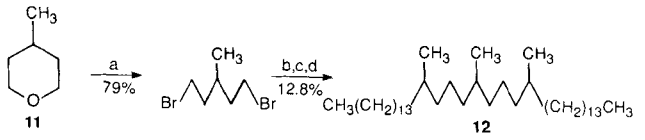

Fig. 4. (a) 48% hydrogen bromide + 98% sulfuric acid; (b) magnesium + tetrahydrofuran, $CH_2{=}CH(CH_3)CH_2Cl$ + copper(I) iodide + 2,2′-bipyridyl; (c) diborane + tetrahydrofuran, 0°C; methanol, −15°C; bromine; sodium methoxide + methanol, 5–25°C; (d) 1-bromotridecane + magnesium + copper(I) iodide + 2,2′-bipyridyl + tetrahydrofuran, 2–20°C.

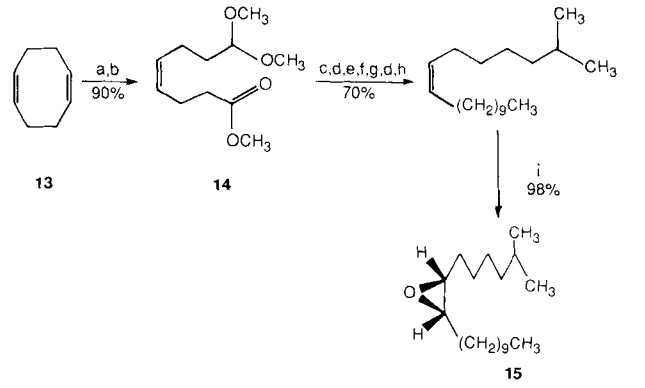

Fig. 5. (a) ozone + cyclohexane, acetic anhydride + acetic acid + sodium acetate; (b) *p*-toluene sulfonic acid + methanol; (c) di-*iso*butyl aluminium hydride + toluene + tetrahydrofuran; (d) *p*-toluene sulfonyl chloride + pyridine; (e) heptyl magnesium bromide + tetrahydrofuran + lithium cuprochloride; (f) hydrochloric acid + acetone; (g) sodium borohydride + methanol; (h) *iso*-butyl magnesium bromide + tetrahydrofuran + lithium cuprochloride; (i) 4-carboxymethylperbenzoic acid + chloroform, 2°C, 1 h.

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Non-Steroidal Analogues of Veratridine: Model-Based Design, Synthesis and Insecticidal Activity*

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Plant-derived chemicals have been used for centuries to combat insect pests and more recently as model compounds for development of (semi) synthetic insecticides with favourable toxicological and environmental properties.[1–3] The major commercial insecticides, both

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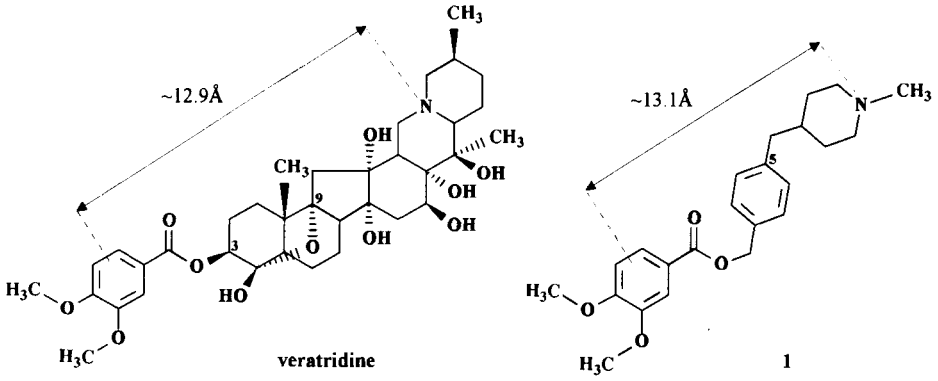

Fig. 1. Structures of veratridine and its piperidine mimic **1**.

natural and synthetic, act at only a few target sites, one of which is the voltage-dependent sodium channels in excitable membranes.[4] Veratridine (Fig. 1), one of the steroid alkaloid insecticide components of sabadilla preparations from the seeds of *Schoenocaulon officinale* L. (Liliaceae),[5] has been shown to activate the sodium-ion channel, sharing a common binding site with aconitine, batrachotoxin and grayanotoxin.[6] Structural similarities of veratridine and these natural products suggested a toxin–receptor interaction model[7–9] that has been useful in partially probing various regions of the proposed pharmacophore.[10–12]

