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A General Synthesis of 1-Aryl Carbamoyl-2-alkyl-4-aryl Substituted Semicarbazides as Nonbasic Factor Xa Inhibitors

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This paper is dedicated to the memory of the late Prof. Dr. Joachim Gante

Abstract—An efficient four-step synthesis of 1-aryl-carbamoyl-2-alkyl-4-aryl-semicarbazides starting from benzophenone hydrazone is described leading to moderately active neutral factor Xa inhibitors.

The serine protease factor Xa (fXa) is involved in the process of blood coagulation and has emerged as an important therapeutic target in the search for an ideal anticoagulant. The inhibtion of fXa may allow the effective control of thrombogenesis with a minimal effect upon bleeding.[1] Most of the known factor Xa inhibitors[2] are benzamidine derivatives that contain a polar basic group which is associated with poor pharmacokinetic properties. As part of our research program to obtain orally active factor Xa inhibitors, we have synthesized and evaluated amino acid derivatives such as 4-chorophenyl carbamoyls **1**–**4** (Fig. 1).[3] A feature of these nonbasic compounds is the chlorophenyl as a surrogate for benzamidine in the S1 binding pocket, a D-amino acid as the central scaffold and a phenyl morpholinone as the P4 ligand, respectively. The D-norvaline analogue **3** is one of the most potent compounds in this series (Fig. 1).

In order to extend the scope of this class of compounds structurally related semicarbazide derivatives **5** were envisaged (Fig. 1). Semicarbazides as modifications of the peptide structure in peptidomimetics have found increasing use in drug design.[4] The replacement of a C(2) tetrahedral atom with a trivalent nitrogen atom results in asymmetry loss and a configuration midway between the corresponding D- and L-amino acids. This replacement should permit the semicarbazides **5** to adopt a conformation approximate to **1**–**4** and provide fXa binding inhibition in a similar range.

A retrosynthetic analysis of **5** led to the commercially available 4-chlorophenyl isocyanate **6**, the 4-aminophenyl morpholinone **7**[5] and different alkyl hydrazines (Fig. 1). However, due to the restrictive availability of these hydrazines the synthetic route was slightly modified.

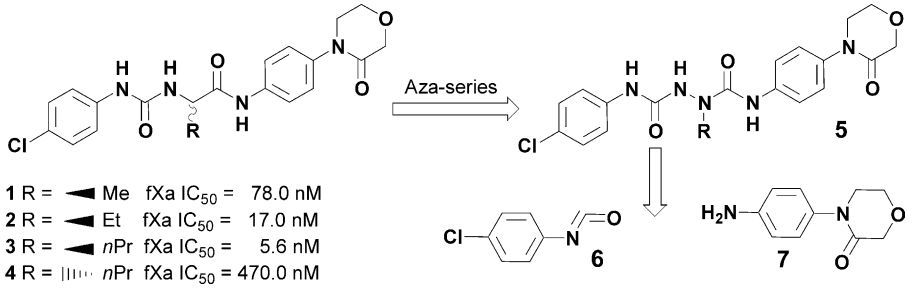

Figure 1. Selected potent factor Xa inhibitors **1**–**4** and retrosynthetic analysis of semicarbazide analogues **5** leading to starting molecules **6** and **7**.

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As a result of this 2-alkyl-4-aryl semicarbazides were envisaged which have to be reacted with isocyanate **6** to give the final products **5**. A literature survey of the synthesis of such semicarbazides revealed that the reaction of monoalkyl hydrazines with isocyanates took place at the α-nitrogen atom giving rise to the targeted compounds (Scheme 1, method A).[6] Hydrazines not easily available were readily accessible by hydrogenation of the hydrazones formed from *t*-butyl carbazate (Scheme 1, method B).[7] A more flexible approach to different α-aza-alkyl amino acid derivatives was described by Ronco et al.[8] Ethylesters of this type were prepared in moderate yields by alkylation of ethyl carbazate, using the diacetyl for amino-protection (Scheme 1, method C). This alkylation method was successfully applied to higher amino acids by O'Donnell et al. The syntheses were accomplished via stable Schiff bases from glycine ester and benzophenone (Scheme 1, method D).[9]

Comparing the different existing reaction pathways depicted in Scheme 1 a decision was made on pursuing a modification of method C. Therefore, the diacetyl moiety was replaced by the cheaper and stable benzophenone and the ethyl ester by an anilide derived from morpholinone **7**.

