Original TDAE reactivity in benzoxa- and benzothiazolone series

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Abstract
We present herein an extension of the TDAE strategy using original heterocyclic carbaldehyde as electrophiles. We also evaluate the influence of the presence of nitro group on the reactivity. The TDAE-initiated reactions of various halomethyl and *gem*-dihalomethyl derivatives with non-nitrated carbaldehyde **1** or **2** formed the expected products accompagnied by original rearranged products while the presence of a nitro group just like the carbaldehyde **21** furnished only the expected products in good yields.

Keywords: TDAE, benzoxazolone, benzothiazolone, electron transfer, rearrangement

Introduction

Since the discovery of its hypnotic properties, the 2(3*H*)-benzoxazolone ring became an important building block in medicinal chemistry and led to the discovery of a number of derivatives endowed with antiepileptic, analgesic, antiinflammatory, antispasmodic, antitubercular, antibacterial, antimicrobial, antifungal and normolipemic effects.[1-9] Moreover, 2(3*H*)-benzothiazolone, the sulfur bioisoster of 2(3*H*)-benzoxazolone, led to the synthesis of various serotonine receptor ligands.[10,11]

Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent[12] which reacts with haloalkyl derivatives to generate an anion under mild conditions *via* two sequential transfers of one electron.[13] Since 2003, we have introduced a new program directed toward the development of original synthetic methods using TDAE methodology in medicinal chemistry.[14] According to

this strategy, we have recently developed several reactions between nitrobenzylic, heterocyclic and quinonic substrates and a series of carbonyl electrophiles such as aldehydes, ketones, α-ketoesters, α-ketolactams and ketomalonates leading to the corresponding alcohol adducts.

Due to the importance of benzoxazolone building block in medicinal chemistry and in continuation of our research program directed toward the development of original synthetic methods,[14] we report herein the study of the behavior of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone carbaldehyde derivatives with various carbanions which are formed *via* the TDAE strategy.

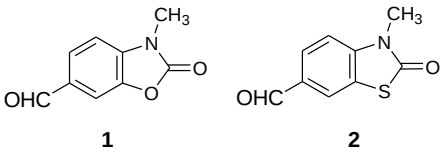


Figure 1. Structures of aldehydes **1** and **2.**

Results and Discussion

In order to explore this reactivity, we have synthesized 2,3-dihydro-3-methyl-2-oxobenzo[*d*]oxazole-6-carbaldehyde **1** and the 2,3-dihydro-3-methyl-2-oxobenzo[*d*]thiazole-6-carbaldehyde **2** (Figure 1) in one step from commercially available 3-methyl-2(3*H*)benzoxazolone and 3-methyl-2(3*H*)benzothiazolone *via* a formylation reaction using hexamethylenetetramine and polyphosphoric acid.[15,16]

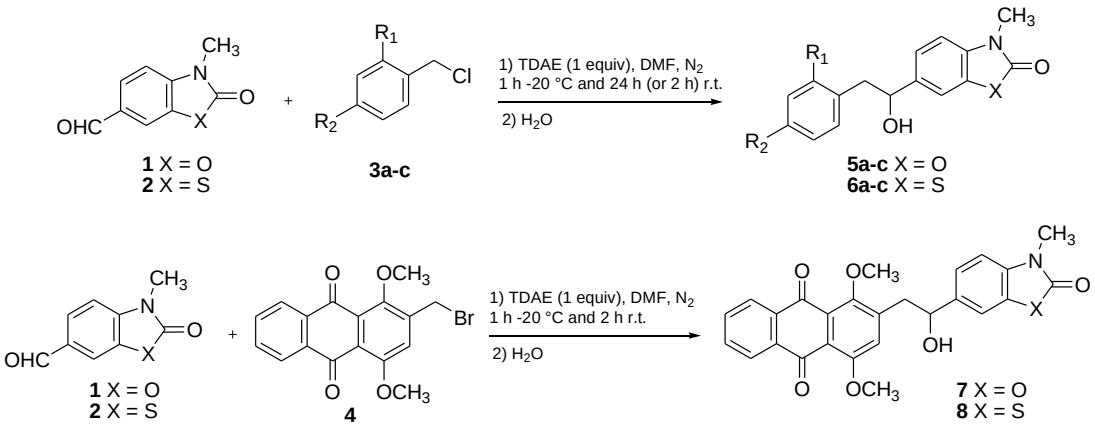


Figure 1

We used four monohalomethyl substrates (nitrobenzylic and anthraquinonic) and two *gem*-dihalomethyl ones (anthraquinonic and quinoxalinic) which are known to form anions under

TDAE strategy.[14] The first attempts concern the reactions of halomethyl derivatives **3a-c**, **4** with 3 equiv of heterocyclic aldehyde **1** or **2** in DMF and in the presence of TDAE at -20 °C for 1 h, followed by 24 h or 2 h at r.t., which furnished the corresponding alcohol derivatives **5a-c**, **6a-c**, **7**, **8** in moderate to good yields. The optimized yields are reported in Table 1.

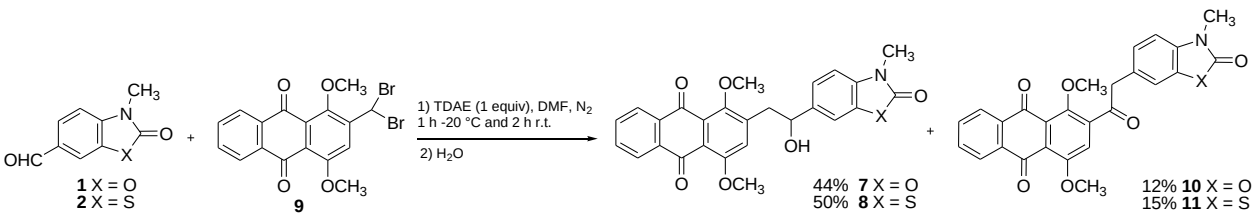
Table 1. TDAE-initiated reactions of halomethyl derivatives **3a-c** and **4** with heterocyclic aldehyde **1** or **2**[a]

