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Design and synthesis of 4-benzylpiperidine carboxamides as dual serotonin and norepinephrine reuptake inhibitors

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ABSTRACT

A series of 4-benzylpiperidine carboxamides were designed and synthesized, and tested for their dual (serotonin and norepinephrine) reuptake inhibition. The synthesis of 4-benzylpiperidine carboxamides involved two main steps: amidation and substitution. Derivatives with 3 carbon linker displayed better activity than with 2 carbon linker. 4-Biphenyl- and 2-naphthyl-substituted derivatives **7e** and **7j** showed greater dual reuptake inhibition than standard drug venlafaxine HCl.

1. Introduction

Depression is a common and severe illness.[1,2] Chronic sadness, loss of interest, disruption in sleep patterns, fatigue and sometimes suicidal intension are common features observed in depressed individuals.[3–5] The primary cause of depression is deficiency of monoamine neurotransmitters, serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in the brain. Monoamine reuptake inhibitors maintain the concentration of neurotransmitters in the brain through inhibition of presynaptic monoamine reuptake transporter.[6–10] Drugs that inhibit dual (5-HT and NE) neurotransmitters reuptake are prescribed for the treatment of several central nervous system (CNS) illnesses including depression.[11–16]

Drawbacks of the selective 5-HT reuptake inhibitors fluoxetine (**1**), paroxetine (**2**) and sertraline (**3**) include delayed onset of action and side effects of insomnia and sexual dysfunction (Fig. 1).[17] Trazodone (**4**), which has a different chemical scaffold than the other antidepressant drugs, works as a 5-HT reuptake inhibitor and is devoid of these limitations and side effects.[18,19] The drug essentially consists of heterocyclic amine (A), linker (B) and aromatic region (C) (Fig. 2). Arylpiperazine-containing pyrimidine 4-carboxamide derivatives **5** that have three fundamental components also display good binding affinity for 5-HT transporter and may work as serotonin reuptake inhibitors.[20] Furthermore, arylalkanol-piperidine derivatives **6** with similar structural moieties also possess serotonin and norepinephrine reuptake inhibition.[21] Thus, considering the structure of trazodone, **5** and **6**, we designed 4-benzylpiperidine carboxamides **7**, **8** as possible dual reuptake inhibitors (Fig. 2). 4-Benzylpiperidine carboxamides **7** and **8** which differ in the length of linker were considered to explore their impact on inhibition of neurotransmitters reuptake. The synthesis, biological evaluation and detailed structure–activity relationship (SAR) of the 4-benzylpiperidine carboxamides are detailed below.

2. Chemistry

Various aromatic carboxylic acids **9a–9i** were refluxed overnight with excess thionyl chloride and the residue obtained by evaporating the solvent was further reacted with 3-bromopropylamine hydrobromide or 2-chloroethylamine hydrochloride in the presence of triethylamine (TEA) to give different amides **10a–10i** and **11a–11i** (Scheme 1). Alternatively, amidation reaction between aromatic carboxylic acid **9j–9l** and 3-bromopropylamine hydrobromide or 2-chloroethylamine hydrochloride using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI·HCl) as a coupling reagent gave corresponding amides **10j–10l** and **11j–11l**. The substitution reaction of **10a–10l** and **11a–11l** with 4-benzylpiperidine gave carboxamides derivatives **7a–7l** and **8a–8l**.

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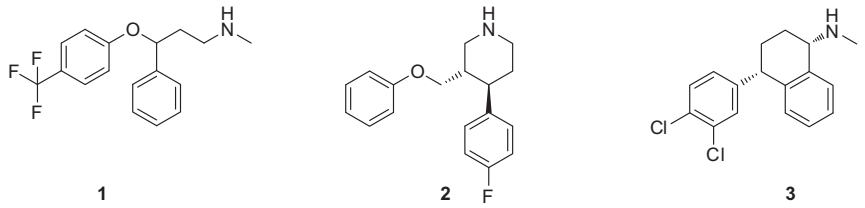


Figure 1. Some marketed antidepressants (selective 5-HT reuptake inhibitors)—fluoxetine (**1**), paroxetine (**2**) and sertraline (**3**).

