Expansion of First-in-Class Drug Candidates That Sequester Toxic All-Trans-Retinal and Prevent Light-Induced Retinal Degeneration


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ABSTRACT

All-trans-retinal, a retinoid metabolite naturally produced upon photoreceptor light activation, is cytotoxic when present at elevated levels in the retina. To lower its toxicity, two experimentally validated methods have been developed involving inhibition of the retinoid cycle and sequestration of excess of all-trans-retinal by drugs containing a primary amine group. We identified the first-in-class drug candidates that transiently sequester this metabolite or slow down its production by inhibiting regeneration of the visual chromophore, 11-cis-retinal. Two enzymes are critical for retinoid recycling in the eye. Lecithin:retinol acyltransferase (LRAT) is the enzyme that traps vitamin A (all-trans-retinal) from the circulation and photoreceptor cells to produce the esterified substrate for retinoid isomerase (RPE65), which converts all-trans-retinyl ester into 11-cis-retinol. Here we investigated retinylamine and its derivatives to assess their inhibitor/substrate specificities for RPE65 and LRAT, mechanisms of action, potency, retention in the eye, and protection against acute light-induced retinal degeneration in mice. We correlated levels of visual cycle inhibition with retinal protective effects and outlined chemical boundaries for LRAT substrates and RPE65 inhibitors to obtain critical insights into therapeutic properties needed for retinal preservation.

Introduction

Highly expressed in rod and cone photoreceptor cells of the retina, visual pigments are G protein–coupled receptors composed of an opsin apoprotein combined with a universal chromophore, 11-cis-retinal, through a protonated Schiff base (Palczewski et al., 2000; Palczewski, 2006). Upon absorption of a photon of light, the retinylidene chromophore is photoisomerized to an all-trans configuration with subsequent activation of the photoreceptor. Spontaneous hydrolysis of the Schiff base bond subsequently liberates all-trans-retinal from the opsin. Because visual pigments are densely packed at a local concentration up to 5 mM (Nickell et al., 2007), an intense stream of photons can result in high levels of all-trans-retinal. Even at low micromolar concentrations, this aldehyde is toxic (Maeda et al., 2008, 2009a; Chen et al., 2012) and primarily affects photoreceptor cells as demonstrated by novel imaging techniques (Maeda et al., 2014).

To restore photoreceptor sensitivity to light, a constant supply of 11-cis-retinal is required, and vertebrates use a metabolic pathway called the retinoid (visual) cycle, by which all-trans-retinal is enzymatically reisomerized back to the 11-cis configuration (Kiser et al., 2014). This process is facilitated by two nonredundant enzymes: lecithin:retinol acyltransferase (LRAT) and retinoid isomerase, a retinal pigmented epithelium-specific 65 kDa protein (RPE65) (Ruiz et al., 1999; Jin et al., 2005; Moiseyev et al., 2005) (Fig. 1). Retinylamine was the first described potent inhibitor of RPE65 (Golczak et al., 2005b). This retinoid is retained in the eye by the action of LRAT that produces its amidated precursors, and then the resulting retinyl amides are slowly hydrolyzed to evoke long-lasting suppression of retinoid isomerase activity (Golczak et al., 2005a). This mechanism revealed the possibility of targeting hydrophobic drugs to the eye and retaining them within the ocular tissue (Palczewski, 2010).

An operative visual cycle is critical for sustaining continuous vision and maintaining the health of photoreceptor cells

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ABBREVIATIONS: DMF, dimethylformamide; ERG, electroretinography; HPLC, high-performance liquid chromatography; LRAT, lecithin:retinol acyltransferase; OCT, optical coherence tomography; ONL, outer nuclear layer; RPE, retinal pigment epithelium; RPE65, retinoid isomerase.
Proper homeostasis of retinoid metabolism supports visual function under a variety of lighting conditions. However, certain environmental insults including prolonged exposure to intense light in combination with an unfavorable genetic background can overcome the adaptive capabilities of the visual cycle and thus compromise retinal function (Travis et al., 2007; Maeda et al., 2008). A clinical example is Stargardt disease, an inherited form of juvenile macular degeneration that results in progressive vision loss associated with mutations in the photoreceptor-specific ATP-binding cassette transporter (ABCA4) that causes a delay in all-trans-retinal clearance (Azarian et al., 1998; Tsybovsky et al., 2010). The resulting increased concentrations of all-trans-retinal exert a direct cytotoxic effect on photoreceptors (Maeda et al., 2009b) in addition to contributing to formation of side products such as N-retinylidene-N-retinylethanolamine (A2E) and retinal dimer. Importantly, all-trans-retinal itself is cytotoxic to photoreceptors. Formation of a transient Schiff base with primary amines can sequester the excess of this toxic aldehyde. Alternatively, cytoprotection can be achieved by inhibiting the visual cycle to slow down the supply of all-trans-retinal. all-trans-RAL, all-trans-retinol; all-trans-RP, all-trans-retinyl palmitate; 11-cis-RAL, 11-cis-retinal; 11-cis-ROL, 11-cis-retinol; ROS, rod outer segments.

Because retinylamine was highly protective against retinal degeneration in mice after short exposure to bright light, direct interaction and persistent suppression of RPE65 by retinylamine may not be the only protective mechanism involved (Maeda et al., 2008, 2009a, 2012). An alternative explanation is trapping the excess all-trans-retinal with primary amines (Maeda et al., 2012, 2014). Aldehyde-selective chemistry was used to reversibly conjugate all-trans-retinal with primary amine containing compounds structurally unrelated to retinylamine (Maeda et al., 2012). Several potential therapeutic compounds were identified that exhibited protective effects against retinal degeneration in animal models. However, potential improvements upon this approach could involve a search for molecules with extended half-lives in vivo, hijacking an eye-selective mechanism for their uptake and retention, and further lowering the concentration needed to achieve a therapeutic effect.

In this study, we investigated many derivatives of retinylamine to assess their substrate/inhibitor binding specificities for RPE65 and LRAT, the mechanism(s) of their action, potency, retention in the eye, and protection against acute light-induced retinal degeneration in mice. Such information could be critical for understanding the modes of action for current and future visual cycle modulators.

**Materials and Methods**

**Chemicals and Synthesis.** Unless otherwise stated, solvents and reagents were purchased from Sigma-Aldrich (St. Louis, MO). QEA-A-002 and QEA-A-003 were obtained from Toronto Research.
Chemicals Inc. (Toronto, Canada). Other aldehydes were synthesized as described in the Supplemental Methods. Syntheses of primary alcohols and amines were performed by previously described procedures (Golczak et al., 2005a,b). 1H NMR spectra (300, 400, or 600 MHz) and 13C NMR spectra (100 or 150 MHz) were recorded with Varian Gemini and Varian Inova instruments (Varian, Palo Alto, CA).

Because retinal is much more stable than retinylamine or retinol, all novel retinoid derivatives were synthesized and stored in their aldehyde forms, and then were converted to primary alcohols/amines just prior to compound screening. The general scheme of synthesis began with building the β-ionone ring analogs, and was followed by elongating the polyene chain with an aldol condensation, a Wittig-Horner reaction, or Suzuki coupling (Supplemental Methods). Synthesized retinal analogs were categorized as QEA, TEA, and PEA based on their polyene chain length (Fig. 2A). Among 35 synthesized aldehydes, four—QEA-E-001, QEA-E-002, QEA-F-001, and QEA-F-002—were unstable and decomposed before proper NMR spectra were completed. Structures and purities of all other compounds were confirmed by 1H and 13C NMR as well as by mass spectrometry (Supplemental Methods).

**Fig. 2.** Schematic representation of retinoid-based amines and their biologic activities. (A) Retinal analogs. For QEA, R1 and R4 represent H or methyl; R2 and R3 are H, hydroxyl; R5 is H, methyl, t-butyl, benzyl, or p-methoxy benzyl; and X corresponds to H, methyl, or t-butyl; and X could be C, O, or N. When X is O, there is no R3 group. For QEA-D and QEA-G-001, R5 represents a -(CH2)3- bridge connecting C7 and C9. For TEA, R1 and R4 can be H or methyl, whereas R2 and R3 are H or hydroxyl; R5 is H or t-butyl; R6 can be H, methyl, t-butyl, or benzyl; and R7 corresponds to H or methyl. For PEA, R1 and R2 are H or hydroxyl. These compounds were converted to primary amines prior to the tests. (B) Schematic representation of the experimental design used to test the biologic activity of amines. The black arrows represent the chemical conversions of tested compounds, whereas blue arrows represent the candidate compound selection. (C) Fraction of tested compounds that serve as substrates of LRAT. (D) Extent of inhibition displayed by tested amines against RPE65 enzymatic activity.
Retinal Pigment Epithelium Microsomal Preparations. Bovine retinal pigment epithelium (RPE) microsomes were isolated from RPE homogenates by differential centrifugation as previously described (Stecher and Palczewski, 2000). The resulting microsomal pellet was resuspended in 10 mM Bis-Tris propane/HCl buffer, pH 7.4, to achieve a total protein concentration of ~5 mg·mL⁻¹. Then the mixture was placed in a quartz cuvette and irradiated for 6 minutes at 4°C with a ChromatoUVE transilluminator (model TM-15; UVP, Upland, CA) to eliminate residual retinoids. After irradiation, dihydroretinol was added to the RPE microsomal mixture to achieve a final concentration of 5 mM.

LRAT Activity Assays. Two microliters of a synthesized primary alcohol or amine dissolved in dimethylformamide (DMF) (final concentration 10 mM) and 2 μL of 1,2-diheptanoyl-sn-glycerol-3-phosphocholine (water, final concentration 1 mM) were added to 200 μL of 10 mM Bis-Tris propane/HCl buffer, pH 7.4, containing 150 μg of RPE microsomes and 1% (v/v) bovine serum albumin. The resulting mixture was incubated at 37°C for 1 hour. The reaction was quenched by adding 300 μL of methanol. Most reaction products were extracted with 300 μL of hexanes, except for products from the QEA-C-006 and QEA-G groups, which were extracted by adding 300 μL of ethyl acetate and 300 μL of water. Reaction products were separated and quantified by normal-phase high-performance liquid chromatography (HPLC) (Agilent Sil, 5 μm, 4.6 × 250 mm; Agilent Technologies, Santa Clara, CA) in a stepwise gradient of ethyl acetate (in hexanes) for 15 minutes. The resulting mixture was extracted with 4 ml of hexanes. Extracts were dried in vacuo, reconstituted in 300 μl of hexanes, and 100 μl of extract was injected into an HPLC for analysis with 10% (v/v) ethyl acetate in hexanes.

Statistical Analyses. Data representing the means ± S.D. for the results of at least three independent experiments were compared by the one-way analysis of variance Student’s t test. Differences with P values of <0.05 were considered to be statistically significant.

Results

Design and Synthesis of Novel Retinal Analogos. To find primary amines that could serve as substrates of LRAT without imposing a strong inhibitory effect on retinoid isomerization, we designed and synthesized a series of retinoid analogs (Fig. 2A; Supplemental Methods). Prior to this study, the only known primary amine acting as a substrate for LRAT was retinylamine (Golczak et al., 2005a). Thus, retinylamine was chosen as a starting model for further chemical modifications. Although LRAT was shown to have a broad substrate specificity (Canada et al., 1990), chemical boundaries that determine the substrate selectivity for this enzyme had not been clarified. In contrast, the crystal structure of RPE65 was elucidated in detail (Kiser et al., 2009, 2012), revealing a narrow tunnel that leads into the active site of this enzyme. Indeed, a relatively small structural modification of the retinoid moiety could effectively abolish binding of an inhibitor to this enzyme. Thus, we hypothesized that a subset of primary amines and LRAT substrates would not inhibit RPE65 enzymatic activity.

In Vitro Screening to Identify the Boundary between Substrates of LRAT and RPE65 Inhibitors. Properties of retinoid derivatives were examined with two standard enzymatic assays: the acylation by LRAT and retinoid isomerization by RPE65. To identify substrates of LRAT, aldehydes were first reduced by sodium borohydride to their corresponding primary alcohols that then were used directly in the esterification assay. Retinoid derivatives were examined with two standard enzymatic assays: the acylation by LRAT and retinoid isomerization by RPE65. To identify substrates of LRAT, aldehydes were first reduced by sodium borohydride to their corresponding primary alcohols that then were used directly in the esterification assay. The ratio between a substrate and its esterified form was used to measure enzymatic activity, based on equivalent UV absorption of the substrate and product at their specific UV maximum wavelengths. Compounds classified as “good” LRAT substrates converted at least 50% of their available alcohol substrates into corresponding esters under these experimental conditions, whereas marginal LRAT substrates were converted at less than 5%. Alcohols with a 5–50% conversion ratio were
classified as weak substrates. An example is shown in Fig. 3A for QEB-B-001. Among 35 tested compounds, 23 were categorized as good and nine as weak substrates; three compounds were not esterified by LRAT (Fig. 2C; Table 1). Based on these data, we conclude that the conformation of the β-ionone ring is a critical structural feature for LRAT substrate recognition. Importantly, various modifications within the β-ionone ring, including incorporation of heteroatoms, deletion of methyl groups, or addition of functional groups, did not significantly alter ester formation. Moreover, elongating double bond conjugation along the polyene chain or deletion of a C9 and/or a C13 methyl group also was allowed. In contrast, exchange of the C13 methyl with a bulky t-butyl group strongly inhibited substrate binding. Interestingly, the C9 methyl could be replaced with a variety of substituents, including a t-butyl, benzene, and its derivatives or even an alkyl chain bridging to C7, which resulted in a rigid configuration of the polyene chain. Reduced enzymatic activity was observed with ionylidene analogs of fewer than 12 carbons in length (Supplemental Table 1; Table 1).

Primary amines of compounds derived from the aldehydes were subsequently tested for their ability to inhibit the RPE65-dependent retinoid isomerization reaction in a dose- and time-dependent manner, as exemplified by QEB-B-001 (Fig. 3B). Amines were incubated with RPE microsomes in the presence of all-trans-retinol and the 11-cis-retinoid binding protein, retinaldehyde-binding protein 1. Progress of the enzymatic reaction was monitored by HPLC separation of retinoids and quantification of 11-cis-retinol, with a decrease of 11-cis-retinol production reflecting inhibition of RPE65 by a tested amine. Compounds with an IC50 below 10 μM were defined as strong inhibitors, those with an IC50 between 10 and 100 μM were categorized as moderate inhibitors, and compounds with an IC50 above 100 μM were viewed as noninhibitors (Table 1). Among the 32 amines serving as substrates of LRAT, 11 exhibited strong inhibition of RPE65, four showed moderate inhibition, and 17 did not affect this isomerization reaction. Those amines exhibiting no inhibition had two common features: an altered β-ionone ring structure characterized by the absence of methyl groups and the presence of one bulky group such as a t-butyl or benzyl group at the C9 position. For example, QEA-B-001-NH2 was a good LRAT substrate but a modest or noninhibitor of RPE65 (Fig. 3). Compounds containing only one of these modifications (QEA-A-006-NH2 and QEA-B-003-NH2) showed moderate inhibition of RPE65, implying a synergistic effect of both changes in RPE65 inhibitory effect (Table 1). This moderate inhibition could be enhanced by shortening the polyene chain length (TEA amines) or diminished by introducing an extra positive charge into the tested compounds (QEA-G amines) (Supplemental Table 1).

Protective Effects of Primary Amines against Light-Induced Retinal Degeneration. Our in vitro screening identified 17 candidates which could be acylated by LRAT and yet did not inhibit RPE65. For practical reasons, only eight of these lead compounds (QEA-B-001-NH2, QEA-B-002-NH2, QEA-C-001-NH2, QEA-C-003-NH2, QEA-C006-NH2, QEA-E-002-NH2, TEA-B-002-NH2, and TEA-C00-2-NH2) along with these lead compounds (QEA-B-001-NH2, QEA-B-002-NH2, QEA-C-001-NH2, QEA-C-003-NH2, QEA-C006-NH2, QEA-E-002-NH2, TEA-B-002-NH2, and TEA-C00-2-NH2) were selected for further testing in Abca4<sup>−/−</sup>Rdh8<sup>−/−</sup> mice, an animal model for light-induced retinal degeneration (Maeda et al., 2008) (Table 2). Additionally, two novel amines with moderate inhibition of RPE65 (QEA-A-006-NH2 and QEA-B-003-NH2) and one with strong inhibition (QEA-A-005-NH2) were added to the first test group

![Fig. 3. Amidation of QEA-B-001-NH2 and inhibition of RPE65. Primary amines were preincubated with bovine RPE microsomes at room temperature for 5 minutes; then all-trans-retinol was added and the mixture was incubated at 37°C. (A) HPLC chromatogram showing acylation of QEA-B-001-NH2 by LRAT in RPE microsomes; chromatograms “a” and “b” correspond to extracts of RPE microsomes in the absence and presence of QEA-B-001-NH2, respectively. Asterisks indicate a step change in the ethyl acetate mobile phase concentration (from 10 to 30% hexane). Under these chromatographic conditions, the free amine of QEA-B-001-NH2 did not elute from the normal-phase HPLC column without addition of ammonia to the mobile phase. (B) UV-Visible absorbance spectrum of a peak at 26 minutes of elution. This spectrum corresponds to QEA-B-001-NH2 amide. (C) Effect of inhibitor concentrations on the production of 11-cis-retinol. Inhibition of RPE65 enzymatic activity was measured as a decline in 11-cis-retinol production. (D) 11-cis-Retinol production in the presence of 5 μM QEA-B-001-NH2, 30 μM QEA-B-001-NH2, 5 μM Ret-NH2, and control.](molpharm.aspetjournals.org)
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<th>Structure</th>
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<th>Inhibition of RPE65 ( ^b )</th>
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(continued)
for comparison. Mice were treated by oral gavage with 2 mg of a test compound and then kept in the dark for 24 hours prior to being exposed to bright light (~10,000 lux) for 1 hour (Maeda et al., 2012). Retinal damage was assessed with OCT by measuring the thickness of the outer nuclear layer and by determining 11-cis-retinal levels in the eye (Fig. 4). Additionally, extracts of livers obtained from treated mice were analyzed by HPLC to estimate the amounts of corresponding amides (Fig. 4D).

Among tested compounds, only inhibitors of RPE65, including QEA-A-005-NH$_2$ and retinylamine, provided significant protection against light-induced retinal degeneration (Table 2). Remaining compounds characterized as weak inhibitors did not prevent retinal deterioration. One possible explanation is that instability of these compounds in vivo caused their failure to protect. Despite being substrates for LRAT, seven compounds (QEA-A-006-NH$_2$, QEA-B-002-NH$_2$, QEA-B-003-NH$_2$, QEA-C-003-NH$_2$, QEA-C-006-NH$_2$, QEA-E-002-NH$_2$,

<table>
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$^a$LRAT substrates were assessed as percentages of their corresponding primary alcohols that were esterified by LRAT in 1 hour at 37°C.

$^b$“Strong” inhibition indicates that the IC$_{50}$ of the tested amine was below 10 μM, “moderate” inhibition means that IC$_{50}$ was between 10 and 100 μM, and “none” signifies that the IC$_{50}$ was above 100 μM.

$^c$Not tested.

$^d$LRAT substrates were assessed as percentages of their corresponding primary alcohols that were esterified by LRAT in 1 hour at 37°C.
TABLE 2
Protective effects of primary amines against intense light-induced retinal degeneration in 4-week-old Abca4−/−Rdh8−/− mice

*Abca4−/−Rdh8−/−* mice treated with tested amines were kept in the dark for 24 hours, and then bleached with 10,000 lux light for 1 hour as described in the Materials and Methods section.

<table>
<thead>
<tr>
<th>Compound Structure Ocular Protection</th>
<th>Amide Formation in Liver</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>QEA-A-001-NH₂ (retinylamine)</td>
<td>Strong</td>
<td>None</td>
</tr>
<tr>
<td>QEA-A-005-NH₂</td>
<td>Strong</td>
<td>None</td>
</tr>
<tr>
<td>QEA-A-006-NH₂</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>QEA-B-001-NH₂</td>
<td>Strong</td>
<td>Yes</td>
</tr>
<tr>
<td>QEA-B-002-NH₂</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>QEA-B-003-NH₂</td>
<td>Weak</td>
<td>None</td>
</tr>
<tr>
<td>QEA-C-001-NH₂</td>
<td>Strong</td>
<td>Yes</td>
</tr>
<tr>
<td>QEA-C-003-NH₂</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>QEA-C-006-NH₂</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>QEA-E-002-NH₂</td>
<td>Weak</td>
<td>None</td>
</tr>
</tbody>
</table>
and TEA-B-002-NH₂) were not efficiently amidated in vivo, as shown by a lack of accumulation of their amide forms in mouse liver. Whether these compounds were removed from the biologic system before or after amidation by LRAT is not clear. Nonetheless, inadequate levels of primary amines in vivo would have resulted from either scenario. Thus, it was not surprising to observe retinal degeneration in OCT images of mice treated with these amines (Fig. 4, A and B). In contrast, compounds QEA-B-001-NH₂, QEA-C-001-NH₂, and TEA-C-002-NH₂, which did not inhibit RPE65, were efficiently converted into amides in vivo, as was apparent from their intense amide peaks present in liver. Notably, none of these compounds protected against retinal degeneration either. Levels of 11-cis-retinal quantified 3 days after light exposure indicated that only 50% of photoreceptors remained as compared with those in control healthy mice (Fig. 4C). The relatively high levels of residual 11-cis-retinal in examined samples may indicate that the disorganization of the outer nuclear layer (ONL) seen in OCT images did not reflect the death of all photoreceptor cells. Additionally, rod outer segments of the compromised photoreceptors loaded with rhodopsin could persist in the retina for some time before they are cleared. Although QEA-B-001-NH₂ was stored as amides in the liver, its inability to prevent light-induced retinal degeneration could be attributed to an insufficient concentration of free amine in eyes needed to sequester the excess all-trans-retinal produced by photobleaching.

