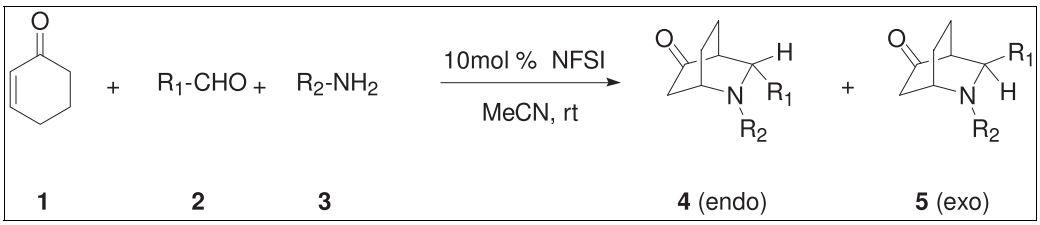
# *N*-Fluorobenzenesulfonimide as Catalyst for the Three-Component Synthesis of Isoquinuclidines



D. Wu,[a,b] Y.-H. He,[a] X. Deng,[a,b] and Z. Guan[a]*

[a]School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, People's Republic of China
[b]Department of Chemistry and Chemical Engineering, Sichuan University of Arts and Science, Sichuan, Dazhou 635000, People's Republic of China
*E-mail: guanzhi@swu.edu.cn

Received October 24, 2010
DOI 10.1002/jhet.1544
Published online 29 March 2013 in Wiley Online Library (wileyonlinelibrary.com).




*N*-Fluorobenzenesulfonimide was used for the first time as a catalyst to carry out the three-component synthesis of isoquinuclidines with the use of various cyclohexenone (**1**), benzaldehydes (**2**), and anilines (**3**). The yields up to 80% and the endo/exo stereoselectivity ratios up to 19:81 were achieved.

*J. Heterocyclic Chem.*, **50**, 425 (2013).

## INTRODUCTION

The aza[4 + 2] reaction is one of the most powerful synthetic methods in organic chemistry for the construction of nitrogen heterocycles such as pyridines, quinolines, isoquinuclidine, azabicycloalkanes, and others. Among them, isoquinuclidine (azabicyclo[2.2.2]octane) has generated considerable attention as a result of their presence in numerous complex natural products and pharmaceuticals such as the alkaloids of dioscorea hispida, dioscorine [1], and the alkaloid ibogaine [2], which possesses the ability to diminish self-administration of cocaine, heroin, and alcohol. Despite their importance, the number of available methodologies for their preparation remained scarce. The methods reported mainly used metal catalysts such as indium trichloride ($InCl_3$) [3], environmentally friendly bismuth trichloride ($BiCl_3$) [4], and α-zirconium hydrogen phosphate, which allow easy recovery and reuse [5]. Some organocatalysts were also used as catalysts such as triphenylphosphonium perchlorate, which is inexpensive, easy to prepare, and only a small amount is required [6]. The chiral organocatalysts such as 1,1′-Bi-2-naphthol (BINOL) [7] and proline derivative [8] were used to achieve high stereoselectivity of the products. Typically, these catalysts are metal-based Lewis acids or complex molecules. Therefore, alternative catalyst that is powerful, easily available, and is low cost would be highly desirable.

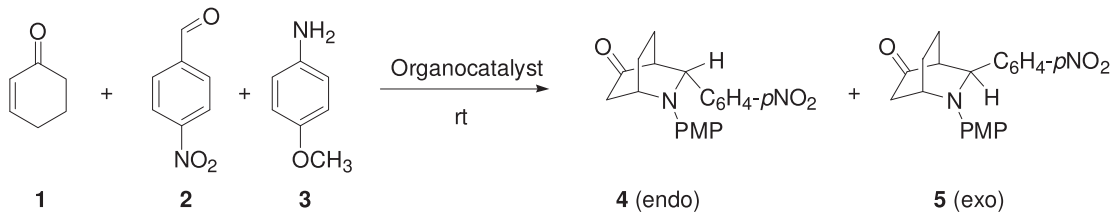
More recently, N–F electrophilic fluorinating agents such as Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2,2,2]octane bis(tetrafluoro-borate)) and *N*-fluoropyridinium triflate have been employed as a powerful Lewis acid in the one-pot allylation reactions of imines [9], the synthesis of *cis*-fused pyrano and furanotetrahydroquinolines [10], and the stereoselective synthesis of N-substituted aziridines [11]. The investigations have shown that N–F electrophilic fluorinating agents, as the alternative to metal-based Lewis acids or the highly electrophilic Brønsted acids, could help the activation of imine and the attack of subsequent nucleophile. With the attributes described previously, we attempted the possibility of the three-component synthesis of isoquinuclidines catalyzed by *N*-fluorobenzenesulfonimide (NFSI) and Selectfluor. Herein, we describe the results of the aza[4 + 2] reaction using cyclohexenone (**1**) and various benzaldehydes (**2**) and anilines (**3**) in a one-pot operation with catalytic amount of NFSI at room temperature. To the best of our knowledge, NFSI was used for the first time as a catalyst to carry out the aza[4 + 2] reaction.

## RESULTS AND DISCUSSION

In our initial experiments, three-component coupling of 4-nitrobenzaldehyde, 4-methoxyaniline, and cyclohexenone (mole ratio 1:1:1) was performed in the presence of catalysts NFSI and Selectfluor, respectively in MeCN at room temperature (Table 1, entries 1 and 3). The reaction catalyzed by NFSI gave the desired product in the yield of 69% with the endo : exo ratio of 27:73 after 8 h, whereas the reaction catalyzed by Selectfluor gave the desired product in the yield of 63% with the endo : exo ratio of 34:66 after 6 h. Next, we also investigated the reactions with the use of these two catalysts respectively under solvent-free conditions. It was found that the reactions proceeded smoothly in shorter reaction times and gave good yields (81 and 72%, respectively; Table 1, entries 2 and 4), which indicated that the catalytic activities of NFSI and Selectfluor increased under solvent-free conditions. However, the stereoselectivity of product decreased (55:45 and 52:48 endo : exo ratios,

**Table 1**

Optimization of catalysts and reaction conditions for the three-component reaction.




