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Synthesis of *N*-Propargylphenelzine and Analogues as Neuroprotective Agents

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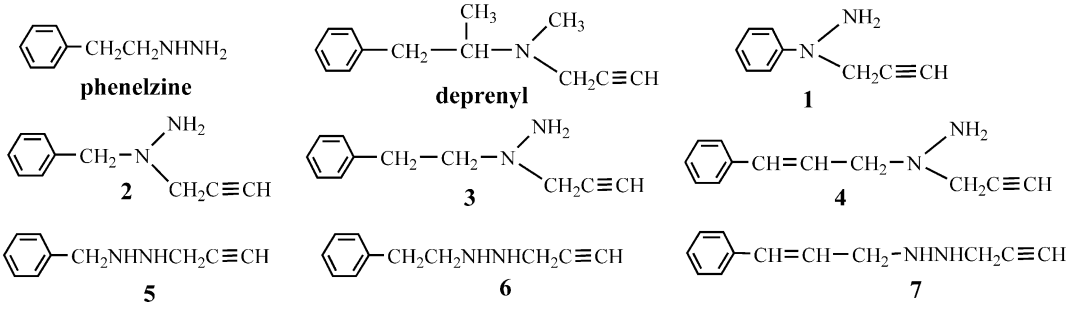
Abstract—A series of N^1- and N^2-propargylphenelzine derivatives and analogues (**1**–**7**) was synthesized. In addition to their activity as monoamine oxidase inhibitors, two of the compounds, N^1- and N^2-propargylphenelzines (**3** and **6**), were found to be potent at preventing DSP-4-induced noradrenaline (NA) depletion in mouse hippocampus, suggesting that they have neuroprotective properties.

Monoamine oxidase (MAO, EC 1.4.3.4) is an enzyme that oxidizes many monoamines, including important neurotransmitter amines, such as noradrenaline (NA), dopamine, and 5-hydroxytryptamine (5-HT).[1] Numerous MAO inhibitors have been synthesized and evaluated, and some of them have proven to be useful for treatment of psychiatric disorders such as depression, panic disorder, and social phobia.[2,3] Phenelzine, a non-selective MAO inhibitor that inhibits both the A and B isozymes of MAO, has been used clinically for such purposes for many years.[4] *R*-(−)-Deprenyl (*N*-methyl-*N*-propargylamphetamine), a selective MAO-B inhibitor, has proven to be effective in alleviating symptoms of Parkinson's disease[5] and has also been shown to be capable of protecting animals from DSP-4 [*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine]-induced neuronal degeneration.[5] Pargyline, another MAO inhibitor that also contains an *N*-propargyl group, is also capable of protecting against DSP-4-induced neurotoxicity.[6] Because both deprenyl and pargyline inhibit MAO and apparently have neuroprotective activity, many other potential MAO inhibitors with the propargyl group have been synthesized and evaluated as neuroprotective agents.[5b,7] In order to study structure–activity relationships and to discover new potent neuroprotective agents, we have recently synthesized a series of N^1- and N^2-propargylphenelzine derivatives and analogues of these compounds that contain different spacer groups between the aromatic ring and the hydrazine moiety. The compounds synthesized are shown in Scheme 1. The effects of these propargylated phenelzine derivatives and their analogues on protection from DSP-4-induced



Scheme 1.

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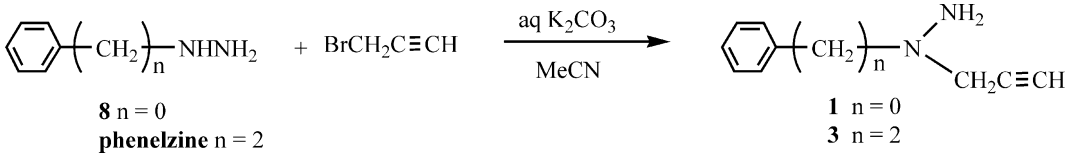
depletion of NA in mouse hippocampus were investigated in preliminary studies. The chemical syntheses and preliminary experimental results are reported here.

