SYNTHESIS AND STRUCTURAL ANALYSIS OF NOVEL ISOMERIC AMIDINO-SUBSTITUTED 2-AMINOPHENOLS

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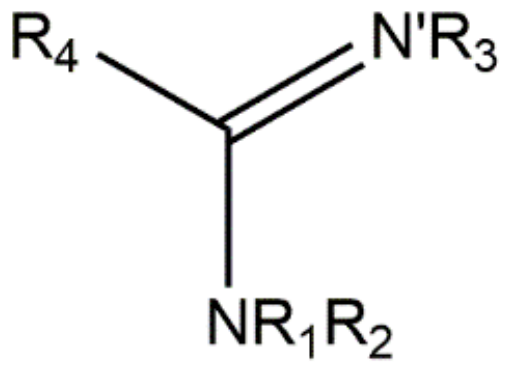
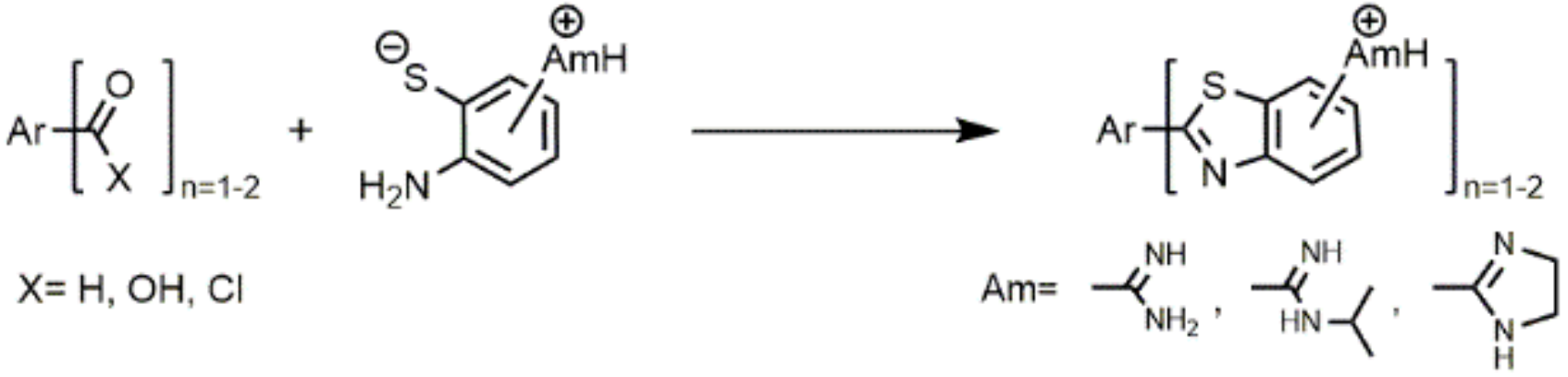
Amidines (Am)



- Nitrogen analogues of carboxylic acids
- Strong organic bases
- Protonated at physiological pH value (7.4)
- Acyclic and cyclic
- Unsubstituted, N- or N’-substituted, N,N’-disubstituted, N,N-disubstituted, N,N,N’-trisubstituted, N,N,N’,N’-tetrasubstituted cation

Background

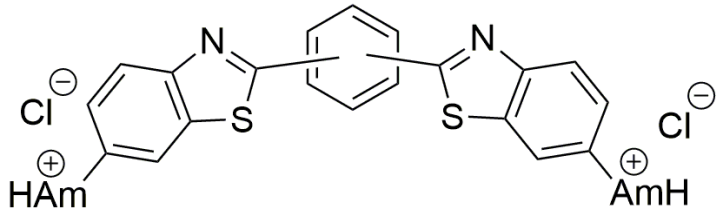
- Interesting due to their potential for diverse pharmaceutical uses
- Substituted benzothiazoles are associated with antimicrobial, antifungal and antitumor activity
- Amidines are often a part of important medical and biochemical agents