The structural complexity of veratridine has restricted structure–biological activity studies to synthetically accessible portions of the skeletal ring system.[13,14] The construction of the cyclic hemiacetal system characteristic to batrachotoxin and Veratrum alkaloids related to veratridine has been the subject of some recent chemical studies,[15,16] but no total synthesis of the complete steroid skeleton of this type has been achieved. Early attempts toward finding simple structural models of hypotensive Veratrum alkaloids led to pharmacologically inactive indanone[17] and quinolizine derivatives.[18,19] Recently prepared hydroxylated norbornane and bicyclooctane derivatives as truncated steroid core mimics lacked insecticidal activity[20] and this is partly explained by our studies with semi-synthetic veratridine analogue insecticides[14] which revealed the significance of the hydrophobic ester group at C-3 of the steroid skeleton.

Chemistry: design and synthesis

Veratridine contains three structural characteristics thought to be important in receptor binding: these are an aromatic ester side chain, a basic nitrogen atom in a quinolizidine ring system, and several hydroxyl groups. The objective of the present work was to find simple, non-steroidal structures containing two of these pharmacophore elements, namely the lipophilic ester side chain and the basic nitrogen atom in a heterocyclic ring that are linked by a suitable moiety.

Modelling studies used molecular mechanics calculations (HyperChem version 3·0, Autodesk, Inc.) and relied on structural information of available molecular probes e.g. the X-ray structure of veratridine.[8] Intuition-guided disconnection of various carbon–carbon bonds of the rigid steroid skeleton followed by energy minimisation of the resulting fragments suggested that 4-{(4-hydroxymethyl)benzyl}piperidine derivatives, such as compound **1** (Fig. 1), in their extended, low-energy conformation could serve as an appropriate template fixing the overall geometry of the molecule in a bent shape characteristic of veratridine. The central, *para*-substituted aromatic ring functions as an isostere of the *cis*-decalin type A/B ring system of the natural product. The average distances between the respective carbon atoms of the 3,4-dimethoxybenzoyl groups and the basic nitrogen atoms in the energy-minimised conformations of the two types of molecules are very similar, i.e. ~13 Å. Furthermore, superimposition of the structures of veratridine and the piperidine derivative **1** shows that the aromatic ester and the amino moieties of the two compounds match reasonably well (Fig. 2). These modelling experiments prompted us to prepare a

Fig. 2. Superposition of MM+ calculated minimum-energy structures of veratridine and its piperidine mimic **1** (thick line) generated using HyperChem's (version 3.0. Autodesk, Inc.) 'Overlay' command by matching the following atomic pairs: (1) the C-9 atom of veratridine and the aryl C-5 of compound **1**, (2) the *N*-atom, and (3) the carbonyl *O*-atoms, respectively. The illustration on the right originates from a 90° rotation of the compounds. Hydrogen atoms are not shown.

TABLE 1
Structures, Synthetic Methods and Insecticidal Activities of Piperidines and Related Derivatives

Compound No.	*Structure*[a]				*Synthesis*		LD_{50}[c] ($\mu g\ g^{-1}$)
	X	*Y*	*R1*	*R2*	*Method*[b]	*Yield* (%)	
1		O	CH_3	3,4-$(CH_3O)_2C_6H_5$	E	38	NA[d]
2	$COOCH_3$						—
3	CN						—
4	$COOCH_3$				A	75	—
5	CN				A	80	—
9	$COOCH_3$		CH_3		B	40	—
10	$COOCH_3$		C_2H_5		B	55	13 000 (Pc)[d,e]
11	$COOCH_3$		C_6H_5		B	65	NA[d]
12	CN		C_2H_5		B	35	7000 (Pc)[d,e]
13	$COOCH_3$		CH_3		C	99	—
14	$COOCH_3$		C_2H_5		C	100	16 000i (Pc)[f]
15	$COOCH_3$		C_6H_5		C	87	NA[d]
16	CN		C_2H_5		C	99	18 000 (Pc)[d,e]
17		O	CH_3		D	98	—
18		O	C_2H_5		D	95	—
19		O	C_6H_5		D	100	—
20		NH	C_2H_5		D	80	—
21		O	C_2H_5	3,4-$(CH_3O)_2C_6H_5$	E	25	200 (Pa)[g]
22		O	C_2H_5	3,5-$(CH_3O)_2C_6H_5$	F	73	NA[d]
23		O	C_2H_5	$(CH_3)_3C$	E	67	NA
24		O	C_2H_5	2,4,5-$(CH_3)_3$ pyrrolyl	G	20	NA[d]
25		O	C_2H_5	(1*R*,*cis*)-3-$(Br_2C{=}CH)$-2,2-$(CH_3)_2$-cyclopropyl	F	25	NA
26		O	C_6H_5	3,4-$(CH_3O)_2C_6H_5$	F	56	NA
27		O	C_6H_5	3,5-$(CH_5O)_2C_6H_5$	F	66	NA[d]
28		O	C_6H_5	$(CH_3)_3C$	E	78	NA[d]
29		NH	C_2H_5	3,5-$(CH_3O)_2C_6H_5$	F	45	NA
30		O	C_2H_5	3,5-$(CH_3O)_2C_6H_5$[h]	H, I	37	NA
31			C_2H_5	3,5-$(CH_3O)_2C_6H_5$	D, F	60	NA[d]
32				3,5-$(CH_3O)_2C_6H_5$	B, D, F	15	NA[d]
33				3,5-$(CH_3O)_2C_6H_5$	B, D, F	18	NA[d]
34				3,4-$(CH_3O)_2C_6H_5$	H, D, F	35	NA
35				$(CH_3)_3C$	1H, D, E	22	NA
36				3,5-$(CH_3O)_2C_6H_5$	[b]	45	—[i]
37				3,5-$(CH_3O)_2C_6H_5$	K	13	NA

