

SYNTHESIS OF TRANS-8-CHLORO-5-METHYL-1-[4-(PYRIDIN-2-YLOXY)-
CYCLOHEXYL]-5,6-DIHYDRO-4H-2,3,5,10B-TETRAAZA-BENZO[E]AZULENE AND
CRYSTALLINE FORMS THEREOF

Field of the invention

5 The present invention provides processes to manufacture substituted 1-[4-(Pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulenes. Also disclosed are compounds useful as intermediates in the methods of the invention.

Background of the invention

10 Autistic Spectrum Disorders (ASD) are a clinically heterogeneous condition characterized by defects in socialization and language. ASD include a wide range of abnormalities including a genuine incapacity to organize affective relations, behavioral anomalies in reciprocal social interactions, verbal and non-verbal communication, limited interest in the surrounding environment associated with stereotyped movements and repetitive plays (Bourreau *et al*, 2009)¹. Research to date indicates that a genetic predisposition may be involved, but also environmental
15 factors have to be taken into consideration (Bourgeron, 2009)². There is at present no efficient biological/ pharmaceutical treatment of ASD.

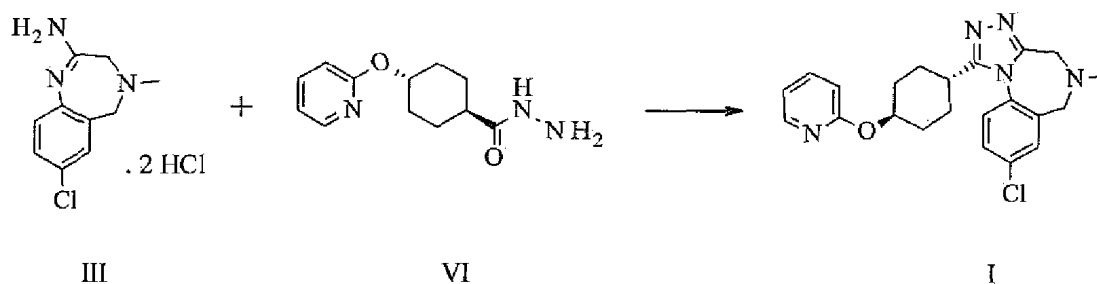
1-[4-(Pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulenes have previously been described in the art³.

20 Further WO2004074291 and WO2005068466⁴ describe triazole compounds and a process of manufacturing the same.

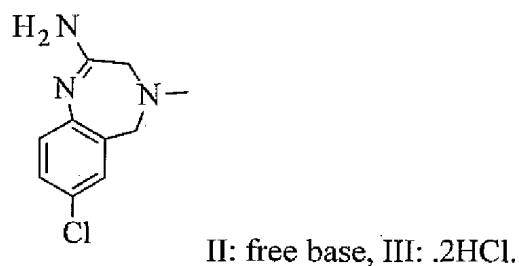
It has surprisingly been found that by using the processes according to the present invention 8-chloro-5-methyl-1-[4-(2-pyridyloxy)cyclohexyl]-4,6-dihydro-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine and its pharmaceutically acceptable salts can be prepared more economically with less process steps under moderate reaction conditions with an outstanding
25 yield. Further, crude intermediate products can mostly be used in subsequent reaction steps without the need of any additional purification steps.

Further, several forms have been identified and it has surprisingly been found that form F is the most preferred one.

In one aspect, there is provided a process to synthesize a compound of formula I, comprising reacting a compound of formula III with a compound of formula VI



5 In another aspect, there is provided an intermediate compound II or a salt thereof III:

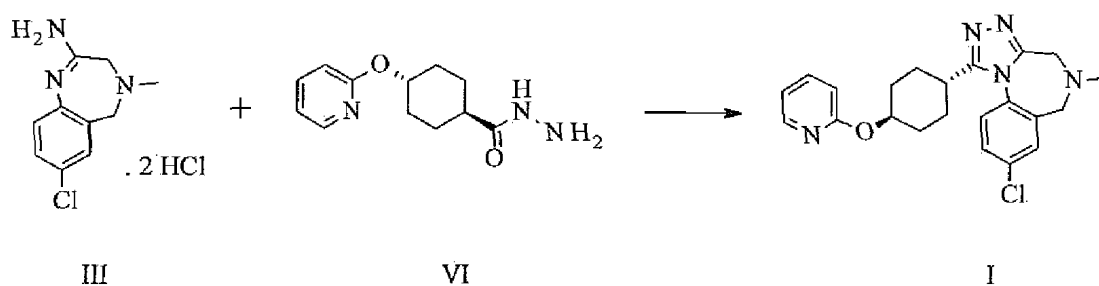


Definitions

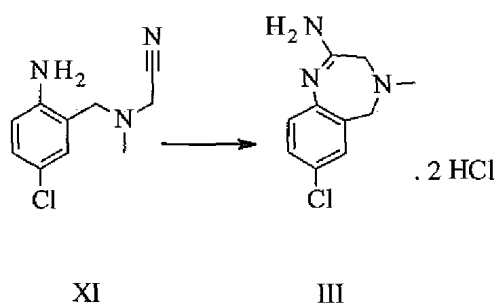
The following definitions of the general terms used in the present description apply
 10 irrespectively of whether the terms in question appear alone or in combination with other groups.

