APPLICATIONS SUBSTITUTED 2-AMINOTHIOPHENES IN DRUG DESIGN

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Abstract. Highly substituted thiophene derivatives are important heterocycles found in numerous biologically active compounds. Title compounds are attractive derivatives because their applications in pharmaceuticals, agriculture and pesticides. They exhibit antimicrobial activity against various Gram(+) and Gram(-) bacteria and fungi. Many of these molecules act as allosteric enhancers of A_1-adenosine receptor, glucagon antagonists as well as antioxidant and anti-inflammatory agents.

Key words: Substituted 2-aminothiophenes, Gewald reaction, thieno[2,3-*d*][1,3]oxazin-4-ones, allosteric enhancers, 3-deazathiadiamine, drug design

1. Introduction

The chemistry of 2-aminothiophenes has received much attention upon their convenient availability through the most versatile synthetic method developed by Gewald and his co-workers (GEWALD *et al*., 1988,). There are four basic variations originally described by Gewald and co-workers and about up to fifteen modifications to accomplish the synthesis of highly functionalized 2-aminothiophenes (SABNIS *et al.,* 1999; GRONOWITZ and HÖRNFELDT, 2004). The improvements of the Gewald synthesis are based in diminution of the reaction time using microwave technology (HUANG *et al.,* 2005, HESSE *et al*., 2007). The recent information of synthesis of title compounds is reviewed in our recent chapter (PUTEROVÁ and KRUTOŠÍKOVÁ, 2009). This article details about the use of substituted 2-aminothiophenes in the synthesis of thieno- type heterocycles as a group of precursors applied in pharmaceuticals and in drug design.

2. Synthesis of pharmaceuticals and drugs

The ultimate positions of substituted 2-aminothiophenes in the field of drug design and synthesis of pharmaceuticals comes from their advantageous properties – the thiophene ring as is bioisosteric replacement for phenyl group broadly present in an active drugs, the thiophene core exists in many natural and synthetic pharmaceuticals.

Moreover, they act as active precursors in broad range of synthetic pathways towards compounds used in therapy and biodiagnostic (JARVEST *et al*., 1999; DORÉ *et al*., 2004).

2.1 5-Substituted 2-aminothiophenes as A_1 adenosine receptor allosteric enhancers

Adenosine is an important endogenous tissue-protective compound released during ischemia, hypoxia or inflammation. Four receptor subtypes (A_1, A_{2A}, A_{2B}, A_3) have been defined based on pharmacological properties (LINDEN, 1997). Considerable effort has been directed towards developing therapeutic agents targeting these receptors (BRUNS and FERGUS, 1990). Substituted 2-aminothiophenes of structure **1** – **4**, with alkyl, aryl and cycloalkyl substituents in C-4 and C-5 position and aroyl substituent in C-3 position (Fig. 1), maintained the best allosteric enhancer activity (NIKOLAKOPOULOS *et al.,* 2006; FERGUSSON *et al*., 2008).

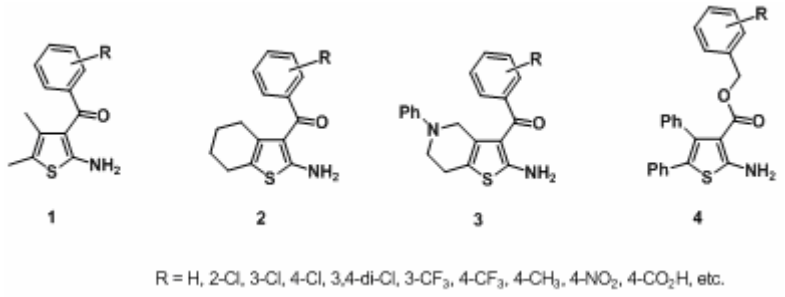


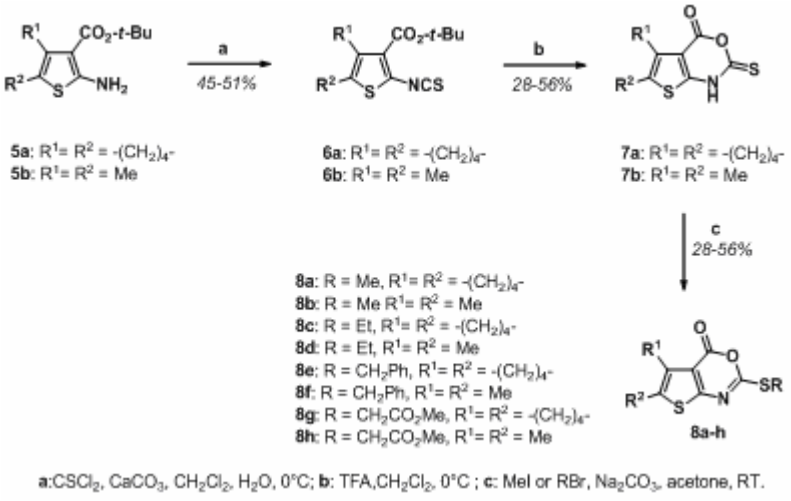
Fig. 1. Structure of some aminothiophene-based allosteric enhancers.

