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Synthesis of five and six-membered heterocycles bearing an arylpiperazinylalkyl side chain as orally active antinociceptive agents

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ABSTRACT

A number of heterocycles bearing an arylpiperazinylalkyl side chain and structurally related to the previously described lead **ET1** (4-amino-6-methyl-2-[3-(4-*p*-tolylpiperazin-1-yl)propyl]-5-vinylpyridazin-3(2*H*)-one) was synthesized and tested for their antinociceptive activity in Writhing Test. Many compounds, tested at doses of 20–40 mg/kg po were able to reduce the number of abdominal constrictions by more than 47% and, in same cases, the potency is comparable to lead **ET1** as for **5e**, **24a**, **27b** and **27c**. The analgesia induced by the active compounds was completely prevented by pretreatment with α_2-antagonist yohimbine, confirming the involvement of the adrenergic system in the mechanism of action for these new compounds.

1. Introduction

Pain relief continues to be an important medical and community problem and millions of people worldwide use drugs for different pain intensity. The identification of new analgesic agents with limited side effects, as for acute and chronic pain, represents an important research field for pharmaceutical industry and academic. In fact the two major classes of analgesic drugs, the traditional non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, showed severe side effects.

NSAIDs, primarily used for the treatment of mild to moderate inflammatory pain[1] induce gastrointestinal lesions, such as ulcerations and perforations, nephrotoxicity and inhibition of platelet aggregation.[2] Development of potent and selective COX-2 inhibitors[3] only partially solved the problem, since recent studies correlated the use of these inhibitors with an elevated risk of acute myocardial infarction.[4,5] On the other hand, the clinical use of opioid, for moderate to severe pain, is associated with very strong and use-limiting side effects, including respiratory depression, constipation, tolerance and physical dependence.[6]

A particular search field regards compounds active on neuropatic pain, which is often resistant to conventional analgesic drugs.[7] Recently defined by the International Association for the Study of Pain (IASP) as 'pain caused by a lesion or disease of the somatosensory system',[8] neuropathic pain is a complex phenomenon characterized by burning pain coupled with hyperalgesia and allodynia involving both the peripheral and central nervous system.[9] At present, first-line drugs recommended for this pathology include anticonvulsant, as gabapentin and pregabalin,[10,11] antidepressants, as amitriptyline and nortriptyline[12,13] and serotonin-norepinephrine reuptake inhibitor antidepressant as duloxetine[14,15] and milnacipran[16] as well as compounds belonging to different therapeutic classes.[17,18]

Our studies in the field of analgesic agents let us to identify a large number of potent compounds, with pyridazine scaffold[19–28] and the most interesting term is **ET1** (Fig. 1), belonging to the series of arylpyperazinylalkyl pyridazinones.[28] It results a potent and orally active antinociceptive agent showing an ED_{50} = 0.5 mg/kg in the hot plate test and a comparable activity in the tail flick test (ED_{50} = 0.8 mg/kg). The adrenergic system is involved in the analgesic activity of **ET1** as demonstrated by its ability to act as α_2AR agonist.[28] Recent studies show its activity in a model of peripheral neuropathy (data not shown).

We report here the synthesis and the antinociceptive evaluation of a series of pyridazinones derivatives as elaboration of the lead **ET1**. At the same time, we designed and synthesized new compounds bearing an arylpiperazinyl moiety linked to different heterocyclic system through alkyl chains.

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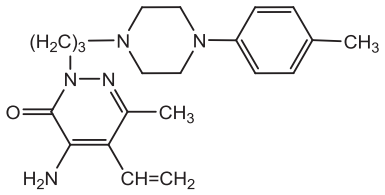


ET$_1$

4-Amino-6-methyl-2-[3-(4-*p*-tolylpiperazin-1-yl)propyl]-5-vinylpyridazin-3(2H)-one

Figure 1.