Herein, we report on a short and flexible synthesis of a 2-propyl-3-aryl substituted semicarbazide with diphenylmethylene as a stable amino-protecting group and subsequent condensation of this intermediate to carbamoyl derivative **5a**.

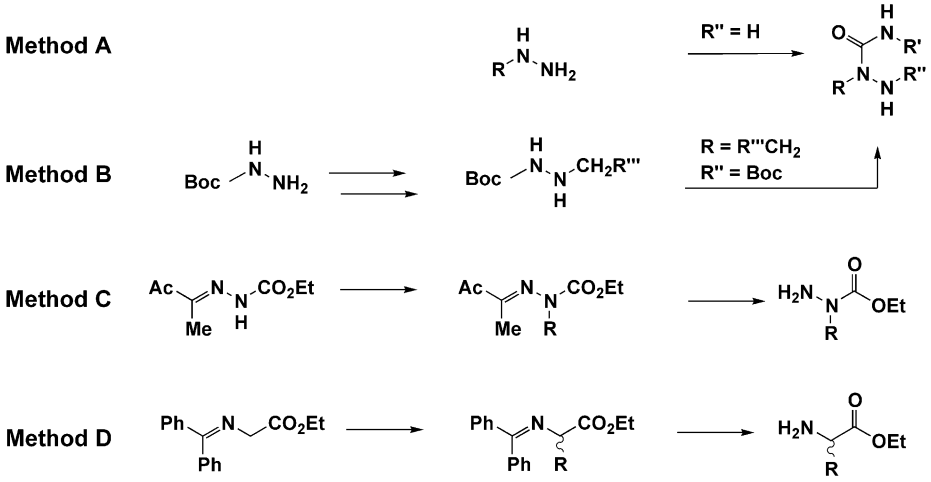
At the outset of this study the synthesis of the 1-amino protected semicarbazide key intermediate **10** (cf. method C, Scheme 1) was investigated. As illustrated in Scheme 2, the commercially available benzophenone hydrazone **9** and the parent anilino heterocycle **7**[5] were chosen as the starting materials. Therefore, both compounds had to be condensed with a phosgene equivalent such as DP, TP, CDI or DSC. Carbonyl diimidazole (CDI) is a well-known phosgene substitute, particularly in carbonylation reactions. However, the carbodiimide mediated condensation of both compounds **7** and **9** led predominantly to the symmetric and dimeric carbonyl analogue of benzophenone hydrazone (not shown in Scheme 2) together with the targeted semicarbazide **10** as the minor compound. This preliminary result caused us to activate the aniline **7** with *p*-nitrophenyl chloroformate to the intermediate *p*-nitrophenyl ester because such carbamic acid esters are prone to react with amines to generate ureas.[10] In our case **7** was converted into the *p*-nitrophenyl ester **8** in situ and then transformed with benzophenone hydrazone **9** to semicarbazide **10** in good yield.[11]

Subsequent to this condensation, the *N*-alkylation of **10** with *n*-propyl iodide had to be examined. To establish the viability of this coupling process, a short screening of reaction variables were undertaken. For room temperature reactions cesium carbonate in acetonitrile was found to be most effective. Other bases such as potassium carbonate or potassium *tert*-butoxide in tetrahydrofuran or dimethylformamide were less successful. Thus, treatment of **10** and *n*-propyl iodide with cesium carbonate in acetonitrile afforded the *N*-propyl semicarbazide **11** in excellent yield.[12] Other reactive halides such as benzyl bromide or propargyl bromide were also found to be suitable *N*-alkylating reagents (data not shown in Scheme 2).

