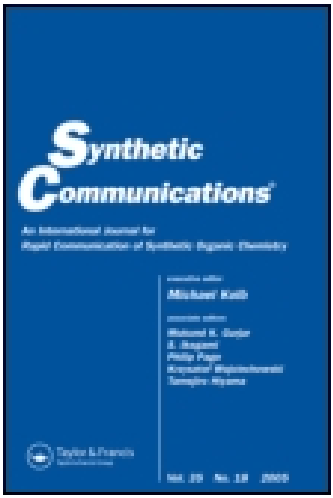

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of Various Nitro-Substituted Derivatives of Semaxinib (SU5416)

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Published online: 28 Aug 2008.

To cite this article: Torsten Kniess, Manuela Kuchar & Frank Wuest (2008) Facile Synthesis of Various Nitro-Substituted Derivatives of Semaxinib (SU5416), Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:17, 3017-3022, DOI: 10.1080/00397910802044256

To link to this article: http://dx.doi.org/10.1080/00397910802044256

Synthetic Communications®, 38: 3017–3022, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802044256

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Facile Synthesis of Various Nitro-Substituted Derivatives of Semaxinib (SU5416)

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Abstract: The synthesis of novel nitro-substituted derivatives of the tyrosine kinase inhibitor Semaxinib (SU5416) is described. The reaction of various substituted oxindoles with 3,5-dimethylpyrrol-2-carbaldehyde derivatives under Knoevenagel conditions gave an array of nitro-substituted derivatives of Semaxinib (SU5416) in high yields of 72–87%.

Keywords: Nitration, semaxinib, tyrosine kinase

Semaxinib (3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]-indolin-2-on, SU5416) is a potent inhibitor of signaling activity of the receptor tyrosine kinases (RTKs) for the vascular endothelial growth factor (VEGF) and has been investigated up to now in clinical phase II studies as anti-angiogenic agent.[1–4] A broad arsenal of substituted SU5416 derivatives has been designed and synthesized, and their potency and selectivity against RTKs and VEGF was tested.[5,6]

SU5416 derivatives, which are appropriately labeled with the short-lived positron emitter ^{18}F ($t_{1/2} = 109.8$ min) as a bioisosteric substitution for hydrogen, would allow noninvasive in vivo studies of RTKs and VEGF by means of positron emission tomography (PET).[7] The introduction of ^{18}F into aromatic compounds is usually accomplished via nucleophilic substitution of aromatic nitro compounds with [^{18}F]fluoride.[8] In the course of our research efforts to prepare ^{18}F-labeled SU5416 derivatives, it became obvious that a facile synthesis of nitro-substituted SU5416 compounds has not been reported yet. Herein,

Received November 16, 2007.
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we describe an approach for the facile and convenient synthesis of various nitro-substituted SU5416 derivatives.

Commonly, Semaxinib is synthesized by a Knoevenagel condensation of oxindole **1a** with 3,5-dimethylpyrrol-2-carbaldehyde **2a** as the key reaction step.[5]

Direct nitration of parent SU5416 to obtain nitro-substituted SU5416 is not feasible, because this reaction leads to the formation of a complex mixture of different nitro-substituted isomers. Hence, we envisaged an alternative approach consisting of (1) nitration of oxindole and pyrrolcarbaldehyde derivatives followed by (2) Knoevenagel condensation to afford various nitro-substituted SU5416 derivatives (Fig. 1).

Nitration is usually carried out by the reaction of oxindole **1a** with fuming nitric acid in concentrated sulphuric acid at 0 °C.[9] However, application of this method afforded 5-nitro-oxindole **1c** in very low yield of 9%. Alternatively, reaction of potassium nitrate in concentrated sulphuric acid as described by Baeyer[10] gave the desired 5-nitro compound **1c** in satisfactory 67% yield.

