Research Article

Shasline Gedeon, Laila M. Boyd, Marlee Avril, Madhavi Gangapuram, Kinfe K. Redda, Tiffany W. Ardley*

Synthesis of new analogs of N-substituted (benzoylamino)-1,2,3,6-tetrahydropyridines

https://doi.org/10.1515/chem-2023-0183
received August 3, 2023; accepted March 1, 2024

Abstract: The tetrahydropyridine (THP) moiety is notably present in synthetic and natural products, playing a cardinal role in the food, cosmetic, and pharmaceutical industries. The THP structure is an instrumental constituent and is widely found in alkaloids that have therapeutic properties against inflammation, cancer, the nervous system, and bacterial infections. The use of THPs has gained traction, so it is imperative to increase the structural database through the synthesis of THP derivatives. The focus of this study is to make structural modifications to the benzene ring portion of the lead compound while keeping the pyridine ring constant. Eleven novel THP analogs were synthesized using a four-step synthetic approach involving partial reduction of N-substituted ylides into 1,2,3,6-THPs. The results illustrate that 11 THPs were successfully synthesized in low to moderate yields. Flash chromatography was utilized for purification. Proton nuclear magnetic resonance, deuterium oxide exchange, carbon nuclear magnetic resonance, infrared spectroscopy, and CHN elemental analysis were utilized to characterize the THP analogs. This study aids in contributing knowledge to the THP database.

Keywords: synthesis, tetrahydropyridines, ylides, partial reduction

*** Corresponding author: Tiffany W. Ardley,** College of Pharmacy and Pharmaceutical Sciences, Institute of Public Health, Florida A&M University, Tallahassee, FL 32307, United States of America, e-mail: tiffany.ardley@famu.edu
Shasline Gedeon, Laila M. Boyd, Marlee Avril, Madhavi Gangapuram, Kinfe K. Redda: College of Pharmacy and Pharmaceutical Sciences, Institute of Public Health, Florida A&M University, Tallahassee, FL 32307, United States of America

1 Introduction

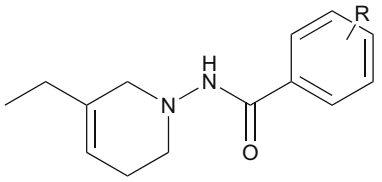
The tetrahydropyridine (THP) moiety is a six-membered, unsaturated, nitrogen-containing heterocycle that succeeds pyridine and dihydropyridine reduction [1,2]. The THP moiety is notably present in synthetic and natural products, playing a cardinal role in the food, cosmetic, and pharmaceutical industries [3–5]. THPs have also been investigated as potential food additives within the food industry [3]. They possess odorant properties likened to crackers or biscuits [6], which are exhibited in certain foods, including tortillas [7], baked desserts, and popcorn [8]. Mycosporin-like amino acid-derived THPs, extracted from cyanobacteria, are potential UV protectants and protect against harmful solar radiation; they are used as sunscreen pigments to prevent UV damage and suppress inflammation [9].

The THP structure is an instrumental constituent and is widely found in alkaloids that have therapeutic properties against inflammation, cancer, the nervous system, and bacterial infections [10–13]. Lozano et al. identified a widespread gene cluster in several *Pseudomonas* spp. necessary for THP alkaloid production, expanding the known repertoire of THP-containing antibiotics [14]. This heterocyclic structure has distinctive and attractive characteristics that have gained interest in the eyes of medicinal chemists. THP can be utilized as a scaffold and a pharmacophoric substituent in drug design, and strategies have been employed in drug design to take advantage of its properties [15]. They have been used as a scaffold to synthesize biologically active molecules, having been recounted in several pharmacological scopes, including dopamine-2 receptor agonists, used in sedation capacities such as antiemetics, antipsychotics, and migraine remedies [16,17]. They act as gamma-aminobutyric acid (GABA) receptor agonists [18], selective serotonin reuptake inhibitors [19], and acetylcholinesterase inhibitors [20]. THP compounds also exhibit antimicrobial [21], antiviral [22], antibacterial [23], antioxidant [24], anticancer [25], and anti-inflammatory properties [26]. The THP motif has been utilized as a scaffold for various studies to increase biological activity, and it has

been confirmed that the biological activity depends on the substituents on the ring site system [27]. The use of THPs has gained traction, so it is imperative to increase the structural database through the synthesis of THP derivatives.

1,2,3,6-THPs are important heterocyclic compounds that find utility in various pharmaceutical and synthetic applications. Several synthetic approaches to 1,2,3,6-THPs have been established by researchers as its significance as a critical structural moiety and lead compound increased, offering distinct advantages and versatility to the drug development process. Das and Njardarson postulated an anionic cascade strategy to retrieve the 1,2,3,6-THP heterocycle. Modification of this strategy originally created for thiopyrans was completed by uncovering a feasible nitrogen-leading group to undergo a Staudinger reaction followed by a Grignard addition [28]. Visseq et al. prepared 2,6-disubstituted-1,2,3,6-THPs in an efficient way. This method highlights the utilization of a diastereoselective palladium catalyst on non-activated alcohols to endure intramolecular allylic amination, providing 2,6-*trans*-1,2,3,6-THPs in moderate to good yields [29]. The diverse array of synthetic approaches for 1,2,3,6-THPs underscores the significance of these heterocycles in synthetic chemistry. Researchers continue to explore and refine these methods, ensuring the availability of powerful tools to access this important class of compounds.

Previous research done by Choi et al. [30] revealed that the ethyl group on the fifth position of the THP ring within the N-substituted(benzoylamino)-5-ethyl-1,2,3,6-THP structure (Figure 1) yielded promising anti-inflammatory activity compared to indomethacin. The focus of this study is to make structural modifications to the benzene ring portion of the lead compound while keeping the pyridine ring constant. Eleven novel THP analogs were synthesized using a four-step synthetic approach involving partial reduction of N-substituted ylides into 1,2,3,6-THPs.



1

Figure 1: N-Substituted(benzoylamino)-5-ethyl-1,2,3,6-THP lead compound from the previous research paper by Choi et al. [30].

2 Results and discussion

2.1 Methodology

This reaction scheme was previously established by Gangapuram and Redda [31] and can be viewed in Scheme 1. In the first step of the reaction, ethyl-*O*-(mesitylenesulfonyl)-acetohydroxymate was hydrolyzed using 70% perchloric acid ($HClO_4$) and *p*-dioxane. The reaction was left to run for 45 min in an ice bath. Ice was used to quench the reaction and was washed with distilled water. The mesitylenesulfonyl hydroxamate (MSH) product was collected and set to completely dry by vacuum filtration for 20–30 min. MSH is a white solid that has explosive properties.

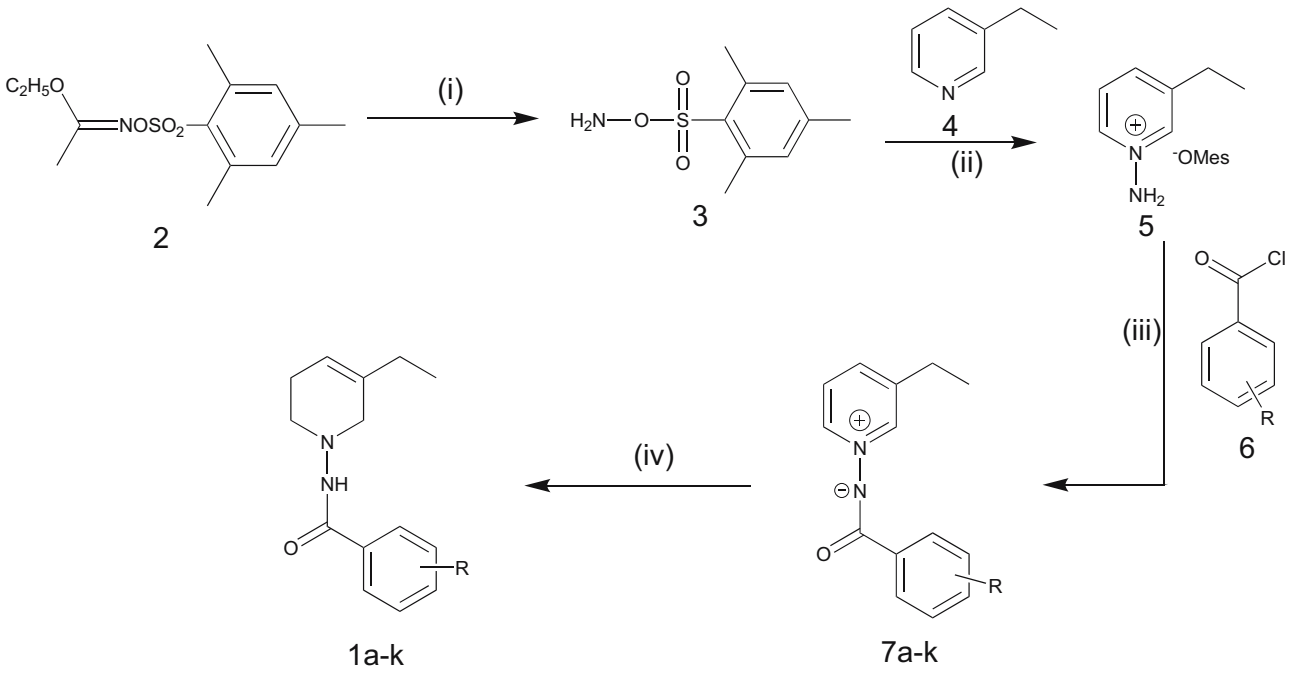
In the second step, MSH is dissolved in anhydrous dichloromethane (DCM) and is added to 3-ethyl pyridine dropwise. MSH is allowed to react at ice bath temperature overnight to form 3-ethylpyridinium mesitylenesulfonate. The 3-ethyl pyridinium salt was extracted with diethyl ether and concentrated under reduced pressure.

