Brief Articles

Potential Nicotinic Acetylcholine Receptor Ligands from 2,4-Methanoproline Derivatives

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Potential nicotinic acetylcholine receptor (nAChR) ligands have been synthesized in which a methylisoxazole substituent is attached to the 1-position (**26**) of the 2-azabicyclo[2.1.1]hexane ring system or separated by "spacer" atoms (**21** and **23**). With ABT-594 as a model, a range of pyridine heterocycles have been attached to the 1-position via a $-CH_2O-$ spacer (**11**, **14**, and **6**). The biological evaluation of target compounds showed there was no binding affinity at the $\alpha4\beta2$ and $\alpha3\beta4$ nAChR subtypes.

Introduction

We recently described the conversion of derivatives of the nonproteinogenic amino acid 2,4-methanoproline (2-azabicyclo-[2.1.1]hexane-1-carboxylic acid)[1−3] into potential nicotinic acetylcholine receptor[a] (nAChR) ligands having heterocycles attached to the 1-position of the 2-azabicyclo[2.1.1]hexane system via a methylene "spacer" (**1**).[4,5] We now describe variants in which heterocycles are directly attached to the 1-position (**2**) and examples in which the heterocycle is separated by two spacer units (**3**, **4**, and **5**, Figure 1).

Various methods available for the construction of the 2-azabicyclo[2.1.1]hexane system exist[2,6−12] and functionality has been studied at different positions around the bicyclic system.[7,13−20] We[4,5,21] used a [2 + 2] photocycloaddition[22−24] strategy, as this allows incorporation of a carboxylic ester substituent at the bridgehead (C_1) position. This opens the way for further functionalization at C_1, leading to the formation of epibatidine ((4*S*,6*R*)-6-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]-heptane) analogues[25−28] in the search for high affinity and subtype selectivity for nAChRs (Figure 2).[29−32] We are aware of no other examples of the incorporation of heterocycles into this azabicyclic system as potential nAChR ligands.

There has been much recent interest concerning 3-pyridyl ether analogues of various azabicyclic systems.[33−37] Variants synthesized at Abbott Laboratories,[34,38,39] include ABT-594 (5-([(2*R*)-azetidin-2-yl]methoxy)-2-chloropyridine), a first-generation nAChR agonist.[35] During clinical trials, this compound was shown to have analgesic properties with improved separation of antinociceptive effects and nicotinic side effects. The chloro substituent and the azetidine ring were found to be important structural elements for potent analgesic activity. ABT-594 was found to have high affinity for nAChRs, although it was 180-fold less potent than (±)-epibatidine in activating peripheral skeletal muscle-type nAChRs. In designing potential ABT-594 variants, we expected the rigid 2-azabicyclo[2.1.1]hexane system to provide a framework for maintaining the structural requirements and orientation necessary for activity at the nAChR. We hoped that this rigid, strained azabicyclic system might emulate the azetidine ring of ABT-594 and that attachment of a chloropyridyl heterocycle at the C_1 position, linked by a $-CH_2O-$ spacer (as in **6**), would reproduce the key pyr−O−CH_2−CHR−NHR moiety in ABT-594 (Figure 3). It was also anticipated that it would give extra flexibility once in the receptor, as opposed to traditional compounds that have the heterocycles directly attached to the bicycle. Certainly, according to simple molecular modeling studies, the ideal internitrogen distance for the nAChR pharmacophore may be attained.

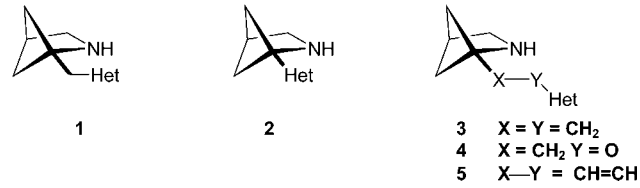

Figure 1. Target 2,4-methanoproline derivatives.