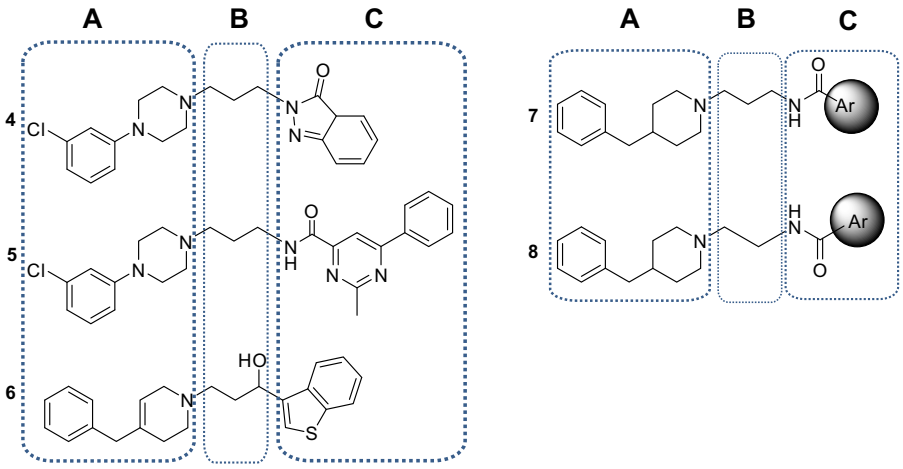
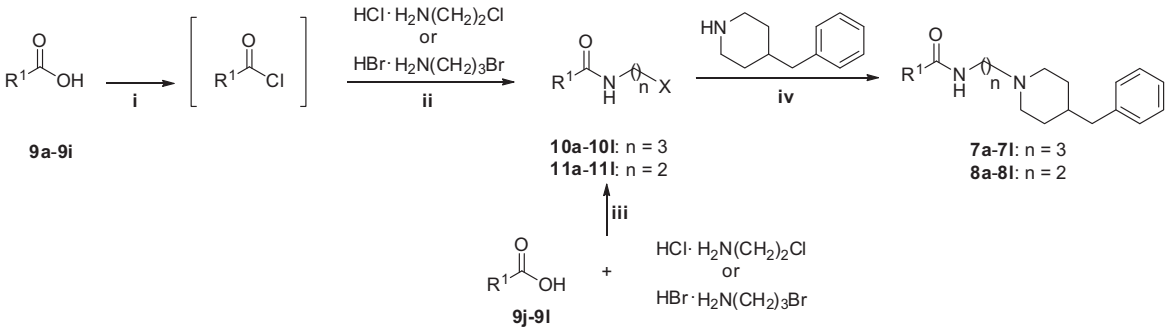
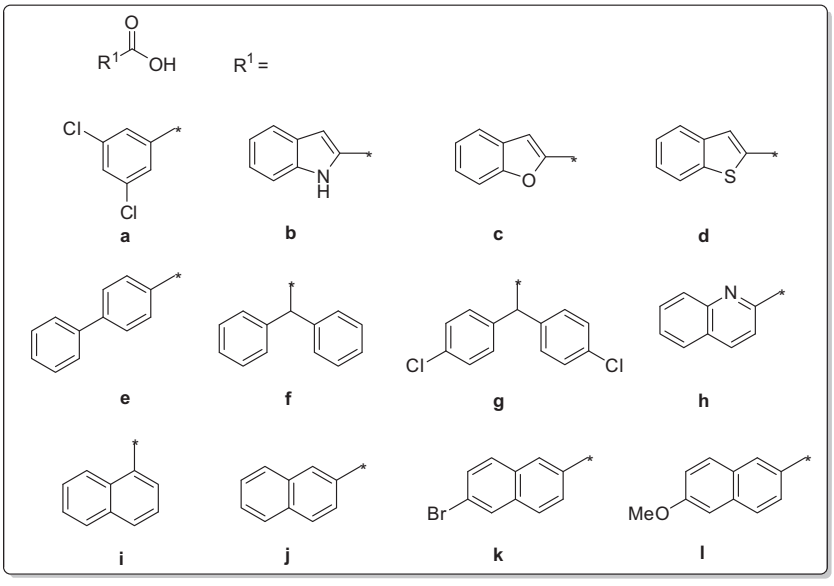


Figure 2. Design of 4-benzylpiperidine carboxamides.





Scheme 1. Reagents and conditions: (i) $SOCl_2$, benzene/toluene/tetrahydrofuran, reflux; (ii) CH_2Cl_2, TEA, 0 °C–rt; (iii) EDCI·HCl, DMAP, TEA, rt; (iv) DMSO, TEA, 100 °C.