Next, the pyridinium salt product reacted with various substituted benzoyl chlorides in tetrahydrofuran (THF) and triethylamine (Et_3N) as the base at 70°C for 5–7 h and then overnight at room temperature. The course of the reaction was monitored using thin-layer chromatography (TLC). Saturated sodium bicarbonate ($NaHCO_3$) was utilized to quench the reaction, followed by extraction with DCM three times. It was dried over sodium sulfate (Na_2SO_4), and the solvent was evaporated. This yields the ylide product that was purified by flash column chromatography.

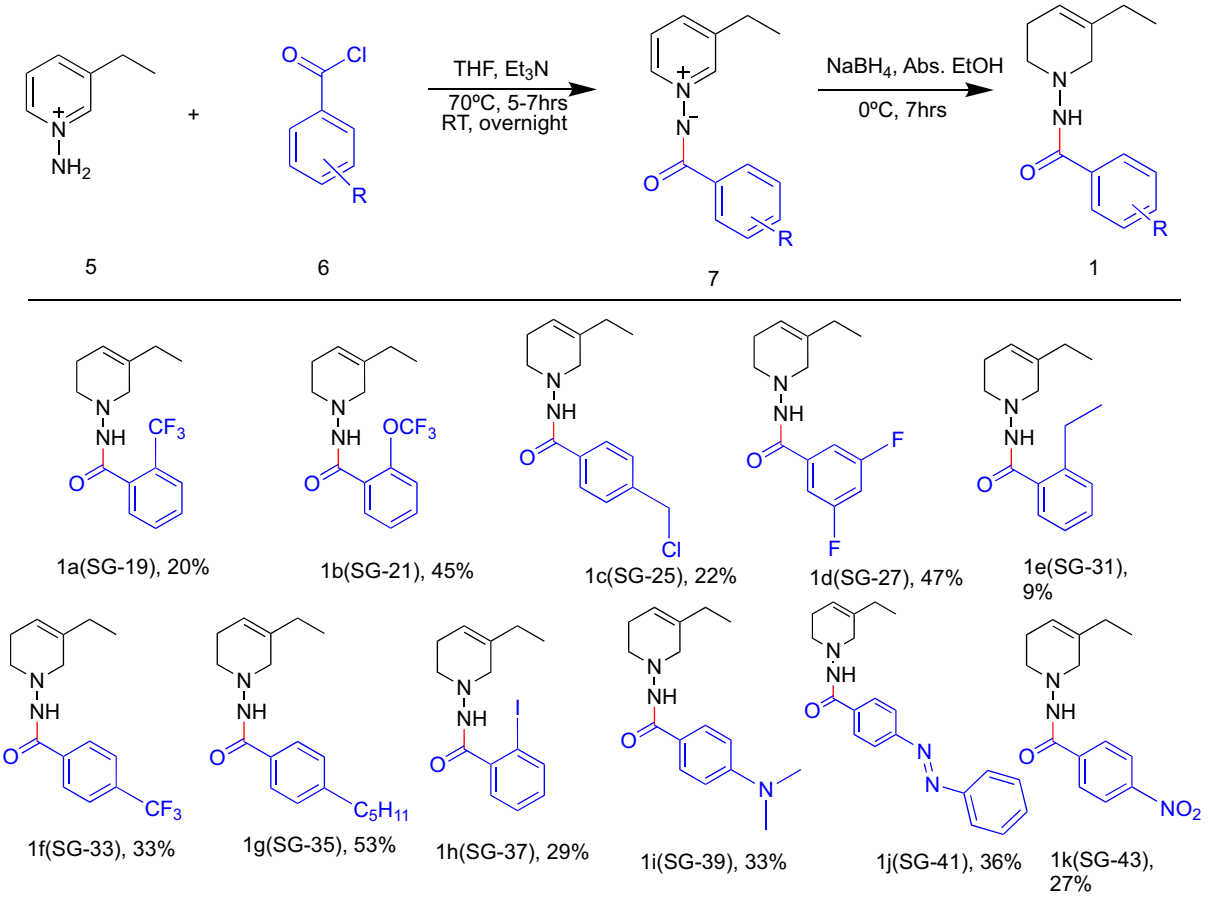
The final step involves the reduction of the ylide using sodium borohydride ($NaBH_4$) and absolute ethanol (Abs. EtOH). The reaction is run for 7 h under ice bath temperature while the course of the reaction is monitored utilizing TLC. Upon completion, the reaction was quenched with ice and extracted three times with DCM. It was then dried over Na_2SO_4, and the solvent was evaporated to afford the final THP product. Purification was done using flash column chromatography. This substrate scope for the novel THP derivatives can be viewed in Scheme 2. The ylide and THPs were characterized using ^{1}H NMR spectroscopy, carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy, infrared (IR) spectroscopy, and elemental analysis.

2.2 Synthesis

The synthetic pathway utilized for the preparation of the 11 THP analogs involved four main steps. The synthesis of these 1,2,3,6-THP analogs primarily involves the hydrolysis of ethyl-*o*-(mesitylenesulfonyl) acetohydroxymate with 70% $HClO_4$ and *p*-dioxane at 0°C for 45 min to render *O*-(mesitylsulfonyl)hydroxylamine (MSH). MSH, acting as an aminating



Scheme 1: General reaction scheme of N-substituted(benzoylamino)-5-ethyl 1,2,3,6-THPs. R = 2-CF_3, 2-OCF_3 4-CH_2Cl, 3,5-F, 2-C_2H_5, 4-CF_3, 4-C_5H_{11}, 2-I, 4-$N(CH_3)_2$, 4-$C_6H_5N_2$, 4-NO_2. (i) *p*-Dioxane; 70% $HClO_4$, 0°C, 45 min; (ii) 3-ethylpyridine, anhydrous CH_2Cl_2; 0°C, 45 min, then room temperature overnight; (iii) substituted benzoyl chlorides, anhydrous THF, Et_3N; 70°C, 6 h, then room temperature overnight (substituted ylide yields: shown in Table 1); and (iv) $NaBH_4$, Abs. EtOH; 0°C, 5–7 h (substituted THP yields: shown in Table 2).



Scheme 2: Substrate scope of N-substituted(benzoylamino)-5-ethyl 1,2,3,6-THPs.

agent, reacts with 3-ethyl pyridine in anhydrous methylene chloride at 0°C for 45 min, then at room temperature overnight. This amination reaction afforded the mesitylene salt, 1-amino-3-ethylpyridin-1-ium. Next, the salt product undergoes acylation with various substituted benzoyl chlorides in anhydrous THF and Et_3N as the base at 70°C for 5–7 h, then at room temperature overnight to generate stable N-ylide products. Finally, the partial reduction of the ylides utilizing $NaBH_4$ at 0°C while monitoring the reaction every hour yielded the desired final THP products.