More recent work has exploited the bioisosteric replacement the chloropyridyl heterocycle of (±)-epibatidine by the methylisoxazole group to form (±)-epiboxidine ((1*R*,4*S*,6*S*)-6-(3-methyl-5-isoxazolyl)-7-azabicyclo[2.2.1]heptane).[40] Epiboxidine is a potent nAChR agonist with antinociceptive activity and binds to ganglionic $\alpha4\beta2$ subtype receptors. More importantly, (±)-epiboxidine was 20-fold less toxic than epibatidine, demonstrating that it is possible to synthesize potent compounds with lowered toxicity. There have been reports of the construction of epiboxidine analogues[41−45] of various azabicyclic systems including those from α,β-unsaturated esters.[46] There have been no recent reports of functional group interconversion at the C_1 position of the 2-azabicyclo[2.1.1] system other than our own,[4,5] and we now add to the range with examples in which the heterocycle is attached by alkenyl and ethano linkages.

Discussion

As described previously,[4,5] we have utilized the [2 + 2] photocycloaddition approach established by Pirrung[22] and Clardy[23] to synthesize the key precursor **7** (Figure 3).

In the approach to analogues based on structure **4**, the *N*-benzoyl compound **7** was converted into the *N*-Cbz alcohol

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[a] Abbreviations: nAChR, nicotinic acetylcholine receptor; Het, heterocycle; Cbz, benzyloxycarbonyl; DEAD, diethyl azodicarboxylate; TPP, triphenylphosphine; THF, tetrahydrofuran, TMSI, iodotrimethylsilane; DCM, dichloromethane; Boc, *t*-butoxycarbonyl; DMSO, dimethylsulfoxide; TEA, triethylamine; BuLi, *t*-butyllithium; HEK, human embryonic kidney; BCA, bicinchoninic acid; SPA, scintillation proximity assay; WGA, wheat germ agglutinin; PVT, polyvinyltoluene.

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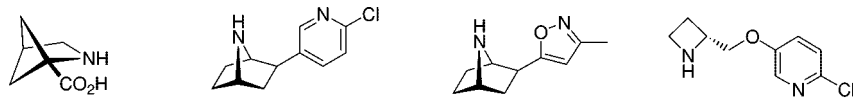


Figure 2. 2,4-Methanoproline and selected current nAChR agonists.

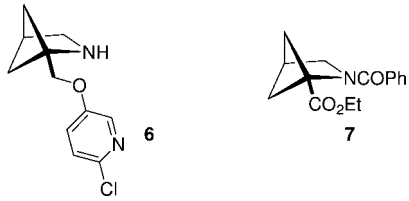


Figure 3. ABT-594 analogue **6** and key precursor compound **7**.

8 as described previously,[4,5] and this was, in turn, reacted with the appropriate phenol (**9**) under Mitsunobu conditions[47] (Scheme 1).

Unlike previous reports concerning the formation of ABT-594 analogues,[34,36,37] we found it necessary to heat the reaction mixture to reflux conditions to achieve coupling. The primary alcohol group in **8** is adjacent to the bridgehead position and it is likely that steric hindrance leads to the need for harsher conditions and also the modest yields (22−27%) obtained. We were pleasantly surprised to be able to achieve ready displacement at the 1-methylene position. Following the successful attachment of a phenoxy substituent, similar reaction conditions were used to attach hydroxy-pyridine derivative (**12**, **15**) to give **13** and **16** in similar yields. A simple deprotection step gave the respective products **11**, **14**, and **6** in good yield (81−87%); compound **6** is the desired azabicyclic analogue of ABT-594.

The literature[40−46] provides a wide array of epibatidine analogues containing the methylisoxazole heterocycle; the most potent of these is epiboxidine. Our initial aim was to synthesize 2-azabicyclo[2.1.1]hexane epiboxidine analogues having the methylisoxazole attached by a bis-methylene chain. The synthesis of these compounds would allow us to investigate the effects of an increase of the carbon chain length on binding to the nAChR. The *N*-Boc alcohol **17** was oxidized to the aldehyde **18** using Swern conditions in 97% yield (Scheme 2).

