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Synthesis of aminated xanthones: exploiting chemical routes to reach for bioactive compounds

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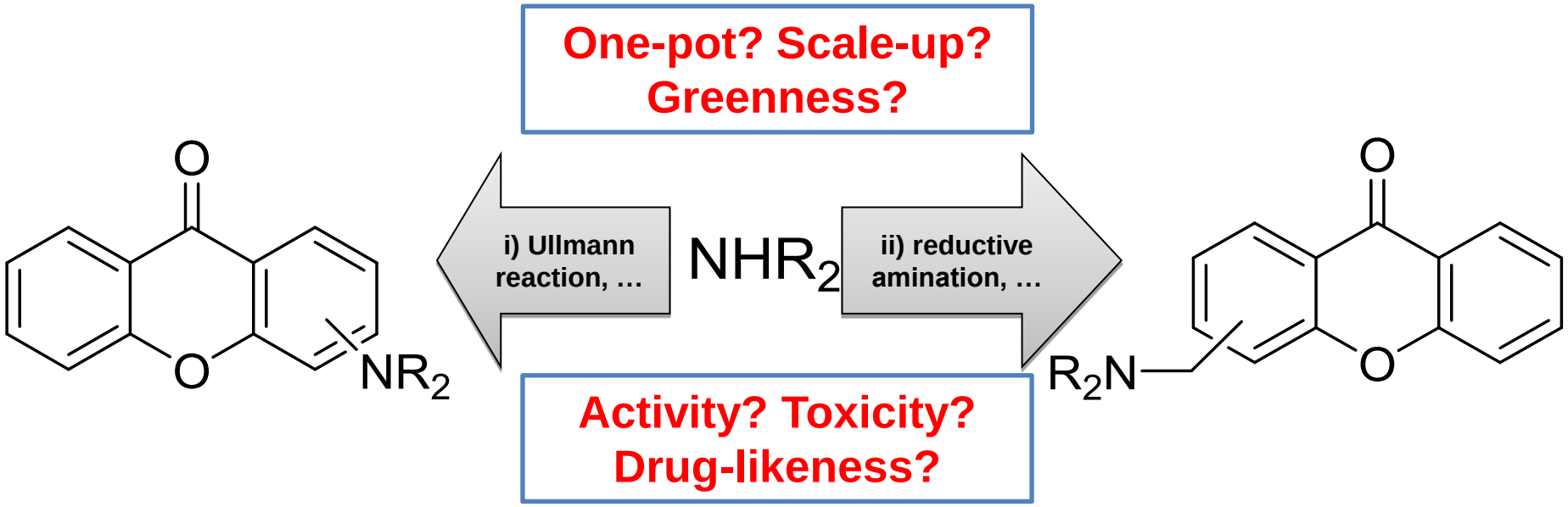
Synthesis of aminated xanthones: exploiting chemical routes to reach for bioactive compounds

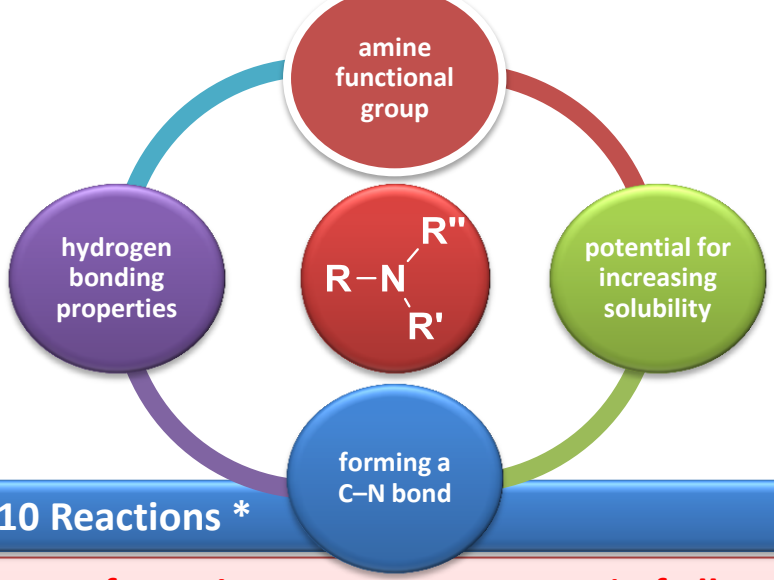
Graphical Abstract



Abstract:
Typically, about 90% of drug candidates are N-containing, and an even higher amount are O-containing. As a consequence, it is not surprising that alkylation and arylation of groups with nitrogen and oxygen emerge as major reactions to obtain bioactive compounds. Xanthones are a class of O-heterocycles characterized by a dibenzo-γ-pyrone nucleus. This scaffold may be considered a “privileged structure” able of providing useful ligands for several types of receptors and/or enzymes targets by judicious structural modifications. In our search for potential anticancer drugs we pursuit with a hybridization approach of N-containing xanthones.
Herein, exploiting chemical routes to reach for bioactive N-containing xanthones with will be shared. The synthesis of new xanthone derivatives proceeds by both strategies and the respective strengths and weakness will be presented in a “medchem” perspective. Although chemical route (i) (SN2 reactions and nucleophilic aromatic substitutions) provided interesting antitumor derivatives, the reductive amination (ii) furnished a library of potential p53:MDM2 inhibitors with noticeable advantages such as: high-yield reactions, one-pot conversions, aliphatic amines with low potential to form reactive metabolites.
The use of a variety of (thio)xanthone building blocks, with various substituents, and different reaction conditions allowed us to develop a repertoire of N-transformations.

