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Synthesis of a new tetracyclic ring system: pyrrolotriazepinoquinazolinone derivatives

Tamás Földesi, András Dancsó, Gyula Simig, Balázs Volk, Mátyás Milen *

Egis Pharmaceuticals Plc., Directorate of Drug Substance Development, PO Box 100, H-1475 Budapest, Hungary

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ABSTRACT

Compounds containing a new tetracyclic ring system, pyrrolotriazepinoquinazolinone derivatives were synthesized by the reaction of 1-aryl-4-(methylsulfanyl)-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepines with substituted anthranilic acids. Both building blocks of the tetracycle, i.e., the pyrrolotriazepine and the quinazolinone unit have biological relevance.

1. Introduction

Quinazolinone (quinazolin-4(3*H*)-one, **1**, Fig. 1) derivatives constitute an important class of natural and synthetic compounds.[1–3] A number of simple or more complex quinazolinones have been isolated and characterized from various plants, animals and microorganisms.[4–7] For instance, loutonin A (**2**) extracted from the Chinese medicinal plant *Peganum nigellastrum* showed potent anti-tumor activity.[8,9] Another important representative of the quinazolinone-type alkaloids is the pentacyclic rutaecarpine (**3**), which was isolated from the dried fruit of *Evodia rutaecarpa*.[10] This herb has been used for a long time in Chinese medical practice as a remedy for cholera, dysentery and worm infestations.[11] Quinazolinobenzodiazepine alkaloids have been isolated from several fungus species.[12] Among these, benzomalvin A (**4**) exhibits potent inhibitory activity against substance P at the neurokinin NK1 receptor.[13]

Moreover, many quinazolinone derivatives were synthesized exhibiting significant biological and pharmaceutical activities including antibacterial,[14] anticancer,[15–17] antihypertensive,[18,19] anti-inflammatory,[20] antidiabetic,[21] and anticonvulsant[22] properties. Methaqualone (**5**, Fig. 1), a synthetic quinazoline derivative, is a widely used anxiolytic and sedative-hypnotic drug.[23] The immense biological significance of quinazolinones has led to extensive studies towards various possible constructions of this core and the synthesis of new derivatives.[24–28]

Recently, we have disclosed the synthesis of 1-aryl-3*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-4(5*H*)-ones (**6**) starting from pyrrole (**7**, Scheme 1).[29] These compounds are bioisosteres[30] of 1-aryl-2,3-benzodiazepin-4-one (**8**, Fig. 2) and its derivatives, a compound family exhibiting an anxiolytic effect due to their AMPA-antagonist activity. Compounds **6** were then further transformed (Scheme 1) to the corresponding thiones (**9**) and their *S*-methyl derivatives

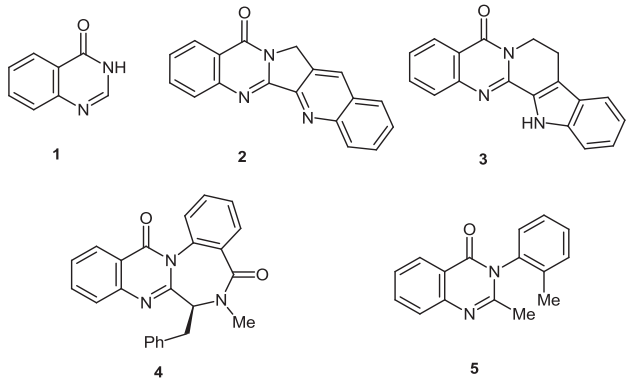

Fig. 1. Structures of some important quinazolinone derivatives.

* Corresponding author. Tel.: +36 1 8035874; e-mail address: milen.matyas@egis.hu (M. Milen).

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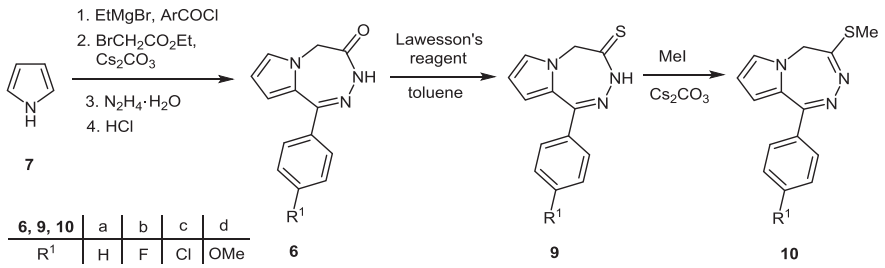


Scheme 1. Synthesis of 4-(methylsulfanyl)-1-aryl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepines **10a**–**d**.