The syntheses of compounds **1** and **3** are shown in Scheme 2. The corresponding starting materials, phenylhydrazine (**8**) and phenelzine, were subjected to direct propargylation with propargyl bromide in a biphasic system of acetonitrile and a saturated aqueous potassium carbonate solution. The reaction was carried out overnight at room temperature. Because of the electron-donating property of the alkyl group, the N^1 atom of each starting material was selectively propargylated to give products N^1-propargylphenylhydrazine (**1**) and N^1-propargylphenelzine (**3**). These products (**1** and **3**) were isolated from the organic layer by silica gel chromatography in yields of 44 and 84%, respectively.[8]

Due to the lack of availability of the direct starting materials, N^1-propargyl-N^1-benzylhydrazine (**2**) and N^1-propargyl-N^1-*trans*-cinnamylhydrazine (**4**) were synthesized from hydrazine. The synthesis is shown in Scheme 3. Both of the N-atoms of hydrazine were protected by reacting with di-*tert*-butyl-dicarbonate [$(BOC)_2O$] in methanol at room temperature to produce compound **9** (96% yield). Benzyl or *trans*-cinnamyl groups were introduced onto the protected hydrazine in the presence of sodium hydride in anhydrous THF to give compounds **10** and **11** in yields of 99 and 76%, respectively. Removal of the protective group of **10** and **11** by anhydrous HCl (in dioxane) produced the intermediates **12** and **13** as their HCl salts (96 and 61% yields, respectively). The precipitates of **12** and **13** were isolated by filtration and subjected to propargylation under the same conditions as in Scheme 2 to give products **2** and **4** (40 and 28% yields, respectively). The final products **1**–**4** were converted to their HCl salts by treatment with anhydrous hydrogen chloride (1 N, in ether). The precipitates formed were collected and washed with ether to produce the final products.[8]

The syntheses of the N^2-propargyl compounds (**5**–**7**) are shown in Scheme 4. Starting material **14** was prepared from phenelzine by reacting with di-*tert*-butyl-dicarbonate. Introduction of the propargyl group to **10**, **11**, and **14** was carried out in the presence of sodium hydride. All reactions proceeded smoothly to give the products **15**, **16**, and **17** in high yields. Removal of the protective group with HCl (4 N in dioxane) gave the final products N^1-benzyl-N^2-propargylhydrazine (**5**), N^2-propargylphenelzine (**6**), and N^1-*trans*-cinnamyl-N^2-propargylhydrazine (**7**) as their HCl salts.[9]

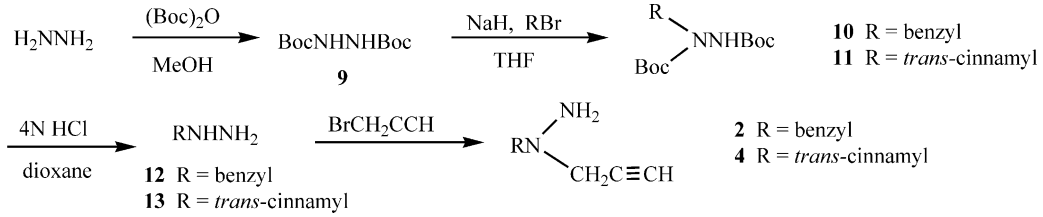
Compounds **1**–**7** were examined for their effect on DSP-4-induced depletion of NA in mouse hippocampus ex vivo and for their ability to inhibit MAO activity in rat whole brain in vitro according to reported literature methods.[7b,10] The effect of the propargylated phenelzine derivatives and their analogues (10 mg/kg, ip) on DSP-4-induced NA depletion is expressed as percentage of NA restoration by comparing mice that received drug prior to DSP-4 administration with mice that received only vehicle prior to the DSP-4. Higher percentages of restoration indicate higher levels of neuroprotection. The results are shown in Table 1 and are compared with those obtained with the same doses of phenelzine and deprenyl. All of the synthesized compounds were relatively potent inhibitors of MAO-A and -B. More importantly, both N^1- and N^2-propargylphenelzine



8 n = 0
phenelzine n = 2

1 n = 0
3 n = 2

Scheme 2.

