Ligand-based drug design (LBDD) approaches are applied when the three-dimensional structure of the target is unknown or when it is not fully reliable (i.e., homology models of the target are based on poor sequence identity) [1].Con- ventional 3D QSAR models consider the ensemble of conformations, orientations, tautomers, Fig.8 An example of apharmacophoremodelof(R)-roscovitine,which tightly bindsCDK5[23].Crucialinteractingresidues of CDK5 are shown in green (hydrophobic residues), blue (H-bond acceptors), and magenta (H-bond donors).That is, for a given molecular structure, properties such as solubility, membrane permeability, partition coefficients, blood-brain barrier penetration, plasma protein binding, and metabolite formation are computed and compared against a database of known drugs.The same principles are valid for molecular similarity methods, where similitudes in geometrical or physicochemical properties among active compounds are used to identify new active compounds from among the many that can be virtually screened.Typical descriptors are physicochemical features such as molecular weight, geometry, surface accessible area, aromaticity index, electronegativity, polarizability, and solvation properties.Absorption, distribution, metabolism, excretion, and toxicity (ADMET) are the key parameters that can be optimized with QSAR approaches to get a drug candidate with a proper drug-like pharmacokinetic (PK) profile.Despite its practical utility for quickly evaluating drug-likeness, it is nowadays clear that this rule can only estimate the compound's probable success by highlighting potentially problematic aspects of its physicochemical and structural profile [22].This says that an optimal orally bioavailable drug should have a molecular weight less than 500, less than 5 H- bond donor sites, and less than 10 H-bond acceptor sites, while the log of the octanol/water partition coefficient (logP), a measure of hydrophobicity, should be below 5.Additionally, interactions with influx/efflux transporter proteins or metabolic enzymes can greatly affect the final therapeutic effect and should be considered in the early phases of a drug discovery program.For example, activity data of active molecules can be used to extract mathematical models for early prediction of activity or, more often, metabolic properties that could generate toxicity problems. 8).