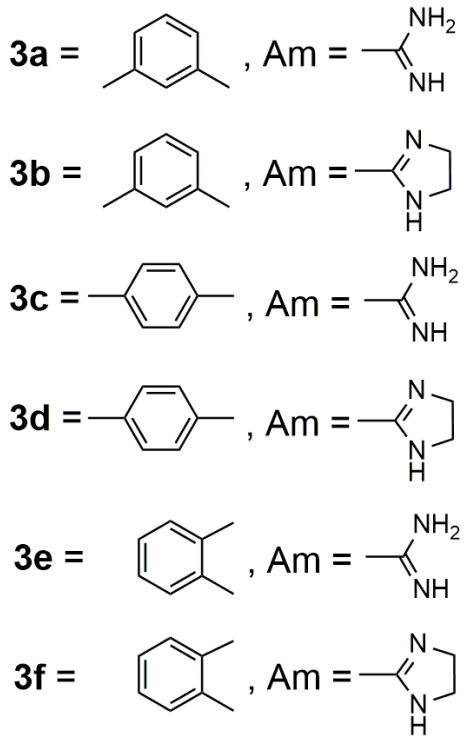
Racané, L. et al., *Eur. J. Med. Chem.* **55**, (2012) , 108-116
Racané, L. et al., *Eur. J. Med. Chem.* **86**, (2014) , 406-419

Background

- Antiproliferative effect of compounds **3a – 3f** on growth of tumor cells in vitro.



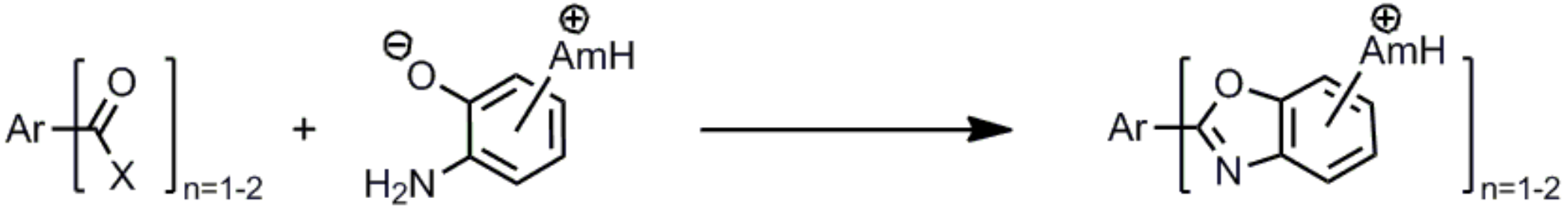
Substance	IC_{50}[a] (μM)					
	Cell lines					
	MCF-7	SK-BR-3	SW620	MiaPaCa-2	WI38	HeLa
3a	5.34	83.2	6.01	>100	0.99	>100
3b	>100	0.04	0.47	0.26	0.15	2.06
3c	9.01	8.55	>100	20.4	41.93	9.6
3d	3.07	1.18	7.65	3.54	>100	7.75
3e	30.9	86.6	>100	44.8	86.4	63.6
3f	10.14	1.86	24.7	14.6	8.99	26.8