A result summary for synthesizing the pyridinium ylides is shown in Table 1. The ylides were successfully synthesized in low to moderate yields. The ylides were purified using flash column chromatography. ^{1}H NMR, ^{13}C NMR, deuterium oxide (D_2O) exchange, IR, and CHN elemental analysis (Atlantic Microlab, Norcross, GA) were utilized to confirm that the analogs were successfully synthesized. The IR spectra note the absorbents for the amino (NH) and carbonyl (CO) functional groups that characterize the ylides. The 11 ylides had sharp melting points (mp), and the theoretical CHN (carbon, hydrogen, nitrogen) elemental analysis (obtained from ChemDraw software) correlated with the experimentally found values. They all fell within the acceptable ± 0.4 deviations.

The result summary for the synthesis of the THP derivatives is shown in Table 2. The table illustrates that 11 THPs were successfully synthesized in low to moderate yields and purified using flash column chromatography. The ^{1}H NMR, ^{13}C NMR, D_2O exchange, IR, and CHN elemental analysis were utilized to characterize the THP analogs. The IR spectra note the absorbents for the amino (NH) and carbonyl (CO) functional groups that characterize the THPs. The 11 THPs had sharp mp, and the theoretical CHN elemental analysis (obtained from ChemDraw software) correlated with the experimentally found values. They all fell within the acceptable ± 0.4 deviations.

2.3 Conclusion

This study aimed to synthesize, purify, and characterize N-substituted(benzoylamino)-5-ethyl-1,2,3,6-tetrahydropuridines. Eleven novel THPs were successfully synthesized, purified, and characterized. The THP derivatives were purified using flash column chromatography and recrystallization when needed. ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis were implemented for compound characterization. The mps were sharp, and the yields were low to fair. This study serves to increase knowledge and expand the database of THPs for the use of structural activity relationship studies as potential anti-inflammatory and anticancer agents.

3 Experimental section

3.1 Chemicals

The chemicals and solvents used for this research were commercially available through Sigma-Aldrich chemical company. Silica gel (200-425 Sigma mesh) was used as the solid phase for the flash column chromatographic separations.

3.2 Instrumentation

- The Stuart SMP10 melting point apparatus was used to determine the mp; they were uncorrected.
- Unless otherwise stated, the ^{1}H NMR spectra were recorded on Oxford Instruments 300 MHz and Bruker Ascend 600 MHz instruments using deuterated chloroform ($CDCl_3$). The internal standard was tetramethylsilane (TMS), and chemical shifts were reported in parts per million (ppm). Multiplicity abbreviations: doublet (d), triplet (t), quartet (q), quintet (quint), doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), and multiplet (m).
- Unless otherwise stated, the carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker Ascend 150 MHz instrument using deuterated chloroform ($CDCl_3$). The internal standard was TMS.
- The elemental analysis was executed by Atlantic Microlab Inc., Norcross, GA.
- The Fourier transform infrared spectroscopy (FTIR) spectra were acquired by Agilent Technologies Cary 630 FTIR.
- The reaction homogeneity of the intermediates and products was observed by TLC on Whatman 60F-245 plates. Visualization of the TLC plates was under ultraviolet (UV) light.

4 The chemistry

4.1 Preparation of *N*-(2-trifluoromethylbenzoylimino)-3-ethylpyridinium ylide (7a)

4.1.1 General procedure 1

Ethyl-*O*-mesitylenesulfonyl acetohydroxymate (5 g, 17.52 mmol) was hydrolyzed with 3 mL of *p*-dioxane and 2 mL of 70% $HClO_4$ and was allowed to run for 45 min at ice bath temperature. The reaction was quenched by 25 g of ice, yielding an off-white

Table 1: Synthetic data of pyridinium ylides

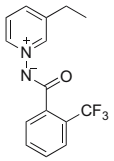
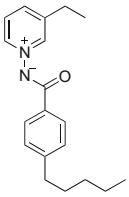
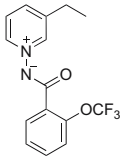
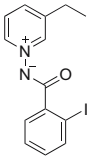
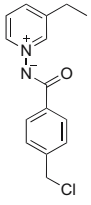
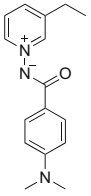
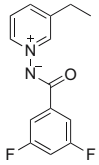
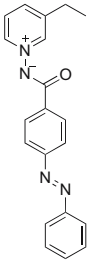
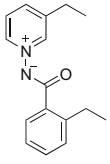
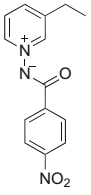
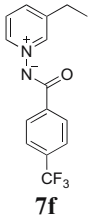
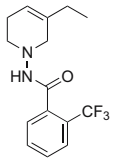
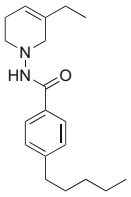
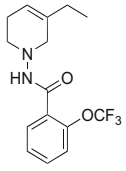
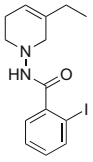
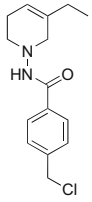
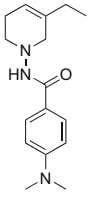
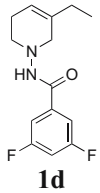
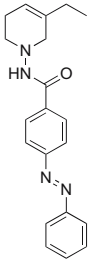
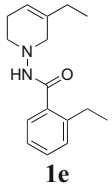
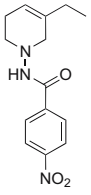
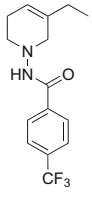
Compound	% Yield	MP	Compound	% Yield	MP
 **7a**	42	67–68°C	 **7g**	27	114–115°C
 **7b**	38	N/A	 **7h**	37	71–72°C
 **7c**	37	123–124°C	 **7i**	36	187–188°C
 **7d**	26	107–108°C	 **7j**	30	178–179°C
 **7e**	36	N/A	 **7k**	14	169–170°C
 **7f**	38	173°C			

Table 2: Synthetic data of THPs

Compound	% Yield	MP	Compound	% Yield	MP
 **1a**	20	122–123°C	 **1g**	53	109–110°C
 **1b**	45	86–87°C	 **1h**	29	126–127°C
 **1c**	22	130–131°C	 **1i**	33	160–161°C
 **1d**	47	144–145°C	 **1j**	36	190–191°C
 **1e**	9	128–129°C	 **1k**	27	159–160°C
 **1f**	33	154–155°C			

solid, MSH. MSH was washed with 800 mL of distilled water, collected by vacuum filtration, and dried for 20–30 min. MSH was completely dried and dissolved in 30 mL of methylene chloride. About 2.1 mL of 3-ethylpyridine was dissolved in 5 mL of methylene chloride and stirred at ice bath temperature for 10 min. Afterward, MSH was added to the 3-ethylpyridine

solution dropwise. The reaction was left to run overnight and afforded 3-ethylpyridinium mesitylenesulfonate, a yellow viscous product. It was extracted with diethyl ether three times and concentrated under reduced pressure.

3-Ethylpyridinium mesitylenesulfonate (1.55 g, 4.77 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.33 mL, 2.39 mmol) and was stirred for 10 min. Then, 2-trifluoromethylbenzoyl chloride (1.41 mL, 9.54 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(2-trifluoromethylbenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-18) was an off-white solid (1.19 g, 42%); FWT: 294.28; mp: 67–68°C; Anal. Calcd for $C_{15}H_{13}F_3N_2O$: C, 61.22; H, 4.45; N, 9.52. Found: C, 61.28; H, 4.54; N, 9.41. ir (potassium bromide): υ 1,592 (CO) cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) (δ): 1.34 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.83 (q, J = 7.6 Hz, 2H, CH_2CH_3), 7.46 (t, J = 7.7 Hz, 1H, C_3–H), 7.56 (t, J = 7.0 Hz, 1H, $C_{3'}$–H), 7.63 (t, J = 6.2 Hz, 1H, $C_{4'}$–H), 7.73 (d, J = 7.6 Hz, 1H, C_2–H), 7.80 (d, J = 0.6 Hz, 1H, C_4–H), 7.81 (d, J = 1.0 Hz, 1H, C_2–H), 8.59 (s, 1H, C_6–H), 8.62 (d, J = 1.3 Hz, 1H, $C_{5'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 26.0, 125.8, 126.11, 126.14, 126.17, 128.2, 129.2, 131.5, 137.4, 138.8, 140.6, 142.1, 143.3, 172.3; R_f = 0.33, ethyl acetate:methanol (9:1 v/v).

