

Racetam candidates based on "Pyrrolidone" Dimers

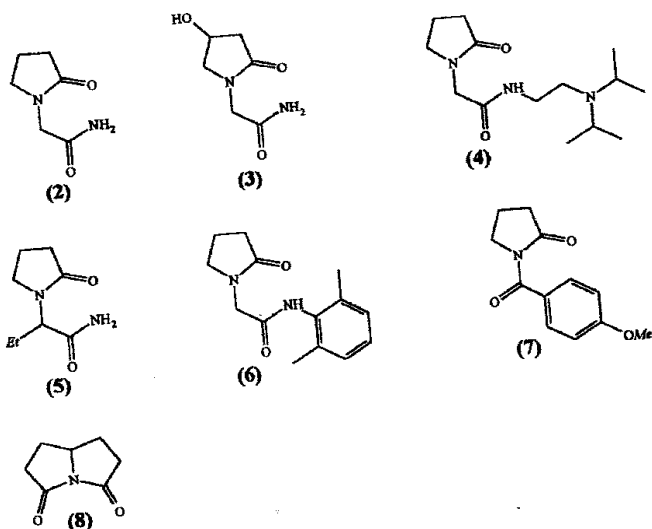
By: Robert B. Login

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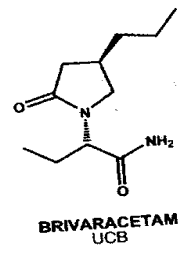
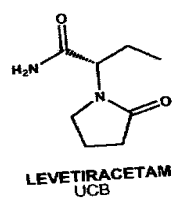
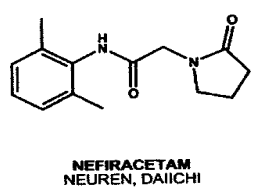
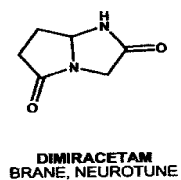
Racetams are pyrrolidone based drugs that can function as stimulants (oxiracetam and phenylpiracetam) and anticonvulsants (levetiracetam and seletracetam). Piracetam, the first one, is considered to be a nootropic (Margineanu, *Revue des Questions Scientifiques*, 2011, 182(I): 33-52) that improves cognition. Reversal of dementia is the real goal of this chemistry.

The discovery of piracetam in the 1960's led to the search for even more effective nootropics. All that showed activity contained the pyrrolidone ring usually as N-substituted derivatives but many other substitutions have been tried. The structures below are reproduced from Gouliarov and Senning (*Brain Research Reviews*, 19, 1994, pp180-222)

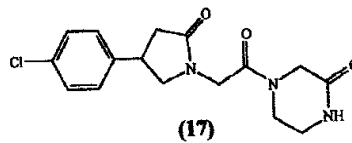
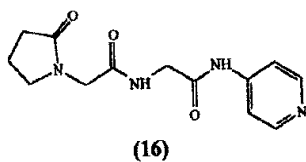
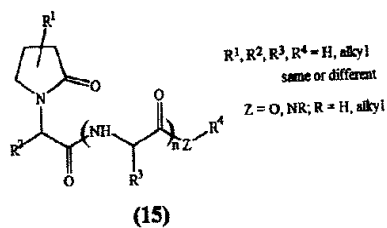
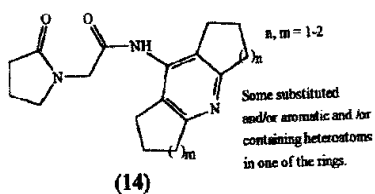
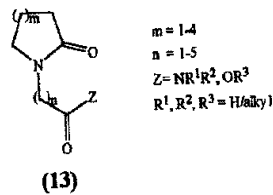
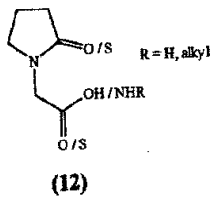
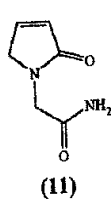
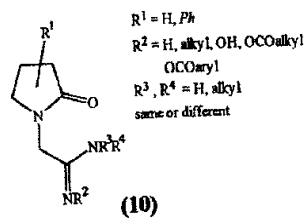
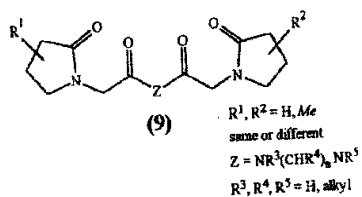
these (see also the nootropic monographs)

