European Journal of Medicinal Chemistry 108 (2016) 347–353

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Design, synthesis and antitrypanosomal activities of 2,6-disubstituted-4,5,7-trifluorobenzothiophenes

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ARTICLE INFO

Article history:
Received 5 August 2015
Received in revised form
23 November 2015
Accepted 25 November 2015
Available online 30 November 2015

Keywords:
Benzothiophenes
Fluorinated drugs
Antitrypanosomal activity
Sleeping sickness
Human African Trypanosomiasis
Trypanosoma brucei rhodesiense

ABSTRACT

Current treatments for Human African Trypanosomiasis (HAT) are limited in their application, have undesirable dosing regimens and unsatisfactory toxicities highlighting the need for the development of a safer drug pipeline. Our medicinal chemistry programme in developing rapidly accessible and modifiable heterocyclic scaffolds led to the design and synthesis of novel substituted benzothiophenes, with 6-benzimidazol-1-ylbenzothiophene derivatives demonstrating significant antitrypanosomal activities (IC_{50} < 1 μM) against *Trypanosoma brucei rhodesiense* and no toxicity towards mammalian cells.

1. Introduction

Human African Trypanosomiasis, also known as sleeping sickness is caused by infection with *Trypanosoma brucei rhodesiense* (*T.b.r*) or *Trypanosoma brucei gambiense* (*T.b.g*) parasites. During the haemolymphatic phase, trypomastigotes circulate within the blood and lymphatic system. If not treated sufficiently, the neurological phase ensues as parasites penetrate the blood brain barrier thus infecting the central nervous system from which patient recovery is unlikely. Current treatment for *T.b.r* is dated and potentially lethal consisting of Suramin for the haemolymphatic phase and arsenic based melarsoprol for the neurological phase. These treatments require complicated dosing regimens and related side-effects such as reactive encephalopathy have proven fatal in up to 9% of patients [1]. Clinical advancements in antitrypanosomal drug development have been limited and resistance is increasing requiring the development of a new drug pipeline to replace existing therapies. Recent literature findings have included the development of 3-nitrotriazole based piperazides exhibiting appreciable *in vitro* activity against *T.b.r* parasites as well as series of hybrids of bile acids and *Cinchona* alkaloids demonstrating high *in vitro* activities against *Trypanosoma brucei brucei* [2,3].

Developing rapidly accessible fluorinated heterocyclic scaffolds [4,5] with potential for further elaboration is thematic of our medicinal chemistry programme. Benzothiophene ring systems represent privileged scaffolds in medicinal chemistry and have been incorporated into: reverse transcriptase inhibitors; tubulin binders to inhibit microtubule formation; and antiprotozoal agents [6–10]. Our investigations highlighted in this article yielded diversely substituted fluorinated benzothiophene scaffolds using aromatic nucleophilic substitution reactions (S_NAr) of perfluorinated building blocks [11]. S_NAr of perfluorinated arenes

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http://dx.doi.org/10.1016/j.ejmech.2015.11.043
0223-5234/

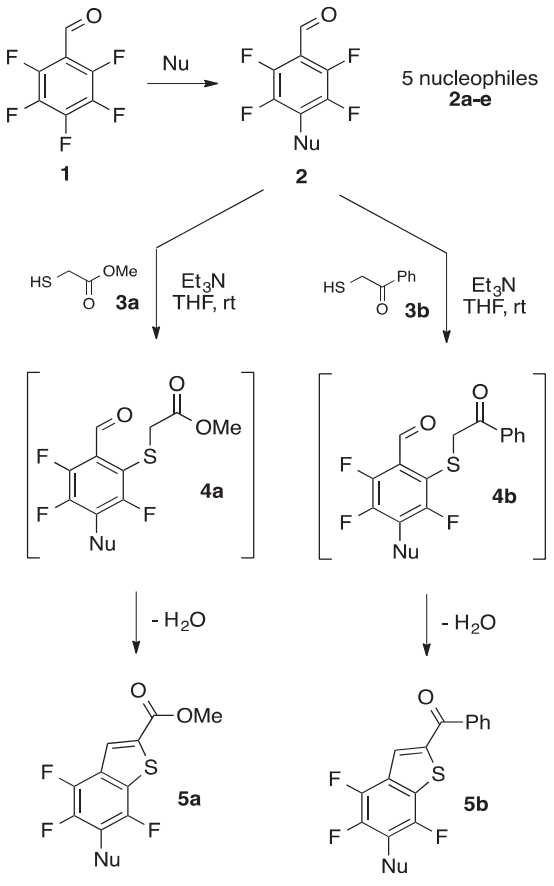
occur readily with a wide range of nucleophiles and often proceed under mild conditions without the need for transition metal catalysis [12]. The substitution patterns available by sequential replacement of fluorine differ from those afforded by electrophilic reaction protocols and allow structurally diverse derivatives to be prepared according to drug design strategies [13,14]. Retaining fluorine is also desirable property in drug design since fluorine can improve metabolic stability due to the strength of the C–F bond (ca. 480 kJ mol^{-1}), whilst its small size (van der Waals radius, 147 pm) and high electronegativity impart desirable properties to a molecule which can significantly alter biological response [15,16].