**1** **2** **3** **4** (endo) **5** (exo)

| Entry | Catalyst | Solvent | Time (h) | Yield[a](%) | **4/5** |
|---|---|---|---|---|---|
| 1 | NFSI (10 mol%) | MeCN | 8 | 69 | 27/73 |
| 2 | NFSI (10 mol%) | None | 6 | 81 | 55/45 |
| 3 | Selectfluor (10 mol%) | MeCN | 6 | 63 | 34/66 |
| 4 | Selectfluor (10 mol%) | None | 5 | 72 | 52/48 |
| 5 | None | MeCN | 24 | 0 | |
| 6 | NFSI (10 mol%) | THF | 8 | 69 | 47/53 |
| 7 | NFSI (10 mol%) | $CHCl_3$ | 10 | 71 | 44/56 |
| 8 | NFSI (10 mol%) | $EtO_2$ | 12 | 79 | 52/48 |
| 9 | NFSI (10 mol%) | Toluene | 12 | 84 | 52/48 |
| 10 | NFSI (5 mol%) | MeCN | 18 | 67 | 30/70 |
| 11 | NFSI (1 mol%) | MeCN | 48 | 60 | 28/72 |

[a]Isolated yields.

respectively) in comparison with that in MeCN. The experiments showed that NFSI was a better catalyst than Selectfluor for this three-component coupling reaction. In addition, to validate the effectiveness of the catalyst, a control reaction of 4-nitrobenzaldehyde, 4-methoxyaniline, and cyclohexenone in MeCN was performed in the absence of catalyst at room temperature. No product was detected even after 24 h (Table 1, entry 5). Furthermore, we optimized the reaction conditions for catalyst NFSI. It was found that solvents had an important effect on the yield and stereoselectivity. Nonpolar solvents, such as toluene and $Et_2O$, resulted in higher yields but lower stereoselectivity compared with polar solvents, such as MeCN, THF, and $CHCl_3$ (Table 1, entries 1 and 6–9). Among the tested solvents, MeCN was found to be the best in consideration of both catalytic activity and stereoselectivity. Moreover, catalyst loading also affected the yield and stereoselectivity (Table 1, entries 1, 10, and 11). Therefore, 10 mol % of NFSI in MeCN at room temperature was chosen as the optimized conditions.

The general scope of the organocatalytic three-component reaction was examined in the presence of NFSI under the optimized conditions. As shown in Table 2, both benzaldehydes and anilines with a wide range of substituent groups on the aromatic rings, including electron-withdrawing, electron-donating, and neutral groups, could be readily tolerated (Table 2, products **a–o**). Good yields (67–80%) and acceptable stereoselectivities (39:61–19:81) were obtained. It was noteworthy that the relatively unreactive 4-nitroanilines (Table 2, product **o**) also gave the desired product in 69% yield with stereoselectivity of 33:67, which indicated that NFSI was a broadly applicable and mild catalyst for the reaction. We also investigated the influence of steric hindrance of the substituents on the reaction (Table 2, products **f–h**). No significant difference was observed between substituents on 2-, 3-, and 4-position of aromatic ring of aldehyde such as 2-chloro-, 3-chloro-, and 4-chlorobenzaldehyde.

## CONCLUSIONS

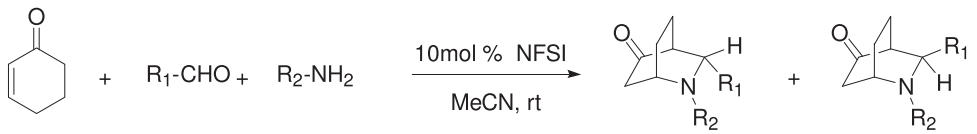
In summary, we have successfully developed a convenient, effective, and mild strategy for the synthesis of isoquinuclidine derivatives by the three-component aza[4 + 2] reaction of cyclohexenone with a number of aromatic aldehydes and amines catalyzed by NFSI (10 mol%). The reactions generated the desired products in good yields at room temperature in 8–32 h with acceptable stereoselectivity (endo/exo ratios up to 19/81). The present method employed user-friendly and commercially available NFSI as catalyst and avoided using metals and complex molecules.

## EXPERIMENTAL

**General procedure for aza[4 + 2] reaction.** Aldehyde **2** (0.5 mmol), anilines **3** (0.5 mmol), and NFSI (0.05 mmol) were separately added to a mixture of cyclohexenone **1** (0.5 mmol) and MeCN (2 mL). The mixture was stirred at room temperature for a specified reaction time. After completion (monitored by TLC), water was added into the reaction mixture and the resulting solution was extracted with $CH_2Cl_2$ ($3 \times 10$ mL). The combined organic layers were dried over $MgSO_4$, and the

**Table 2**

*N*-Fluorobenzenesulfonimide-catalyzed one-pot three-component synthesis of isoquinuclidines.[a]




**1** **2** **3** **4** (endo) **5** (exo)

| Product **4**,**5** | $R_1$ | $R_2$ | Time (h) | Yield[b](%) | **4/5** |
|---|---|---|---|---|---|
| **a** | 4-$NO_2C_6H_4^-$ | 4-$MeOC_6H_4^-$ | 8 | 69 | 27/73 |
| **b** | $C_6H_5^-$ | 4-$MeOC_6H_4^-$ | 12 | 71 | 28/72 |
| **c** | 4-$MeC_6H_4^-$ | 4-$MeOC_6H_4^-$ | 8 | 68 | 35/65 |
| **d** | 4-$MeOC_6H_4^-$ | 4-$MeOC_6H_4^-$ | 8 | 68 | 24/76 |
| **e** | 4-$FC_6H_4^-$ | 4-$MeOC_6H_4^-$ | 8 | 67 | 20/80 |
| **f** | 2-$ClC_6H_4^-$ | 4-$MeOC_6H_4^-$ | 12 | 72 | 37/63 |
| **g** | 3-$ClC_6H_4^-$ | 4-$MeOC_6H_4^-$ | 12 | 80 | 39/61 |
| **h** | 4-$ClC_6H_4^-$ | 4-$MeOC_6H_4^-$ | 8 | 67 | 21/79 |
| **i** | 4-$BrC_6H_4^-$ | 4-$MeOC_6H_4^-$ | 8 | 69 | 19/81 |
| **j** | 4-$CNC_6H_4^-$ | 4-$MeOC_6H_4^-$ | 8 | 72 | 32/68 |
| **k** | $C_6H_5^-$ | $C_6H_5^-$ | 8 | 72 | 38/62 |
| **l** | $C_6H_5^-$ | 4-$MeC_6H_4^-$ | 8 | 77 | 32/68 |
| **m** | $C_6H_5^-$ | 4-$ClC_6H_4^-$ | 10 | 80 | 31/69 |
| **n** | $C_6H_5^-$ | 4-$BrC_6H_4^-$ | 10 | 72 | 33/67 |
| **o** | $C_6H_5^-$ | 4-$NO_2C_6H_4^-$ | 32 | 69 | 33/67 |

[a]For general procedure of aza[4 + 2] reaction.
[b]Isolated yields.

solvents were removed under reduced pressure. The crude material was purified via flash column chromatography of silica gel (petroleum ether/AcOEt = 12:1 to 8:1) to give **4** and **5**. Compound **4** was further purified by recrystallization.