Racané, L. et al., *Eur. J. Med. Chem.* **63**, (2013), 882-891

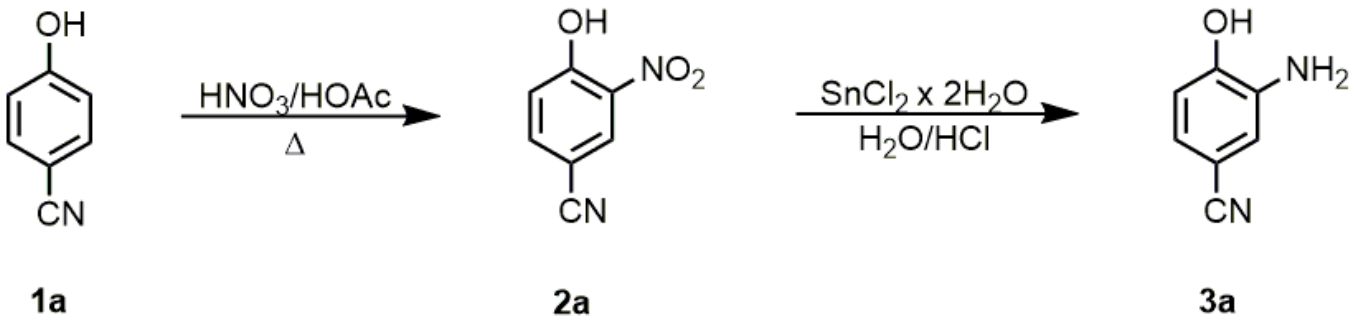
Synthetic approach – amidino-substituted benzoxazoles

- Efficient general method for benzoxazole preparation?
- Condensation reaction of amidino-substituted 2-aminophenols with aldehydes, carboxylic acids and carboxylic acid derivatives