The significant effort in the area of synthetic aminothiophene-based allosteric enhancer is directed to development and synthesis of adenosine receptor agonists with limited side-effects. Since the active compounds with potential and utility are substituted 2-aminothiophenes their synthesis in principal based on the Gewald reaction.

2.2 Synthesis thieno[2,3-d][1,3]oxazin-4-ones as inhibitors of Human Leukocyte Elastase

A series of thieno[2,3-*d*][1,3]oxazin-4-ones **8a** – **h** was synthesized and evaluated *in vitro* for inhibitory activity toward Human Leukocyte Elastaze (HLE). The strategy presented by authors (GÜTSCHOW and NEUMAN, 1998; GÜTSCHOW *et al*., 1999) is base on the replacement of the benzene ring in benzoxazinones by thiophene. The study demonstrates the versatility of 2-aminothiophenes prepared by Gewald reaction as a synthetic entry to serine protease-inhibiting, fused 1,3-oxazin-4-ones. The synthetic route to novel thieno[2,3-*d*][1,3]oxazin-4-ones **8a** – **h** using alkyl 2-aminothiophenecarboxylates **5a,b** as substrates exhibits a facile three step synthesis, as is presented on Scheme 21. Aminothiophenes **5a,b** were converted to isothiocyanato-

thiophenes **6a,b** by the action of thiophosgene. Deprotection of *tert*-butoxycarbonyl group resulted directly to ring closure of the intermediates isothiocyanatothiophenecarboxylic acids **7a,b**. These key intermediates were alkylated with appropriate alkyl halides to furnish the final derivatives **8a** – **h** (Scheme 1).



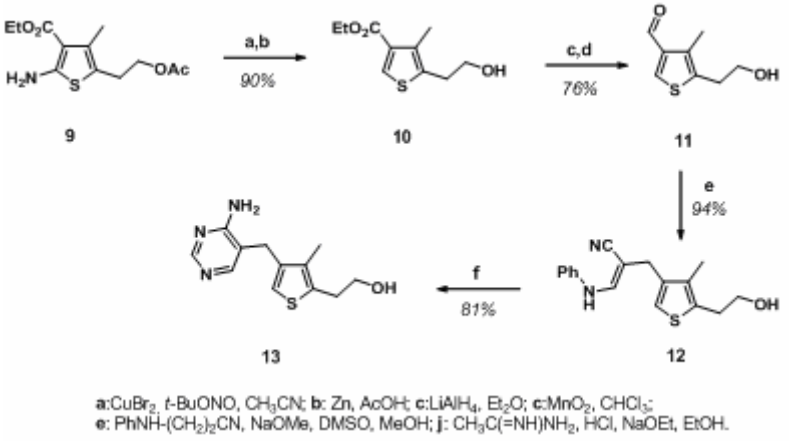
Scheme 1. Synthesis of substituted thieno[2,3-*d*][1,3]oxazin-4-ones **8a**–**h**

Extracellurar HLE is a serine protease contained in the azurophilic granules of human neutrophils and has been shown to contribute to the pathogenesis of destructive lung diseases, such as pulmonary emphysema, cystic fibrosis, adult respiratory distress syndrome and inflammatory disorders such as rheumatoid arthritis. For that reason, much attention is focused on the inhibition of HLE by low-molecular-weight inhibitors that might serve as therapeutic agents.

2.3 Synthesis of 3-deazathiamine

Authors (HAWSKEY *et al.,* 2001) outlined the synthesis of 3-deazathiamine (**13**) in ten chemical steps, through key intermediate substituted 2-aminothiophene **9**. On the Scheme 2 we have outlined the synthesis of target compound **13** starting from appropriate aminothiophene **9**. Deamination of aminothiophene **9** *via* the bromide and following cleavage with Zn in acid media to afford derivative **10** was very efficient, displaying none of side reactions. Conversion of formed ester **10** to final 3-deazathiamine (**12**) was accomplished in four subsequent steps isolating the crucial intermediates – aldehyde **11** and nitrile **12**. The readily available and inexpensive starting materials and reagents, and the lack of protection and de-protection steps make this synthesis very fashionable (Scheme 2).

Deazathiamine diphosphate (deaza-TDP) is an analogue of thiamine diphosphate (TDP), the biologically active for of thiamin (vitamin B_1), with a neutral thiophene replacing positively charged thiazolium ring. TDP is co-enzyme present in a number of enzymes, including pyruvate decarboxylase, transketolase, pyruvate oxidase.



Scheme 2. Reaction sequence towards 3-deazathiamine **13**.

