Synthesis and pharmacological evaluation of *N*-substituted 6,7-benzomorphans

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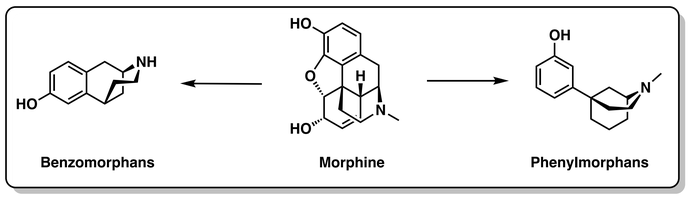
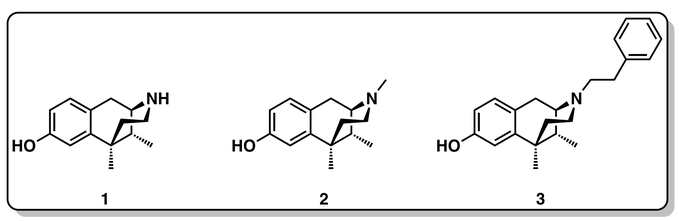
Introduction

The structure of morphine can be made smaller and simpler and still retain its activity. One such class of less complex compounds are the 6,7-benzomorphans. Some of them were found to be much more potent than morphine and were thought to have fewer side effects.[1,2]



Structural relationship between morphine, benzomorphans and phenylmorphans

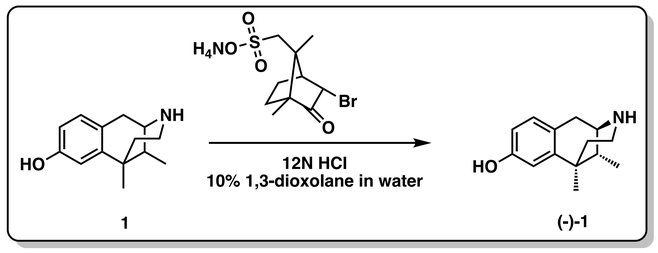
Various studies have shown that the nature of the substituent at the secondary nitrogen of normetazocine (**1**) affects the biological response of the molecule. Metazocine (**2**) was found to be just as potent as morphine. Replacing the methyl group with a saturated alkyl chain like ethyl, propyl and butyl resulted in loss of analgesia. However, phenazocine (**3**) in which the methyl group is replaced by a phenethyl substituent was found to be 20 times more potent than morphine.[3]



In this work, a series of (-)-*N*-phenethyl-6,7-benzomorphans have been synthesized with electron withdrawing or donating substituents on the aromatic ring of the *N*-phenethyl moiety. The compounds were examined for agonist activity in a cAMP assay.

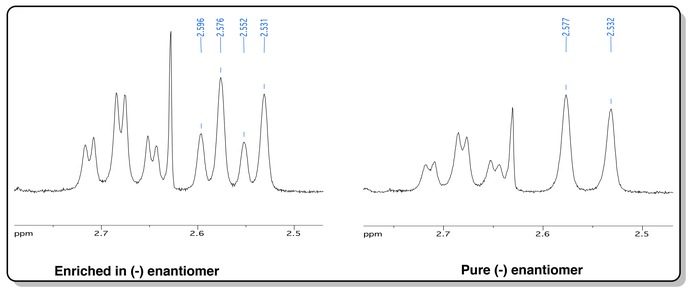
Synthesis

Optical resolution



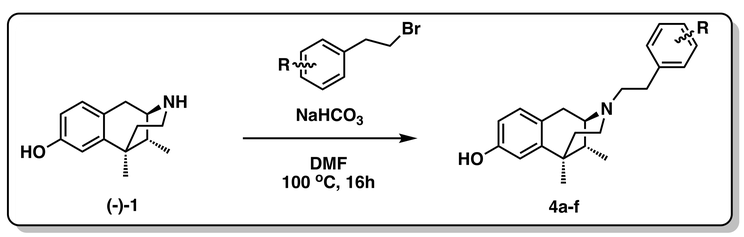
Optical resolution of normetazocine[4]

Optical purity of the product was determined by NMR using (R)-methylbenzylisocyanate as a chiral derivatizing agent.



Comparison of NMR after adding (*R*)-methylbenzylisocyanate to enriched and pure product

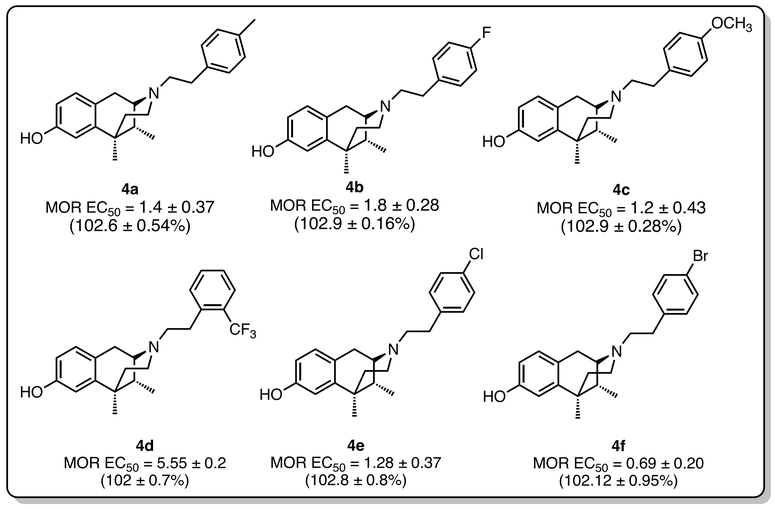
N-alkylation with substituted phenethyl bromides



Synthesis of substituted N-phenethyl-6,7-benzomorphans

Optically resolved (-)-**1** was then subjected to N-alkylation with various substituted phenethyl bromides to give a series of substituted N-phenethyl analogs of 6,7-benzomorphans.

μ opioid receptor (MOR) activity



MOR activity of **4a-f** in cAMP assay

4a-f were tested for MOR activity in a cAMP assay. All analogs were found to be highly potent, fully efficacious μ opioid receptor (MOR) agonists with the exception of the *ortho* trifluoromethyl substituted analog (**4d**) that had potency similar to that of morphine. The *para* bromo substituted analog (**4e**) was 7 times more potent than morphine.

Conclusion

- A series of substituted N-phenethyl analogs **4a-f** were prepared.
- Substituents at the *para* position led to more potent compounds.
- Substituents at the *ortho* position led to lower potency.
- Synthesis of other *ortho* and *meta* substituted analogs is currently underway.

REFERENCES

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3.) Weijland, J., Orahovats, P. D., Sullivan, A. P., Purdue, G., Heath, F. K., Pfister, K., J. Chem. Soc, **1956**, 78, 2342.
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