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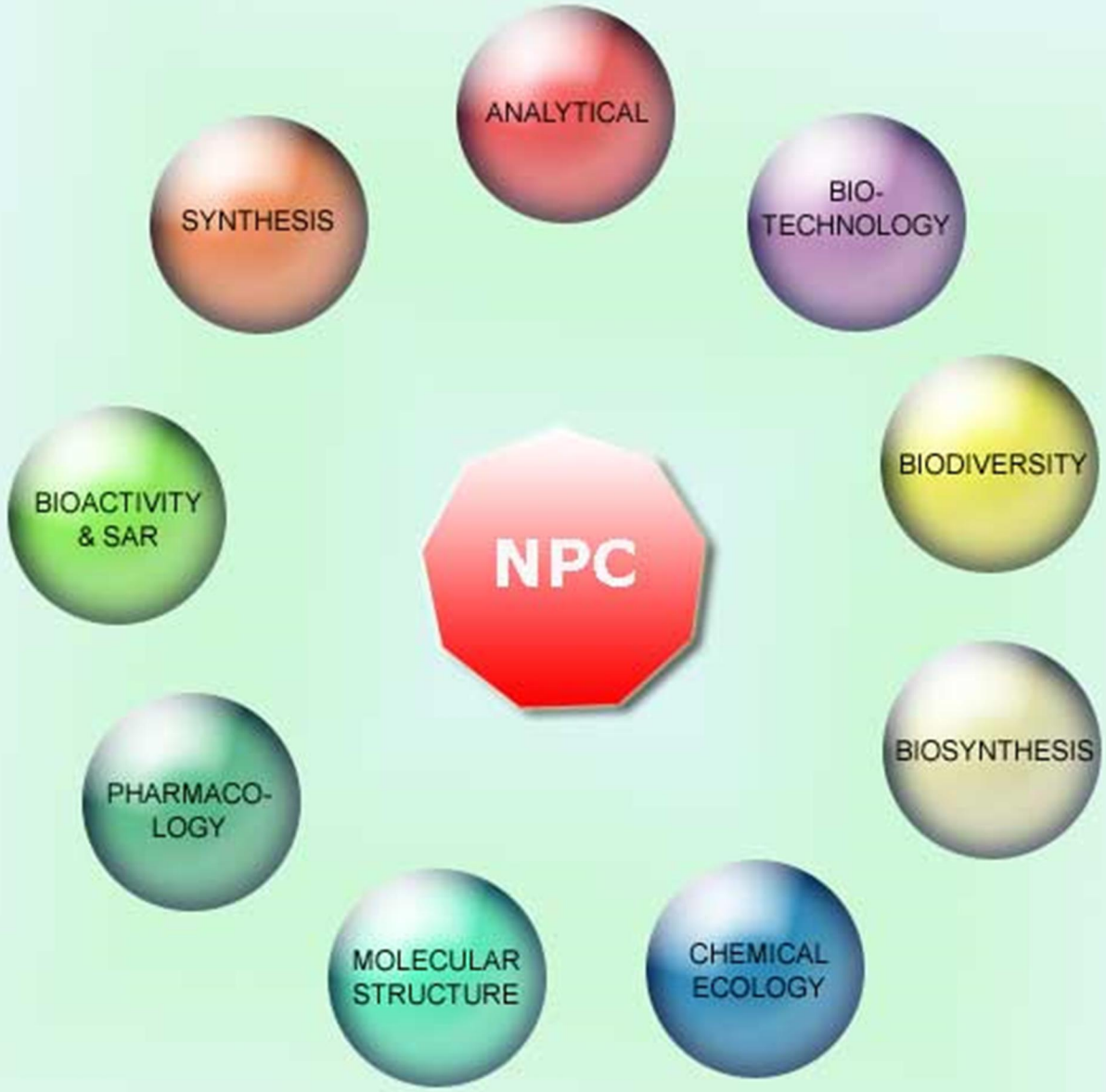

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Synthetic and Structure-Activity Relationship of Insecticidal Bufadienolides

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A new synthetic analog of bufadienolide, methyl isobryophyllinate A (**1**), and a known synthetic analog, methyl isobersaldegenate-1,3,5-orthoacetate (**2**), were obtained by methanolysis of bryophyllin A (**3**) and bersaldegenin-1,3,5-orthoacetate (**5**) in basic solution. Structure-insecticidal activity relationship studies revealed both orthoacetate and α-pyrone moieties seemed to be essential structural elements for exhibiting insecticidal activity, whereas oxygenated substituents in the C ring enhanced the insecticidal activity against the third instar larvae of silkworm (*Bombyx mori*).

