APB, and lacosamide.[93] The '464 application also describes the administration of the compounds of the invention with various pharmaceutical carriers for anticonvulsant activity.[94]

117. The '464 application discloses that "[t]he present compounds obviously exist in stereoisomeric forms and the products obtained thus can be mixtures of the isomers which can be resolved."[95] Consistent with the literature discussed above, the '464 application reports data showing that the D stereoisomer[96] was tenfold more potent than the L stereoisomer for the compounds reported.[97]

g. Harold Kohn et al., Marked Stereospecificity in a New Class of Anticonvulsants, 457 Brain Res. 371-375 (1988) ("Kohn 1988")

118. Kohn 1988 is prior art to the '551 patent because it published in 1988, which is prior to March 15, 1996.

[93] *Id.* at cl. 1.

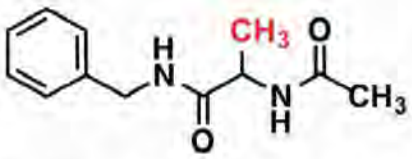
[94] *Id.* at 5:41-6:35; 5:30-32; 6:45-46.

[95] *Id.* at 5:27-28.

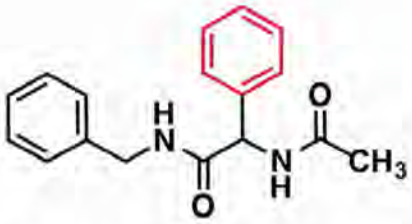
[96] In this case, the D-enantiomers for which data was reported correspond the R configuration, which a POSA would have known.

[97] *Id.* at 12, Tbl. 1.

119. Kohn 1988 reports studies of anticonvulsant potency of the racemates and individual enantiomers of N-acetyl-alanine-N-benzylamide ("AAB") and N-acetyl-phenylglycine-N-benzylamide ("APB"), which are depicted below, and which differ only in the substituent attached to the stereocenter (methyl in AAB and phenyl in APB):[98]



N-acetyl-DL-alanine-N-benzylamide (DL-AAB)



N-acetyl-DL-phenylglycine-N-benzylamide (DL-APB)

The main conclusions of the study were that "the anticonvulsant activity is due to the D-stereoisomer,[99] and the L-stereoisomer is virtually inactive as an anticonvulsant."[100]

[98] Ex. 1021 at 371, abstr.

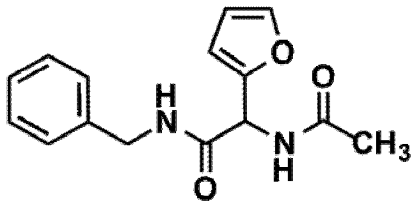
[99] In this case, the D-stereoisomers referred to correspond to the R configuration, which a POSA would have known.

[100] *Id.* at 371, abstr.; *see also id.* at 372-74.

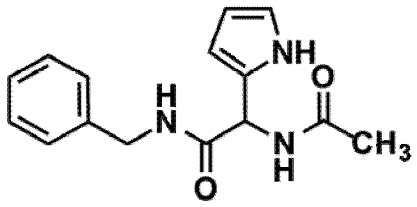
h. Harold Kohn et al., Preparation and Anticonvulsant Activity of a Series of Functionalized α-Aromatic and α-Heteroaromatic Amino Acids, 33 J. Med. Chem. 919-926 (1990) ("Kohn 1990")

120. Kohn 1990 is prior art to the '551 patent because it published in 1990, which is prior to March 15, 1996.

121. The Kohn 1990 study used APB as a starting point and explored replacement of the phenyl group attached to the α-carbon by a number of other aromatic or heteroaromatic groups.[101] After evaluating 23 analogs of APB, Kohn and coworkers concluded that "the most active compounds are (R,S)-α-acetamido-N-benzyl-2-furanacetamide (2g) and (R,S)-α-acetamido-N-benzyl-2-pyrroleacetamide (2i)," the structures of which are shown below:[102]



Kohn 1990 Furanyl Derivative (2g)



Kohn 1990 Pyrrolyl Derivative (2l)

On the basis of this SAR study, Kohn and coworkers concluded that "[e]vidence is presented that placement of a relatively small, electron-rich, heteroaromatic moiety at the α-site leads to a substantial enhancement in the anticonvulsant activity of the

[101] Ex. 1022 at 919.

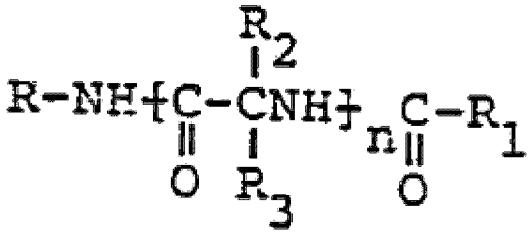
[102] *Id.* at 919 abstr., Tbl. I.

drug candidate" relative to APB.[103] As with AAB and APB, the "[e]valuation of the two individual enantiomers of 2g demonstrated that the anticonvulsant activity resided in the R stereoisomer."[104]

i. European Patent Application No. 0 263 506 ("The '506 application")

122. The '506 application is prior art to the '551 patent because it published on April 13, 1988, which is prior to March 15, 1996.

123. The '506 application discloses "compounds having central nervous system (CNS) activity which are useful in the treatment of epilepsy…having the following general formula:"[105]



The '506 application further discloses that R_2 can include lower alkyl groups, substituted or unsubstituted, where the substitution can be an alkoxy group, which

[103] *Id.* at 919, 922.

[104] *Id.* at 919, 922, Tbl. III.

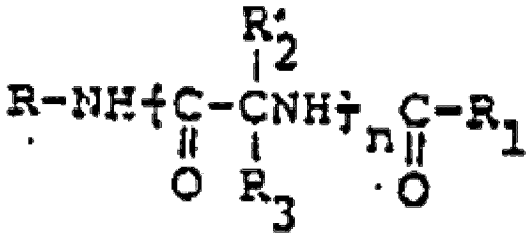
[105] Ex. 1023 at 2:2-10; *see also id.* 3:18-21, 8:8-10.

would include the methoxymethyl of lacosamide.[106] The '506 application reported the same data discussed above demonstrating that the D-enantiomer[107] possessed about tenfold greater anticonvulsant activity than the L-enantiomer.[108]

j. European Patent Application No. 0 400 440 ("The '440 application)

124. The '440 application is prior art to the '551 patent because it was published on December 5, 1990, which is prior to March 15, 1996.

125. The '440 application discloses "compounds exhibiting central nervous system (CNS) activity which are useful in the treatment of epilepsy…[of] the following general formula:"[109]



According to the '440 application, these compounds "exhibit excellent anticonvulsant activity."[110]

[106] *Id.* at 2:51 – 3:14.

[107] In this case, the D-enantiomers for which data was reported correspond to the R configuration, which a POSA would have known.

[108] *Id.* at 18, Tbl. 1.

[109] Ex. 1024 at 3:2-12.

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