	3a $R_1 = H$, $R_2 = NO_2$	**3b** $R_1 = NO_2$, $R_2 = H$	**3c** $R_1 = NO_2$, $R_2 = CH_3$	**4**
1	52% **5a**	49% **5b**	73% **5c**	64% **7**
2	61% **6a**	54% **6b**	63% **6c**	78% **8**

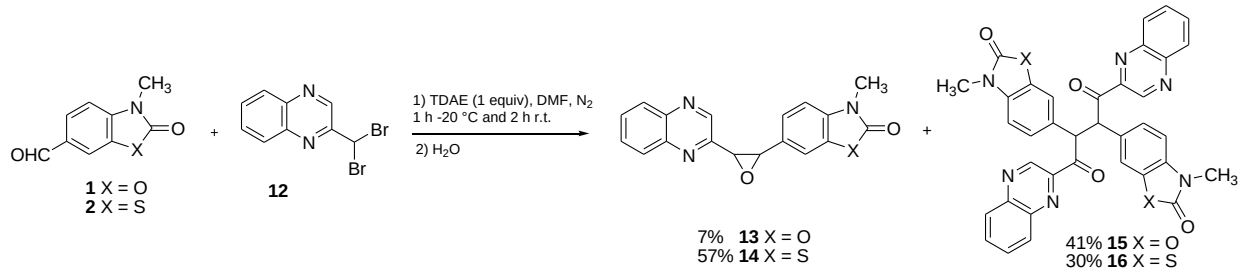
[a]All the reactions were performed using 3 equiv of aldehyde **1** or **2**, 1 equiv of halomethyl derivative **3a-c** and **4** and 1 equiv of TDAE in anhydrous DMF, 1 h at -20 °C followed by 24 h at r.t. for **3a** and **3b** or 2 h for **3c** and **4**. % All yields refer to chromatographically isolated pure products and are relative to halomethyl derivatives **3a-c** and **4**.

The reaction time at r.t. has been optimized according to the corresponding halomethyl derivatives *i.e.* 24 h for derivatives **3a** and **3b** and 2 h for derivatives **3c** and **4**. Increasing time for compounds **3c** and **4** for 24h at r.t. caused to decrease the yield of product. The reason of this phenomenon was not clear to us but maybe arose from the low stability of the corresponding carbanions.

We have continued our study by using *gem*-dibromomethyl derivatives such as 2-(dibromomethyl)-1,4-dimethoxy-anthracene-9,10-dione **9** and 2-(dibromomethyl)quinoxaline **12**. Surprisingly, the reaction of **1** or **2** with these two dibromomethyl substrates **9**, **12** under TDAE-initiated conditions produced original compounds. The reactions of **9** with **1** or **2** led to the formation of observed alcohol **7** or **8** and ketone **10** or **11**. The yield of compounds **7**, **8**, **10** and **11** were 44, 50, 12 and 15% respectively (Scheme 1). The formation of alcohol derivatives **7** and **8** may be explained by the reduction of dibromomethyl substrate **9** by the TDAE in the monobromomethyl derivative **4** which reacts under TDAE conditions with **1** or **2**. The formation of the ketone derivatives **10**-**11** could be explain by the rearrangement of the expected oxirane during the purification process.[17] Effectively, in the ^{1}H-NMR spectra of the crude product we have observed the alcohol and the signal of oxirane but after purification by column chromatography (silica gel) we have obtained these original ketone products. The position of the carbonyl group in **10** and **11**, between the two aromatic rings, has been determined after comparison of NMR spectra with those of the ketones formed by oxidation of **7** or **8**. For example, the oxidation of **7** using CrO_3/H_2SO_4 in acetone led to a new ketone with a CH_2 signal at 4.41 ppm while the CH_2 signal appears at 4.35 ppm for the ketone **10**.



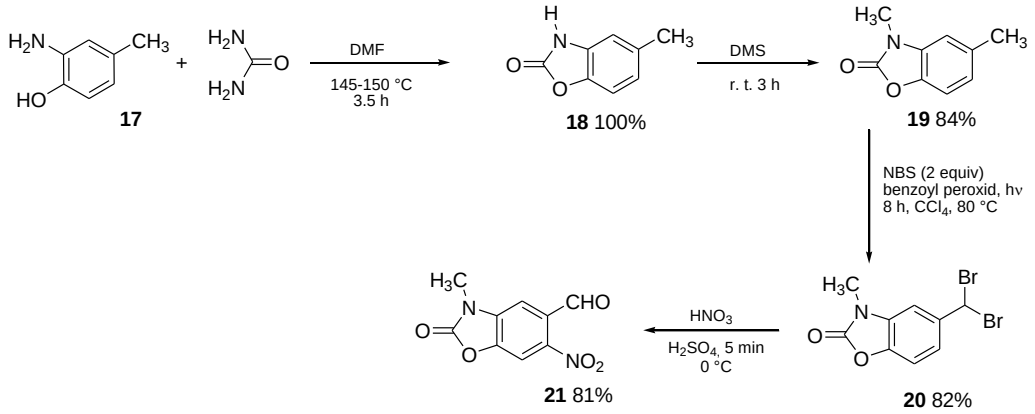
Scheme 1. TDAE-initiated reactions of dibromomethyl **9** with aldehyde **1** or **2.**



Scheme 2 TDAE-initiated reactions of dibromomethyl **12** with aldehyde **1** or **2.**

