NEW 2*H*-PYRAZOLO[4,3-*c*]PYRIDINES: SYNTHESIS, OPTICAL PROPERTIES AND ELUCIDATION OF ANTI-CANCER ACTIVITY

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Introduction

Pyrazole is a common structural unit in many pharmaceuticals and a central axis of numerous ongoing studies devoted to the synthesis and biological evaluation of novel pyrazole moiety-bearing molecules. Annelated pyrazoles are of particular interest as they constitute the core of several well-known drugs, including Sildenafil, Zaleplon and Allopurinol. Among the vast variety of up to now developed biologically active annelated pyrazole derivatives, synthetically demanding 2*H*-pyrazolo[4,3-*c*]pyridines are, however, relatively understudied. Thus, the aim of this work was to synthesize and evaluate the biological acitivity of novel 2*H*-pyrazolo[4,3-*c*]pyridine derivatives.

Firstly, 1-phenyl-3-(2-phenylethynyl)-1*H*-pyrazole-4-carbaldehyde was prepared from 1-phenyl-1*H*-pyrazol-3-ol by consecutive alkylation, formylation and Sonogashira cross-coupling reactions (**scheme 1**). Then the pyrazolo[4,3-*c*]pyridine core was obtained *via* a three step route (**scheme 2**). Firstly, carbaldehyde **4** was converted to alcohols **5** and **6** using either Gringnard reagent or reduction conditions and then transformed into azide-alkynes **7** and **8**. The latter were used in electrophilic cyclization reaction to obtain 7-iodo-2,6-diphenyl-2*H*-pyrazolo[4,3-*c*]pyridines **9** and **10**. The library of 2,4,6,7-tetrasubstituted-2*H*-pyrazolo[4,3-*c*]pyridine derivatives was obtained *via* palladium catalysed Suzuki-Miyaura cross-coupling reactions.

The newly synthesized compounds were evaluated for their cytotoxicity against two human cancer cell lines: K562 (chronic myeloid leukemia cells) and MCF-7 (breast cancer cells). In general, most tested compounds exhibited moderate cytotoxicity, with GI_{50} values in the micromolar range (**table 1**).

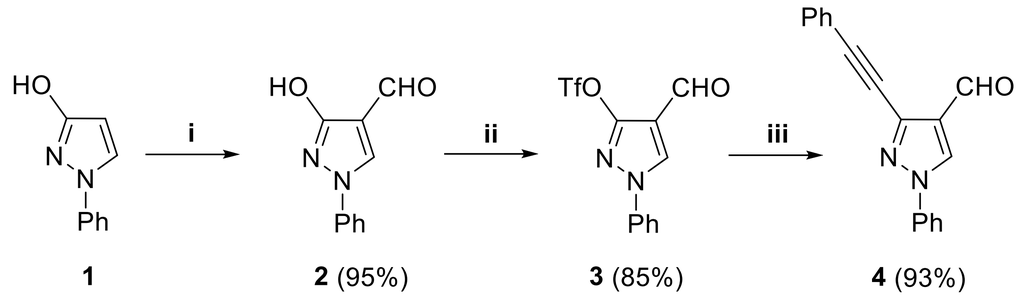
The optical properties of new derivatives were also assessed in THF solutions (**table 2**).

Optical properties

Compound	Emision λ_{em} (nm) ($\lambda_{ex\ 350nm}$)	Stokes shift (nm)	Quantum yield Φ_f (%)
11	442	130	18.91
12	461	151	71.77
13	437	126	53.21
14	447	136	26.15
15	478	167	56.84
16	449	138	17.65
17	466	117	72.21
18	450	140	48.67
19	449	139	30.03
20	481	125	62.84

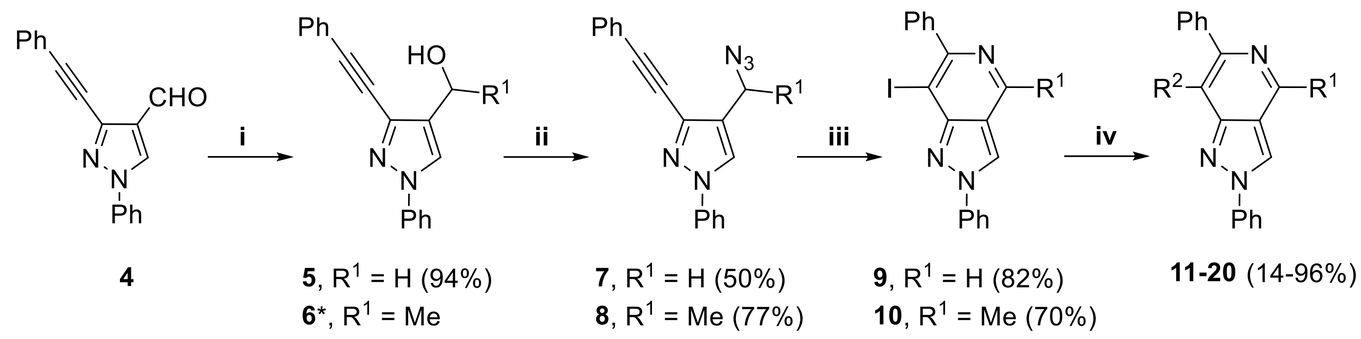
Table 2. Fluorescence parameters in THF.

Synthesis of 1-phenyl-3-(2-phenylethynyl)-1*H*-pyrazole-4-carbaldehyde



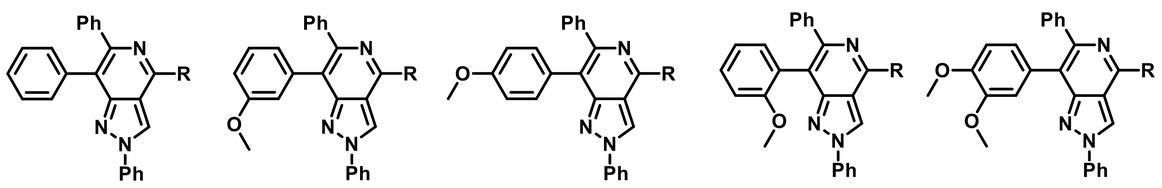
Scheme 1. *Reagents*: i: (a) NaH, BnCl; (b) $POCl_3$, DMF; (c) TFA, toluene. ii: Tf_2O, TEA. iii: Phenylacetylene, TEA, CuI, $Pd(PPh_3)_2Cl_2$.

Synthesis of 2,4,6,7-tetrasubstituted-2*H*-pyrazolo[4,3-*c*]pyridines



Scheme 2. *Reagents:* i: MeMgBr (for **6**) or $NaBH_4$ (for **5**); ii: $TMSN_3$, $BF_3{\cdot}Et_2O$; iii: $NaHCO_3$, I_2 (for **10**) or K_3PO_4, I_2 (for **9**); iv: $R^2B(OH)_2$, $Pd(OAc)_2$, Cs_2CO_3. *compound **6** was used in the next step without further purification.

Biological Activity



GI_{50}, μM	**11**	**12**	**13**	**14**	**15**
K562	>50	17	41	>100	8,6
MCF-7	>50	18	89	>100	18.2
R=Me					
	16	**17**	**18**	**19**	**20**
K562	10.2	2,3	4	4,5	3,9
MCF-7	>12.5	>12.5	17.5	17.5	9.4
R=H					

Table 1. *In vitro* citotoxicity of 2,4,6,7-tetrasubstituted-2*H*-pyrazolo[4,3-*c*]pyridines against breast carcinoma MCF-7 and leukemia K562 cell lines.

Acknowledgements

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