4.2 Preparation of *N*-(2-trifluoromethoxybenzoylimino)-3-ethylpyridinium ylide (7b)

3-Ethylpyridinium mesitylenesulfonate (1.78 g, 5.48 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.38 mL, 2.74 mmol) and was stirred for 10 min. Then, 2-trifluoromethoxybenzoyl chloride (1.72 mL, 10.96 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(2-trifluoromethoxybenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-20) was a yellow viscous liquid (1.30 g, 38%); FWT: 310.28; mp: N/A; Anal. Calcd for $C_{15}H_{13}F_3N_2O_2$: C, 58.07; H, 4.22; N, 9.03. Found: C, 57.85; H, 4.17; N, 8.84. ir (potassium bromide): υ 1,593 (CO) cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) (δ): 1.32 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.79 (q, J = 7.6 Hz, 2H, CH_2CH_3), 7.46 (t, J = 7.7 Hz, 1H, C_3–H), 7.56 (t, J = 7.0 Hz, 1H, $C_{3'}$–H), 7.63 (t, J = 6.2 Hz, 1H, $C_{4'}$–H), 7.73 (d, J = 7.6 Hz, 1H, C_2–H), 7.80 (d, J = 0.6 Hz, 1H, C_4–H), 7.81 (d, J = 1.0 Hz, 1H, C_2–H), 8.59 (s, 1H, C_6–H), 8.62 (d, J = 1.3 Hz, 1H, $C_{5'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 26.0, 121.5, 121.7, 125.7, 126.7, 129.9, 130.4, 133.2, 137.2, 140.7, 142.3, 143.2, 146.5, 170.0; R_f = 0.36, ethyl acetate:methanol 9:1 (v/v).

4.3 Preparation of *N*-(4-chloromethylbenzoylimino)-3-ethylpyridinium ylide (7c)

3-Ethylpyridinium mesitylenesulfonate (2.04 g, 6.28 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.44 mL, 3.14 mmol) and was stirred for 10 min. Then, 4-chloromethylbenzoyl chloride (2.37 mL, 12.56 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. *N*-(2-Chloromethylbenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-24) was a white solid (1.27 g, 37%); FWT: 274.75; mp: 123–124°C; Anal. Calcd for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; N, 10.20. Found: C, 64.83; H, 5.57; N, 9.85. ir (potassium bromide): υ 1,592 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.34 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.81 (q, J = 7.5 Hz, 2H, CH_2CH_3), 4.63 (s, 2H, CH_2Cl), 7.43 (d, J = 8.4 Hz, 2H, C_2–H, C_6–H), 7.60 (t, J = 6.3 Hz, 1H, C_3–H), 7.77 (d, J = 7.5 Hz, 1H, C_4–H), 8.15 (d, J = 8.1 Hz, 2H, C_3–H, C_5–H), 8.62 (d, J = 6.9 Hz, 2H, C_2–H, C_6–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 26.0, 40.1, 125.5, 128.1, 128.4, 136.8, 137.5, 139.2, 140.8, 142.5, 143.0, 170.1; R_f = 0.25, ethyl acetate:methanol (9:1 v/v).

4.4 Preparation of *N*-(3,5-difluorobenzoylimino)-3-ethylpyridinium ylide (7d)

3-Ethylpyridinium mesitylenesulfonate (3.27 g, 10.07 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.70 mL, 5.04 mmol) and was stirred for 10 min. Then, 3,5-difluorobenzoyl chloride (2.37 mL, 20.14 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(3,5-difluorobenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL

of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-26) was a pale-yellow solid (1.35 g, 26%); FWT: 262.26; mp: 107–108°C; Anal. Calcd for $C_{14}H_{12}F_2N_2O$: C, 64.12; H, 4.61; N, 10.68. Found: C, 63.66; H, 4.57; N, 10.43. ir (potassium bromide): υ 1,560 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.29 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.81 (q, J = 7.5 Hz, 2H, CH_2CH_3), 6.85 (tt, J = 2.4, 8.7 Hz, 1H, $C_{4'}$–H), 7.58–7.70 (m, 3H, C_3–H, $C_{2'}$–H, $C_{6'}$–H), 7.79 (d, J = 8.1 Hz, 1H, C_4–H), 8.61 (d, J = 5.4 Hz, 2H, C_2–H, C_6–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 26.0, 105.1, 110.7, 110.9, 125.6, 137.1, 140.6, 142.3, 143.2, 161.8, 163.4, 163.5, 168.3; R_f = 0.63, ethyl acetate:methanol (9:1 v/v).

4.5 Preparation of *N*-(2-ethylbenzoylimino)-3-ethylpyridinium ylide (7e)

3-Ethylpyridinium mesitylenesulfonate (3.14 g, 9.67 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.67 mL, 4.84 mmol) and was stirred for 10 min. Then, 2-ethylbenzoyl chloride (2.89 mL, 19.34 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(2-ethylbenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-30) was a light-orange liquid (1.76 g, 36%); FWT: 254.33; mp: N/A; Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 72.38; H, 7.05; N, 10.37. ir (potassium bromide): υ 1,549 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.34 (t, J = 6.0 Hz, 3H, CH_2CH_3), 1.34 (t, J = 7.8 Hz, 3H, $CH_{2'}CH_{3'}$), 2.81 (q, J = 7.5 Hz, 2H, $CH_{2'}CH_{3'}$), 2.97 (q, J = 7.5 Hz, 2H, CH_2CH_3), 7.16–7.31 (m, 3H, C_3–H, $C_{4'}$–H, $C_{5'}$–H), 7.56–7.66 (m, 2H, $C_{2'}$–H, $C_{3'}$–H), 7.75 (d, J = 8.1 Hz, 1H, C_4–H), 8.65 (t, J = 6.3 Hz, 2H, C_2–H, C_6–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 16.0, 26.0, 26.8, 125.3, 125.6, 128.2, 128.6, 129.0, 136.9, 138.3, 140.7, 142.2, 142.5, 143.1, 174.2; R_f = 0.29, ethyl acetate:methanol (9:1 v/v).

4.6 Preparation of *N*-(4-trifluoromethylbenzoylimino)-3-ethylpyridinium ylide (7f)

3-Ethylpyridinium mesitylenesulfonate (1.94 g, 5.98 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.42 mL, 2.99 mmol) and was stirred for 10 min. Then, 4-trifluoromethylbenzoyl chloride (1.78 mL, 11.96 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(4-trifluoromethylbenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-32) was a fine, white solid (1.34 g, 27%); FWT: 294.28; mp: 173°C; Anal. Calcd for $C_{15}H_{13}F_3N_2O$: C, 61.22; H, 4.45; N, 9.52. Found: C, 60.99; H, 4.36; N, 9.38. ir (potassium bromide): υ 1,599 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.35 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.82 (q, J = 7.8 Hz, 2H, CH_2CH_3), 7.59–7.67 (m, 3H, C_3–H, $C_{3'}$–H, $C_{5'}$–H), 7.79 (d, J = 8.1 Hz, 1H, C_4–H), 8.26 (d, J = 8.1 Hz, 2H, $C_{2'}$–H, $C_{6'}$–H), 8.62 (d, J = 6.3 Hz, 2H, C_2–H, C_6–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 26.0, 124.3, 124.7, 125.6, 128.3, 131.6, 131.8, 137.1, 140.7, 141.0, 142.4, 143.2, 169.4; R_f = 0.37, ethyl acetate:methanol (9:1 v/v).

4.7 Preparation of *N*-(4-pentylbenzoylimino)-3-ethylpyridinium ylide (7g)

3-Ethylpyridinium mesitylenesulfonate (4.36 g, 13.43 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.94 mL, 6.72 mmol) and was stirred for 10 min. Then, 4-pentylbenzoyl chloride (5.46 mL, 26.86 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(4-pentylbenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-34) was an off-white solid (2.14 g, 27%); FWT: 296.41; mp: 114–115°C; Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.80; H, 8.11; N, 9.30. ir (potassium bromide): υ 1,590 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 0.88 (t, J = 6.3 Hz, 3H, CH_3–C_5H_{11}), 1.29–1.35 (m, 7H, CH_2CH_3, C_3H–C_5H_{11}, C_4H–C_5H_{11}), 1.63 (quint, J = 7.8 Hz, 2H, C_2H–C_5H_{11}), 2.64 (t, J = 7.5 Hz, 2H, C_1H–C_5H_{11}), 2.79 (q, J = 7.8 Hz, 2H, CH_2CH_3), 7.21 (d, J = 7.8 Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.56 (t, J = 6.3 Hz, 1H, C_3–H), 7.73 (d, J = 7.8 Hz, 1H, C_4–H), 8.06 (d, J = 8.4 Hz, 2H, $C_{2'}$–H, $C_{6'}$–H), 8.63 (d, J = 7.5 Hz, 2H, C_2–H, C_6–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.0, 14.3, 22.5, 26.0, 31.0, 31.4, 35.8, 125.4, 128.0, 134.7, 136.5, 140.9, 142.6, 142.9, 145.1, 170.9; R_f = 0.38, ethyl acetate:methanol (9:1 v/v).