Keywords: Ullmann Coupling; Reductive Amination; Xanthones; Bioactive compouds

Introduction



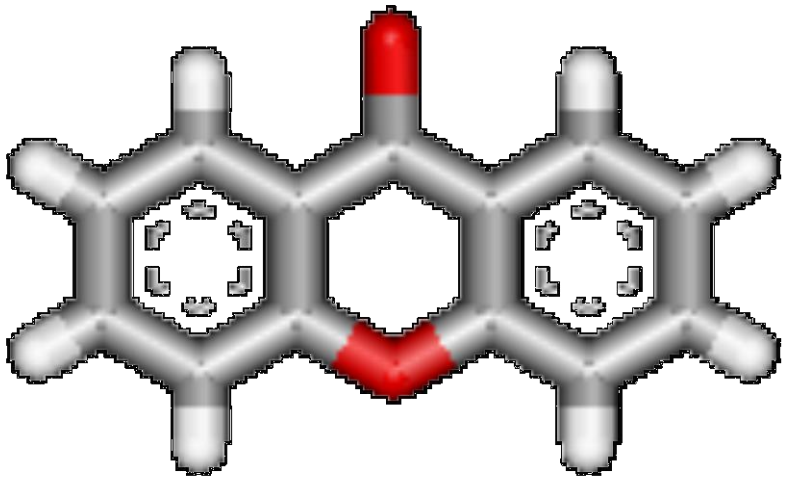
Top 10 Reactions *

reaction	no. of reactions	% of all reactions
N-acylation to amide	1165	16.0
N-containing heterocycle formation	537	7.4
N-arylation with Ar-X	**458**	**6.3**
RCO_2H deprotection	395	5.4
N-subs with alkyl-X	**390**	**5.3**
reductive amination	**386**	**5.3**
N-Boc deprotection	357	4.9
Suzuki cross-coupling reaction	338	4.6
O-substitution	319	4.4
other NH deprotection	212	2.9
total	4557	62.4

*by Frequency in the 2008 Data Set, J. Med. Chem. 2011, 54, 3451–3479

Common approach of most medicinal chemistry programs

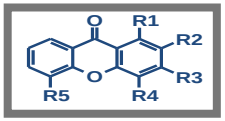
- synthesizing a common core motif
- performing multiple derivatizations of this core



Dibenzo-gamma-pirone

Pedro, M. M.; Cerqueira, F.; Sousa, M. E.; Nascimento, M. S. J.; Pinto, M. M. M. *Bioorg. Med. Chem.* 2002, *10*, 3725–3730.

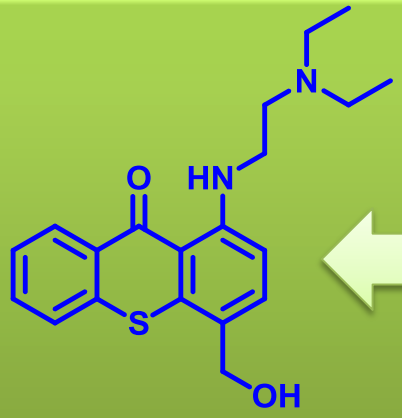
useful structure-activity relationships (SAR)



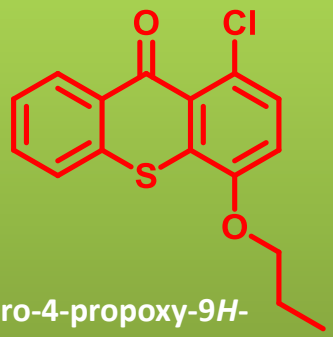
R1	R2	R3	R4	R5
OH	H	H	H	H
H	OH	H	H	H
H	H	OH	H	H
H	H	H	OH	H
OCH_3	H	H	H	H
H	OCH_3	H	H	H
H	H	OCH_3	H	H
H	H	H	OCH_3	H
OH	OH	H	H	H
H	OH	OH	H	H
H	H	OH	OH	H
H	H	OCH_3	OH	H
H	H	OH	OCH_3	H
H	H	OH	H	OH
H	H	OCH_3	H	OCH_3
H	H	OCH_3	H	OH
OH	CH_3	OH	H	H
H	OH	OH	OCH_3	H
CHO	H	OCH_3	OH	H
H	CHO	OH	OCH_3	H

Two projects of hit-to-lead optimization

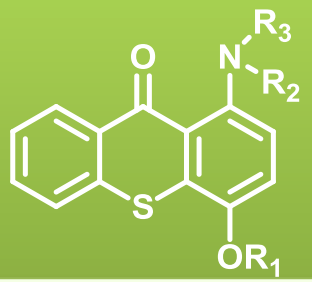
1. Optimization of an antitumor thioxanthone



lucanthone

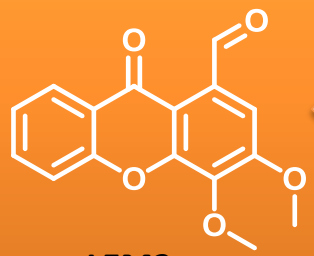


1-chloro-4-propoxy-9*H*-thioxanthen-9-one



development of P-glycoprotein inhibitors with antitumor activity

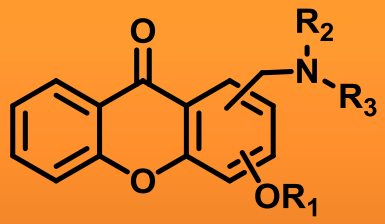
2. Optimization of a potent inhibitor of p53-MDM2 interaction



LEM2

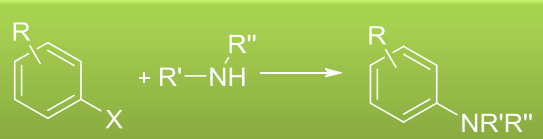
cis-Imidazoline
Morpholinone
Piperidinone
Pyrrolidine
Quinolinol

