, final concentrations of DNA and AAPH were kept at 2.0 mg/mL and 40.0 mM, respectively. The mixture was dispatched into test tubes with each one containing 2.0 mL. All of the

test tubes were incubated at 37°C for initiating the DNA oxidation. Three of them were taken out at every 2 hours and cooled immediately, and 1.0 mL of thiobarbituric acid (TBA, 1.00 g of TBA and 0.40 g of NaOH dissolved in 100 mL of PBS) and 1.0 mL of 3.0% trichloroacetic acid aqueous solution were added. The mixture was then heated in boiling water for 15 min and cooled to room temperature; 1.5 mL of *n*-butanol was added and shaken vigorously to extract thiobarbituric acid reactive species (TBARS) for measuring the absorbance at 535 nm. The absorbance of TBARS was plotted *vs* the reaction period (see Supporting Information).

4.6. Cyclic voltammetry.

The cyclic voltammetry (CV) was measured on a CHI 604C voltammetric analyzer with a platinum button and a wire as the working and counter electrodes, respectively, along with a saturated calomel electrode (SCE) as the reference electrode. A solution of 10 mL of CH_2Cl_2 (dehydration by CaH_2 in advance) consisting of ~1 mM corresponding compounds was scanned at the rate of 50 $mV{\cdot}s^{-1}$ with ferrocene as the internal reference and 0.1 M $(n\text{-}C_4H_9)_4NPF_6$ as the supporting electrolyte.

4.7. Statistical analysis.

All of the data were the average value from at least three independent measurements with the experimental error within 10%. Equations were analyzed by one-way ANOVA in Origin 6.0 professional Software, and $p<0.001$ indicated a significance difference.

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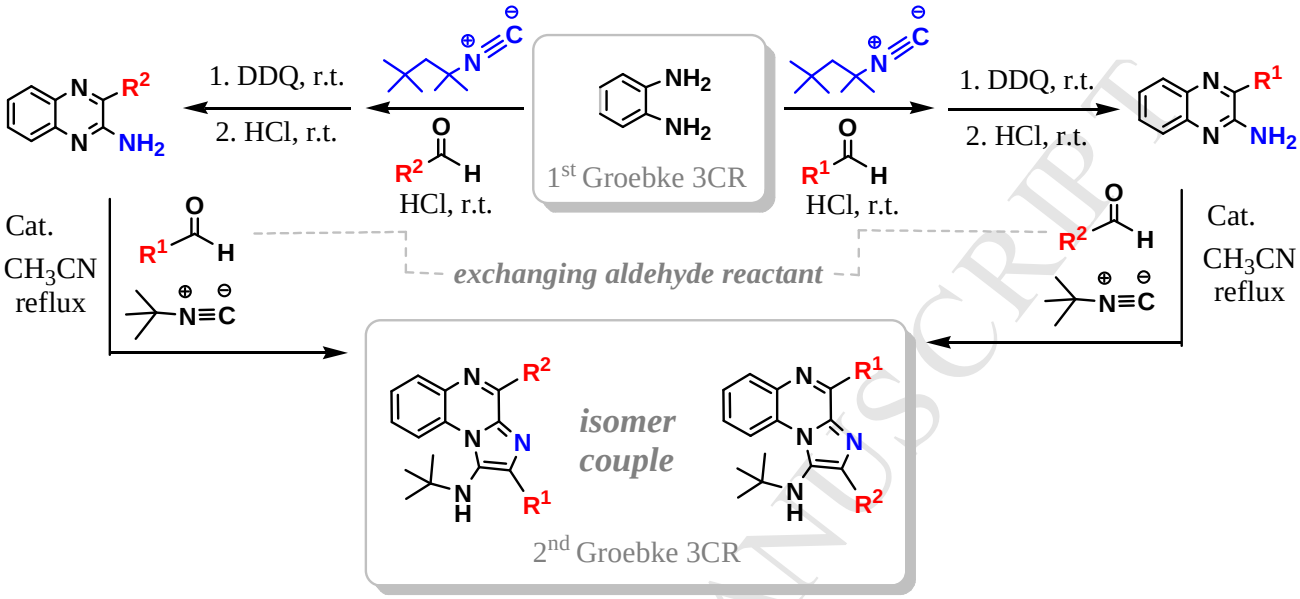
Graphic Abstract



for inhibiting DNA oxidation
for quenching radicals