[a] For basic structures, see Fig. 3.
[b] For details, see text and Fig. 3; compounds **2** and **3** are commercially available.
[c] Topical LD_{50} values estimated by probit analysis from mortalities at 24 h after treatment. Pc = *Phaedon cochleariae*; Pa = *Periplaneta americana*; Md = *Musca domestica*. NA = not active at the discriminatory dose used against any species, unless otherwise noted; '—' = not tested. Topical LD_{50} values ($\mu g\ g^{-1}$) for veratridine: Pc: 4,800; Pa: 52; Md: 18 (from Ref. 14).
[d] Not tested against Md.
[e] Not active against Pa.
[f] Not active against Pa and Md.
[g] Not active against Pc and Md.
[h] 'Reverse ester'.
[i] This reactive benzylic bromide was not assayed.

series of compounds related to **1**, i.e. esters of para-substituted benzyl alcohols containing a piperidine heterocycle, as a basic moiety, for biological evaluation (Table 1 and Fig. 3). The 3,4- and 3,5-dimethoxybenzoyl, as well as the pivaloyl groups, shown to confer improved insecticidal activity and selectivity in the Veratrum alkaloid series,[14] were selected as the preferred acyl moieties. Compounds of type **1** are all new, although various neuroactive compounds containing a similar, 4-substituted piperidine ring are known in the