***3-endo-(4-Nitrophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (4a)*** *[5].* Yield 19%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.80 (m, 1H), 2.07 (m, 1H), 2.16 (m, 1H), 2.25 (m, 1H), 2.51 (d, *J* = 18.7 Hz, 1H), 2.76 (d, *J* = 18.7 Hz, 2H), 3.72 (s, 3H), 4.46 (s, 1H), 4.68 (s, 1H), 6.58 (d, *J* = 8.9 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 2H) ppm.

***3-exo-(4-Nitrophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (5a)*** *[5].* Yield 50%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.63–1.70 (m, 2H), 1.94 (m, 1H), 2.26 (m, 1H), 2.42 (d, *J* = 18.8 Hz, 1H), 2.75 (t, *J* = 18.9 Hz, 2H), 3.71 (s, 3H), 4.46 (s, 1H), 4.80 (s, 1H), 6.51 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 8.25 (d, *J* = 8.5 Hz, 2H) ppm.

***3-exo-Phenyl-2-(4-methoxyphenyl)-2-aza-bicyclo[2.2.2] octan-5-one (5b)*** *[5].* Yield 51%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.65 (m, 1H), 1.73 (m, 1H), 1.89 (m, 1H), 2.26 (m, 1H), 2.38 (d, *J* = 18.8 Hz, 1H), 2.66 (d, *J* = 2.7 Hz, 1H), 2.76 (d, *J* = 18.8 Hz, 1H), 3.70 (s, 3H), 4.44 (s, 1H), 4.70 (s, 1H), 6.51 (d, *J* = 9.1 Hz, 2H), 6.74 (d, *J* = 9.1 Hz, 2H), 7.29–7.44 (m, 5H) ppm.

***3-endo-(4-Methylphenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (4c)*** *[5].* Yield 24%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.72 (m, 1H), 2.01 (m, 1H), 2.12 (m, 1H), 2.30 (s, 3H), 2.37 (m, 1H), 2.44 (d, *J* = 20.3 Hz, 1H), 2.76 (d, *J* = 21.4 Hz, 2H), 3.72 (s, 3H), 4.42 (s, 1H), 4.54 (s, 1H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H) ppm.

***3-exo-(4-Methylphenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (5c)*** *[5].* Yield 44%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.65 (m, 1H), 1.75 (m, 1H), 1.88 (m, 1H), 2.01 (m, 1H), 2.23 (s, 3H), 2.41 (s, 1H), 2.63 (s, 1H), 2.75 (d, *J* = 18.8 Hz, 1H), 3.70 (s, 3H), 4.43 (s, 1H), 4.67 (s, 1H), 6.56 (d, *J* = 9.1 Hz, 2H), 6.75 (m, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H) ppm.

***3-endo-(4-Methoxyphenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo[2.2.2]octan-5-one (4d)*** *[5].* Yield 16%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.72 (m, 1H), 2.05 (m, 1H), 2.11 (m, 1H), 2.25 (m, 1H), 2.45 (d, *J* = 18.7 Hz, 1H), 2.74 (d, *J* = 22.0 Hz, 2H), 3.72 (s, 3H), 3.77 (s, 3H), 4.42 (s, 1H), 4.53 (s, 1H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H) ppm.

***3-exo-(4-Methoxyphenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (5d)*** *[5].* Yield 52%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.72 (m, 1H), 1.75 (m, 1H), 1.88 (m, 1H), 2.25 (m, 1H), 2.37 (d, *J* = 18.7 Hz, 1H), 2.61 (d, *J* = 2.4 Hz, 1H), 2.74 (d, *J* = 18.8 Hz, 1H), 3.70 (s, 3H), 3.78 (s, 3H), 4.42 (s, 1H), 4.66 (s, 1H), 6.56 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H) ppm.

***3-exo-(4-Fluorophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (5e)*** *[5].* Yield 54%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.71 (m, 2H), 1.89 (m, 1H), 2.24 (m, 1H), 2.37 (d, *J* = 18.8 Hz, 1H), 2.62 (d, *J* = 2.0 Hz, 1H), 2.75 (d, *J* = 18.8 Hz, 1H), 3.71 (s, 3H), 4.43 (s, 1H), 4.68 (s, 1H), 6.54 (d, *J* = 9.0 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 2H), 7.07 (t, *J* = 8.3 Hz, 2H), 8.25 (m, 2H) ppm.

***3-endo-(2-Chlorophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (4f)*** *[5].* Yield 27%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.79 (m, 1H), 2.01 (m, 1H), 2.22 (m, 2H), 2.51

(d, $J$ = 18.7 Hz, 1H), 2.84 (d, $J$ = 18.0 Hz, 2H), 3.71 (s, 3H), 4.47 (s, 1H), 4.95 (s, 1H), 6.57 (d, $J$ = 9.0 Hz, 2H), 6.76 (d, $J$ = 8.9 Hz, 2H), 7.17 (m, 2H), 7.38 (d, $J$ = 6.4 Hz, 2H) ppm.

***3-exo-(2-Chlorophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (5f)*** *[5].* Yield 45%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.70–1.76 (m, 2H), 1.91 (m, 1H), 2.33 (m, 1H), 2.39 (dd, $J$ = 1.23, 18.8 Hz, 1H), 2.78 (d, $J$ = 18.8 Hz, 1H), 2.90 (d, $J$ = 2.5 Hz, 1H), 3.70 (s, 3H), 4.47 (s, 1H), 5.06 (s, 1H), 6.52 (d, $J$ = 9.1 Hz, 2H), 6.75 (d, $J$ = 9.1 Hz, 2H), 7.26 (m, 2H), 7.43 (t, $J$ = 3.7 Hz, 1H), 7.67 (t, $J$ = 4.9 Hz, 1H) ppm.

***3-endo-(3-Chlorophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (4g)*** *[5].* Yield 31%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.75 (m, 1H), 2.03 (m, 1H), 2.12 (m, 1H), 2.25 (m, 1H), 2.48 (d, $J$ = 18.8 Hz, 1H), 2.76 (d, $J$ = 18.8 Hz, 2H), 3.73 (s, 3H), 4.43 (s, 1H), 4.54 (s, 1H), 6.60 (d, $J$ = 8.9 Hz, 2H), 6.78 (d, $J$ = 8.9 Hz, 2H), 7.17–7.29 (m, 4H) ppm.

***3-exo-(3-Chlorophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (5g)*** *[5].* Yield 49%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.66–1.71 (m, 2H), 1.89 (m, 1H), 2.25 (m, 1H), 2.37 (d, $J$ = 18.8 Hz, 1H), 2.64 (d, $J$ = 2.5 Hz, 1H), 2.75 (d, $J$ = 18.8 Hz, 1H), 3.71 (s, 3H), 4.42 (s, 1H), 4.66 (s, 1H), 6.54 (d, $J$ = 9.0 Hz, 2H), 6.75 (d, $J$ = 9.0 Hz, 2H), 7.29 (m, 3H), 7.43 (s, 1H) ppm.

