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Discovery of small molecules with vasodilating characteristics and adjustable hydrolytic behavior

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ABSTRACT

In this contribution the development of a new class of vasodilating compounds obtained by lead structure optimization is described. Three groups of compounds were synthesized and tested for their activity on various smooth muscle preparations of the guinea pig. Beside the lead compound **3a**, the most interesting derivative was 1*H*-imidazole-1-carbothioic acid *O*-cyclohexyl ester hydrochloride (**5b**) with a good selective vasodilating potential on aorta and pulmonary artery rings (EC_{50} 14 μM and 24 μM, respectively). Due to the properties of small molecules the hydrolysis behavior of the compounds can be easily adapted hence opening a new route in terms of duration of the agent's effect. With the aid of structure–activity relationship studies, structural motifs influencing the biological activity on isolated smooth muscle cell preparations of the synthesized compounds were proposed. The presented compounds offer good tools in identifying promising molecules as emergency therapy in myocardial infarction.

1. Introduction

In developed countries, the leading cause of death and source of disability are myocardial infarction and arterial thrombosis (stroke). The main determinant of clinical outcome is well established as the fast and complete restoration of blood flow to the blocked artery[1] either by thrombolysis or by acute percutaneous coronary interventions and reopening of the occluded vessel using a stent.[2] As a consequence anti-platelet drugs such as aspirin, clopidogrel and its recently developed follow-up drugs are used to preserve the open vessel.[3] Additionally, vasoactive drugs like nitrates are used to improve coronary blood flow and the hunt for the development of new nitric oxide (NO) releasing compounds still continues.[4] Whereas there have been a couple of new anti-platelet drugs promoted on the market, no new vasodilators have been clinically introduced.[5]

In this contribution, a unique collection of small sulfur-containing compounds was synthesized and tested for vasodilating activity, with their characteristics designed to act as emergency drugs in the treatment of ischemia. The main idea is that the presented compounds are supposed to act immediately as vasoactive compounds, which can for instance be applied in the status of acute ischemia. In this case, after controlling the initial phase the compounds should facilitate the body's duty to get rid of the xenobiotics via degrading themselves through hydrolysis into more polar compounds that can be excreted more easily. This seems contradictory to the general aim of medicinal chemists which is to prolong the duration of a compound's activity within the body by making it more metabolically stable.[6] We present compounds offering the possibility to adjust their hydrolysis properties but still keep the desired biological activity. Thinking ahead, this is—to the best of our knowledge—a new concept, which may open the way to the application of a specific compound/medication depending on how long the patient needs the agent's action.

Previous studies in which we showed that dithio- and thiobenzanilides act as potent spasmolytic agents compared to their benzanilide derivatives[7,8] and that the sulfur present in their scaffold was responsible for the increased activity[9] led us to investigate the biological activity of the small molecule **3a**. The base was commercially available and its short synthesis (conversion to the hydrochloride salt) as well as biological profile on smooth muscle cell preparations made it an attractive candidate for lead structure optimization. Conversion of the compound into its hydrochloride salt resulted in a change of the aggregation state from fluid to solid thus providing a better accessibility to the biological investigation (scaling, solubility). In order to obtain compounds showing the ability to widen selectively blood vessels we modified the structure around the thiocarbonyl group, which was synthetically achieved by 'growing' of compound **3a**. Thus we gained three different groups of compounds with partly high vasodilating activity on aorta and pulmonary artery rings of the guinea pig as assessed

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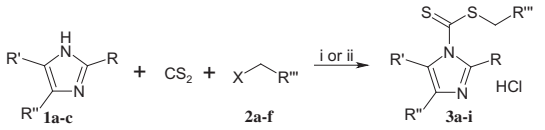


1a R,R',R'': H
1b R: CH_3; R'-R'': CH=CH-CH=CH
1c R: CH_3; R',R'': H

2a X: I; R''': H
2b X: Cl; R''': C_6H_5
2c X: Cl; R''': $(4\text{-}OCH_3)C_6H_4$
2d X: Cl; R''': $(3,4,5\text{-}(OCH_3)_3)C_6H_2$
2e X: Br; R''': $C_2H_4COOC_2H_5$
2f X: Br; R''': $C_2H_4OCOCH_3$

3a R, R', R'', R''': H
3b R, R', R'': H; R''': C_6H_5
3c R, R', R'': H; R''': $(4\text{-}OCH_3)C_6H_4$
3d R, R', R'': H; R''': $(3,4,5\text{-}(OCH_3)_3)C_6H_2$
3e R, R', R'': H; R''': $CH_2COOC_2H_5$
3f R, R', R'': H; R''': CH_2OCOCH_3
3g R: CH_3; R'-R'': CH=CH-CH=CH; R'''=H
3h R: CH_3; R', R'', R''': H
3i R: CH_3; R',R'':H; R''': C_6H_5

Scheme 1. Conditions: (i) NaH, THF, 0 °C; diethylether, 1 M HCl; (ii) K_3PO_4, acetone, room temp; diethylether, 1 M HCl.

by isometric tension recording. Hydrolysis studies, studies concerning their mechanisms of action as well as information of the chemical space covered by the compounds using ChemGPS-NP[10–12] are presented.