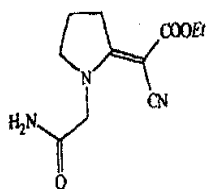


Piracetam(2) oxiracetam(3) pramiracetam (4) etiracetam (5) nefiracetam (6)
aniracetam(7) rolziracetam (8) and more recently developed:
levetiracetam, brivaracetam, dimiracetam, nefiracetam

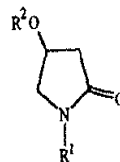


Many other pyrrolidone containing structures have been evaluated. For example;





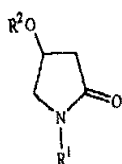
(18)



$R^1 = Et, allyl, CH_2CCH, CH_2COOEt, CH_2CONH_2,$
 $CH_2CH_2CONH_2, CONHEt, CH(allyl)CONH_2$

$R^2 = H, Me, allyl, Ac, benzoyl$; all with (±)-configuration

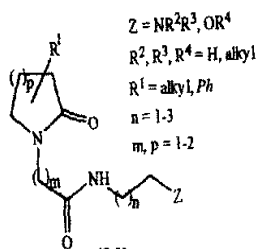
(19)



$R^1 = H, Ac, CH_2COOH, CH_2COOEt, CH_2CONH_2,$
 $CH_2CH_2CONH_2$

$R^2 = H, allyl, Ac, benzoyl$; all with (±)-configuration

(20)



$Z = NR^2R^3, OR^4$

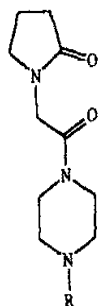
$R^2, R^3, R^4 = H, alkyl$

$R^1 = alkyl, Ph$

$n = 1-3$

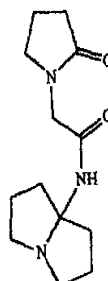
$m, p = 1-2$

(21)



$R = H, alkyl, aryl,$
 $COalkyl, COOalkyl$

(22)



(23)

Fig. 3 (continued).

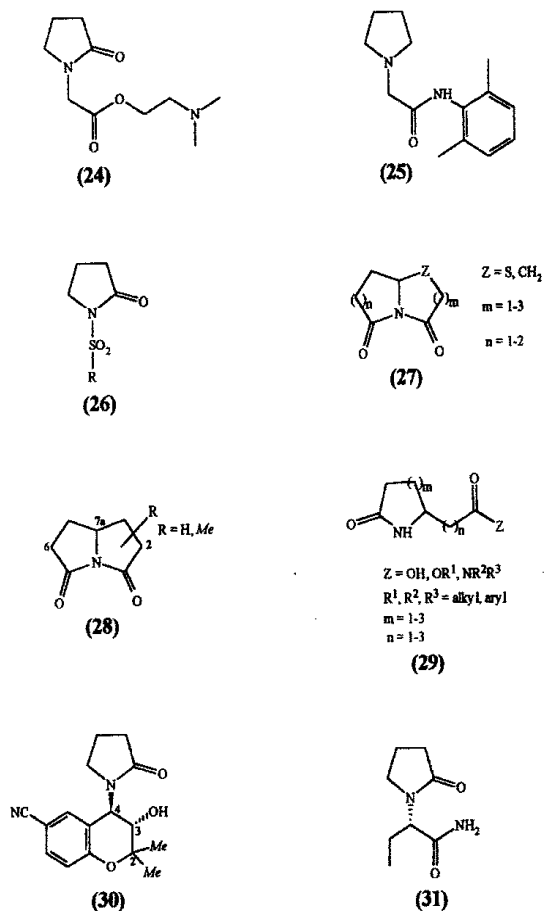
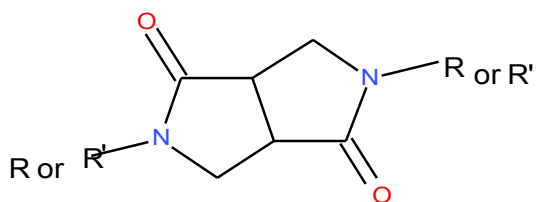


Fig. 3 (continued).

When this review was published, the authors found 660 2-oxopyrrolidineacetic acid variants. Only those with the “racetam” name have become drug candidates.