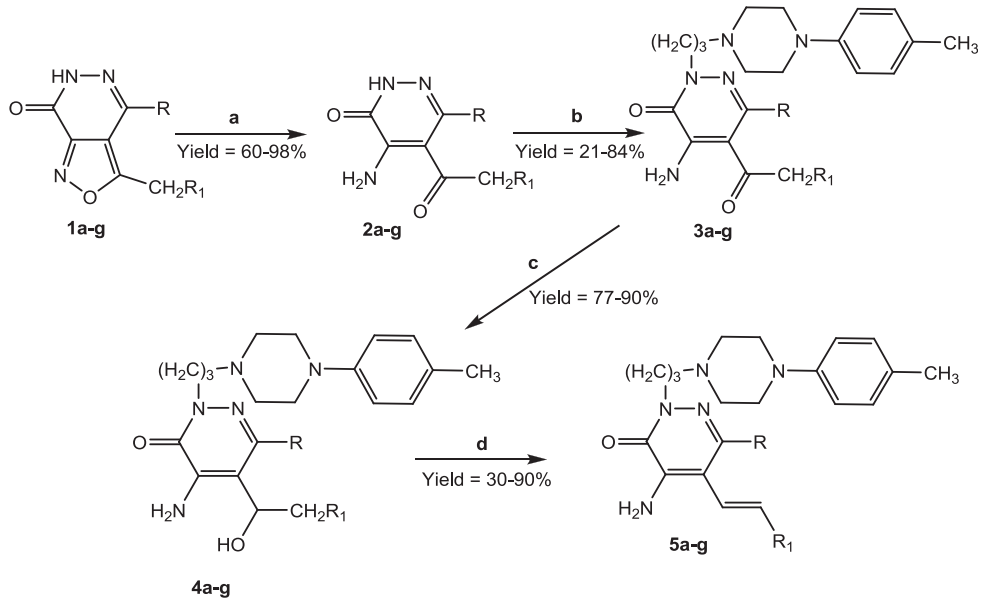
2. Chemistry

All new compounds were synthesized as reported in Schemes 1–4 and the structures were confirmed on the basis of the analytical and spectral data.

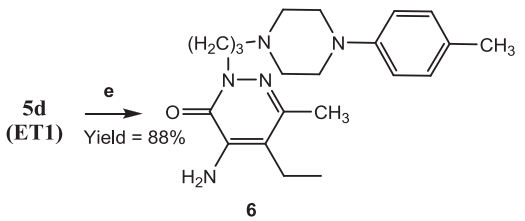
Scheme 1 shows the synthetic pathway affording the final compounds **5a–g** (**5d**[28], alias **ET1**) and **6**, in which we reported modifications at position 5 or 6 of lead **ET1**. The 4-amino-5-acyl derivatives **2a–g** (**2d–g**[29,30]) were obtained starting from isoxazolo[3,4-*d*]pyridazinones **1a–g**[30–32] by reductive cleavage with ammonium formate and Pd/C and represent the key intermediates of the reported synthetic pathway. The alkylation of **2a–g** with 1-(3-bromopropyl)-4-(*p*-tolyl)-piperazine[28] under standard conditions afforded compounds **3a–g** (**3d**[28]) which were reduced with sodium borohydride in methanol to give the corresponding secondary alcohols (**4a–g**, **4d**[28]), which finally were transformed into the final 4-amino-5-vinyl derivatives **5a–g** (**5d**[28]) with polyphoshoric acid (PPA) (**5a–e**, **5g**) or with sulfuric acid adsorbed on silica gel (**5f**). The vinyl group of **5d** was further reduced with Parr instrument to afford compound **6**.

In Schemes 2 and 3 are depicted the synthesis of **ET1** analogues bearing a different N-2 basic side chain with respect to lead compound.

In Scheme 2 compounds **8a–c** were obtained from 4-amino-5-acetylpyridazinone **2d**,[29] following two different procedures: a direct alkylation of **2d** with 1-(3-bromopropyl)-4-(4-fluorophenyl)piperazine[24] in anhydrous DMF and K_2CO_3 at room temperature, for **8a**, or through the synthesis of *N*-butylbromide **7** followed by condensation with the appropriate R-arylpiperazine for **8b**,**c**. Final compounds **10a–c** were then obtained following the same synthetic procedure described in Scheme 1.



1-5	R	R_1
a	C_2H_5	H
b	nC_3H_7	H
c	nC_4H_9	H
d	CH_3	H
e	CH_3	CH_3
f	CH_3	C_2H_5
g	CH_3	nC_3H_7



Scheme 1. Reagents and conditions: (a) 10% Pd/C, $HCOONH_4$, EtOH abs, reflux, 2 h; (b) 1-(3-bromopropyl)-4-(*p*-tolyl)-piperazine, K_2CO_3, anhydrous DMF, rt, 16 h; (c) $NaBH_4$, anhydrous MeOH, rt, 1 h; (d) for **5a–e** and **5g**: PPA, 90 °C, 5 h; for **5f**: H_2SO_4 on silica gel, anhydrous toluene, 40–50 °C, 5 h, then rt, 16 h; (e) 10% Pd/C, EtOH abs, H_2, Parr, 60 PSI, 5 h.