Wittig methodology[48−50] was then employed to form the α,β-unsaturated ester **19** (24% yield). The α,β-unsaturated methylisoxazole **20** was then constructed using the method of Daly and co-workers[41] in 30% yield. Deprotection of the Boc group with 3 M hydrochloric acid gave the desired product **21** in 97% yield. The ^{1}H NMR spectrum confirmed the construction of the methylisoxazole heterocycle in **20**. The singlet at δ 2.21 corresponds to the methyl group, and the singlet at δ 5.95 is the olefinic proton in the ring system. The alkene protons at δ 6.28 and 6.46 showed mutual coupling of 16 Hz, confirming the trans stereochemistry. The double bond of **20** was selectively reduced using potassium azodicarboxylate to give the saturated methylisoxazole **22** in 34% yield. Removal of the Boc group gave the product **23** in a 99% yield (Scheme 3).

Next we aimed to construct the methylisoxazole heterocycle attached directly at the C_1 position of the 2-azabicyclo[2.1.1] hexane system (type **2**). Other groups[46,51] have incorporated heterocycles directly at the bridgehead position of other azabicyclic systems in an attempt to create nAChR ligands. The methylisoxazole synthesis was attempted on the bridgehead ethyl ester **7** in the hope of making **24** (Scheme 4).

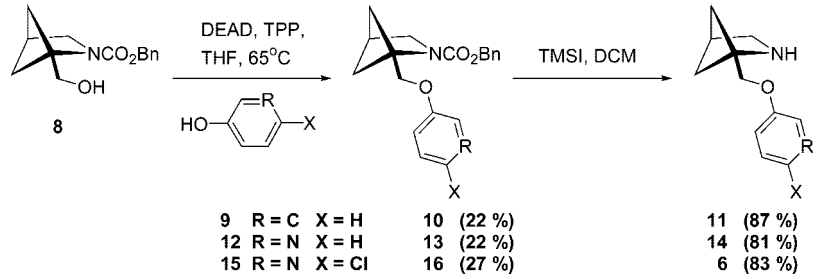
Bizarrely, we isolated the novel intermediate **25** (61% yield, based on recovered starting material) instead; such a nonaromatized intermediate has not previously been reported during methylisoxazole synthesis. The formation of **25** was confirmed by X-ray crystallography, which indicated hydrogen bonding between the carbonyl-oxygen and -hydrogen from the alcohol. This stabilization is thought to be the reason for the interesting isolation of **25**. *N*-Deprotection of **25** with 6 M hydrochloric acid led to concomitant elimination of water, achieving conversion into the target **26**. Daly and co-workers[41] have reported the isolation of a minor byproduct while constructing the methylisoxazole ring, but there are no reports of compounds akin to **25**.

Biological Evaluation. The *p*-toluenesulfonate salts of racemic ABT-594 analogues **11**, **14**, and **6** and hydrochloride salts of racemic epiboxidine analogues **21**, **23**, and **26** were evaluated for binding to the high affinity nicotine binding site in human brain (at the α4β2 and α3β4 nAChR subtypes). Unexpectedly, for all of the compounds, the K_i values could not be recorded even at a concentration of 1000 nM, showing that there was no significant binding at the nAChR subtypes. *Membrane preparation*. Cell pastes from large-scale production of HEK-293 cells expressing cloned human α4β2 or α3β4 nAChR were homogenized in 4 volumes of buffer (50 mM Tris-HCl, 150 mM NaCl, and 5 mM KCl, pH 7.4). The homogenate was centrifuged twice (40000*g*, 10 min, 4 °C) and the pellets resuspended in 4 volumes of Tris-HCl buffer after the first spin and 8 volumes after the second spin. The resuspended homogenate was centrifuged (100*g*, 10 min, 4 °C) and the supernatant kept and recentrifuged (40000*g*, 20 min, 4 °C). The pellet was resuspended in Tris-HCl buffer supplemented with 10% w/v sucrose. The membrane preparation was stored in 1 mL aliquots at −80 °C until required. The protein concentration of the membrane preparation was determined using a BCA protein assay reagent kit. *Nicotinic receptor radioligand binding scintillation proximity assay (SPA)*. SPA radioligand binding assays were performed in 96-well plates in a final volume of 250 μL Tris-HCl buffer (50 mM Tris-HCl, 150 mM NaCl, 5 mM KCl, pH 7.4) using the following conditions: [^{3}H]epibatidine (53 Ci/mmol; Amersham) α4β2 = 1 nM, α3β4 = 2 nM; WGA-coated PVT SPA beads (Amersham) α4β2 = 1 mg/well, α3β4 = 1.5 mg/ well; membrane protein = 30 μg/well for both assay types. Nonspecific binding (<10% for both assay types) was determined using 10 μM epibatidine. Reactions were allowed to equilibrate for 2−4 h at room temperature prior to reading on a Trilux Scintillation counter (Perkin-Elmer). Data were analyzed using a standard 4-parameter logistic equation (Multicalc, Perkin-Elmer) to provide IC_{50} values that were converted to K_i values using the Cheng−Prusoff equation.[52]