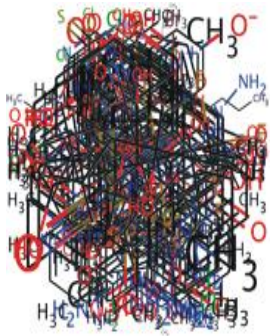
Classes of known p53:MDM2 inhibitors



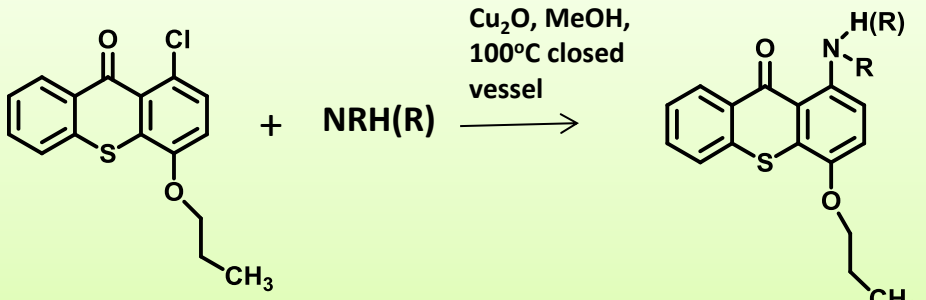
development of hybrids

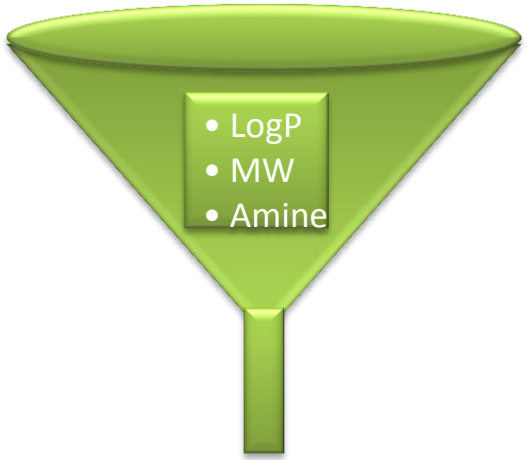
1. N-Arylation with Ar-X



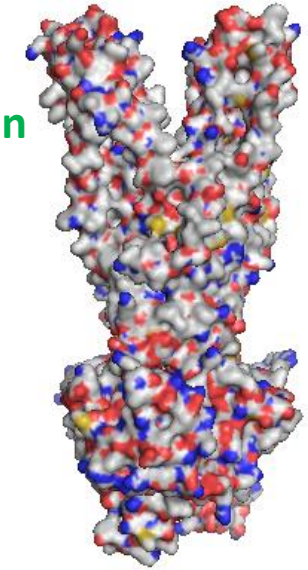


~ 1000 designed thioxanthones (Tx)



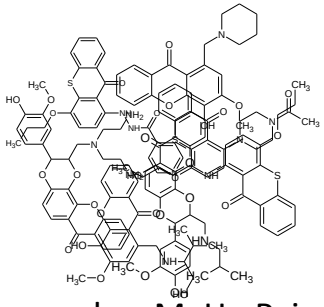


P-glycoprotein



Molecules with the best scores

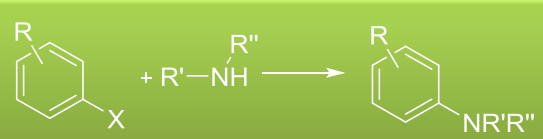
Hundreds…



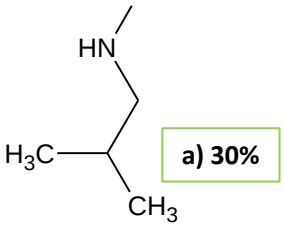
Docking

Palmeira, A.; Vasconcelos, M. H.; Paiva, A.; Fernandes, M. X.; Pinto, M.; Sousa. E. *Biochem. Pharmacol.* **2012**, *83*, 57–68.

1. N-Arylation with Ar-X



a) Cu_2O, MeOH, 100°C closed vessel, 2 days



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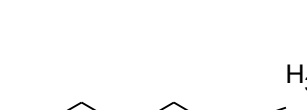

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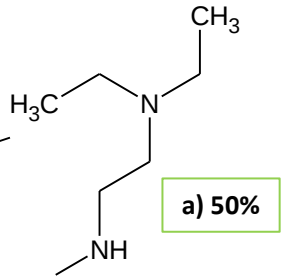

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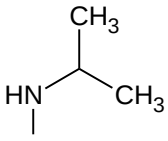

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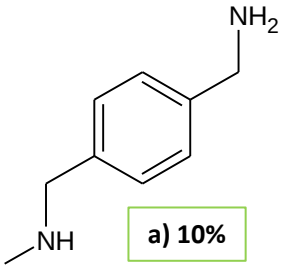

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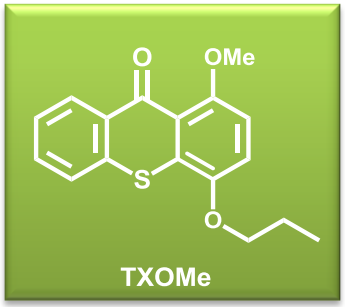
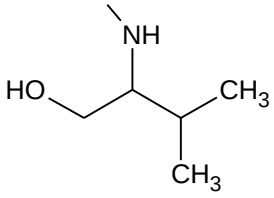
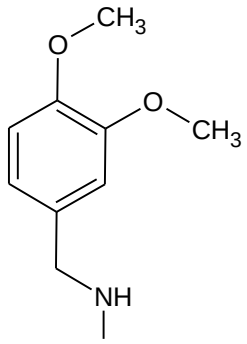
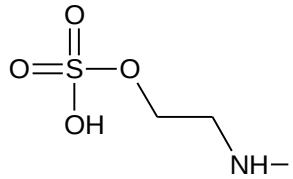
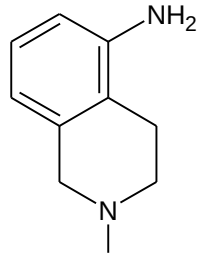
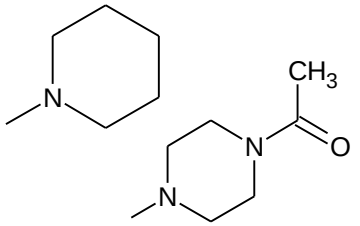