**Functional Relationship between Inhibition of the Visual Cycle and Retinal Protection.** As indicated earlier, inhibition of RPE65 can protect the retina against light-induced damage. However, a fundamental question is to what extent RPE65 enzymatic activity needs to be affected to achieve this therapeutic effect. To answer this question, we measured the rate of the visual chromophore recovery in wild-type mice pretreated with retinylamine and exposed to light illumination that activated ~90% of rhodopsin yet failed to trigger retinal degeneration. As demonstrated in Fig. 5A, mice without treatment had recovered ~85 ± 5% of the prebleached 11-cis-retinal level in the eye at 6 hours, whereas mice exposed to light 2 hours after administration of 0.2 mg of retinylamine recovered only 50 ± 13%. Importantly, animals treated with the same amount of retinylamine but exposed to light 24 hours later exhibited a much slower recovery of 11-cis-retinal in the eye—namely, only 22 ± 5.0% of the prebleached level (Fig. 5B). When the retinylamine inhibitory effect was investigated over a broader time period (Fig. 5C), 24 hours postadministration was found to be the time point with the strongest inhibition, regardless of a 5-fold difference in the retinylamine dose. The inhibitory effect observed for the 0.2-mg dose decreased by day 3, resulting in 61 ± 2.2% of recovered 11-cis-retinal, and nearly disappeared by day 7. In contrast, 0.5 mg of retinylamine still strongly affected the rate of 11-cis-retinal regeneration at day 7, allowing only a partial recovery (56 ± 9.1%).

Once the time course of retinylamine’s inhibitory effect was established, we investigated the correlation between the level of inhibition and the protective effect on the retina. Four-week-old Abca4<sup>−/−</sup>/Rdh8<sup>−/−</sup> mice were treated by oral gavage with 0.1, 0.2, and 0.5 mg of retinylamine, respectively, and kept in the dark for 24 hours. Mice then were bleached with 10,000 lux bright light for 1 hour. Measured as described earlier, the recovery of visual chromophore was inhibited by about 40, 80, and 95%, respectively, by these tested doses (Fig. 5, B and C). Bleached mice were kept in the dark for 3 days, and then imaged by OCT (Fig. 6, A and B). Mice treated with only 0.1 mg of retinylamine developed severe retinal degeneration, similar to that observed in mice without treatment, whereas mice treated with 0.5 mg of retinylamine showed a clear intact ONL image. The average ONL thickness in the latter group was 51.1 ± 5.8 μm, well within the range of healthy retinas. Concurrently, OCT imaging revealed that mice treated with the 0.2-mg dose were partially protected. Their average ONL thickness was 94.4 ± 17.4 μm. In an equivalent experiment, mice were kept in the dark for 7 days prior to quantification of visual chromophore levels. Mice treated with 0.2 mg of retinylamine showed the same 11-cis-retinal levels (445 ± 37 pmol/eye) as control mice not exposed to light (452 ± 43 pmol/eye), whereas mice treated by oral gavage with a 0.1-mg dose and untreated animals had 323 ± 48 and 301 ± 8 pmol/eye, respectively, suggesting damage to the retina (Fig. 6C). Furthermore, mice treated with the 0.2- and 0.5-mg doses of retinylamine showed the same ERG scotopic a-wave responses, whereas animals provided with 0.1 mg of the compound revealed attenuated ERG responses similar to those of untreated controls (Fig. 6D). Thus, the 0.1-mg dose failed to protect against retinal degeneration under the bright light exposure conditions described in this study.

**Discussion**

Development of safe and effective small-molecule therapeutics for blinding retinal degenerative diseases still remains a major
challenge. Ophthalmic drugs comprise a special category of therapeutics. Their site of action is limited to a relatively small organ protected by both static and dynamic barriers, including different layers of the cornea, sclera, and retina and blood-retinal barriers, in addition to choroidal blood flow, lymphatic clearance, and dilution by tears (Gaudana et al., 2010). Thus, designing efficient drug delivery systems, especially those directed to the posterior segment of the eye, has been a major problem. This challenge certainly applies to therapeutics administered systemically. Oral delivery is definitely the most feasible noninvasive and patient-preferred route for treating chronic retinal diseases. But inadequate accessibility of targeted ocular tissues after oral administration often requires high drug doses that cause unwanted systemic side effects. Examples are acetazolamide and ethoxzolamide, carbonic anhydrase inhibitors, and antiglaucoma drugs that have been discontinued due to their systemic toxicity (Kaur et al., 2002; Shirasaki, 2008).

Recently, the first-in-class drug candidates were discovered that transiently sequester the toxic all-trans-retinal metabolite produced in excess under adverse conditions. These compounds do not inhibit enzymes, channels, or receptors, but instead react with all-trans-retinal to form a Schiff base and thus reduce peak concentrations of this potentially toxic aldehyde. Because this reaction is readily reversible, there is no discernable diminution in the total amount of all-trans-retinal needed to replenish the visual chromophore. Present at high micromolar levels, all-trans-retinal is uniquely concentrated in the eye and constitutes an ideal target for primary amine-containing drugs that do not interact with cellular machinery and processes. But to be an effective drug, the primary amine also must be delivered to and be retained in the eye. Primary amines can be amidated with fatty acids by LRAT and retained in the eye, but then the similar substrate/product profile shown by another key enzyme of the retinoid cycle, RPE65, can produce the undesirable side effect of severely delayed dark

![Fig. 4. Protective effects of selected amines against light-induced retinal degeneration. Four-week-old Abca4+/−Rdh8−/− mice treated with tested amine compounds were kept in the dark for 24 hours and then bleached with 10,000 lux light for 1 hour. (A) Representative OCT images of retinas from mice treated by oral gavage with 2 or 4 mg of different amines. (B) Quantification of the protective effects of QEA-B-001-NH₂, QEA-B-003-NH₂, QEA-A-005-NH₂, and retinylamine (Ret-NH₂) is shown by measuring the averaged thickness of the ONL. A dramatic decrease in ONL thickness indicates advanced retinal degeneration. Ret-NH₂ (2 mg) and QEA-A-005-NH₂ (4 mg) protected the ONLs of these mice. (C) Quantification of 11-cis-retinal in the eyes of mice kept in dark for 7 days after bleaching. The decreased amount of 11-cis-retinal in damaged eyes reflects the loss of photoreceptors. (D) HPLC chromatograph showing acylation of QEA-B-001-NH₂ in mouse liver; “a” is a representative chromatogram of a liver extract from mice treated with dimethylsulfoxide (DMSO, vehicle) only, whereas “b” corresponds to an extract from mice treated with 2 mg of QEA-B-001-NH₂.](https://molpharm.aspetjournals.org/content/488)
adaptation. In this study, we performed enzymatic tests that delineated the chemical boundaries for LRAT substrate and RPE65 inhibitor specificities. Next, we tested the role of LRAT enzymatic activity in ocular tissue uptake and in establishing an equilibrium between primary amines and their acylated forms together with their retention in vivo. A similar protocol was used to assess the inhibition of RPE65 and corresponding levels of visual chromophore production and the duration of their suppression. Finally, we used the Abca4<sup>−/−</sup>Rdh8<sup>−/−</sup> mouse model of Stargardt disease to assess the ocular tissue uptake and mechanism of action of several retinoid-derived amines in vivo. These new compounds were examined for their therapeutic protection against bright light–induced retinal damage. This extensive search has yielded a new class of compounds for the treatment of retinal degeneration.

Extensive studies on animals, including rats as well as wild-type and Abca4<sup>−/−</sup>Rdh8<sup>−/−</sup> double knockout mice that

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**Fig. 5.** Inhibitory effects of retinylamine on the visual cycle in vivo. Inhibition of the retinoid cycle was measured by recovery of 11-cis-retinal in the eyes of wild-type mice after exposure to bright light. Recovery of 11-cis-retinal in the eyes of mice when retinylamine was administered 2 hours (A) or 24 hours (B) prior to light exposure (C, control; ●, 0.2 mg retinylamine; ▼, 0.5 mg retinylamine; ▲, 0.5 mg retinylamine). Mice treated with vehicle only achieved over 80% of 11-cis-retinal recovery by 6 hours after bleaching. (C) Temporal profile of the retinylamine effect on the retinoid cycle. Mice were treated by oral gavage with retinylamine 2 hours to 7 days before light exposure. Amounts of 11-cis-retinal in the eye were measured 6 hours after bleaching. Inhibition achieved a maximum at 24 hours after bleaching and lasted more than 7 days. Symbols represent doses of retinylamine (○, 0.1 mg; ●, 0.2 mg; ▲, 0.5 mg). Since inhibition of the visual cycle at the 0.1-mg dose did not offer sufficient protection against retinal degeneration, it could be considered as a reference point for higher doses. Thus, we decided to collect data only for a time point at which the inhibitory effect was the most profound. The slow decrease of the inhibitory effect after day 2 reflects delayed clearance of retinylamine or retinylamide from the RPE.

**Fig. 6.** Protective effects of retinylamine against light-induced retinal degeneration. Mice treated by oral gavage with different doses of retinylamine were kept in the dark for 24 hours and then bleached with 10,000 lux light for 1 hour. (A) Representative OCT images of mouse retinas 3 days after bleaching. (B) Quantification of ONL thickness by OCT. (C) Recovery of 11-cis-retinal in retinas of mice kept in the dark for 7 days after bleaching. The decreased amounts of 11-cis-retinal in the damaged eyes reflect the loss of photoreceptors. (D) Representative scotopic ERG responses of mice kept in the dark for 7 days after bleaching. ○, 0.1 mg; ▲, 0.2 mg; ●, 0.5 mg; ■, vehicle [dimethylsulfoxide (DMSO)].
closely mimic many features of human retinal degeneration, have shown that retinylamine exhibits a protective effect against light-induced damage by preventing the buildup of all-trans-retinol and its condensation products (Golczak et al., 2005b, 2008; Maeda et al., 2008; Berkowitz et al., 2009). However, prolonged complete inhibition of 11-cis-retinoid production would cause accumulation of unliganded opsin, a condition that resembles Leber congenital amaurosis and leads to retinal dystrophies. Thus, a partial slowing but not a complete blockage of visual chromophore regeneration offers an optimal therapeutic window for prevention of many degenerative retinal diseases.

Many drug side effects could be minimized by improving tissue-specific drug uptake through the use of existing nutrient transport systems. Visual functions of the eye, unlike any other tissue, depend on vitamin A. In fact, retinoids are preferentially taken up by the eye at the expense of other peripheral tissues (Amengual et al., 2012). This selectivity offers the opportunity of designing compounds that use vitamin A transport machinery and thus benefit from efficient and active uptake into the eye, low systemic toxicity, and dramatically improved pharmacokinetics (Moise et al., 2007). Retinylamine well illustrates this concept. This inhibitor of RPE65 has a reactive amine group instead of an alcohol, yet similar to vitamin A, it can also be acylated and stored in the form of a corresponding fatty acid amide. Solely responsible for catalyzing amide formation, LRAT is a critical enzyme in determining cellular uptake (Batten et al., 2004; Golczak et al., 2005a). Conversion of retinylamine to pharmacologically inactive retinylamides occurs in the liver and RPE, leading to safe storage of this inhibitor as a prodrug within these tissues (Maeda et al., 2006). Retinylamides are then slowly hydrolyzed back to free retinylamine, providing a steady supply and prolonged therapeutic effect for this active retinoid with lowered toxicity.

To investigate whether the vitamin A-specific absorption pathway can be used by drugs directed at protecting the retina, we examined the substrate specificity of the key enzymatic component of this system, LRAT. Over 35 retinoid derivatives were tested that featured a broad range of chemical modifications within the β-ionone ring and polyene chain (Supplemental Table 1; Table 1). Numerous modifications of the retinoid moiety, including replacements within the β-ionone ring, elongation of the double-bond conjugation, as well as substitution of the C9 methyl with a variety of substituents including bulky groups, did not abolish acylation by LRAT, thereby demonstrating a broad substrate specificity for this enzyme. These findings are in a good agreement with the proposed molecular mechanism of catalysis and substrate recognition based on the crystal structures of LRAT chimeric enzymes (Golczak et al., 2005b, 2015). Thus, defining the chemical boundaries for LRAT-dependent drug uptake offers an opportunity to improve the pharmacokinetic properties of small molecules targeted against the most devastating retinal degenerative diseases. This approach may help establish treatments not only for ocular diseases but also other pathologies such as cancer in which retinoid-based drugs are used.

Two experimentally validated methods for prevention of light-induced retinal degeneration involve 1) sequestration of excess of all-trans-retinal by drugs containing a primary amine group, and 2) inhibition of the retinoid cycle (Maeda et al., 2008, 2012). The unquestionable advantage of the first approach is the lack of adverse side effects caused by simply lowering the toxic levels of free all-trans-retinal. LRAT substrates persist in tissue in two forms: free amines and their acylated (amide) forms. The equilibrium between an active drug and its prodrug is determined by the efficiency of acylation and breakdown of the corresponding amide. Our data suggest that compounds that are fair LRAT substrates but did not inhibit RPE65 were efficiently delivered to ocular tissue. However, their free amine concentrations were too low to effectively sequester the excess of free all-trans-retinal and thus failed to protect against retinal degeneration. In contrast, potent inhibitors of RPE65 that were acylated by LRAT revealed excellent therapeutic properties. Therefore, it became clear that LRAT-aided tissue-specific uptake of drugs is therapeutically beneficial only for inhibitors of the visual cycle.

The ultimate result of our experiments was a determination of key structural features of RPE65 inhibitors that determine their function. The narrow hydrophobic tunnel leading to the active site of RPE65 explains why introduction of a bulky group such as a t-buty1 or benzyl at the C9 position should weaken the inhibitory effect. However, it was surprising to find that methyl groups on the β-ionone ring contributed significantly to inhibitory binding (QEA-A-006-NH₂). In contrast, the conformation of the β-ionone ring had only a slight impact (TEA-A-002-NH₂). Interestingly, introduction of an extra nitrogen atom (QEA-G-001-NH₂ and QEA-G-002-NH₂) moderately recovered the inhibitory properties. This observation supports the previous hypothesis that the isomerization occurs via a carbocation intermediate, and that the positively charged compound inhibits the reaction (Golczak et al., 2005b; Kiser et al., 2009, 2012, 2014).

Finding effective treatments for ocular degenerative diseases is an ongoing task. Challenges in designing the most effective drugs are not limited to optimization of drug-target interactions but also involve understanding routes of eye-specific drug absorbance and storage. We believe that investigating the specificity of natural eye delivery systems and the mode of action of primary amines will shed new light on the prospects and limitations associated with the development of novel small-molecule ocular therapies.

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Authorship Contributions
Participated in research design: Zhang, Golczak, Palczewski, Seibel, Papoian.
Conducted experiments: Zhang, Dong, Golczak.
Contributed new reagents or analytic tools: Zhang, Dong, Mundla, Hu, Seibel, Papoian.
Performed data analysis: Zhang, Dong, Palczewski, Golczak.
Wrote or contributed to the writing of the manuscript: Zhang, Palczewski, Golczak.

References


Sequestration of Toxic All-Trans-Retinal in the Retina 491


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Expansion of first-in-class drug candidates that sequester toxic all-
trans-retinal and prevent light-induced retinal degeneration

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**Supplemental Table S1.**

**Summary of structure factors that affect LRAT substrates and RPE65 inhibitors *in vitro.***

<table>
<thead>
<tr>
<th>Modifications to the structure of retinylamine</th>
<th>LRAT substrate</th>
<th>RPE65 inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removing of methyl groups on the polyene chain</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Introducing hydroxyl group on the β-ionone ring</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Elongating polyene chain</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Introducing oxygen on the β-ionone ring</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Removing of methyl groups on the β-ionone ring</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>+</td>
</tr>
<tr>
<td>Introducing bulky group at C9</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>+</td>
</tr>
<tr>
<td>Shortening polyene chain</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>+</td>
</tr>
<tr>
<td>Changing the conformation of β-ionone ring</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>++</td>
</tr>
<tr>
<td>Introducing bulky group at C13</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>+++</td>
</tr>
</tbody>
</table>

Effects of structural modifications of retinylamine on the acylation by LRAT or their RPE65 inhibitory properties are represented by the following symbols: 0 – not affect, + – minor, ++ – moderate, and +++ – severe decrease, N – data not available.
Supplemental Methods

Chemical synthesis of compounds used in this study.

TEA-A-001 (5-Methyl-7-(2,6,6-trimethyl-cyclohex-1-enyl)-hepta-2,4,6-trienal)

Preparation of Compound-2: To a stirred solution of Compound-1 (20 g, 10 mmol) in benzene (120 mL) at 0 ºC was added a solution of cyanoacetic acid (17.6 g, 20 mmol) followed by piperidine (20 mL) and the resulting mixture was refluxed for 18 h. After cooling to room temperature, the mixture was diluted with water (200 mL) and the aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried over anhydrous Na2SO4 and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-2 (19.3 g, 86%). MS (m/z): [M + H]+, 216.

Preparation of Compound-3: To a stirred solution of Compound-2 (19.3 g, 89.6 mmol) in dry toluene (96 mL) at -5 ºC was slowly added DIBAL-H (1 M in toluene, 89.6 mL) and the reaction mixture was stirred at 0 ºC for 1 h. A chilled 1 M H2SO4 solution was added and the resulting mixture was extracted thrice with ether. The combined organic layers were dried over anhydrous Na2SO4 and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-3 (15.6 g, 79.7%). MS (m/z): [M + H]+, 219.

Preparation of Compound-4: To a stirred solution of Compound-3 (8.3 g, 38 mmol) in benzene (50 mL) cooled to 0 ºC was slowly added a solution of cyanoacetic acid (7.12 g, 76 mmol) followed by piperidine (82 mL). The resulting mixture was refluxed for 18 h, and then evaporated under vacuum. The residue was dissolved in piperidine (25 mL) and pyridine (25 mL). The resulting solution was refluxed for 8 h, and then evaporated under vacuum. The residue was washed with cold 1 M HCl solution and brine, dried over anhydrous Na2SO4 and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel...
and eluted with 40% DCM/petroleum ether to obtain Compound-4 (3.4 g, 37%). MS (m/z): [M + H]+, 242.

**Preparation of TEA-A-001:** To a stirred solution of Compound-4 (3.4 g, 14 mmol) in dry toluene (17.5 mL) at -5 °C was slowly added DIBAL-H (1 M in toluene, 14 mL) and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with a chilled 1 M H2SO4 solution and extracted thrice with ether. The combined organic layers were dried over anhydrous Na2SO4 and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 30% of DCM/petroleum ether to obtain TEA-A-001 (800 mg, 23.3%). 1H NMR (CDCl3, 400 MHz): δ 1.04 (s, 6H), 1.46-1.49 (m, 2H), 1.58-1.64 (m, 2H), 1.73 (d, J = 0.8 Hz, 3H), 2.04 (t, J = 6.4 Hz, 2H), 2.09 (d, J = 0.8 Hz, 3H), 6.14-6.23 (m, 2H), 6.29 (d, J = 12 Hz, 1H), 6.50 (d, J = 16.4 Hz, 1H), 7.54 (dd, J = 12 Hz, 15.2 Hz, 1H), 9.61 (d, J = 8 Hz, 1H); 13C NMR (CDCl3, 100 MHz): δ 10.79, 16.75, 19.44, 26.61, 30.85, 31.91, 37.21, 125.1, 128.4, 129.3, 130.2, 134.1, 135.0, 144.5, 145.8, 191.4. MS (m/z): [M + H]+, 245.3.

TEA-A-002 (5-Methyl-7-(2,6,6-trimethyl-cyclohexa-1,3-dienyl)-hepta-2,4,6-trienal) and TEA-A-003 (7-(3-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-5-methyl-hepta-2,4,6-trienal)

**Preparation of Compound-2:** To a stirred solution of Compound-1 (8 g, 41.6 mmol) in dry DCM (120 mL) at 0 °C was slowly added m-CPBA (15.8 g, 91 mmol). The resulting mixture was stirred at room temperature for 2 h. Then the mixture was filtered and the precipitate was washed with DCM. The combined filtrate was washed serially with 10% aq. Na2SO3, 5% aq. NaOH, water and brine, dried over anhydrous Na2SO4 and concentrated to obtain Compound-2 (10.2 g). The crude material was used for the next step without further purification. MS (m/z): [M + H]+, 209.2.