The Dimer “pyrrolidones” I described in previous reports (see pdfs on my web page rloginconsulting.com) can be reacted with reagents that can produce derivatives like the racetam drugs or their congeners. For example:

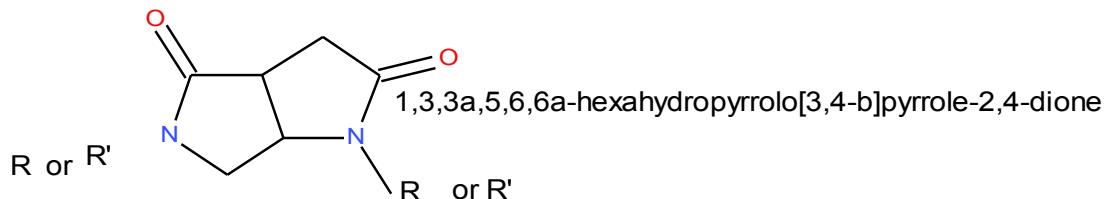


R=R'=Any of the N-R derivatives of the Racetams

R≠R'=" " "

R or R' can be H

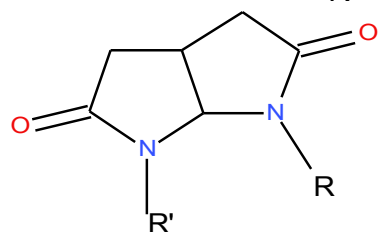
2,5-alkyl-1,3a,4,6a-tetrahydropyrrolo[3,4-c]pyrrole-3,6-dione



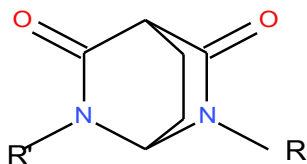
R or R'

1,3,3a,5,6,6a-hexahydropyrrolo[3,4-b]pyrrole-2,4-dione

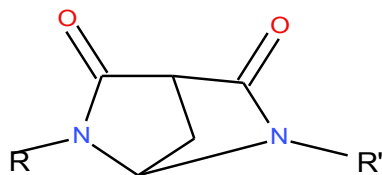
R or R'



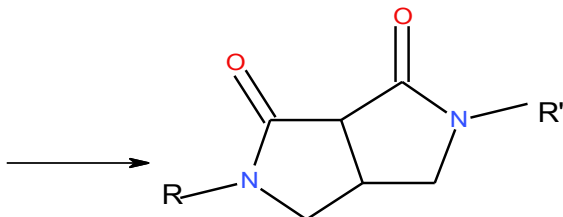
1,3,3a,4,6,6a-hexahydropyrrolo[2,3-b]pyrrole-2,5-dione