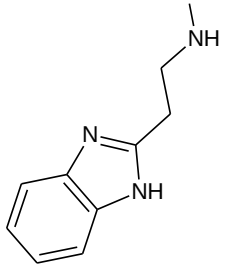


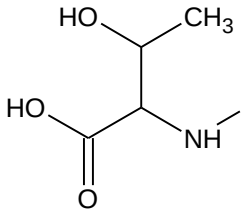


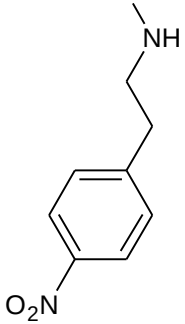


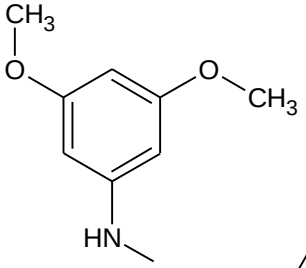


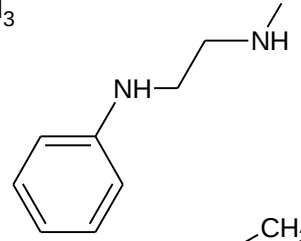


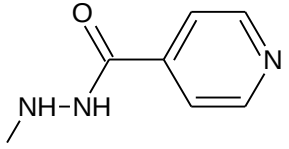


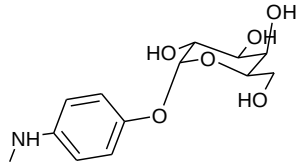


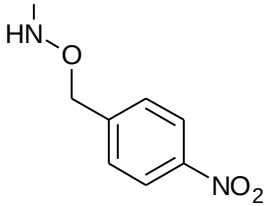


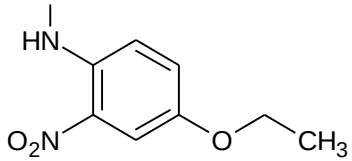


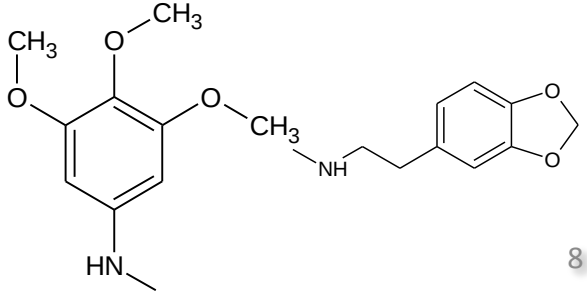




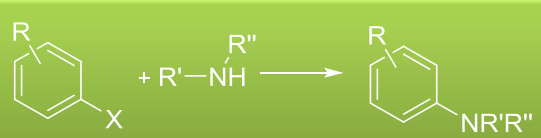








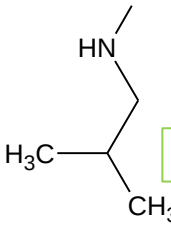
1. N-Arylation with Ar-X



a) Cu_2O, MeOH, 100°C closed vessel, 2 days

b) Cu_2O, K_2CO_3, MeOH closed vessel, 100°C, 2 days

c) Cu_2O, K_2CO_3, NMP, MW 205°C, 50 min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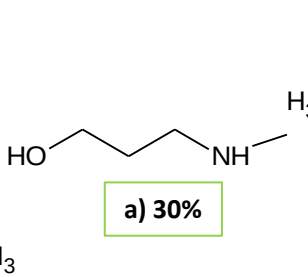
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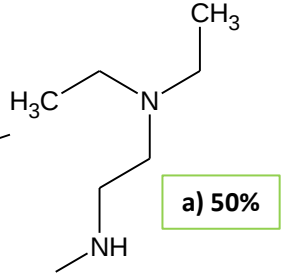
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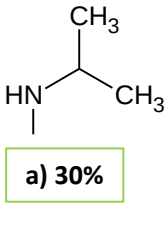
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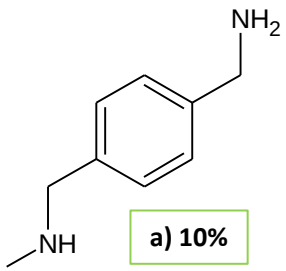
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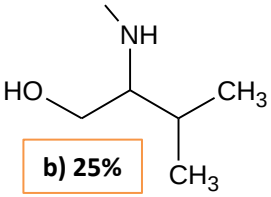
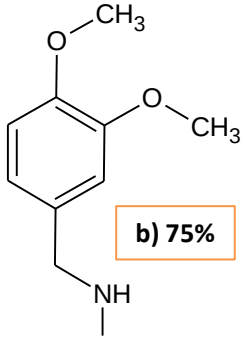
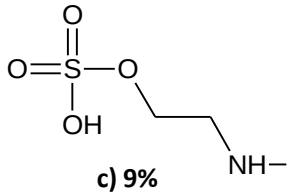
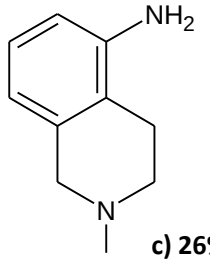

b) 25%


b) 75%


c) 9%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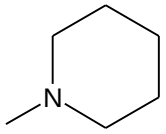
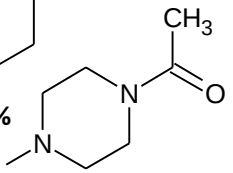
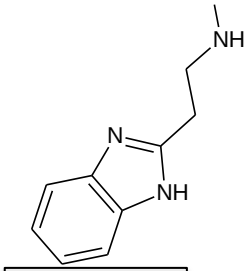
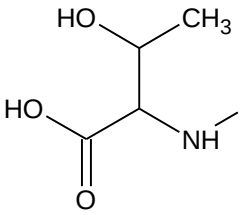
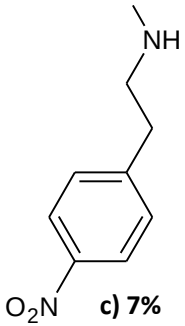
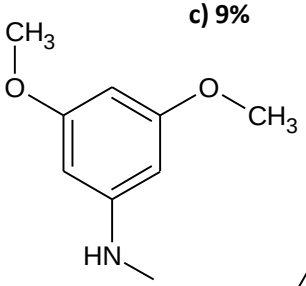