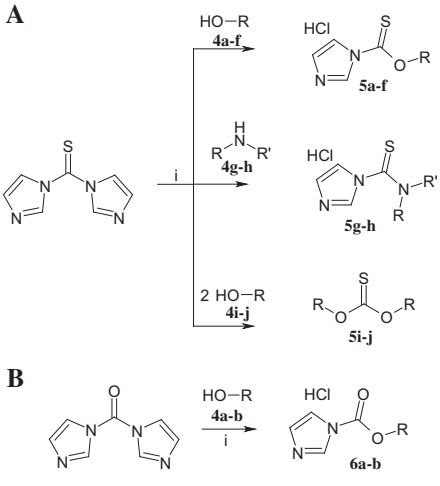
2. Results and discussion

2.1. Chemistry

Applying the approach of lead structure optimization to obtain selectively vasodilating small molecules, we forwarded our studies and designed three different groups of compounds: dithiocarbamide derivatives, *O*-thiocarbamate/carbamide derivatives as well as diesters of thiocarbonic acid. The synthetic routes used to prepare the dithiocarbamide derivatives are summarized in Scheme 1. In general, two routes were available to obtain the desired compounds. The first protocol includes the conversion of imidazole or an imidazole derivative to the corresponding imidazolide under the influence of sodium hydride in tetrahydrofuran (THF) under argon atmosphere at 0 °C followed by adding carbonyl disulfide (CS_2). The end products were obtained by addition of the appropriate alkyl halide at room temperature.[13] This procedure was applied for the preparation of compounds **3a–d** and **3h**. The preparation of compounds **3e–g** and **3i** required the use of potassium phosphate in acetone as described by Wang et al.[14] An excess of CS_2 was added at room temperature followed by the corresponding alkyl halide. In both cases, the compounds were further converted to their hydrochloric salt by using 1 M hydrochloric acid in diethylether to improve water solubility, which represented an advantage in the following biological assays in terms of reproducibility. The compound **3d** was not able to be converted into the salt form and therefore was tested as its free base. The *O*-thiocarbamates **5a–f** as well as the thiocarbamides **5g** and **5h** were synthesized by reaction of 1,1′-thiocarbonyldiimidazole (TCDI) and the corresponding alcohol and amine component, respectively, in dry THF. The reaction worked equally well for both the thiocarbamates and -carbamides with yields above 60%. For the synthesis of the symmetric diesters **5i** and **5j** the same synthetic procedure was applied but with 2 equiv of the corresponding alcohol component. The oxygen analogs of **5a** and **5b**, **6a** and **6b**, were obtained by the same procedure but with 1,1′-carbonyldiimidazole as starting material (Scheme 2). The synthesis of the compounds **8a–h** required replacing the imidazolide moiety against an alkyloxy and -amino substituent, respectively, thus obtaining either symmetrical or asymmetrical diester/-amides of the thiocarbonic acid (Scheme 3). Elemental analysis was used for characterization as well as purity confirmation of the compounds. For the compounds **5a**, **6a**, **8c**, **8d** and **8g** the elemental analysis provided unconvincing data and therefore the bases of these compounds were used and characterized by HRMS.

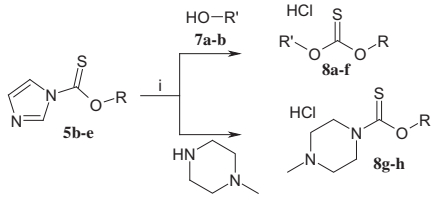
2.2. Activities on smooth and heart muscle preparations and SAR

The vasodilating potency of the compounds was assessed on isolated aorta and pulmonary artery rings of the guinea pig precontracted by 90 mM potassium chloride. A possible spasmolytic activity was studied on terminal ileum preparations



a R: $CH(CH_3)_2$
b R: cyclohexyl
c R: CH_2CH_3
d R: $(CH_2)_2CH_3$
e R: $(CH_2)_3CH_3$
f R: cyclopentyl
g R-R': $(CH_2)_5$
h R, R': $CH_2CH(CH_3)_2$
i R: $(CH_2)_2N(CH_3)_2$; HCl
j R: $(CH_2)_2N(CH_3)_3{}^+Cl^-$

Scheme 2. Conditions: (i) THF, reflux; diethylether, 1 M HCl.



7a R': $(CH_2)_3N(CH_3)_2$
7b R': $(CH_2)_2N(CH_3)_2$

8a R: hexyl; R': $(CH_2)_3N(CH_3)_2$
8b R: CH_2CH_3; R': $(CH_2)_2N(CH_3)_2$
8c R: CH_2CH_3; R': $(CH_2)_3N(CH_3)_2$
8d R: $(CH_2)_2CH_3$; R': $(CH_2)_2N(CH_3)_2$
8e R: $(CH_2)_2CH_3$; R': $(CH_2)_3N(CH_3)_2$
8f R: $(CH_2)_3CH_3$; R': $(CH_2)_3N(CH_3)_2$
8g R: CH_2CH_3
8h R: $(CH_2)_2CH_3$

Scheme 3. Conditions: (i) THF, reflux; diethylether, 1 M HCl.