[redacted] 23-95 # 152-102 44-103 110-115 12c

1202

PATENT
20-3326P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Ikutaro SAJI et al.

Serial No. : 08/113,320 Group: 1202

Filed : August 30, 1993 Examiner: R. Bond

For : IMIDE DERIVATIVES AND THEIR PRODUCTION AND USE

AMENDMENT

Commissioner of Patents
and Trademarks
Washington, D. C. 20231

December 29, 1994

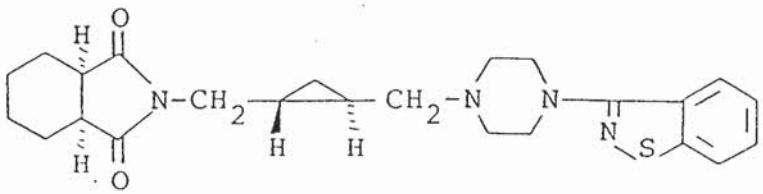
Sir:

In response to the Office Action dated August 30, 1994, the due date for response having been extended one (1) month to December 30, 1994, the following amendments and remarks are respectfully submitted in connection with the above application.

In The Claims:

Please add new claims 28 and 29 as follows.

15 28. The imide compound of the formula:



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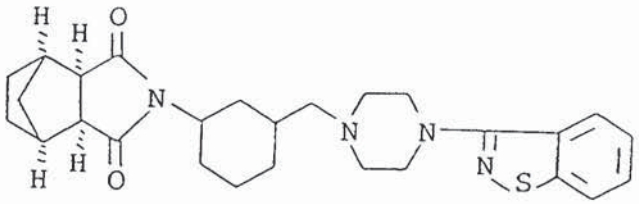
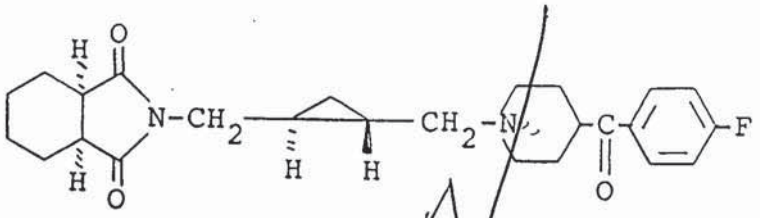
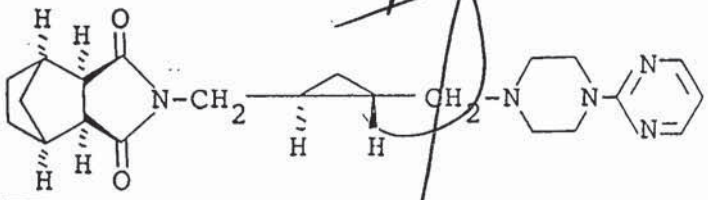
-- 16. The imide compound of one of the following formulae:





.HCl



.HCl

Remarks

Claims 11-27 have been rejected under 35 U.S.C. 112, first paragraph. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

While the Examiner has urged that the specification fails to adequately teach "how to use" the claimed subject matter, applicants submit that the specification does indeed provide a fully enabling disclosure. Pages 23 and 24 of the specification specifically describe pharmaceutical compositions and dosages for use of the compounds. Numerous examples are then provided for how

to make various of the compounds encompassed by the claims. Applicants submit that these and other teachings in the specification fully enable one skilled in the art how to use the compounds as presently claimed and in full compliance with 35 U.S.C. 112.

However, from the Examiner's discussion of the rejection, it appears that the Examiner's true criticism is an alleged lack of proof of utility, properly asserted under 35 U.S.C. 101. Assuming this to be the true basis for the Examiner's rejection, applicants submit that the test results in the specification, taken together with the knowledge of one skilled in the art, sufficiently establishes the utility of the claimed compounds as required under 35 U.S.C. 101.

The compounds of the present invention are useful as anti-psychotic agents (neuroleptic agents, anti-anxiety agents) particularly useful for therapy of schizophrenia, senile insanity, manic-depressive psychosis, neurosis, and similar disorders. Various drugs are commercially available for treatment of these conditions and applicants submit that the test results in the specification show that the compounds of the present invention have in vitro and in vivo activities similar to those of the known compounds, such that one skilled in the art would accept the asserted utility for the claimed compounds. The following discusses the evidence with respect to four major categories of therapy.

1. Schizophrenia

It is well known to those skilled in the art that anti-psychotic drugs block the dopamine D_2 receptors in the brain, to thereby effect improvement in the symptoms of schizophrenia, such as improvements in excitation, hallucination and delusions. This phenomenon is known in the art as the "dopamine hypothesis".

1.1 **Philip Seeman: SYNAPSE 1, 133-152 (1987)** (Exhibit 1) discusses this dopamine hypothesis of schizophrenia and reports the results of tests to determine the affinity of various known anti-psychotic drugs to the dopamine D_2 receptors. The authors report that "the clinical doses of neuroleptics for anti-psychotic action correlated very well with their ability to block the D_2 receptors" (see the first full paragraph in the right hand column of page 137 and the results reported in Figure 2 of the publication).

The compounds of the present invention have similarly been shown to have high affinity to the dopamine D_2 receptors. Pages 24-26 of the specification report the results of the dopamine D_2 receptor binding assays for the compounds of the present invention and show that the compounds are even more active than the known compound haloperidol. Applicants submit that these test results would be sufficient to one skilled in the art to establish that the claimed compounds have anti-psychotic activity and would be useful for the treatment of schizophrenia.

1.2 **Philip Seeman: Pharmacological Reviews, 32 (3), 229-230, 232 (1981)** (Exhibit II) also discusses the hypothesis of

neuroleptic blockade of dopamine receptors. In particular, at page 232, the left hand column, line 9 from the bottom, through the right hand column, line 5, the publication discusses that compounds having anti-psychotic activity (i.e. neuroleptics) inhibit the action of animals caused by the administration of dopamine-mimetic drugs, such as apomorphine.

Similarly, page 26, line 5 through page 28 of the present specification reports the results of in vivo tests on the anti-climbing activity of the claimed compounds, such climbing action being typical of the action caused by apomorphine as a dopamine-mimetic drug. Applicants submit that these test results additionally support the utility of the claimed compounds as anti-psychotic drugs against schizophrenia, establishing the utility additionally by means of in vivo tests.

2. Senile Insanity

Senile insanity is a psychotic disorder of aging humans, and various anti-psychotic agents are frequently used for treatment of the disorder. **Thomas A. Ban: Psycho Pharmacology for the Aged, 42-43 and 62-73 (1980)** (Exhibit III) states that "it is estimated that one out of every three individuals over 60 years of age in the United states is treated with one or more psychotropic drugs" (cf. Chapter IV, page 42, first paragraph). Thus, many aged people are treated with psychotropic drugs for therapy of this psychotic disorder. Page 62, line 6 from the bottom to page 73 in the same

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