c) 30%

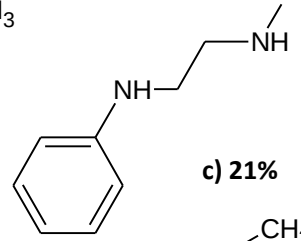

c) 65%

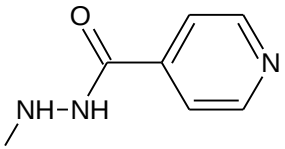

c +H_2O) 10%

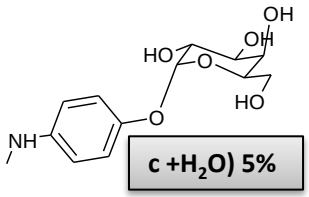

c +H_2O) 85%

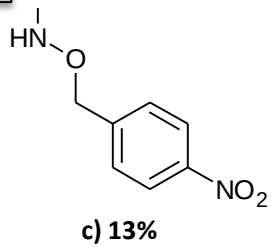

c) 7%

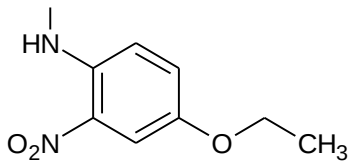

c) 28%

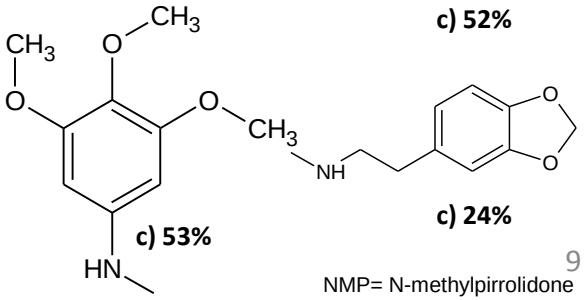

c) 21%


c) 52%


c +H_2O) 5%


c) 13%

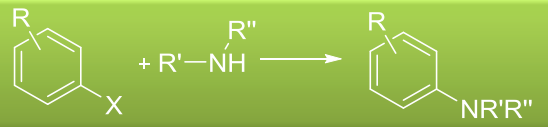

c) 47%


c) 53%

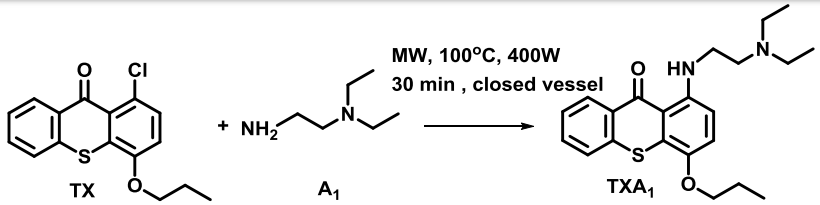
c) 24%

NMP= N-methylpirrolidone
MW= microwave

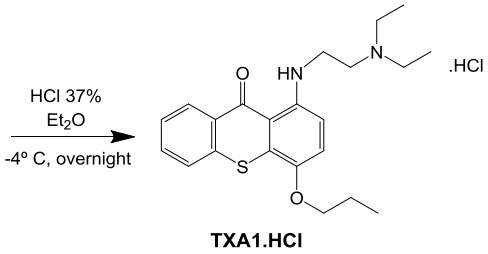
1. N-Arylation with Ar-X



Results and discussion



Catalyst	Amount of catalyst	Ligand	Base	Solvent	Yield (HPLC)	
					TXA1	TXOMe
Cu_2O	5% mol		K_2CO_3	Methanol	trace	
Cu(0)	5% mol		K_2CO_3	Methanol	trace	
CuI	5% mol		K_2CO_3	Methanol	**26**	**1**
CuI	**10% mol**		K_2CO_3	Methanol	**55**	**11**
CuI	5% mol		K_2CO_3	**Acetonitrile**	trace	
CuI	5% mol		K_2CO_3	**Isopropanol**	trace	
CuI	5% mol		K_2CO_3	**Propanol**	trace	
CuI	5% mol		K_2CO_3	**NMP**	trace	
CuI	5% mol		K_2CO_3	**Water**	trace	
CuI	5% mol		K_2CO_3	**Ethanol**	**12**	**2 (TXOEt)**
CuI	5% mol		K_2CO_3	**Formamide**	trace	
CuI	5% mol		K_2CO_3	**neat**	trace	
CuI	5% mol		**Et_3N**	**neat**	trace	
CuI	5% mol		K_2CO_3	**Ethylenoglycol**	**10**	
$Pd(dppf)Cl_2.CH_2Cl_2$	5% mol		K_2CO_3	Methanol	trace	
$Pd_2(dba)_3$:BINAP	5% mol		**tBuONa**	Methanol	trace	n.d.
$Pd_2(dba)_3$: BINAP	5% mol		**$CsCO_3$**	Methanol	trace	
CuI	5% mol	**Picolinic acid 20% mol**	K_2CO_3	Methanol	trace	
CuI	5% mol	***N,N*-dimethylglicine 20% mol**	**K_2CO_3**	**Methanol**	**43**	**4**
CuI	5% mol	N,N-dimethylglicine 20% mol	K_2CO_3	**neat**	9	
CuI	5% mol	N,N-dimethylglicine 20% mol	K_2CO_3	**Ethylenoglycol**	trace	
CuI + **Montmorillonite K10**	5% mol **+ 10eq**		K_2CO_3	Methanol	**16**	n.d.

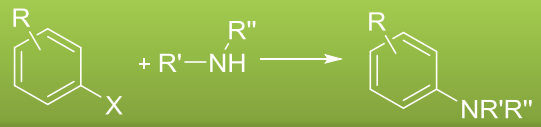


TXA1.HCl

50% overall yield (~10g)

