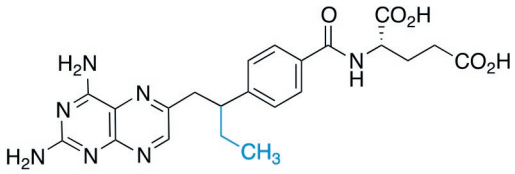
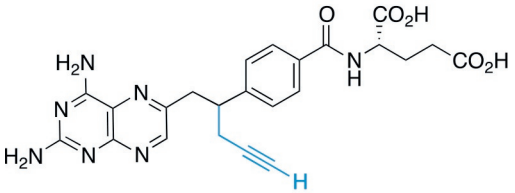
clinical investigations.[65,66] The latter compound, under the trade name Folotyn®, was the first drug approved for the treatment of relapsed or refractory peripheral T-cell lymphoma, or peripheral T-cell lymphoma.



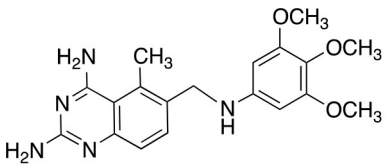
Edatrexate



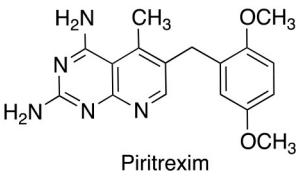
Pralatrexate (PDX)

5.2 NONCLASSICAL (LIPOPHILIC) DHFR INHIBITORS

Suppression of the glutamic chain of the folic acid skeleton leads to compounds that are not substrates for the folate active transport systems and enter the cells by passive diffusion. They have the advantage of being active in cancer cells that are resistant to methotrexate because of transport defects. On the other hand, the lack of the glutamic acid side chain prevents polyglutamation, and therefore these compounds are not retained within the cells and require more prolonged treatments. Among these compounds, trimetrexate is mainly used to treat pneumonias by *Pneumocystis carinii* and *Toxoplasma gondii*, although it is also used in the treatment of certain cancers, including colon cancer, as its glucuronate salt (Neutrexin®).[67] Piritrexim has been assayed for the treatment of psoriasis, pneumonia, and several cancers, including phase II studies for the treatment of advanced carcinoma of the urotelium.[68]



Trimetrexate



Piritrexim

6 INHIBITORS OF THE *DE NOVO* PURINE BIOSYNTHESIS PATHWAY

In contrast to pyrimidine nucleotide biosynthesis, in which a preformed heterocyclic moiety is attached to PRPP, in the case of purine nucleotides the purine ring is constructed gradually. The complete route comprises 10 steps and is summarized in Figures 2.39 and 2.40. This *de novo* pathway