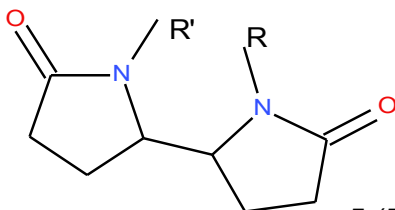
3,5-diazabicyclo[2.2.2]octane-2,6-dione



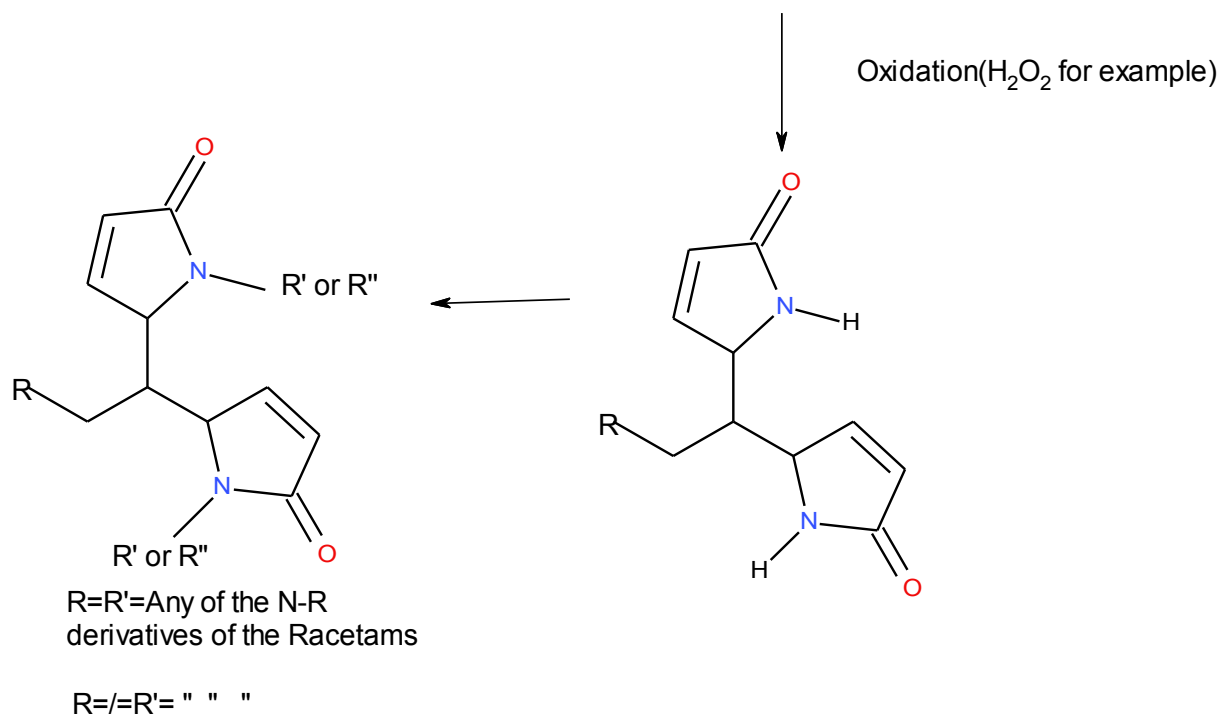
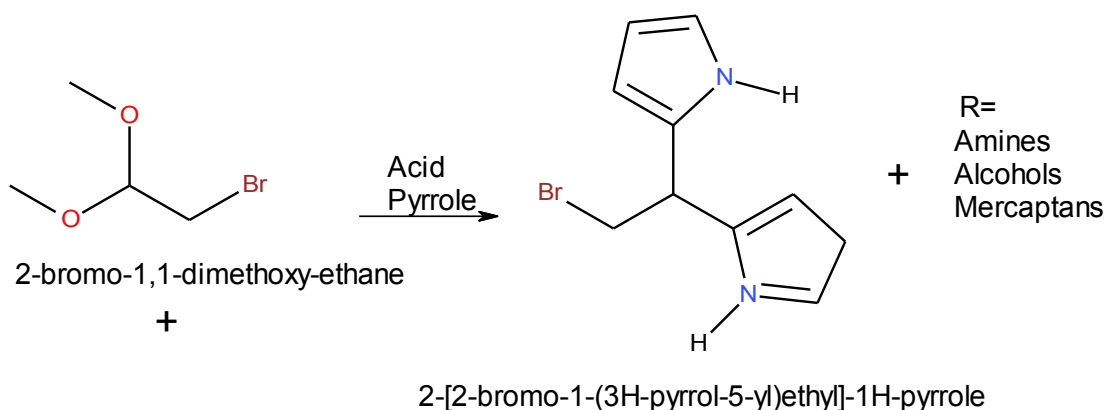
3,5-diazabicyclo[2.2.1]heptane-2,6-dione



1,2,3a,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole-3,4-dione



5-(5-oxopyrrolidin-2-yl)pyrrolidin-2-one



R or R' can be H

The above scheme shows how potentially to prepare pyrrolinones from pyrromethanes. Pyrrolinones shown are known Michael acceptors therefore, unique 4-pyrrolidone derivatives can be prepared. I would think that with the scourge of dementia and Alzheimer, no structure should be ignored until a cure is found.

The above shows that it is possible to have bridge head isomers where the protons are either cis or trans. In addition, enantiomers are possible for some of the above. My proposed synthesis methods most likely will produce mixtures.

As an example of how N-substituted pyrrolidones are synthesized let's consider the synthesis of piracetam (N-acetamide pyrrolidone derivative) can be readily achieved by known reactions (For example; M. Verona et. al. Chem of Heterocyclic Compounds, Vol. 48, No. 5, p.720, 2012). In this case, the N sodium salt of the pyrrolidone reacts with chloroacetonitrile or haloacetamide or 2-bromoacetate etc. in each case further well known reactions leads to acetamide derivative. Likewise any of the other racetams N-derivatives can be reproduced with the Dimer "Pyrrolidones" by identical or similar reactions.

In conclusion, the extensive current racetam literature reveals the tremendous value of pyrrolidone derivatives. What is most enlightening, is the growing volume of literature revealing the search for more effective derivatives. This is driven by the scourge of dementia afflicting our aging population.

Claims:

1. Dimer "pyrrolidones" comprising the structures prepared as shown in provisional patent application 61987222.
2. The said dimer "pyrrolidones" exhibiting nootropic activity.
3. Pharmaceutical formulations of said dimer "pyrrolidones" comprising excipients such as solvents, solubilizers, tableting auxiliaries all designed by those of ordinary skill in the art for delivering active ingredients in a safe acceptable formulation suitable for human beings.
4. The processes revealed in 61987222 for the synthesis of said dimers of claim 1.
5. N-substituted derivatives of said dimer "pyrrolidones" with identical R groups selected from the racetams singly or in combination from different racetams.
6. The compounds of claim 5 wherein the "pyrrolidone" nitrogens are completely or partially substituted with said racetams derivatives.