Synthesis of α-Phenyl β-Enamino γ-Sultims: the New Horizon of the CSIC Reaction

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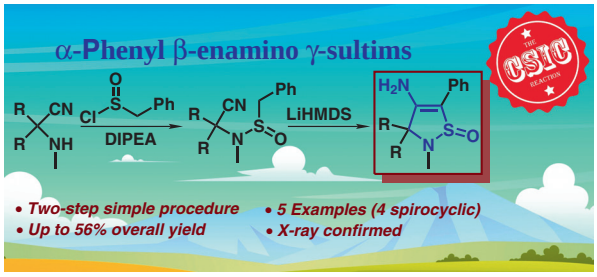

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Abstract Herein, we report the novel strategy for the synthesis of 4-enamino-5-phenyl-2,3-dihydroisothiazole 1-oxides (in other words α-phenyl β-enamino γ-sultims) based on the CSIC reaction. Particularly, readily available α-amino nitriles (the Strecker products) reacted with benzyl sulfinyl chloride to give the corresponding sulfinamides, which upon treatment with excess of LiHMDS converted into the target α-phenyl β-enamino γ-sultims. The method works well and tolerates strained 3- and 4-membered spirocyclic substituents. A preliminary *in silico* study indicated that the γ-sultim scaffold can be considered a promising pharmacophore template.

Key words sulfinamides, enamines, sultims, CSIC reaction, cyclization

The application of novel and uncommon structural motifs in lead-oriented synthesis[1] opens up new avenues for the development of innovative pharmaceuticals. The unique structural frameworks allow the creation of new chemical entities (NCE) for tackling previously intractable diseases and drug-resistant pathogens. In this regard, sulfinamides[2] and their cyclic congeners, regarded as a separate class, *sultims*,[3] can be considered as chiral bioisosteres of carboxamides and lactams, respectively.[4]

Despite γ-sultims having been known since the early 1920s,[5] they have triggered attention as novel pharmacological templates only in the last decades. This is especially indicative for (en)amino derivatives. The antibacterial candidate[6] and gastric secretion inhibitors[7] may serve as examples (Figure 1).

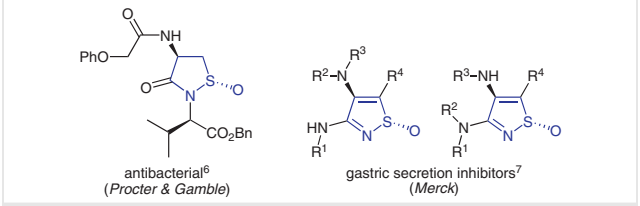
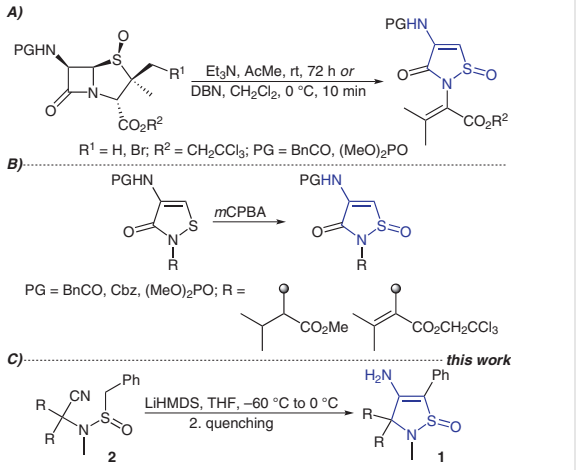


Figure 1 Biologically active β-(en)amino γ-sultims

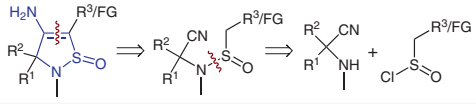
Surprisingly, only two approaches to the construction of β-enamino γ-sultim framework have been reported to date. The first one is underlain on the base-mediated rearrangement of penicillin sulfoxides (Scheme 1, A).[8a,b] However, this strategy appeared synthetically useless since it provided the complex mixture of product so that the desired sultims were isolated in low yields through the tedious purification procedures. The second approach looked more reliable in that it implied the oxidation of the appropriately substituted isothiazolones with *m*CPBA (Scheme 1, B).[8] With that, neither general procedures for both approaches nor isolated yields of pure products have been provided.



