translational bridges between *in vitro* screening results, animal models, and the human condition facilitated the discovery of new therapies such as Januvia® (Sitagliptin),[48] Onglyza® (Saxagliptin),[49] and Tradjenta® (Linagliptin) (Figure 10.7).[50] DPP-IV plays an indirect role in blood glucose

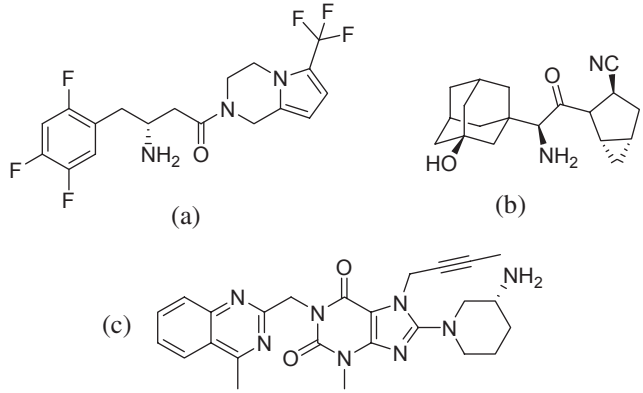

FIGURE 10.7 (a) Januvia® (Sitagliptin) (b) Onglyza® (Saxagliptin) (c) Tradjenta® (Linagliptin).

concentration, a key aspect in diabetes, through its ability to inactivate the incretin hormone glucagon-like peptide-1 (GLP-1). This hormone is released from the gut in response to food intake, stimulates insulin synthesis and secretion, and suppresses glucagon release.[51] Inhibiting DPP-IV would effectively slow the inactivation of GLP-1 (extend its half-life), prolonging its impact on glucose regulation.

When the aforementioned drugs were being developed, the link between DPP-IV, insulin, glucagon, glucose, and diabetes had not been firmly established. It was, therefore, necessary to develop animal models capable of predicting the impact of DPP-IV inhibitors on diabetes progression. Biomarkers played a key role in this process. Although blood glucose concentration could certainly be measured in animals, this assessment is not capable of demonstrating that a hypothetical DPP-IV inhibitor is actually engaging the target or that target engagement is actually a useful course of action. In the absence of an assay capable of demonstrating target engagement *in vivo*, the meaning of a negative result in a glucose tolerance test (a standard diabetes animal model) would not be clear. A negative result of this type could have been an indication that the hypothesis linking DPP-IV to diabetes progression was incorrect, that DPP-IV was not on the critical path of disease progression, or that the compound was simply not capable of reaching the target. The first two interpretations would have led to questioning of the utility of DPP-IV inhibitors as a whole for the treatment of diabetes,