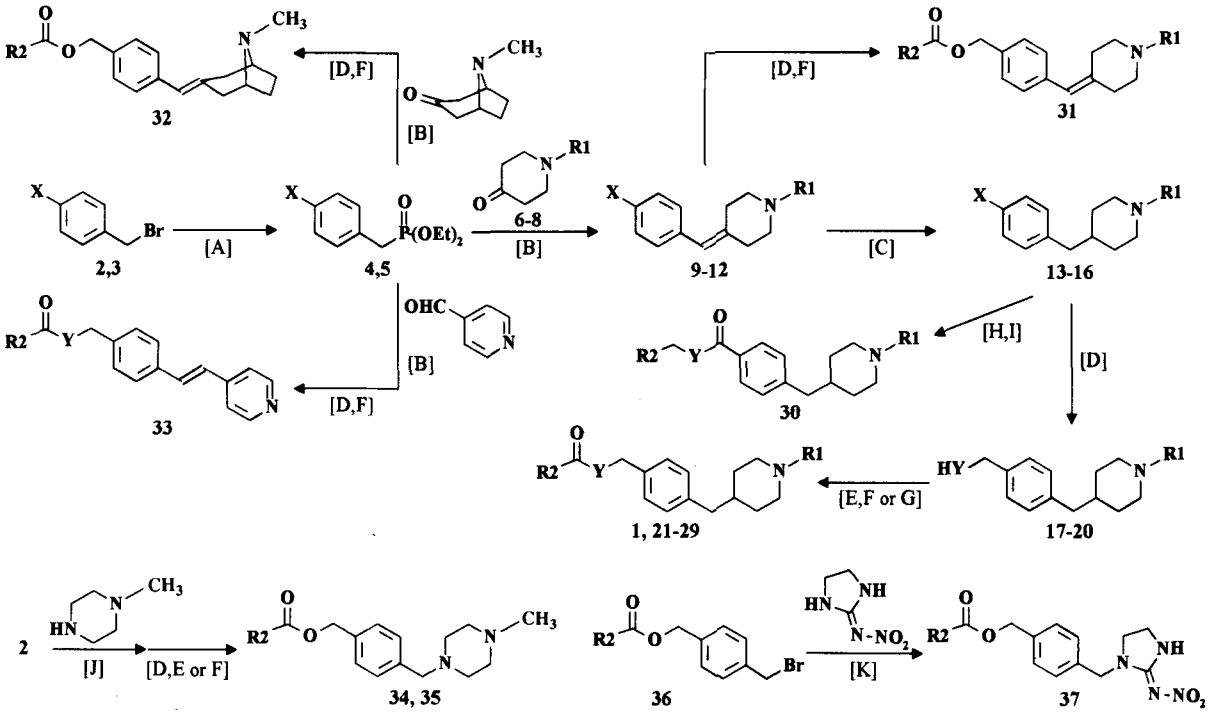

Fig. 3. General synthesis of piperidine and related derivatives. Methods: [A] $(C_2H_5O)_3P$, 160°C; [B] NaH, THF; [C] H_2-Pd/C, C_2H_5OH; [D] $LiAlH_4$, THF; [E] acid chloride, CH_2Cl_2, pyridine; [F] carboxylic acid, DCCD, CH_2Cl_2, pyridine, DMAP; [G] 2,4,5-trimethylpyrrolecarboxylic acid, $(CF_3CO)_2O$, benzene; [H] KOH, H_2O-C_2H_5OH, then HCl; [I] 3,5-dimethoxybenzyl alcohol, DCCD, CH_2Cl_2, pyridine, DMAP; [J] DMF, K_2CO_3; [K] CH_3CN, K_2CO_3.

pharmacological literature as analgesics,[21] anticonvulsants,[22] and antihypertensives.[23]

The target compounds and their synthetic intermediates listed in Table 1 were prepared using methodologies developed for simple (arylmethyl)piperidines[24] followed by conventional functional group transformations as shown in Fig. 3. Specifically, Wadsworth–Emmons condensation of 1-methyl-, 1-ethyl- or 1-phenyl-4-piperidone (**6**, **7** or **8**,[25] respectively) with appropriately substituted benzylphosphonates, [prepared from methyl 4-(bromomethyl)benzoate (**2**) or 4-(bromomethyl)benzonitrile (**3**) by Arbuzov rearrangement] gave the corresponding alkenes **9–12** with an exocyclic double bond which, in turn, underwent smooth catalytic hydrogenation. Reduction of the ester or nitrile functionality of **13–16** thus obtained, followed by acylation of the respective alcohols (**17–19**) or amine (**20**), afforded the desired products (**1**, **21–29**). Compounds **30–33** were obtained by suitable variations of these procedures as indicated in Fig. 3. Compound **24**, containing the acyl component of a synthetic homologue of batrachotoxin, could be obtained only if the mixed anhydride of trifluoroacetic and 2,4,5-trimethylpyrrole-3-carboxylic acids was used for acylation.[26]

Heterocylic derivatives **34** and **35** were synthesised by alkylation of *N*-methylpiperazine with the benzyl bromide **2** and subsequent functional group transformations. Similarly, compound **37** was prepared by *N*-alkylation of 2-nitroimino-imidazolidine, a toxophore moiety of novel nicotinoid insecticides,[27] with the substituted benzyl bromide **36** that was obtained from the reaction of potassium 3,5-dimethoxybenzoate with 1·2 equivalents of α,α′-dibromo-*p*-xylene in acetonitrile at ambient temperature.

The crude products were purified either by preparative TLC on silica gel plates using chloroform or chloroform + methanol (9 + 1 by volume) for development, or by column chromatography using silica gel and chloroform containing methanol (0–50 ml litre^{-1}) as eluent. The melting points (where appropriate) and proton magnetic resonance data of the target compounds are shown in Table 2.

Biological evaluation

LD_{50} values were determined by topical application of the test compounds in acetone solution to the following three insect species: mustard beetle (*Phaedon cochleariae* Fab.) (0 to 8000 μg g^{-1} dose range, two replicates, 20 third-instar larvae per dose, average weight 2·2 mg); American cockroach (*Periplaneta americana* L.) (0 to 160 μg g^{-1} dose range, two replicates, 10 last-instar nymphs per dose, average weight 0.50 g) and housefly (*Musca domestica* L.) (0 to 500 μg g^{-1} dose range, three replicates, 10 adult females per dose, average weight 20 mg). When needed, further assays using appropriate higher doses were carried out to determine the LD_{50} values.