**Preparation of Compound-3:** To a stirred solution of NaOMe (18 mmol) in methanol (50 mL) was slowly added a solution of Compound-2 (12.5 g, 60 mmol) in methanol (15 mL) and the solution was refluxed for 4 h. Then the solution was neutralized to pH 7 with diluted acetic acid
and evaporated under vacuum. The residue was poured into water (300 mL) and the aqueous layer was extracted with ethyl acetate (5 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 15% of ethyl acetate/petroleum ether to obtain Compound-3 (3.7 g, 42.7% for 2 steps). MS (m/z): [M + H]⁺, 209.2.

Preparation of Compound-4: To a stirred solution of Compound-3 (8.5 g, 40.8 mmol) in benzene (15 mL) at 0 ºC was added cyanoacetic acid (6.94 g, 81 mmol) followed by piperidine (8.1 mL, 81 mmol). The reaction mixture was refluxed for 18 h and then cooled to room temperature. Water (100 mL) was added and the resulting aqueous layer was extracted with ethyl acetate (5 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 12% ethyl acetate/petroleum ether to obtain Compound-4 (8.2 g, 86.9%). MS (m/z): [M - OH]⁺, 214.2.

Preparation of Compound-5: To a stirred solution of Compound-4 (8.3 g, 35 mmol) in dry toluene (45 mL) at -10 ºC under a nitrogen atmosphere was added dropwise DIBAL-H (1 M in toluene, 71.8 mL). The reaction mixture was stirred at -10 ºC for 30 min. Then 1 M H₂SO₄ (20 mL) solution was added and the resulting mixture was extracted with ether (6 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 15% ethyl acetate/petroleum ether to obtain Compound-5 (3 g, 35.7%). MS (m/z): [M - OH]⁺, 217.1.

Preparation of Compound-6: To a stirred solution of Compound-5 (3.0 g, 12.8 mmol in benzene (10 mL) at 0 ºC was added a solution of cyanoacetic acid (2.17 g, 25 mmol) followed by piperidine (3 mL, 25 mmol). The reaction mixture was refluxed for 16 h and then evaporated under vacuum. A solution of piperidine (20 mL) and pyridine (20 mL) was added and the resulting solution was refluxed for 8 h before being evaporated again under vacuum. The residue was diluted with water and extracted with ethyl acetate (200 mL). The combined organic layers were washed with chilled 1 M HCl solution, dried over anhydrous Na₂SO₄ and concentrated to obtain Compound-6 (750 mg, 22.7%). MS (m/z): [M - OH]⁺, 240.3.

Preparation of TEA-A-002 and TEA-A-003: To a stirred solution of Compound-7 (750 mg, 2.9 mmol) in dry toluene (4 mL) at -10 ºC was slowly added DIBAL-H (1 M in toluene, 5.83 mL). The reaction mixture was stirred for at 0 ºC for 30 min, quenched with a cooled saturated sodium potassium tartrate solution and filtered through celite. The filtrate was extracted twice with chloroform. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 6% ethyl acetate/petroleum ether to obtain TEA-A-002 (60 mg, 2.4% based on Compound- 5) and TEA-A-003 (80 mg, 2.6% based on Compound-5). TEA-A-002: ¹H NMR
(CDCl₃, 400 MHz): δ 1.05 (s, 6H), 1.88 (s, 3H), 2.09 (m, 2H), 2.11 (d, J = 0.8 Hz, 3H), 5.79 (m, 1H), 5.87 (d, J = 7.6 Hz, 1H), 6.18 (dd, J = 14.8 Hz, 8 Hz, 2H), 6.34 (m, 2H), 6.51 (d, J = 16 Hz, 1H), 7.54 (dd, J = 14.8 Hz, 12 Hz, 1H), 9.61 (d, J = 8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 13.27, 20.60, 26.97, 29.92, 34.25, 40.10, 126.5, 128.1, 129.1, 130.0, 131.0, 131.5, 135.9, 138.0, 146.8, 148.1, 193.9. IR: 1676 cm⁻¹. MS (m/z): [M + H]+, 243.2

TEA-A-003: ¹H NMR (CDCl₃, 400 MHz): δ 1.02 (s, 3H), 1.05 (s, 3H), 1.40-1.48 (m, 1H), 1.62-1.76 (m, 2H), 1.83 (s, 3H), 1.84-1.96 (m, 1H), 2.09 (d, J = 1.2 Hz, 3H), 4.02 (t, J = 4.8 Hz, 1H), 6.15-6.24 (m, 2H), 6.30 (d, J = 11.6 Hz, 1H), 6.44 (d, J = 16 Hz, 1H), 7.53 (dd, J = 12 Hz, 15.2 Hz, 1H), 9.61 (d, J = 8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 13.36, 18.88, 27.76, 28.62, 29.25, 29.92, 34.73, 35.04, 70.33, 128.4, 131.4, 131.7, 137.8, 141.4, 146.3, 148.0, 194.0. IR: 3418, 1677 cm⁻¹. MS (m/z): [M + H]+, 243.2.

TEA-A-004 (7-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-5-methyl-hepta-2,4,6-trienal)

Preparation of Compound-3: To a stirred suspension of NaH (141 g, 3.52 mol) in THF (7.4 L) at 0 ºC was added dropwise a solution of Compound-2 (571.7 g, 3.23 mol) in dry THF (10 mL). The reaction mixture was stirred at 0 ºC for 30 min and a solution of Compound-1 (370 g, 2.937 mol) in THF (10 mL) was slowly added. The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with diluted HCl and the resulting mixture was extracted
thrice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-3 (370 g, 84.4%). MS (m/z): [M + H]+, 150.2

**Preparation of Compound-4:** To a solution of conc. H2SO4 (360 mL) at 0 ºC was added dropwise a solution of compound-3 (120 g, 0.8 mole) in nitromethane (3 L). The mixture was stirred for 1 h at 0 ºC. Then the reaction was quenched with ice and the resulting mixture was extracted thrice with ether. The combined organic layers were washed with NaHCO3 solution, dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-4 (82 g, 68.7%). MS (m/z): [M + H]+, 150.2.

**Preparation of Compound-5:** To a stirred solution of m-CPBA (217 g, 0.88 mol) in ethyl acetate (787 mL) cooled to 0 ºC was added a solution of Compound-4 (65.6 g, 0.44 mol) and the solution was stirred at room temperature overnight. Then the reaction was quenched with TEA at 0 ºC. The resulting mixture was diluted with ethyl acetate and washed twice with water. The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 4-5% ethyl acetate/petroleum ether to obtain Compound-5 (30 g, 41.2%). MS (m/z): [M + H]+, 166.2.

**Preparation of Compound-6:** To a stirred solution of sodium (1.25 g, 54 mmol) in methanol (10 mL) at 0 ºC was slowly added methanol (450 mL) followed by Compound-5 (30 g, 180 mmol) in methanol (10 mL). The resulting solution was stirred at room temperature overnight, and then evaporated under vacuum. The residue was diluted with water, neutralized with acetic acid and extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-6 (23 g, 77.3%). MS (m/z): [M + H]+, 166.2.

**Preparation of Compound-7:** To a stirred solution of Compound-6 (16 g, 96 mmol) in dry toluene (160 mL) was added PTSA (6.47 g, 37.6 mmol) and the reaction mixture was refluxed for 6 h. Then the solution was cooled to room temperature and water (200 mL) was added. The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with an aq. NaHCO3 solution, then brine, dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 4% ethyl acetate/petroleum ether to obtain Compound-7 (6.5 g, 45.6%). MS (m/z): [M + H]+, 148.2.

**Preparation of Compound-8:** To a stirred solution of m-CPBA (12 g, 48 mmol) in chloroform (72 mL) cooled to 0 ºC was added a solution of Compound-7 (6 g, 40 mmol) in chloroform (10 mL) and the solution was stirred at room temperature overnight. The solution was cooled to 4 ºC...
and both TEA and water were added. The resulting mixture was extracted with DCM. The organic layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 4% ethyl acetate/petroleum ether to obtain Compound-8 (4.9 g, 73.8%). MS (m/z): [M + H]\textsuperscript{+}, 164.2.

**Preparation of Compound-9:** To a stirred solution of Compound-8 (4.9 g, 30 mmol) in ether (49 mL) cooled to -60 °C under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 62 mL), and the resulting solution was stirred at room temperature for 3 h before cooling to -70 °C. Then wet silica gel was added at -70 °C and the resulting mixture was stirred for 1 h. The mixture was filtered and the filtrate was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-9 (3.5 g, 70%). IR: 3406, 1668, 1611 cm\textsuperscript{-1}. MS (m/z): [M + H]\textsuperscript{+}, 169.2.

**Preparation of Compound-11:** To a stirred suspension of NaH (750 mg, 35 mmol) in dry THF (30 mL) at 0 °C was added a solution of Compound-10 (6.76 g, 35 mmol) in dry THF (10 mL). The resulting solution was stirred for 1 h, cooled to 0 °C and then a solution of Compound-9 (1.5 g, 8.9 mmol) in dry THF (10 mL) was slowly added. The reaction mixture was further stirred at room temperature for 3 h. The reaction was quenched with an NH\textsubscript{4}Cl solution and the resulting mixture was extracted thrice with ether. The combined organic layers were washed with brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-11 (1 g, 48.6%). IR: 3407, 2211, 1617 cm\textsuperscript{-1}. MS (m/z): [M + H]\textsuperscript{+}, 214.3.

**Preparation of Compound-12:** To a stirred solution of Compound-11 (1 g, 4.3 mmol) in dry toluene (10 mL) at -60 °C under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 8.9 mL). After addition, the solution was stirred at -60 °C for 2 h and cooled to -70 °C. Wet silica gel was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-12 (830 mg, 83%). MS (m/z): [M + H]\textsuperscript{+}, 235.3.

**Preparation of Compound-13:** To a stirred suspension of NaH (149 mg, 6 mmol) in dry THF (10 mL) cooled to 0 °C under nitrogen was added a solution of Compound-2 (1.1 g, 6 mmol) in dry THF (10 mL). This solution was stirred for 30 min. A solution of Compound-12 (730 mg, 3.1 mmol) in dry THF (10 mL) was added at 0 °C and the resulting mixture was further stirred at room temperature for 3 h. The reaction was quenched with NH\textsubscript{4}Cl solution, and the mixture was extracted with ether twice. The combined organic layers were washed with brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-14 (530 mg, 66.4%). MS (m/z): [M + H]\textsuperscript{+}, 258.2.
Preparation of TEA-A-004: To a stirred solution of Compound-14 (530 mg, 2 mmol) in toluene (5.3 mL) cooled to -60 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 4.24 mL) and the solution was stirred at room temperature for 2 h. Then reaction mass was cooled to -70 ºC, wet silica gel was added and the mixture was stirred for 1 h. The mixture was filtered and the filtrate was dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain TEA-A-004 (230 mg, 44%). 1H NMR (CDCl3, 400 MHz): δ 1.08 (s, 6H), 1.48 (t, J = 12 Hz, 1H), 1.74 (s, 3H), 1.76-1.81 (m, 1H), 2.02-2.08 (m, 1H), 2.09 (s, 3H), 2.41 (dd, J = 6 Hz, 17.2 Hz, 1H), 4.00 (m, 1H), 6.15-6.21 (m, 2H), 6.29 (d, J = 12 Hz, 1H), 6.43 (d, J = 15.6 Hz, 1H), 7.53 (dd, J = 12 Hz, 14.8 Hz, 1H), 9.61 (d, J = 8 Hz, 1H), 13C NMR (CDCl3, 100 MHz): δ 13.36, 21.85, 28.94, 30.43, 37.31, 42.76, 48.51, 65.07, 128.1, 128.4, 131.2, 131.6, 137.37, 137.39, 146.5, 148.1, 194.0. IR: 3413, 1667 cm⁻¹. MS (m/z): [M + H]⁺, 261.2.

PEA-A-003 (11-(4-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-5,9-dimethyl-undeca-2,4,6,8,10-pentaenal)

Preparation of Compound-3: To a stirred suspension of NaH (190 mg, 7.9 mmol) in dry THF (20 mL) cooled to 0 ºC under nitrogen was added a solution of Compound-2 (1.68 g, 7.9 mmol) in dry THF (10 mL). The solution was stirred for 10 min and a solution of Compound-1 (530 mg, 2.2 mmol) in dry THF (10 mL) was added. The resulting solution was stirred at room temperature for 3 h, and then the reaction was quenched with an NH4Cl solution. The mixture was extracted thrice with ether. The combined organic layers were washed with brine, dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-3 (580 mg, 86.3%). MS (m/z): [M + H]⁺, 298.4.

Preparation of Compound-4: To a stirred solution of Compound-3 (580 mg, 1.95 mmol) in toluene (6 mL) at -60 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 4 mL) and the mixture was stirred at room temperature for 2 h. Then the solution was cooled to -20 ºC, and poured onto wet silica gel. The resulting mixture was stirred for 1 h, and filtrated. The filtrate was dried over anhydrous Na2SO4 and concentrated. The crude compound was purified
by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-4 (250 mg, 42.6%). MS (m/z): [M + H]$^+$, 301.4.

**Preparation of Compound-6:** To a stirred suspension of NaH (40 mg, 1.66 mmol) in dry THF (8 mL) cooled to 0 ºC under nitrogen was added a solution of Compound-5 (295 mg, 1.66 mmol) in dry THF (10 mL). The mixture was stirred for 30 min and cooled to 0 ºC. A solution of Compound-4 (250 mg, 0.83 mmol) in dry THF (10 mL) was added and the mixture was stirred at room temperature for 2 h. The reaction was quenched with NH$_4$Cl solution and the resulting mixture was extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-6 (200 mg, 74.5%). MS (m/z): [M + H]$^+$, 323.4.

**Preparation of PEA-A-003:** To a stirred solution of Compound-6 (200 mg, 0.6 mmol) in toluene (5 mL) at -60 ºC under nitrogen was added DIBAL-H (1.7 M in toluene, 1.2 mL). The resulting solution was stirred at room temperature for 2 h, cooled to -20 ºC and poured onto wet silica gel. This mixture was stirred for 1 h and filtered. The filtrate was dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain PEA-A-003 (100 mg, 49.6%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.07 (s, 6H), 1.48 (t, $J = 12$ Hz, 1H), 1.74 (s, 3H), 1.76-1.80 (m, 1H), 2.00 (s, 3H), 2.01-2.09 (m, 1H), 2.11 (s, 3H), 2.39 (dd, $J = 6$ Hz, 17 Hz, 1H), 4.00 (m, 1H), 6.12-6.16 (m, 4H), 6.35 (d, $J = 12.4$ Hz, 1H), 6.39 (d, $J = 15.2$ Hz, 1H), 6.91 (dd, $J = 11.4$ Hz, 15 Hz, 1H), 7.51 (dd, $J = 12$ Hz, 14.8 Hz, 1H), 9.61 (d, $J = 8$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 13.14, 13.51, 21.85, 28.95, 30.46, 37.33, 42.76, 48.58, 65.21, 127.1, 127.8, 128.9, 129.9, 130.6, 131.1, 136.1, 137.8, 138.3, 139.3, 146.8, 147.9, 193.8. MS (m/z): [M + H]$^+$, 327.3.

PEA-A-002 (11-(3-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-5,9-dimethyl-undeca-2,4,6,8,10-pentaenal)
Preparation of Compound-3: To a stirred solution of t-BuOK (4.3 g, 38 mmol) in methanol (150 mL) at 0 °C was added a solution of Compound-2 (6.0 g, 25 mmol) in methanol (10 mL) followed by a solution of Compound-1 (7.8 g, 51 mmol) in methanol (10 mL). The solution was stirred at room temperature overnight and then evaporated. The residue was poured into water (100 mL) and the resulting aqueous layer was extracted twice with ether. Then the aqueous layer was acidified with diluted HCl and extracted thrice with ether. The combined ether organic layers were dried over anhydrous Na₂SO₄ and concentrated to obtain Compound-3 (6.0 g, 70%).

Preparation of Compound-4: A solution of Compound-3 (6.0 g, 17.5 mmol) in piperidine (120 mL) and pyridine (120 mL) was refluxed for 3 h, and then evaporated under vacuum. The residue was diluted with ethyl acetate and washed with a diluted HCl solution. The organic layer was dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 10% ethyl acetate/petroleum ether to obtain Compound-4 (2.7 g, 51.7%). MS (m/z): [M - OH]⁺, 280.4.

Preparation of Compound-5: To a stirred solution of Compound-4 (2.7 g, 9 mmol) in dry toluene (22 mL) at -5 °C under nitrogen was added dropwise DIBAL-H (1M in toluene, 13.6 mL) and the solution was stirred at 0 °C for another hour. The reaction was slowly quenched with a cold saturated sodium potassium tartrate solution, and the resulting mixture was filtered through celite. The filtrate was extracted with chloroform. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 10% acetone/petroleum ether to obtain Compound-5 (1.77 g, 65.5%). MS (m/z): [M - OH]⁺, 283.4.

Preparation of Compound-6: To a stirred solution of Compound-5 (1.77 g, 5.9 mmol) in benzene (10.6 mL) cooled to 10 °C was added a solution of cyanoacetic acid (1.0 g, 11 mmol) followed by piperidine (1.4 mL, 11 mmol). The reaction mixture was refluxed for 4 h and
evaporated under vacuum. The residue was dissolved in a solution of piperidine (25 mL) and pyridine (25 mL). The reaction mixture was refluxed for 16 h and then concentrated under vacuum. The residue was re-dissolved in ethyl acetate and washed with a diluted HCl solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 10% acetone/petroleum ether to obtain compound-6 (650 mg, 34.2%). MS (m/z): [M - OH]$^+$, 307.4.

**Preparation of PEA-A-002:** To a stirred solution of Compound-7 (650 mg, 2 mmol) in toluene (4 mL) at -5 °C under nitrogen was added DIBAL-H (1 M in toluene, 3 mL) dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then the reaction was slowly quenched with a cold saturated sodium potassium tartrate solution. The resulting mixture was filtered through celite. The filtrate was extracted with chloroform. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude compound was column chromatography on 230-400 mesh silica gel and eluted with 5% acetone/petroleum ether to obtain PEA-A-002 (240 mg, 36.8%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.02 (s, 3H), 1.05 (s, 3H), 1.40-1.46 (m, 1H), 1.61-1.73 (m, 2H), 1.84 (s, 3H), 1.88-1.92 (m, 1H), 2.01 (d, $J = 0.8$ Hz, 3H), 2.11 (d, $J = 0.8$ Hz, 3H), 4.01 (t, $J = 4.6$ Hz, 1H), 6.14-6.21 (m, 4H), 6.36 (d, $J = 13.6$ Hz, 1H), 6.40 (d, $J = 15.2$ Hz, 1H), 6.91 (dd, $J = 11.6$ Hz, 14.8 Hz, 1H), 7.51 (dd, $J = 12$ Hz, 14.8 Hz, 1H), 9.61 (d, $J = 8$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 13.13, 13.52, 18.93, 27.74, 28.67, 29.31, 34.75, 35.04, 70.47, 127.9, 129.0, 129.8, 130.5, 131.0, 131.2, 136.3, 138.6, 139.1, 141.9, 146.7, 147.8, 193.8. MS (m/z): [M - OH]$^+$, 309.

**QEA-A-005 (9-(2,6,6-Trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal)**
Preparation of Compound-2: To a stirred solution of NaOH (112 g, 2.8 mol) in water (480 mL) at 0 °C was added bromine (36.2 mL, 1.4 mol) and the reaction mixture was stirred for 2 h. Then a solution of Compound-1 (30 g, 156 mmol) in dioxane (60 mL) was slowly added. The mixture was stirred at room temperature for 4 h. The reaction was quenched with sodium sulphite solution and the resulting mixture was washed twice with ether. The aqueous layer was cooled to 0 °C, acidified with diluted HCl and extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to obtain Compound-2 (30 g, 99%). MS (m/z): [M + H]+, 195.2.

Preparation of Compound-3: To a solution of LAH (8.2 g, 216 mmol) in anhydrous ether (168 mL) at 0 °C was added a solution of Compound-2 (21 g, 108 mmol) in anhydrous ether. The reaction mixture was stirred at 0 °C for 2 h. Then the reaction was quenched with a cold saturated NH₄Cl solution and the resulting mixture was filtered through celite. The organic layer was separated from the filtrate, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on silica gel and eluted with 15-20% ethyl acetate/hexane to obtain Compound-3 (19 g, 97.5%). MS (m/z): [M - OH]+, 163.3.

Preparation of Compound-4: To a stirred solution of Compound-3 (19 g, 105 mmol) in DCM (20 mL) at 0 °C was added PDC (119 g, 316 mmol) in portions. The reaction mixture was stirred at 0 °C for 4 h, diluted with ether and filtered through silica gel and concentrated. The crude
compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 4% ethyl acetate/hexane to obtain Compound-4 (10.7 g, 57.2%). MS (m/z): [M + H]^+, 179.3.