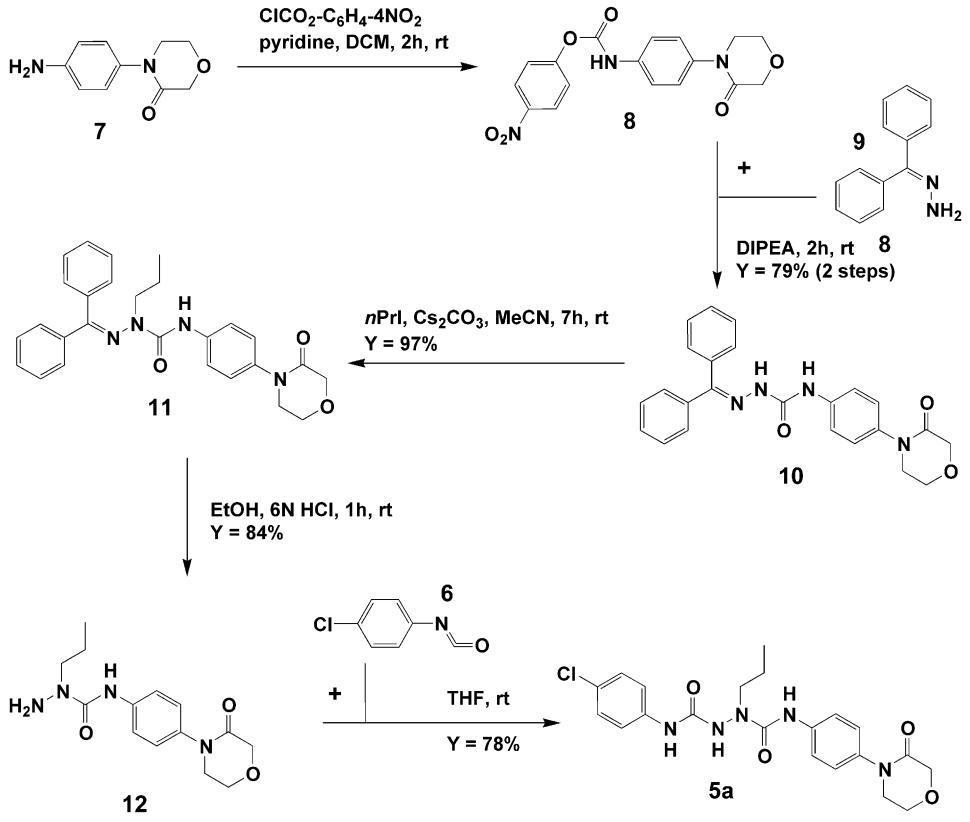
Next, the benzophenone derived protecting group of semicarbazide **11** had to be removed.[13] The imine functionality in compound **11** could be selectively cleaved to benzophenone and 2-propyl semicarbazide **12** by the hydrolysis of **11** with hydrochloric acid in ethanol.[14]

Finally, for the incorporation of a carbamoyl moiety at the N-terminus of semicarbazide **12**, 4-chlorophenyl isocyanate **6** was treated with **12** in tetrahydrofuran to provide the corresponding coupling product **5a** in good yield.[15]

Compound **5a** was tested for its ability to inhibit human factor Xa in a purified enzyme system and compared to carba-analogues **3** and **4**. The hypothesis of a configuration midway could be confirmed (**5a**: IC_{50} fXa = 85.0 nM; cf. **3** and **4** in Fig. 1). This diminished in vitro



Scheme 1. Synthetic pathways to 2-alkyl-semicarbazides (A, B), α-aza-alkyl amino acids (C) and α-alkyl amino acids (D).



Scheme 2. General synthesis of carbamoyl semicarbazide **5a**.

potency in comparison to the D-amino acid series caused us to suspend the synthesis of further 2-alkyl semicarbazides.

In conclusion, we have described the selective and efficient three step synthesis of a 2-propyl-4-aryl semicarbazide and the subsequent condensation to carbamoyl analogue **5a** which gave rise to a moderately active factor Xa inhibitor. Although some more alkyl derivatives have been prepared the application to other 2-alkyl and/or 4-aryl compounds has to be confirmed.

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11. Experimental procedure for 1-diphenylmethylen-4-[4-(3-oxo-4-morpholinyl)-phenyl]-semicarbazide **10**: A mixture of 4-(4-amino-phenyl)-morpholin-3-one **7** (2.0 g, 10.4 mmol), 4-nitro-phenyl chloroformate (2.1 g, 10.4 mmol), pyridine (0.84 mL, 10.4 mmol), and dichloromethane (50 mL) was stirred at ambient temperature for 1 h. This mixture was treated with benzophenone hydrazone **9** (2.04 g, 10.4 mmol) and ethyl-diisopropyl-amine (5.3 mL, 31.2 mmol). The resulting suspension was allowed to stir at room temperature for 2 h. On diluting with ethyl acetate (100 mL) the organic phase was washed with sodium hydroxide (0.5 N, 100 mL) and dried over sodium sulfate. The organic solution was evaporated under reduced pressure and the residue was purified by recrystallization from ethyl acetate to yield **10** (3.94 g, 79%) as a colourless solid: mp 241–243 °C; ^{1}H NMR (DMSO-d_6) δ 9.20 (s, 1H), 8.71 (s, 1H), 7.65–7.54 (m, 5H), 7.56 (d, J = 8.9 Hz, 2H), 7.40–7.31 (m, 5H), 7.29 (d, J = 8.9 Hz, 2H), 4.18 (s, 2H), 3.96 (dd, J = 3.8 and 4.7 Hz, 2H), 3.70 (dd, J = 3.8 and 4.9 Hz); MS (EI) m/z 414 (8, M^+), 165 (100). HRMS calcd for $C_{24}H_{22}N_4O_3$ (M^+) m/e 414.1692, found m/e 414.1687.
12. Experimental procedure for 1-diphenylmethylen-4-[4-(3-oxo-4-morpholinyl)-phenyl]-2-propylsemicarbazide **11**: A suspension of semicarbazide **10** (1.0 g, 2.4 mmol) and cesium carbonate (0.98 g, 3.0 mmol) in acetonitrile (30 mL) was stirred at room temperature for 0.5 h. This mixture was treated with 1-iodo-propane (0.29 mL, 3.0 mmol) and stirred for additional 7 h. After treatment with cold water (150 mL) the