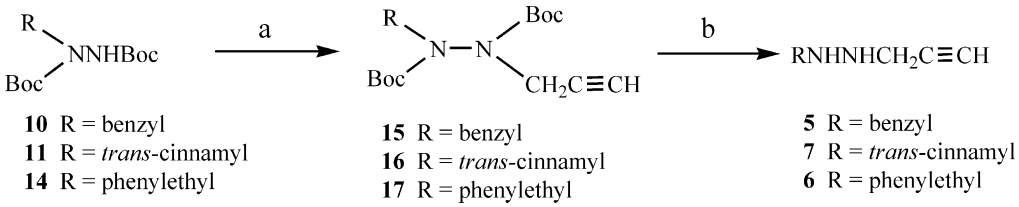


10 R = benzyl
11 R = *trans*-cinnamyl

12 R = benzyl
13 R = *trans*-cinnamyl

2 R = benzyl
4 R = *trans*-cinnamyl

Scheme 3.



10 R = benzyl
11 R = *trans*-cinnamyl
14 R = phenylethyl

15 R = benzyl
16 R = *trans*-cinnamyl
17 R = phenylethyl

5 R = benzyl
7 R = *trans*-cinnamyl
6 R = phenylethyl

Scheme 4. (a) NaH, propargyl bromide; (b) 4 N HCl in dioxane.

Table 1. Effect of the synthesized compounds on prevention of DSP-4-induced NA depletion ex vivo and on MAO activity in vitro

Compd	DSP-4 (% NA restoration)[a]	IC_{50} for inhibition of MAO-A (M)[a]	IC_{50} for inhibition of MAO-B (M)[a]
Phenelzine	43.48±9.13	3.31×10^{-8}[b]	7.63×10^{-8}[b]
(−)-Deprenyl	79.71±7.89	5.16×10^{-7}[b]	2.76×10^{-9}[b]
1	−49.82±5.39	1.13×10^{-5}	1.01×10^{-6}
2	33.58±6.57	1.56×10^{-6}	1.21×10^{-7}
3	56.38±8.80	2.04×10^{-6}	7.65×10^{-8}
4	−39.20±7.68	1.17×10^{-6}	3.53×10^{-6}
5	31.74±7.31	3.62×10^{-7}	2.84×10^{-6}
6	76.83±8.49	1.85×10^{-6}	3.18×10^{-6}
7	−7.21±5.17	7.90×10^{-6}	1.02×10^{-5}

[a]Data represent means±SEM ($n=5$) unless otherwise indicated.
[b]Data represent means±SEM of seven experiments.

(**3** and **6**), compounds with two-carbon chain spacer between aromatic ring and hydrazine moiety, showed considerable activity at preventing DSP-4-induced NA depletion. Compound **3** was similar in neuroprotective potency to phenelzine, while compound **6** provided substantially more protection from DSP-4-induced neurodegeneration, similar to the activity of (−)-deprenyl. This suggests that compounds **3** and **6** may be effective neuroprotective agents.

In summary, a series of N^1- and N^2-propargylphenelzine derivatives and analogues was synthesized. Both N^1- and N^2-propargylphenelzine were relatively potent in preventing DSP-4-induced NA depletion. These findings suggest that some of these analogues should undergo further screening to evaluate their potential use as antidepressant agents and/or for use in prevention or treatment of neurodegenerative disorders.

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8. ^{1}H NMR of compound **3** in $CDCl_3$: δ 2.30 (t, 1H, $J=2.45$ Hz, CH), 2.85 (m, 4H, $CH_2\times2$), 3.20 (brs, 2H, NH_2), 3.59 (d, 2H, $J=2.45$ Hz, CH_2 of propargyl group), 7.18–7.33 (m, 5H, aromatic); HCl salt in D_2O: δ 2.95 (m, 3H, CH_2 and CH), 3.37 (t, 2H, $J=7.02$ Hz, CH_2), 3.97 (m, 2H, CH_2 of propargyl group), 7.28–7.39 (m, 5H, aromatic).
9. ^{1}H NMR of compound **6** (HCl salt in D_2O): δ 2.81 (m, 1H, CH), 3.04 (m, 2H, CH_2), 3.45 (m, 2H, CH_2), 3.82 (m, 2H, CH_2 of propargyl group), 7.33–7.39 (m, 5H, aromatic).
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