***3-endo-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (4h)*** *[5].* Yield 14%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.75 (m, 1H), 2.06 (m, 1H), 2.13 (m, 1H), 2.23 (m, 1H), 2.47 (d, $J$ = 18.8 Hz, 1H), 2.74 (d, $J$ = 20.1 Hz, 2H), 3.72 (s, 3H), 4.43 (s, 1H), 4.55 (s, 1H), 6.59 (d, $J$ = 8.9 Hz, 2H), 6.77 (d, $J$ = 8.9 Hz, 2H), 7.23 (d, $J$ = 8.6 Hz, 2H), 7.28 (d, $J$ = 8.9 Hz, 2H) ppm.

***3-exo-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (5h)*** *[5].* Yield 53%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.67 (m, 2H), 1.87 (m, 1H), 2.22 (m, 1H), 2.38 (d, $J$ = 18.8 Hz, 1H), 2.62 (s, 1H), 2.75 (d, $J$ = 18.8 Hz, 1H), 3.71 (s, 3H), 4.43 (s, 1H), 4.67 (s, 1H), 6.53 (d, $J$ = 8.7 Hz, 2H), 6.75 (d, $J$ = 8.7 Hz, 2H), 7.35 (s, 4H) ppm.

***3-endo-(4-Bromophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (4i)*** *[5].* Yield 13%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.74 (m, 1H), 2.07 (m, 1H), 2.12 (m, 1H), 2.25 (m, 1H), .2.47 (d, $J$ = 18.6 Hz, 1H), 2.73 (d, $J$ = 19.9 Hz, 2H), 3.72 (s, 3H), 4.42 (s, 1H), 4.53 (s, 1H), 6.59 (d, $J$ = 8.9 Hz, 2H), 6.77 (d, $J$ = 8.8 Hz, 2H), 7.18 (d, $J$ = 8.1 Hz, 2H), 7.43 (d, $J$ = 8.1 Hz, 2H) ppm.

***3-exo-(4-Bromophenyl)-2-(4-methoxyphenyl)-2-aza-bicyclo [2.2.2]octan-5-one (5i)*** *[5].* Yield 56%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.68 (m, 2H), 1.89 (m, 1H), 2.22 (m, 1H), 2.38 (d, $J$ = 18.7 Hz, 1H), 2.62 (s, 1H), 2.75 (d, $J$ = 18.8 Hz, 1H), 3.71 (s, 3H), 4.42 (s, 1H), 4.66 (s, 1H), 6.53 (d, $J$ = 8.7 Hz, 2H), 6.75 (d, $J$ = 8.7 Hz, 2H), 7.30 (d, $J$ = 8.0 Hz, 2H), 7.51 (d, $J$ = 8.0 Hz, 2H) ppm.

***4-endo-[2-(4-Methoxy-phenyl)-5-oxo-2-aza-bicyclo[2.2.2]oct-3-yl]-benzonitrile (4j)*** *[5].* Yield 23%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.78 (m, 1H), 2.06 (m, 1H), 2.14 (m, 1H), 2.24 (m, 1H), 2.50 (d, $J$ = 18.9 Hz, 1H), 2.74 (d, $J$ = 19.2 Hz, 2H), 3.72 (s, 3H), 4.44 (s, 1H), 4.63 (s, 1H), 6.57 (d, $J$ = 9.0 Hz, 2H), 6.77 (d, $J$ = 9.0 Hz, 2H), 7.43 (d, $J$ = 8.0 Hz, 2H), 7.61 (d, $J$ = 8.1 Hz, 2H) ppm.

***4-exo-[2-(4-Methoxy-phenyl)-5-oxo-2-aza-bicyclo[2.2.2]oct-3-yl]-benzonitrile (5j)*** *[5].* Yield 49%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.64–1.66 (m, 2H), 1.94 (m, 1H), 2.22 (m, 1H), 2.41 (d, $J$ = 18.8 Hz, 1H), 2.66 (d, $J$ = 2.4 Hz, 1H), 2.77 (d, $J$ = 18.8 Hz, 1H), 3.71 (s, 3H), 4.45 (s, 1H), 4.75 (s, 1H), 6.50 (d, $J$ = 9.0 Hz, 2H), 6.75 (d, $J$ = 8.9 Hz, 2H), 7.56 (d, $J$ = 8.0 Hz, 2H), 7.69 (d, $J$ = 8.0 Hz, 2H) ppm.

***3-endo-Phenyl-2-phenyl-2-aza-bicyclo[2.2.2]octan-5-one (4k)*** *[4].* Yield 27%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.74 (m, 1H), 2.04–2.14 (m, 2H), 2.29 (m, 1H), 2.47 (dd, $J$ = 2.3, 18.8 Hz, 1H), 2.77 (dd, $J$ = 2.9 Hz, 22.2 Hz, 2H), 4.56 (s, 1H), 4.67 (d, $J$ = 2.2 Hz, 1H), 6.67 (d, $J$ = 8.2 Hz, 2H), 6.75 (t, $J$ = 7.2 Hz, 1H), 7.18 (t, $J$ = 8.4 Hz, 1H), 7.24–7.35 (m, 4H) ppm.

***3-exo-Phenyl-2-phenyl-2-aza-bicyclo[2.2.2]octan-5-one (5k)*** *[4].* Yield 45%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.71 (m, 2H), 1.89 (m, 1H), 2.05 (m, 1H), 2.44 (m, 1H), 2.70–2.73 (m, 2H), 4.56 (s, 1H), 4.78 (s, 1H), 6.59–6.74 (m, 3H), 7.15 (m, 1H), 7.27–7.43 (m, 5H) ppm.

***3-exo-Phenyl-2-(4-methylphenyl)-2-aza-bicyclo[2.2.2]octan-5-one (5l)*** *[6].* Yield 52%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.63–1.73 (m, 2H), 1.91 (m, 1H), 2.21 (s, 3H), 2.26 (m, 1H), 2.40 (d, $J$ = 18.7 Hz, 1H), 2.70 (s, 1H), 2.77 (d, $J$ = 18.8 Hz, 1H), 4.52 (s, 1H), 4.75 (s, 1H), 6.53 (d, $J$ = 7.9 Hz, 2H), 6.97 (d, $J$ = 8.0 Hz, 2H), 7.28–7.44 (m, 5H) ppm.

***3-endo-Phenyl-2-(4-chlorophenyl)-2-aza-bicyclo[2.2.2] octan-5-one (4m)*** *[6].* Yield 25%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.76 (m, 1H), 2.05–2.24 (m, 3H), 2.47 (d, $J$ = 18.8 Hz, 1H), 2.76 (d, $J$ = 19.0 Hz, 2H), 4.49 (s, 1H), 4.60 (s, 1H), 6.57 (d, $J$ = 8.8 Hz, 2H), 7.10 (d, $J$ = 8.8 Hz, 2H), 7.24–7.34 (m, 5H) ppm.