Keywords: Bufadienolide, Insecticidal activity, Methyl isobryophyllinate A, Methyl isobersaldegenate-1,3,5-orthoacetate, *Bombyx mori*.

The bufadienolides are an important group of steroids containing the α-pyrone moiety [1]. They are characterized by an α-pyrone connected at the five position to a steroid nucleus [2]. This class of α-pyrones can be found in several families of plants and animals and the biological activity of the bufadienolides is diverse [3]. The plant sources include the families Crassulaceae, Hyacinthaceae, Iridaceae, Melianthaceae, Ranunculaceae and Santalaceae [4]. Those from the family Crassulaceae can cause the symptoms of cardiac poisoning in animals [5].

In the course of our continuing search for novel insecticidal compounds from Indonesian plants, we isolated and described two insecticidal bufadienolides, bryophyllin A (**3**) and C (**4**), along with an inactive bufadienolide, bersaldegenin-3-acetate (**7**), from the leaves of *Kalanchoe pinnata* [6]. In a further search for insecticidal compounds from Indonesian *Kalanchoe* (syn. *Bryophyllum*) species, we found that the methanolic extract of *K. daigremontiana* x *tubiflora* produced three insecticidal bufadienolides, bersaldegenin-1,3,5-orthoacetate (**5**), daigremontianin (**6**), and methyl daigremonate (**9**), together with an inactive bufadienolide, bersaldegenin-1-acetate (**8**) (Figure 1) [7].

In order to further confirm the functional groups responsible for insecticidal activity, two synthetic bufadienolides were prepared from bryophyllin A (**3**) and bersaldegenin-1,3,5-orthoacetate (**5**) by reacting them with a base in methanol, followed by treatment with an acid, according to the partially modified procedure of a previous report [8,9]. We now record the preparation of two synthetic bufadienolides by chemical transformation of insecticidal bufadienolides, their isolation, structural elucidation and the structure-insecticidal activity relationship against the third instar larvae of silkworm (*Bombyx mori*) of the two synthetic products in comparison with the naturally occurring compounds.

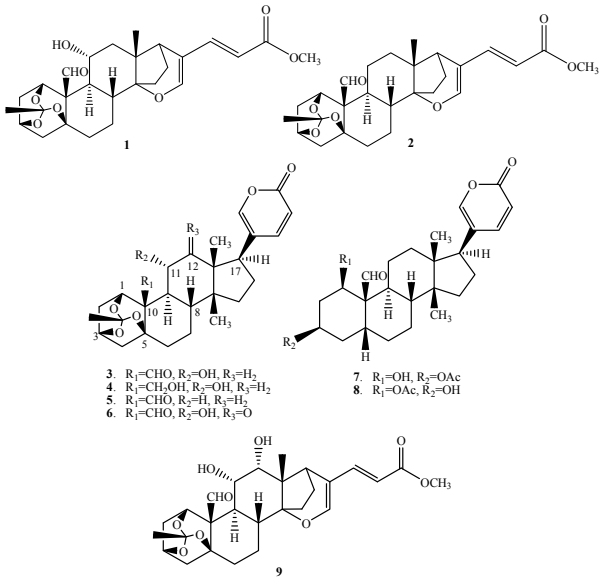

Figure 1: Chemical structures of synthetic (**1**-**2**) and naturally-occurring bufadienolides (**3**-**9**).

Bryophyllin A (**3**), after treatment with a methanolic solution of sodium hydroxide, followed by acidification, extraction with chloroform, and column chromatographic purification, gave a synthetic product **1**. The molecular formula of **1** was established as $C_{27}H_{34}O_8$ from the $[M+H]^+$ ion at *m/z* 487.2251 in the HR-ESI-TOFMS, and its NMR spectroscopic data (Table 1), thus requiring 11 degrees of unsaturation. Its UV spectrum showed an absorption maximum at 298 nm (ε 5900), indicating the presence of a conjugated carbonyl group. The IR spectrum of **1** showed the