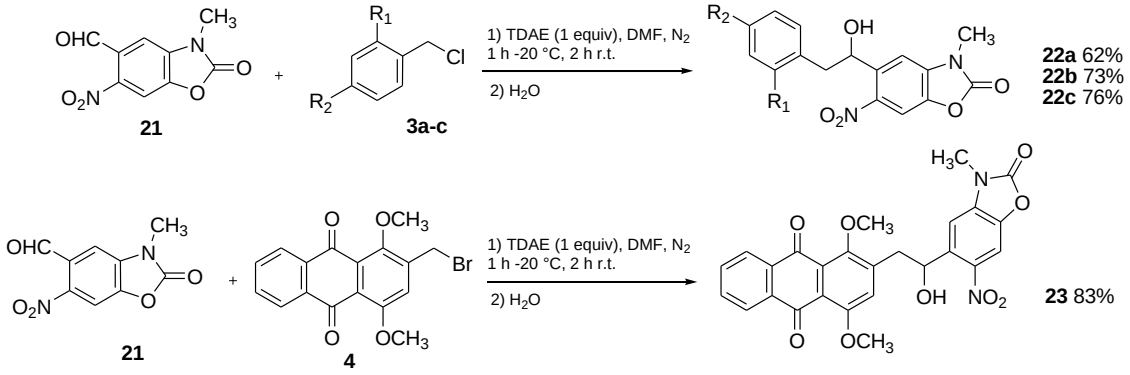
In the reaction of 2-(dibromomethyl)-quinoxaline **12** with **1** or **2**, we have observed the expected *cis-trans* mixture of oxirane **13** or **14** in respectively 7 or 57% and an original dimeric compound **15** or **16** in respectively 41 and 30% yields (Scheme 2). This difference of reactivity could be explained by a stronger unstability of oxiranes in benzoxazolone series. Formation of compounds **15** and **16** arises from the dimer of ketone analogs, this dimerization could occurs during the rearrangement of oxirane.[12e] This versatile reactivity observed with these two heterocyclic carbaldehydes could be explained by the low electrophilicity of carbonyl allowing the development of side reactions. In order to activate the carbonyl group of these heterocyclic carbaldehydes, we have used an analog of these carbaldehydes containing an electron withdrawing group such as the nitro group.

Indeed, we have prepared the 2,3-dihydro-3-methyl-6-nitro-2-oxobenzo[*d*]oxazole-5-carbaldehyde from 2-amino-4-methylphenol **17** by a procedure containing four steps (Scheme 3). The condensation of **17** with urea followed by a methylation using dimethylsulfate has furnished the 3,5-dimethylbenzo[*d*]oxazol-2(3*H*)-one **19**.[11,18] The radical bromination of **19** with 2 equiv of NBS led to the 5-(dibromomethyl)-3-methyl-benzo[*d*]oxazol-2(3*H*)-one **20** which was converted into the desired nitrocarbaldehyde **21** by action of a mixture of nitric and sulfuric acids (Scheme 3).

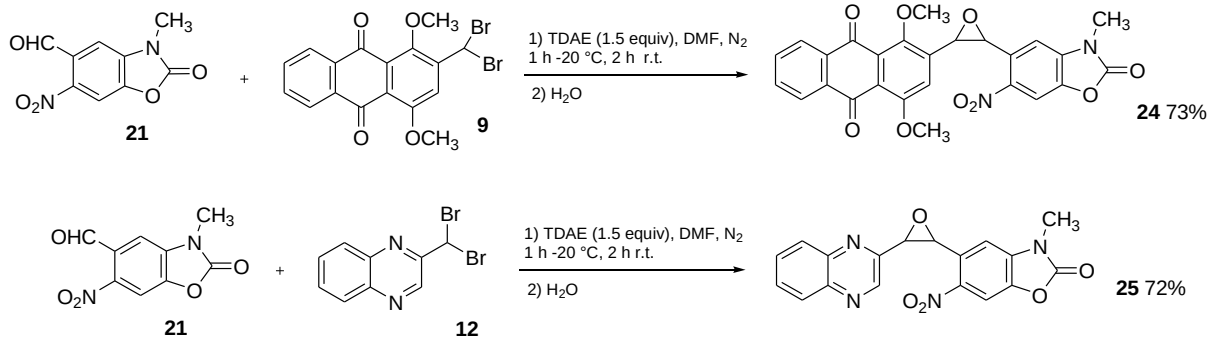


Scheme 3. Synthesis of aldehyde **21.**

The reaction of aldehyde **21** with mono- and bis-halomethyl substrates **3a-c**, **4** and **9**, **12** under TDAE-initiated conditions furnished the expected alcohols **22a-c, 23** (Scheme 4) and oxiranes **24**, **25** (Scheme 5), in good yields.



Scheme 4. TDAE-initiated reactions of halomethyl derivatives **3a-c, 4** with aldehyde **21.**



Scheme 5. TDAE-initiated reactions of dibromomethyls **9** and **12** with aldehyde **21**.

In order to optimize reaction conditions, we have studied the influence of the chloride/aldehyde/TDAE ratio and the reaction time. The best reaction conditions for the halomethyl derivatives **3a-c**, **4** have been found with 3 equiv of aldehyde **21,** 1 equiv of halomethyl derivatives **3a-c**, **4** and 1 equiv of TDAE in anhydrous DMF, 1h at -20 °C followed by 2 h at r.t. (Scheme 5). The corresponding alcohols have been isolated.

Concerning the formation of oxiranes *via* the reaction of the dibromomethyl derivatives **9**, **12** with **21** under TDAE conditions, the optimized protocol was defined with 3 equiv of aldehyde **21**, 1 equiv of dibromomethyl derivatives **9**, **12** and 1.5 equiv of TDAE in anhydrous DMF, 1h at -20 °C followed by 2 h at r.t. (Scheme 6). Only the *trans* isomers of the oxiranes **24** and **25** have been obtained in respectively 73 and 72% yields. This stereoselectivity is in agreement with the previous results in which the dibromomethyl derivative **9** furnished only the *trans* isomer of corresponding oxirane with *o*-nitro and *o*-bromo-benzaldehydes.[14g]

Conclusions

We present herein an extension of the TDAE strategy using original heterocyclic carbaldehydes with great biological interest. This method furnished two series of new benzoxazolone and benzothiazolone derivatives. This study allowed us to discover new original reactivity and to define some limits of the TDAE strategy. We have shown the importance of the electrophily of carbaldehyde to obtain classical TDAE reactivity and to limit the development of secondary reactions. Moreover, as observed in our previous studies,[14e] we have shown the unstability of some diaromatic oxiranes. In continuation of our program directed toward the preparation of new bioactive compounds as anti-infectious agents, the pharmacological evaluation of all these synthesized compounds is under active investigation in this area.