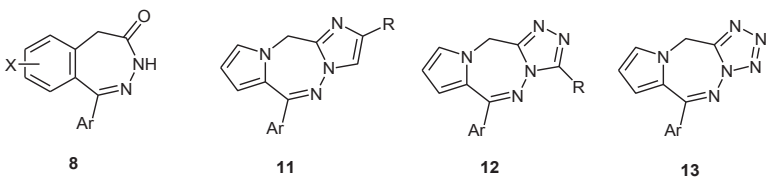


Fig. 2. Related structures: 1-aryl-2,3-benzodiazepin-4-ones (**8**), and pyrrolotriazepines condensed with nitrogen heterocycles (**11**–**13**).

(**10**).[31] Using these latter as starting materials, we have also described the synthesis of three new ring systems (Fig. 2), pyrrolotriazepines condensed with an imidazole (**11**), a triazole (**12**) or a tetrazole (**13**) ring.[31]

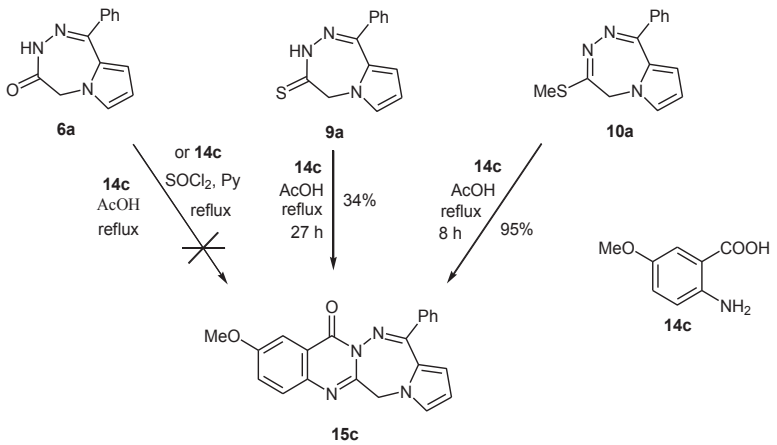
2. Results and discussion

In continuation of our efforts to develop new scaffolds, which may serve as starting points to new compound families exhibiting various pharmaceutical activities, we now present the synthesis of new tetracyclic compounds containing both the pyrrolotriazepine and the quinazolinone fragments. The main approach for the synthesis of quinazolinones involves condensation of anthranilic acids with various carboxylic acid derivatives (e.g., amides, thioamides, amidines, imino esters). All these reactions can be considered as modifications of the classical Niementowski reaction.[1–3,32]

Theoretically, compounds **6**, **9** and **10** all seemed to be suitable to act as an electrophilic centre in the reaction with anthranilic acids. At first, pyrrolotriazepinone **6a** was treated with anthranilic acid **14c** in boiling glacial acetic acid, but no reaction was observed (Scheme 2). The reaction was unsuccessful even under more drastic conditions, i.e., using $SOCl_2$ in pyridine at reflux temperature.[33] When the corresponding thione **9a** was applied as the starting material, the reaction with anthranilic acid **14c** in refluxing acetic acid afforded the desired product **15c**. Nevertheless, the reaction was sluggish and only 34% of the product was obtained after 27 h, and 62% of **9a** was recovered. Finally, *S*-methyl derivative **10a** proved to be the suitable compound for our purpose: refluxing with **14c** in acetic acid for 8 h resulted in tetracycle **15c** in 95% yield.

The extension of the latter reaction to *S*-methyl derivatives **10b**–**d** with anthranilic acids **14a**–**c** in refluxing glacial acetic acid afforded fused tetracyclic compounds **15a**–**g** in moderate to good yields (34–95%) after purification by chromatography (Scheme 3). All reactions were monitored by LC-MS and preparative TLC, and continued until the starting material **10** disappeared (4–8 h). The results are summarized in Table 1.

The structure assignment of products **15a**–**g** was based on IR, ^{1}H NMR and ^{13}C NMR spectral data and on single-crystal X-ray structure of **15a**. While the IR spectrum of the starting anthranilic acid **14a** exhibits intense absorption bands of N–H and H-bonded O–H groups in the range of 3150–2200 cm^{-1}, and a broad absorption peak of the carboxylate group at 1670–1600 cm^{-1}, in the product **15a** an amide C=O stretch absorption can be observed at 1688 cm^{-1}. The ^{13}C NMR signal of atom C11 at 158.5 ppm in **15a** corresponds to the newly formed amide moiety. Moreover, the fusion of B and C rings is detected by the doublet signal of carbon



Scheme 2. Reactions of pyrrolotriazepine derivatives **6a**, **9a** and **10a** with 2-amino-5-methoxybenzoic acid (**14c**).