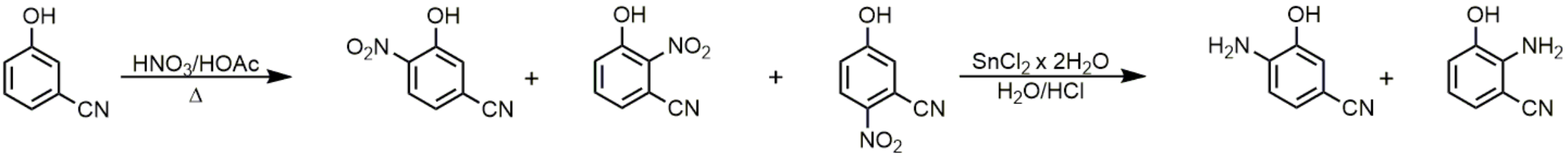


X= H, OH, Cl

Synthesis of isomeric cyano-substituted 2-aminophenols



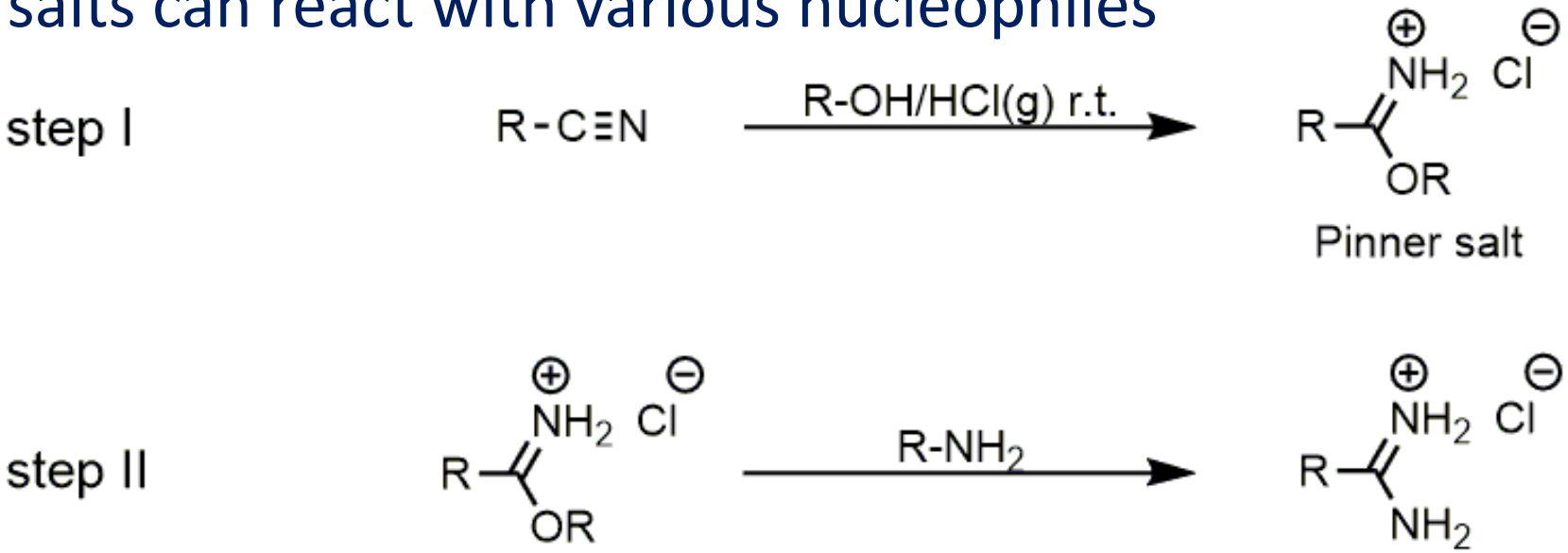
1a **2a** **3a**



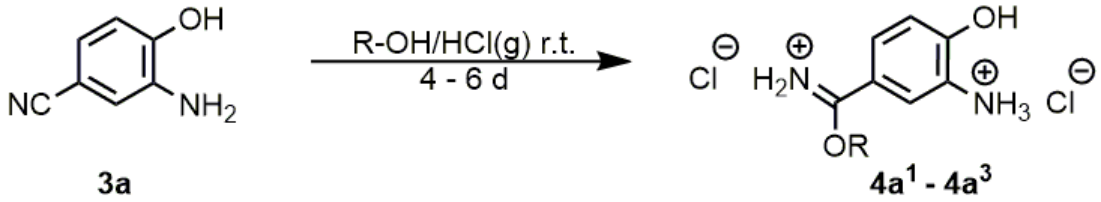
1b **2b** **2c** **2d** **3b** **3c**

Pinner reaction

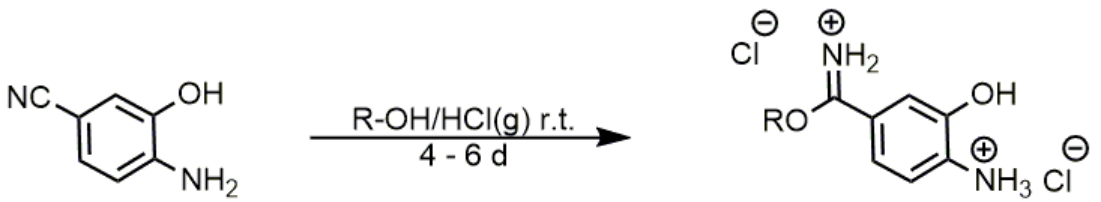
- Partial solvolysis of a nitrile to yield an imidate (imino ether) by acid catalyzed addition of alcohol to nitrile
- Treatment of nitrile with gaseous hydrochloride acid in a mixture of anhydrous alcohol produces the hydrochloride salt of an imidate
- Pinner salts can react with various nucleophiles