Experimental Section

General. Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the spectropole (Aix-Marseille University). Both ^{1}H and ^{13}C NMR spectra were determined on a Brucker AC 200 spectrometer. The ^{1}H chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvents peaks: $CDCl_3$ (76.9 ppm) or Me_2SO-d_6 (39.6 ppm). Absorptions are reported with the following notations: s, singulet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets. The solid-state ^{13}C NMR spectrum was obtained on a Bruker Avance-400 MHz NMR spectrometer operating at a ^{13}C resonance frequency of 106 MHz and using a commercial Bruker double-bearing probe. The following adsorbents were used for column chromatography: silica

gel 60 (Merck, particule size 0.063-0.200 mm, 70-230 mesh ASTM). TLC were performed on 5 cm x 10 cm aluminium plates coated with silica gel 60 F-254 (Merck) in an appropriate solvent.
The following materials were prepared and purified according to reported procedures: 2,3-dihydro-3-methyl-2-oxobenzo[*d*]oxazole-6-carbaldehyde **1**,[15,16] 2,3-dihydro-3-methyl-2-oxobenzo[*d*]thiazole-6-carbaldehyde **2**,[15,16] 2-(bromomethyl)-1,4-dimethoxyanthracene-9,10-dione **4**,[14g] 2-(dibromomethyl)-1,4-dimethoxyanthracene-9,10-dione **9**,[14g] 2-(dibromomethyl) quinoxaline **12**,[14d] 5-methylbenzo[*d*]oxazol-2(3*H*)-one **18**,[18] 3,5-dimethylbenzo[*d*]oxazol-2(3*H*)-one **19**.[11]

General procedure for the reaction of halomethyl or dihalomethyl derivatives (3a-c, 4, 9, 12) and carbaldehydes (1, 2) using TDAE

Into a two-necked flask equipped with a drying tube (silica gel) and a nitrogen inlet was added 10 mL of anhydrous DMF solution of halomethyl (dihalomethyl) derivative **3a-c**, **4**, **9**, **12** (1 mmol) and carbaldehyde **1, 2** (3 mmol). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (1 mmol). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at -20 °C for 1 h and then warmed up to r.t. for 24 h **3a**, **3b** or for 2 h **3c**, **4**, **9**, **12**. After this time TLC analysis (CH_2Cl_2) clearly showed that compound **3a-c**, **4**, **9**, **12** was totally consumed. The solution was filtered (to remove the octamethyl-oxamidinium dihalide) and hydrolyzed with 80 mL of H_2O. The aqueous solution was extracted with chloroform (3x40 mL), the combined organic layers washed with H_2O (2x40 mL) and dried over $MgSO_4$. Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography and recrystallization from appropriate solvent gave corresponding products.

6-[1-Hydroxy-2-(4-nitrophenyl)ethyl]-3-methylbenzo[*d*]oxazol-2(3*H*)-one (5a). Beige solid; mp 174 °C (propan-2-ol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.80 (bs, 1H, OH), 3.07 (dd, *J* = 5.9, 13.4 Hz, 1H, CH_2), 3.17 (dd, *J* = 7.2, 13.4 Hz, 1H, CH_2), 3.39 (s, 3H, N-CH_3), 4.98 (dd, *J* = 5.9, 7.2 Hz, 1H, CH), 6.88 (d, *J* = 8.1 Hz, 1H, CH), 7.07 (dd, *J* = 1.1, 8.1 Hz, 1H, CH), 7.23 (d, *J* = 1.1 Hz, 1H, CH), 7.30 (d, *J* = 8.6 Hz, 2H, CH), 8.13 (d, *J* = 8.6 Hz, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.2, 45.7, 74.7, 107.6, 107.7, 121.5, 123.5, 130.4, 131.4, 138.3, 142.8, 145.4, 146.8, 154.8. Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 60.57; H, 4.59; N, 8.71.

6-[1-Hydroxy-2-(2-nitrophenyl)ethyl]-3-methylbenzo[*d*]oxazol-2(3*H*)-one (5b). Pale yellow solid; mp 178 °C (propan-2-ol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.19 (dd, *J* = 8.4, 13.4 Hz, 1H, CH_2), 3.36 (dd, *J* = 4.1, 13.4 Hz, 1H, CH_2), 3.40 (s, 3H, N-CH_3), 5.08 (dd, *J* = 4.1, 8.4 Hz, 1H, CH), 6.92 (d, *J* = 8.0 Hz, 1H, CH), 7.20-7.24 (m, 1H, CH), 7.28 (d, *J* = 1.3 Hz, 1H, CH), 7.30-7.34 (m, 1H, CH), 7.38-7.44 (m, 1H, CH), 7.52-7.56 (m, 1H, CH), 7.95 (dd, *J* = 1.3, 8.0 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.2, 43.2, 73.9, 107.5, 107.8, 121.3, 124.9, 127.9, 131.2, 132.8, 132.9, 133.6, 139.0, 142.8, 149.8, 154.9. Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.04; H, 4.54; N, 8.53.