resultant solution was allowed to stand to precipitate. The solid was collected by filtration, washed with water and dried under high vacuum to give **11** (1.07 g, 97%): mp 75–77 °C; ^{1}H NMR (DMSO-d_6) δ 9.00 (s, 1H), 7.62 (d, J = 8.9 Hz, 2H), 7.58–7.36 (m, 10H), 7.28 (d, J = 8.9 Hz, 2H), 4.18 (s, 2H), 3.96 (dd, J = 3.9 and 4.7 Hz, 2H), 3.69 (dd, J = 3.9 and 4.9 Hz, 2H), 3.16 (t, J = 7.3 Hz, 2H), 1.24–1.19 (m, J = 7.3 Hz, 2H), 0.59 (t, J = 7.3 Hz, 3H); MS (EI) m/z 456 (2, M^+), 180 (100). HRMS calcd for $C_{27}H_{28}N_4O_3$ (M^+) m/e 456.2161, found m/e 456.2156.

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14. Experimental procedure for 4-[4-(3-oxo-4-morpholinyl)-phenyl]-2-propylsemicarbazide **12**: A solution of semicarbazide **11** (0.5 g, 1.1 mmol) in ethanol (20 mL) was treated at room temperature with hydrogen chloride (37%, 5.0 mL) for 1 h. The reaction mixture was diluted with water (30 mL) and extracted with *tert*-butyl methyl ether. The pH of the water phase was adjusted to 8.0 by addition of aqueous sodium hydroxide and extracted with dichloromethane. After drying over sodium sulfate, the organic solvent was evaporated to provide **12** (0.27 g, 84%) as a colourless solid: mp 127–129 °C; ^{1}H NMR (DMSO-d_6) 9.05 (s, 1H), 7.55 d, J = 8.9 Hz, 2H), 7.21 (d, J = 8.9 Hz, 2H), 4.67 (s, 2H), 4.16 (s, 2H), 3.94 (dd, J = 3.6 and 4.4 Hz, 2H), 3.67 (dd, J = 3.6 and 4.6 Hz, 2H), 3.39 (t, J = 7.3 Hz, 2H), 1.65–1.50 (m, J = 7.3 Hz, 2H), 0.84 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 293 [(M + H)$^+$].

15. Experimental procedure for 1-[*N*-(4-chlorophenyl)-carbamoyl]- 4-[4-(3-oxo-4-morpholinyl)-phenyl]-2-propylsemicarbazide **5a**: A solution of semicarbazide **12** (0.25 g, 0.86 mmol) in tetrahydrofuran (5 mL) was treated at room temperature with 4-chlorophenyl isocyanate **6** (0.13 g, 0.86 mmol) for 18 h. On diluting with water (20 mL) the precipitated product was filtered off, washed with water and dried to give **5a** (0.3 g, 78%) as a colourless solid: mp 131–133 °C; ^{1}H NMR (DMSO-d_6) δ 8.97 (s, 1H), 8.88 (s, 1H), 8.38 (s, 1H), 7.58 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 8.9 Hz, 2H), 7.31 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 4.16 (s, 2H), 3.95 (t, J = 5.0 Hz, 2H), 3.68 (t, J = 5.0 Hz, 2H), 3.52–3.34 (m, 2H), 1.60.1.50 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); MS (FAB) m/z 447 [(M + H)$^+$].