Pinner reaction: step I



3a **4a^1 - 4a^3**

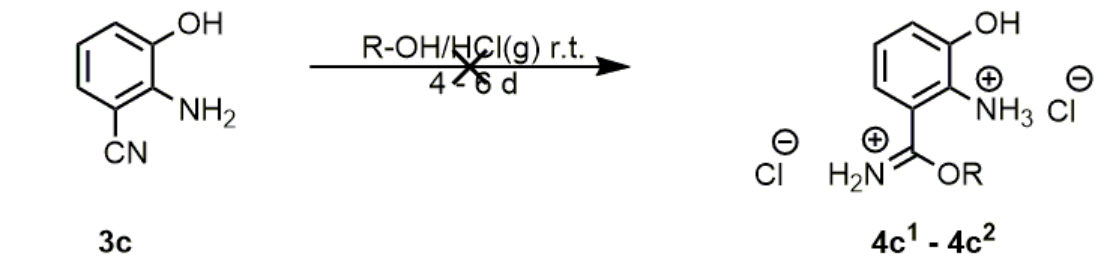


3b **4b^1 - 4b^3**

R^1=— $CH_2CH_2OCH_3$

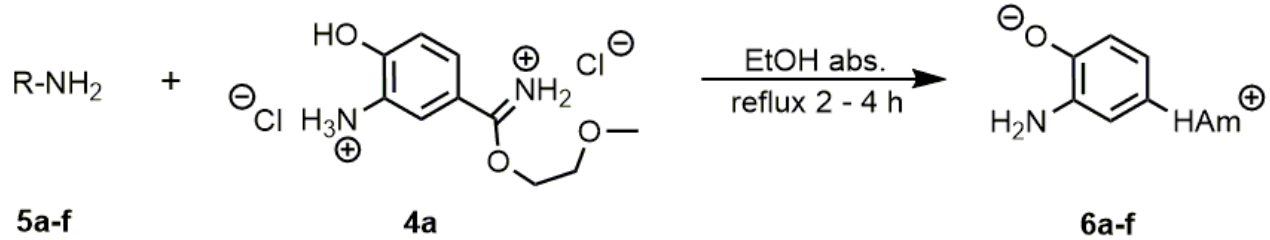
R^2=— CH_3

R^3=— $CH_2CH_2OCH_2CH_2OCH_2CH_3$



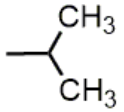
3c **4c^1 - 4c^2**

Pinner reaction: step II from 2-amino-4-cyanophenol



5a-f **4a** **6a-f**

5a; R= H

5b; R= 

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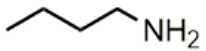
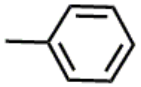
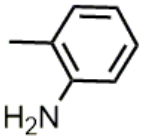
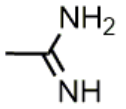
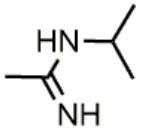
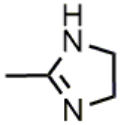
5d; R= 