Scheme 1 Synthetic approaches toward β-enamino γ-sultims

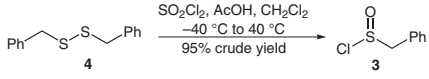
The present work is devoted to the synthesis of α-phenyl β-enamino γ-sultims through the LiHMDS-mediated cyclization of *N*-sulfinylated α-amino nitriles (Scheme 1, C).

While syntheses for sultams (cyclic sulfonamides) are relatively common,[9] sultims still have remained an underrepresented class that can be accessed through the quite limited set of synthetic strategies.[3,10] Recently we have described the synthesis of differently substituted/functionalized β-enamino γ-sultams[11] through the carbanion-mediated sulfonate (or sulfonamide) intermolecular coupling and intramolecular cyclization (CSIC) reaction.[12] Inspired by this, we assumed that the logic inherent in the above synthetic strategy can be extended to access similarly substituted/functionalized β-enamino γ-sultims. In turn, the direct precursors for the sulfa-Thorpe cyclization can be prepared by the simple sulfinylation of readily available *N*-monosubstituted α-amino nitriles, the Strecker products (Scheme 2).



Scheme 2 Retrosynthetic disconnection for the assembly of α-phenyl β-enamino γ-sultims

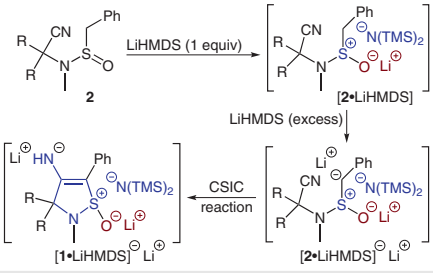
We initiated our study with the synthesis of the model sulfinylation agent – benzyl sulfinyl chloride (**3**) adopting the literature method on the oxidation of 1,2-dibenzyldisulfane (**4**) with $SOCl_2$ (Scheme 3).[13,14] It should be taken into account that the residual amount of both SO_2Cl_2 and $SOCl_2$ led to a significant loss of yield on the next sulfinylation step. Therefore, it is quite important to rid sulfinyl chloride **3** of these impurities as thoroughly as possible.



Scheme 3 Synthesis of benzyl sulfinyl chloride (**3**)

With the freshly prepared benzyl sulfinyl chloride (**3**) in hand, a set of α-amino nitriles **5** was involved in the sulfinylation step, and the corresponding linear sulfinamides **2** were isolated in fair to good yields (Table 1).[15,16] It should be noted that the crude product can be used in the next step so that up to 20% of impurities are permissible. The overall yields of the target γ-sultims (starting from **5a–c**) were comparable to those when purified precursors **2a–e** were involved in the final cyclization step.

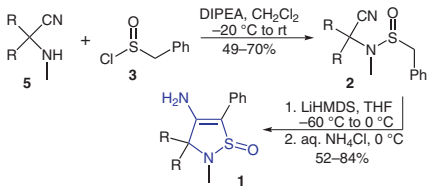
Next, we set out to optimize the reaction conditions for the cyclization step. Initially, we faced synthetically unacceptable yields (not exceeding 10%) when using slight excess (up to 15%) of LiHMDS. After extensive exploration, conditions utilizing 4.5 equivalents of LiHMDS resulted in a dramatic improvement in the yield of the target α-phenyl β-enamino γ-sultims **1** (Table 1). Presumably, this arises from the zwitterionic form of the S=O double bond, which forms a 1:1 complex with LiHDMS, in this way precluding the abstraction of the proton from the $(S{=}O)CH_2Ph$ fragment. Therefore, extra equivalents of the base are required to move the equilibrium reaction towards the formation of the carbanion. It should be also taken into account that a stoichiometric amount of LiHMDS remains coordinated with the sulfinyl group even after the cyclization reaction has taken place (Scheme 4).