**Preparation of Compound-6:** To a stirred suspension of NaH (1.4 g, 58 mmol) in THF (10 mL) cooled to 0 ºC was slowly added a solution of Compound-5 (10.3 g, 58 mmol) in dry THF (10 mL). The reaction mixture was stirred for 10 min, cooled to 0 ºC and a solution of Compound-4 (6.9 g, 38 mmol) in THF (10 mL) was added. The reaction was continued at room temperature for 2 h, quenched with an NH₄Cl solution and the resulting mixture was extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on silica gel and eluted with 5% ethyl acetate/hexane to obtain Compound-6 (4.5 g 57.8%). IR: 2212 cm⁻¹. MS (m/z): [M + H]^+, 202.3.

**Preparation of Compound-7:** To a stirred solution of Compound-6 (9 g, 44 mmol) in toluene (90 mL) at -30 ºC was added dropwise DIBAL-H (1.7 M in toluene, 29 mL) under nitrogen. The reaction solution was stirred at -30 ºC for 30 min, quenched with an ice cold sodium potassium tartrate solution and stirred at -30 ºC for 45 min. The reaction mixture was filtered through celite, the precipitate was washed with ether and the aqueous layer from the filtrate was extracted twice with chloroform. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and was eluted with 1% ethyl acetate/hexane to obtain Compound-7 (1.78 g, 19.5%). MS (m/z): [M + H]^+, 205.3.

**Preparation of Compound-8:** To a stirred suspension of NaH (312 mg, 13 mmol) in THF (10 mL) cooled to 0 ºC was slowly added a solution of Compound-5 (2.3 g, 13 mmol) in dry THF (10 mL) and the reaction mixture was stirred for another 10 min. A solution of Compound-6 (1.78 g, 8.7 mmol) in THF (10 mL) was added and the solution was stirred at room temperature for 2 h. The reaction was quenched with NH₄Cl solution and the resulting mixture was extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% ethyl acetate/hexane to obtain Compound-8 (1.39 g, 70%). MS (m/z): [M + H]^+, 228.3.

**Preparation of Compound-9:** To a stirred solution of Compound-8 (1.39 g, 6.1 mmol) in toluene (10 mL) at -20 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 7.2 mL). The reaction mixture was stirred at -20 ºC for 30 min. Then the reaction was quenched with an ice cold solution of sodium potassium tartrate. The resulting mixture was stirred at -20 ºC for another 45 min, and filtered through celite. The precipitate was washed with ether and the aqueous layer of the filtrate was extracted twice with chloroform. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 2% ethyl acetate/hexane to obtain Compound-9 (490 mg, 35 %). MS (m/z): [M + H]^+, 230.5.
Preparation of Compound-10: To a stirred suspension of NaH (76 mg, 3.19 mmol) in THF (5.6 mL) cooled to 0 °C was slowly added a solution of Compound-5 (566 mg, 3.19 mmol) in dry THF (10 mL). The reaction mixture was stirred for 10 min, cooled to 0 °C. A solution of Compound-9 (490 mg, 2.13 mmol) in THF (10 mL) was added, and the solution was stirred at room temperature for 2 h. The reaction was quenched with NH4Cl solution and the resulting mixture was extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by silica gel column chromatography and eluted with 1% ethyl acetate/hexane to obtain Compound-10 (450 mg, 83.4%). MS (m/z): [M + H]+, 254.4.

Preparation of QEA-A-005: To a stirred solution of Compound-10 (450 mg, 1.77 mmol) in toluene (4.5 mL) at -20 °C under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 2 mL). The reaction mixture was stirred at -20 °C for 30 min. Then the reaction was quenched with an ice cold solution of sodium potassium tartrate and the resulting solution was stirred at -20 °C for another 45 min. The mixture was filtered through celite. The precipitate was washed with ether and the aqueous layer of filtrate was extracted twice with chloroform. The combined organic layers were dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/hexane to obtain QEA-A-005 (80 mg, 17.6%). 1H NMR (CDCl3, 300 MHz): δ 1.04 (s, 6H), 1.45 (m, 2H), 1.61 (m, 2H), 1.74 (s, 3H), 2.04 (t, J = 6.6 Hz, 2H), 6.14 (dd, J = 8 Hz, 15.2 Hz, 1H), 6.20 (dd, J = 10.8 Hz, 15.2 Hz, 1H), 6.30 (dd, J = 11.2 Hz, 14.8 Hz, 1H), 6.38 (d, J = 16 Hz, 1H), 6.43 (dd, J = 11.2 Hz, 14.8 Hz, 1H), 6.55(dd, J = 11 Hz, 15 Hz, 1H), 6.73 (dd, J = 11 Hz, 14.8 Hz, 1H), 7.15 (dd, J = 11.2 Hz, 15.2 Hz, 1H), 9.55 (d, J = 8 Hz, 1H); 13C NMR (CDCl3, 100 MHz): δ 19.31, 22.05, 29.15, 33.65, 34.39, 39.96, 129.18, 129.92, 130.68, 132.55, 132.76, 137.54, 140.45, 152.46, 193.8. MS (m/z): [M + H]+, 257.3.

QEA-A-004 (7-Methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal)

Preparation of Compound-2: To a stirred solution of TEA-A-001 (2.0 g, 8.1 mmol) in benzene (12 mL) at 0 °C was added a solution of cyanoacetic acid (1.4 g, 16.3 mmol) followed by piperidine (1.61 mL, 16.3 mmol). The reaction mixture was stirred for 18 h and then evaporated. A solution of piperidine (25 mL) and pyridine (25 mL) was added. The resulting solution was refluxed for 8 h, and then evaporated under vacuum. The residue was poured into ethyl acetate and washed thrice with a dilute HCl solution. The organic layer was dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by column chromatography on 60-
120 mesh silica gel and eluted with 40% DCM/petroleum ether to obtain Compound-2 (900 mg, 41.5%). MS (m/z): [M + H]$^+$, 268.4.

**Preparation of QEA-A-004:** To a solution of Compound-2 (900 mg, 3.37 mmol) in dry toluene (4.5 mL) at -5 ºC under nitrogen was slowly added DIBAL-H (1 M in toluene, 3.37 mL). The solution was stirred at 0 ºC for 1 h, and then the reaction was quenched with 1 M H$_2$SO$_4$ solution. The resulting mixture was extracted thrice with ether. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 30% DCM/petroleum ether to obtain QEA-A-004 (180 mg, 18%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.03 (s, 9H), 1.45-1.49 (m, 2H), 1.58-1.65 (m, 2H), 1.72 (s, 3H), 2.02 (s, 3H), 2.03 (m, 2H), 6.11-6.19 (m, 3H), 6.35-6.49 (m, 2H), 7.07 (dd, J = 14.4 Hz, 12 Hz, 1H), 7.21 (dd, J = 15 Hz, 11 Hz, 1H), 9.56 (dd, J = 8 Hz, 0.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 13.17, 19.38, 20.01, 29.19, 29.93, 33.39, 34.49, 39.79, 129.2, 129.6, 130.5, 130.7, 131.0, 137.1, 137.8, 139.5, 142.8, 152.7, 193.8. MS (m/z): [M + H]$^+$, 271.4.

**PEA-A-001** (5,9-Dimethyl-11-(2,6,6-trimethyl-cyclohex-1-enyl)-undeca-2,4,6,8,10-pentaenal)

**Preparation of Compound-2:** To a stirred solution of Compound-1 (20 g, 104 mmol) in benzene (120 mL) at 0 ºC was added a solution of cyanoacetic acid (17.6 g, 208 mmol) in benzene (5 mL) followed by piperidine (20.4 mL). The reaction mixture was refluxed for 18 h, cooled to room temperature and diluted with water (200 mL). The aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography on 60-120 mesh silica.
Preparation of Compound-3: To a stirred solution of Compound-2 (19.3 g, 89.6 mmol) in dry toluene (96 mL) at -5 °C was slowly added DIBAL-H (1 M in toluene, 89.6 mL) and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with chilled 1 M H₂SO₄ and the resulting mixture was extracted thrice with ether. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain compound-3 (15.6 g, 79.7%). MS (m/z): [M + H]⁺, 219.3.

Preparation of Compound-5: To a stirred solution of i-BuOK (4.63 g, 41.25 mmol) in methanol (100 mL) at 0 °C was added a solution of Compound-3 (6.0 g, 27.5 mmol) and Compound-4 (8.425 g, 55 mmol). The solution was stirred at room temperature for 2 h and evaporated under vacuum. The residue was poured into water and extracted thrice with ether. The aqueous layer was acidified with a diluted HCl solution and extracted thrice with ether. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to obtain Compound-5 (21.6 g). The crude material was used for the next step without further purification.

Preparation of Compound-6: To a stirred solution of crude Compound-5 (21.6 g, 66 mmol) was added dropwise piperidine (20 mL) followed by pyridine (20 mL). The reaction mixture was refluxed for 3 h, and evaporated under vacuum. The residue was poured into ethyl acetate and washed thrice with a diluted HCl solution. The resulting mixture was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel with 10% ethyl acetate/petroleum ether as to obtain Compound-6 (4.9 g, 63% for two steps). MS (m/z): [M + H]⁺, 282.4.

Preparation of Compound-7: To a stirred solution of Compound-6 (8.7 g, 30 mmol) in dry toluene (43.5 mL) at -5 °C under nitrogen was added dropwise DIBAL-H (1 M in toluene, 31 mL). The reaction mixture was stirred at 0 °C for 1 h. The reaction was slowly quenched with potassium sodium tartrate solution and the resulting mixture was filtered through celite. The filtrate was extracted with chloroform thrice. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 230-400 mesh silica gel and eluted with 10% DCM/petroleum ether to obtain Compound-7 (2.3 g, 26.2%). MS (m/z): [M + H]⁺, 285.4.

Preparation of Compound-9: To a stirred solution of Compound-7 (2.1 g, 7.38 mmol) in benzene (12.6 mL) cooled to at 0 °C was added a solution of cyanoacetic acid (1.2 g, 14.7 mmol) followed by piperidine (1.4 mL). The reaction mixture was refluxed for 5 h and then evaporated. A solution of piperidine (25 mL) and pyridine (25 mL) was added to the residue. The resulting mixture was refluxed for 16 h and then evaporated under vacuum. The residue was washed thrice
with diluted 1 M HCl solution and then brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 20% of DCM/petroleum ether to obtain Compound-9 (600 mg, 26.4%). MS (m/z): [M + H]⁺, 308.4.

Preparation PEA-A-001: To a stirred solution of Compound-9 (600 mg, 1.95 mmol) in dry toluene (3 mL) at -5 ºC under nitrogen was added dropwise DIBAL-H (1 M in toluene, 1.95 mL). The reaction mixture was stirred at 0 ºC for 1 h. The reaction was slowly quenched with potassium sodium tartrate solution and the resulting mixture was filtered through celite. The filtrate was extracted with chloroform. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 230-400 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain PEA-A-001 (75 mg, 12.4%). ¹H NMR (CDCl₃, 400 MHz): δ 1.03 (s, 6H), 1.46 (m, 2H), 1.59-1.63 (m, 2H), 1.72 (d, J = 0.8 Hz, 3H), 2.01 (d, J = 0.8 Hz, 3H), 2.02 (m, 2H), 2.11 (d, J = 0.8 Hz, 3H), 6.13-6.40 (m, 6H), 6.92 (dd, J = 15.2 Hz, 11.6 Hz, 1H), 7.51 (dd, J = 14.8 Hz, 12 Hz, 1H), 6.92 (dd, J = 15.2 Hz, 11.6 Hz, 1H), 9.61 (d, J = 8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 13.16, 13.52, 19.43, 22.01, 29.2, 33.36, 34.49, 39.81, 128.71, 128.92, 130.12, 130.19, 130.37, 130.95, 135.72, 137.54, 137.93, 139.7, 146.94, 147.97, 193.87. MS (m/z): [M + H]⁺, 311.4.

QEA-B-004 (3,7-Di-tert-butyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal)

Preparation of Compound-1: To a suspension of NaH (5 g, 0.2 mol) in dry THF (10 mL) at 0 ºC was added dropwise a solution of β-ionone (10 g, 52 mmol) in dry THF (10 mL). The reaction mixture was stirred at 0 ºC for 1 h. Then a solution of methyl iodide (12.5 mL, 0.2 mol) in dry THF (5 mL) was slowly added and the resulting solution was stirred at room temperature overnight. The reaction was quenched with NH₄Cl solution and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-1 (5 g, 41%). MS (m/z): [M + H]⁺, 235.3
Preparation of Compound-3: To a stirred suspension of NaH (1.54 g, 64 mmol) in dry THF (20 mL) at 0 ºC was added dropwise a solution of Compound-2 (11.4 g, 64 mmol) in dry THF (10 mL). The reaction mixture was stirred at 0 ºC for 10 min. Then a solution of Compound-1 (5 g, 21 mmol) in dry THF (10 mL) was slowly added and the solution was stirred at 50 ºC for 2 h and at room temperature for 12 h. The reaction was quenched with NH₄Cl solution and the resulting mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel l and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-3 (5 g, 91%). MS (m/z): [M + H]+, 258.4.

Preparation of Compound-4: To a stirred solution of compound-3 (5.3 g, 20.6 mmol) in dry toluene (53 mL) at -30 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 24 mL). The solution was cooled to -10 ºC, poured onto wet silica gel and stirred for 30 min. The mixture was filtered through silica gel. The precipitate was washed twice with ether and the filtrate was concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.8% ethyl acetate/petroleum ether to obtain Compound-4 (1.53 g, 28.5%). MS (m/z): [M + H]+, 261.4.

Preparation of Compound-6: To a stirred suspension of NaH (69 mg, 2.88 mmol) in dry THF (20 mL) at 0 ºC was added dropwise a solution of Compound-5 (747 mg, 2.88 mmol) in dry THF (10 mL). The reaction mixture was stirred for 1 h. Then a solution of Compound-4 (300 mg, 1.15 mmol) in dry THF (10 mL) was slowly added at 0 ºC. The resulting solution was stirred for 3 h, the reaction was quenched with NH₄Cl solution and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-6 (320 mg, 76%). IR: 2208 cm⁻¹. MS (m/z): [M + H]+, 366.6.

Preparation of QEA-B-004: To a stirred solution of Compound-6 (320 mg, 0.87 mmol) in dry toluene (10 mL) at -30 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 2.1 mL). The solution was cooled to -10 ºC, poured onto wet silica gel and stirred for 30 min. The mixture was filtered, the precipitate was washed twice with ether and the filtrate was concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain QEA-B-004 (85 mg, 26.4%). ¹H NMR (CDCl₃, 300 MHz): δ 1.14 (s, 9H), 1.15 (s, 9H), 1.42-1.46 (m, 2H), 1.58-1.61 (m, 2H), 1.70 (d, J = 0.4 Hz, 3H), 1.99 (t, J = 6.4 Hz, 2H), 5.89-6.02 (m, 3H), 6.18 (d, J = 10.8 Hz, 1H), 6.31 (d, J = 14.8 Hz, 1H), 6.80 (dd, J = 14.8 Hz, 10.8 Hz, 1H), 9.65 (d, J = 7.6 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 19.42, 22.08, 29.06, 29.47, 29.88, 33.05, 34.25, 36.51, 37.21, 39.60, 121.77, 125.25, 125.8, 129.7, 129.8, 134.9, 137.9, 140.0, 155.8, 173.1, 194.0. MS (m/z): [M + H]+, 369.6.
QEA-B-003 (7-tert-Butyl-3-methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal)

Preparation of Compound-3: To a stirred suspension of NaH (276 mg, 11 mmol) in dry THF (2 mL) at 0 ºC was added dropwise a solution of Compound-2 (2.5 g, 11 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 40 min. Then a solution of Compound-1 (1.2 g, 4.6 mmol) in dry THF (10 mL) was slowly added at 0 ºC and the resulting mixture was stirred for 1 h. The reaction was quenched with NH4Cl solution and the product was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 2 % ethyl acetate/petroleum ether to obtain Compound-3 (1.4 g, 94%). MS (m/z): [M + H]+, 324.4.

Preparation of QEA-B-003: To a stirred solution of Compound-3 (1.4 g, 4.3 mmol) in dry toluene (10 mL) at -30 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 5 mL). The solution was cooled to -10 ºC, poured onto wet silica gel and stirred for 30 min. The mixture was filtered, the precipitate was washed twice with ether and the combined filtrate was concentrated. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 2% ethyl acetate/petroleum ether to obtain QEA-B-003 (840 mg, 59.9%). 1H NMR (CDCl3, 300 MHz): δ 1.05 (s, 6H), 1.15 (s, 9H), 1.4-1.5 (m, 2H), 1.6-1.7 (m, 2H), 1.8 (s, 3H), 2.0-2.1 (m, 2H), 2.2-2.3 (s, 3H), 5.9-6.0(m, 1H), 6.0-6.1 (m, 2H), 6.2-6.3 (d, 1H), 6.4-6.45(d, 1H), 7.3-7.4 (m, 1H), 10.1 (d, 1H). MS (m/z): [M + H]+, 327.3.

QEA-F-001 (3,7-Dimethyl-9-(2,2,6-trimethyl-cyclohexyl)-nona-2,4,6,8-tetraenal)

Preparation of Compound-2: To Ac2O (148 mL, 1.45 mol) cooled to 0 ºC under nitrogen was added NaOAc (4.6 g, 5.5 mmol) followed by TEA (168 mL, 1.2 mol). The solution was heated
to 75 ºC. Then Compound-1 (172 g, 1.11 mol) was added dropwise and the solution was refluxed for 6 h. The reaction was quenched with water (100 mL), and the resulting mixture was extracted with toluene twice. The combined toluene solution was used in the next step without further purification.

**Preparation of Compound-3:** To a stirred solution of the above Compound-2 in toluene (89 mL) was added dropwise a solution of 85% H₃PO₄ (110 g). The solution was refluxed for 3 h, cooled to 5 ºC and poured into cold water. The organic layer was washed with a NaHCO₃ solution, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 5% of ethyl acetate/petroleum ether to obtain Compound-3 (6.5 g, 3.7%). MS (m/z): [M + H]+, 155.2.

**Preparation of Compound-5:** To a stirred suspension of NaH (2.025 g, 84 mmol) in THF (190 mL) at 0 ºC was slowly added a solution of Compound-4 (18.3 g, 84 mmol). The solution was stirred for 45 min and then cooled to 0 ºC. A solution of Compound-3 (6.5 g, 42 mmol) in THF (10 mL) was added, and the solution was stirred at room temperature for 1 h. the reaction was quenched with an NH₄Cl solution. The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 5% ethyl acetate/petroleum ether to obtain Compound-5 (6.1 g, 66.7%). MS (m/z): [M + H]+, 218.2.

**Preparation of Compound-6:** To a stirred solution of Compound-5 (6 g, 27.6 mmol) in dry toluene (60 mL) cooled to -60 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 32.5 mL). The reaction mixture was stirred at -60 ºC for 30 min, then warmed to -30 ºC and poured onto wet silica gel, stirred for 1 h and filtered. The precipitate was washed twice with ether and the filtrate was concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% of ethyl acetate/petroleum ether as to obtain Compound-6 (1.55 g, 25%). MS (m/z): [M + H]+, 221.2.

**Preparation of Compound-8:** To a stirred solution of t-BuOK (1 g, 9 mmol) at 0 ºC was added methanol (25 mL) followed by a solution of Compound-6 (0.8 g, 3.6 mmol) in methanol (10 mL). Then a solution of Compound-7 (1.1 g, 7.2 mmol) in methanol (10 mL) was added under nitrogen. The reaction solution was stirred at room temperature for 16 h and then evaporated. The residue was dissolved in a solution of pyridine (32 mL) and piperidine (32 mL). The mixture was refluxed for 16 h and then evaporated. Then diluted HCl was added to the residue and the resulting mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/hexane to obtain Compound-8 (380 mg, 38%). MS (m/z): [M + H]+, 284.4.
**Preparation of QEA-F-001:** To a stirred solution of Compound-8 (380 mg, 1.3 mmol) in dry toluene (1.9 mL) cooled to -20 ºC under nitrogen was added dropwise DIBAL-H (1 M in toluene, 1.4 mL). The reaction mixture was stirred at -20 ºC for 30 min, poured into an ice cold solution of sodium potassium tartrate and stirred at 0 ºC for 1 h. The resulting mixture was filtered through celite and the filtrate was extracted twice with chloroform. The combined organic layers were dried over anhydrous Na2SO4 and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/hexane to obtain QEA-F-001 (80 mg, 20.8%). 1H NMR (CDCl3, 300 MHz): δ 0.9 (s, 9H), 1.35-1.45 (m, 3H), 1.55-1.65 (m, 4H), 2.1 (m, 3H), 2.2 (m, 1H), 2.3 (s, 3H), 5.9-6.0 (m, 2H), 6.2-6.3 (m, 2H), 6.3-6.4 (m, 1H), 6.6-6.7 (m, 1H), 10.1 (d, 1H). MS (m/z): [M + H]+, 287.4.