2.4 Other important pharmaceuticals developed from2-aminothiophenes

The synthesis and antitumor a potent thieno[2,3-*b*]azepin-4-one antineoplastic agents was reported (KOEBEL *et al*., 1975). The meaningful structure-activity relationships have been established in monocarbonyl and dicarbonyl series of thieno[2, 3-*b*]azepin-4-one **14, 15** (Fig. 2) prepared by Dieckmann ring closure reaction in multi step reaction from substituted 2-aminothiophenes.

Cinnamyl derivatives of thieno[2, 3-*d*]oxazinones **16** (Fig. 3) inhibits herpes protease processing in HSV-2 infected cells. The synthesis and pharmacology of this series of derivatives was presented by authors (JARVEST *et al*., 1997 and 1999) from ethyl 2-amino-4-methylthiophene-3-carboxylate.

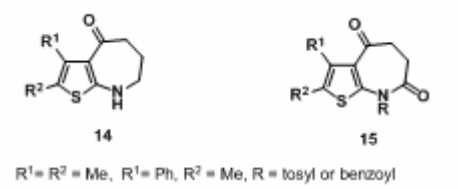


Fig. 2. Structure of potential antineoplastics Thieno (2,3-*b*) azepin-4-ones **14,15**

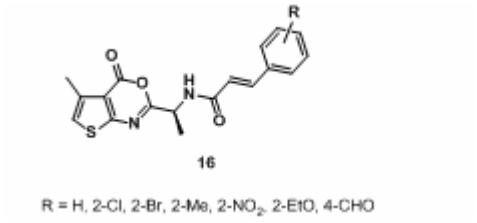


Fig. 3. The family of herpes proteases HSV-2 Thieno (2,3-d) oxazinones **16**

Transglutaminases (TGases) are a family of Ca^{2+} dependent enzymes which are normally expressed at low levels in many different tissues and serve vital roles, such as blood clothing and epithelia formation. Some TGase isoenzymes are involved in diverse pathological conditions like celiac disease, atherosclerosis and neurodegenerative disorders. Thieno[2,3-*d*]pyrimidin-4-hydrazide derivatives related to structure **17** (Fig. 4) were discovered as a moderately potent inhibitors of TGase-2 (tissue transglutaminase) (DUVAL *et al*., 2000).

The RNA polymerase holoenzyme is a proven target for antibacterial agents. A high-throughput screening program based on this enzyme from *Staphylococcus aureus* had identified a 2-ureido-thiophene-3-carboxylate **18** (Fig. 5) as a low micromolar inhibitor. It displayed good antibacterial activity against *S. aureus* and *S. epidermidis*. Based on these observations the authors (AHRIN *et al*., 2006) reported a facile synthesis of the number of analogs of **18** *via* the Gewald reaction and evaluated for cytotoxic activity against Rifampicin-resistant *S. aureus.*

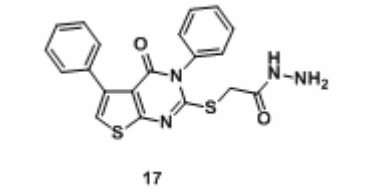


Fig. 4. Thieno (2,3-*d*) pyrimidin-4-hydrazide **17** lead structure in inhibition of TGase-2.

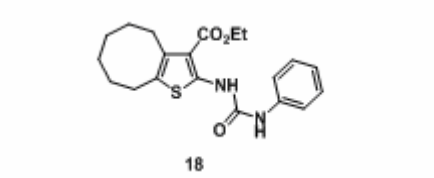


Fig. 5. 2-Ureido-thiophene-3-carboxylate **18** antibacterial agent against *S. aureus.*

A novel class of thiophene-derived antagonists of the human hepatic glucagon receptor (hGCRG) has been discovered (DUFFY *et al*., 2005). The synthesis of derivatives based on the lead structure **19** (Fig. 6) was accomplished using the Gewald reaction. The further investigations of such structures are challenging in development of therapeutics of the diabetes mellitus. Diabetes mellitus is a condition characterized by chronically elevated levels of blood glucose caused by incorrect function of the hormone responsible for the hGCRG activation.

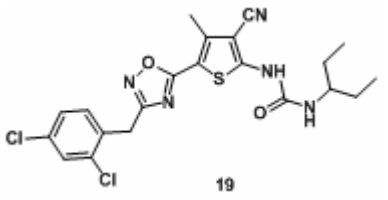


Fig. 6. Thiophene-based antagonist of hGCRG **19**

Because the structure-based drug design program through substituted 2-aminothiophenes has been investigated broadly, up to this date there are many other research works dealing with the synthesis, pharmacology and application of thiophene-based structures in medicinal chemistry (KOUROUNAKIS *et al*., 2000). It is no doubt, that this area of Gewald-like thiophene derivatives exhibits the highest progress in a scope and utilization.

3. Conclusions

In this short review the importance of substituted 2-aminothiophenes in the medicinal chemistry was extended in terms of drug design and synthesis of pharmaceuticals. The scope of this work does not include all of the publications in this field, but the most interesting studies in the subject areas are considered. The further detailed information in the latter aspects can be found within the list of the references.

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