6-[1-Hydroxy-2-(4-methyl-2-nitrophenyl)ethyl]-3-methylbenzo[*d*]oxazol-2(3*H*)-one (5c). Pale green solid; mp 222 °C (propan-2-ol). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.36 (s, 3H, CH_3), 3.12-3.16 (m, 2H, CH_2), 3.32 (s, 3H, CH_3), 4.73-4.82 (m, 1H, CH), 5.46 (d, *J* = 4.8 Hz, 1H, OH), 7.15-7.17 (m, 2H, CH), 7.21-7.29 (m, 3H, CH), 7.79 (d, *J* = 8.0 Hz, 1H, CH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 21.3, 28.5, 42.6, 73.0, 107.3, 109.0, 121.7, 124.9, 128.6, 131.1, 133.8, 134.3, 140.6, 142.4, 144.0, 148.1, 154.8. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.11; H, 5.08; N, 8.43.

6-[1-Hydroxy-2-(4-nitrophenyl)ethyl]-3-methylbenzo[*d*]thiazol-2(3*H*)-one (6a). Yellow solid; mp 201 °C (propan-2-ol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.74 (bs, 1H, OH), 3.11-3.17 (m, 2H, CH_2), 3.44 (s, 3H, N-CH_3), 4.97 (m, 1H, CH), 6.95 (d, *J* = 8.3 Hz, 1H, CH), 7.19 (d, *J* = 8.3 Hz, 1H, CH), 7.29 (d, *J* = 8.1 Hz, 2H, CH), 7.43 (s, 1H, CH), 8.11 (d, *J* = 8.1 Hz, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.1, 45.6, 74.5, 110.3, 120.0, 123.1, 123.6, 124.2, 130.4, 137.5, 138.6, 145.5, 146.9, 169.9. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_2O_4S$: 331.0747; Found: 331.0756.

6-[1-Hydroxy-2-(2-nitrophenyl)ethyl]-3-methylbenzo[*d*]thiazol-2(3*H*)-one (6b). Brown solid; mp 157 °C (propan-2-ol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.18 (dd, *J* = 8.7, 13.5 Hz, 1H, CH_2), 3.36 (dd, *J* = 3.9, 13.5 Hz, 1H, CH_2), 3.42 (s, 3H, N-CH_3), 5.06 (dd, *J* = 3.9, 8.7 Hz, 1H, CH), 6.99 (d, *J* = 8.2 Hz,1H, CH), 7.31-7.38 (m, 2H, CH), 7.40-7.45 (m, 1H, CH), 7.48-7.57 (m, 2H, CH), 7.95 (dd, *J* = 1.4, 8.2 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.1, 43.1, 73.7, 110.2, 119.8, 122.8, 124.0, 124.8, 127.8, 132.8, 133.1, 133.6, 137.2, 139.4, 149.7, 170.1. Anal. Calcd for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48; S, 9.71. Found: C, 57.66; H, 4.34; N, 8.16; S, 9.10.

6-[1-Hydroxy-2-(4-methyl-2-nitrophenyl)ethyl]-3-methylbenzo[*d*]thiazol-2(3*H*)-one (6c). Brown solid; mp 203 °C (propan-2-ol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.61 (bs, 1H, OH), 2.41 (s, 3H, CH_3), 3.11 (dd, *J* = 9.1, 13.5 Hz, 1H, CH_2), 3.41 (dd, *J* = 3.5, 13.5 Hz, 1H, CH_2), 3.46 (s, 3H, N-CH_3), 5.07 (dd, *J* = 3.5, 9.1 Hz, 1H, CH), 7.03 (d, *J* = 8.3 Hz, 1H, CH), 7.16 (m, 1H, CH), 7.21 (d, *J* = 8.3 Hz, 1H, CH), 7.40 (dd, *J* = 1.5, 8.3 Hz, 1H, CH), 7.53 (d, *J* = 1.5 Hz, 1H, CH),7.93 (d, *J* = 8,3 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4, 29.1, 43.5, 73.8, 110.2, 119.8, 122.8, 123.9, 125.2, 128.5, 133.3, 134.1, 137.2, 139.5, 144.2, 147.3, 170.1. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_4S$: 345.0904; Found: 345.0904.

2-[2-Hydroxy-2-(3-methyl-2-oxo-2,3-dihydro-benzo[*d*]oxazol-6-yl)ethyl]-1,4-dimethoxy-anthracene-9,10-dione (7). Yellow solid; mp 240 °C (propan-2-ol). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.03 (dd, *J* = 11.4, 12.5 Hz, 1H, CH), 3.10 (dd, *J* = 6.2, 12.5 Hz, 1H, CH), 3.29 (s, 3H, N-CH_3), 3.78 (s, 3H, O-CH_3), 3.84 (s, 3H, O-CH_3), 4.96 (dd, *J* = 6.2, 11.4 Hz, 1H, CH), 5.50 (d, *J* = 4.7 Hz, 1H, OH), 7.19 (s, 1H, CH), 7.40 (m, 2H, CH), 7.81-7.85 (m, 2H, CH), 8.00-8.09 (m, 2H, CH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 28.2, 40.8, 56.6, 61.8, 72.2, 107.2, 108.5, 120.5, 121.5, 122.5, 126.0, 126.1, 126.4, 130.8, 133.5, 133.6, 133.9, 134.0, 140.5, 142.1, 143.1, 152.3, 154.3, 155.6, 181.7, 182.7. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{22}NO_7$: 460.1391; Found: 460.1395.

2-[2-Hydroxy-2-(3-methyl-2-oxo-2,3-dihydro-benzo[*d*]thiazol-6-yl)ethyl]-1,4-dimethoxy-anthracene-9,10-dione (8). Yellow solid; mp 221 °C (ethanol/propan-2-ol; 5/5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.87 (bs, 1H, OH), 3.07 (dd, *J* = 8.1, 13.4 Hz, 1H, CH_2), 3.25 (dd, *J* = 4.4, 13.4 Hz, 1H, CH_2), 3.43 (s, 3H, N-CH_3), 3.92 (s, 6H, 2×O-CH_3), 5.07 (dd, *J* = 4.4, 8.1 Hz, 1H, CH), 6.95 (d, *J* = 8.1 Hz, 1H, CH), 7.10 (s, 1H, CH), 7.25 (d, *J* = 8.1 Hz, 1H, CH), 7.50 (s, 1H, CH), 7.70-7.75 (m, 2H, CH), 8.14-8.18 (m, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.1, 41.5, 56.7, 62.1, 73.6, 110.2, 119.8, 121.8, 122.9, 124.1, 126.4, 126.5, 127.6, 133.3, 133.7, 133.8, 134.3, 137.2, 138.6, 139.4, 141.6, 152.5, 156.2, 169.3, 182.8, 183.4. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{22}NO_6S$: 476.1162; Found: 476.1172.