**QEA-A-006 (9-Cyclohex-1-enyl-3,7-dimethyl-nona-2,4,6,8-tetraenal)**

![Chemical Reaction Diagram]

**Preparation of Compound-2:** To a stirred solution of trichloroethylene (5 mL) and DMF (101.5 mL, 1.314 mol) at 0 ºC was added dropwise POCl3 and the solution was stirred at room temperature for 30 min. Then a solution of Compound-1 (100 g, 1.01 mol) in trichloroethylene (5 mL) was added. The solution was stirred at 55-60 ºC for 3 h. A solution of sodium acetate (375 g, 4.57 mol) in water (800 mL) was added to the mixture at 35 ºC. The resulting organic layer was dried on anhydrous Na2SO4 and concentrated. The crude compound (122 g, 844 mmol) was taken to the next step without further purification.

**Preparation of Compound-3:** To a stirred solution of Compound-2 (122 g, 844 mmol) in ethanol (9.6 mL) at room temperature was added Zn dust (496 g, 7.59 mol). The reaction mixture was refluxed for 2 h, and then cooled to room temperature. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in water and ethyl acetate, then filtered...
through celite. The organic layer of filtrate was washed with water, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by fractional distillation to obtain Compound-3 (17 g, 15%). MS (m/z): [M + H]⁺, 111.2.

**Preparation of Compound-5:** To a stirred solution of t-BuOK (30.55 g, 272 mmol) in methanol (10 mL) under nitrogen at 0 ºC was added a solution of Compound-3 (12 g, 108 mmol) in methanol (10 mL) followed by Compound-4 (33.36 g, 210 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature overnight, and then evaporated. The residue was poured into diluted HCl and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to obtain Compound-5 (40 g). The crude material was used for the next step without further purification.

**Preparation of Compound-6:** A solution of crude Compound-5 (40 g) in piperidine (20 mL) and pyridine (20 mL) was refluxed overnight. Then the solution was evaporated under vacuum. The residue was poured into diluted HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/hexane to obtain Compound-6 (4.71 g, 25% in 2 steps). MS (m/z): [M + H]⁺, 174.2.

**Preparation of Compound-7:** To a stirred solution of Compound-6 (3.6 g, 20 mmol) in dry toluene (5 mL) at -10 ºC was slowly added DIBAL-H (1 M in toluene, 23 mL) and the reaction mixture was stirred at 0 ºC for 30 min. Then the mixture was poured into an ice cold solution of sodium potassium tartrate and stirred at 0 ºC for 1 h and filtered through celite. The filtrate was extracted twice with chloroform. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 2% ethyl acetate/hexane to obtain Compound-7 (750 mg, 20%). MS (m/z): [M + H]⁺, 177.1.

**Preparation of Compound-9:** To a stirred suspension of NaH (395 mg, 16 mmol) in dry THF (20 mL) at 0 ºC was added dropwise a solution of Compound-8 (3.8 g, 16 mmol) in dry THF (10 mL). A solution of Compound-7 (950 mg, 5 mmol) in dry THF (10 mL) was slowly added at 0 ºC. The reaction solution was stirred at room temperature for 3 h. The reaction was quenched with an NH₄Cl solution and the resulting mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 2% ethyl acetate/hexane to obtain Compound-9 (750 mg, 58.1%). MS (m/z): [M + H]⁺, 240.3.

**Preparation of QEA-A-006:** To a stirred solution of Compound-9 (0.83 g, 3 mmol) in dry toluene (5 mL) at -10 ºC was slowly added DIBAL-H (1 M in toluene, 3.8 mL). The reaction mixture was stirred at -10 ºC for 30 min, poured into an ice cold solution of sodium potassium tartrate. The resulting mixture was stirred at 0 ºC for 1 h, and filtered through celite. The filtrate
was extracted twice with chloroform. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/hexane to obtain **QEA-A-006** (120 g, 14.2%).

\[ ^1H \text{ NMR (CDCl}_3, 400 \text{ MHz): } \delta 1.6-1.7 \text{ (m, 4H), 2.01 (d, } J = 0.8 \text{ Hz, 3H), 2.19 (m, 4H), 2.32 (d, } J = 0.8 \text{ Hz, 3H), 5.9 (t, } J = 3.6 \text{ Hz, 1H), 5.97 (d, } J = 8.4 \text{ Hz, 1H), 6.22-6.43 \text{ (m, 4 H), 7.12 (dd, } J = 11.4 \text{ Hz, 15.4 Hz, 1H), 10.1 (d, } J = 8 \text{ Hz, 1H); } ^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz): } \delta 13.33, 13.35, 22.65, 24.74, 26.54, 129.22, 129.38, 130.18, 132.59, 132.81, 134.60, 134.62, 136.32, 141.61, 155.09, 191.35. MS (m/z): [M + H]^{+}, 243.2.\]

**QEA-F-002 (9-Cyclopentyl-3,7-dimethyl-nona-2,4,6,8-tetraenal)**

![Chemical structure of QEA-F-002](image)

**Preparation of Compound-2:** To a stirred suspension of Mg metal (13.8 g, 0.57 mol) in dry THF (100 mL) at room temperature was slowly added a catalytic amount of iodine followed by Compound-1 (86 g, 0.57 mol) in ether (6 mL). Then a solution of N-formylpiperidine in ether was added. The resulting solution was stirred at room temperature for 1.5 h. The reaction was quenched with 3 M HCl, and the resulting mixture was extracted twice with ether. The combined organic layers were washed serially with aq. NaHCO₃ and brine, dried over anhydrous Na₂SO₄ and concentrated to obtain Compound-2 (24.2 g, 37.8%). IR: 1723 cm⁻¹.

**Preparation of Compound-4:** To a solution of t-BuOK (41.41 g, 369 mmol) in methanol (25 mL) cooled to 0 °C under nitrogen was added a solution of Compound-2 (24.2 g, 246 mmol) in methanol (10 mL) followed by Compound-3 (75.5 g, 493 mmol) in methanol (10 mL). The solution was stirred at room temperature overnight, and then evaporated. The residue was dissolved in water and washed with ethyl acetate. The resulting aqueous layer was acidified with diluted HCl and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to obtain Compound-4 (84.6 g). The crude material was used for the next step without further purification.
Preparation of Compound-5: A solution of Compound-4 (84.6 g, 412 mmol) in piperidine (20 mL) and pyridine (20 mL) was refluxed overnight. The resulting solution was evaporated, and the residue was poured into diluted HCl and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% of ethyl acetate/hexane to obtain Compound-5 (4 g, 11.4%). MS (m/z): [M + H]⁺, 162.2.

Preparation of Compound-6: To a stirred solution of Compound-5 (3.5 g, 21 mmol) in dry toluene (5 mL) at -10 ºC was slowly added DIBAL-H (1 M in toluene, 2.4 mL). The reaction mixture was stirred at -10 ºC for 30 min, poured into a solution of sodium potassium tartrate and stirred at 0 ºC for 1 h. Then the mixture was filtered through celite and the filtrate was extracted twice with chloroform. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/hexane to obtain Compound-6 (600 mg, 16.8%). MS (m/z): [M + H]⁺, 165.2.

Preparation of Compound-7: To a stirred solution of t-BuOK (1 g, 9.1 mol) in methanol at 0 ºC under nitrogen was added a solution of Compound-3 (1.119 g, 7.3 mmol) and then Compound-6 (600 mg, 3.65 mmol) in methanol (10 mL). The resulting solution was stirred at room temperature overnight and then evaporated. The residue was diluted with water, washed with ethyl acetate, acidified with diluted HCl, and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to obtain Compound-7. The crude material was used for the next step without further purification. MS (m/z): [M + H]⁺, 272.3.

Preparation of Compound-8: To the above crude Compound-7 were added both piperidine (20 mL) and pyridine (20 mL) and the reaction mixture was refluxed overnight. Then the solution was evaporated, and the residue was poured into diluted HCl and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/hexane to obtain Compound-8 (340 mg, 41.0 %). MS (m/z): [M + H]⁺, 228.3.

Preparation of QEA-F-002: To a stirred solution of Compound-8 (340 mg, 1.5 mmol) in dry toluene (5 mL) at -10 ºC was slowly added DIBAL-H (1 M in toluene, 1.65 mL). The reaction mixture was stirred at -10 ºC for 30 min and then poured into a solution of sodium potassium tartrate and stirred at 0 ºC for 1 h. The resulting mixture was filtered through celite and the filtrate was extracted twice with chloroform. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.3% ethyl acetate/hexane to obtain QEA-F-002 (40 mg, 11.6%). ¹H NMR (CDCl₃, 300 MHz): δ 1.2-1.4 (m, 8H), 1.9 (s, 3H), 2.1 (m, 1H), 2.3 (s, 3H),
5.8-5.9 (m, 1H), 5.9-6.0 (d, 1H), 6.1-6.2 (m, 2H), 6.3-6.4 (m, 1H), 7.1-7.2 (m, 1H), 10.1 (d, 1H). MS (m/z): [M + H]^+, 231.2.

QEA-B-001 (7-tert-Butyl-9-cyclohex-1-enyl-3-methyl-nona-2,4,6,8-tetraenal)

Preparation of Compound-3: To a stirred suspension of NaH (435 mg, 18 mmol) in dry THF (10 mL) at room temperature was added dropwise a solution of Compound-2 (3.53 g, 136 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 1 h. Then a solution of Compound-1 (1 g, 9.0 mmol) in dry THF (10 mL) was slowly added and the resulting solution was stirred at room temperature for 1 h. the reaction was quenched with a saturated NH₄Cl solution and the resulting mixture was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/hexane to obtain Compound-3 (590 mg, 37%). MS (m/z): [M + H]^+, 216.3.

Preparation of Compound-4: To a solution of Compound-3 (590 mg, 2.7 mmol) in dry toluene (5.9 mL) cooled to -60 ºC under nitrogen was slowly added DIBAL-H (1 M in toluene, 3.2 mL) and the reaction mixture was stirred at -60 ºC for 30 min. The mixture was then poured into a saturated sodium potassium tartrate solution and extracted with ethyl acetate. The organic layer was washed with water, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1.2% ethyl acetate/petroleum ether to obtain compound-4 (250 mg, 41.8%). MS (m/z): [M + H]^+, 219.3.

Preparation of Compound-6: To a stirred suspension of NaH (132 mg, 5.5 mmoles) in dry THF at 0 ºC under nitrogen was added a solution of Compound-5 (895 mg, 4.12 mmol) in dry THF (6 mL). The reaction solution was stirred at room temperature for 1 h and then cooled to 0 ºC. A solution of Compound-4 (600 mg, 2.75 mmol) in dry THF (6 ml) was slowly added, and the solution stirred at room temperature for 2 h. The reaction was quenched with a saturated NH₄Cl solution, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue
was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-6 (660 mg, 85.3%). MS (m/z): [M + H]⁺, 282.4.

**Preparation of QEA-B-001:** To a stirred solution of Compound-6 (660 mg, 2.35 mmol) in dry toluene at -70 °C under nitrogen was added dropwise DIBAL-H (1 M in toluene, 2.76 mL). The reaction mixture was stirred at -70 °C for 30 min. Wet silica gel was added to the reaction mixture at -30 °C. The resulting mixture was stirred at same temperature for 1 h, and then filtered. The filtrate was extracted thrice with ether. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain QEA-B-001 (150 mg, 22.48%). ¹H NMR (CDCl₃, 400 MHz): δ 1.11 (s, 9H), 1.62-1.74 (m, 4H), 2.16-2.23 (m, 4H), 2.24 (d, J = 1.2 Hz, 3H), 5.80 (t, J = 4 Hz, 1H), 5.93 (d, J = 8.4 Hz, 1H), 6.04-6.19 (m, 3H), 6.35 (d, J = 15.6 Hz, 1H), 7.13 (dd, J = 10.8 Hz, 15.6 Hz, 1H), 10.07 (d, J = 8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 13.50, 22.60, 22.65, 24.65, 26.28, 29.92, 36.80, 121.7, 122.7, 128.5, 131.5, 133.6, 135.9, 136.2, 140.1, 156.0, 157.4, 191.5. MS (m/z): [M + H]⁺, 285.3

**TEA-B-002 (5-tert-Butyl-7-cyclohex-1-enyl-hepta-2,4,6-trienal)**

![Chemical structure]

**Preparation of Compound-1:** To a stirred suspension of NaH (168 mg, 7.0 mmol) in dry THF (10 mL) at room temperature was slowly added dropwise a solution of Compound-2 (1.24 g, 7.0 mmol) in THF (15 mL) over 30 min. A solution of Compound-1 (770 mg, 3.5 mmol) in THF (15 mL) was slowly added at 0 °C and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/hexane to obtain Compound-3 (770 mg, 91%). MS (m/z): [M + H]⁺, 282.4.

**Preparation of TEA-B-002:** To a stirred solution of Compound-3 (770 mg, 3.1 mmol) in dry toluene (10 mL) cooled to -70 °C under nitrogen was slowly added DIBAL-H (3.75 mL, 6.3 mmol) and the reaction mixture was stirred at -70 °C for 30 min. Then the solution was poured onto silica gel, stirred at 0 °C for 1 h and filtered. The filtrate was dried over Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.4% ethyl acetate/hexane to give TEA-B-002 (220 mg, 28.2%). ¹H NMR (CDCl₃, 400 MHz): δ 1.14 (s, 9H), 1.62-1.76 (m, 4H), 2.21 (m, 4H), 5.88 (t, J = 4 Hz, 1H), 6.06-6.20(m, 3 H), 6.3 (d, J = 11.2 Hz, 1H),7.148 (dd, J = 11.2 Hz, 15.2 Hz, 1H),
9.54 (d, J = 8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 22.53, 22.56, 24.64, 26.3, 29.76, 37.23, 121.11, 121.3, 130.74, 132.83, 135.64, 141.34, 152.23, 163.67, 194.61. IR: 1681.49 cm$^{-1}$. MS (m/z): [M + H]$^+$, 285.4.

QEA-D-001 (6-Bicyclohexyl-1,1'-dien-3-ylidene-3-methyl-hexa-2,4-dienal)

Preparation of Compound-3: To a stirred solution of NaH (245 mg, 10 mmol) in dry THF (10 mL) at room temperature was added dropwise a solution of Compound-2 (1.80 g, 10.0 mmol) in dry THF (10 mL). A solution of Compound-1 (900 mg, 5.1 mmol) in dry THF (10 mL) was slowly added at room temperature. The reaction mixture was stirred at room temperature for 1 h and the reaction was quenched with a saturated NH$_4$Cl solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 2% ethyl acetate/hexane to obtain Compound-3 (960 mg, 94.4%). MS (m/z): [M + H]$^+$, 200.3.

Preparation of Compound-4: To a solution of Compound-3 (100 mg, 0.5 mmol) in dry toluene (10 mL) cooled to -60 ºC under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 0.59 mL) and the reaction mixture was stirred at -60 ºC for 30 min. Then the solution was poured onto wet silica gel and filtered. The filtrate was dried over Na$_2$SO$_4$ and concentrated to obtain compound-4 (115 mg). The crude material was used for the next step without further purification. MS (m/z): [M + H]$^+$, 203.3.

Preparation of Compound-6: To a stirred suspension of NaH (108 mg, 4.5 mmol) in dry THF (10 mL) at 0 ºC under nitrogen was added a solution of Compound-5 (740 mg, 3.4 mmol) in dry THF (10 mL). The resulting solution was stirred at room temperature for 1 h. Then a solution of Compound-4 (460 mg, 2.2 mmol) in dry THF (10 mL) was slowly added at 0 ºC. The mixture was stirred at room temperature for 1 h and the reaction was quenched with a saturated NH$_4$Cl solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers
were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% ethyl acetate/hexane to obtain Compound-6 (550 mg, 96%). MS (m/z): [M + H]$^+$, 266.4.

**Preparation of QEA-D-001:** To a stirred solution of Compound-6 (550 mg, 2 mmol) in toluene (5.5 mL) at -60 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 2.4 mL). The reaction mixture was stirred at -60 ºC for 30 min. Wet silica gel was added at 0 ºC, and the suspension was stirred at same temperature for 90 min. The mixture was filtered, and the precipitate was washed thrice with ether. The combined filtrate was dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 2% ethyl acetate/hexane to obtain QEA-D-001 (140 mg, 25.2%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.56-1.62 (m, 6H), 1.68-1.74 (m, 2H), 1.76-1.84 (m, 2H), 2.18-2.26 (m, 4H), 2.31 (s, 3H), 2.37 (t, $J = 6.2$ Hz, 2H), 2.52 (m, 2H), 5.96 (d, $J = 8$ Hz, 1H), 6.04 (t, $J = 4.2$ Hz, 1H), 6.09 (d, $J = 12$ Hz, 1H), 6.25 (s, 1H), 6.32 (d, $J = 15.2$ Hz, 1H), 7.11 (dd, $J = 11.6$ Hz, 15 Hz, 1H), 10.09 (d, $J = 8$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 13.32, 22.43, 22.72, 23.11, 25.64, 25.9, 26.13, 26.53, 125.1, 126.42, 126.53, 128.81, 132.76, 133.66, 136.61, 143.02, 144.24, 155.33, 191.3. MS (m/z): [M + H]$^+$, 269.2.

**TEA-B-004 (7-Cyclohex-1-enyl-5-phenyl-hepta-2,4,6-trienal)**

Preparation of Compound-3: To a stirred suspension of NaH (1.5 g, 62.4 mmol) in THF (25 mL) at 0 ºC was added dropwise a solution of Compound-2 (11 g, 62.4 mmol) in dry THF (10 mL) and the reaction mixture was stirred for 20 min. Then a solution of Compound-1 (5 g, 41.6 mmol) in THF (25 mL) was slowly added and the resulting solution was stirred at room temperature for 3 h. The reaction was quenched with a saturated NH$_4$Cl solution and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-3 (5.4 g, 90.7%). MS (m/z): [M + H]$^+$, 144.1.
Preparation of Compound-4: To a stirred solution of Compound-3 (500 mg, 3.49 mmol) in CCl₄ (3.5 mL) at room temperature was added NBS (1.65 g, 13.9 mmol) followed by AIBN (57 mg, 0.35 mmol) and the mixture was refluxed overnight. Then the reaction mixture was filtered and the filtrate was concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-4 (340 mg, 43.9%). MS (m/z): [M + H]⁺, 223.1.

Preparation of Compound-5: To a stirred solution of Compound-4 (340 mg, 1.53 mmol) in toluene (3.4 mL) at room temperature was added dropwise a solution of P(OEt)₃ (TEP, 0.38 g, 2.29 mmol). The solution was refluxed overnight and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 30% ethyl acetate/petroleum ether to obtain Compound-5 (380 mg, 89%). MS (m/z): [M + H]⁺, 279.2.

Preparation of Compound-7: To a stirred suspension of NaH (327 mg, 13.6 mmol) in dry THF (15 mL) at 0 ºC was added dropwise a solution of Compound-5 (3.79 g, 13.6 mmol) in THF (10 mL). The reaction mixture was stirred for at 55 ºC for 40 min. Then a solution of Compound-6 (1 g, 9.1 mmol) in THF (15 mL) was slowly added and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-7 (940 mg, 44%). MS (m/z): [M + H]⁺, 235.3.

Preparation of Compound-8: To a stirred solution of Compound-7 (940 mg, 3.9 mmol) in dry toluene (9.4 mL) at -70 ºC was added dropwise DIBAL-H (1.7 M in toluene, 4.7 mL). The reaction mixture was stirred for 1 h and the reaction was quenched with wet silica gel at 0 ºC. The resulting mixture was stirred for 1 h and filtered. The filtrate was dried over Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-8 (410 mg, 44%). MS (m/z): [M + H]⁺, 239.3.

Preparation of Compound-9: To a stirred suspension of NaH (82.5 mg, 0.1 mmol) in dry THF (4.1 mL) at 0 ºC under nitrogen was added dropwise a solution of Compound-2 (609 mg, 3.4 mmol) in dry THF (4.1 mL). The reaction mixture was stirred at 0 ºC for 20 min and a solution of Compound-8 (410 mg, 1.7 mmol) in THF (10 mL) was slowly added. The resulting reaction solution was stirred at room temperature for 45 min. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layer was washed with brine solution, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-9 (282 mg, 62.7%). MS (m/z): [M + H]⁺, 262.2.
Preparation of TEA-B-004: To a stirred solution of Compound-9 (282 mg, 1 mmol) in toluene (3 mL) cooled to -70 °C under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 1.27 mL). This reaction solution was stirred at -70 °C for 30 min, poured onto wet silica gel at 0 °C and stirred for 1h. The reaction mixture was filtered through silica gel, dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain TEA-B-004 (80 mg, 28%). ¹H NMR (CDCl₃, 400 MHz): δ 1.58-1.78 (m, 4H), 2.12-2.22 (m, 4H), 5.78 (t, J = 4 Hz, 1H), 6.05 (d, J = 16 Hz, 1H), 6.16 (dd, J = 8.2 Hz, 15 Hz, 1H), 6.46 (d, J = 15.6 Hz, 1H), 6.53 (d, J = 11.6 Hz, 1H), 9.97 (dd, J = 11.6 Hz, 15.6 Hz, 1H), 7.17-7.19 (m, 2H), 7.41-7.47 (m, 3H), 8.21 (d, J = 9 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 22.46, 22.53, 24.65, 25.68, 128.15, 128.2, 128.36, 128.6, 129.8, 131.11, 135.17, 136.63, 141.15, 149.9, 153.09, 194.0. MS (m/z): [M+H]⁺, 265.2.