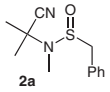
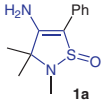
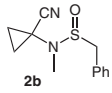
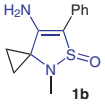
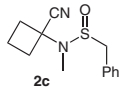
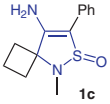
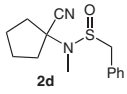
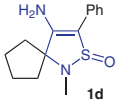
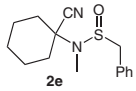
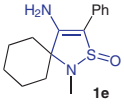


Scheme 4 Coordination of LiHDMS with the sulfinyl group of the precursor **2**, intermediate carbanion, and the target β-enamino γ-sultim **1**

These optimized reaction conditions allowed us to convert sulfinamide precursors **2** into the desired α-phenyl β-enamino γ-sultims **1** with synthetically valuable yields (Table 1).[17,18] It transpired that the nature of the substituent in the α-position of amino nitriles **5** had some impact on the yield of both the linear sulfinamides **2** and target products. Thus, sultims **1b**,**c** possessing strained 3- and 4-membered spirocyclic substituents were isolated in lower yields than their unstrained counterparts **1a**,**d**,**e** (Table 1).

Table 1 Synthesis of α-Phenyl β-Enamino γ-Sultims **1**



Entry	Starting α-amino nitrile **5**	*N*-sulfinylated α-amino nitrile **2**	Yield (%)	β-Enamino γ-sultim **1**	Yield (%)
1	 **5a**	 **2a**	70	 **1a**	80
2	 **5b**	 **2b**	49	 **1b**	52
3	 **5c**	 **2c**	55	 **1c**	65
4	 **5d**	 **2d**	53	 **1d**	73
5	 **5e**	 **2e**	62	 **1e**	84

The presence of the sulfur(IV) atom endowed precursors **2** and β-enamino γ-sultims **1** with chirality and caused a chemical anisotropy shift of the signals of the (spiro)alkyl substituent in NMR spectra (attributable to deshielding effect by S=O and to shielding one by the lone pair). For instance, two methyl groups in the 3rd position of sultim **1a** exhibited a moderate chemical anisotropy shift both in ^{1}H ($\Delta\delta$ = 0.22 ppm) and ^{13}C ($\Delta\delta$ = 2.9 ppm) NMR spectra.

The structure of β-enamino γ-sultim **1c** was established unambiguously by the X-ray crystal structure analysis (Figure 2).[19]

To further demonstrate the potential utility of β-enamino γ-sultim scaffold we estimated their probable biological activity resorting to *in silico* methods. To accomplish this, molecular docking of sultim **1c** into the aldehyde dehydrogenase ALDH1A1 (pdb id: 5L2M) active site was performed. The docking grid was established centered on the co-crystallized ligand (BUC11).[20] The obtained results showed that **1c** has predicted affinity to ALDH1A1 (Figure 3). The recent studies showed that ALDH1A1 inhibitors acted as the tumor suppressors in certain cancers and therefore ALDH1A1-targeted therapy has become widespread in cancer treatment.[21] Apart from that, ALDH1A1 downregulation in reti-

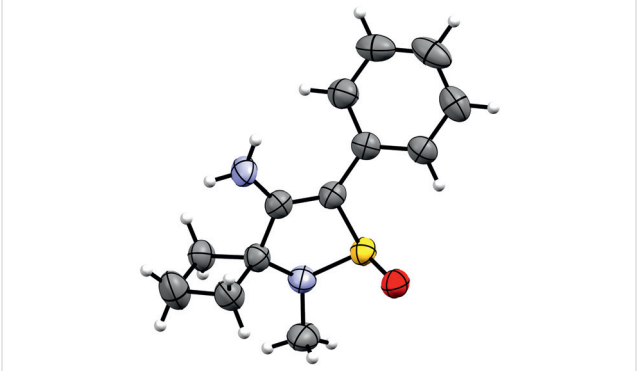


Figure 2 Molecular structure of α-phenyl β-enamino γ-sultim **1c** according to results of X-ray crystal-structure analysis. Thermal ellipsoids are shown at the 50% probability level.