***3-exo-Phenyl-2-(4-chlorophenyl)-2-aza-bicyclo[2.2.2]octan-5-one (5m)*** *[6].* Yield 55%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.59–1.72 (m, 2H), 1.91 (m, 1H), 2.26 (m, 1H), 2.41 (d, $J$ = 18.7 Hz, 1H), 2.71 (m, 2H), 4.49 (s, 1H), 4.72 (s, 1H), 6.50 (d, $J$ = 8.9 Hz, 2H), 7.08 (d, $J$ = 9.0 Hz, 2H), 7.29–7.39 (m, 5H) ppm.

***3-endo-Phenyl-2-(4-bromophenyl)-2-aza-bicyclo[2.2.2]octan-5-one (4n)*** *[6].* Yield 24%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.74 (m, 1H), 2.05–2.24 (m, 3H), 2.46 (d, $J$ = 18.8 Hz, 1H), 2.76 (d, $J$ = 21.5 Hz, 2H), 4.49 (s, 1H), 4.60 (s, 1H), 6.52 (d, $J$ = 8.8 Hz, 2H), 7.22–7.37 (m, 7H) ppm.

***3-exo-Phenyl-2-(4-bromophenyl)-2-aza-bicyclo[2.2.2]octan-5-one (5n)*** *[6].* Yield 48%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.71 (m, 2H), 1.91 (m, 1H), 2.25 (m, 1H), 2.41 (d, $J$ = 18.6 Hz, 1H), 2.70 (s, 1H), 2.71 (d, $J$ = 18.3 Hz, 1H), 4.49 (s, 1H), 4.72 (s, 1H), 6.46 (d, $J$ = 8.7 Hz, 2H), 7.21 (d, $J$ = 8.7 Hz, 2H), 7.31–7.37 (m, 5H) ppm.

***3-endo-Phenyl-2-(4-nitrophenyl)-2-aza-bicyclo[2.2.2]octan-5-one (4o).*** Yield 23%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.82 (m, 1H), 2.06 (m, 1H), 2.12 (m, 1H), 2.14 (m, 1H), 2.50 (d, $J$ = 18.9 Hz, 1H), 2.78 (d, $J$ = 19.0 Hz, 1H), 2.90 (d, $J$ = 2.0 Hz, 1H), 4.69 (s, 1H), 4.82 (s, 1H), 6.61 (d, $J$ = 9.2 Hz, 2H), 7.20 (d, $J$ = 7.3 Hz, 2H), 7.30 (m, 3H), 8.02 (d, $J$ = 9.1 Hz, 2H) ppm.

***3-exo-Phenyl-2-(4-nitrophenyl)-2-aza-bicyclo[2.2.2]octan-5-one (5o).*** Yield 46%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.69–1.74 (m, 2H), 1.98 (m, 1H), 2.27 (m, 1H), 2.52 (d, $J$ = 18.4 Hz, 1H), 2.77 (d, $J$ = 15.8 Hz, 1H), 2.80 (d, $J$ = 2.7 Hz, 1H), 4.71 (s, 1H), 4.90 (s, 1H), 6.56 (d, $J$ = 9.2 Hz, 2H), 7.32 (m, 3H), 7.41 (t,$J$ = 6.6 Hz, 2H), 8.03 (d, $J$ = 9.2 Hz, 2H) ppm.

**Acknowledgments.** This work was funded in 2007 as a selected project in scientific and technological activities for returned scholars by the State Personnel Ministry and supported by the Natural Science Foundation Project of CQ CSTC of 2009BA5051.

## REFERENCES AND NOTES

[1] Leete, E.; Michelson, R. H. Phytochemistry 1988, 27, 3793.

[2] (a) Broadbent, J. L.; Schnieden, H. Br J Pharmacol 1958, 13, 213; (b) Page, C. B.; Pinder, A. R. J Chem Soc 1964, 4811; (c)Nagata, K.; Aistrup, G. L.; Honda, H.; Shono, T.; Narahashi, T. Pestic Biochem Physiol 1999, 64, 157.

[3] Babu, G.; Perumal, P. T. Tetrahedron 1998, 54, 1627.

[4] Astudillo, S. L.; Vallejos, G. A.; Correa, N.; Gutierrez, C. M.; de la Guarda, W.; Kouznetsov, V. V. Lett Org Chem 2008, 5, 559.

[5] Costantino, U.; Fringuelli, F.; Orrù, M.; Nocchetti, M.; Piermatti, O.; Pizzo, F. Eur J Org Chem 2009, 1214.

[6] Shanthi, G.; Perumal, P. T. Synth Commun 2005, 35, 1319.

[7] (a) Rueping, M.; Azap, C. Angew Chem Int Ed 2006, 45, 7832; (b) Liu, H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. Org Lett 2006, 8, 6023.

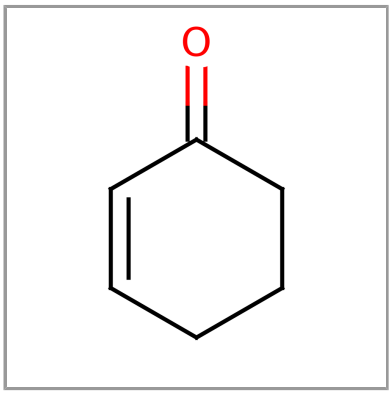
[8] (a) Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. Angew Chem Int Ed 2005, 44, 4877; (b) Yang, H.; Carter, R. G. J. Org Chem 2009, 74, 5151.

[9] Liu, J.; Wong, C.-H. Tetrahedron Lett 2002, 43, 3915.

[10] Yadav, J. S.; Reddy, B. V. S.; Sunitha, V.; Reddy, K. S. Adv Synth Catal 2003, 345, 1203.

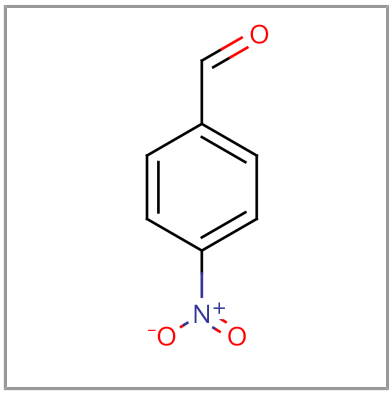
[11] Bew, S. P.; Fairhurst, S. A.; Hughes, D. L.; Legentil, L.; Liddle, J.; Pesce, P.; Nigudkar, S.; Wilson, M. A. Org Lett 2009, 11, 4552.