QEA-C-002 (7-tert-Butyl-3-methyl-9-(5,6,7,8-tetrahydro-naphthalen-2-yl)-nona-2,4,6,8-tetraenal)

Preparation of Compound-3: To a stirred suspension of NaH (1.795 g, 74.8 mmol) in dry THF (10 mL) at room temperature was added dropwise a solution of Compound-2 (11.6 g, 45.0 mmol) in dry THF (10 mL). This reaction mixture was stirred at room temperature for 45 min when a solution of Compound-1 (6.0 g, 37.4 mmol) in dry THF (10 mL) was slowly added and the reaction was stirred at room temperature for 1 h. Then the reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 2% ethyl acetate/petroleum ether to obtain Compound-3 (8.0 g, 80.6%). MS (m/z): [M+H]⁺, 266.3.

Preparation of Compound-4: To a solution of Compound-3 (8 g, 30 mmol) in DCM (80 mL) cooled to -70 °C under nitrogen, DIBAL-H (1.7 M in DCM, 32 mL) was slowly added and the mixture was stirred at -70 °C for 20 min. The reaction solution was poured into 0.3 M H₂SO₄
solution at 0 ºC, stirred at room temperature for 20 min, and extracted thrice with ethyl acetate. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.6% ethyl acetate/petroleum ether to obtain Compound-4 (3.14 g, 38.8%). MS (m/z): [M + H]$^+$, 269.3.

Preparation of Compound-6: To a stirred suspension of NaH (89 mg, 3.7 mmol) in dry THF (10 mL) at 0 ºC under nitrogen was added a solution of Compound-5 (606 mg, 2.79 mmol) in dry THF (11 mL). The reaction solution was stirred at room temperature for 1 h and then a solution of Compound-4 (500 mg, 1.86 mmol) in dry THF (11 mL) was slowly added at 0 ºC. The mixture was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH$_4$Cl solution and the resulting mixture was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-6 (580 mg, 93.9%). MS (m/z): [M + H]$^+$, 332.3.

Preparation of QEA-C-002: To a stirred solution of Compound-6 (580 mg, 1.75 mmol) in dry toluene at -70 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 1.85 mL). The reaction mixture was stirred at -70 ºC for 20 min, and poured into a 0.3 M H$_2$SO$_4$ solution at 0 ºC. This mixture was stirred at room temperature for 30 min and extracted thrice with ethyl acetate. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified column chromatography on 60-120 mesh silica gel and eluted with 0.4-0.5% ethyl acetate/petroleum ether to obtain QEA-C-002 (200 mg, 34.2%).$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.17 (s, 9H), 1.82 (m, 4H), 2.20 (d, $J$ = 0.8 Hz, 3H), 2.79 (d, $J$ = 3.6 Hz, 4H), 5.95 (d, $J$ = 8 Hz, 1H), 6.27 (d, $J$ = 10.8 Hz, 1H), 6.41 (d, $J$ = 15.6 Hz, 1H), 6.47 (d, $J$ = 16 Hz, 1H), 6.73 (d, $J$ = 16 Hz, 1H), 7.08 (d, $J$ = 16 Hz, 1H), 7.16-7.26 (m, 3H), 10.07 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 13.43, 23.38, 29.52, 29.67, 29.90, 36.91, 107.5, 123.4, 123.8, 125.0, 128.8, 129.8, 134.2, 134.5, 135.8, 136.2, 137.8, 155.8, 156.8, 191.5. MS (m/z): [M + H]$^+$, 335.2.

TEA-C-001 (5-tert-Butyl-7-(5,6,7,8-tetrahydro-naphthalen-2-yl)-hepta-2,4,6-trienal)

Preparation of Compound-3: To a stirred suspension of NaH (65 mg, 2.79 mmol) in dry THF (5 mL) at room temperature was added dropwise a solution of Compound-2 (495 mg, 2.79 mmol) in dry THF (5 mL) and the resulting solution was stirred for 30 min. Then a solution of Compound-1 (500 mg, 1.86 mmol) in THF (5 mL) was slowly added at 0 ºC and the solution
was stirred at room temperature for 30 min. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-3 (470 mg, 86.6%). MS (m/z): [M + H]⁺, 292.3.

**Preparation of TEA-C-001:** To a stirred solution of Compound-3 (470 mg, 1.60 mmol) in dry toluene cooled to -70 ºC under nitrogen was slowly added DIBAL-H (1.7 M, 1.71 mL) and the reaction mixture was stirred for 20 min. The reaction was quenched with a cold 3 M H₂SO₄. The resulting mixture was stirred at room temperature for 10 min and then extracted thrice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 2% ethyl acetate/petroleum ether to obtain **TEA-C-001** (180 mg, 38.2%). ¹H NMR (CDCl₃, 400 MHz): δ 1.20 (s, 9H), 1.82 (m, 4H), 2.80 (m, 4H), 6.21 (dd, J = 15.2 Hz, 8.4 Hz, 1H), 6.39 (d, J = 10.8 Hz, 1H), 6.47 (d, J = 16 Hz, 1H), 6.76 (d, J = 15.6 Hz, 1H), 7.10 (d, J = 8 Hz, 1H), 7.18 (s, 1H), 7.24 (m, 1H), 7.55 (dd, J = 15.2 Hz, 10.8 Hz 1H), 9.50 (d, J = 8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 23.36, 29.55, 29.65, 29.78, 37.35, 122.0, 124.0, 124.1, 127.9, 129.9, 131.2, 133.9, 137.5, 137.9, 138.2, 151.8, 163.0, 194.6. MS (m/z): [M + H]⁺, 295.3.

**QEA-C-001 (7-tert-Butyl-3-methyl-9-phenyl-nona-2,4,6,8-tetraenal)**

![Chemical structure of QEA-C-001](image)

**Preparation of Compound-3:** To a stirred suspension of NaH (1.36 g, 56.6 mmol) in dry THF (10 mL) at 0 ºC was slowly added a solution of Compound-2 (8.8 g, 34 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 20 min. Then a solution of Compound-1 (3.0 g, 28.3 mmol) in dry THF (10 mL) was added and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 2% ethyl acetate/petroleum ether to obtain Compound-3 (4.0 g, 67%). MS (m/z): [M + H]⁺, 212.2.
Preparation of Compound-4: To a solution of Compound-4 (3.0 g, 14.2 mmol) in DCM (30 mL) cooled to -70 °C under nitrogen was slowly added DIBAL-H (1.7 M in DCM, 12.5 mL) and the mixture was stirred for 10 min. The reaction solution was poured into a 0.3 M H2SO4 solution at 0 °C and stirred for 15 min. The aqueous layer was extracted thrice with ethyl acetate, and the combined organic layers were dried over anhydrous Na2SO4 and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.8% ethyl acetate/petroleum ether to obtain Compound-4 (920 mg, 30.6%). MS (m/z): [M + H]+, 215.2.

Preparation of Compound-6: To a stirred suspension of NaH (84 mg, 3.45 mmol) in dry THF (10 mL) at 0 °C under nitrogen was added a solution of Compound-5 (608 mg, 2.80 mmol) in dry THF (5 mL). The reaction mixture was stirred at room temperature for 1 h and then a solution of Compound-4 (500 mg, 2.33 mmol) in dry THF (11 mL) was slowly added at 0 °C. The solution was stirred at room temperature for 1 h. Then the reaction was quenched with a saturated NH4Cl solution and the mixture was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na2SO4 and concentrated under reduced pressure. The residue was purified by column chromatography on 100-200 mesh silica gel eluted with 0.3% ethyl acetate/petroleum ether to obtain Compound-6 (560 mg, 86.5%). MS (m/z): [M + H]+, 278.3.

Preparation of QEA-C-001: To a stirred solution of Compound-6 (560 mg, 2.0 mmol) in dry toluene (2 mL) at -78 °C under nitrogen was added dropwise DIBAL-H (1.7 M solution in toluene, 1.78 mL). The resulting solution was stirred at -78 °C for 30 min, poured into a 0.3 M H2SO4 solution at 0 °C and stirred at room temperature for 30 min. The mixture then was extracted thrice with ethyl acetate, dried over Na2SO4 and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.6-1% ethyl acetate/petroleum ether to obtain QEA-C-001 (200 mg, 35%). 1H NMR (CDCl3, 400 MHz): δ 1.18 (s, 9H), 2.21 (d, J = 1.2 Hz, 3H), 5.96 (d, J = 8.4 Hz, 1H), 6.30 (d, J = 10.8 Hz, 1H), 6.42 (d, J = 15.2 Hz, 1H), 6.54 (d, J = 16 Hz, 1H), 6.80 (d, J = 16 Hz, 1H), 7.21 (dd, J = 15.2 Hz, 10.8 Hz, 1H), 7.31 (m, 1H), 7.38 (m, 2H), 7.46 (m, 2H), 10.08 (d, J = 8 Hz, 1H); 13C NMR (CDCl3, 100 MHz): δ 13.41, 29.90, 36.91, 123.7, 126.1, 126.7, 128.2, 128.9, 129.0, 134.4, 135.5, 136.0, 137.1, 155.6, 156.4, 191.5. MS (m/z): [M + H]+, 281.3.

QEA-C-003 (3-Methyl-7-phenyl-9-(4-trifluoromethyl-phenyl)-nona-2,4,6,8-tetraenal)
Preparation of Compound-3: To a stirred suspension of NaH (393 mg, 16.3 mmol) in dry THF (10 mL) at 0 ºC under nitrogen was added dropwise a solution of Compound-2 (3.65 g, 13.0 mmol) in dry THF (10 mL). The resulting mixture was stirred at room temperature for 45 min. Then a solution of Compound-1 (1.9 g, 11.0 mmol) in dry THF (10 mL) was slowly added and the reaction solution was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-3 (1.34 g, 41%). MS (m/z): [M + H]⁺, 300.2.

Preparation of Compound-4: To a solution of Compound-3 (1.34 g, 44 mmol) in toluene (10 mL) cooled to -70 ºC under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 5.26 mL) and the reaction mixture was stirred at -70 ºC for 20 min. Then the solution was poured into a 0.3 M H₂SO₄ solution at 0 ºC and stirred for 20 min at room temperature. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.2% ethyl acetate/petroleum ether to obtain Compound-4 (1.15 g, 85%). MS (m/z): [M + H]⁺, 303.2.

Preparation of Compound-6: To a stirred suspension of NaH (60 mg, 2.48 mmol) in dry THF at 0 ºC under nitrogen was slowly added a solution of Compound-5 (467 mg, 2.15 mmol) in dry THF (10 mL). The reaction solution was stirred at room temperature for 45 min and then a solution of Compound-4 (500 mg, 1.6 mmol) in dry THF (10 mL) was slowly added at 0 ºC and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution, extracted thrice with ethyl acetate, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 60-120
mesh silica gel and eluted with 1.5% ethyl acetate/petroleum ether to obtain Compound-6 (310 mg, 51.3%). MS (m/z): [M + H]⁺, 366.3.

**Preparation of QEA-C-003:** To a stirred solution of Compound-6 (310 mg, 0.84 mmol) in dry toluene (10 mL) at -78 °C under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 0.99 mL). The reaction mixture was stirred at -78 °C for 20 min. The mixture was poured into a 0.3 M H₂SO₄ solution at 0 °C, stirred at room temperature for 30 min, extracted thrice with ethyl acetate, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 230-400 mesh silica and eluted with 1.4% ethyl acetate/petroleum ether to obtain QEA-C-003 (100 mg, 32%). ¹H NMR (CDCl₃, 400 MHz): δ 2.07 (d, J = 1.2 Hz, 3H), 5.96 (d, J = 8 Hz, 1H), 6.29 (d, J = 14 Hz, 1H), 6.47 (d, J = 14.4 Hz, 1H), 6.60-6.65 (m, 2H), 7.14 (d, J = 16 Hz, 1H), 7.23 (m, 1H), 7.42-7.54 (m, 8H). 10.05 (d, J = 8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 13.20, 125.8 (m), 127.0, 128.3, 128.8, 129.9, 130.0, 132.3, 133.1, 133.6, 134.6, 136.7, 137.1, 140.6, 146.6, 154.4, 191.4. MS (m/z): [M + H]⁺, 369.3.

**PEA-B-001 (3,9-Di-tert-butyl-11-cyclohex-1-enyl-undeca-2,4,6,8,10-pentaenal)**

**Preparation of Compound-3:** To a stirred suspension of NaH (1.74 g, 72.6 mmol) in dry THF (30 mL) at 0 °C was slowly added dropwise a solution of Compound-2 (14.1 g, 54.0 mmol) in dry THF (5 mL). The reaction mixture was stirred at room temperature for 1 h. Then a solution of Compound-1 (4 g, 36.0 mmol) in dry THF (5 mL) was slowly added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.2% ethyl acetate/petroleum ether to obtain Compound-3 (3.6 g, 46%). MS (m/z): [M + H]⁺, 216.2.

**Preparation of Compound-4:** To a solution of Compound-3 (3 g, 13.0 mmol) in dry toluene (10 mL) cooled to -70 °C under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 16.4 mL) and the solution was stirred at -70 °C for 30 min. The reaction mixture was poured onto silica gel at 0 °C, stirred for 1 h and filtered. The filtrate was washed with ether, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column
chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-4 (640 mg, 21%). MS (m/z): [M + H]+, 219.2.

**Preparation of Compound-6:** To a stirred suspension of NaH (103 mg, 4.3 mmol) in dry THF (10 mL) at 0 ºC under nitrogen was added a solution of Compound-5 (456 mg, 4.3 mmol) in dry THF (10 mL). The reaction mixture was stirred at 0 ºC for 30 min, then a solution of Compound-4 (640 mg, 2.9 mmol) in dry THF (10 mL) was slowly added and stirred at room temperature for 1 h. The reaction mixture was quenched with a saturated NH₄Cl solution, extracted thrice with ethyl acetate, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-6 (580 mg, 82%). MS (m/z): [M + H]+, 242.2.

**Preparation of Compound-7:** To a stirred solution of Compound-6 (540 mg, 2.1 mmol) in dry toluene (10 mL) at -70 ºC under nitrogen was added DIBAL-H (1.7 M solution in Toluene, 2.6 mL). The reaction mixture was stirred at -70 ºC for 30 min, then poured onto silica gel at 0 ºC and stirred for 2 h before filtration. The precipitate was washed with ether, and the filtrate was dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-7 (230 mg, 42%). MS (m/z): [M + H]+, 245.2.

**Preparation of Compound-8:** To a stirred suspension of NaH (45 mg, 1.8 mmol) in dry THF (10 mL) at 0 ºC under nitrogen was added a solution of Compound-8 (487 mg, 1.8 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 45 min. A solution of Compound-7 (230 mg, 0.9 mmol) in dry THF (10 mL) was slowly added at 0 ºC and stirred at room temperature for 2 h. The reaction mixture was quenched with a saturated NH₄Cl solution, extracted thrice with ethyl acetate, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-8 (210 mg, 64%). MS (m/z): [M + H]+, 350.3.

**Preparation of PEA-B-001:** To a stirred solution of Compound-8 (210 mg, 0.6 mmol) in dry toluene (10 mL) at -70 ºC under nitrogen DIBAL-H (1.7 M solution in toluene, 0.53 mL) was added dropwise. This reaction mixture was stirred at -70 ºC for 30 min, then the reaction was quenched with a 0.3 M H₂SO₄ solution at 0 ºC. The aqueous layer was extracted thrice with ethyl acetate, and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.4-0.5% ethyl acetate/petroleum ether to obtain PEA-B-001 (100 mg, 47.3%).

1H NMR (CDCl₃, 300 MHz): δ 1.10 (s, 9H), 1.14 (s, 9H), 1.61-1.74 (m, 4H), 2.19 (m, 4H), 5.82 (t, J = 8 Hz, 1H), 6.00-6.16 (m, 4H), 6.23-6.44 (m, 3H), 6.74 (dd, J = 14Hz, 11.2 Hz, 1H), 9.66 (d, J = 7.2 Hz, 1H); 13C NMR (CDCl₃, 100 MHz): δ 22.63, 22.88, 24.63, 26.21, 29.47, 29.92, 36.56, 37.19, 107.4, 121.7, 125.3, 125.9, 130.2, 131.1, 135.8, 136.3, 139.2, 141.9, 154.9, 172.7, 194.2. MS (m/z): [M + H]+, 353.3.
QEA-E-001 (9-Cyclohex-1-enyl-3-methyl-7-phenyl-nona-2,4,6,8-tetraenal)

Preparation of Compound-3: To a stirred suspension of NaH (362 mg, 15 mmol) in dry THF (10 mL) at 0 ºC, a solution of Compound-2 (3.6 g, 12 mmol) in dry THF (10 mL) was added dropwise. The reaction mixture was stirred at 45 ºC for 45 min, then a solution of Compound-1 (1.2 g, 10 mmol) in dry THF (10 mL) was slowly added and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-3 (720 mg, 28%). MS (m/z): [M + H]+, 236.2.

Preparation of Compound-4: To a solution of Compound-3 (720 mg, 3.0 mmol) in dry toluene (10 mL) cooled to -70 ºC under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 3.5 mL) and the reaction mixture was stirred for 30 min. Then the solution was poured into a 0.3 M H₂SO₄ solution at 0 ºC and the resulting aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-4 (530 mg, 72.7%). MS (m/z): [M + H]+, 239.2.

Preparation of Compound-6: To a stirred suspension of NaH (75 mg, 3.13 mmol) in dry THF (10 mL) at 0 ºC under nitrogen was added a solution of Compound-5 (590 mg, 2.7 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 40 min and then a solution of Compound-4 (500 mg, 2.09 mmol) in dry THF (10 mL) was slowly added at 0 ºC. This mixture was stirred at room temperature for 1 h. Then the reaction was quenched with a saturated NH₄Cl solution, and extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-6 (400 mg, 63.2%). MS (m/z): [M + H]+, 302.2.
Preparation of QEA-E-001: To a stirred solution of Compound-6 (400 mg, 1.3 mmol) in dry toluene (10 mL) at -70 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 1.12 mL). The reaction mixture was stirred at -70 ºC for 20 min. The reaction was quenched with a 0.3 M H₂SO₄ solution at 0 ºC. The aqueous layer was extracted thrice with ethyl acetate, and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain QEA-E-001 (60 mg, 14.8%). ¹H NMR (CDCl₃, 300 MHz): δ 1.6-1.8 (m, 4H), 2-2.3 (m, 7H), 5.7-5.8 (m, 1H), 5.9-6.0 (m, 2H), 6.4-6.5 (m, 2H), 6.5-6.7 (m, 1H), 7.1-7.2 (d, 2H), 7.3-7.5 (m, 4H), 10.0-10.1 (d, 1H). MS (m/z): [M + H]+, 305.2.

QEA-E-002 (9-Cyclohex-1-enyl-7-(4-methoxy-phenyl)-3-methyl-nona-2,4,6,8-tetraenal)

Preparation of Compound-3: To a stirred suspension of NaH (1.44 g, 59 mmol) in dry THF (10 mL) at room temperature under nitrogen was added a solution of Compound-2 (8.5 g, 47 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 45 min. A solution of Compound-1 (6 g, 39 mmol) in dry THF (10 mL) was slowly added at room temperature. The resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with a saturated NH₄Cl solution and extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-3 (6.8 g, 98.3%). MS (m/z): [M + H]+, 174.2.

Preparation of Compound-4: To a stirred solution of Compound-3 (1 g, 5.7 mmol) in CCl₄ (20 mL) at room temperature was added NBS followed slowly by AIBN. The reaction mixture was stirred at 90 ºC for 18 h and diluted with DCM. The mixture was washed with water (90 mL), the
organic layer was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 5-8% ethyl acetate/petroleum ether to obtain compound-4 (1.1 g, 75.8%). MS (m/z): [M + H]⁺, 253.1.

**Preparation of Compound-5:** To a stirred solution of Compound-4 (1.1 g, 4.3 mmol) in dry toluene (2 mL) at room temperature was slowly added triethyl phosphate (1.6 g, 6.9 mmol) and the reaction mixture was stirred at 150 ºC overnight. After the excessive triethyl phosphate was evaporated, the residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 40% ethyl acetate/petroleum ether to obtain Compound-5 (600 mg, 44.7%). MS (m/z): [M + H]⁺, 310.3.

**Preparation of Compound-7:** To a stirred suspension of NaH (456 mg, 19 mmol) in dry THF (10 mL) at 0 ºC was added dropwise a solution of Compound-5 (4.7 g, 15.2 mmol) in dry THF (10 mL). This reaction mixture was stirred at 0 ºC for 30 min. A solution of Compound-6 (1.4 g, 12 mmol) in dry THF (10 mL) then was slowly added and the solution was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution, the resulting aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-7 (830 mg, 24.6%). MS (m/z): [M + H]⁺, 266.2.