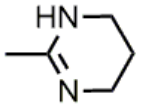
5e; R= 

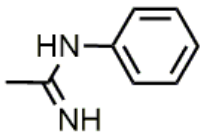
5f; R= 

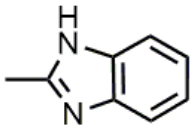
6a; Am= 

6b; Am= 

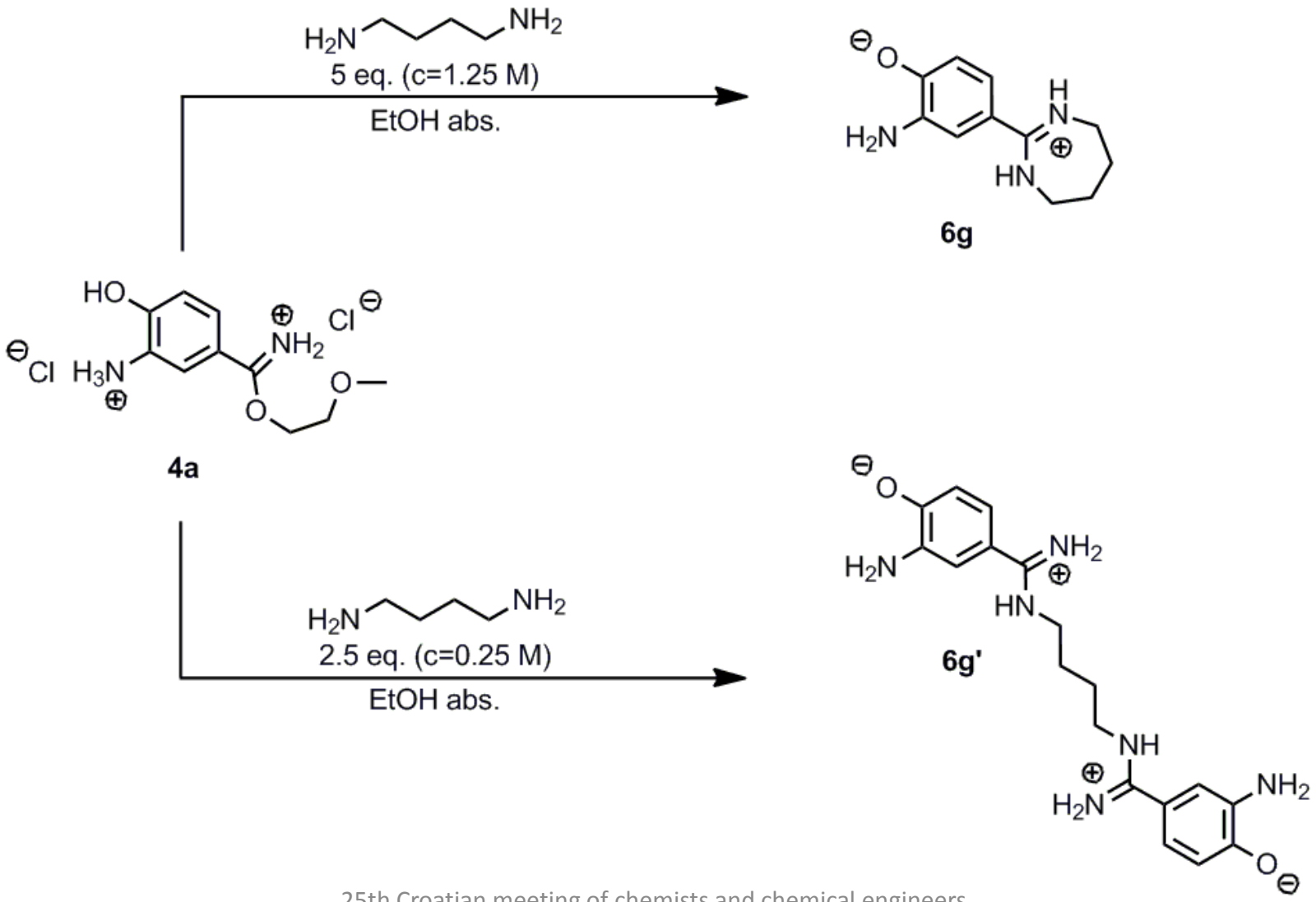
6c; Am= 

6d; Am= 

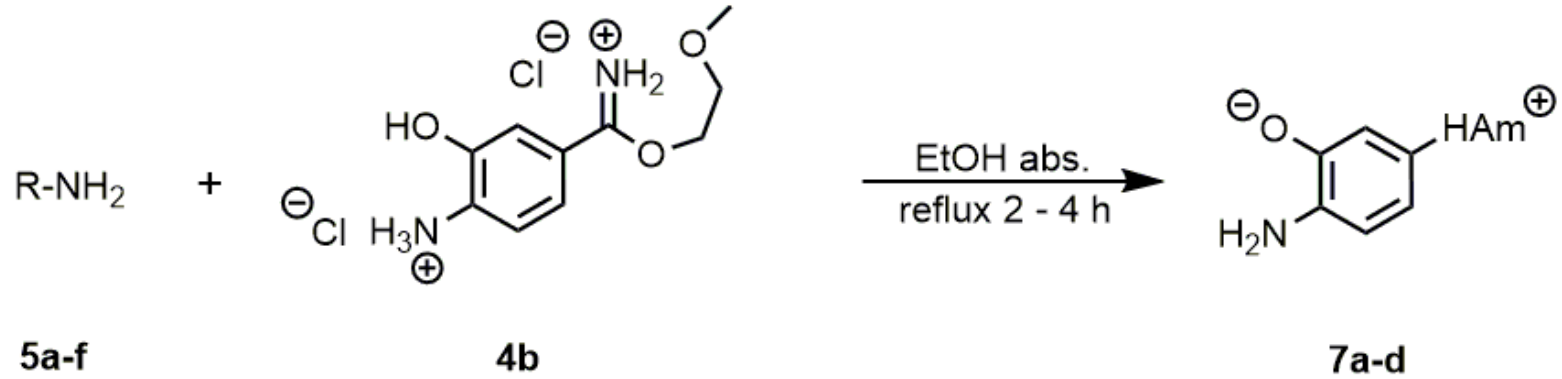
6e; Am= 

6f; Am= 

Pinner reaction: step II from 2-amino-4-cyanophenol

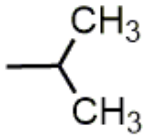


Pinner reaction: step II from 2-amino-5-cyanophenol

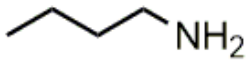