**1**



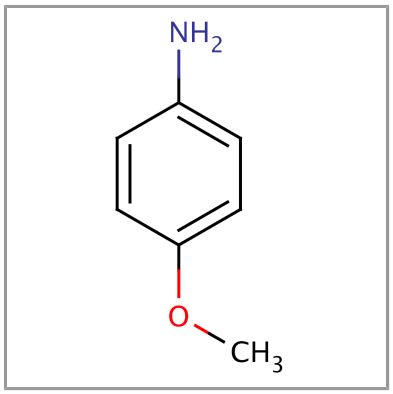
Compound Details Structure Search

**2a**



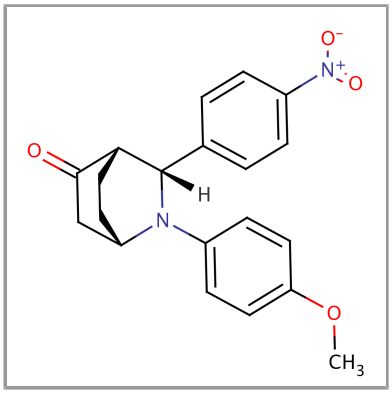
Compound Details Structure Search

**3a**



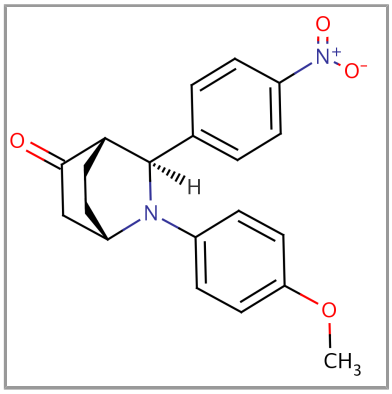
Compound Details Structure Search

**4a**



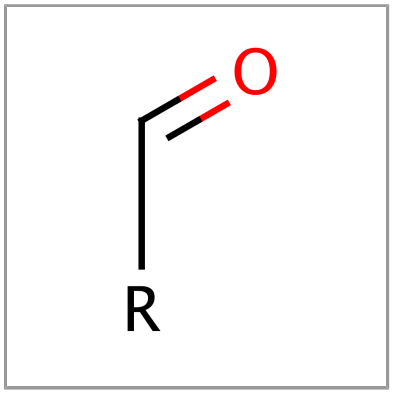
Compound Details Structure Search

**5a**



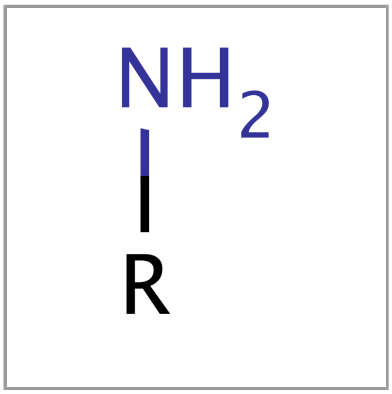
Compound Details Structure Search

**2**



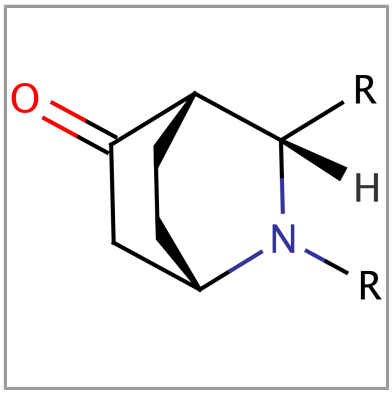
Compound Details Structure Search

**3**



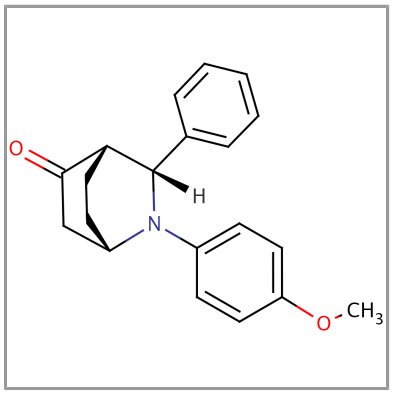
Compound Details Structure Search

**4**



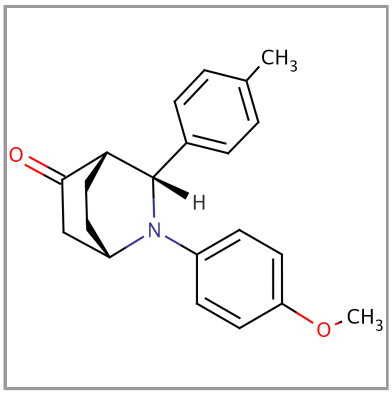
Compound Details Structure Search

**4b**



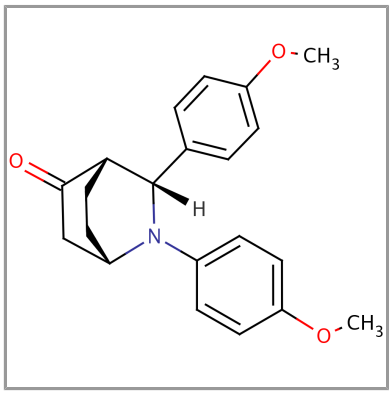
Compound Details Structure Search

**4c**



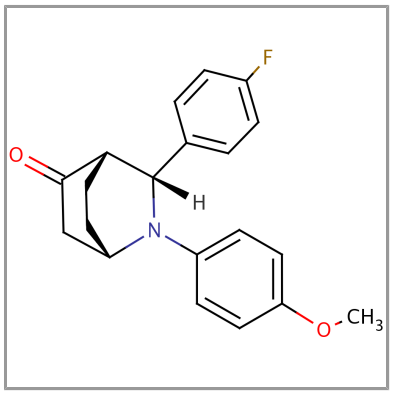

Compound Details Structure Search

**4d**



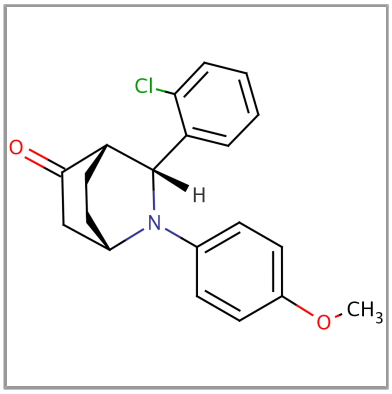

Compound Details Structure Search

**4e**



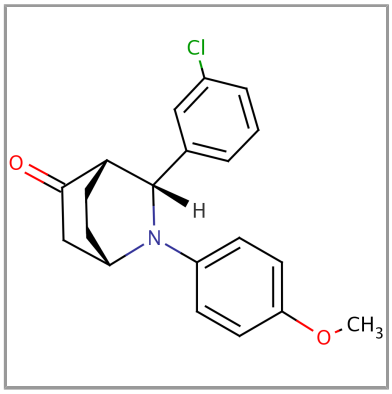

Compound Details Structure Search