**Preparation of Compound-8:** To a solution of Compound-7 (1 g, 3.7 mmol) in dry toluene (10 mL) cooled to -78 ºC under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 4.43 mL). The reaction mixture was stirred at -78 ºC for 30 min and then quenched with a cold 0.3 M H₂SO₄ solution. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% with ethyl acetate/petroleum ether to obtain Compound-8 (640 mg, 63.3%). MS (m/z): [M + H]⁺, 269.2

**Preparation of Compound-10:** To a stirred suspension of NaH (57 mg, 2.4 mmol) in dry THF (2 mL) at 0 ºC under nitrogen was added a solution of Compound-9 (456 mg, 2.1 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 1 h. Then a solution of Compound-8 (440 mg, 1.6 mmol) in dry THF (10 mL) was slowly added at 0 ºC. The resulting reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution, the resulting mixture was extracted thrice with ethyl acetate, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-10 (400 mg, 73.7%). MS (m/z): [M + H]⁺, 332.3.

**Preparation of QEA-E-002:** To a stirred solution of Compound-10 (400 mg, 1.1 mmol) in dry toluene (10 mL) at -78 ºC under nitrogen was added drops of DIBAL-H (1.7 M in toluene, 1.42
mL). This reaction mixture was stirred at -78 °C for 30 min, and the reaction was quenched with a 3 M H2SO4 solution at 0 °C. The solution was stirred at room temperature for 30 min. The aqueous layer was extracted thrice with ethyl acetate, and the combined organic layers were dried over anhydrous Na2SO4 and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.4-0.5% ethyl acetate/petroleum ether to obtain QEA-E-002 (120 mg, 29.7%). 1H NMR of major isomer (CDCl3, 300 MHz): δ 1.6-1.8 (m, 4H), 2.1 (s, 3H), 2.2-2.45 (m, 4H), 3.8 (s, 3H), 5.7 (s, 1H), 5.95-6.1 (m, 2H), 6.2-6.3 (m, 1H), 6.4-6.5 (m, 2H), 6.6-6.8 (m, 1H), 6.9-7.0 (d, 2H), 7.1-7.2 (d, 2H), 10.1-10.25 (d, 1H). MS (m/z): [M + H]+, 335.3.

QEA-D-002 (3-Methyl-6-[3-(tetrahydro-pyran-3-yl)-cyclohex-2-enylidene]-hexa-2,4-dienal)

Preparation of Compound-2: To a stirred mixture of Compound-1 (40 g, 713 mmol) in DCM (105 mL) and H2O (2.3 mL) at room temperature, H3PO4 (12.7 mL) was slowly added and the reaction mixture was refluxed overnight. The mixture was purified by fractional distillation at 110-150 ºC/20 mmHg to obtain Compound-2 (12.6 g, 15.7%). MS (m/z): [M + H]+, 113.1.

Preparation of Compound-3: 10% Pd/C (600 mg) was slowly added to a solution of Compound-2 (6 g, 53.5 mmol) in methanol (10 mL) and the mixture was stirred under hydrogen (40 psi). The reaction mixture was filtered through celite, the precipitate was rinsed with methanol and the filtrate was concentrated under vacuum. The residue was purified by fractional distillation at 125 ºC/20 mm Hg to obtain Compound-3 (5.5 g, 91.6%). MS (m/z): [M + H]+, 115.1.

Preparation of Compound-4: To a stirred suspension of Mg (2 g, 84 mmol) with cat. I2 in dry THF (20 mL) under nitrogen was slowly added 5-bromopentene (9.9 mL, 84 mmol). The reaction was stirred for 1 h. Then Compound-3 (8 g, 70 mmol) was added at -5 ºC, and the
reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with a saturated NH₄Cl solution and extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 8% ethyl acetate/petroleum ether to obtain Compound-4 (9.5 g, 74.3%). MS (m/z): [M + H]⁺, 185.1.

**Preparation of Compound-5:** To a stirred solution of Compound-4 (980 mg, 5.3 mmol) in DCM (10 mL) at 0 ºC, PDC (3.98 g, 10.6 mmol) was slowly added. The reaction mixture was stirred at room temperature overnight. The mixture then was poured onto a 60-120 mesh silica gel, the precipitate was rinsed with ether and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 10% ethyl acetate/petroleum ether to obtain Compound-5 (80 mg, 8.25%). MS (m/z): [M + H]⁺, 183.1.

**Preparation of Compound-6:** To a stirred suspension of PdCl₂ (18.6 mg, 0.1 mmol), CuCl (138.6 mg, 1.4 mmol) in H₂O (10 mL) and DMF (10 mL) at room temperature was slowly added a solution of Compound-5 (80 mg, 0.4 mmol) in dry DMF (16.6 mL). The reaction mixture was stirred under oxygen atmosphere for 3 h, then quenched with a 5% HCl solution and extracted thrice with ether. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to obtain Compound-6 (220 mg, 64%). MS (m/z): [M + H]⁺, 199.2.

**Preparation of Compound-7:** To a stirred solution of Compound-6 (3 g, 15.1 mmol) in ethanol (5 mL) and water (5 mL) at 40 ºC, NaOH solution (1 M, 30 mL) was slowly added and the reaction mixture was stirred at 40 ºC for 1 h. The resulting aqueous layer was extracted thrice with ethyl acetate. The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-7 (2 g, 73.3%). MS (m/z): [M + H]⁺, 181.1.

**Preparation of Compound-9:** To a stirred suspension of NaH (475 mg, 19.8 mmol) in dry THF (10 mL) at 0 ºC was slowly added a solution of Compound-8 (2.93 g, 16.6 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 1h until it turned into light cream color. To the reaction mixture was added a solution of Compound-7 (2 g, 11 mmol) in dry THF (10 mL) and the solution was stirred at room temperature for 30 min. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 10% ethyl acetate/petroleum ether to obtain Compound-9 (2 g, 88.8%). MS (m/z): [M + H]⁺, 204.2.

**Preparation of Compound-10:** To a stirred solution of Compound-9 (2 g, 9.8 mmol) in dry toluene (10 mL) cooled to -78 ºC under nitrogen was slowly added DIBAL-H (1.7 M, 11.5 mL) and the reaction mixture was stirred at -78 ºC for 30 min. The reaction was quenched with 3 M
H$_2$SO$_4$ solution at -78 °C and stirred at room temperature for 30 min. The resulting mixture was extracted thrice with ethyl acetate, and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 20% ethyl acetate/petroleum ether to obtain Compound-10 (1.5 g, 73.9%). MS (m/z): [M + H]$^+$, 207.2.

**Preparation of Compound-12:** To a stirred suspension of NaH (86 mg, 3.6 mmol) in dry THF (10 mL) at room temperature was added Compound-11 (781 mg, 3.6 mmol). The reaction mixture was stirred at 50 °C for 30 min. Then Compound-10 (500 mg, 2.4 mmol) in dry THF (10 mL) was slowly added at 0 °C. The resulting reaction mixture was stirred at room temperature for 30 min and the reaction was quenched with a saturated NH$_4$Cl solution. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 10% ethyl acetate/petroleum ether to obtain Compound-12 (600 mg, 92%). MS (m/z): [M + H]$^+$, 270.3.

**Preparation of QEA-D-002:** To a solution of Compound-12 (500 g, 1.8 mmol) in dry toluene (10 mL) cooled to -70 °C under nitrogen was slowly added DIBAL-H (1.7 M, 2.18 mL) and the reaction mixture was stirred at -70 °C for 30 min. The reaction was quenched with 3 M H$_2$SO$_4$ solution at -70 °C and the mixture was stirred at room temperature for 30 min. The resulting aqueous layer was extracted thrice with ethyl acetate, and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 10% ethyl acetate/petroleum ether to obtain of QEA-D-002 (102 mg, 23.8%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.64-1.68 (m, 2H), 1.73-1.78 (m, 1H), 1.88-1.92 (m, 1H), 2.12-2.16 (m, 1H), 2.17-2.31 (m, 1H), 2.28 (s, 3H), 2.48-2.52 (m, 1H), 3.25-3.37 (m, 2H), 3.90-3.98 (m, 2H), 5.97 (m, 3H), 6.31 (d, J = 15.6 Hz, 1H), 7.07 (m, 2H), 10.09 (d, J = 6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 13.10, 22.56, 25.68, 25.91, 28.13, 28.58, 44.31, 68.30, 71.87, 125.1, 126.3, 128.7, 132.3, 133.6, 142.8, 146.4, 155.1, 191.2. MS (m/z): [M + H]$^+$, 273.3.

**QEA-G-001 (3-Methyl-6-(3-pyridin-3-yl-cyclohex-2-enylidene)-hexa-2,4-dienal)**
Preparation of Compound-3: To a stirred solution of Compound-1 (8 g, 50.6 mmol) in DMF (10 mL) at room temperature were added Compound-2 (9.8 mL, 101.26 mmol), KF (5.88 g, 101.26 mmol) and Pd(OAc)$_2$ (227 mg, 1.012 mmol). The reaction mixture was stirred at 130 ºC for 2 d, then diluted with water and extracted with diethyl ether. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with ethyl acetate to obtain Compound-3 (1.8 g, 20.5%). MS (m/z): [M + H]$^+$, 174.2.

Preparation of Compound-5: To a stirred suspension of NaH (80 mg, 2.8 mmol) in dry THF (20 mL) at 10 ºC was slowly added a solution of Compound-4 (380 mg, 2.1 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 30 min. Then a solution of Compound-3 (250 mg, 1.4 mmol) in dry THF (10 mL) was slowly added and the resulting solution was stirred at room temperature for 2 h. The reaction was quenched with a saturated NH$_4$Cl solution. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 40-50% ethyl acetate/petroleum ether to obtain Compound-5 (50 mg, 17.7%). MS (m/z): [M + H]$^+$, 197.2.

Preparation of Compound-6: To a stirred solution of Compound-5 (1.18 g, 6.0 mmol) in dry toluene (10 mL) cooled to -70 ºC under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 7 mL) and the reaction mixture was stirred at -70 ºC for 1 h. Then the solution was poured into a saturated potassium tartrate solution at 10 ºC and stirred at room temperature for 1 h. The mixture was alkylated with NaHCO$_3$, extracted with ethyl acetate, dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude compound was purified by column chromatography on neutral alumina and eluted with 15% ethyl acetate/petroleum ether to obtain of Compound-6 (330 mg, 27.5%). MS (m/z): [M + H]$^+$, 200.2.

Preparation of Compound-8: To a stirred suspension of NaH (79 mg, 3.3 mmol) in dry THF (10 mL) cooled to 10 ºC was slowly added a solution of Compound-7 (719 mg, 3.3 mmol) in dry
THF (10 mL). This reaction mixture was stirred at room temperature for 1 h. Then Compound-6 (330 mg, 1.6 mmol) was added at 10 ºC. The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution, the aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 30% ethyl acetate/tet ether to obtain Compound-8 (350 mg, 80.6%). MS (m/z): [M + H]+, 263.2.

**Preparation of QEA-G-001:** To a stirred solution of Compound-8 (350 mg, 1.33 mmol) in dry toluene (10 mL) cooled to -70 ºC under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 2.35 mL). The reaction mixture was stirred at -70 ºC for 1 h, and then poured into a saturated sodium potassium tartrate solution at 0 °C and stirred at room temperature for 1 h, extracted with ethyl acetate, dried over Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on neutral alumina and eluted with 12-15% ethyl acetate/petroleum ether to obtain QEA-G-001 (120 mg, 33.8%). ¹H NMR of major isomer (CDCl₃, 300 MHz): δ 1.95-2.01 (m, 2H), 2.34 (s, 3H), 2.59-2.65 (m, 4H), 6.02 (d, J = 8 Hz, 1H), 6.29 (d, J = 12 Hz, 1H), 6.46 (d, J = 11.2 Hz, 1H), 6.78 (s, 1H), 7.09 (dd, J = 11.6 Hz, 15.6 Hz, 1H), 7.64 (m, 1H), 8.15 (d, J = 7.6 Hz, 1H), 8.53 (bs, 1H), 8.79 (bs, 1H), 10.13 (d, J = 8 Hz, 1H); ¹³C NMR (CDCl₃, 150 MHz): δ 13.33, 22.25, 25.15, 27.38, 125.3, 130.1, 130.5, 131.3, 132.2, 135.1, 136.8, 137.1, 139.0, 140.9, 141.2, 142.2, 154.1, 191.2. MS (m/z): [M + H]+, 266.2.

**QEA-C-006 (Acetic acid 4-[3-(4-methoxy-phenyl)-7-methyl-9-oxo-nona-1,3,5,7-tetraenyl]-phenyl ester)**
Preparation of Compound-2: To a stirred solution of Compound-1 (10 g, 81.8 mmol) in DCM (10 mL) at 0 ºC was slowly added TBDMSCl (24.66 g, 163.6 mmol). Then the reaction was quenched with water and the aqueous layer was extracted thrice with DCM. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 5% ethyl acetate/petroleum ether to obtain Compound-2 (11 g, 56.8%). MS (m/z): [M + H]^+, 237.2.

Preparation of Compound-4: To a stirred suspension of NaH (1.56 g, 65 mmol) in dry THF (10 mL) at room temperature under nitrogen was added dropwise a solution of Compound-3 (17.2 g, 55.6 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 30 min. Then a solution of Compound-2 (11 g, 46.5 mmol) in dry THF (10 mL) was slowly added and the resulting reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with a saturated with NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 10% ethyl acetate/petroleum ether to obtain Compound-4 (3.5 g, 27%). MS (m/z): [M + H]^+, 278.2.

Preparation of Compound-5: To a solution of Compound-4 (3.5 g, 12.6 mmol) in toluene/DCM (4 : 1) cooled to -78 ºC under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 25.9 mL) and the reaction mixture was stirred for 30 min. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 30% ethyl acetate/petroleum ether to obtain compound-5 (1.5 g, 42.4%). MS (m/z): [M + H]^+, 281.2.

Preparation of Compound-7: To a stirred suspension of NaH (0.3 g, 2.5 mmol) in dry THF (10 mL) at room temperature under nitrogen was added dropwise a solution of Compound-6 (1.62 g, 7.5 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 30 min. A solution of Compound-5 (1.4 g, 5 mmol) in dry THF (10 mL) was slowly added and the solution was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 15% ethyl acetate/petroleum ether to obtain Compound-7 (1.6 g, 93.2%). MS (m/z): [M + H]^+, 344.3.

Preparation of Compound-8: To a solution of Compound-7 (1.6 g, 4.65 mmol) in mixture of toluene (5 mL) and DCM (5 mL) cooled to -70 ºC under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 9.6 mL) and the reaction mixture was stirred for 1 h. The reaction was quenched with a 0.3 M H₂SO₄ solution and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and evaporated under vacuum.
The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 12% ethyl acetate/petroleum ether to obtain Compound-8 (1 g, 62%). MS (m/z): [M + H]+, 347.3.

**Preparation of QEA-C-006:** To a stirred solution of compound-7 (1 g, 2.8 mmol) in DCM at 0 °C under nitrogen was added DMAP (512 mg, 4.2 mmol) followed by acetyl chloride (329 mg, 4.2 mmol). The reaction mixture was stirred at room temperature for 45 min, diluted with water, extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na2SO4 and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain QEA-C-006 (330 mg, 29.4%). 1H NMR (CDCl3, 400 MHz): δ 2.11 (d, J = 1.2 Hz, 3H), 2.29 (s, 3H), 3.89 (s, 3H), 5.95 (d, J = 8 Hz, 1H), 6.31 (d, J = 16 Hz, 1H), 6.44 (d, J = 15.2 Hz, 1H), 6.53 (d, J = 11.2 Hz, 1H), 6.55-6.69 (m, 1H), 6.71 (dd, J = 11.2 Hz, 15.2 Hz, 1H), 6.98-7.05 (m, 4H), 7.16 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 11.2 Hz, 2H), 10.06 (d, J = 8.4 Hz, 1H); 13C NMR (CDCl3, 100 MHz): δ 13.28, 21.39, 55.53, 114.0, 122.1, 127.9, 129.1, 129.6, 131.3, 131.8, 132.8, 133.0, 134.2, 135.1, 136.0, 146.9, 150.5, 154.9, 159.5, 169.7, 191.4. MS (m/z): [M + H]+, 389.3.

**QEA-C-005 (7-(4-Methoxy-phenyl)-3-methyl-9-(4-nitro-phenyl)-nona-2,4,6,8-tetraenal)**

**Preparation of Compound-3:** To a suspension of NaH (633 mg, 26.4 mmol) in dry DMF (10 mL) cooled to 0 °C under nitrogen was added dropwise a solution of Compound-2 (6.12 g, 19.8 mmol) in dry DMF (10 mL). The reaction mixture was stirred at room temperature for 30 min. To the reaction mixture was slowly added a solution of Compound-1 (2 g, 13.2 mmol) in dry DMF (10 mL) at 10 °C and the resulting mixture was stirred at room temperature for 10 min. The reaction was quenched with a saturated NH4Cl solution. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous Na2SO4 and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 10% ethyl acetate/petroleum ether to obtain Compound-3 (2.5 g, 62%). MS (m/z): [M + H]+, 307.3.

**Preparation of Compound-4:** To a solution of Compound-3 (2.18 g, 7.1 mmol) in DCM (5 mL) cooled to -70 °C under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 8.4 mL) and the
reaction mixture was stirred at for 30 min. The reaction was quenched with a 0.3 M H₂SO₄ solution and stirred at room temperature for 30 min. The mixture was extracted thrice with ethyl acetate, and the combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 13-15% ethyl acetate/petroleum ether to obtain Compound-4 (1 g, 45.4%). MS (m/z): [M + H]^+, 310.2.

**Preparation of Compound-6:** To a stirred suspension of NaH (115 mg, 4.8 mmol) in dry THF (10 mL) at room temperature under nitrogen was added dropwise a solution of Compound-5 (825 mg, 3.8 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 30 min. Then a solution of Compound-4 (1 g, 3.2 mmol) in dry THF (10 mL) was slowly added and the solution was stirred at room temperature for 30 min. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 8-10% ethyl acetate/petroleum ether to obtain Compound-6 (1.09 g, 90.8%). MS (m/z): [M + H]^+, 373.3.

**Preparation of QEA-C-005:** To a solution of Compound-6 (1.09 g, 2.9 mmol) dissolved in mixture of toluene (10 mL) and DCM (5 mL) cooled to -70 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 3.44 mL). The reaction mixture was stirred at -70 ºC for 30 min and then poured into a 0.3 M H₂SO₄ solution at 0 ºC. The reaction mixture was stirred at room temperature for 30 min, extracted thrice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 10-12% ethyl acetate/petroleum ether to obtain QEA-C-005 (700 mg, 63.7%). ¹H NMR of major isomer (CDCl₃, 400 MHz): δ 2.12 (s, 3H), 3.91 (s, 3H), 5.99 (d, J = 8 Hz, 1H), 6.36 (d, J = 16 Hz, 1H), 6.51(d, J = 14.8 Hz, 1H), 6.64-6.72 (m, 2H), 7.02 (dd, J = 6.4 Hz, 2 Hz, 2H), 7.17 (dd, J = 8.4 Hz, 2 Hz, 2H), 7.48 (d, J = 9.2 Hz, 2H), 7.48 (m, 1H), 8.16 (d, J = 8.8 Hz, 2H), 10.07 (d, J = 8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 13.27, 55.55, 114.2, 114.3, 124.3, 127.2, 130.2, 131.2, 143.8, 145.9, 154.3, 159.7, 133.5, 134.3, 137.0, 137.6, 191.3. MS (m/z): [M + H]^+, 376.3.

**QEA-G-002 (7-(4-Methoxy-phenyl)-3-methyl-9-pyridin-3-yl-nona-2,4,6,8-tetraenal)**
Preparation of Compound-3: To a stirred suspension of NaH (892 mg, 37.2 mmol) in dry DMF (10 mL) at 0 °C under nitrogen was added dropwise a solution of Compound-2 (6.89 g, 22.3 mmol) in dry DMF (10 mL). The reaction mixture was stirred at room temperature for 1 h. Then a solution of Compound-1 (2 g, 18.6 mmol) in dry THF (10 mL) was slowly added at 10 °C and the solution was stirred at room temperature for 2 h. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 50% ethyl acetate/petroleum ether to obtain Compound-3 (4.5 g, 91.8%). MS (m/z): [M + H]+, 263.1.

Preparation of Compound-4: To a solution of Compound-3 (3.8 g, 14.4 mmol) in DCM (10 mL) cooled to -78 °C under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 17 mL) and the reaction mixture was stirred for 20 min. Then the reaction was quenched with a saturated potassium sodium tartrate solution. The mixture was stirred at room temperature for 1 h. The resulting aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 40% ethyl acetate/petroleum ether to obtain Compound-4 (950 mg, 25%). MS (m/z): [M + H]+, 266.2.

