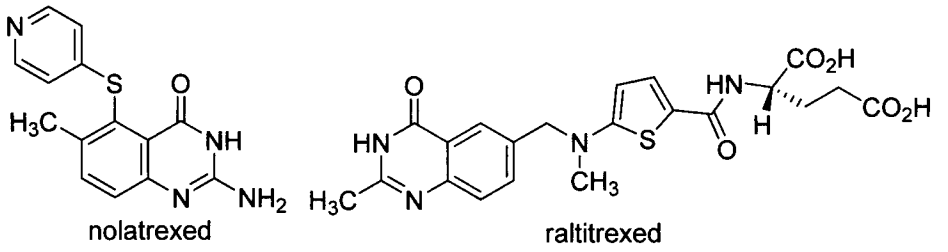
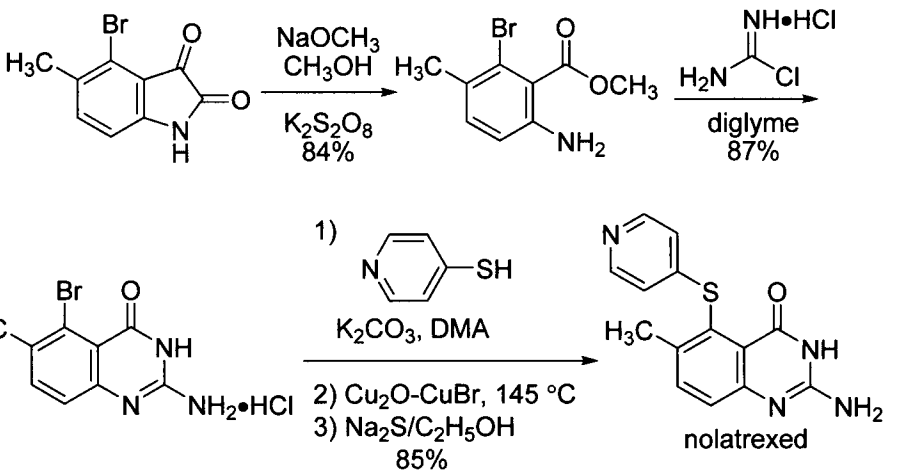


The original synthesis of nolatrexed, reported by Webber and co-workers,[46] was recently improved by Fang and co-workers.[47] Base-catalyzed hydrolysis of 4-bromo-5-methylisatin proceeded in 84% yield to produce the corresponding methyl ester. Niementowski reaction of the ester with chloroformamidine hydrochloride in diglyme gave the corresponding quinazolinone-hydrochoride in 87% yield. Finally, Ullmann reaction of the hydrochloride with 4-mercaptopyridine produced nolatrexed in 85% yield (62% over five steps).



Cao and co-workers[48] reported a facile synthesis to raltitrexed that helped to overcome many of the unwanted *N,N*-dialkylation side products reported in the previous syntheses of this compound.[49] Their synthesis began with the coupling of commercially available 2,5-thiophenedicarboxylic acid and diethyl L-glutamate in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) to produce the desired product in 60% yield.[48] Conversion of the carboxylic acid using diphenylphosphoryl azide (DPPA) in the presence of *t*-butanol gave the Boc protected amine in 56% yield, which was subsequently converted under standard alkylating conditions using TBAB as a phase transfer catalyst to the methyl amine in 90% yield. Removal of the Boc protecting group using TFA, followed by coupling of the amine with 6-