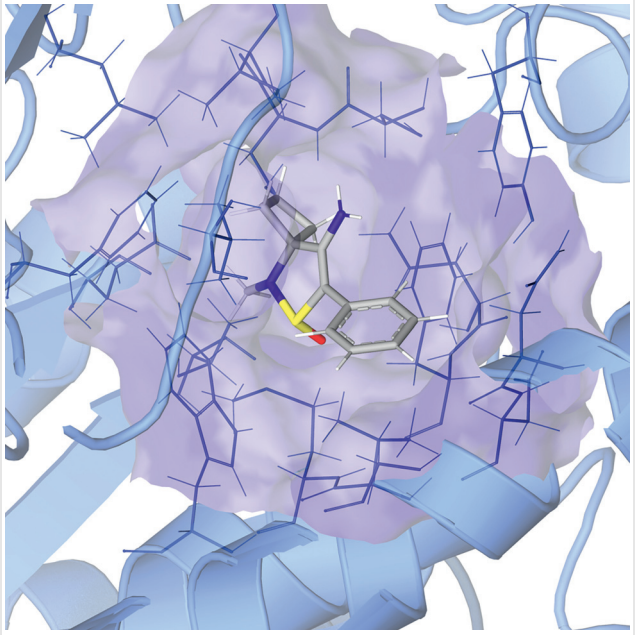


Figure 3 3D binding mode of sultim **1c** in the active site of ALDH1A1

nal Müller glia could contribute to the inner blood retinal barrier (iBRB) breakdown during diabetic retinopathy, the main cause of vision loss in this disease.[22]

In conclusion, the CSIC reaction strategy appeared as an appropriate and, apparently, the most reliable tool for the construction of β-enamino γ-sultim framework. The method worked well and tolerated strained 3- and 4-membered spirocyclic substituents. Having developed the synthesis of α-phenyl β-enamino γ-sultims, we would extend this protocol to other substituted and α-functionalized sultims. Owing to low molecular weight, sp^3-enrichment, and conformational restriction, β-enamino γ-sultims meet the criteria for lead-oriented synthesis.[1a] Preliminary *in silico* study indicated that γ-sultim scaffold can be considered a promising template and therefore might be useful for early drug discovery programs.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0043-1763751.