4.8 Preparation of *N*-(2-iodobenzoylimino)-3-ethylpyridinium ylide (7h)

3-Ethylpyridinium mesitylenesulfonate (4.18 g, 12.87 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.90 mL, 6.44 mmol) and was stirred for 10 min. Then, 2-iodomethylbenzoyl chloride (6.86 mL, 25.75 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(2-iodomethylbenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-36) was a light-yellow solid (3.37 g, 37%); FWT: 352.18; mp: 71–72°C; Anal. Calcd for $C_{14}H_{13}IN_2O$: C, 47.75; H, 3.72; N, 7.95. Found: C, 47.46; H, 3.65; N, 7.74. ir (potassium bromide): υ 1,566 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.34 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.82 (q, J = 7.8 Hz, 2H, CH_2CH_3), 7.02 (td, J = 1.8, 7.5 Hz, 1H, C_3–H), 7.35 (td, J = 1.2, 7.5 Hz, 1H, $C_{4'}$–H), 7.58–7.64 (m, 2H, $C_{4,}$–H, $C_{3'}$–H), 7.78 (d, J = 8.1 Hz, 1H, $C_{5'}$–H), 7.85 (dd, J = 0.9, 8.1 Hz, 1H, C_2–H), 8.66 (s, 1H, $C_{2'}$–H), 8.70 (d, J = 6.3 Hz, C_6–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 26.0, 94.5, 125.7, 127.8, 128.6, 129.6, 137.3, 139.4, 140.5, 142.1, 143.2, 144.2, 173.6; R_f = 0.37, ethyl acetate:methanol (9:1 v/v).

4.9 Preparation of *N*-(4-dimethylaminobenzoylimino)-3-ethylpyridinium ylide (7i)

3-Ethylpyridinium mesitylenesulfonate (3.51 g, 10.81 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.75 mL, 5.41 mmol) and was stirred for 10 min. Then, 4-dimethylaminobenzoyl chloride (3.97 mL, 21.62 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(4-dimethylaminobenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-38) was a pale-yellow solid (2.07 g, 36%); FWT: 269.35; mp: 187–188°C; Anal. Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 70.46; H, 7.10; N, 15.24. ir (potassium bromide): υ 1,579 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.32 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.77 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.00 (s, 6H, $(CH_3)_2N$), 6.71 (dt, J = 2.7, 9.6 Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.52 (t, J = 6.3 Hz, 1H, C_3–H), 7.69 (d, J = 7.8 Hz, 1H, C_4–H), 8.05 (dt, J = 2.7, 9.0 Hz, 2H, $C_{2'}$–H, $C_{6'}$–H), 8.63 (t, J = 6.0 Hz, 2H, C_2–H, C_6–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 26.0, 40.3, 111.1, 124.9, 125.3, 129.2, 136.0, 140.9, 142.6, 152.0, 170.9; R_f = 0.33, ethyl acetate:-methanol (9:1 v/v).

4.10 Preparation of *N*-(4-phenylazobenzoylimino)-3-ethylpyridinium ylide (7j)

3-Ethylpyridinium mesitylenesulfonate (1.69 g, 5.21 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.36 mL, 2.61 mmol) and was stirred for 10 min. Then, 4-phenylazobenzoyl chloride (2.55 mL, 10.42 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(4-phenylazobenzoylimino)-3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-40) was an orange solid (1.04 g, 30%); FWT: 330.39; mp: 178–179°C; Anal. Calcd for $C_{20}H_{18}N_4O$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.56; H, 5.41; N, 16.84. ir (potassium bromide): υ 1,593 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.35 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.82 (q, J = 7.8 Hz, 2H, CH_2CH_3), 7.45–7.56 (m, 3H, $C_{3''}$–H, $C_{4''}$–H, $C_{5''}$–H), 7.61 (t, J = 5.7 Hz, 1H, C_3–H), 7.78 (d, J = 7.5 Hz, 1H, C_4–H), 7.93–7.97 (m, 4H, $C_{3'}$–H, $C_{5'}$–H, $C_{2''}$–H, $C_{6''}$–H), 8.31 (dd, J = 1.5, 8.7 Hz, 2H, $C_{2'}$–H, $C_{6'}$–H), 8.66 (d, J = 6.9 Hz, 2H, C_2–H, C_6–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 26.0, 122.4, 122.9, 125.6, 128.9, 129.1, 136.9, 139.8, 140.7, 142.5, 143.1, 152.8, 153.7, 170.0; R_f = 0.32, ethyl acetate:methanol (9:1 v/v).

4.11 Preparation of *N*-(4-nitrobenzoylimino)-3-ethylpyridinium ylide (7k)

3-Ethylpyridinium mesitylenesulfonate (4.28 g, 13.18 mmol) was dissolved in 15 mL of anhydrous THF at 70°C with Et_3N (0.92 mL, 6.60 mmol) and was stirred for 10 min. Then, 4-nitrobenzoyl chloride (4.89 mL, 26.36 mmol) was added. The reaction proceeded for 5 h at 70°C and then overnight at room temperature. About 100 mL of $NaHCO_3$ was used to quench the reaction. The product *N*-(4-nitrobenzoylimino)-

3-ethylpyridinium ylide was extracted with 3 × 70 mL of methylene chloride and dried over Na_2SO_4. The ylide was retrieved by filtration and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol (9:1 v/v). The result (SG-42) was an off-white solid (1.02 g, 14%); FWT: 271.28; mp: 169–170°C; Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.62; H, 4.83; N, 15.42. ir (potassium bromide): υ 1,571 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.35 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.83 (q, J = 7.8 Hz, 2H, CH_2CH_3), 7.63 (t, J = 6.9 Hz, 1H, C_3–H), 7.82 (d, J = 8.1 Hz, 1H, C_4–H), 8.24 (dt, J = 1.8, 8.7 Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 8.26 (d, J = 1.8, 9.6 Hz, 2H, $C_{2'}$–H, $C_{6'}$–H), 8.62 (d, J = 5.7 Hz, 2H, C_2–H, C_6–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 14.3, 26.0, 123.0, 125.7, 129.0, 137.4, 140.5, 142.3, 143.3, 143.8, 148.9, 168.6; R_f = 0.35, ethyl acetate:methanol (9:1 v/v).

4.12 $NaBH_4$ reduction of *N*-(2-trifluoromethylbenzoylimino)-3-ethylpyridinium ylide (7a) to produce N-(2-trifluoromethylbenzoylamino)-3-ethyl-1,2,3,6-THP (1a)

4.12.1 General procedure 2

$NaBH_4$ (0.35 g, 9.35 mmol) was added to a solution of **7a** (0.55 g, 1.87 mmol) in 60 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with methylene chloride (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was solid white crystals (0.11 g, 20%); FWT: 298.31; mp: 122–123°C; Anal. Calcd for $C_{15}H_{17}F_3N_2O$: C, 60.40; H, 5.74; N, 9.39. Found: C, 60.12; H, 5.78; N, 9.28. ir (potassium bromide): υ 3,178 (NH), 1650 (CO) cm^{-1}; ^1H NMR (600 MHz $CDCl_3$) (δ): 1.34 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.83 (q, J = 7.6 Hz, 2H, CH_2CH_3), 7.46 (t, J = 7.7 Hz, 1H, C_3–H), 7.56 (t, J = 7.0 Hz, 1H, $C_{3'}$–H), 7.63 (t, J = 6.2 Hz, 1H, $C_{4'}$–H), 7.73 (d, J = 7.6 Hz, 1H, C_2–H), 7.80 (d, J = 0.6 Hz, 1H, C_4–H), 7.81 (d, J = 1.0 Hz, 1H, C_2–H), 8.59 (s, 1H, C_6–H), 8.62 (d, J = 1.3 Hz, 1H, $C_{5'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 11.9, 23.9, 27.6, 27.7, 51.3, 56.6, 117.4, 126.3, 127.0, 128.9, 129.2, 130.0, 132.1, 136.2, 165.6; R_f = 0.53, ethyl acetate:hexane (6:4 v/v).