**4f**



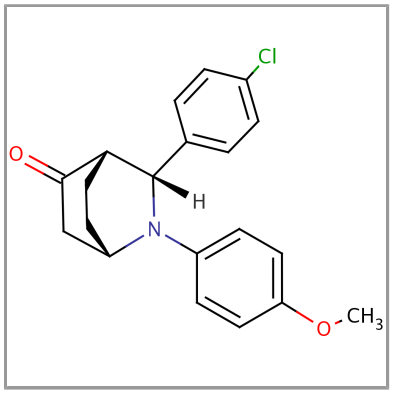

Compound Details Structure Search

**4g**



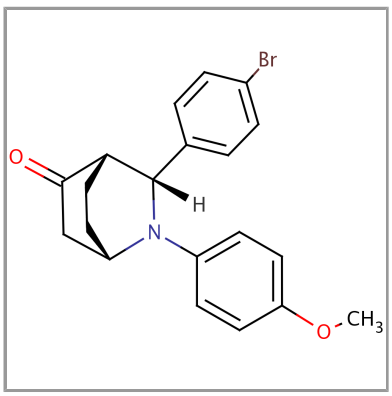

Compound Details Structure Search

**4h**



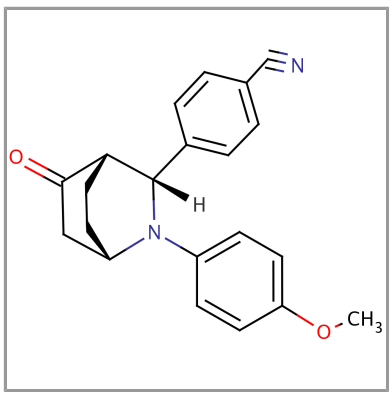

Compound Details Structure Search

**4i**



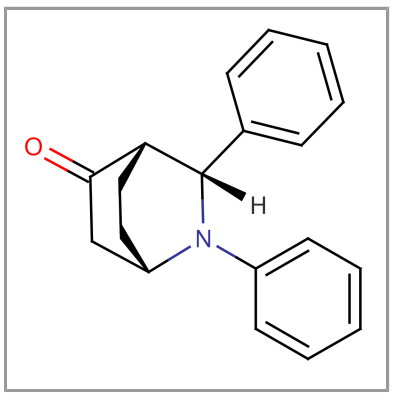

Compound Details Structure Search

**4j**



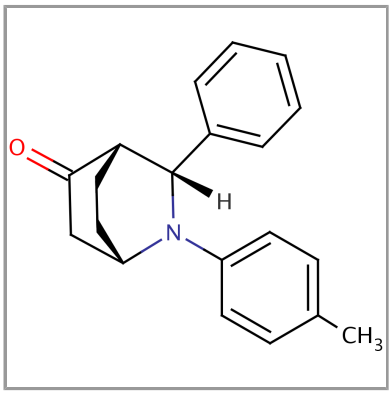

Compound Details Structure Search

**4k**



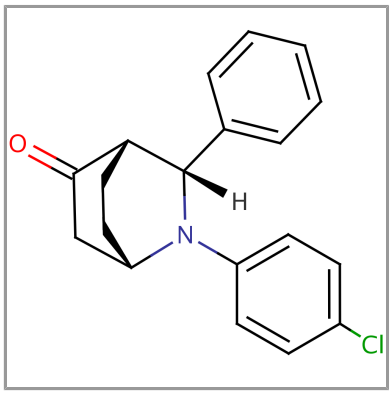

Compound Details Structure Search

**4l**



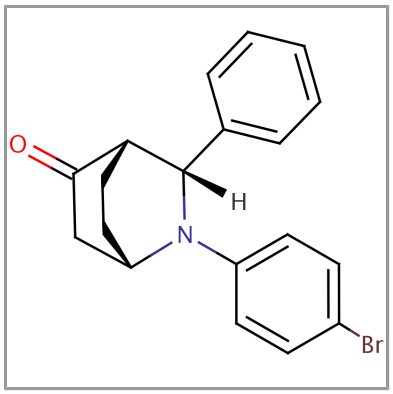

Compound Details Structure Search

**4m**



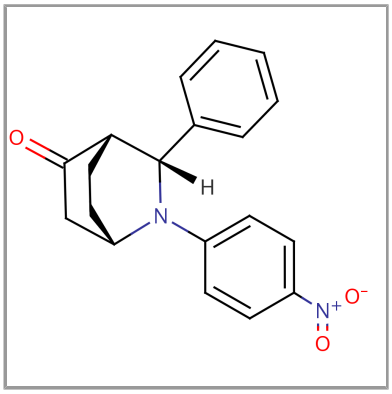

Compound Details Structure Search

**4n**



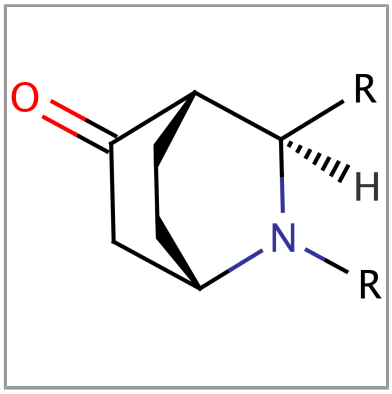

Compound Details Structure Search

**4o**



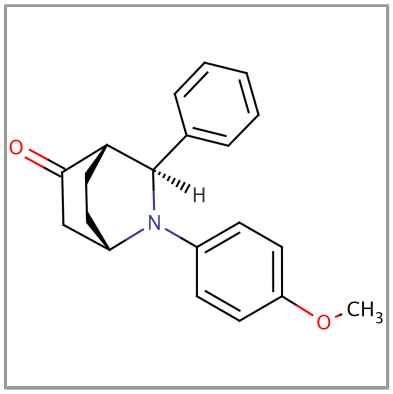

Compound Details Structure Search

**5**



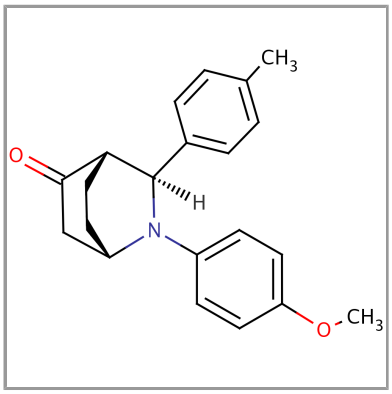

Compound Details Structure Search

**5b**



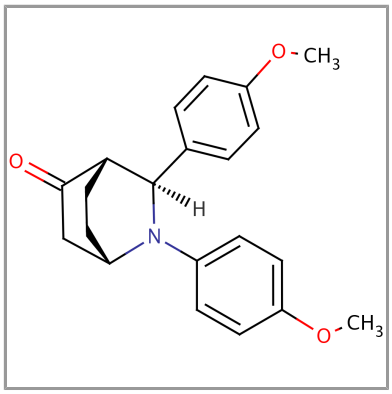

Compound Details Structure Search

