The synthesis of pyrazolopyrimidines and aminopyrazoles as a potent CDK inhibitors

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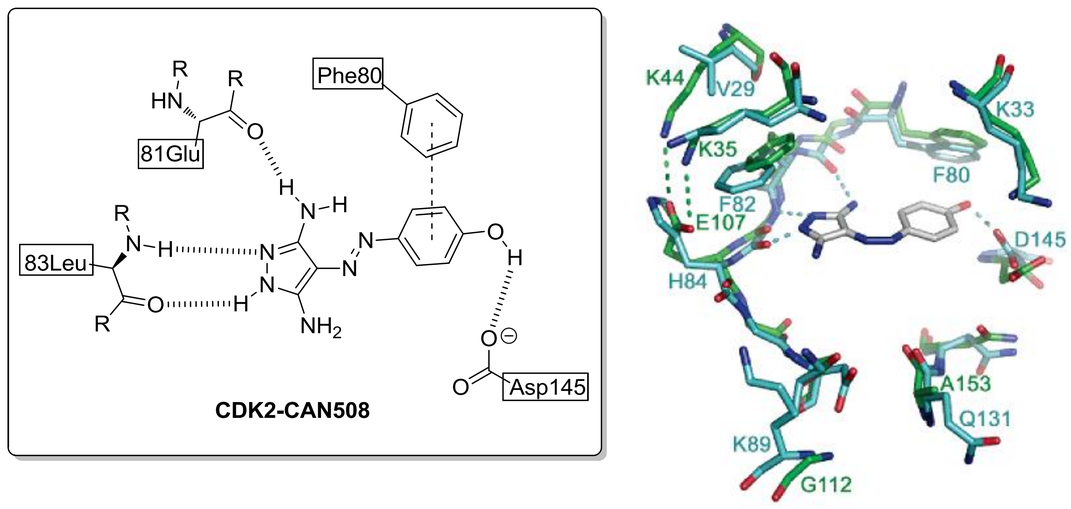
INTRODUCTION

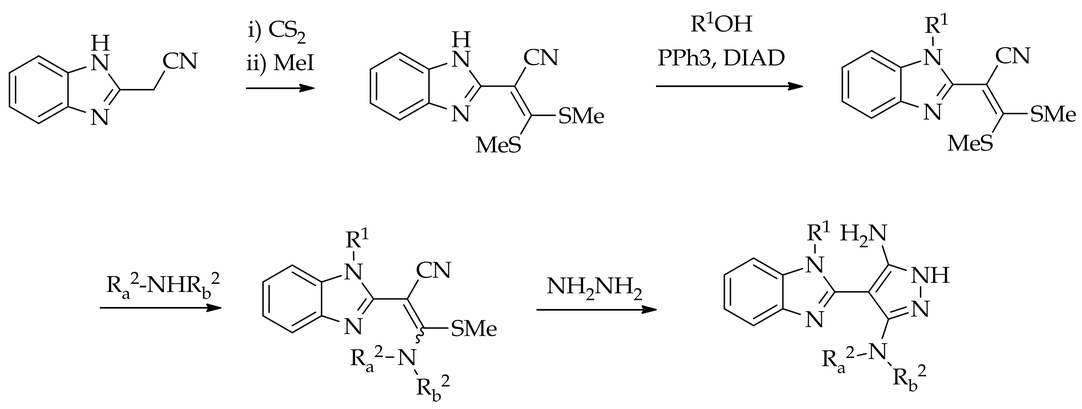
In 2006 Krystof *et al.* [1] found novel CDK inhibitor CAN508. This pyrazole showed modest inhibitory activity against several CDK, including CDK1/B, CDK2/E, CDK2/A, CDK4/D1, CDK7/H, and CDK9/T1. Therefore, aminopyrazole 508 represents a good starting point for the development of novel CDK inhibitors, which are considered useful tools for an anticancer therapy. In this work, we present synthesis and biological activity evaluation of the derivatives of aminopyrazole CAN508.

The interactions of CAN508 with CDK2/E



THE SYNTHESIS OF AMINOPYRAZOLES A1-26

Heterocyclic compounds containing both aminopyrazole and benzimidazole core were prepared via multi-step synthesis. The reaction steps include the addition of carbon disulfide, methylation, Mitsunobu alkylation, substitution of thiomethyl group by an amine and cyclisation with hydrazine.



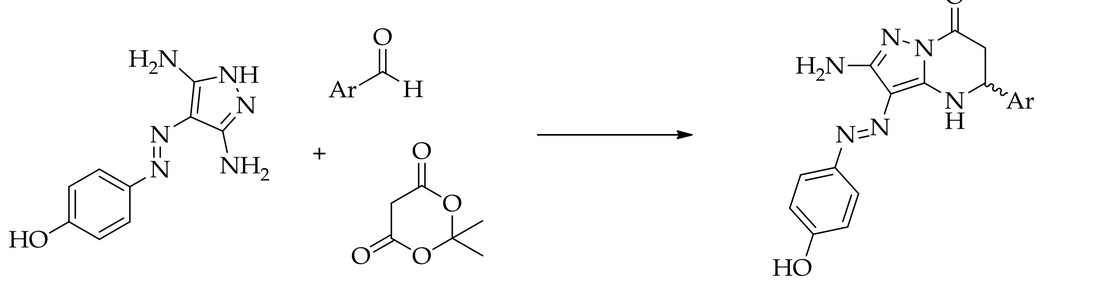
aminopyrazoles **A1-26**

R^1 = hydrogen, alkylamine, alkylpyridine

R^2 = propylamine, piperidine, morpholine, aniline...