1,4-Dimethoxy-2-[2-(3-methyl-2-oxo-2,3-dihydro-benzo[*d*]oxazol-6-yl)-2-oxo-ethyl]anthracene-9,10-dione (10). Orange solid; mp 189 °C (ethanol/propan-2-ol, 5/5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.39 (s, 3H, N-CH_3), 3.93 (s, 3H, O-CH_3), 3.99 (s, 3H, O-CH_3), 4.35 (s, 2H, CH_2), 6.90 (d, *J* = 8.1 Hz, 1H, CH), 7.09 (d, *J* = 8.1 Hz, 1H, CH), 7.15 (s, 1H, CH), 7.32 (s, 1H, CH), 7.74-7.79 (m, 2H, CH), 8.16-8.22 (m, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.6, 49.5, 57.0, 63.8, 108.0, 111.4, 118.5, 119.5, 124.8, 125.3, 126.5, 126.7, 128.2, 130.9, 133.6, 133.7, 134.0, 134.2, 141.6, 142.8, 156.4, 182.5, 182.9, 200.6. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{20}NO_7$: 458.1234; Found: 458.1231.

1,4-Dimethoxy-2-[2-(3-methyl-2-oxo-2,3-dihydro-benzo[*d*]thiazol-6-yl)-2-oxo-ethyl]anthracene-9,10-dione (11). Orange solid; mp 162 °C (ethanol/propan-2-ol; 5/5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.44 (s, 3H, N-CH_3), 3.93 (s, 3H, O-CH_3), 3.98 (s, 3H, O-CH_3), 4.35 (s, 2H, CH_2), 6.99 (d, *J* = 8.3 Hz, 1H, CH), 7.23 (dd, *J* = 1.7, 8.3 Hz, 1H, CH), 7.32 (s, 1H, CH), 7.36 (d, *J* = 1.7 Hz, 1H, CH), 7.74-7.79 (m, 2H, CH), 8.16-8.22 (m, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.0, 49.2, 56.9, 63.8, 110.5, 118.6, 123.1, 123.7, 126.6, 126.8, 127.9, 128.6, 128.7, 133.6, 133.7, 134.0, 134.2, 137.0, 141.6, 151.9, 156.4, 169.9, 178.7, 182.5, 182.9, 200.6. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{20}NO_6S$: 474.1006; Found: 474.1005.

3-Methyl-6-[3-(quinoxalin-2-yl)oxiran-2-yl]benzo[*d*]thiazol-2(3*H*)-one (14). *trans*-Isomer. Pale brown solid; mp 147 °C (ethanol/propan-2-ol; 5/5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.48 (s, 3H, N-CH_3), 4.27-4.29 (m, 2H, 2×CH), 7.06 (d, *J* = 8.3 Hz, 1H, CH), 7.37 (dd, *J* = 1.5, 8.3 Hz, 1H, CH), 7.47 (d, *J* = 1.5 Hz, 1H, CH), 7.78-7.83 (m, 2H, CH), 8.07-8.17 (m, 2H, CH), 8.87 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.2, 61.6; 62.0, 110.5, 119.8, 123.3, 124.2, 129.1, 129.4, 130.2, 130.7, 131.2, 138.2, 141.8, 142.2, 142.6, 150.8, 169.8. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}N_3O_2S$: 336.0801; Found: 336.0802.

***cis*-Isomer.** Pale brown solid; mp 170 °C (ethanol/propan-2-ol; 5/5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.33 (s, 3H, N-CH_3), 4.61 (d, *J* = 4.3 Hz, 1H, CH), 4.65 (d, *J* = 4.3 Hz, 1H, CH), 6.83 (d, *J* = 8.3 Hz, 1H, CH), 7.27 (dd, *J* = 1.5, 8.3 Hz, 1H, CH), 7.43 (d, *J* = 1.5 Hz, 1H, CH), 7.70-7.78 (m, 2H, CH), 7.97-8.05 (m, 2H, CH), 8.62 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.0, 59.2, 59.5, 110.1, 120.9, 122.8, 124.8, 128.3, 128.8, 129.3, 130.0, 130.4, 137.5, 141.5, 141.9, 142.9, 149.6, 169.7. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}N_3O_2S$: 336.0801; Found: 336.0803.

2,3-Bis(2,3-dihydro-3-methyl-2-oxo-benzo[*d*]oxazol-6-yl)-1,4-di(quinoxalin-2-yl)butane-1,4-dione (15). Yellow solid; mp 292 °C (ethanol/propan-2-ol, 5/5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.28 (s, 6H, N-CH_3), 6.36 (s, 2H, CH), 6.77 (d, *J* = 8.4 Hz, 2H, CH), 7.24-7.27 (m, 4H, CH), 7.86-7.91 (m, 4H, CH), 8.11-8.16 (m, 2H, CH), 8.23-8.28 (m, 2H, CH), 9.41 (s, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.1, 55.2, 108.1, 111.4, 124.7, 129.2, 130.1, 130.6, 131.0, 131.1, 132.7, 141.0, 142.7, 143.3, 143.5, 145.2, 154.4, 199.1. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{25}N_6O_6$: 637.1830; Found: 637.1838.