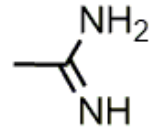
5a-f **4b** **7a-d**

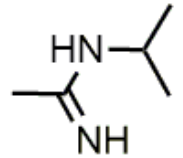
5a; R= H

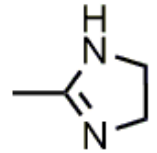
5b; R= 

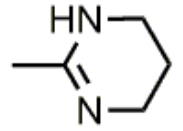
5c; R= 

5d; R= 

7a; Am= 

7b; Am= 

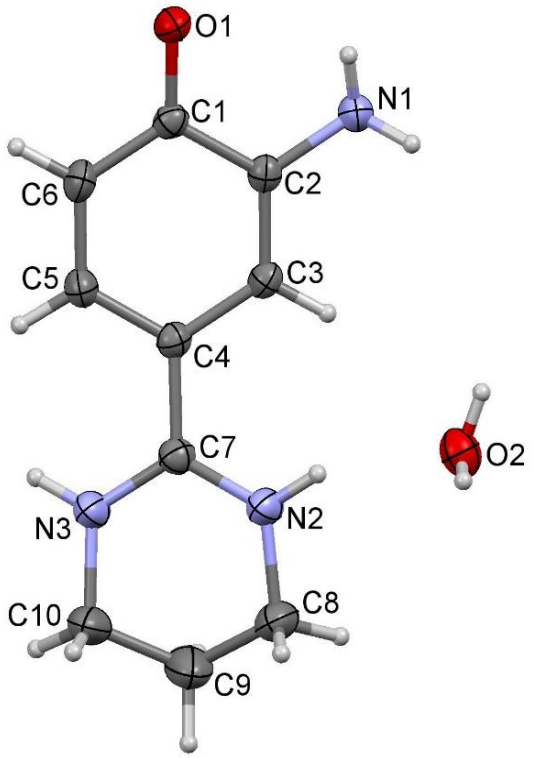
7c; Am= 

7d; Am= 

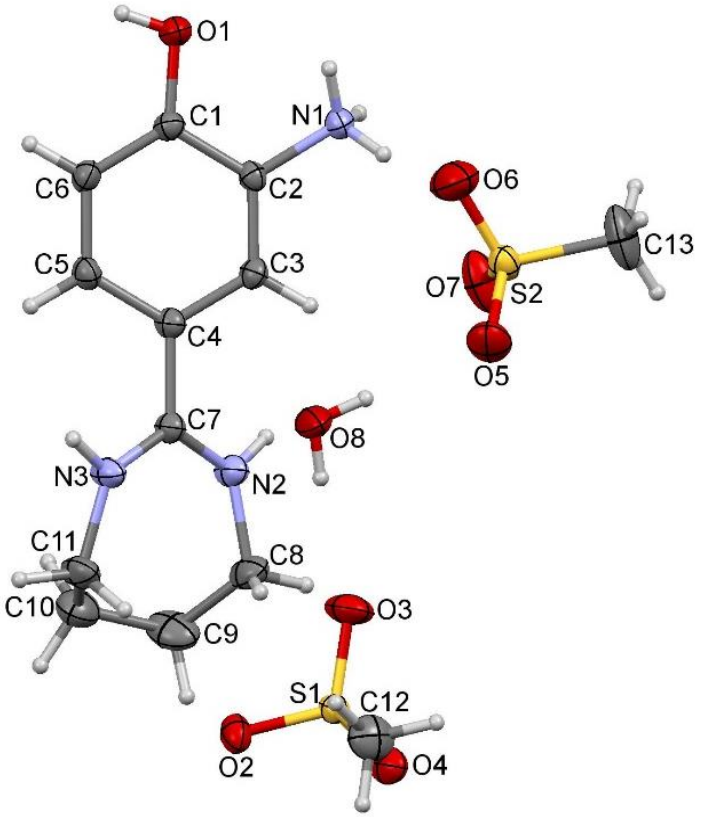
X – ray structural analysis

Selected bonds	Compound	
	7d	6g
C7 – N2	1.322 (3)	1.313 (2)