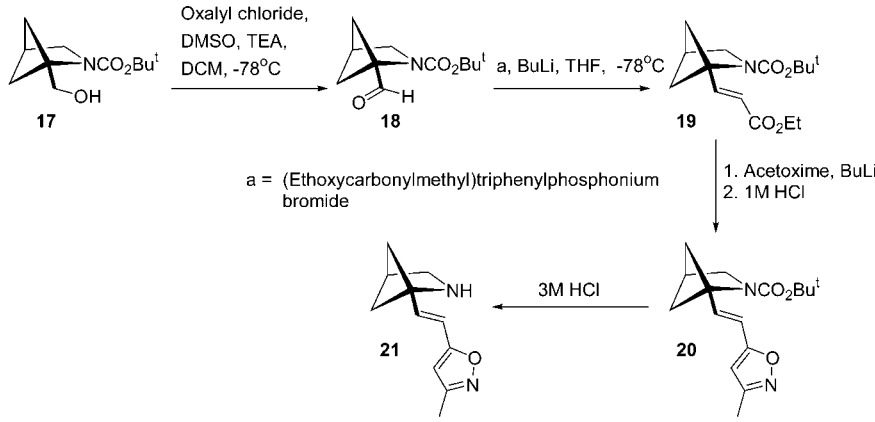
Conclusion

In conclusion, we have been successful in the synthesis of a range of nAChR ligands with either the pyridyl ether moiety or the methylisoxazole heterocycle attached to the 2-azabicyclo[2.1.1]hexane. The Mitsunobu reaction has been effectively performed in order to synthesize a range of ABT-594 analogues; **11**, **14**, and **6**. Methylisoxazole compounds have also been synthesized on the 2-azabicyclo[2.1.1]hexane framework, with

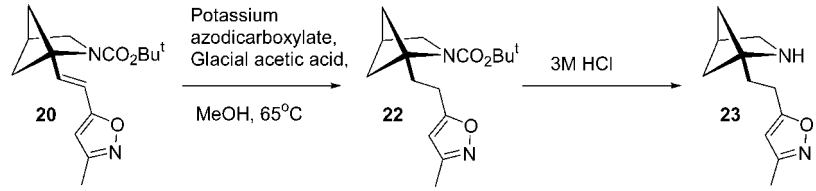
Scheme 1. Synthesis of 1-Substituted 2-Azabicyclo[2.1.1]hexane Derivatives



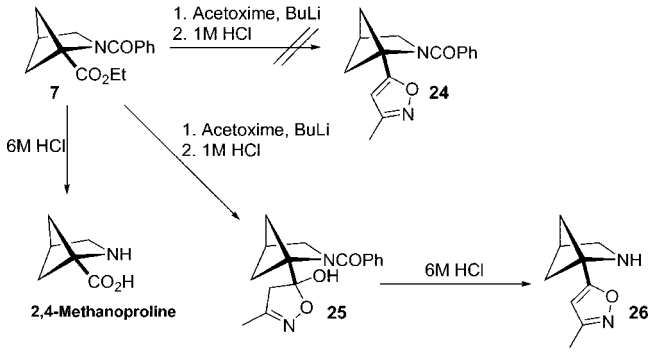
Scheme 2. Synthesis of Methylisoxazole Compound **21**