Preparation of Compound-6: To a stirred suspension of NaH (261.8 mg, 55%, 6 mmol) in dry THF (10 mL) at room temperature under nitrogen was added dropwise a solution of Compound-5 (653 mg, 3 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 30 min. A solution of Compound-4 (800 mg, 3.01 mmol) in dry THF (10 mL) was slowly added and the mixture was stirred at room temperature for 1 h. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and
eluted with 25% ethyl acetate/petroleum ether to obtain Compound-6 (500 mg, 50.5%). MS (m/z): [M + H]⁺, 329.2.

**Preparation of QEA-G-002:** To a stirred solution of Compound-6 (1.2 g, 3.65 mmol) in dry toluene (10 mL) cooled to -70 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 4.3 mL). The reaction mixture was stirred at -70 ºC for 30 min, and then the reaction was quenched with a potassium sodium tartrate solution at 0 ºC. The resulting mixture was stirred for at room temperature for 30 min and extracted thrice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain QEA-G-002 (210 mg, 17.3%). ¹H NMR of major isomer (CDCl₃, 300 MHz): δ 2.09 (s, 3H), 3.90 (s, 3H), 5.98 (d, J = 8 Hz, 1H), 6.30 (d, J = 15.6 Hz, 1H), 6.50 (d, J = 14.8 Hz, 1H), 6.58-6.71 (m, 2H), 7.15-7.19 (m, 3H), 7.87 (dd, J = 2 Hz, 8.4 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.61 (s, 1H), 10.07 (d, J = 8.4 Hz, 1H); ¹³C NMR (CDCl₃, 150 MHz): δ 13.27, 55.54, 114.2, 124.6, 128.3, 128.7, 129.2, 130.1, 131.1, 133.5, 133.8, 134.4, 135.3, 136.0, 137.4, 145.7, 145.9, 154.3, 159.7, 191.3. MS (m/z): [M + H]⁺, 332.2.

**QEA-C-004 (9-(4-Chloro-phenyl)-3-methyl-7-phenyl-nona-2,4,6,8-tetraenal)**

\[
\begin{align*}
\text{Cl} & \quad \text{CHO} \\
\text{Cl} & \quad \text{CN} \\
\text{Cl} & \quad \text{CHO} \\
\text{Cl} & \quad \text{CN} \\
\text{Cl} & \quad \text{CHO} \\
\text{Cl} & \quad \text{CN} \\
\end{align*}
\]

**Preparation of Compound-3:** To a stirred suspension of NaH (715 mg, 29.8 mmol) in dry THF (10 mL) at room temperature under nitrogen was added dropwise a solution of Compound-2 (7.1 g, 25 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 40 min. Then a solution of Compound-1 (3 g, 21.3 mmol) in dry THF (10 mL) was slowly added at 0 ºC and the mixture was stirred at room temperature for 1 h. Then the reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-3 (2 g, 35.2%). MS (m/z): [M + H]⁺, 266.1.
Preparation of Compound-4: To a solution of Compound-3 (2 g, 7.5 mmol) in toluene (20 mL) cooled to -78 °C under nitrogen was slowly added DIBAL-H (1.7 M in toluene, 8.8 mL) and the reaction mixture was stirred for 30 min. The reaction was quenched with a saturated potassium sodium tartrate solution at -70 °C. The resulting mixture was stirred at room temperature for 1 h. and extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na2SO4 and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-4 (1.6 g, 79.2%). MS (m/z): [M + H]+, 269.1.

Preparation of Compound-6: To a stirred suspension of NaH (132 mg, 5.5 mmol) in dry THF (10 mL) at room temperature under nitrogen was added dropwise a solution of Compound-5 (955 mg, 4.4 mmol) in dry THF (10 mL). This reaction mixture was stirred at room temperature for 20 min. Then a solution of Compound-4 (1 g, 3.7 mmol) in dry THF (10 mL) was slowly added and the reaction was stirred at room temperature for 30 min. The reaction mixture was quenched with a saturated NH4Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na2SO4 and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-6 (430 mg, 35%). IR: 2206 cm⁻¹. MS (m/z): [M + H]+, 332.1.

Preparation of QEA-C-004: To a stirred solution of Compound-6 (580 mg, 1.74 mmol) in dry toluene at -78 °C under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 4.3 mL). The reaction mixture was stirred at -78 °C for 30 min and then poured into a 0.3 M H2SO4 solution at 0 °C. The reaction mixture was quenched with a potassium sodium tartrate solution at 0 °C. The mixture was stirred at room temperature for 30 min, and extracted thrice with ethyl acetate. The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain QEA-C-004 (210 mg, 36%). ¹H NMR of major isomer (CDCl3, 400 MHz): δ 2.08 (d, J = 1.2 Hz, 3H), 5.96 (d, J = 8 Hz, 1H), 6.23 (d, J = 15.6 Hz, 1H), 6.46 (d, J = 14.8 Hz, 1H), 6.54-6.65 (m, 2H), 7.05 (d, J = 15.6 Hz, 1H), 7.23-7.30 (m, 6H), 7.43-7.48 (m, 3H). 10.05 (d, J = 8 Hz, 1H); 13C NMR (CDCl3, 150 MHz): δ 13.20, 128.1, 128.2, 128.7, 129.1, 129.8, 130.0, 132.2, 132.7, 132.9, 133.8, 135.7, 136.5, 136.9, 147.0, 154.7, 191.4. MS (m/z): [M + H]+, 335.2.

TEA-C-002 (3,8,8-Trimethyl-7-naphthalen-2-yl-nona-2,4,6-trienal)
Preparation of Compound-2: To a stirred solution of nitrobenzene (23 mL) and AlCl₃ at room temperature were slowly added Compound-1 (10 g, 78 mmol) and a solution of isobutyryl chloride (9.3 mL, 88 mmol) in nitrobenzene (20 mL) at 40 ºC. This reaction mixture was stirred at room temperature overnight and then poured into a diluted HCl solution. The resulting white precipitate was removed by filtration. The filtrate was extracted thrice with diethyl ether, and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel I and eluted with 2-5% ethyl acetate/petroleum ether to obtain Compound-3 (10 g, 64.6%). MS (m/z): [M + H]⁺, 199.1.

Preparation of Compound-3: To a stirred solution of Compound-2 (3 g, 15.1 mmol) in benzene (8.4 mL) was added NaH (1.3 g, 60%, 30.2 mmol) and the resulting solution was refluxed for 3 h. Then CH₃I (3.7 mL, 59 mmol) was slowly added at 0 ºC. The reaction mixture was refluxed for 3 h. The reaction mixture was quenched with 2 M HCl solution at 0 ºC. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain compound-4 (2.5 g, 78%). MS (m/z): [M + H]⁺, 213.1.

Preparation of Compound-5: To a stirred suspension of NaH (444 mg, 18.5 mmol) in dry THF (10 mL) at room temperature was added dropwise a solution of Compound-4 (3.3 g, 18.5 mmol) in dry THF (10 mL). The reaction mixture was refluxed for 30 min. A solution of Compound-3 (2.2 g, 10.3 mmol) in dry THF (10 mL) was slowly added at 0 ºC and the solution was stirred at room temperature for 30 min. The reaction was quenched with a saturated NH₄Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-5 (650 mg, 26.8%). IR: 2218 cm⁻¹. MS (m/z): [M + H]⁺, 236.2.

Preparation of Compound-6: To a stirred solution of Compound-5 (650 mg, 2.68 mmol) in DCM (10 mL) at -70 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 3.25 mL). The reaction mixture was stirred at -70 ºC for 30 min and the reaction was quenched with a
saturated potassium sodium tartrate solution at -70 °C. The mixture was stirred at room
temperature for 30 min and extracted thrice with ethyl acetate. The combined organic layers
were dried over Na2SO4 and concentrated under vacuum. The residue was purified by column
chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to
obtain Compound-6 (480 mg, 73%). MS (m/z): [M + H]+, 239.2.

Preparation of Compound-8: To a stirred suspension of NaH (96 mg, 4 mmol) in dry THF (10
mL) at room temperature was added dropwise a solution of Compound-7 (868 mg, 3.5 mmol) in
dry THF (10 mL). The reaction mixture was stirred at room temperature for 20 min. Then a
solution of Compound-6 (480 mg, 2.0 mmol) in dry THF (10 mL) was slowly added and the
solution was stirred at room temperature for 30 min. The reaction was quenched with a saturated
NH4Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined
organic layers were dried over anhydrous Na2SO4 and concentrated under vacuum. The crude
compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 1%
ethyl acetate/petroleum ether to obtain Compound-8 (480 mg, 79%). IR: 2208 cm⁻¹. MS (m/z):
[M + H]+, 302.2.

Preparation of TEA-C-002: To a stirred solution of Compound-8 (480 mg, 1.59 mmol) in dry
toluene at -78 °C under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 1.87 mL). The
reaction mixture was stirred at -78 °C for 20 min. The reaction was quenched with a saturated
potassium sodium tartrate solution at 0 °C. The resulting mixture was stirred at room temperature
for 30 min, and then extracted thrice with ethyl acetate. The combined organic layers were dried
over Na2SO4 and concentrated under vacuum. The residue was purified by column
chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to
obtain TEA-C-002 (110 mg, 22.8%). \(^1\)H NMR (CDCl3, 400 MHz): \(\delta\) 1.18 (s, 9H), 1.88 (s, 3H),
5.89 (d, \(J = 8.4\) Hz, 1H), 6.18-6.45 (m, 2H), 6.46 (d, \(J = 14.4\) Hz, 1H), 7.20 (dd, \(J = 1.6\) Hz, 8.4
Hz, 1H), 7.53 (m, 3H), 7.86 (m, 3H), 9.98 (d, \(J = 8\) Hz, 1H); \(^{13}\)C NMR (CDCl3, 100 MHz): \(\delta\)
13.17, 29.88, 37.34, 125.0, 126.1, 126.4, 127.4, 127.9, 128.2, 128.5, 129.2, 132.5, 133.0, 134.5,
135.0, 135.9, 137.2, 155.4, 159.1, 191.5. MS (m/z): [M + H]+, 305.2.

QEA-B-002 (7-tert-Butyl-3-methyl-9-(2-methyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal)
Preparation of Compound-2: To a solution of DCM (10 mL) and triethyl orthoformate (60.3 g, 407.4 mmol) cooled to -35 ºC was added dropwise a solution of BF$_3$Et$_2$O (69 g, 488 mmol) in DCM (10 mL) over a period of 30 min. The reaction mixture was stirred at room temperature for 15 min. Compound-1 (20 g, 204 mmol) and diisopropylethyl amine (79 g, 611.1 mmol) were slowly added to the reaction mixture over a period of 30 min at -78 ºC. Then the reaction mixture was warmed to -15 ºC and stirred at -15 ºC to -5 ºC for 2 h. The reaction was quenched with aqueous NaHCO$_3$. The aqueous layer was extracted thrice with DCM. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with petroleum ether to obtain Compound-2 (9 g, 22%). MS (m/z): [M + H]$^+$, 201.1.

Preparation of Compound-3: To a solution of Compound-2 (9 g, 44.9 mmol) in diethyl ether (10 mL) cooled to 0 ºC under nitrogen was slowly added CH$_3$MgBr (3 M in diethyl ether, 59.9 mL). The reaction mixture was stirred at 0 ºC for 1 h and then at room temperature overnight. The reaction was quenched with 6 M HCl and the solution was stirred at room temperature for 3 h. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 2-5% ethyl acetate/petroleum ether to obtain compound-3 (2.5 g, 44.8%). MS (m/z): [M + H]$^+$, 125.1.

Preparation of Compound-5: To a stirred suspension of NaH (1.76 g, 55%, 40.4 mmol) in dry THF (10 mL) at room temperature under nitrogen was added dropwise a solution of Compound-4 (6.27 g, 24.2 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 30 min. Then a solution of Compound-3 (2.52 g, 20.2 mmol) in dry THF (10 mL) was slowly added and the mixture was stirred at room temperature for 20 min. The reaction was quenched with a saturated NH$_4$Cl solution and the aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-5 (3.3 g, 70.9%). MS (m/z): [M + H]$^+$, 230.1.

Preparation of Compound-6: To a stirred solution of compound-5 (2.7 g, 11.7 mmol) in toluene (10 mL) at -78 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 13.87 mL). The reaction mixture then was stirred at -78 ºC for 20 min. and poured into 0.3N H$_2$SO$_4$ at -10 ºC. Ethyl acetate was added and the mixture was stirred at room temperature for 30 min. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 1% ethyl acetate/petroleum ether to obtain Compound-6 (840 mg, 30.7%). MS (m/z): [M + H]$^+$, 233.2.

Preparation of Compound-8: To a stirred suspension of NaH (111 mg, 4.64 mol) in dry THF (10 mL) at room temperature under nitrogen was added dropwise a solution of Compound-7 (603
mg, 2.78 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 20 min. Then a solution of Compound-6 (540 mg, 2.32 mmol) in dry THF (10 mL) was slowly added and the solution was stirred at room temperature for 30 min. The reaction was quenched with a saturated NH₄Cl solution. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.3% ethyl acetate/petroleum ether to obtain Compound-8 (430 mg, 62.6%). MS (m/z): [M + H]⁺, 296.2.

Preparation of QEA-B-002: To a stirred solution of compound-8 (430 mg, 1.45 mmol) in toluene (10 mL) at -78 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 1.71 mL). The reaction mixture was stirred at -78 ºC for 20 min and then poured into 0.3N H₂SO₄ at -10 ºC. Ethyl acetate was then added and the mixture was stirred at room temperature for 30 min. The aqueous layer was extracted thrice with ethyl acetate, and the combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain QEA-B-002 (140 mg, 32.2%). ¹H NMR (CDCl₃, 400 MHz): δ 1.13 (s, (H), 1.63-1.70 (m, 4H), 2.11-2.14 (m, 2H0, 2.21- 2.25 (m, 2H0, 2.25 (s, 3H), 5.95 (d, J = 8 Hz, 1H), 5.97 (d, J = 8.4 Hz, 1H), 6.11 (d, J = 16 Hz, 1H), 6.23 (d, J = 10.8 Hz, 1H), 6.38 (d, J = 15.6 Hz, 1H), 6.71 (d, J = 15.6 Hz, 1H), 7.18-7.27 (m, 1H), 10.08 (d, J = 8.4 Hz, 1H). MS (m/z): [M + H]⁺, 299.2.

TEA-B-003 (5-tert-Butyl-7-(2-methyl-cyclohex-1-enyl)-hepta-2,4,6-trienal)

Preparation of Compound-3: To a stirred suspension of NaH (69 mg, 2.87 mmol) in dry THF (10 mL) at room temperature under nitrogen was added dropwise a solution of Compound-2 (517 mg, 2.9 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 15 min. Then a solution of Compound-1 (450 mg, 1.93 mmol) in dry THF (10 mL) was slowly added and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated NH₄Cl solution. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-3 (430 mg, 86.9%). MS (m/z): [M + H]⁺, 256.3.

Preparation of TEA-B-003: To a stirred solution of Compound-3 (430 mg, 1.68 mmol) in toluene (10 mL) at -78 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 2 mL). The reaction mixture was stirred at -78 ºC for 30 min and poured into 0.3 M H₂SO₄ at -30
ºC. Ethyl acetate was added and the mixture then was stirred at room temperature for 1 h. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.3% ethyl acetate/petroleum ether to obtain TEA-B-003 (180 mg, 41.3%). ¹H NMR (CDCl₃, 400 MHz): δ 1.15 (s, 9H), 1.58-1.74 (m, 4H), 1.78 (s, 3H), 2.08-2.16 (m, 2H), 2.19-2.24 (m, 2H), 6.11 (d, J = 15.6 Hz, 1H), 6.17 (dd, J = 8 Hz, 15.2 Hz, 1H), 6.33 (d, J = 11.2 Hz, 1H), 6.68 (d, J = 16 Hz, 1H), 7.56 (dd, J = 10.8 Hz, 15.2 Hz, 1H), 9.66 (d, J = 7.2 Hz, 1H) ¹³C NMR (CDCl₃, 100 MHz): δ 19.67, 22.89, 25.65, 29.84, 33.40, 37.23, 121.1, 121.4, 127.9, 130.4, 136.7, 152.7, 164.6, 194.6. MS (m/z): [M + H]⁺, 259.3.

TEA-B-001 (5-tert-Butyl-7-(2,6,6-trimethyl-cyclohex-1-enyl)-hepta-2,4,6-trienal)

Preparation of Compound-1: To a stirred suspension of NaH (5 g, 0.2 mol) in dry THF (10 mL) at 0 ºC was added dropwise a solution of β-ionone (10 g, 52 mmol) in dry THF (10 mL). The reaction mixture was stirred at 0 ºC for 2 h. A solution of CH₃I (12.5 mL, 0.2 mol) in dry THF (10 mL) was slowly added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with an NH₄Cl solution and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.5% ethyl acetate/petroleum ether to obtain Compound-1 (5 g, 41%). MS (m/z): [M + H]⁺, 235.2.

Preparation of Compound-3: To a stirred suspension of NaH (1.54 g, 64 mmol) in dry THF (20 mL) at 0 ºC was added dropwise a solution of Compound-2 (11.4 g, 64 mmol) in dry THF (10 mL). The reaction mixture was stirred at 0 ºC for 10 min. Then a solution of Compound-1 (5 g, 21 mmol) in dry THF (10 mL) was slowly added. The resulting reaction mixture was stirred at 50 ºC for 2 h and then at room temperature for 12 h. The reaction was quenched with an NH₄Cl solution and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.5 % ethyl acetate/petroleum ether to obtain Compound-3 (5 g, 91%). MS (m/z): [M + H]⁺, 258.2.
Preparation of Compound-4: To a stirred solution of Compound-3 (5.3 g, 20.6 mmol) in dry toluene (53 mL) at -30 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 24 mL). The reaction mixture was cooled to -10 ºC and poured onto wet silica gel. The resulting mixture was stirred for 30 minutes and filtered. The silica bed was washed twice with ether and the filtrate was concentrated. The residue was purified by column chromatography on 60-120 mesh silica gel and eluted with 0.8% ethyl acetate/petroleum ether to obtain Compound-4 (1.53 g, 28.5%). MS (m/z): [M + H]+, 261.2.

Preparation of Compound-6: To a stirred suspension of NaH (133 mg, 5.54 mmol) in dry THF (20 mL) at room temperature under nitrogen was added dropwise a solution of Compound-2 (0.98 g, 5.53 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 15 min and then a solution of Compound-4 (970 mg, 3.72 mmol) in dry THF (10 mL) was slowly added. The reaction mixture was stirred at room temperature for 15 min and the reaction was quenched with an NH₄Cl solution. The mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.2% ethyl acetate/petroleum ether to obtain Compound-6 (550 mg, 51.5%). MS (m/z): [M + H]+, 284.3.

Preparation of TEA-B-001: To a stirred solution of Compound-6 (550 mg, 1.94 mmol) in dry toluene (10 mL) cooled to -78 ºC under nitrogen was added dropwise DIBAL-H (1.7 M in toluene, 2.28 mL). The reaction mixture was was stirred at -78 ºC for 30 min and quenched with a 0.3 M H₂SO₄ solution and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude compound was purified by column chromatography on 100-200 mesh silica gel and eluted with 0.1% ethyl acetate/petroleum ether to obtain TEA-B-001 (180 mg, 32.4%). ¹H NMR (CDCl₃, 400 MHz): δ 1.05 (s, 6H), 1.16 (s, 9H), 1.47-1.51 (m, 2H), 1.62-1.66 (m, 2H), 1.79 (s, 3H), 2.04 (t, J = 6.4 Hz, 2H), 6.04 (s, 1H), 6.05 (m, 1H), 6.19 (dd, J = 8 Hz, 15.2 Hz, 1H), 6.33 (d, J = 11.2 Hz, 1H), 7.64 (dd, J = 11.2 Hz, 15.2 Hz, 1H), 9.53 (d, J = 8 Hz, 1H);¹³C NMR (CDCl₃, 100 MHz): δ 19.37, 22.14, 29.16, 29.77, 33.14, 34.46, 37.17, 39.60, 110.0, 121.3, 129.3, 130.6, 130.7, 136.9, 137.8, 152.5, 163.9, 194.5. MS (m/z): [M + H]+, 287.2.
List of abbreviations:

DIBAL-H: diisobutylaluminium hydride;
DCM: dichloromethane;
\textit{m}-CPBA: \textit{m}-chloroperbenzoic acid
Met: methanol;
THF: tetrahydrofuran;
\textit{p}-TSA: \textit{p}-toluenesulfonic acid;
TEA: triethylamine;
t-BuOK: potassium tert-butoxide;
LAH\textsubscript{4}: lithium aluminum hydride;
PDC: pyridium dichromate;
NBS: \textit{N}-bromosuccinimide;
AIBN: azobisisobutyronitrile;
TEP: triethylphosphate;
Pd/C: palladium on carbon;
DMF: dimethylformate;
TBDMSCl: \textit{tert}-butyldimethylsilyl chloride;
DMAP: dimethylaminopyridine;
\textit{i}-PrCOCl: isobutyryl chloride;
BF\textsubscript{3}Et\textsubscript{2}O: boron trifluoride diethyl etherate;
\textit{i}-PrNEt: diisopropylethyl amine;
CH\textsubscript{3}MgBr: methylmagnesium bromide.