TABLE 2
Melting Points and Nuclear Magnetic Resonance Data for the Target Compounds

Compound No.[a]	*Melting point (°C)*	*[^1H]NMR (300 MHz, deuterochloroform) δ values (ppm) and assignments*[b]
1	Gum	1·39 (m, 2H), 1·6 (m, 3H), 1·85 (broad t, 2H), 2·30 (s, 3H), 2·57 (d, J = 6·7 Hz, 2H), 2·95 (d, J = 11·5 Hz, 2H), 3·92 (s, 6H), 5·33 (s, 2H), 6·86 (d, J = 8·3 Hz, 1H), 7·14 (d, J = 8·0 Hz, 2H), 7·35 (d, J = 8·0 Hz, 2H), 7·58 (d, J = 2·0 Hz, 1H), 7·72 (dd, J = 2·0 and 8·3 Hz, 1H).
10	Oil	1·11 (t, J = 7·2 Hz, 3H), 2·43 (m, 6H), 2·53 (m, 4H), 3·89 (s, 3H), 6·29 (s, 1H), 7·25 (d, J = 8·0 Hz, 2H), 7·97 (d, J = 8·0 Hz, 2H).
14	Oil	1·10 (t, J = 7·2 Hz, 3H), 1·39 (m, 2H), 1·56 (m, 1H), 1·64 (d, J = 13·6 Hz, 2H), 1·88 (t, J = 11·5 Hz, 2H), 2·41 (q, J = 7·2 Hz, 2H), 2·59 (d, J = 6·6 Hz, 2H), 2·96 (d, J = 11·5 Hz, 2H), 3·90 (s, 3H), 7·20 (d, J = 8·3 Hz, 2H), 7·95 (d, J = 8·3 Hz, 2H).
18	Oil	1·09 (t, J = 7·2 Hz, 3H), 1·37 (m, 2H), 1·54 (m, 1H), 1·63 (d, J = 13·0 Hz, 2H), 1·87 (dt, J = 2·2 and 11·7 Hz, 2H), 2·40 (q, J = 7·2 Hz, 2H), 2·58 (d, J = 6·8 Hz, 2H), 2·96 (d, J = 11·7 Hz, 2H), 3·44 (s, OH), 4·64 (s, 2H), 7·12 (d, J = 8·0 Hz, 2H), 7·27 (d, J = 8·0 Hz, 2H).
21	105–7	1·10 (t, J = 7·2 Hz, 3H), 1·38 (m, 2H), 1·62 (m, 3H) 1·87 (t, J = 11·7 Hz, 2H), 2·38 (q, J = 7·2 Hz, 2H), 2·58 (d, J = 6·8 Hz, 2H), 2·95 (d, J = 11·7 Hz, 2H), 3·91 (s, 6H), 5·33 (s, 2H), 6·86 (d, J = 8·3 Hz, 1H), 7·18 (d, J = 8·0 Hz, 2H), 7·38 (d, J = 8·0 Hz, 2H), 7·58 (d, J = 2·0 Hz, 1H), 7·72 (dd, J = 2·0 and 8·3 Hz, 1H).
22	Gum	1·10 (t, J = 7·2 Hz, 3H), 1·37 (m, 2H), 1·54 (m, 1H), 1·63 (d, J = 13·0 Hz, 2H), 1·87 (dt, J = 2·2 and 11·7 Hz, 2H), 2·40 (q, J = 7·2 Hz, 2H), 2·58 (d, J = 6·8 Hz, 2H), 2·96 (d, J = 11·7 Hz, 2H), 3·80 (s, 6H), 5·33 (s, 2H), 6·64 (t, J = 2·3 Hz, 1H), 7·18 (d, J = 8·0 Hz, 2H), 7·22 (d, J = 2·3 Hz, 2H), 7·38 (d, J = 8·0 Hz, 2H).
23	182-5	1·10 (t, J = 7·2 Hz, 3H), 1·22 (s, 9H), 1·38 (m, 2H), 1·54 (m, 1H), 1·65 (d, J = 13·0 Hz, 2H), 1·90 (t, J = 11·7 Hz, 2H), 2·45 (q, J = 7·2 Hz, 2H), 2·52 (d, J = 6·8 Hz, 2H, 2·99 (d, J = 11·7 Hz, 2H), 5·09 (s, 2H),), 7·12 (d, J = 8·0 Hz, 2H), 7·27 (d, J = 8·0 Hz, 2H).
24	Oil	1·10 (t, J = 7·2 Hz, 3H), 1·38 (m, 2H), 1·54 (m, 1H), 1·65 (d, J = 13·0 Hz, 2H), 1·90 (broad t, J = 11·7 Hz, 2H), 2·10 (s, 3H), 2·15 (s, 3H), 2·44 (s, 3H), 2·45 (q, J = 7·2 Hz, 2H), 2·52 (d, J = 6·8 Hz, 2H), 2·99 (d, J = 11·7 Hz, 2H), 5·24 (s, 2H), 7·10 (d, J = 7·9 Hz, 2H), 7·31 (d, J = 7·9 Hz, 2H), 8·26 (bs, 1H).
25	Oil	1·10 (t, J = 7·2 Hz, 3H), 1·24 (s, 3H), 1·27 (s, 3H), 1·38 (m, 2H), 1·54 (m, 1H), 1·66 (d, J = 13·0 Hz, 2H), 1·90 (m, 4H), 2·42 (q, J = 7·2 Hz, 2H), 2·54 (d, J = 6·8 Hz, 2H), 2·97 (d, J = 11·7 Hz, 2H), 5·07 (s, 2H), 6·79 (d, J = 8·2 Hz, 1H), 7·15 (d, J = 8·0 Hz, 2H), 7·27 (d, J = 8·0 Hz, 2H).