Synthesis of 3,5-dimethyl-4-nitro-pyrrol-2-carbaldehyde **2b** can be performed via two distinct synthetic routes. The first route commenced with a nitration reaction of 2-ethoxycarbonyl-3,5-dimethyl-pyrrole in a mixture of nitric acid and acetic acid to give ethyl-3,5-dimethyl-4-nitro-1H-pyrrole-2-carboxylate. Conversion of the ester into carbaldehyde **2b** was accomplished via McFadyen–Stevens reaction, which consists of the base-catalyzed thermal decomposition of acylbenzenesulfonylhydrazines to aldehydes.[11] For this purpose, ethyl-3,5-dimethyl-4-nitro-1H-pyrrole-2-carboxylate was reacted with benzenesulfonylhydrazide to give the corresponding acylsulfonylhydrazine derivative, which was further treated with Na_2CO_3 in ethylene glycol at 160 °C to afford the desired carbaldehyde. However, application of this three-step synthesis sequence gave compound **2b** in only a very low total yield of

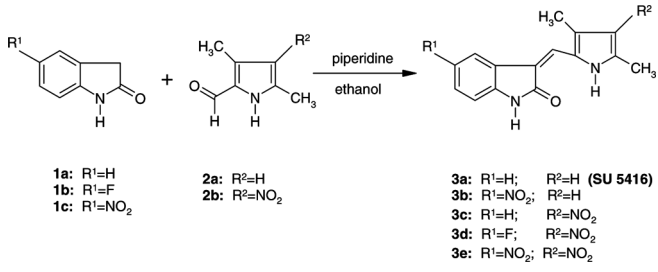

Figure 1. Synthesis of nitrosubstituted Semaxinib.

2%. Consequently, this approach is not suitable for the synthesis of sufficient amounts of 3,5-dimethyl-4-nitro-pyrrol-2-carbaldehyde **2b**.

A second synthetic route is based on the direct nitration of the 3,5-dimethylpyrrol-2-carbaldehyde **2a**. However, direct nitration of **2a** in acetic anhydride and fuming nitric acid at $-40\ ^{\circ}C$ as reported in the literature for pyrrole-2-carbaldehyde[12] gave a complex reaction mixture containing various oxidized by-products. Finally we were very pleased to find that substitution of fumic nitric acid with potassium nitrate, the use of concentrated sulphuric acid as the solvent, and performance of the reaction at $-5^{\circ}C$ gave the desired 3,5-dimethyl-4-nitro-pyrrol-2-carbaldehyde **2b** in 74% yield without formation of by-products.

The synthesis of nitro-substituted SU5416 derivatives **3b–e** was conducted through application of a Knoevenagel reaction between carbaldehydes **2a** and **2b** and oxindoles **1a–c** in boiling ethanol. This procedure gave the SU 5416 derivatives **3b–e** derivatives in very good yield of 72–87%.

The submitted synthetic route represents a convenient and reliable approach for the preparation of an array of different nitro-substituted SU5416 derivatives **3b–e**. The use of nitro-substituted compounds **3b–e** as labeling precursors for the radiolabeling with [^{18}F]fluoride is currently in progress.

EXPERIMENTAL

All chemicals as oxindole (2-indolinon) **1a**, 5-fluoro-oxindole **1b**, 3,5-dimethylpyrrol-2-carbaldehyde **2a**, potassium nitrate, and solvents were purchased from commercial suppliers. Melting points were determined with an apparatus Galen^{TM}III (Cambridge Instruments) and are uncorrected. ^{1}H NMR spectra were recorded on an Inova-400 spectrometer (Varian) at 400 MHz in DMSO-d_6; chemical shifts (δ) were determined relative to the solvent and converted to the TMS scale. Mass spectra were obtained on a Quattro/LC mass spectrometer (Micromass).

5-Nitro-oxindole 1c

Oxindole **1a** (1.33 g, 10 mmol) was dissolved in 13.3 g (7.26 mL) of cold concentrated sulphuric acid at $0\ ^{\circ}C$. After complete dissolution 1.01 g (10 mmol) of potassium nitrate was added portion for portion. The temperature of the mixture should not exceed $5\ ^{\circ}C$. After further stirring for 30 min, the mixture was added to 200 mL of crushed ice. The precipitate was collected by filtration, washed with water, and dried. The raw product was purified by recrystallization from acetic acid (50%) to give

1.2 g of **1c** as an orange solid. Yield: 67%, mp 249–254 °C (lit.[7] 240–241 °C]. ^{1}H NMR δ (ppm): 3.62 (s, 2H, CH_2), 6.96 (d, 1H, H_7), 8.07 (s, 1H, H_4), 8.14 (d, 1H, H_6), 11.04 (s, 1H, NH). ESI-MS (ES+): m/z 201 $[M + Na]^+$.