2,3-Bis(2,3-dihydro-3-methyl-2-oxo-benzo[*d*]thiazol-6-yl)-1,4-di(quinoxalin-2-yl)butane-1,4-dione (16). Yellow pale solid; mp 294 °C (ethanol/propan-2-ol, 5/5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.32 (s, 6H, N-CH_3), 6.39 (s, 2H, CH), 6.84 (d, *J* = 8.3 Hz, 2H, CH), 7.34 (dd, *J* = 1.7, 8.3 Hz, 2H, CH), 7.49 (d, *J* = 1.7 Hz, 2H, CH), 7.86-7.94 (m, 4H, CH), 8.12-8.17 (m, 2H, CH), 8.24-8.29 (m, 2H, CH), 9.42 (s, 2H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.0, 54.9, 110.6, 123.1, 123.2, 127.9, 129.4, 130.5, 130.6, 130.8, 132.6, 137.1, 141.0, 143.6, 143.8, 145.2, 169.7, 199.4. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{25}N_6O_4S_2$: 669.1373; Found: 669.1347.

5-(Dibromomethyl)-3-methylbenzo[*d*]oxazol-2(3*H*)-one (20). To a solution of 3,5-dimethylbenzo[*d*]oxazol-2(3*H*)-one **19** (1 g, 6.13 mmol, 1 eq) in CCl_4 (125 mL) was added NBS (2.18 g, 12.25 mmol, 2 equiv) followed by benzoylperoxide in catalytic quantity, the mixture was gradually heated to reflux for 9 h and cooled to r.t. The succinimide was filtered off and the filtrate was concentrated under reduced pressure. 1.61 g (82%) of **20** was isolated by crystallization from propan-2-ol. Beige crystals; mp 165 °C (propan-2-ol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.46 (s, 3H, N-CH_3), 6.68 (s, 1H, CH), 7.12 (d, *J* = 8.2 Hz, 1H, CH), 7.24 (dd, *J* = 1.7, 8.2 Hz, 1H, Ar-H), 7.31 (d, *J* = 1.7 Hz, 1H, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3, 40.0, 107.2, 109.2, 120.3, 132.3, 138.3, 143.3, 154.5. Anal. Calcd for $C_9H_7Br_2NO_2$: C, 33.68; H, 2.20; N, 4.36. Found: C, 33.99; H, 2.21; N, 4.34.

2,3-Dihydro-3-methyl-6-nitro-2-oxobenzo[*d*]oxazole-5-carbaldehyde (21). To concentrated H_2SO_4 (7 mL) was added, with stirring, 5-(dibromomethyl)-3-methylbenzo[*d*]oxazol-2(3*H*)-one **20** (1g, 3.11 mmol, 1 eq). The mixture was cooled to 0 °C in an ice bath and to the cold stirred solution was added fuming HNO_3 (0.26 mL). After 5 min, the solution was poured into ice and a light yellow precipitate appeared. The solid was filtered and recrystallized (propan-2-ol) to give 1.11 g (81%) of 2,3-dihydro-3-methyl-6-nitro-2-oxobenzo[*d*]oxazole-5-carbaldehyde **21**. Pale green needels; mp 161 °C (propan-2-ol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.53 (s, 3H, N-CH_3), 7.53 (s, 1H, CH), 8.01 (s, 1H, CH), 10.45 (s, 1H, CHO). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.8, 106.9, 107.7, 129.5, 136.5, 144.6, 153.6, 181.8, 187.0. Anal. Calcd for $C_9H_6N_2O_5$: C, 48.66; H, 2.72; N, 12.61. Found: C, 48.65; H, 2.71; N, 12.25.

General procedure for the reaction of halomethyl or dihalomethyl derivatives (3a-c, 4, 9, 12) and carbaldehydes 21 using TDAE

Into a two-necked flask equipped with a drying tube (silica gel) and a nitrogen inlet was added 10 mL of anhydrous DMF solution of halomethyl (dihalomethyl) derivatives **3a-c**, **4**, **9**, **12** (1 mmol) and carbaldehyde **21** (3 mmol). The solution was stirred and maintained at this

temperature for 30 min and then was added dropwise (via a syringe) the TDAE (1 mmol for reaction with **3a-c**, **4** or 1.5 mmol for **9**, **12**). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at -20 °C for 1 h and then warmed up to r.t. for 2 h. After this time TLC analysis (CH_2Cl_2) clearly showed that compound **3a-c**, **4**, **9**, **12** was totally consumed. The solution was filtered (to remove the octamethyl-oxamidinium dihalide) and hydrolyzed with 80 mL of H_2O. The aqueous solution was extracted with chloroform (3x40 mL), the combined organic layers washed with H_2O (2x40 mL) and dried over $MgSO_4$. Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography and recrystallization from appropriate solvent gave corresponding products.

5-[1-Hydroxy-2-(4-nitrophenyl)ethyl]-3-methyl-6-nitrobenzo[*d*]oxazol-2(3*H*)-one (22a). Pale pink solid; mp 231 °C (ethanol). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.94 (dd, *J* = 9.0, 13.5 Hz, 1H, CH_2), 3.15 (dd, *J* = 2.4, 13.5 Hz, 1H, CH_2), 3.41 (s, 3H, N-CH_3), 5.37 (dd, *J* = 2.4, 9.0 Hz, 1H, CH), 5.86 (bs, 1H, OH), 7.55 (d, *J* = 8.7 Hz, 2H, CH), 7.66 (s, 1H, CH), 8.09 (s, 1H, CH), 8.20 (d, *J* = 8.7 Hz, 2H, CH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 28.7, 44.7, 69.2, 106.3, 107.6, 123.4, 130.8, 136.8, 139.7, 140.5, 141.3, 146.4, 147.5, 154.4. Anal. Calcd for $C_{16}H_{13}N_3O_7$: C, 53.49; H, 3.65; N, 11.70. Found: C, 53.49; H, 3.59; N, 11.51.