26	109–10	1·41 (dq, J = 3·5 and 12·0 Hz, 2H), 1·64 (m, 1H), 1·68 (m, 2H), 2·62 (m, 4H), 3·64 (d, J = 12·4 Hz, 2H), 3·91 (s, 6H), 5·32 (s, 2H), 6·81 (t, J = 7·2 Hz, 1H), 6·88 (m, 2H), 7·18 (d, J = 8·0 Hz, 2H), 7·23 (m, 3H), 7·36 (J = 8·0 Hz, 2H), 7·58 (d, J = 2·0 Hz, 1H), 7·72 (dd, J = 2·0 and 8·3 Hz, 1H).
27	88–9	1·41 (dq, J = 3·5 and 11·7 Hz, 2H), 1·67 (m, 3H), 2·62 (m, 4H), 3·64 (d, J = 12·3 Hz, 2H), 3·77 (s, 6H), 5·32 (s, 2H), 6·64 (t, J = 2·3 Hz, 1H), 6·81 (t, J = 7·0 Hz, 1H), 6·92 (d, J = 8·0 Hz, 2H), 7·14 (d, J = 8·0 Hz, 2H), 7·22 (m, 4H), 7·36 (d, J = 8·0 Hz, 2H).
28	74–5	1·22 (s, 9H), 1·41 (dq, J = 3·5 and 11·7 Hz, 2H), 1·70 (m, 3H), 2·61 (m, 4H), 3·64 (d, J = 12 Hz, 2H), 5·08 (s, 2H), 6·81 (t, J = 7·0 Hz, 1H), 6·91 (d, J = 8·3 Hz, 2H), 7·14 (d, J = 8·0 Hz, 2H), 7·23 (m, 4H).
29	Oil	1·10 (t, J = 7·2 Hz, 2H), 1·40 (m, 2H), 1·60 (m, 3H), 1·90 (t, J = 12·0 Hz, 2H), 2·48 (m, 4H), 3·00 (d, J = 12·0 Hz, 2H), 3·79 (s, 6H), 4·54 (d, J = 5·6 Hz, 2H), 6·54 (t, J = 2·2 Hz, 1H), 6·84 (t, J = 5·6 Hz, 1H), 6·94 (d, J = 2·2 Hz, 1H), 7·08 (d, J = 8·0 Hz, 2H), 7·23 (d, J = 8·0 Hz, 2H).
30	Gum	1·07 (t, J = 7·2 Hz, 3H), 1·36 (m, 2H), 1·54 (m, 1H), 1·62 (d, J = 13·3 Hz, 2H), 1·80 (t, J = 11·0 Hz, 2H), 2·34 (q, J = 7·2 Hz, 2H), 2·59 (d, J = 6·7 Hz, 2H), 2·93 (d, J = 11·0 Hz, 2H), 3·80 (s, 6H), 5·28 (s, 2H), 6·43 (t, J = 2·2 Hz, 1H) 6·58 (d, J = 2·2 Hz, 2H), 7·21 (d, J = 8·2 Hz, 2H), 7·98 (d, J = 8·2 Hz, 2H).
31	Oil	1·10 (t, J = 7·2 Hz, 3H), 2·43 (m, 6H), 2·55 (m, 4H), 3·81 (s, 6H), 5·33 (s, 2H), 6·23 (s, 1H), 6·64 (t, J = 2·3 Hz, 1H), 7·21 (d, J = 8·0 Hz, 2H), 7·22 (d, J = 2·3 Hz, 2H), 7·38 (d, J = 8·0 Hz, 2H).
32	Oil	1·51 (t, = 10·0 Hz, 1H), 1·74 (t, J = 10·0 Hz, 1H), 2·02 (m, 2H), 2·17 (d, J = 14·6 Hz, 1H), 2·54 (s, 3H), 2·79 and 2·61 (AB system, J_{AB} = 56·8 Hz, 2H), 3·05 (d, J = 14·6 Hz, 1H), 3·46 (d, J = 32·0 Hz, 2H), 3·81 (s, 6H), 5·32 (s, 2H), 6·42 (s, 1H), 6·64 (t, J = 2·3 Hz, 1H), 7·19 (d, J = 8·0 Hz, 2H), 7·22 (d, J = 2·3 Hz, 2H), 7·38 (d, J = 8·0 Hz, 2H).
33	143–5	3·81 (s, 6H), 5·36 (s, 2H), 6·65 (t, J = 2·3 Hz, 1H), 7·01 (d, J = 16·2 Hz, 1H), 7·22 (d, J = 2·3 Hz, 2H), 7·29 (d, J = 16·2 Hz, 1H), 7·36 (d, J = 5·3 Hz, 2H), 7·45 and 7·55 (AB system, J_{AB} = 27·3 Hz, 4H), 8·57 (d, J = 5·3 Hz, 2H).
34	Oil	2·33 (s, 3H), 2·52 (m, 8H), 3·53 (s, 2H) 3·92 (s, 6H), 5·33 (s, 2H), 6·86 (d, J = 8·3 Hz, 1H), 7·36 (m, 4H), 7·58 (d, J = 2·0 Hz, 1H), 7·72 (dd, J = 2·0 and 8·3 Hz, 1H).
35	Oil	1·22 (s, 9H), 2·33 (s, 3H), 2·52 (m, 8H), 3·53 (s, 2H), 5·08 (s, 2H), 7·35 (m, 4H).
37	149-50	3·70 (m, 4H), 3·80 (s, 6H), 4·50 (s, 2H), 5·33 (s, 2H), 6·64 (t, J = 2·3 Hz, 1H), 7·20 (d, J = 8·0 Hz, 2H), 7·22 (d, J = 2·3 Hz, 2H), 7·35 (d, J = 8·0 Hz, 2H).