4.13 $NaBH_4$ reduction of *N*-(2-trifluoromethoxybenzoylimino)-3-ethylpyridinium ylide (7b) to produce *N*-(2-trifluoromethoxybenzoylamino)-3-ethyl-1,2,3,6-THP (1b)

$NaBH_4$ (0.80 g, 20.95 mmol) was added to a solution of **7b** (1.3 g, 4.19 mmol) in 80 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:-hexane (6:4 v/v). The result was an off-white solid (0.59 g, 45%); FWT: 314.31; mp: 86–87°C; Anal. Calcd for $C_{15}H_{17}F_3N_2O_2$: C, 57.32; H, 5.45; N, 8.91. Found: C, 57.62; H, 5.44; N, 8.85. ir (potassium bromide): υ 3,215 (NH), 1651 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.02 (t, J = 6.3 Hz, 3H, CH_2CH_3), 1.96 (q, J = 6.6 Hz, 2H, CH_2CH_3), 2.30 (s, 2H, C_3–H), 3.08 (s, 2H, C_2–H), 3.41 (s, 2H, C_6–H), 5.49 (s, 1H, C_4–H), 7.27–7.50 (m, 3H, $C_{2'}$–H, $C_{3'}$–H, $C_{4'}$–H), 7.95 (d, J = 6.9 Hz, 1H, $C_{5'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 11.9, 23.7, 27.7, 51.4, 56.8, 117.4, 121.1, 127.5, 127.8, 131.6, 132.2, 136.1, 145.7, 162.4; R_f = 0.51, ethyl acetate:hexane (6:4 v/v).

4.14 $NaBH_4$ reduction of *N*-(4-chloromethylbenzoylimino)-3-ethylpyridinium ylide (7c) to produce *N*-(4-chloromethylbenzoylamino)-3-ethyl-1,2,3,6-THP (1c)

$NaBH_4$ (0.83 g, 31.74 mmol) was added to a solution of **7c** (1.2 g, 6.35 mmol) in 75 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was white solid recrystallized with DCM and hexane (20 mL) (0.27 g, 22%); FWT: 278.78; mp: 130–131°C; Anal. Calcd: $C_{15}H_{19}ClN_2O$: C, 64.63; H, 6.87; N, 10.05. Found: C, 64.55; H, 6.87; N, 9.99. ir

(potassium bromide): υ 3,189 (NH), 1,646 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.02 (t, J = 6.9 Hz, 3H, CH_2CH_3), 1.97 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.31 (s, 2H, C_3–H), 3.08 (t, J = 6.0 Hz, 2H, C_2–H), 3.43 (s, 2H, C_6–H), 4.60 (s, 2H, CH_2Cl), 5.50 (s, 1H, C_4–H), 7.45 (d, J = 8.1 Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.74 (d, J = 8.1, 2H, $C_{2'}$–H, $C_{6'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 12.0, 24.3, 27.7, 45.4, 51.7, 57.0, 117.3, 127.6, 128.6, 133.9, 136.3, 140.9, 165.2; R_f = 0.44, ethyl acetate:hexane (6:4 v/v).

4.15 $NaBH_4$ reduction of *N*-(3,5-difluorobenzoylimino)-3-ethylpyridinium ylide (7d) to produce *N*-(3,5-difluorobenzoylamino)-3-ethyl-1,2,3,6-THP (1d)

$NaBH_4$ (0.22 g, 5.72 mmol) was added to a solution of **7d** (0.30 g, 1.14 mmol) in 50 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was solid white crystals (0.14 g, 47%); FWT: 266.29; mp: 144–145°C; Anal. Calcd for $C_{14}H_{16}F_2N_2O$: C, 63.15; H, 6.06; N, 10.44. Found: C, 62.85; H, 6.00; N, 10.47. ir (potassium bromide): υ 3,204 (NH), 1,646 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.02 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.97 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.31 (s, 2H, C_3–H), 3.07 (t, J = 5.7 Hz, 2H, C_2–H), 3.41 (s, 2H, C_6–H), 5.50 (s, 1H, C_4–H), 6.95 (tt, J = 2.4 Hz, 8.1 Hz, 1H, $C_{4'}$–H), 7.27 (d, J = 5.1 Hz, 2H, $C_{2'}$–H, $C_{6'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 12.0, 24.4, 27.7, 51.8, 57.0, 106.9, 110.4, 110.5, 117.4, 136.2, 137.2, 162.2, 163.8; R_f = 0.56, ethyl acetate:hexane (6:4 v/v).

4.16 $NaBH_4$ reduction of *N*-(2-ethylbenzoylimino)-3-ethylpyridinium ylide (7e) to produce *N*-(2-ethylbenzoylamino)-3-ethyl-1,2,3,6-THP (1e)

$NaBH_4$ (0.42 g, 11.01 mmol) was added to a solution of **7e** (0.56 g, 2.20 mmol) in 60 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was solid white crystals (0.05 g, 9%); FWT: 258.37; mp: 128–129°C; Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.32; H, 8.59; N, 10.86. ir (potassium bromide): υ 3,178 (NH), 1,638 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.02 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.25 (t, J = 7.5 Hz, 3H, $CH_{2'}CH_{3'}$), 1.97 (q, J = 6.9 Hz, 2H, CH_2CH_3), 2.31 (m, 2H, C_3–H), 2.82 (q, J = 7.8 Hz, 2H, $CH_{2'}CH_{3'}$), 3.08 (t, J = 6.0 Hz, 2H, C_2–H), 3.42 (s, 2H, C_6–H), 5.48 (m, 1H, C_4–H), 7.18–7.39 (m, 4H, $C_{2'}$–H, $C_{3'}$–H, $C_{4'}$–H, $C_{5'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 12.0, 15.9, 24.1, 26.3, 27.7, 51.2, 57.0, 117.4, 125.7, 127.0, 129.4, 130.1, 134.9, 136.2, 142.5, 168.0; R_f = 0.70, ethyl acetate:hexane (6:4 v/v).

4.17 $NaBH_4$ reduction of *N*-(4-trifluoromethylbenzoylimino)-3-ethylpyridinium ylide (7 f) to produce *N*-(4-trifluoromethylbenzoylamino)-3-ethyl-1,2,3,6-THP (1f)

$NaBH_4$ (0.64 g, 16.99 mmol) was added to a solution of **7f** (1.0 g, 3.40 mmol) in 80 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was solid white crystals (0.33 g, 33%); FWT: 298.31; mp: 154–155°C; Anal. Calcd for $C_{15}H_{17}F_3N_2O$: C, 60.40; H, 5.74; N, 9.39. Found: C, 60.45; H, 5.71; N, 9.36. ir (potassium bromide): υ 3,196 (NH), 1,644 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.02 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.97 (q, J = 6.9 Hz, 2H, CH_2CH_3), 2.32 (s, 2H, C_3–H), 3.09 (t, J = 6.0 Hz, 2H, C_2–H), 3.44 (s, 2H, C_6–H), 5.50 (s, 1H, C_4–H), 7.69 (d, J = 8.1 Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.86 (d, J = 8.1, 2H, $C_{2'}$–H, $C_{6'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 12.0, 24.4, 27.6, 51.7, 57.0, 117.3, 125.5, 127.7, 136.2, 137.2, 164.5; R_f = 0.64, ethyl acetate:hexane (6:4 v/v).

4.18 $NaBH_4$ reduction of *N*-(4-pentylbenzoylimino)-3-ethylpyridinium ylide (7g) to produce *N*-(4-pentylbenzoylamino)-3-ethyl-1,2,3,6-THP (1g)

$NaBH_4$ (0.64 g, 16.87 mmol) was added to a solution of **7g** (1.0 g, 3.37 mmol) in 75 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was white solid crystals (0.54 g, 53%); FWT: 300.45; mp: 109–110°C; Anal. Calcd for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.32. Found: C, 75.90; H, 9.48; N, 9.18. ir (potassium bromide): υ 3,193 (NH), 1,638 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 0.886 (t, J = 6.9 Hz, 3H, C_5H_{11}) 1.02 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.23–1.37 (m, 4H, C_5H_{11}) 1.61 (q, J = 7.5 Hz, 2H, C_5H_{11}), 1.96 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.30 (s, 2H, C_3–H), 2.64 (t, J = 7.5 Hz, 3H, C_5H_{11}), 3.07 (t, J = 5.7 Hz, 2H, C_2–H), 3.42 (s, 2H, C_6–H), 5.48 (s, 1H, C_4–H), 7.22 (d, J = 8.1 Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.66 (d, J = 7.5, 2H, $C_{2'}$–H, $C_{6'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 12.0, 13.9, 22.4, 24.4, 27.7, 30.8, 31.3, 35.8, 51.7, 57.0, 117.3, 127.1, 128.5, 131.3, 136.4, 146.9, 165.8; R_f = 0.67, ethyl acetate:hexane (6:4 v/v).