Buchwald-Hartwig reaction

1. N-Arylation with Ar-X

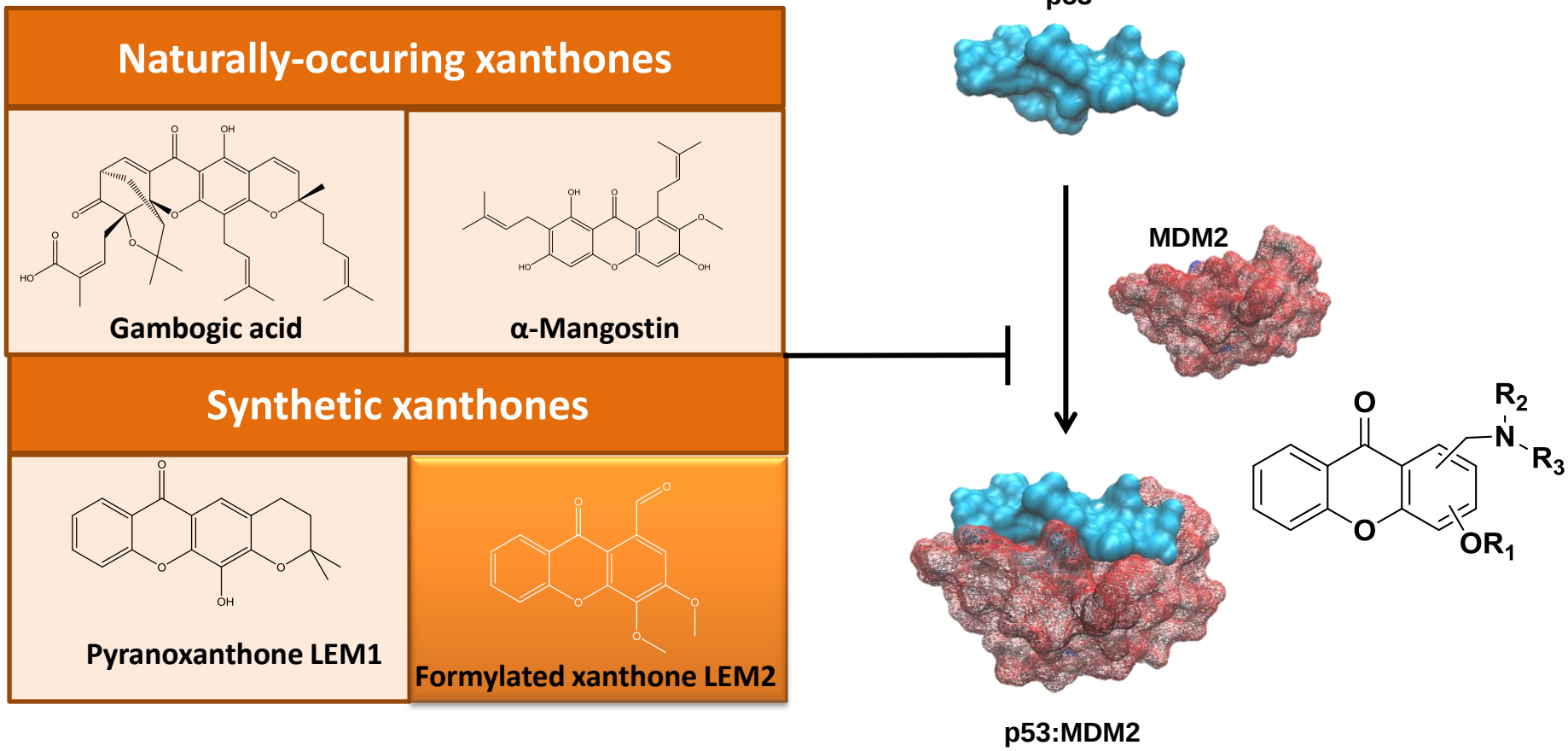


- Widespread commercial **availability halogenated** heterocyclic moieties precursor (one-pot reactions)
- **Catalysis and microwave**-assisted chemistry (CuI/*N,N*-dimethylglycine is a cheap and efficient catalytic system)
- Strategy in obtaining directly **hydrochlorides** fruitful

- Difficulty of coupling electron-rich and **low reactive** aryl chlorides and hindered, **unreactive** amine substrates (low-yield reactions)
- Only vanishingly small levels of **residual alkylating** agents and **metals** should be present in drug candidates
- N-aromatics **risks of metabolizing to anilines**

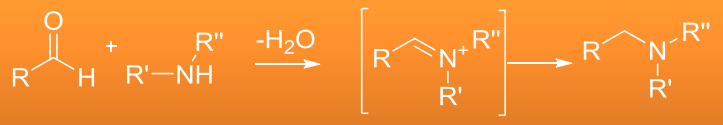
2. Optimization of a potent inhibitor of p53-MDM2 interaction

- Xanthone derivatives represent a priviliged scaffold for antitumor agents with the ability to activate p53 pathway

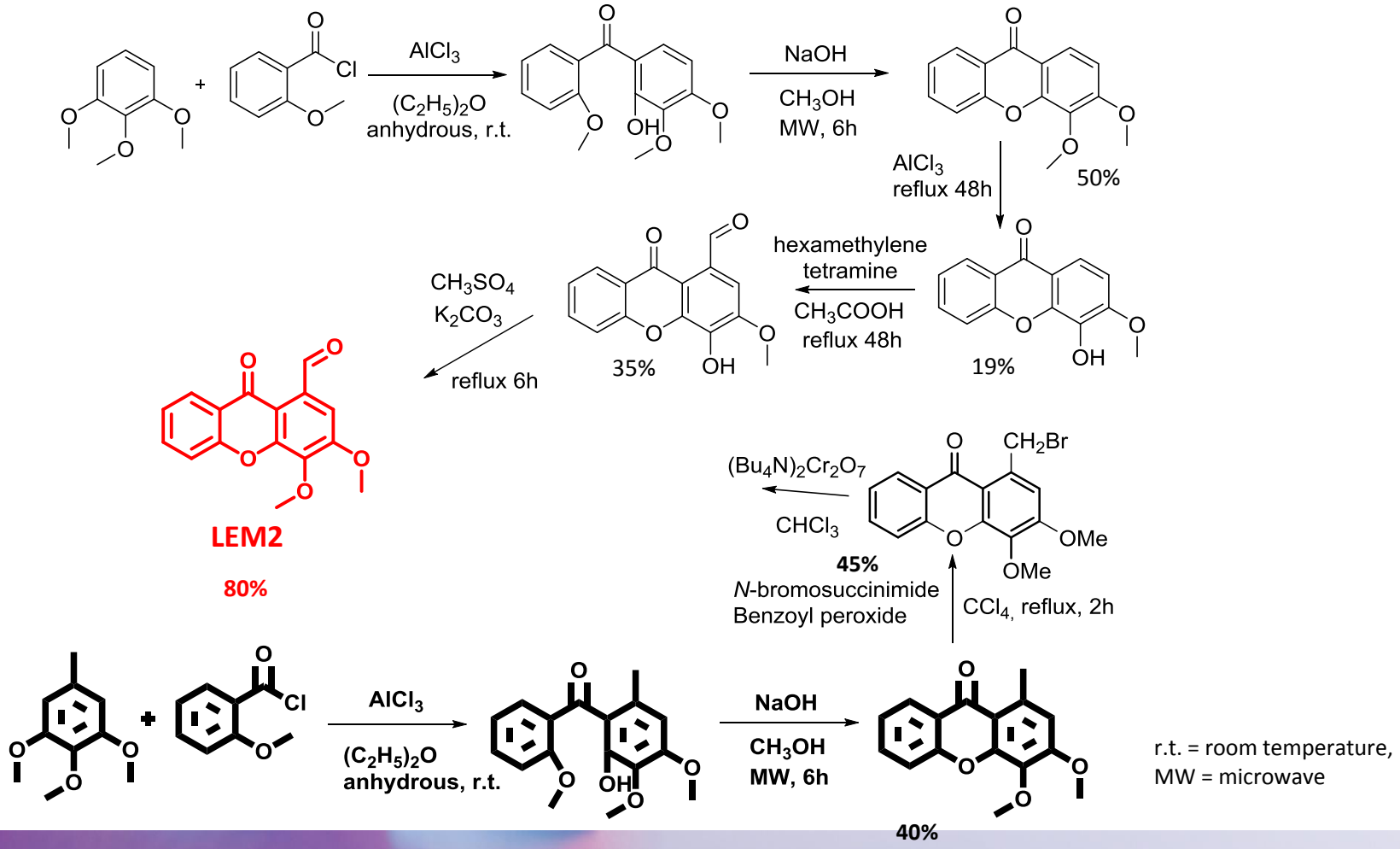


M. Leão, et al. Biochemical Pharmacology 2013, 85(9), 1234-1245.
M. Leão, et al. Journal of Natural Products 2013, 76 (4), 774–778.

Reductive Amination

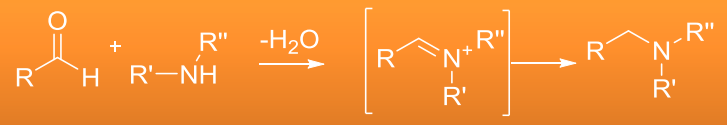


Obtaining the functionalized aldehyde was the 1st drawback for a rapid synthetic protocol

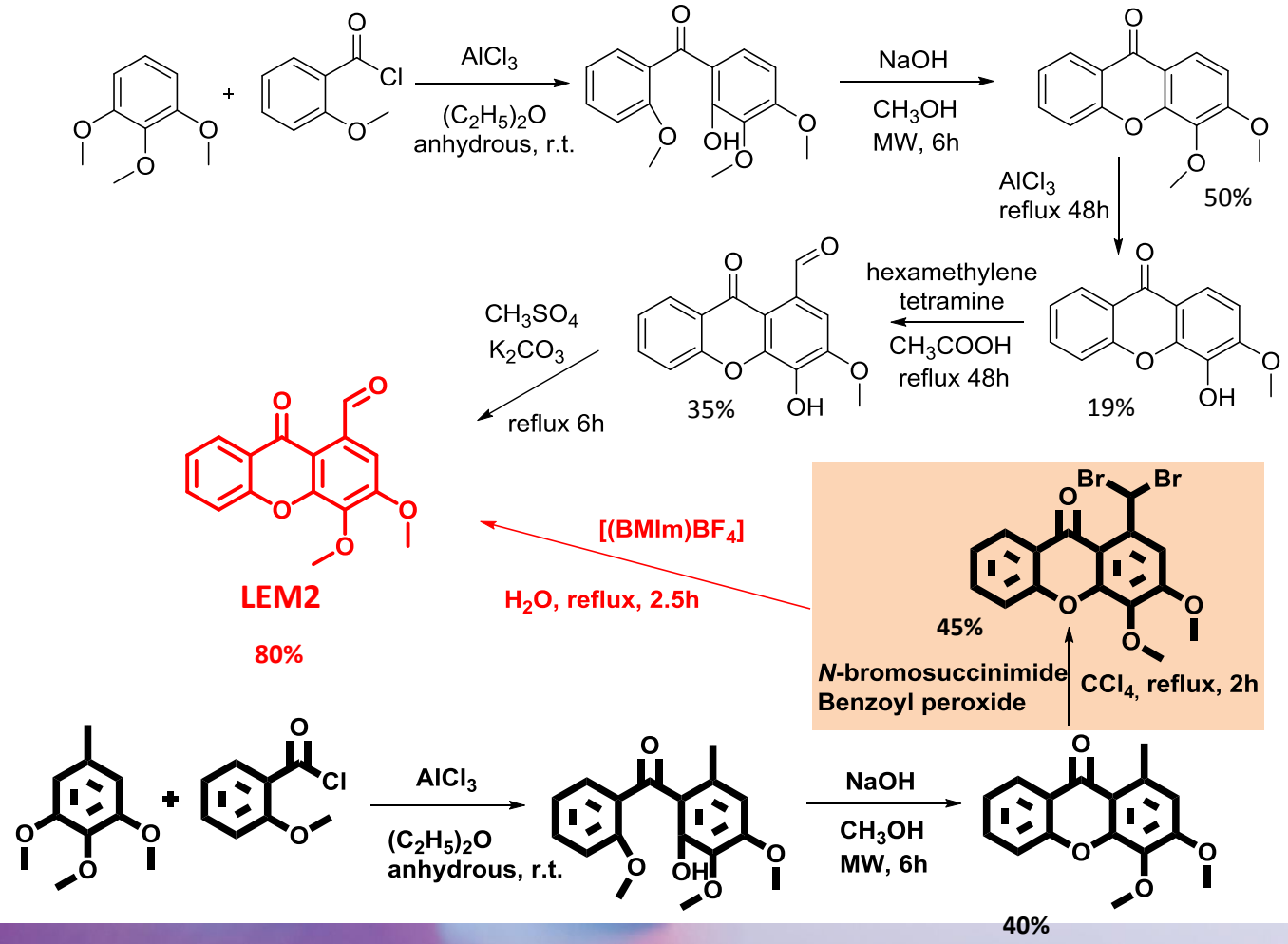


r.t. = room temperature,
MW = microwave

Reductive Amination

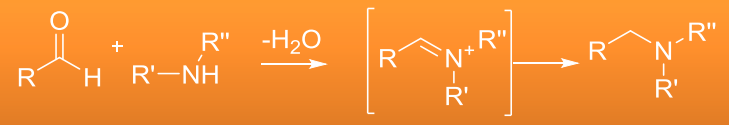


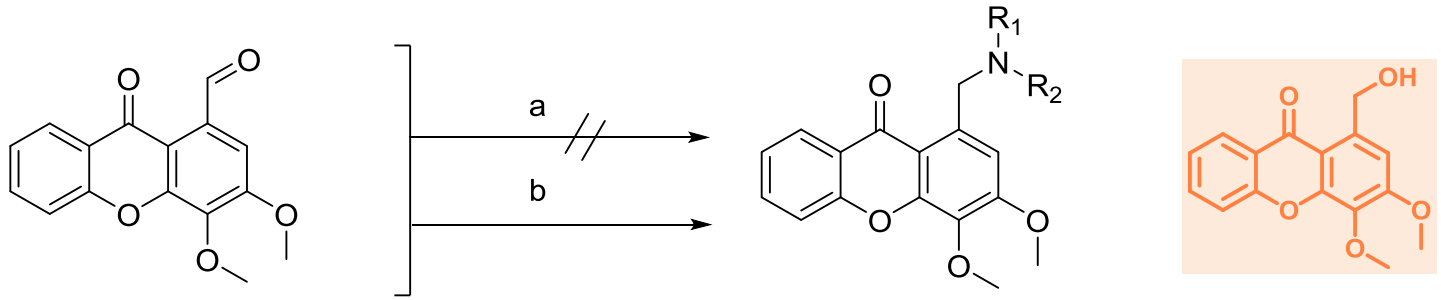
Obtaining the functionalized aldehyde was the 1st drawback for a rapid synthetic protocol



[(BMIm)BF4] = 1-butyl-3-methylimidazolium tetrafluoroborate

Reductive Amination

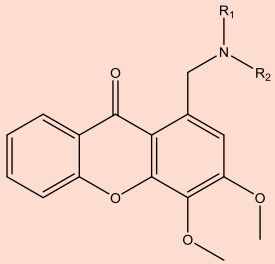




LEM2

a) MP-$CNBH_3$, CH_3COOH, CH_3OH, r.t., overnight
b) STAB, CH_3COOH , THF, r.t., overnight

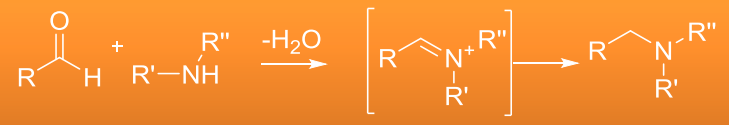
Table 1. Reaction yields (%) of the new aminoxanthone derivatives*

LEM2	Compounds	Yield (%)	Compounds	Yield (%)	Compounds	Yield (%)
	ALX1	56	ALX5	40	ALX9	35
	ALX2	57	ALX6	63	ALX10	36
	ALX3	70	ALX7	68	ALX11	58
	ALX4	41	ALX8	62		

MP-$CNBH_3$ = Solid-supported cyanoborohydride, STAB = Sodium triacetoxyborohydride, THF = tetrahydrofuran, r.t. = room temperature

*Due to confidentiality issues, the compounds are not shown.

Reductive Amination



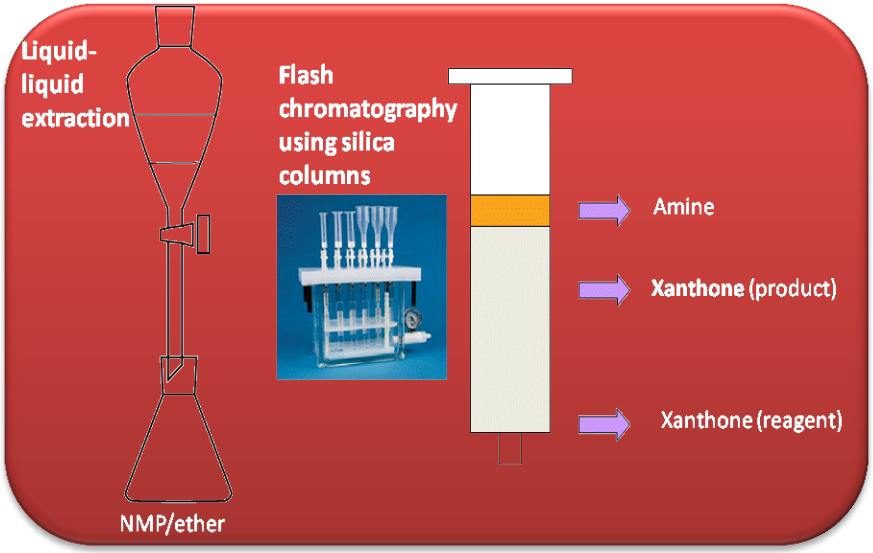
- **Preparation of aldehyde** heterocyclic moieties precursors difficult /restrains
- Aldehydes less commercial availability than halogenated precursors
- highly **sensitive to solvent/reagents** modifications

- **high-yield** reactions (the intermediate imine does not suffer from the issues of over-reaction)
- **metal-free** reactions
- aliphatic amines with **low potential to form reactive metabolites**

Conclusions

a variety of (thio)xanthone building blocks, pendent functionalities, and different reaction conditions allowed us to develop a repertoire of *N*-transformations

Importance the use of enabling techniques in synthesis



- Microwave irradiation
- New solvents
- Catalysis

Acknowledgments

national funds from FCT—Fundação para a Ciência e a Tecnologia under the project CEQUIMED—PEst-OE/SAU/UI4040/2014 and ERDF through COMPETE and national funds from FCT, PEst-C/MAR/LA0015/2013.