[a] For structural formulae see Fig. 3 and Table 1.
[b] Assignments in parentheses.

The results of the bioassays are shown in Table 1. From the target ester derivatives only 4-[4-(*N*-ethylpiperidinyl)methyl]benzyl 3,4-dimethoxybenzoate (**21**) had significant activity against *P. americana* (LD_{50} = 200 μg g^{-1}, compared with 52 μg g^{-1} for veratridine). Interestingly, however, intermediates methyl 4-[4-(*N*-ethylpiperidinyl)methyl]benzoate (**10**) and its piperidinylidene precursor **14** were found to have LD_{50} values of 13 000 and 16 000 μg g^{-1}, respectively, against *P. cochleariae* larvae, but were inactive against *P. americana* nymphs; compound **14** was inactive against *M. domestica* adults. Similarly, the related benzonitriles **12** and **16** had LD_{50} values of 7000 and 18 000 μg g^{-1}, respectively, against *P. cochleariae* larvae. Methyl benzoate analogues **11** and **15**, both containing an *N*-phenyl substituent, were inactive against this latter insect species. It is also notable that combination of the piperidinylmethylaryl moiety of compounds of type **1** with toxophore structural units such as 2,4,5-trimethylpyrrole or dibromovinylcyclopropane carboxylic

acids and the nitroimino-imidazolidine moiety led to inactive derivatives (**24**, **25** and **37**, respectively). Moreover, 8-(diethylamino)octyl 3,4,5-trimethoxybenzoate (**38**) (Aldrich Chemical Co.), an open-chain analogue in which the distance of the aromatic ring and the *tert*-amino group is 14·8 Å in its fully extended conformation, was also devoid of any activity at the doses tested against *P. cochleariae* and *P. americana* (data not shown).

Conclusion

Molecular modelling experiments demonstrate that the new piperidinylmethylbenzyl esters can adopt a low-energy conformation that mimics the shape of the structurally rigid prototype veratridine and places the hydrogen bond donor/acceptor heterocyclic amino group and the electron-rich aromatic ring at positions similar to those in the natural insecticide. However, the finding of low insecticidal activity of even the best analogues indicates that simple, flexibly linked aromatic and piperidine ring systems, although capable of providing the proper geometry, are not sufficient for target-oriented transport and/or strong receptor binding. The most notable structural difference between the piperidine derivatives and veratridine is the lack of hydrogen bonding hydroxyl groups. Clearly, certain hydroxyl groups (the 'oxygen triad'[6,7]) found in the natural sabadilla components and related sodium-channel activators, must be present for high biological activity. Further evaluation and qualitative comparison of the structures of the natural compounds and these analogues should be useful in suggesting particular sites for the introduction of hydroxyl groups positioned according to those in the hypothetical veratridine pharmacophore.