**5c**



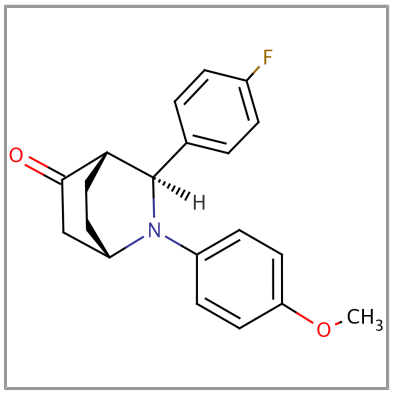

Compound Details Structure Search

**5d**



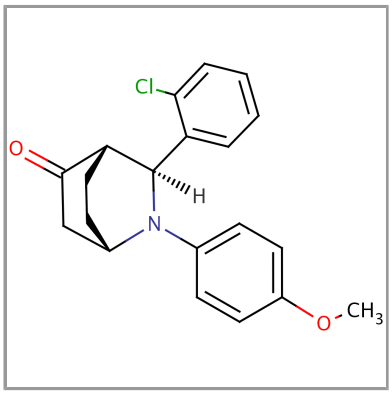

Compound Details Structure Search

**5e**



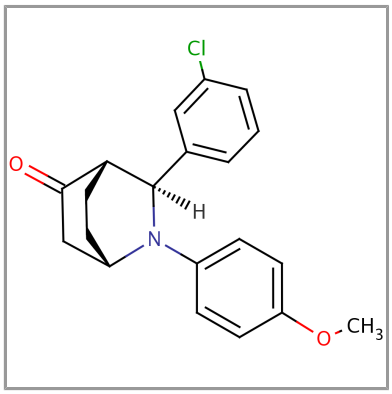

Compound Details Structure Search

**5f**



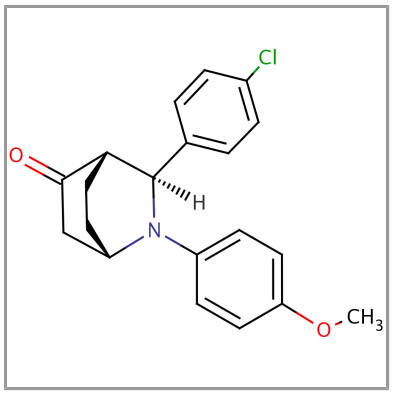

Compound Details Structure Search

**5g**



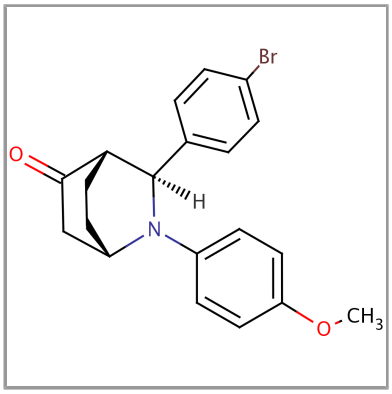

Compound Details Structure Search

**5h**



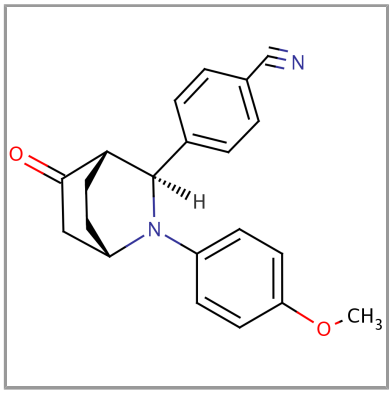

Compound Details Structure Search

**5i**



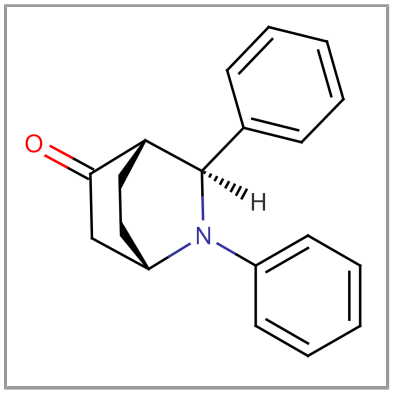

Compound Details Structure Search

**5j**



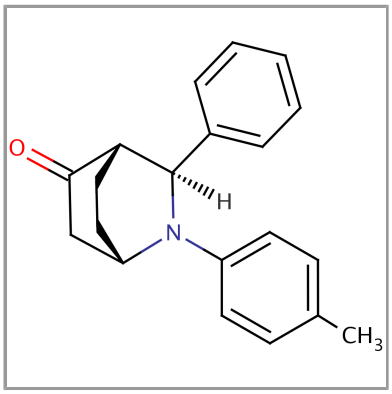

Compound Details Structure Search

**5k**



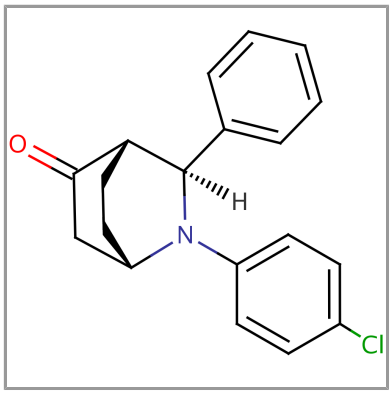

Compound Details Structure Search

**5l**



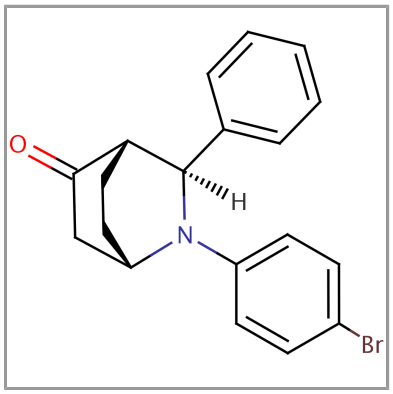

Compound Details Structure Search

**5m**



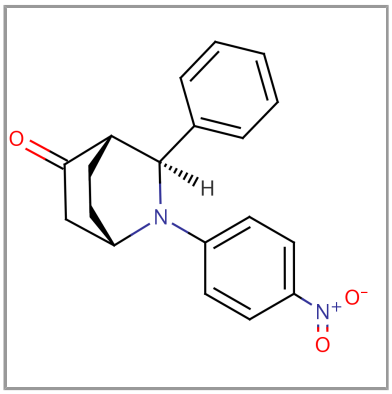

Compound Details Structure Search

**5n**




Compound Details Structure Search

**5o**




Compound Details Structure Search