C7 – N3	1.322 (3)	1.316 (2)
C1 – O1	1.303 (3)	1.347 (2)

- **7d**: zwitterionic form

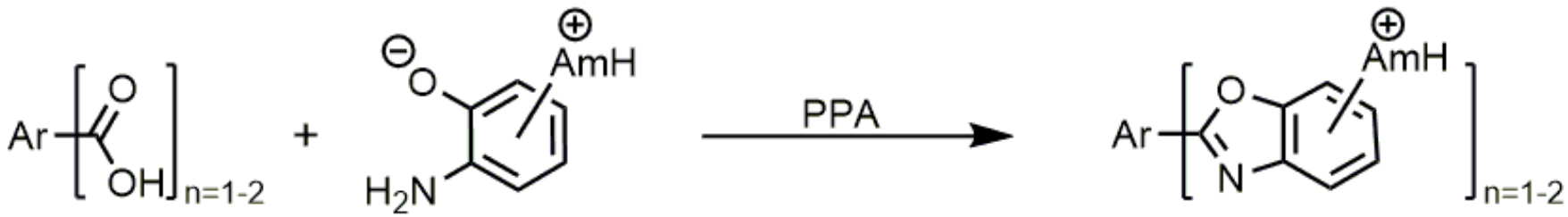


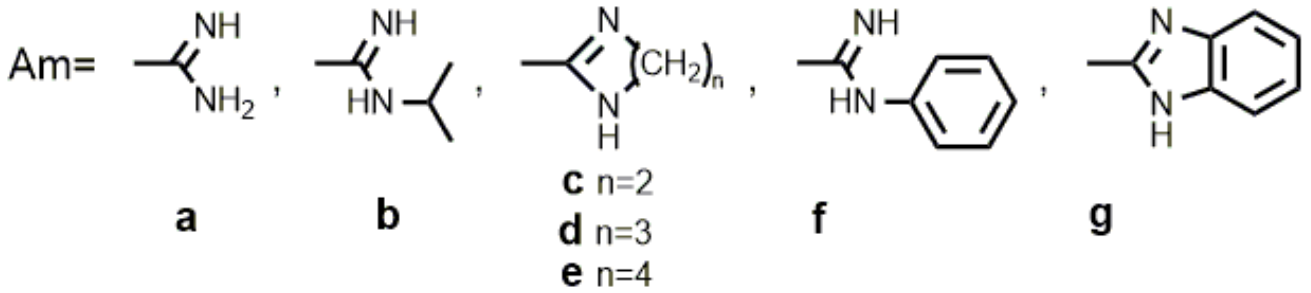
- **6g**: mesylate salt form



Current research and goals

- Preparation of isomeric amidino-substituted benzoxazole derivatives by condensation reaction in PPA and investigation of their biological activity





Thank you for your attention!

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