4.19 $NaBH_4$ reduction of *N*-(2-iodobenzoylimino)-3-ethylpyridinium ylide (7h) to produce *N*-(2-iodobenzoylamino)-3-ethyl-1,2,3,6-THP (1h)

$NaBH_4$ (0.54 g, 14.20 mmol) was added to a solution of **7h** (1.0 g, 2.84 mmol) in 75 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was solid white crystals (0.29 g, 29%); FWT: 356.21; mp: 126–127°C; Anal. Calcd for $C_{14}H_{17}IN_2O$: C, 47.21; H, 4.81; N, 7.86. Found: C, 47.36; H, 4.94; N, 7.92. ir (potassium bromide): υ 3,185 (NH), 1,648 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.02 (t, J = 7.8 Hz, 3H, CH_2CH_3), 1.98 (q, J = 6.6 Hz, 2H, CH_2CH_3), 2.31 (m, 2H, C_3–H), 3.14 (t, J = 6.0 Hz, 2H, C_2–H), 3.47 (s, 2H, C_6–H), 5.49 (m, 1H, C_4–H), 7.08–7.14 (m, 1H, $C_{4'}$–H), 7.33–7.40 (m, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.83(t, J = 7.8 Hz, $C_{2'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 12.0, 24.0, 27.7, 51.4, 56.7, 92.7, 117.4, 128.2, 128.5, 131.1, 136.2, 139.6, 141.1, 167.3; R_f = 0.60, ethyl acetate:hexane (6:4 v/v).

4.20 $NaBH_4$ reduction of *N*-(4-dimethylaminobenzoylimino)-3-ethylpyridinium ylide (7i) to produce *N*-(2-dimethylaminobenzoylamino)-3-ethyl-1,2,3,6-THP (1i)

$NaBH_4$ (0.70 g, 18.56 mmol) was added to a solution of **7i** (1.0 g, 3.71 mmol) in 75 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was solid pale-yellow crystals (0.33 g, 33%); FWT: 273.38; mp: 160–161°C; Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.30; H, 8.48; N, 15.37. Found: C, 70.36; H, 8.55; N, 15.53. ir (potassium bromide): υ 3,200 (NH), 1,634 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.02 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.96 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.30 (s, 2H, C_3–H), 3.02 (s, 6H, $(CH_3)_2N$), 3.09 (t, J = 1.8 Hz, 2H, C_2–H), 3.42 (s, 2H, C_6–H), 5.50 (s, 1H, C_4–H), 6.66 (d, J = 2.4 Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 7.65 (m, 2H $C_{2'}$–H, $C_{6'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 12.0, 24.4, 27.8, 40.1, 51.9, 57.2, 111.0, 117.3, 120.6, 128.5, 136.5, 152.5, 164.9; R_f = 0.36, ethyl acetate:hexane (6:4 v/v).

4.21 $NaBH_4$ reduction of *N*-(4-phenylazobenzoylimino)-3-ethylpyridinium ylide (7j) to produce *N*-(4-phenylazobenzoylamino)-3-ethyl-1,2,3,6-THP (1j)

$NaBH_4$ (0.34 g, 9.08 mmol) was added to a solution of **7j** (0.60 g, 1.82 mmol) in 60 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was

permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was solid orange crystals (0.22 g, 36%); FWT: 334.42; mp: 190–191°C; Anal. Calcd for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.75. Found: C, 71.54; H, 6.58; N, 16.72. ir (potassium bromide): υ 3,194 (NH), 1,638 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.04 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.98 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.33 (s, 2H, C_3–H), 3.02 (s, 6H, $(CH_3)_2N$), 3.11 (t, J = 5.7 Hz, 2H, C_2–H), 3.46 (s, 2H, C_6–H), 5.50 7.14 (s, NH, D_2O Exchange) (s, 1H, C_4–H), 7.52–7.54 (m, 4H, $C_{3''}$–H, $C_{5''}$–H, $C_{2''}$–H, $C_{6''}$–H), 7.92–7.98 (m, 5H, $C_{3'}$–H, $C_{5'}$–H, C_2–H, C_6–H, $C_{4''}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 12.0, 24.3, 27.7, 51.8, 57.1, 117.4, 122.9, 123.1, 128.1, 129.2, 131.6, 135.7, 136.3, 152.6, 154.3, 165.1; R_f = 0.51, ethyl acetate:hexane (6:4 v/v).

4.22 $NaBH_4$ reduction of *N*-(4-bitrobenzoylimino)-3-ethylpyridinium ylide (7k) to produce *N*-(4-nitrobenzoylamino)-3-ethyl-1,2,3,6-THP (1k)

$NaBH_4$ (0.35 g, 9.22 mmol) was added to a solution of **7k** (0.50 g, 1.84 mmol) in 50 mL of Abs. EtOH at 0°C. The reaction continued for 7 h while being monitored by TLC. About 25 g of ice was used to quench the reaction. It was permitted to warm to room temperature. The product was extracted with DCM (3 × 70 mL) and dried over Na_2SO_4. It was filtered, and the solvent was concentrated under reduced pressure. The product purification was done by flash column chromatography with silica gel using ethyl acetate:hexane (6:4 v/v). The result was solid yellow crystals (0.14 g, 27%); FWT: 275.31; mp: 159–160°C; Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.21. Found: C, 60.79; H, 6.13; N, 15.16. ir (potassium bromide): υ 3,196 (NH), 1,642 (CO) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) (δ): 1.03 (t, J = 7.8 Hz, 3H, CH_2CH_3), 1.98 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.32 (s, 2H, C_3–H), 3.11 (t, J = 5.4 Hz, 2H, C_2–H), 3.45 (s, 2H, C_6–H), 5.51 (s, 1H, C_4–H), 7.93 (d, J = 8.4 Hz, 2H, $C_{3'}$–H, $C_{5'}$–H), 8.28 (d, J = 8.1, 2H, $C_{2'}$–H, $C_{6'}$–H); ^{13}C NMR (150 MHz, $CDCl_3$) (δ): 12.0, 24.5, 27.6, 51.7, 56.9, 117.4, 122.9, 123.7, 128.4, 129.8, 136.1, 139.5, 149.6, 163.8; R_f = 0.63, ethyl acetate:hexane (6:4 v/v).

Acknowledgements: We would like to acknowledge FAMU College of Pharmacy & Pharmaceutical Sciences, Institute of Public Health and FAMU Cancer Research Education & Engagement Program – FAMU CaRE^2 Program, the Research Center at Minority Institutions, and Title III Programs.

Funding information: This research was also made possible by Grant Numbers U54CA233396, U54CA233444, and U54CA233465 from the National Institutes of Health (NIH), National Cancer Institute (NCI). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCI. This research was supported by the National Institute on Minority Health and Health Disparities of the National Institutes of Health under Award Number U54 MD007582. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author contributions: S.G. – writing, data curation; L.B. – data curation; M.A. – data curation; M.G. – methodology, supervision; K.R. – methodology, funding acquisition; T.A. – supervision, project administration, funding acquisition.

Conflict of interest: The authors declare no conflict of interest.

Ethical approval: The conducted research is not related to either human or animal use.

Data availability statement: The data presented in this study are available on request from the corresponding author.

References

[1] Vereshchagin AN, Iliyasov TM, Karpenko KA, Akchurin RN, Minyaev ME. Tetrahydropyridines' stereoselective formation, how lockdown assisted in the identification of the features of its mechanism. Molecules. 2022;27(14):4367. doi: 10.3390/molecules27144367.

[2] Balasubramanian M. Chapter 5 – Formation of completely or partially reduced pyridines and quinolines. In Pyridines: from lab to production. In: Scriven EFV, editor.Best synthetic methods. Oxford: Academic Press; 2013. p. 413–58. doi: 10.1016/B978-0-12-385235-9.00005-9.

[3] Calva-Estrada SJ, Jiménez-Fernández M, Lugo-Cervantes E. Betalains and their applications in food: The current state of processing, stability and future opportunities in the industry. Food Chem Mol Sci. 2022;4:100089. doi: 10.1016/j.fochms.2022.100089.