References and Notes

(1) (a) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem. Int. Ed.* **2012**, *51*, 1114. (b) Doveston, R.; Marsden, S.; Nelson, A. *Drug Discovery Today* **2014**, *19*, 813.
(2) (a) Zhang, Q.; Xi, J.; Ze, H.; Qingle, Z. *Synthesis* **2021**, *53*, 2570. (b) Yin, X.; Zhang, Q.; Zeng, Q. *Organics* **2023**, *4*, 173. (c) Wojaczyńska, E.; Wojaczyński, J. *Chem. Rev.* **2020**, *120*, 4578. (d) Achuenu, C.; Carret, S.; Poisson, J.; Berthiol, F. *Eur. J. Org. Chem.* **2020**, 5901. (e) Lo, P. K. T.; Oliver, G. A.; Willis, M. C. *J. Org. Chem.* **2020**, *85*, 5753. (f) Cao, Y.; Abdolmohammadi, S.; Ahmadi, R.; Issakhov, A.; Ebadi, A. G.; Vessally, E. *RSC Adv.* **2021**, *11*, 32394. (g) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.
(3) Dobrydnev, A. V.; Popova, M. V.; Volovenko, Y. M. *Chem. Rec.* **2024**, *24*, e202300221.
(4) (a) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147. (b) Langdon, S. R.; Ertl, P.; Brown, N. *Mol. Inf.* **2010**, *29*, 366. (c) Kubinyi, H. J. *Braz. Chem. Soc.* **2002**, *13*, 717. (d) Wassermann, A. M.; Bajorath, J. *Future Med. Chem.* **2011**, *3*, 425.
(5) Reißert, A. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 858.
(6) Chen, Z.; Demuth, T. P.; Wireko, F. C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2111.
(7) Britcher, S. F.; Lumma, W. C. J. US5171860A, **1992**.
(8) (a) Kamiya, T.; Teraji, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *J. Am. Chem. Soc.* **1975**, *97*, 5020. (b) Fukumura, M.; Hamma, N.; Nakagome, T. *Tetrahedron Lett.* **1975**, *16*, 4123. (c) Morin, R. B.; Gordon, E. M.; Lake, J. R. *Tetrahedron Lett.* **1973**, *14*, 5213.
(9) (a) Rassadin, V. A.; Grosheva, D. S.; Tomashevskii, A. A.; Sokolov, V. V. *Chem. Heterocycl. Compd.* **2013**, *49*, 39. (b) Popova, M. V.; Dobrydnev, A. V. *Chem. Heterocycl. Compd.* **2017**, *53*, 492. (c) Debnath, S.; Mondal, S. *Eur. J. Org. Chem.* **2018**, 933.
(10) Dittmer, D. C.; Hoey, M. D. In *The Chemistry of Sulphinic Acids, Esters and Derivatives*; Patai, S., Ed.; John Wiley & Sons: Chichester, **1990**, 239.
(11) (a) Popova, M. V.; Dobrydnev, A. V.; Dyachenko, M. S.; Duhayon, C.; Listunov, D.; Volovenko, Y. M. *Monatsh. Chem.* **2017**, *148*, 939. (b) Dobrydnev, A. V.; Vashchenko, B. V.; Konovalova, I. S.; Bisikalo, K. O.; Volovenko, Y. M. *Monatsh. Chem.* **2018**, *149*, 1827. (c) Dyachenko, M. S.; Dobrydnev, A. V.; Volovenko, Y. M. *Mol. Diversity* **2018**, *22*, 919. (d) Dyachenko, M. S.; Dobrydnev, A. V.; Chuchvera, Y. O.; Shishkina, S. V.; Volovenko, Y. M. *Chem. Heterocycl. Compd.* **2020**, *56*, 386. (e) Omelian, T. V.; Dobrydnev, A. V.; Utchenko, O. Y.; Ostapchuk, E. N.; Konovalova, I. S.; Volovenko, Y. M. *Monatsh. Chem.* **2020**, *151*, 1759. (f) Dobrydnev, A. V.; Popova, M. V.; Yatsymyrskyi, A. V.; Shishkina, S. V.; Chuchvera, Y. O.; Volovenko, Y. M. *J. Mol. Struct.* **2024**, *1295*, 136745.
(12) (a) Marco, J. L.; Ingate, S. T.; Chinchón, P. M. *Tetrahedron* **1999**, *55*, 7625. (b) Marco, J. L.; Ingate, S. T.; Jaime, C.; Beá, I. *Tetrahedron* **2000**, *56*, 2523. (c) Postel, D.; Van Nhien, A. N.; Marco, J. L.

Eur. J. Org. Chem. **2003**, 3713. (d) Domínguez, L.; Nguyen Van Nhien, A.; Tomassi, C.; Len, C.; Postel, D.; Marco-Contelles, J. *J. Org. Chem.* **2004**, *69*, 843. (e) Dobrydnev, A. V.; Marco-Contelles, J. *Eur. J. Org. Chem.* **2021**, 1229.

(13) Youn, J.-H.; Herrmann, R. *Tetrahedron Lett.* **1986**, *27*, 1493.

(14) **Benzyl Sulfinyl Chloride (3)**
The solution of 1,2-dibenzyldisulfane (**4**, 24.6 g, 100 mmol) and AcOH (12.6 g, 12 mL, 210 mmol) in CH_2Cl_2 (250 mL) was cooled to −40 °C followed by dropwise addition of freshly distilled SO_2Cl_2 (43.2 g, 25.9 mL, 320 mmol) maintaining the above temperature. The resulting mixture was stirred at −40 °C for 30 min, then warmed to rt, and stirred at this temperature for another 30 min. Then the reaction mixture was carefully heated to 35–40 °C (*Caution!* Violent gas release). After gas evolution had ceased, the reaction mixture was evaporated at reduced pressure maintaining the internal temperature below 35 °C, and then dried in a vacuum (0.5 mmHg) with stirring at rt for 2 h. Thus obtained sulfinyl chloride **3** (ca. 33 g, 95% crude yield) was used in the sulfinylation step without additional purification, and the rest was stored at 4 °C.