ACKNOWLEDGEMENT

This work was supported by the US-Hungarian Science and Technology Joint Fund Grant 039-90, and, in part, by Grant No. PO1 ES00049 from the National Institute of Environmental Health Sciences, NIH.

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Quantitative Structure-Activity Relationships and Designed Synthesis of Larvicidal *N,N'*-Dibenzoyl-*N-tert*-butylhydrazines against *Chilo suppressalis*

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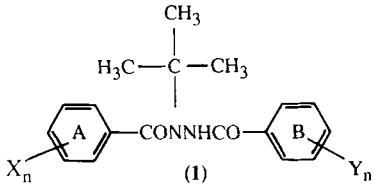
The key steps in insect larval growth are regulated by the steroidal moulting hormone, 20-hydroxyecdysone.[1] External administration of an excessive amount of the moulting hormone induces severe damage in larval growth, leading to death.[2] Although the development of moulting hormone mimics as selective insecticides has been hampered for a long time by the structural complexity of the steroid molecule, the recent disclosure of a non-steroidal ecdysone agonist, RH-5849 (**1**; X_n = Y_n = H) has provided a remedy for this difficulty.[3,4]



(1)

We synthesized a number of dibenzoyl-*N-tert*-butylhydrazines (**1**) with various substituents on the two benzene rings (A and B) and measured the larvicidal activity (*in vivo*)[5,6] and the molting hormone activity (*in vitro*)[7] using the rice stem borer (*Chilo suppressalis* Walker). The structure–larvicidal activity relationships were examined quantitatively using physicochemical substituent and (sub)molecular parameters and regression analysis.[5,6] We also found that there was a linear relationship between in-vivo and in-vitro activities.

Larvicidal activity against the rice stem borer was measured by the topical application method in the presence of piperonyl butoxide (PB) in a manner similar to that described previously,[5,6] and pLD_{50}, (the logarithm of the reciprocal of the dose (mmol per insect) required to kill 50% of the larvae) was used as the larvicidal activity index. For the in-vitro moulting hormone activity, the cultured integument fragments prepared from diapause larvae of the rice stem borer were used.[7] The pEC_{50}, (the logarithm of the reciprocal of the median effective concentration (M)) was used as the moulting hormone activity index. The EC_{50} is that required to stimulate the *N*-acetylglucosamine (GlcNAc) uptake into the cultured integument fragments by 50% of the maximum.

In the QSAR analyses various steric and electronic substituent parameters were used to describe the effects of substituents of the two benzene rings, depending upon the substituent positions and substitution patterns. The molecular hydrophobicity, log *P* (*P* is the partition coefficient in *n*-octanol/water system), was either measured experimentally or estimated empirically. The log *P* values of unsubstituted compound **1** (RH-5849) and the 2-chloro derivative (compound **2**) were used as references to estimate the Δ log *P* for the hydrophobic effect of substituents of the A- and B-ring moieties, respectively.

The Δ log *P* values for substituents on the two benzene rings were analyzed quantitatively leading to eqns (1) and (2). These empirical equations were used to estimate the non-measured Δ log *P* values. For the compounds substituted on the A-ring:

$$\begin{aligned}\Delta \log P &= \log P[\mathrm{Ph(X_n)CON}(\textit{tert}\text{-butyl})\mathrm{NHCOPh}] \\ &\quad - \log P \text{ (compd 1)} \\ &= 0{\cdot}858\ \Sigma\pi(\mathrm{X_i}) + 0{\cdot}690\ \Sigma\sigma^0 - 0{\cdot}726\ \Sigma\sigma_\mathrm{I}^{ortho} \\ &\quad + 0{\cdot}259\ \Sigma E_s^{ortho} + 0{\cdot}079 \\ n = 45 \quad s &= 0{\cdot}159 \quad r = 0{\cdot}958 \quad F_{4,40} = 111{\cdot}91 \quad (1)\end{aligned}$$

For the compounds substituted on the B-ring:

$$\begin{aligned}&\Delta \log P \\ &\quad = \log P[\text{2-Cl-PhCON}(\textit{tert}\text{-butyl})\mathrm{NHCOPh(Y_n)}] \\ &\qquad - \log P \text{ (compd 2)} \\ &\quad = 1{\cdot}008 \log P(\mathrm{Y_n - PhCONH_2}) \\ &\qquad - 0{\cdot}158\ \Sigma Es^{ortho} - 0{\cdot}638 \\ n = 10, \quad s &= 0{\cdot}015, \quad r = 0{\cdot}999, \quad F_{2,7} = 2017{\cdot}2 \quad (2)\end{aligned}$$

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