THE SYNTHESIS OF PYRAZOLOPYRIMIDINES B1-17

Pyrazolopyrimidines were obtained via regioselective three-component synthesis of aminopyrazole CAN508, Meldrum´s acid and arylaldehydes. The regioselectivity of the reaction was proved by X-ray crystallography.



pyrazolopyrimidines **B1-17**

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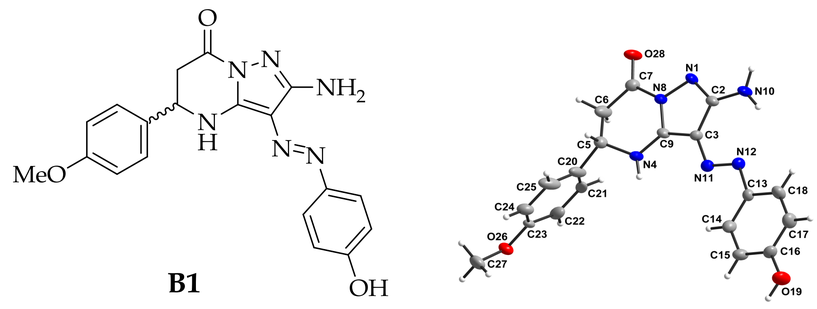
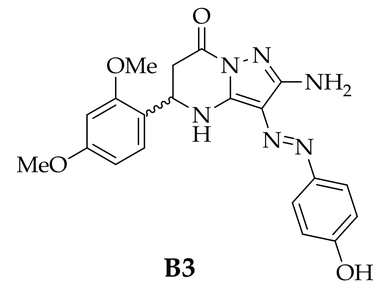
X-ray structure of representative pyrazolopyrimidine **B1**



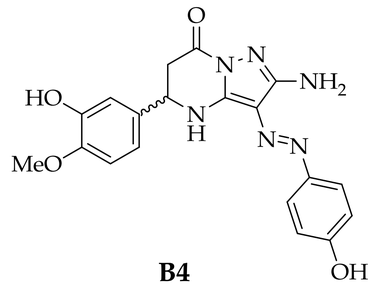
B1

BIOLOGICAL ACTIVITY OF COMPOUNDS A1-A26 AND B1-17

IC_{50} values for the inhibition activity against CDK2/cyclin E, and 50 % growth inhibition (GI_{50}) of cancer cell lines K562, and MCF7 were evaluated. The most potent pyrazolopyrimidines **B3** and **B4** displayed modest inhibition of CDK2/E, but were not active in cells.

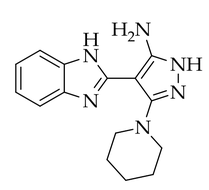


B3
IC_{50} (CDK2/E) = 18 μM
GI_{50} (K562) = >50 μM
GI_{50} (MCF7) = >50 μM

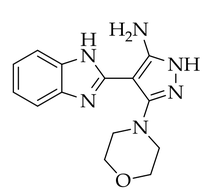


B4
IC_{50} (CDK2/E) = 20 μM
GI_{50} (K562) = >50 μM
GI_{50} (MCF7) = >50 μM

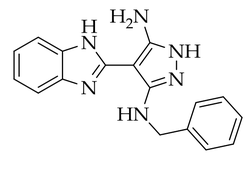
From the aminopyrazole series **A1-26**, only compounds with unsubstituted benzimidazole (R1 = H) showed some activity. Four aminopyrazoles **A21**, **A22**, **A25**, and **A26** were potent inhibitors of CKD2/cyclin E with IC_{50} around 30 μM. Pyrazoles **A25** and **A26** showed 50% growth inhibition of cancer cell lines in a concentration around 20 μM.



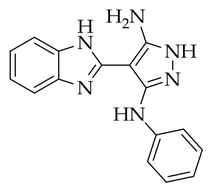
A21
IC50 (CDK2/E) 38 μM
GI50 (K562) >100 μM
GI50 (MCF7) >100 μM



A22
IC50 (CDK2/E) 44 μM
GI50 (K562) >100 μM
GI50 (MCF7) >100 μM



A25
IC50 (CDK2/E) = 62 μM
GI50 (K562) = 41 μM
GI50 (MCF7) = 33 μM



A26
IC50 (CDK2/E) = 23 μM
GI50 (K562) = 20 μM
GI50 (MCF7) = 11 μM

In conclusion, novel pyrazoles and pyrazolopyrimidines with modest inhibitory activity against CDK2/E were synthesized. Pyrazoles **A25** and **A26** showed cell growth inhibition comparable to pyrazole CAN508 and purine derivative Roscovitine.

REFERENCES

1. Krystof, V., *et al.*, *J. Med. Chem.* **2006**, 49, 6500 – 6509.
2. Jedinak, L., *et al.*, *Heterocycles* , **2014**.
3. Schutznerova, *et. al.*, *Tetrahedron* **2012**, 68, 3396 – 4002.

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