(15) **General Procedure for the Synthesis of Sulfinamides 2a–c**
$PhCH_2SOCl$ (**3**, 9.6 g, 55 mmol, 1.1 equiv) was added dropwise to the stirred cold (−20 °C) solution of α-amino nitrile **5a–e** (50 mmol, 1 equiv) and DIPEA (14.2 g, 19.2 mml, 110 mmol, 2.2 equiv) in anhydrous CH_2Cl_2 (100 mL). After the reagent had been added the reaction mixture was stirred at −20 °C for 30 min whereupon was left to react overnight allowing to equilibrate to rt. The resulting reaction mixture was filtered, the filtrate was evaporated at reduced pressure and redissolved in EtOAc (100 mL). The organic layer was sequentially washed with saturated aq. $NaHCO_3$ (1 × 10 mL) and brine (1 × 10 mL), dried (Na_2SO_4), and evaporated at reduced pressure to give the title product **2a–e**. Thus obtained sulfinamides were pure enough to be used in subsequent cyclization step without additional purification. If necessary, sulfinamides **2a–e** can be purified by silica gel flash chromatography (gradient elution from hexanes–*t*-BuOMe (1:1) to *t*-BuOMe).

(16) ***N*-(2-Cyanopropan-2-yl)-*N*-methyl-1-phenylmethanesulfinamide (2a)**
From **5a** (4.9 g); yield 8.27 g (35 mmol, 70%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 3 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 3.94 (dd, *J* = 13.0, 9.6 Hz, 2 H), 2.81 (s, 3 H), 1.40 (s, 3 H), 1.32 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 130.1, 130.0, 128.9, 128.3, 120.5, 60.2, 55.8, 27.1, 26.5, 25.5. MS (APCI): *m/z* = 237 $[M + H]^+$.

(17) **General Procedure for the Synthesis of β-Enamino γ-Sultims 1a–e**
The solution of LiHMDS (15 g, 90 mmol, 4.5 equiv) in THF (85 mL) was added dropwise to the stirred cold (−60 °C) solution of sulfinamide **2a–e** (20 mmol) in THF (40 mL) under Ar atmosphere. After the reagent had been added the reaction mixture was stirred at –60 °C for 30 min whereupon was heated to 0 °C within 90 min. After this time the reaction mixture was quenched by pouring it into cold (0 °C) saturated aq. NH_4Cl (100 mL) followed by extraction with *t*-BuOMe (3 × 50 mL). The combined organic layer was dried (Na_2SO_4) and evaporated at reduced pressure to give the target product **1a–e**. Thus obtained β-enamino γ-sultims were pure enough and if necessary were further purified by silica gel flash chromatography (gradient elution from hexanes–*t*-BuOMe (1:1) to *t*-BuOMe).

(18) **4-Amino-2,3,3-trimethyl-5-phenyl-2,3-dihydroisothiazole 1-oxide (1a)**
From **2a** (4.73 g); yield 3.78 g (16 mmol, 80%); white solid; mp 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.5 Hz, 2 H), 7.36 (t, *J* = 7.5 Hz, 2 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 4.36 (s, 2 H), 2.85 (s, 3 H), 1.54 (s, 3 H), 1.31 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.2, 131.8, 129.2, 128.0, 127.0, 111.8, 69.9, 28.0, 27.0, 24.1. MS (APCI): *m/z* = 237 $[M + H]^+$.

(19) CCDC 2332756 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

(20) Buchman, C. D.; Hurley, T. D. *J. Med. Chem.* **2017**, *60*, 2439.

(21) Yue, H.; Hu, Z.; Hu, R.; Guo, Z.; Zheng, Y.; Wang, Y.; Zhou, Y. *Front. Oncol.* **2022**, *12*, 918778.

(22) (a) McDowell, R. E.; McGahon, M. K.; Augustine, J.; Chen, M.; McGeown, J. G.; Curtis, T. M. *Invest. Opthalmol. Visual Sci.* **2016**, *57*, 4762. (b) Karan, B. M.; Little, K.; Augustine, J.; Stitt, A. W.; Curtis, T. M. *Antioxidants* **2023**, *12*, 1466.