Scheme 3. Synthesis of Methylisoxazole Compound **23**



Scheme 4. Attachment of a Methylisoxazole Substituent to C_1



differing number of carbon atoms in the chain: **21** ($n = 2$ alkene), **23** ($n = 2$ alkane), and **26** ($n = 0$). It is perhaps surprising that none of these compounds show binding despite the very different conformational opportunities open to them, as shown by modeling studies. On the route to constructing **26**, we have reported a novel intermediate, apparently stabilized by H-bonding via a seven-membered ring. This work, together with our earlier studies,[4] has led to the synthesis of a wide range of heterocycle-substituted derivatives of the 2-azabicyclo[2.1.1]-hexane ring system. The incorporation of other heterocycles at the C_7 position of this bicyclic ring system (the CH_2 attached to C_1) is currently under investigation in an attempt to widen the range of potential nAChR ligands.

Experimental Section

NMR spectra were recorded at 300 MHz using a Bruker DPX 300 spectrometer and at 400 MHz using a Bruker DRX 400 spectrometer. Chemical shifts are expressed in ppm (δ) relative to an internal standard tetramethylsilane (TMS). Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), bs (broad singlet), AB (AB-system). Signals in ^{13}C NMR were determined by DEPT experiments. Signals were assigned with assistance of $^{1}H-^{1}H$ COSY and $^{1}H-^{13}C$ COSY spectra. Routine mass spectra were measured on a Micromass Quattro LC triple quadropole spectrometer and were obtained using ionization by electrospray. Accurate mass measurements were measured on a Kratos Concept 1H sector mass spectrometer and were obtained using ionization by fast atom bombardment. Mass spectra were determined in units of mass relative to charge (m/z). IR spectra were recorded on a Perkin-Elmer 298 FT spectrometer. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad). Flash chromatography was carried out using silica gel (60) manufactured by Fisher. Thin layer chromatography was conducted on standard commercial aluminum sheets precoated with 0.2 mm layer of silica gel (Merck Kieselgel 60-254). All the target compounds were unsuitable for elemental analysis as they were obtained as volatile and viscous oils or

unstable salts. Purification by HPLC or other chromatographic methods caused the target compounds to decompose, so were not used.

1-Phenoxymethyl-2-azabicyclo[2.1.1]hexane (11). 10 (110 mg, 0.34 mmol) was dissolved in dry dichloromethane (3 mL) and stirred under a nitrogen atmosphere. TMSI (242 μL, 1.70 mmol) was added and stirred for 7 min, followed by hydrofluoroboric acid−diethyl ether complex (51 μL, 0.68 mmol), stirring for a further 6 min. The reaction mixture was quenched with water (200 μL) and the solvent removed under reduced pressure. Water (3 mL) was added and the solution washed with petroleum ether (bp 40−60 °C) (3 × 1 mL). The solution was neutralized with solid potassium carbonate and the product extracted with dichloromethane (6 × 5 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield **11** (56 mg, 0.29 mmol, 87% yield) as an orange oil. δ_H (300 MHz, $CDCl_3$): 1.36 (dd, J = 4.4, 1.4 Hz, 2 H, H_{5s}, H_{6s}), 1.71 (m, 2 H, H_{5a}, H_{6a}), 2.74 (m, 1 H, H_4), 3.00 (s, 2 H, H_{3x}, H_{3n}), 4.12 (s, 2 H, $C\underline{H}_2O$), 6.82−6.89 (m, 3 H, Ph), 7.17−7.23 (m, 2 H, Ph). δ_C (75.5 MHz, $CDCl_3$): 37.69 (C_4), 40.72 (C_5, C_6), 48.85 (C_3), 68.45 ($\underline{C}H_2O$), 68.77 (C_1), 114.55, 120.86, 129.44 (5 × aryl), 158.87 (aryl C−O). ν_{max} (CH_2Cl_2): 2880w (C−H), 1590w (Ph), 1490w (Ph), 1050w cm^{-1}. *m/z*: 190 (MH^+). $C_{12}H_{16}NO$ [MH^+] requires *m/z* 190.12311; observed 190.12319.