2. Methods and results

2.1. Syntheses

Continuing our interest in preparing condensed sulfur containing heterocycles [17] from perfluoroarene precursors, firstly, tetrafluorobenzaldehydes **2a**–**e** suitable for ring annelation reactions to construct the benzothiophene derivatives were prepared through the reaction of pentafluorobenzaldehyde **1** with a range of nucleophiles (Scheme 1) including two diazoles, a phenol and two thiols [18]. Treatment of the aldehydes **2** with α-mercaptocarbonyl compounds **3a** or **3b** was expected to lead to addition of the thiol to the 2-position of the benzaldehyde and allow condensation of the active methylene group with the adjacent aldehyde to form a fused thiophene ring **5**, since thieno[2,3-*c*]pyridines have been prepared by a related method involving cyclization onto a nitrile [19].

In practice, pentafluorobenzaldehyde reacted smoothly with selected diazoles, arenethiols and 2-bromophenol to the form a series of 4-substituted benzaldehydes **2** in good yields. Addition at the 4-position is in line with the usual orientation of addition observed for perfluorinated arenes [20]. Treatment of the benzaldehydes with either methyl α-mercaptoacetate **3a** or 2′-mercaptoacetophenone **3b** in the presence of triethylamine as base led to the clean conversion to the 6-substituted-4,5,7-trifluorobenzothiophenes **5aa**–**5be** in moderate to excellent yields. Treatment of pentafluorobenzaldehyde **1** with two equivalents of **3a** or **3b** led to direct formation of **5af** and **5bf** in reasonable yields, in which the thiols most likely added consecutively to the 4- and 2-positions of the aldehyde. Subsequently, the intramolecular reaction of the 2-substituent with the adjacent aldehyde group would have resulted in cyclization forming the benzothiophene scaffold in a one-pot procedure. The intermediate 2-sulfanyl benzaldehydes **4a**/**b** were not isolated. The structures of the new compounds were fully in accord with their analytical and spectroscopic properties. Computational studies to predict oral drug-likeness demonstrated no compound within this study violated more than one of the parameters constituting Lipinski's rule of 5 and all fall within acceptable limits of rotational bond count and polar surface area [21–24]. The structure of compound **5bb** was confirmed by single crystal X-ray diffraction analysis, with the molecular structure shown in Fig. 1 [25–27].



Scheme 1. Overall reaction scheme to generate 2,6-disubstituted-4,5,7-trifluorobenzothiophenes.

2.2. Antitrypanosomal and antiproliferative activity

Synthesized compounds (Table 1) were screened in a phenotypic assay against *Trypanosoma brucei rhodesiense* (STIB 900) and cytotoxicities determined against MCF7 cells [28].

2.2.1. 6-Substituted-benzothiophene-2-carboxylate derivatives

Compound 5ad, synthesized bearing a 6-(2-bromophenylsufanyl) group demonstrated moderate trypanocidal activity with an IC_{50} value of 11.9 μM. Compound **5ac** was prepared with a 6-(2-bromophenoxy) group and gave an IC_{50} value of 30 μM, with a similar toxicity value against the MCF7 cell line. The bromophenyl groups in these two compounds were strategically designed to allow further modification of the scaffold by halogen–lithium exchange which would allow ring forming reactions. The results of such reactions will be reported in due course alongside comparative bioactivity data. Compound **5aa**, the 6-imidazolyl substituted analog did not demonstrate trypanocidal activity, nor did the 6-(4-tert-butylphenylsulfanyl) derivative **5ae**. Compound **5af**, the 6-benzoylmethylsulfanyl analog, showed moderate activity but interestingly, the 6-benzimidazolyl analog **5ab** demonstrated respectable trypanocidal activity with an IC_{50} value of 0.60 μM, significantly greater than aforementioned benzothiophene-2-carboxylate derivatives screened. The selectivity ratio of trypanocidal activity against MCF7 cells was greater than 20 fold, making this compound a successful hit within the 2-carboxylate derivatives.

2.2.2. 2-Benzoyl-benzothiophene derivatives

In the ketone series, compound **5bd**, the 2-benzoylbenzothiophene with a bromophenyl sulfanyl substituent showed comparable antiparasitic and cytotoxic activity to **5ad** with an IC_{50} value of 9.8 μM. Similarly, the imidazolyl substituted compound **5ba** showed an increase in trypanocidal activity with an IC_{50} value of 33.0 μM in relation to its carboxylate analog **5aa**, but not to the extent of being classified as a hit compound. Likewise for the pair **5be**/**5ae** the ketone showed 2-fold better antiparasitic activity than the corresponding carboxylate, while for **5bf**/**5af** comparable trypanocidal activity was observed in the region of 10 μM and above. Importantly, the benzimidazole-containing compound **5bb** demonstrated a trypanocidal IC_{50} value of 0.53 μM, comparable to