[4] Chrapusta E, Kaminski A, Duchnik K, Bober B, Adamski M, Bialczyk J. Mycosporine-like amino acids: Potential health and beauty ingredients. Mar Drugs. 2017;15(10):326. doi: 10.3390/md15100326.

[5] Frolov NA, Vereshchagin AN. Piperidine derivatives: recent advances in synthesis and pharmacological applications. Int J Mol Sci. 2023;24(3):2937. doi: 10.3390/ijms24032937.
[6] Takeoka GR, Buttery RG. Preparation and characterisation of 2-formyl-1,4,5,6-tetrahydropyridine, a compound with a cracker-like odour. Food Chem. 2012;132(4):2131–4. doi: 10.1016/j.foodchem.2011.12.023.
[7] Harrison TJ, Dake GR. An expeditious, high-yielding construction of the food aroma compounds 6-acetyl-1,2,3,4-tetrahydropyridine and 2-acetyl-1-pyrroline. J Org Chem. 2005;70(26):10872–74. doi: 10.1021/jo051940a.
[8] Snowdon EM, Bowyer MC, Grbin PR, Bowyer PK. Mousy off-flavor: A review. J Agric Food Chem. 2006;54(18):6465–74. doi: 10.1021/jf0528613.
[9] Chakdar H, Verma S, Pabbi S. Blue green algae for secondary agriculture. Indian J Plant Genet Resour. 2022;35(3):375–80. doi: 10.5958/0976-1926.2022.00103.6.
[10] Nakao A, Ohkawa N, Nagasaki T, Kagari T, Doi H, Shimozato T, et al. Tetrahydropyridine derivatives with inhibitory activity on the production of proinflammatory cytokines: Part 2. Bioorg Med Chem Lett. 2010;20(8):2435–7. doi: 10.1016/j.bmcl.2010.03.022.
[11] Pavale G, Acharya P, Korgavkar N, Ramana MMV. Design, synthesis, and biological evaluation of quinoxaline bearing tetrahydropyridine derivatives as anticancer, antioxidant, and anti- tubercular agents. Curr Comput Aided Drug Des. 2022;18(6):414–24.
[12] Jaen JC, Nickell DG, Reynolds DM, Smith SJ, Wise LD, Wustrow DJ. Substituted tetrahydropyridines as central nervous system agents. 1991;5(45):550.
[13] Vianna JS, Ramis IB, Bierhals D, von Groll A, Ramos DF, Zanatta N, et al. Tetrahydropyridine derivative as efflux inhibitor in Mycobacterium abscessus. J Glob Antimicrob Resist. 2019;17:296–9. doi: 10.1016/j.jgar.2018.12.020.
[14] Lozano GL, Park HB, Bravo JI, Armstrong EA, Denu JM, Stabb EV, et al. Bacterial analogs of plant tetrahydropyridine alkaloids mediate microbial interactions in a rhizosphere model system. Appl Env Microbiol. 2019;85(10):e03058–18. doi: 10.1128/AEM.03058-18.
[15] Gedeon S, Montgomery A, Gangapuram M, Redda KK, Ardley TW. The chemistry and pharmacology of tetrahydropyridines: Part 2. Clin Med Rev Rep. 2023;4(5). doi: 10.31579/2690-8794/135.
[16] Glase SA, Akunne HC, Heffner TG, Jaen JC, MacKenzie RG, Meltzer LT, et al. Aryl 1-but-3-ynyl-4-phenyl-1,2,3,6-tetrahydropyridines as potential antipsychotic agents: synthesis and structure-activity relationships. J Med Chem. 1996;39(16):3179–87. doi: 10.1021/jm950721m.
[17] Robertson AD, Hill AP, Glen RC, Martin GR. Indolyl tetrahydropyridines for treating migraine. US5399574A, Mar. 21, 1995 Accessed: Jul. 27, 2023. [Online]. https://patents.google.com/patent/US5399574A/en.
[18] Krishna PR, Reddy PS. Diversity oriented synthesis' of functionalized chiral tetrahydropyridines: Potential GABA receptor agonists and azasugars from natural amino acids via a sequential Baylis −Hillman reaction and RCM protocol. J Comb Chem. 2008;10(3):426–35. doi: 10.1021/cc700171p.
[19] Nolan TL, Lapinsky DJ, Talbot JN, Indarte M, Liu Y, Manepalli S, et al. Identification of a novel selective serotonin reuptake inhibitor by coupling monoamine transporter-based virtual screening and rational molecular hybridization. ACS Chem Neurosci. 2011;2(9):544–52. doi: 10.1021/cn200044x.
[20] Prasad SBB, Kumar YCS, Kumar CSA, Sadashiva CT, Vinaya K, Rangappa KS. Synthesis of novel 3-aryl-n-methyl-1,2,5,6-tetrahydropyridine derivatives by Suzuki coupling: as acetyl cholinesterase inhibitors. Open Med Chem J. 2007;1:4–10. doi: 10.2174/1874104500701010004.
[21] Prachayasittikul S, Pingaew R, Worachartcheewan A, Ruchirawat S, Prachayasittikul V. A new sulfoxide analog of 1,2,3,6-tetrahydrophenylpyridine and antimicrobial activity. EXCLI J. 2010;9:102–7.
[22] Watanabe R, Mizoguchi H, Oikawa H, Ohashi H, Watashi K, Oguri H. Stereo-controlled synthesis of functionalized tetrahydropyridines based on the cyanomethylation of 1,6-dihydropyridines and generation of anti-hepatitis C virus agents. Bioorg Med Chem. 2017;25(11):2851–5. doi: 10.1016/j.bmc.2017.03.011.
[23] Choi S-H, Im W-B, Choi S-H, CHO C-H, Moon H-S, Park J-S, et al. Tetrahydropyridine derivatives and their use as antibacterial agents. Apr. 05, 2018 Accessed: Oct. 13, 2022. [Online]. https://patentscope.wipo.int/search/en/detail.jsf? docId=WO2018062924.
[24] Aiello D, Jonas H, Carbone A, Carbone D, Pecoraro C, Tesoriere L, et al. Synthesis and antioxidative properties of 1,2,3,4-tetrahydropyridine derivatives with different substituents in 4-position. Mol Basel Switz. 2022;27(21):7423. doi: 10.3390/molecules27217423.
[25] Henderson ED, Gangapuram M, Eyunni SKV, Redda KK, Wilson-Ardley T. Design, synthesis and evaluation of novel N-substituted-[benzoylamino]-5-ethyl-1,2,3,6-tetrahydropyridines as potential anti-cancer agents. Madridge J Pharm Res. 2019;3(1):52–9. doi: 10.18689/mjpr-1000109.
[26] Ghaffari MA, Ardley TW, Gangapuram M, Redda KK. Synthesis of n-substituted carbonylamino-1,2,3,6-tetrahydropyridines as potential anti-inflammatory agents. Synth Commun. 2011;41(7):2615–23. doi: 10.1080/00397911.2010.515335.
[27] Mateeva NN, Winfield LL, Redda KK. The chemistry and pharmacology of tetrahydropyridines. 2005;12(5):551–71. doi: 10.2174/0929867310504050551.
[28] Das P, Njardarson JT. Synthesis of 1,2,3,6-Tetrahydropyridines via aminophosphate enabled anionic cascade and acid catalyzed cyclization approaches. Org Lett. 2015;17(16):4030–3. doi: 10.1021/acs.orglett.5b01937.
[29] Visseq A, Boibessot T, Nauton L, Théry V, Anizon F, Abrunhosa-Thomas I. Diastereoselective synthesis of 2,6-disubstituted-1,2,3,6-tetrahydropyridines through a palladium-catalyzed intramolecular allylic amination. Eur J Org Chem. 2019;2019(47):7686–702. doi: 10.1002/ejoc.201901520.
[30] Choi J, Wilson TL, Ly AM, Okoro CO, Onubogu UC, Redda KK. Synthesis of some n-(phenylsulfonylamino)-1,2,3,6-tetrahydropyridines as potential anti-inflammatory agents. Med Chem Res. 1995;5:281–95.
[31] Gangapuram M, Redda KK. Synthesis of 1-(substituted phenylcarbonyl/sulfonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamides as potential anti-inflammatory agents. J Heterocycl Chem. 2006;43(3):709–18. doi: 10.1002/jhet.5570430327.