1-(Pyridin-3-yloxymethyl)-2-azabicyclo[2.1.1]hexane (14). 13 (101 mg, 0.31 mmol) was dissolved in dry dichloromethane (6 mL) and stirred under a nitrogen atmosphere. TMSI (222 μL, 1.56 mmol) was added and stirred for 7 min, followed by hydrofluoroboric acid−diethyl ether complex (46 μL, 0.62 mmol), stirring for a further 6 min. The reaction mixture was quenched with water (200 μL) and the solvent removed under reduced pressure. Water (5 mL) was added and the solution washed with petroleum ether (bp 40−60 °C) (3 × 3 mL). The solution was neutralized with solid potassium carbonate and the product extracted with dichloromethane (5 × 10 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield **14** (48 mg, 0.25 mmol, 81% yield) as a yellow oil. δ_H (300 MHz, $CDCl_3$): 1.37 (dd, J = 4.4, 2.0 Hz, 2 H, H_{5s}, H_{6s}), 1.72 (m, 2 H, H_{5a}, H_{6a}), 2.77 (m, 1 H, H_4), 3.01 (s, 2 H, H_{3x}, H_{3n}), 4.16 (s, 2 H, $C\underline{H}_2O$), 7.14 (m, 2 H, heterocycle), 8.14 (m, 1 H, heterocycle), 8.24 (m, 1 H, heterocycle). δ_C (75.5 MHz, $CDCl_3$): 37.77 (C_4), 40.65 (C_5, C_6), 48.73 (C_3), 68.32 ($\underline{C}H_2O$), 68.89 (C_1), 120.90, 123.71, 138.07, 142.14 (4 × heterocycle), 154.95 (heterocycle C−O). ν_{max} (CH_2Cl_2): 3000s (C−H), 2950s (C−H), 1420s, 1160s, 900s, 690br cm^{-1}. *m/z*: 191 (MH^+). $C_{11}H_{15}N_2O$ [MH^+] requires *m/z* 191.11844; observed 191.11840.

1-(6-Chloro-pyridin-3-yloxymethyl)-2-azabicyclo[2.1.1]hexane (6). 16 (57 mg, 0.16 mmol) was dissolved in dry dichloromethane (4 mL) and stirred under a nitrogen atmosphere. TMSI (113 μL, 0.79 mmol) was added and stirred for 7 min, followed by hydrofluoroboric acid−diethyl ether complex (24 μL, 0.31 mmol), stirring for a further 6 min. The reaction mixture was quenched with water (100 μL) and the solvent removed under reduced pressure. Water (10 mL) was added and the solution washed with petroleum ether (bp 40−60 °C) (5 × 5 mL). The solution was neutralized with solid potassium carbonate and the product extracted with dichloromethane (5 × 10 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield **6** (30 mg, 0.13 mmol, 83% yield) as a bright-yellow oil. δ_H (300 MHz, $CDCl_3$): 1.41 (dd, J = 4.5, 1.6 Hz, 2 H, H_{5s}, H_{6s}), 1.74 (m, 2 H, H_{5a}, H_{6a}), 2.79 (m, 1 H, H_4), 3.05 (s, 2 H, H_{3x}, H_{3n}), 4.18 (s, 2 H, $C\underline{H}_2O$), 7.15 (m, 2 H, heterocycle), 8.00 (m, 1 H, heterocycle). δ_C (75.5 MHz, $CDCl_3$): 37.68 (C_4), 40.59 (C_5, C_6), 48.76 (C_3), 68.48 ($\underline{C}H_2O$), 69.10 (C_1), 124.39, 124.92, 136.77 (3 × heterocycle), 142.76 (heterocycle C−Cl), 154.19 (heterocycle C−O). ν_{max} (CH_2Cl_2): 3020s (C−H), 2990s (C−H), 2300m, 1420s, 1260s, 900s, 750br (C−Cl) cm^{-1}. *m/z*: 225 (MH^+). $C_{11}H_{14}N_2OCl$ [MH^+] requires *m/z* 225.07944; observed 225.07947.