5-[1-Hydroxy-2-(2-nitrophenyl)ethyl]-3-methyl-6-nitrobenzo[*d*]oxazol-2(3*H*)-one (22b). Yellowish brown solid, mp 216 °C (ethanol). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.18 (dd, *J* = 3.8, 13.7 Hz, 1H, CH_2), 3.40 (s, 3H, CH_3), 3.41 (dd, *J* = 8.4, 13.7 Hz, 1H, CH_2), 5.36 (dd, *J* = 3.8, 8.4 Hz, 1H, CH), 5.88 (d, *J* = 4.6 Hz, 1H, OH), 7.45-7.52 (m, 3H, CH), 7.61-7.68 (m, 1H, CH), 7.86-8.89 (m, 1H, CH), 8.04 (s, 1H, CH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 28.7, 40.2, 68.5, 106.2, 107.5, 124.2, 128.0, 132.5, 132.7, 132.9, 136.6, 139.0, 140.5, 141.6, 150.6, 154.3. Anal. Calcd for $C_{16}H_{13}N_3O_7$: C, 53.49; H, 3.65; N, 11.70. Found: C, 53.44; H, 3.65; N, 11.45.

5-[1-Hydroxy-2-(4-methyl-2-nitrophenyl)ethyl]-3-methyl-6-nitrobenzo[*d*]oxazol-2(3*H*)-one (22c). Pale green solid; mp 244 °C(ethanol). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.37 (s, 3H, CH_3), 3.14 (dd, *J* = 3.8, 13.5 Hz, 1H, CH_2), 3.40 (s, 3H, N-CH_3), 3.42 (dd, *J* = 8.5, 13.5 Hz, 1H, CH_2), 5.36 (dd, *J* = 3.8, 8.5 Hz, 1H, CH), 5.84 (d, *J* = 4.3 Hz, 1H, OH), 7.27 (s, 1H, CH), 7.30 (d, *J* = 8.8 Hz, 1H, CH), 7.50 (s, 1H, CH), 7.78 (d, *J* = 8.8 Hz, 1H, CH), 8.03 (s, 1H, CH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 21.1, 28.6, 40.5, 68.4, 106.1, 107.5, 124.5, 128.3, 132.7, 133.1, 136.6, 139.0, 140.5, 141.6, 143.5, 148.3, 154.3. Anal. Calcd for $C_{17}H_{15}N_3O_7$: C, 54.69; H, 4.05; N, 11.26. Found: C, 54.43; H, 4.03; N, 10.99.

2-[2-Hydroxy-2-(3-methyl-6-nitro-2-oxo-2,3-dihydro-benzo[*d*]oxazol-5-yl)ethyl]-1,4-di-methoxyanthracene-9,10-dione (23). Pale brown solid, mp 242 °C (ethanol/propan-2-ol, 5/5). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.08-3.12 (m, 2H, CH_2), 3.42 (s, 3H, CH_3), 3.78 (s, 3H, O-CH_3), 3.88 (s, 3H, OCH_3), 5.54 (m, 1H, CH), 5.88 (bs, 1H, OH), 7.49 (s, 1H, CH), 7.69 (s, 1H, CH), 7.82-7.87 (m, 2H, CH), 8.01-8.09 (m, 3H, CH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 28.7, 40.9, 56.7, 61.8, 67.7, 106.0, 107.7, 120.8, 122.3, 126.0, 126.1, 126.5, 133.6, 134.1, 136.5, 139.0, 140.4, 141.8, 142.5, 152.6, 154.3, 155.6, 181.7, 182.7. Anal. Calcd for $C_{26}H_{20}N_2O_9$: C, 61.91; H, 4.00; N, 5.55. Found: C, 61.27; H, 4.10; N, 5.51.

***trans*-2-[3-(2,3-Dihydro-3-methyl-6-nitro-2-oxo-benzo[*d*]oxazol-5-yl)oxiran-2-yl]-1,4-dimethoxy-anthracene-9,10-dione (24).** Yellow solid; mp 253 °C (ethanol/propan-2-ol, 5/5). ^{1}H RMN (400 MHz, DMSO-d_6): δ = 3.46 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.37 (d, *J* = 2.0, 1H, CH), 4.84 (d, *J* = 2.0, 1H, CH), 7.40 (s, 1H, CH), 7.47 (s, 1H, CH), 7.76-7.95 (m, 2H, CH), 7.99-8.11 (m, 2H, CH), 8.30 (s, 1H, CH). Solid-state ^{13}C NMR (100MHz): δ = 27.5, 55.4, 59.5, 60.3, 60.4, 106.0, 108.8, 114.5, 121.3, 124.0, 127.3, 128.0, 132.4, 132.5, 134.5, 134.6, 139.1, 139.2, 141.6, 143.5, 153.1, 155.8, 157.1, 157.2, 180.9, 183.3. HRMS (EI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{19}N_2O_9$: 503.1085; Found: 503.1086.

***trans*-3-Methyl-6-nitro-5-[3-(quinoxalin-2-yl)oxiran-2-yl]benzo[*d*]oxazol-2(3*H*)-one (25).** Beige solid, mp 195 °C (propan-2-ol). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.46 (s, 3H, NCH_3), 3.41 (d, *J* = 1.6 Hz, 1H, CH), 5.17 (d, *J* = 1.6 Hz, 1H, CH), 7.51 (s, 1H, CH), 7.90-7.95 (m, 2H, CH), 8.11-8.20 (m, 2H, CH), 8.29 (s, 1H, CH), 9.07 (s, 1H, CH). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 28.8, 59.7, 60.2, 106.5, 107.1, 129.1, 129.3, 130.8, 131.2, 131.3, 137.6, 141.2, 141.3, 141.9, 142.1, 143.7, 151.0, 154.3. Anal. Calcd for $C_{18}H_{12}N_4O_5$: C, 59.34; H, 3.32; N, 15.38. Found: C, 59.33; H, 3.62; N, 14.64.

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