3,5-Dimethyl-4-nitro-pyrrol-2-carbaldehyde 2b

3,5-Dimethylpyrrol-2-carbaldehyde **2a** (246 mg, 2 mmol) was dissolved in 3 mL of concentrated sulphuric acid. The temperature should be kept at 0 °C by an ice–salt mixture. The solution was cooled at −5 °C, and 202 mg (2 mmol) of potassium nitrate were added. The mixture was allowed to warm up to room temperature and then added to 75 mL of crushed ice. The precipitate was separated by filtration, washed with water, and dried. The product was obtained as 250 mg of a grey solid and used without further purification. Yield: 74%, mp 220–229 °C decomp. [Lit.[9] 226–230 °C]. ^{1}H NMR δ (ppm): 2.52 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 9.72 (s, 1H, H_{CO}), 12.87 (s, 1H, NH). ESI-MS (ES −): m/z 167 $[M - H]^-$.

General Procedure for Knoevenagel Condensation

Oxindole **1a**–**c** (2 mmol) and 2.4 mmol of 3,5-dimethylpyrrol-2-carbaldehyde **2a,b** were refluxed in 4 mL of ethanol with four drops of piperidine for 4–5 h. The solvent was removed in vacuum, and the residue was purified by washing with ethyl acetate or recrystallization from dioxane.

Data

Compound **3b**: 3-[(2′,4′-Dimethylpyrrol-5′-yl)methylindenyl]-5-nitro-indolin-2-one, yield: 72%, mp > 280 °C (decomp.). ^{1}H NMR δ (ppm): 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.08 (s, 1H, $H_{3'}$), 7.03 (d, 1H, H_7), 7.93 (s, 1H, H_4), 8.02 (d, 1H, H_6), 8.76 (s, 1H, H_{vinyl}), 11.42 (s, 1H, $NH_{oxindol}$), 13.10 (s, 1H, NH_{pyrrol}). ESI-MS (ES+): m/z 284 [M + H].

Compound **3c**: 3-[(2′,4′-Dimethylpyrrol-3′nitro-5′-yl)methylindenyl]-indolin-2-one, yield: 84%, mp > 330 °C (decomp.). ^{1}H NMR δ (ppm): 2.55 (s, 3H, CH_3), 2.62 (s, 1H, CH_3), 6.90 (d, 1H, H_7), 7.02 (t, 1H, H_6), 7.19 (t, 1H, H_5), 7.71 (s, 1H, H_{vinyl}), 7.86 (d, 1H, H_4), 11.40 (s, 1H, $NH_{oxindol}$), 14.34 (s, 1H, NH_{pyrrol}). ESI-MS (ES+): m/z 306 [M + Na].

Compound **3d**: 3-[(2′,4′-Dimethylpyrrol-3′nitro-5′-yl)methylindenyl] -5-fluoro-indolin-2-one, yield 87%, mp > 340 °C (decomp.). ^{1}H NMR δ (ppm); 2.56 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 6.86 (dd, 1H, H_7), 6.99 (dt, 1H, H_6), 7.80 (s, 1H, H_{vinyl}), 7.85 (dd, 1H, H_4), 11.12 (s, 1H, $NH_{oxindol}$), 14.34 (s, 1H, NH_{pyrrol}).

Compound **3e**: 3-[(2′,4′-Dimethylpyrrol-3′nitro-5′-yl)methylindenyl]-5-nitro-indolin-2-one, yield 76%, mp > 320 °C (decomp.). ^{1}H NMR δ (ppm): 2.62 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 7.06 (d, 1H, H_7), 8.10 (d, 1H, H_6), 8.13 (s, 1H, H_{vinyl}), 8.97 (s, 1H, H_4), 11.73 (s, 1H, $NH_{oxindol}$), 14.36 (s, 1H, NH_{pyrrol}).

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