1-[2-(3-Methyl-isoxazol-5-yl)-vinyl]-2-azabicyclo[2.1.1]hexane (21). 20 (5 mg, 0.02 mmol) was stirred in a solution of 3 M HCl (2 mL) made in situ (dry ethanol (0.43 mL), dry ethyl acetate (1.2 mL), and acetyl chloride (0.36 mL)) at 0 °C for 1 h. The reaction mixture was washed with diethyl ether (3 × 0.5 mL) and then evaporated to dryness to give the hydrochloride salt of **21** (4 mg, 0.02 mmol, 97% yield). δ_H (300 MHz, D_2O): 1.95−2.16 (m, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 2.04 (s, 3 H, CH_3), 2.32 (m, 1 H, H_4), 2.90 (m, 2 H, H_{3x}, H_{3n}), 6.08 (s, 1 H, =CH), 6.28 (d, J = 16.0 Hz, 1 H, $H\underline{C}$=CH-CO_2Et), 6.46 (d, J = 16.0 Hz, 1 H, HC=C$\underline{H}$-CO_2Et). δ_C (75.5 MHz, D_2O): 10.35 (CH_3), 25.69 (C_4), 37.76 ($\underline{C}_5$, C_6), 44.24 (C_3), 102.95 (=$\underline{C}$H), 113.04 (C_8), 141.20 (C_7). *m/z*: 191 (MH^+). $C_{11}H_{19}N_2O$ [MH^+] requires *m/z* 191.17851; observed 191.17847.

1-[2-(3-Methyl-isoxazol-5-yl)-ethyl]-2-azabicyclo[2.1.1]hexane (23). 22 (10 mg, 0.02 mmol) was stirred in a solution of 3 M HCl (2 mL) made in situ (dry ethanol (0.43 mL), dry ethyl acetate (1.2 mL), and acetyl chloride (0.36 mL)) at 0 °C for 1 h. The reaction mixture was washed with diethyl ether (3 × 0.5 mL) and then evaporated to dryness to give the hydrochloride salt of **23** (8 mg, 0.02 mmol, 99% yield). δ_H (300 MHz, D_2O): 1.49 (dd, J = 6.1, 2.2 Hz, 2 H, H_{5s}, H_{6s}), 1.85 (m, 2 H, H_{5a}, H_{6a}), 2.10 (s, 3 H, CH_3), 2.42 (t, J = 7.8 Hz, 2 H, H_7), 2.73 (m, 1 H, H_4), 2.78 (t, J = 7.8 Hz, 2 H, H_8), 3.24 (s, 2 H, H_{3x}, H_{3n}), 6.01 (s, 1 H, =CH). *m/z*: 193 (MH^+). $C_{11}H_{17}N_2O$ [MH^+] requires *m/z* 193.13409; observed 193.13407.

1-(3-Methyl-isoxazole-5-yl)-2-azabicyclo[2.1.1]hexane (26). 25 (20 mg, 0.07 mmol) was stirred in 6 M HCl (10 mL) and heated to reflux for 48 h. The reaction mixture was washed with diethyl ether (3 × 0.5 mL) and then evaporated to dryness to give the hydrochloride salt of evaporated to dryness to give the hydrochloride salt of **26** (14 mg, 0.07 mmol, 99% yield). δ_H (300 MHz, D_2O): 1.84−1.98, 2.08−2.26 (m, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 1.97 (s, 3 H, CH_3), 2.47 (m, 1 H, H_4), 2.83 (m, 2 H, H_{3x}, H_{3n}), 6.04 (s, 1 H, =CH). δ_C (75.5 MHz, D_2O): 10.39 (CH_3), 25.40 (C_4), 38.99 (C_5, C_6), 44.45 (C_3), 68.82 (C_1), 101.56 (=$\underline{C}$H), 155.81 (C_7). *m/z*: 165 (MH^+). $C_9H_{12}N_2O$ [MH^+] requires *m/z* 165.48922; observed 165.48910.

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Supporting Information Available: Experimental details, spectroscopic characterization of all new compounds, and crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

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