Cd^{2+} binds to the ring of four glutamates in the selectivity filter of the pore with much higher affinity than Ca^{2+} itself and thus blocks the pore. Most of the peptide toxins which block Ca_V subtypes with high specificity, also act by producing pore block. Allosteric modulation, on the other hand, is exemplified by the dihydropyridines which selectively affect members of the Ca_V1 family. The binding site for these compounds is located away from the pore and their mechanism of action relies on modification of the gating characteristics of the channel.

13.3.3.1 Ca_V1 Family (L-Type Currents)

The best characterized group of Ca_V modulators is the so-called "organic calcium blockers" or "calcium antagonists," comprising phenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), and the dihydropyridines (e.g., nifedipine; Figure 13.8), with distinct drug bindings sites for the two classes on the α_1 subunit. Several dihydropyridines are widely used clinically for the treatment of cardiovascular disorders such as hypertension, angina pectoris, and cardiac arrhythmia.

The organic calcium channel blockers bind with high affinity and selectivity to α_1 subunits of the Ca_V1 family, and act as allosteric modulators. This is highlighted by the fact that among the dihydropyridine-type compounds, positive modulators of Ca_V1 have also been identified, e.g., the compound (*S*)-Bay-K-8644 (Figure 13.8).

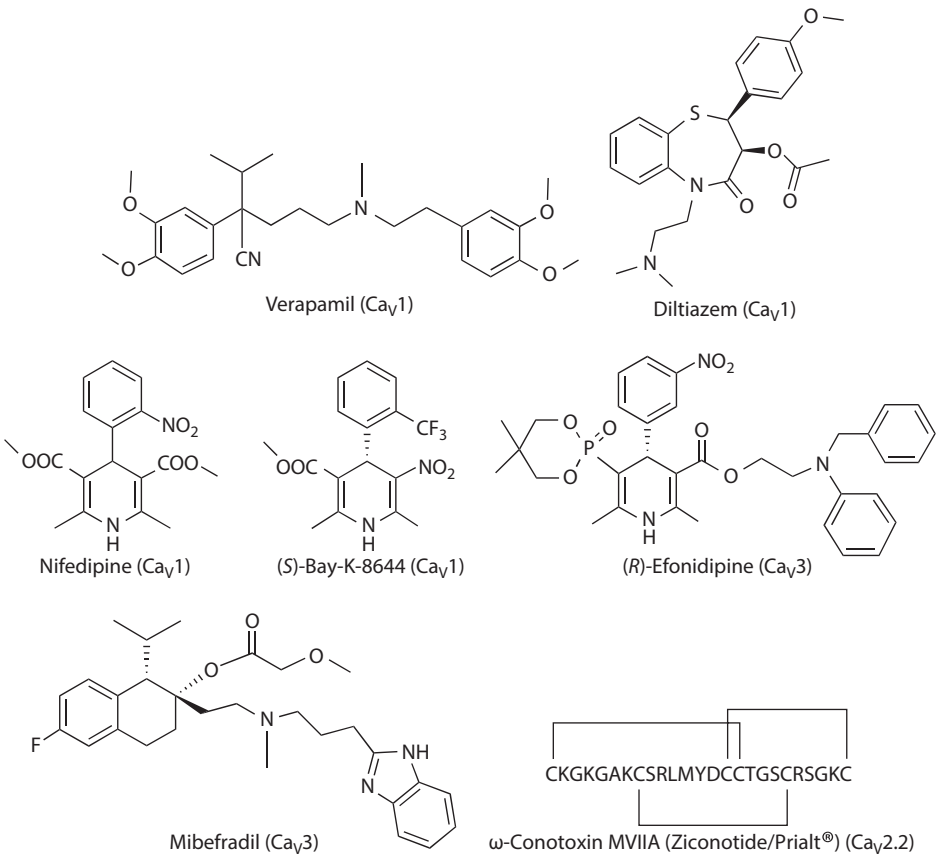

FIGURE 13.8 Chemical structure of drugs acting as blockers of Ca_V1 (L-type) and Ca_V3 (T-type) channels, the Ca_V1 channel activator (*S*)-Bay-K-8644, and the amino acid sequence of the highly specific peptide blocker of $Ca_V2.2$ (N-type) channels, ω-conotoxin MVIIA.