Claims

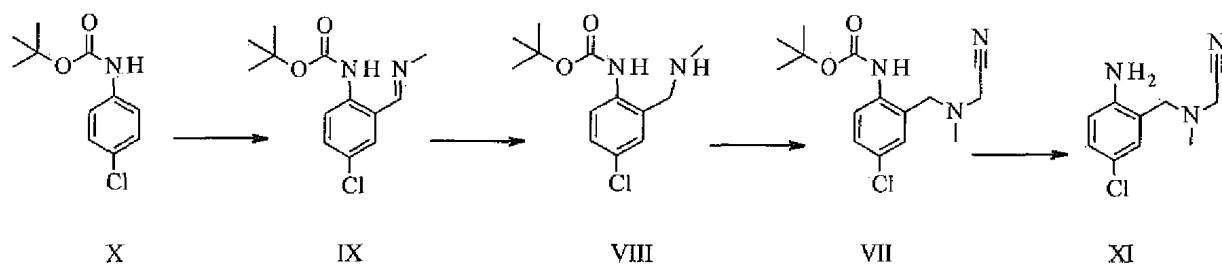
1. A process to synthesize a compound of formula I, comprising reacting a compound of
5 formula III with a compound of formula VI



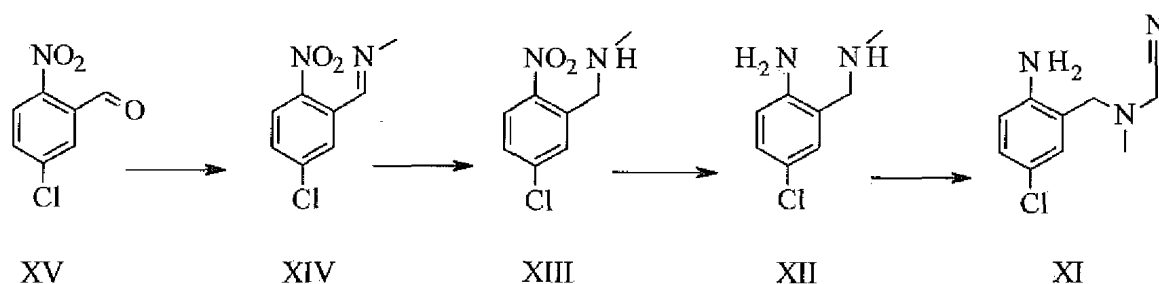
2. The process according to claim 1, further comprising reacting a compound of formula XI to a compound of formula III:



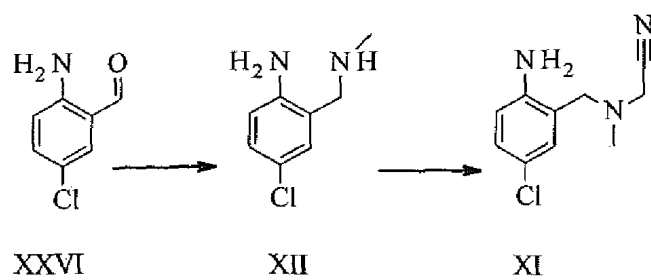
5 3. The process according to any one of claims 1-2 further comprising reacting a compound of formula X to a compound of formula XI or a pharmaceutically acceptable salt thereof via the following steps:



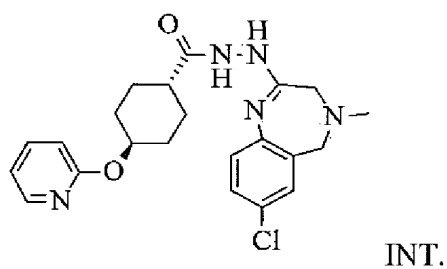
10 4. The process according to any one of claims 1-2 further comprising reacting a compound of formula XV to a compound of formula XI or a pharmaceutically acceptable salt thereof via the following steps:



5. The process according to any one of claims 1-2 further comprising reacting a compound of formula XXVI to a compound of formula XI or a pharmaceutically acceptable salt thereof via the following steps



6. The process according to any one of claims 1-2, whereby a compound of formula INT is formed as intermediate:



7. Intermediate compound II or a salt thereof III:

