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Discovery of novel endocannabinoid level regulators by modifications of old analgesic drugs

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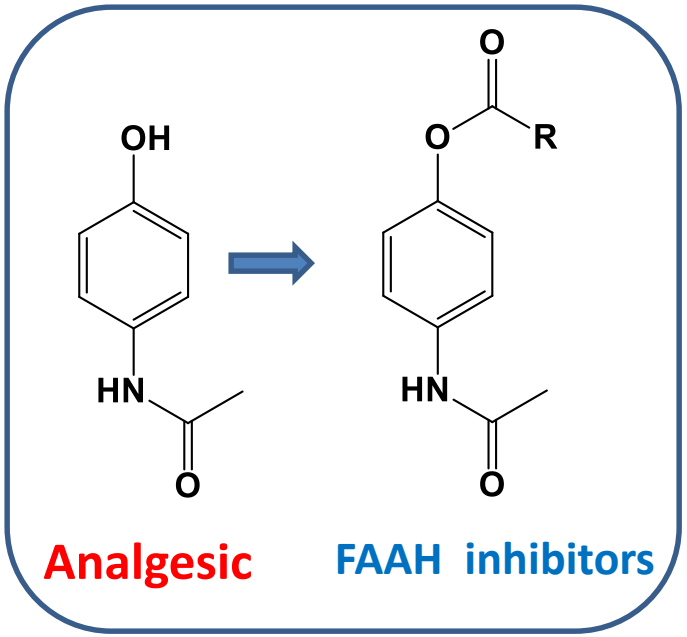
Discovery of novel endocannabinoid level regulators by modification of old analgesic drugs

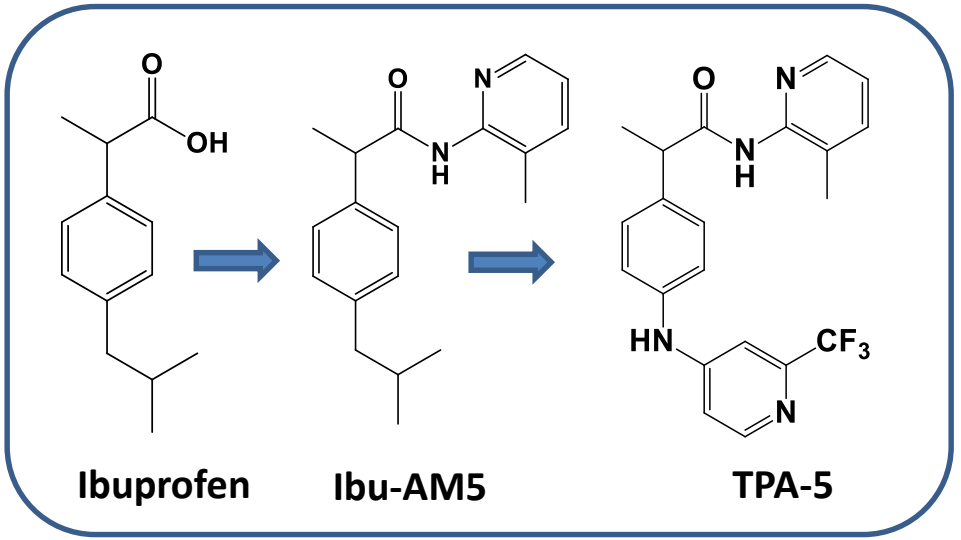
Graphical abstract

Old NSAID

Chemical elaboration

New FAAH inhibitors



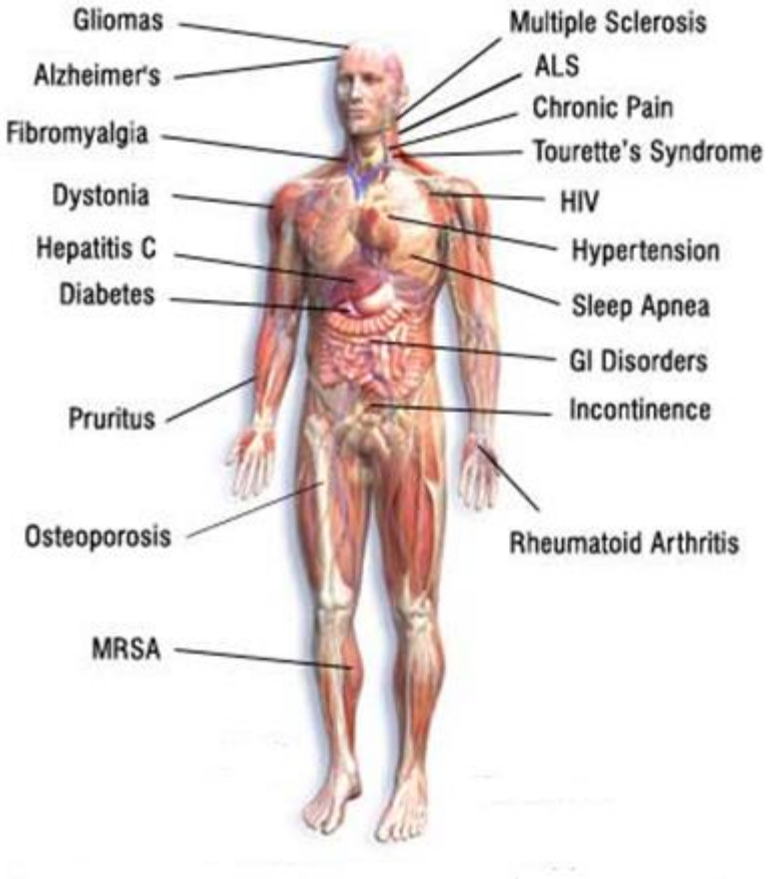


Abstract: Fatty acid amide hydrolase (FAAH) is a serine hydrolase that catalyzes the deactivating hydrolysis of the fatty acid ethanolamide family of signaling lipids, which includes anandamide (AEA), an endogenous ligand for cannabinoid receptors. Endogenous FAAH substrates such as AEA serve key regulatory functions in the body and have been implicated in a variety of pathological conditions including pain, inflammation, sleep disorders, anxiety, depression, and vascular hypertension, and there has been an increasing interest in the development of inhibitors of this enzyme. Different structural classes of FAAH inhibitors have been reported including α-ketoheterocycles, (thio)hydantoins, piperidine/piperazine ureas, and carbamate derivatives. When tested, these compounds have been shown to be efficacious in models of inflammatory, visceral, and in some cases neuropathic pain without producing the central effects seen with directly acting cannabinoid receptor agonists. An intriguing aspect of FAAH inhibition is that some currently marketed nonsteroidal anti-inflammatory drugs (NSAIDs) have also been shown to be weak inhibitors of FAAH, but can be used as a template for the design of more potent compounds. However, structure–activity relationships of analogues of clinically used NSAIDs with respect to FAAH inhibition have been examined scarcely in the literature. These findings led us to design and synthesis of new series of FAAH inhibitors derivable from conjugation of heterocyclic structures with NSAIDs as profens, fenamates, and new their correlate molecules. In this keynote we report on the synthetic pathways to transform old analgesic drugs into FAAH inhibitors and SAR studies on the new inhibitor series.

Keywords: Analgesic drugs, NSAID, FAAH, enzyme inhibitors

Endocannabinoid System

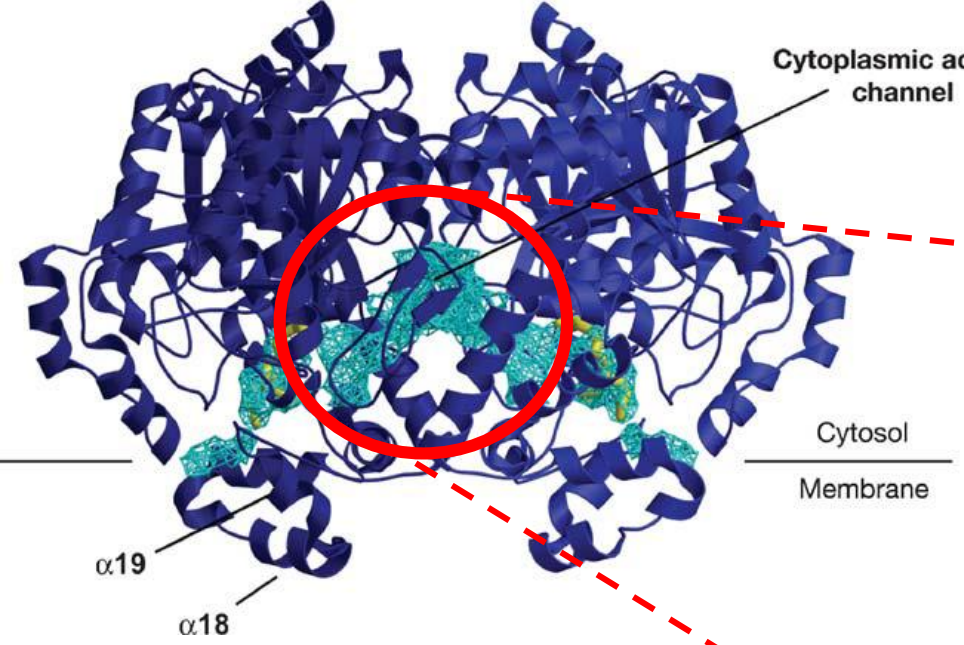
Distribution and Effects Cannabinoid receptors activation

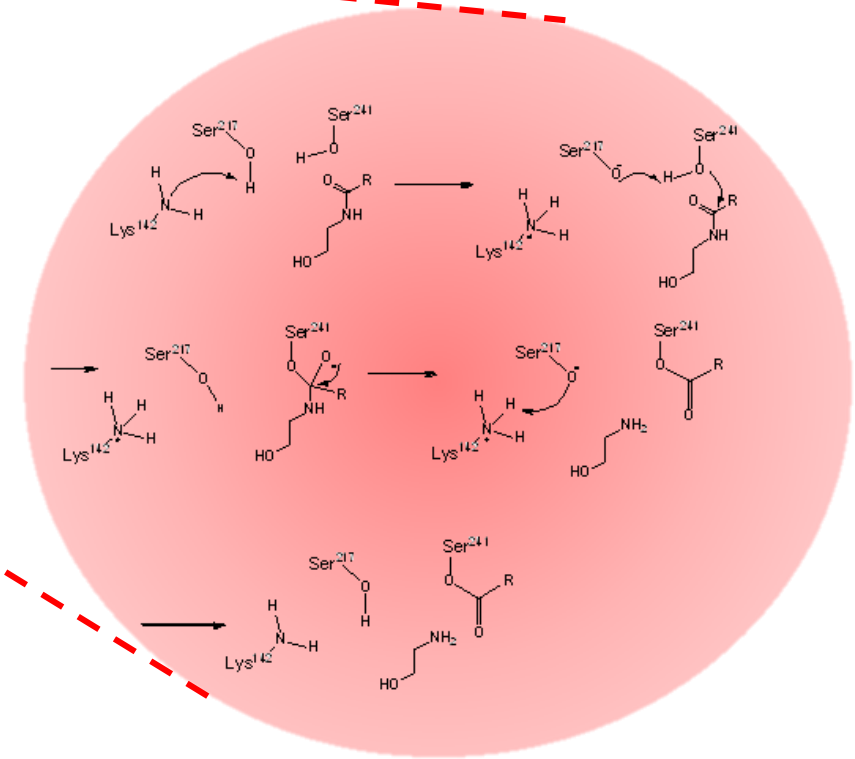


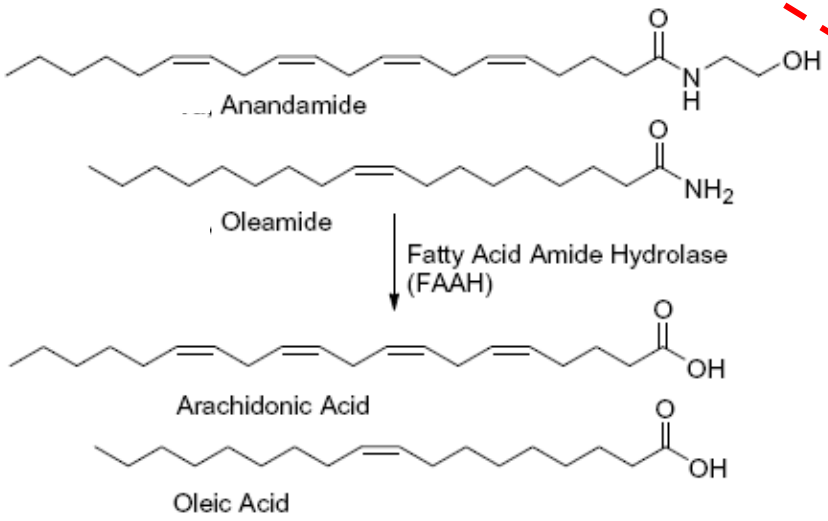
Side Effects of direct stimulations of CB1 and CB2

- CNS: memory disturbs, psychosis, delirium, schizophrenia, apathy
- Immunodeficiency
- Heart
- Lungs

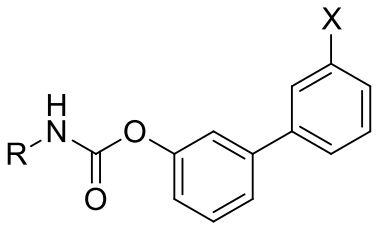
Anandamide metabolism



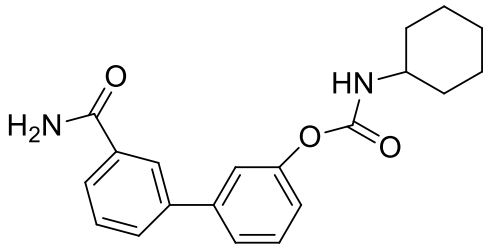




FAAH INHIBITORS



Mor et al. J. Med. Chem., **2008**, 51, 3487-3498



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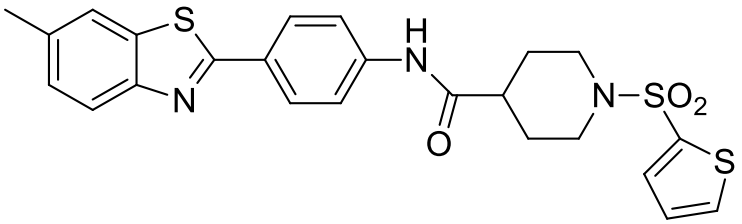
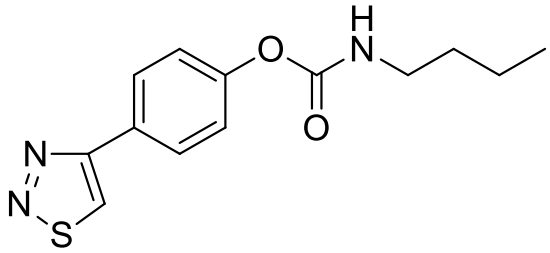
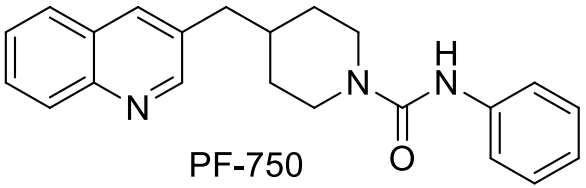


Wang et al. *J. Med. Chem.*, **2009**, 52, 170-180



A. Minkkila et al. Eur. J. Med. Chem. **2009**, 44, 2994-3008



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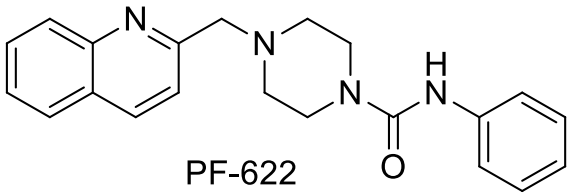

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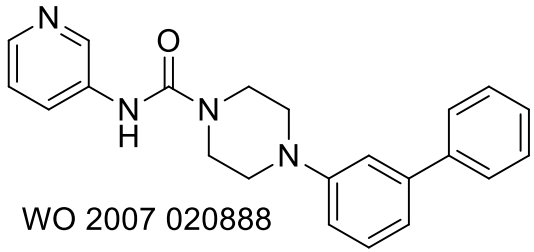
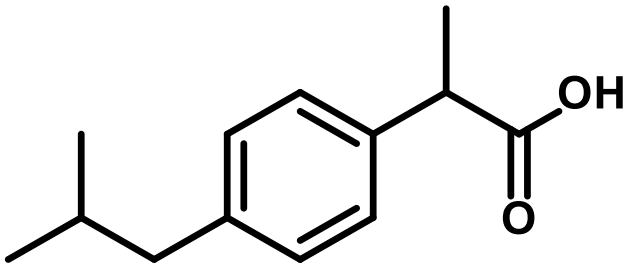


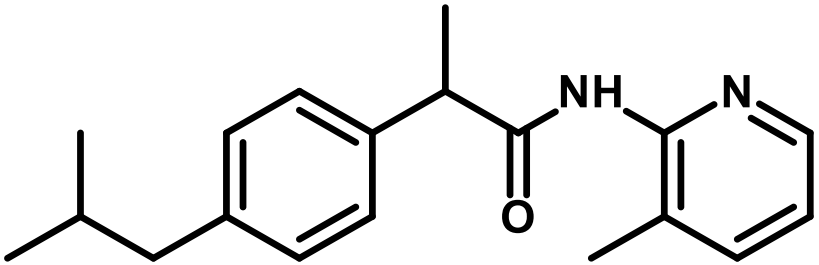
WO 2007 020888

From NSAID to FAAH inhibitor



Ibuprofen

IC_{50} 156 μM



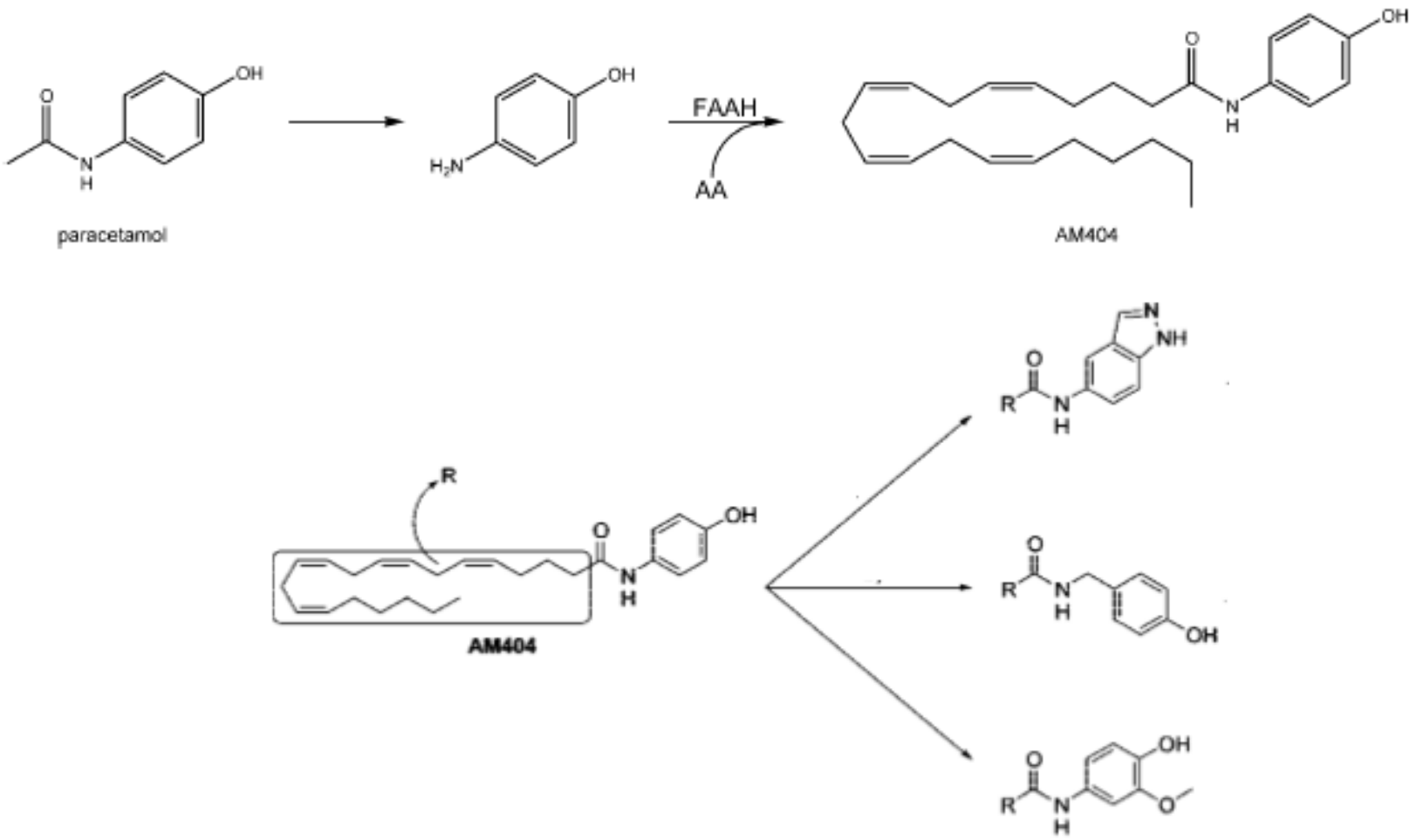
Ibu-AM5

IC_{50} 0.52 μM

- FAAH non competitive inhibitor
- IC_{50} 1.2 μM in C6 glioma cells
- retain ibuprofen COX inhibitory activity
  (COX1: IC_{50} 180nM; COX2 IC_{50} 310nM)
- 10 fold higher potency as CB antagonist
  (CB1: IC_{50} 41 μM; CB2: IC_{50} 24 μM)

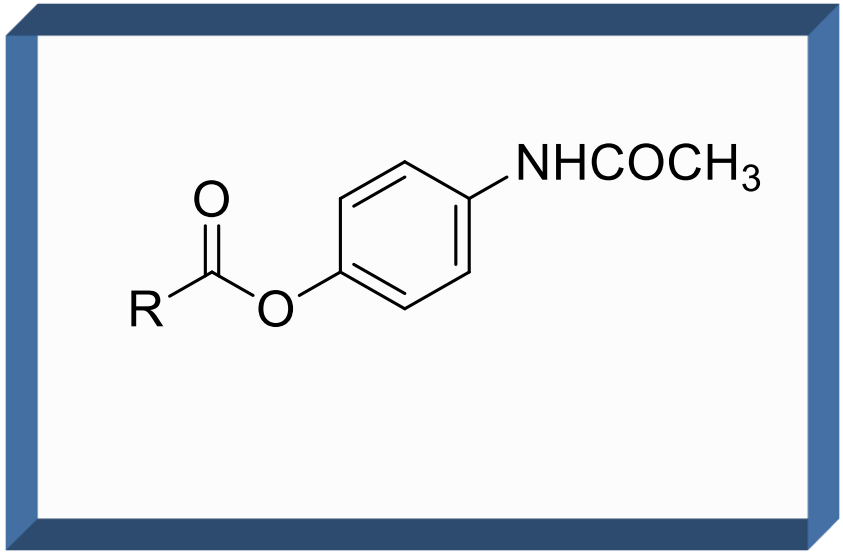
Holt S., Paylor B., Boldrup L., Alajakku K., Vandevoorde S., Sundstrom A., Cocco M.T., Onnis V., Fowler C.J.
Inhibition of fatty acid amide hydrolase, a key endocannabinoid metabolizing enzyme, by analogues of ibuprofen and indomethacin
Eur. J. Pharmacol., 565 (1-3), 26-36 (2007).

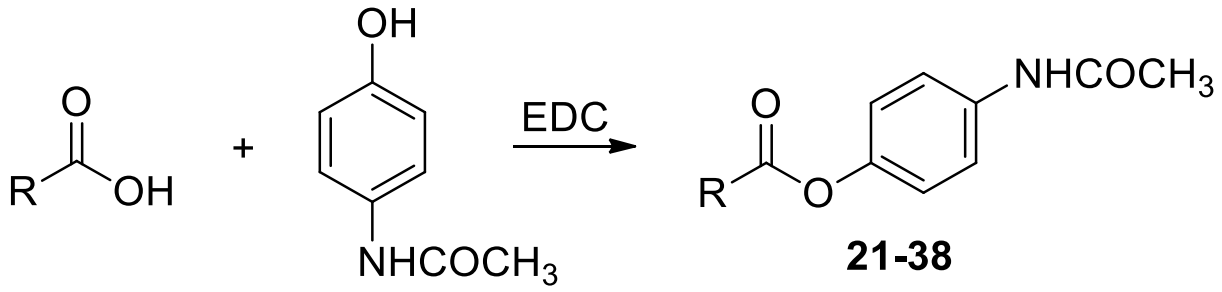
Paracetamol an old drug a new mechanism



Sinning et al. *J. Med. Chem.* **2008,** *51,* 7800–7805

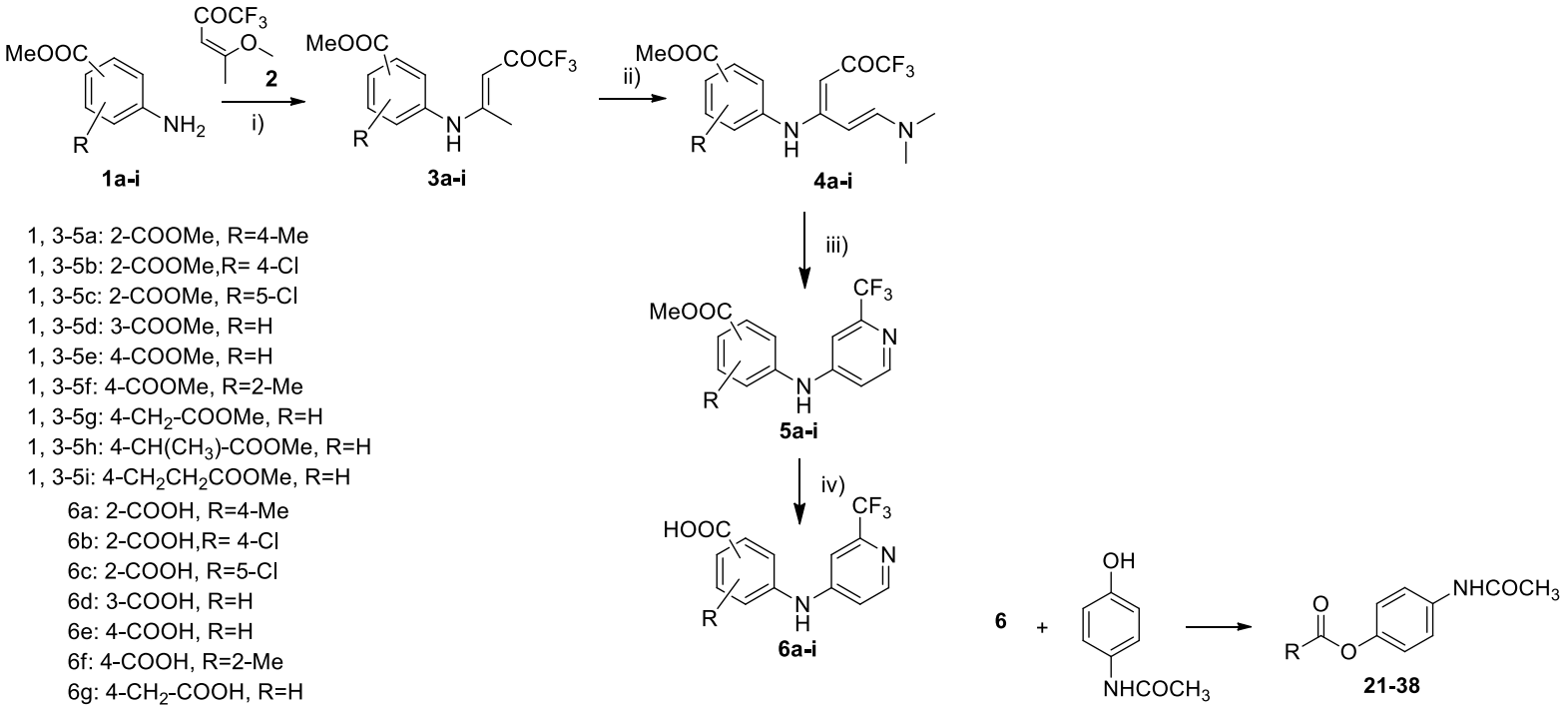
PARACETAMOL ESTERS AS FAAH INHIBITORS





Onnis V. et al. **Synthesis and Evaluation of Paracetamol Esters as Novel Fatty Acid Amide Hydrolase Inhibitors**
J. Med. Chem. *53*, 2286-2298 (2010)

PARACETAMOL ESTERS AS FAAH INHIBITORS



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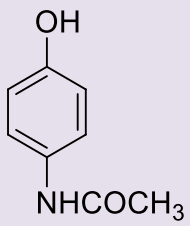
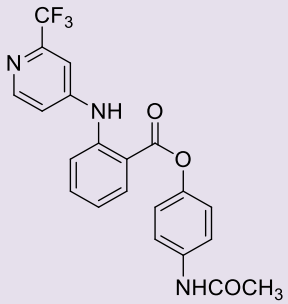
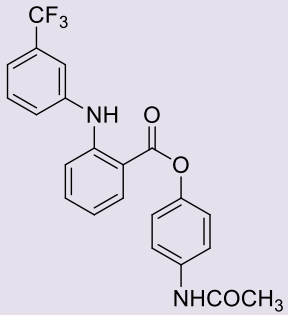
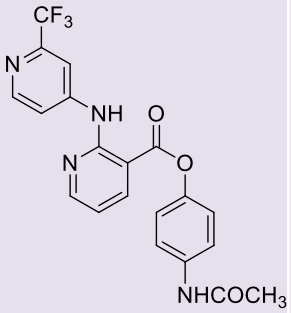
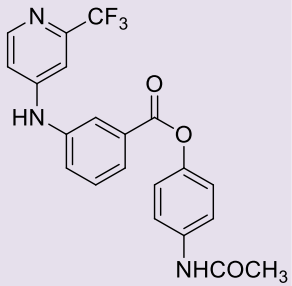
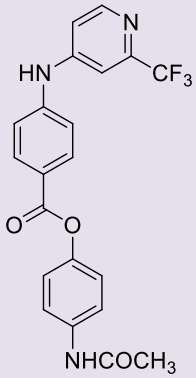
1, 3-5b: 2-COOMe,R= 4-Cl
1, 3-5c: 2-COOMe, R=5-Cl
1, 3-5d: 3-COOMe, R=H
1, 3-5e: 4-COOMe, R=H
1, 3-5f: 4-COOMe, R=2-Me
1, 3-5g: 4-CH_2-COOMe, R=H
1, 3-5h: 4-$CH(CH_3)$-COOMe, R=H
1, 3-5i: 4-CH_2CH_2COOMe, R=H

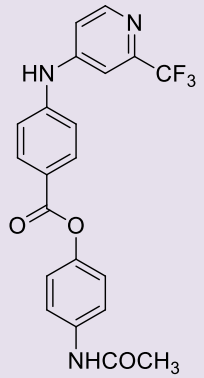
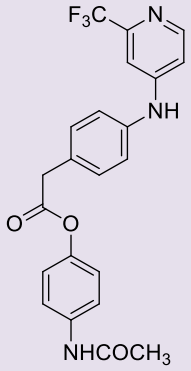
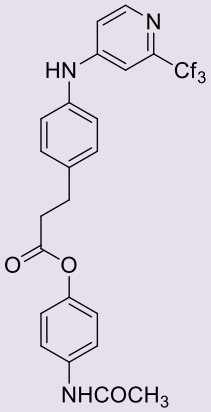
6a: 2-COOH, R=4-Me
6b: 2-COOH,R= 4-Cl
6c: 2-COOH, R=5-Cl
6d: 3-COOH, R=H
6e: 4-COOH, R=H
6f: 4-COOH, R=2-Me
6g: 4-CH_2-COOH, R=H
6h: 4-$CH(CH_3)$-COOH, R=H
6i: 4-CH_2CH_2-COOH, R=H

Scheme 2. Reagents and conditions: (i) MeCN, reflux, 2h; (ii) DMF-DMA, PhMe, reflux, 1h; (iii) NH_4OAc, DMF, reflux, 1.5 h; (iv) 10% aq. NaOH, reflux, 30 min.

Paracetamol-Fenamates hybrids as FAAH inhibitors

Compound	Paracetamol	21	25	26	28	29
						
IC_{50} (μM)	>300	64	8.3	31	48	2.7

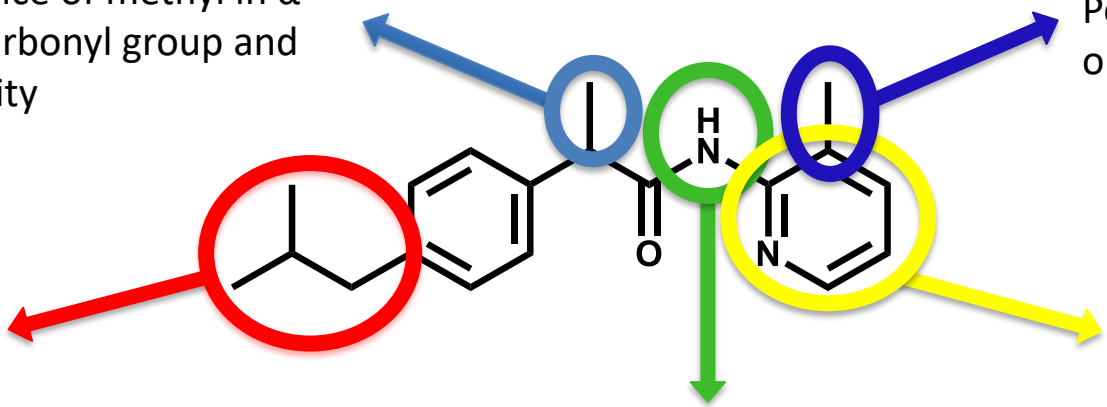
Paracetamol-Fenamates hybrids as FAAH inhibitors

Compound	29	31	38	33
				
IC_{50} (μM)	**2.7**	**0.18**	**8.3**	**0.08**

Paracetamol ester **33**

- FAAH competitive inhibitor
- Same paracetamol inhibition profile against COX
- MAGL IC_{50} 1.9 μM

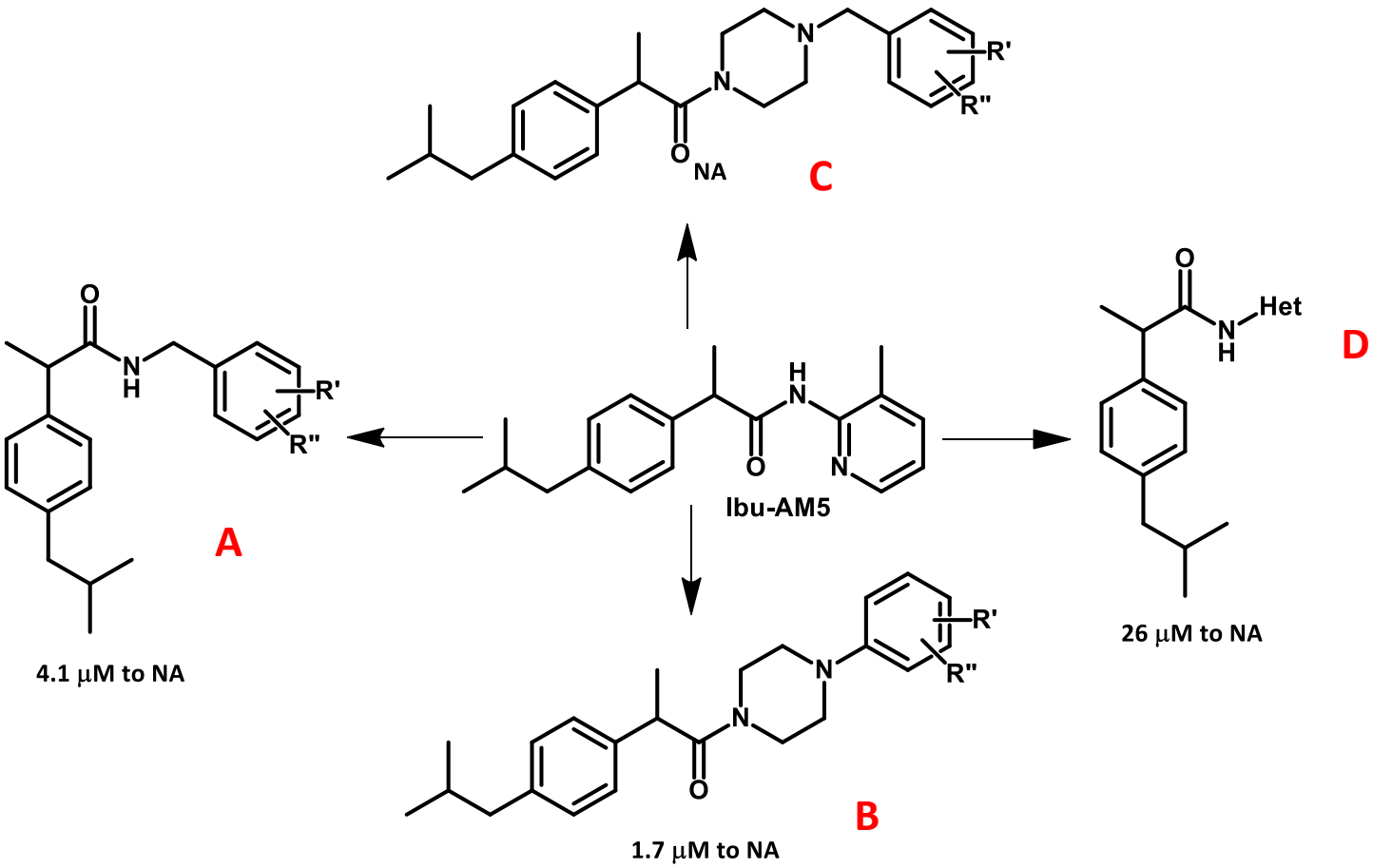
Ibu-AM SAR scheme



Ibu-AM5

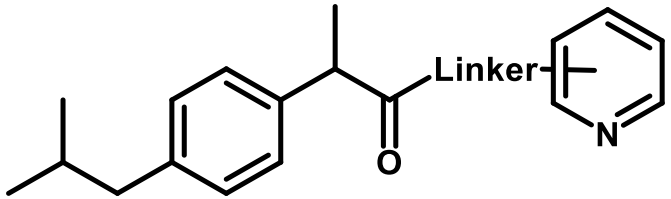
IC_{50} 0.52 µM

Modifications on the amide moiety

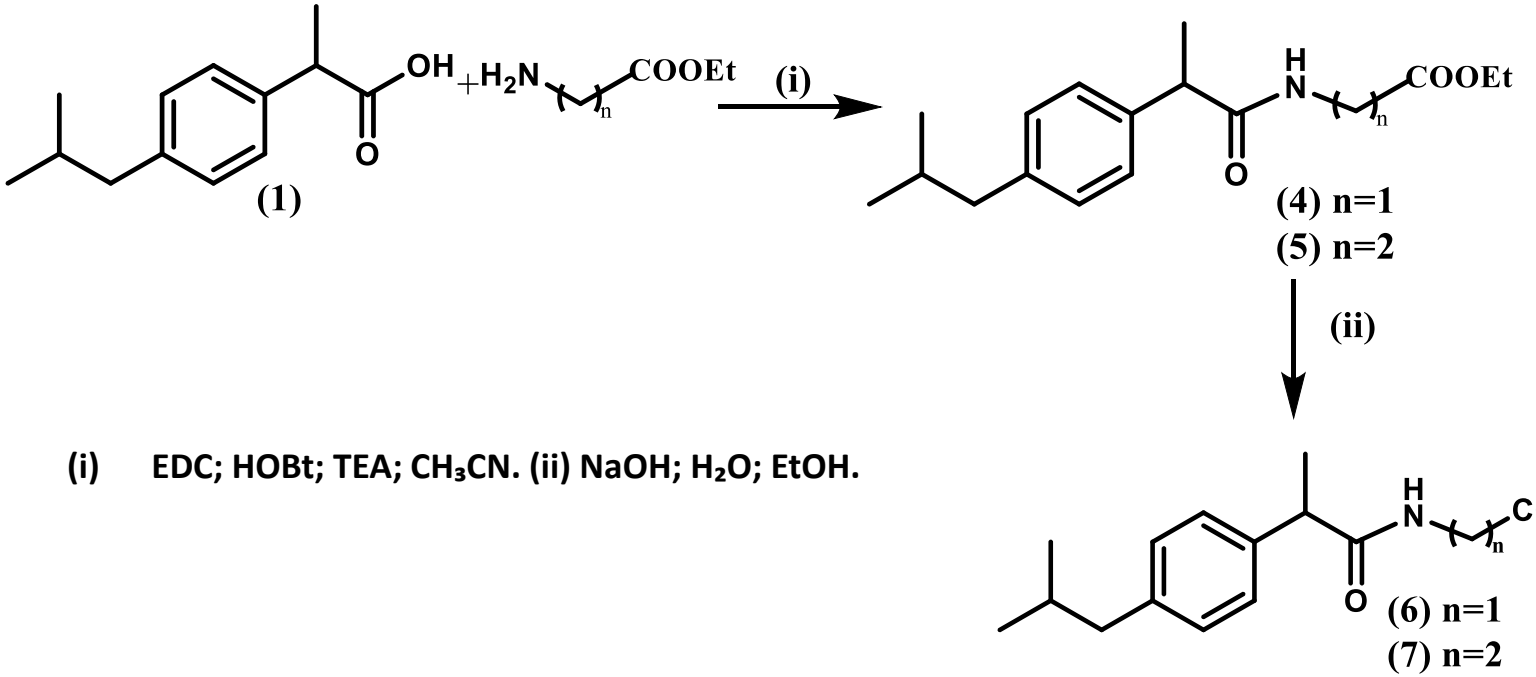


A. Deplano, M. Cipriano, F. Moraca, E. Novellino, B. Catalanotti, C. J. Fowler, V. Onnis **Benzylamides and piperazinoarylamides of ibuprofen as fatty acid amide hydrolase inhibitors**. J. Enz. Inhib. Med. Chem 2018

Modification of linker



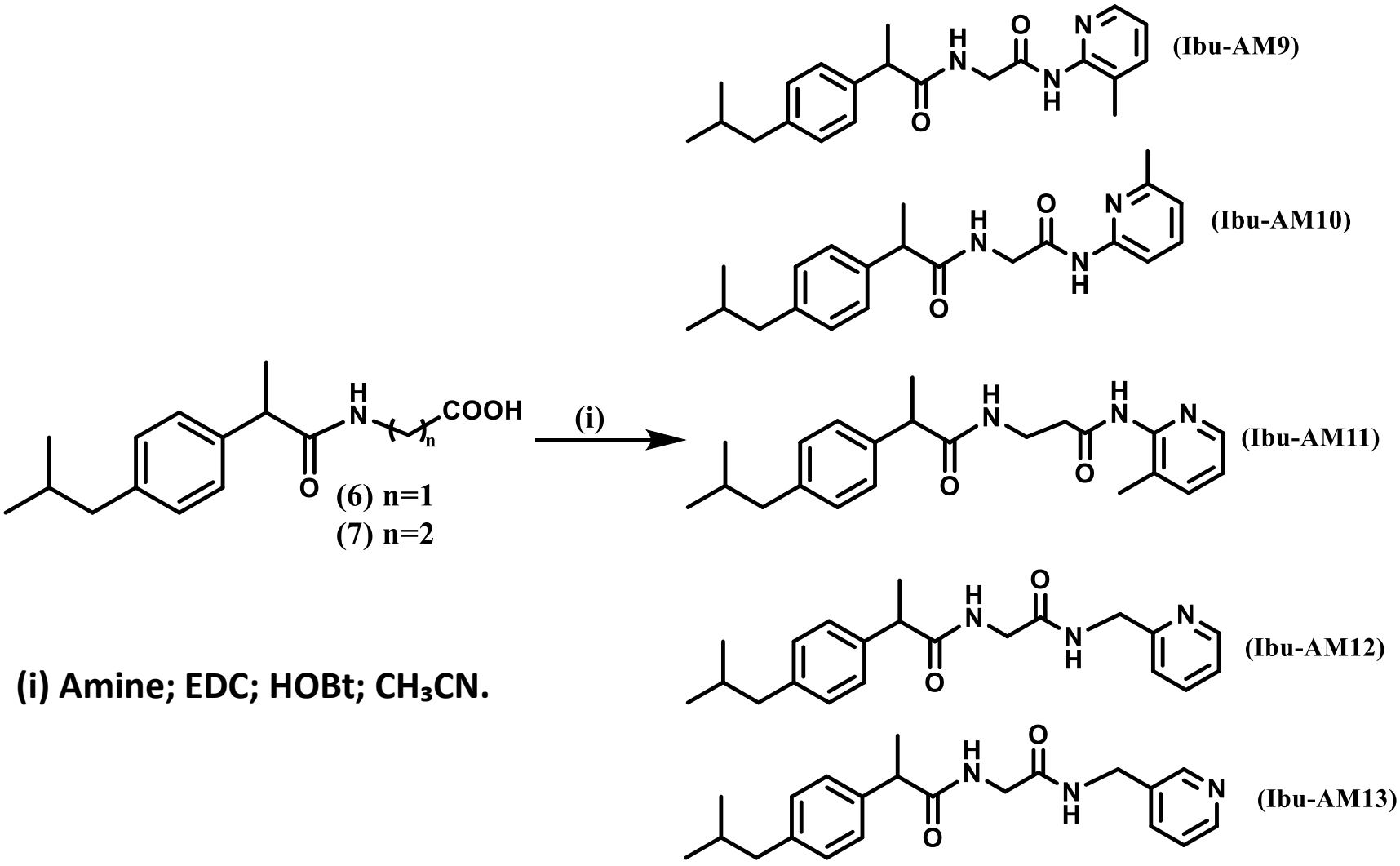
Ibu-AM9-13



(i) EDC; HOBt; TEA; CH_3CN. (ii) NaOH; H_2O; EtOH.

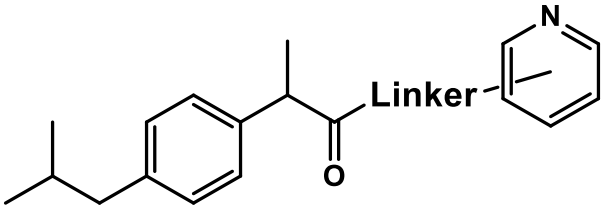
Fowler C.J., Björklund E., Lichtman A. H., Naidu P.S., Congiu C., Onnis V.
Inhibitory properties of ibuprofen and its amide analogues towards the hydrolysis and cyclooxygenation of the endocannabinoid anandamide.
J. Enz. Inhib. Med. Chem, 28 (1) 178-182 (2013)

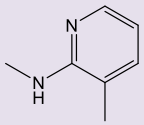
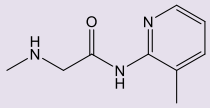
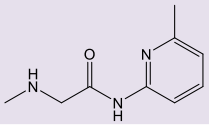
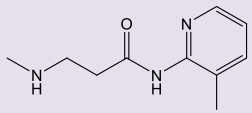
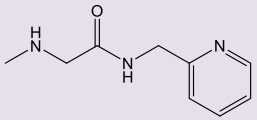
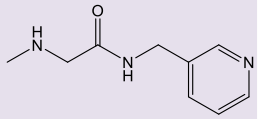
Modification of linker



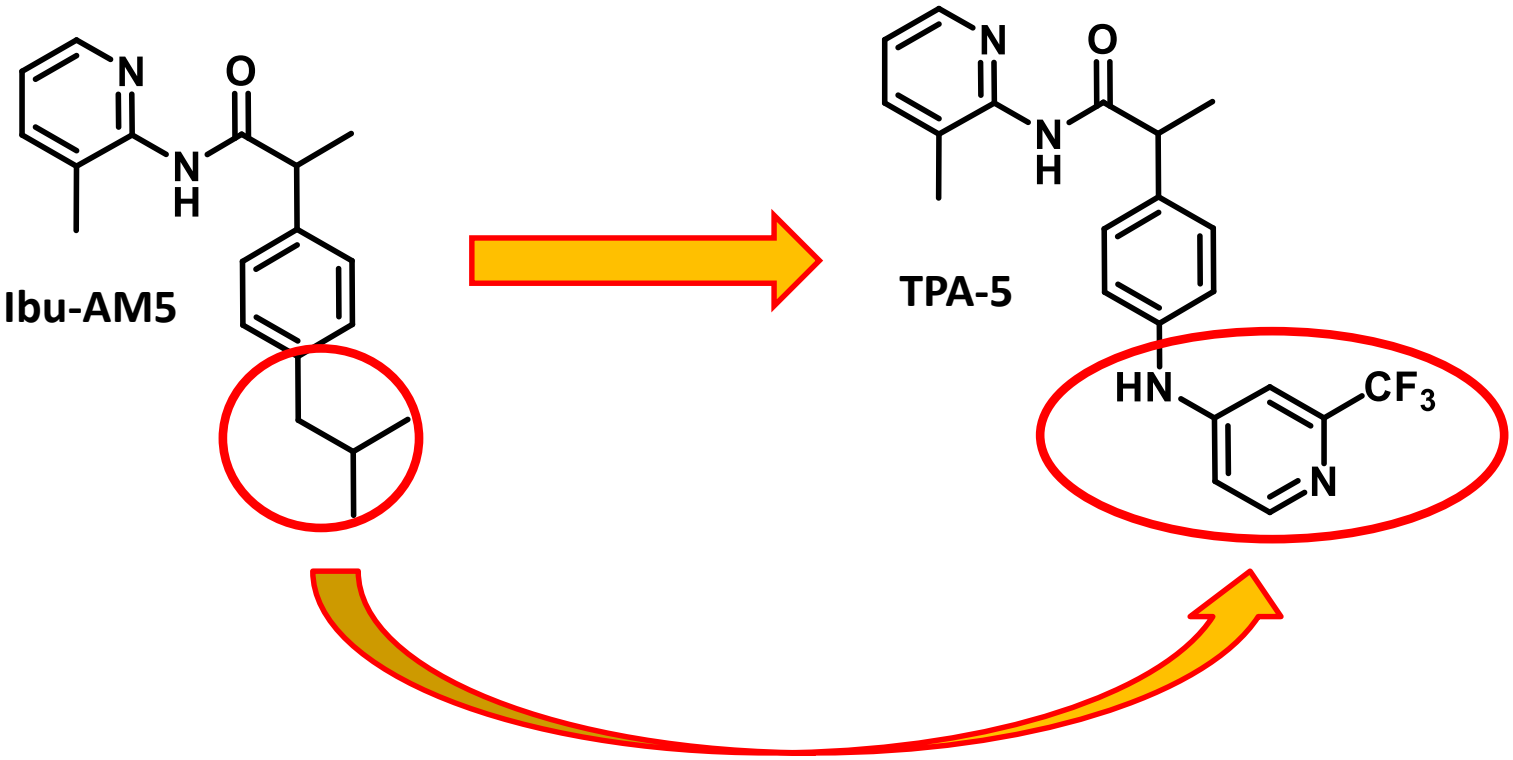
(i) Amine; EDC; HOBt; CH_3CN.

Modification of linker



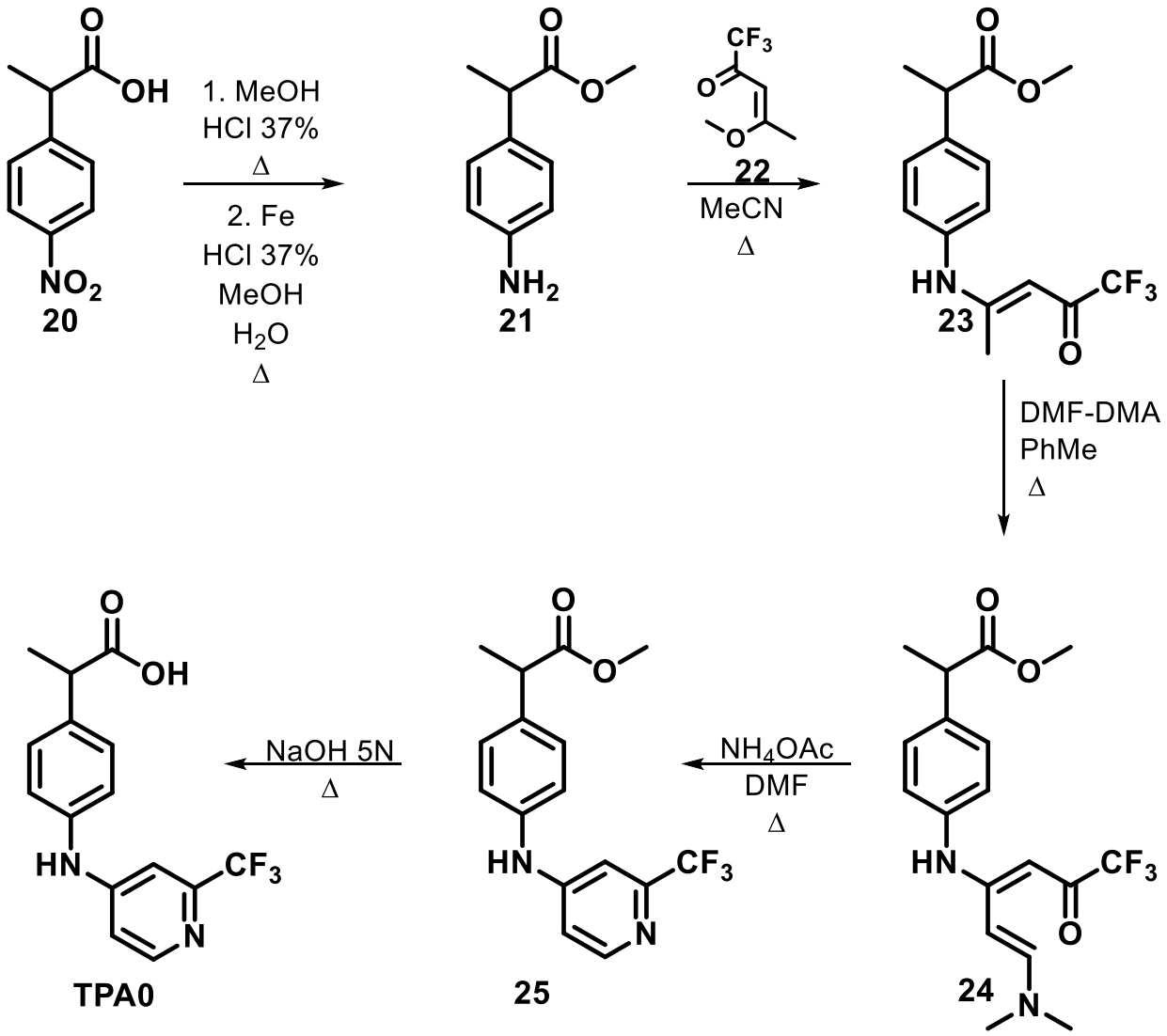
Compound	R	IC_{50} (μM)	Max inhibition (%)
Ibuprofen	OH	156	100
Ibu-AM5		0.52	100
Ibu-AM9		3.2	100
Ibu-AM10		150	100
Ibu-AM11		9.3	90±3
Ibu-AM12		90	100
Ibu-AM13		37	81±8

From Ibu-AM to TPA

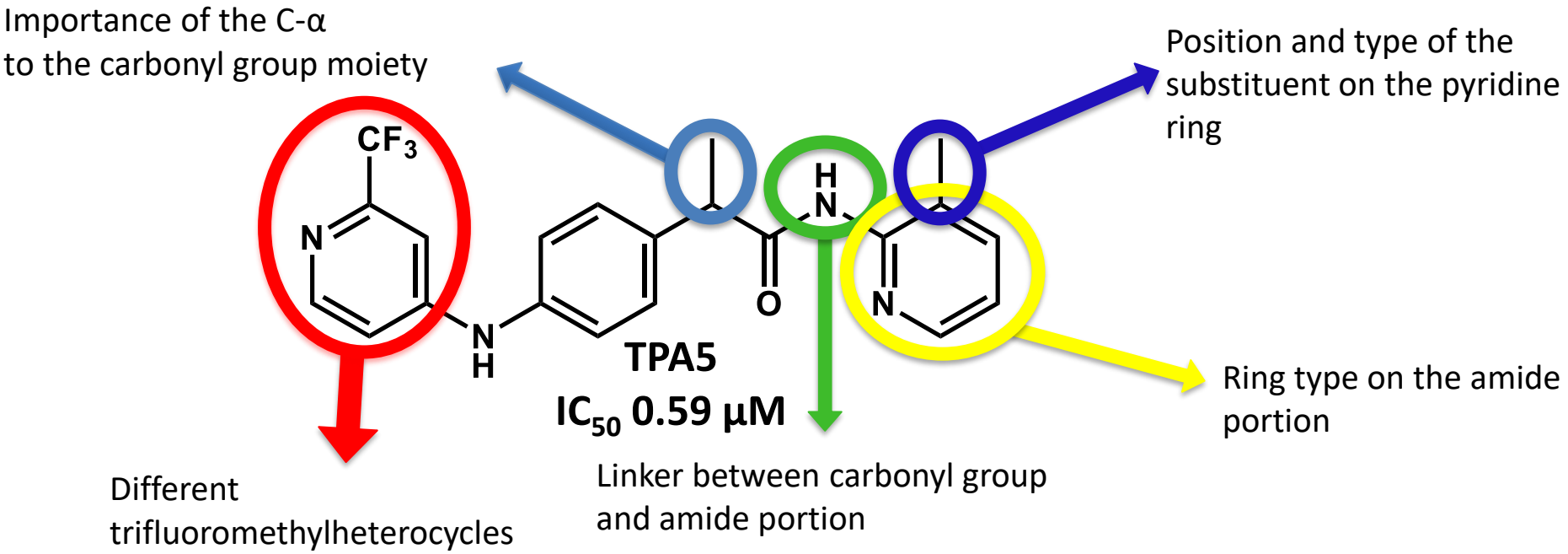


2-(4-((2-(**T**rifluoromethyl)**P**yridin-4-yl)amino)phenyl)propan **A**mides (**TPA**)

TPA synthesis

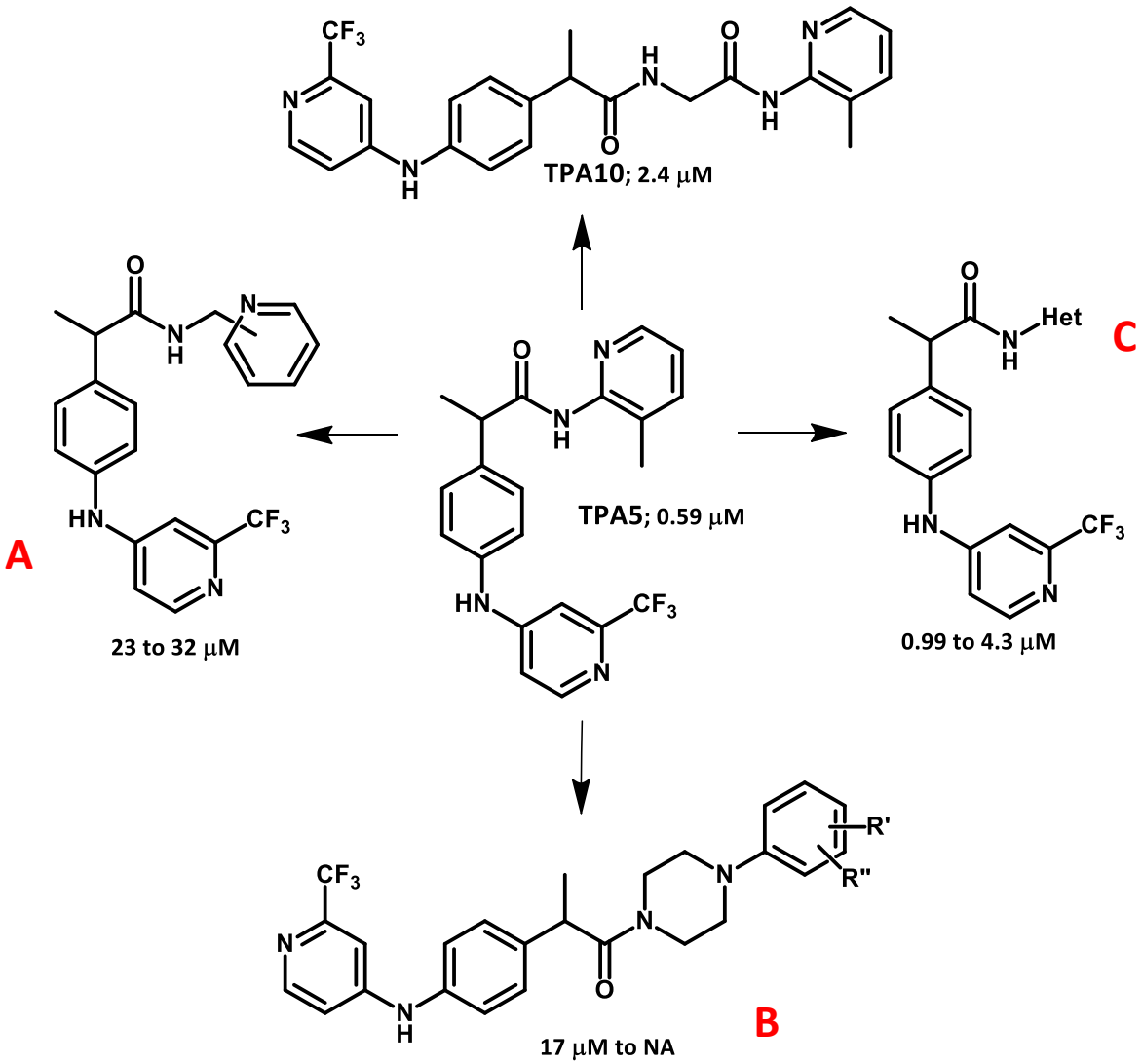


TPA SAR scheme

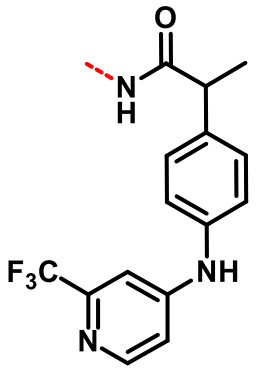


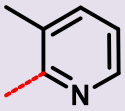
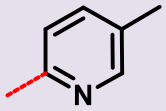
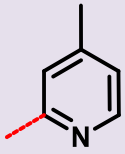
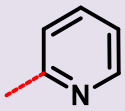
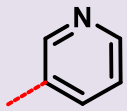
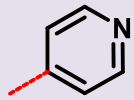
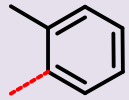
Deplano A. C. M. Morgillo, M. Demurtas, E. Björklund, M. Cipriano, M. Svensson, S. Hashemian, G. Smaldone, E. Pedone, F. J. Luque, M. G. Cabiddu, E Novellino, C. J. Fowler, B. Catalanotti, V. Onnis **Novel propanamides as fatty acid amide hydrolase inhibitors** Eur. J. Med. Chem.136 (2017) 523-542

Modifications on the amide moiety

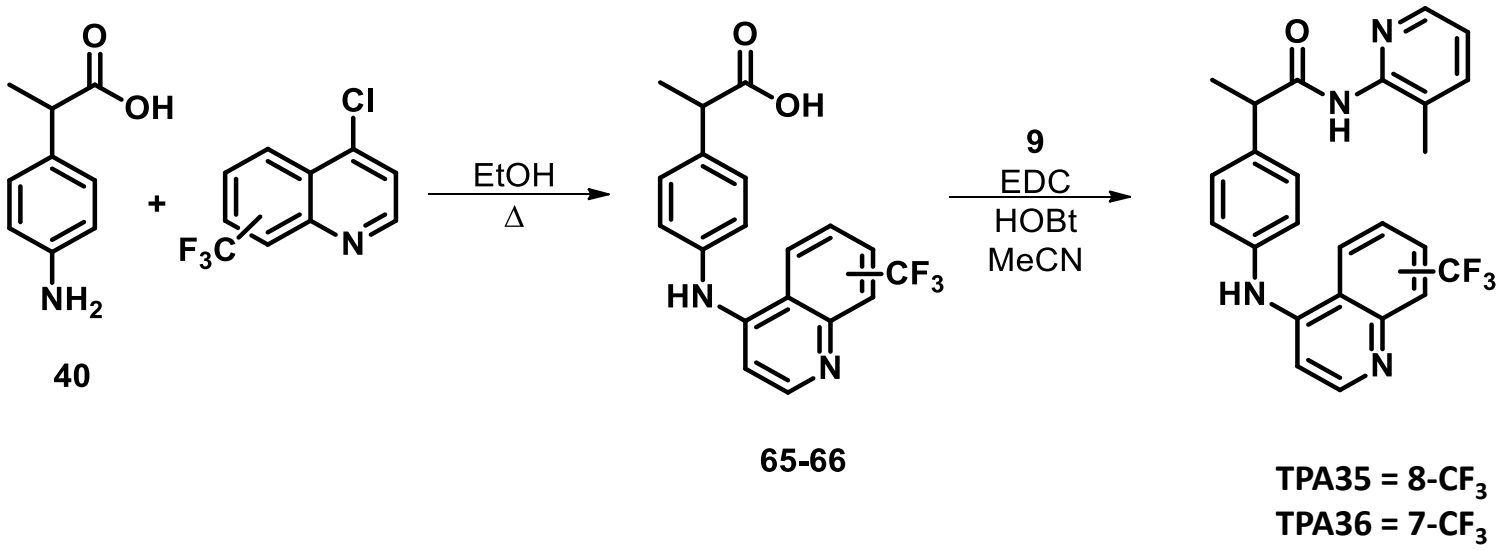


Pyridine nitrogen and methyl position influence

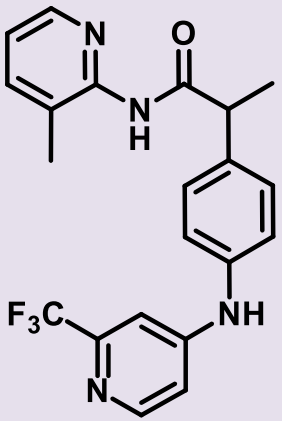
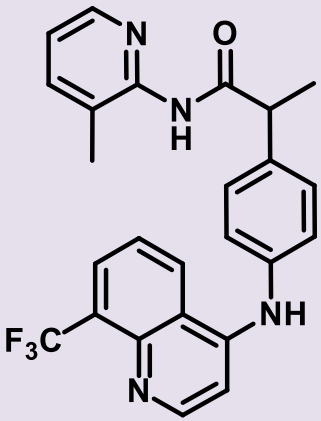
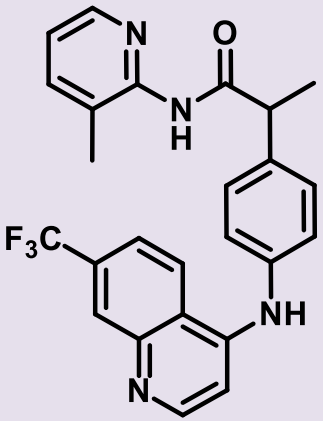


Compound	TPA5	TPA11	TPA12	TPA13	TPA14	TPA15	TPA16
							
IC_{50} (μM)	0.59	11	4.0	12	6.4	52	0.74
Max Inhib (%)	100	68±4	100	93±3	86±2	100	100

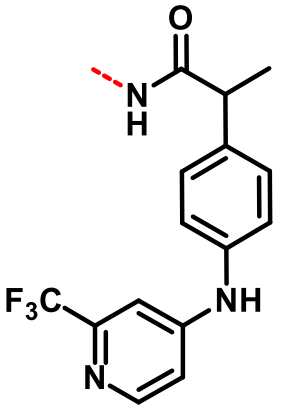
Modification of the trifluoromethyl moiety

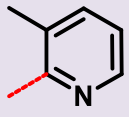
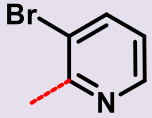
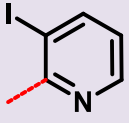
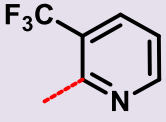
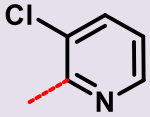


Trifluoromethylpyridine moiety modifications

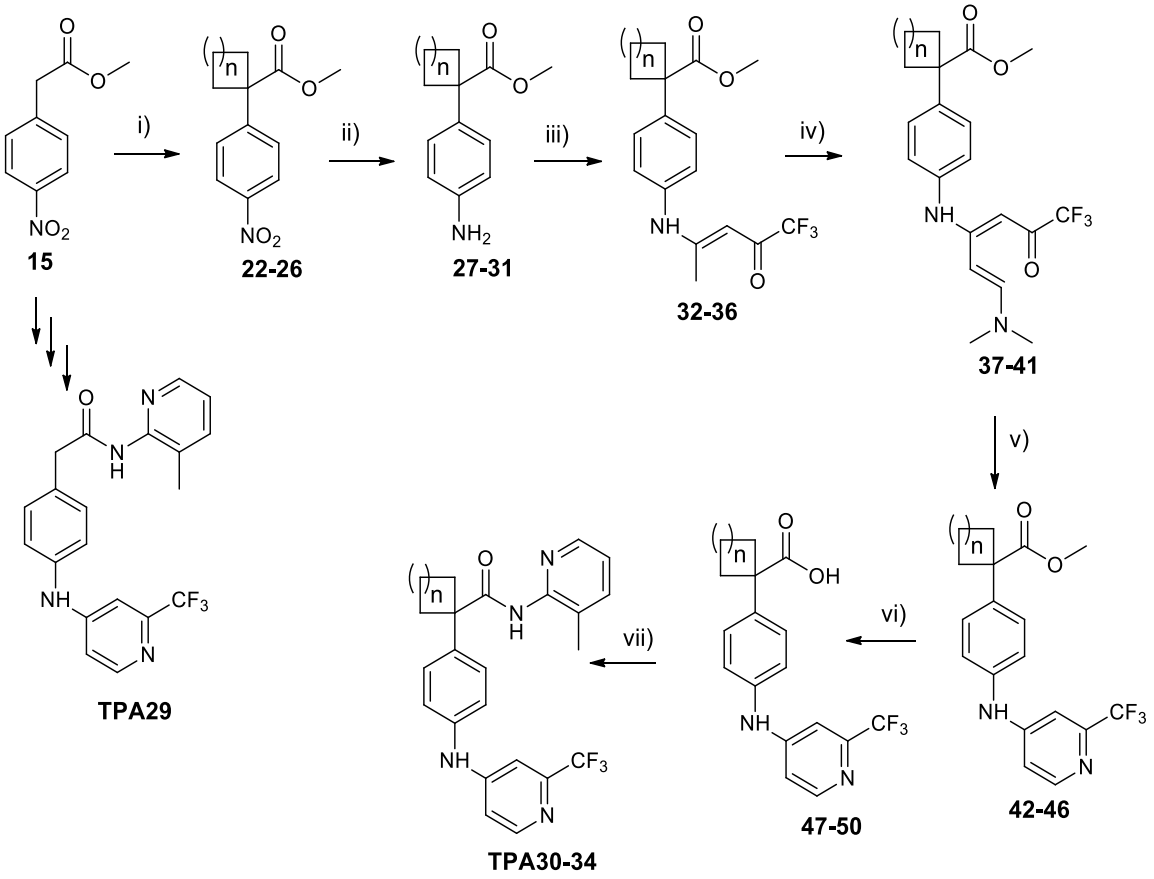
Compound	TPA5	TPA35	TPA36
			
IC_{50} (μM)	0.59	27	3.1

Influence of the substituent type on amide moiety



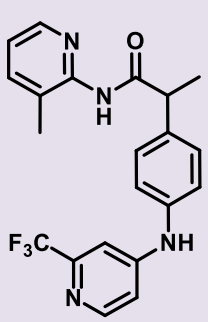
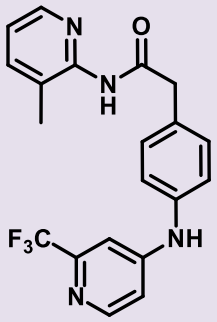
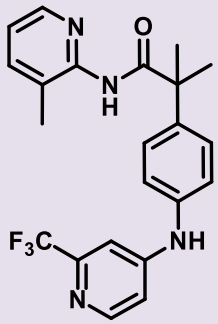
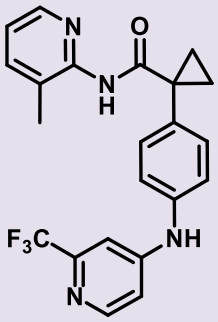
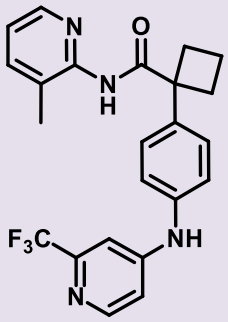
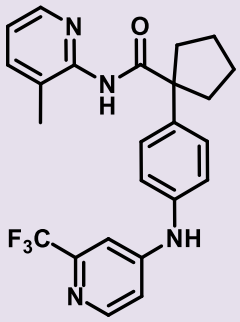
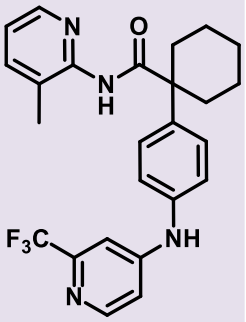
Compound	TPA5	TPA24	TPA25	TPA26	TPA27
					
IC_{50} (μM)	0.59	0.13	0.10	0.33	0.058

Influence of the substituent in α



(i) DMF, NaH, di-haloalkane, 0 °C to r.t.; (ii) AcOEt, $SnCl_2$ $2H_2O$, 75 °C, 4h; (iii) MeCN, reflux, 2h; (iv) DMF-DMA, PhMe, reflux, 1h; (v)) NH_4OAc, DMF, reflux, 1.5 h; (vi) EtOH, 5N aq. NaOH, r.t., 24h; (vii) EDC, HOBt, MeCN, r.t., 36h.

Influence of the substituent in α

Compound	TPA5	TPA29	TPA30	TPA31	TPA32	TPA33	TPA34
							
IC_{50} (μM)	0.59	48	1.8	14	9.1	60	>100
Max Inhib (%)	100	100	100	100	100	100	30±3

Conclusions

- Old drug were modified to obtain new molecules with a different biological activity
- New efficient synthetic procedures were developed
- New FAAH inhibitors with variable IC_{50} were prepared and tested
- SAR of Ibu-AM and TPA series were extesively studied

Acknowledgements

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