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Synthesis and biological evaluation of chalcone and stilbene based acetamidines as Nitric Oxide Synthase inhibitors

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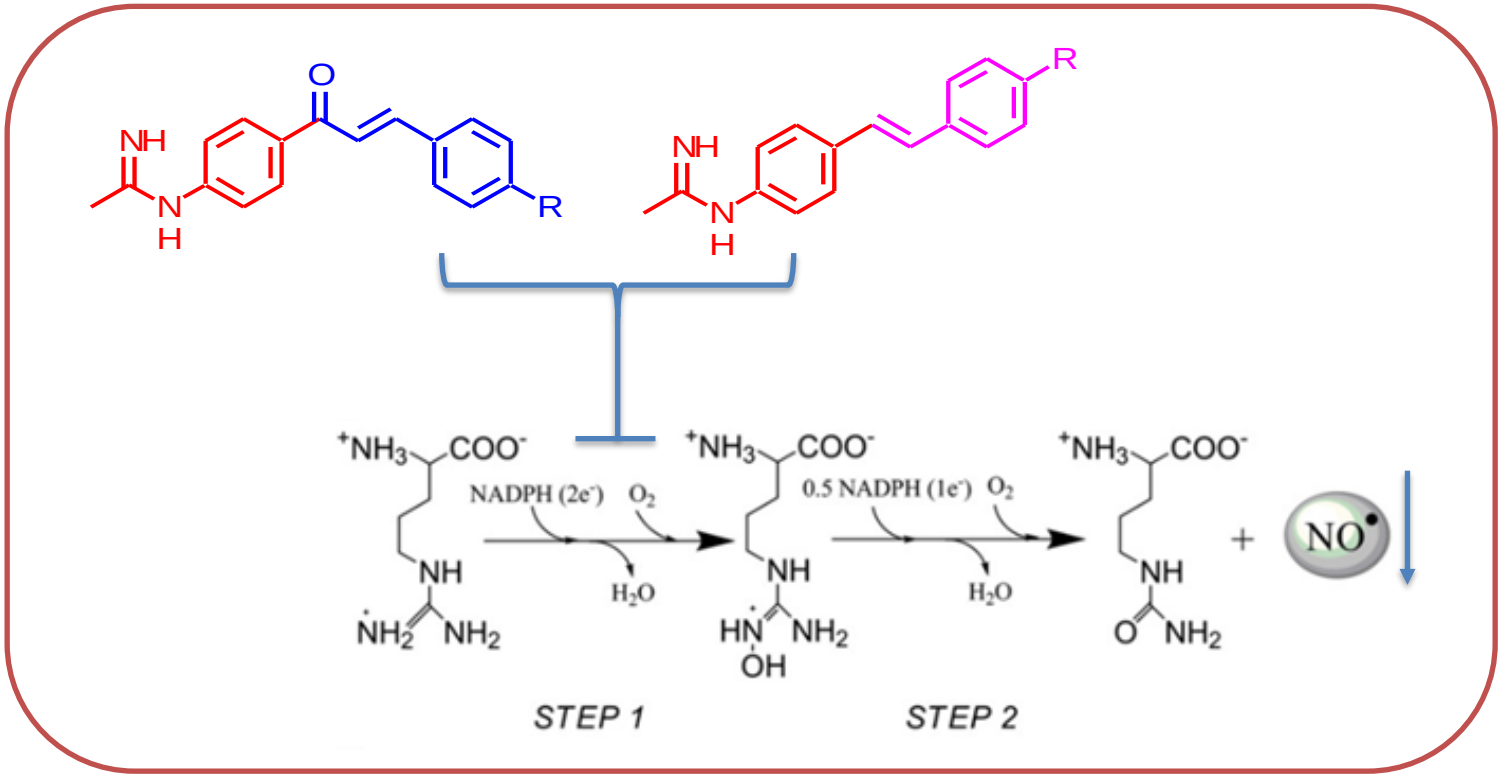
Synthesis and biological evaluation of chalcone and stilbene based acetamidines as Nitric Oxide Synthase inhibitors

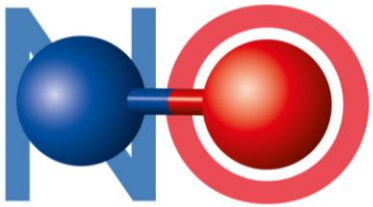
Graphical Abstract

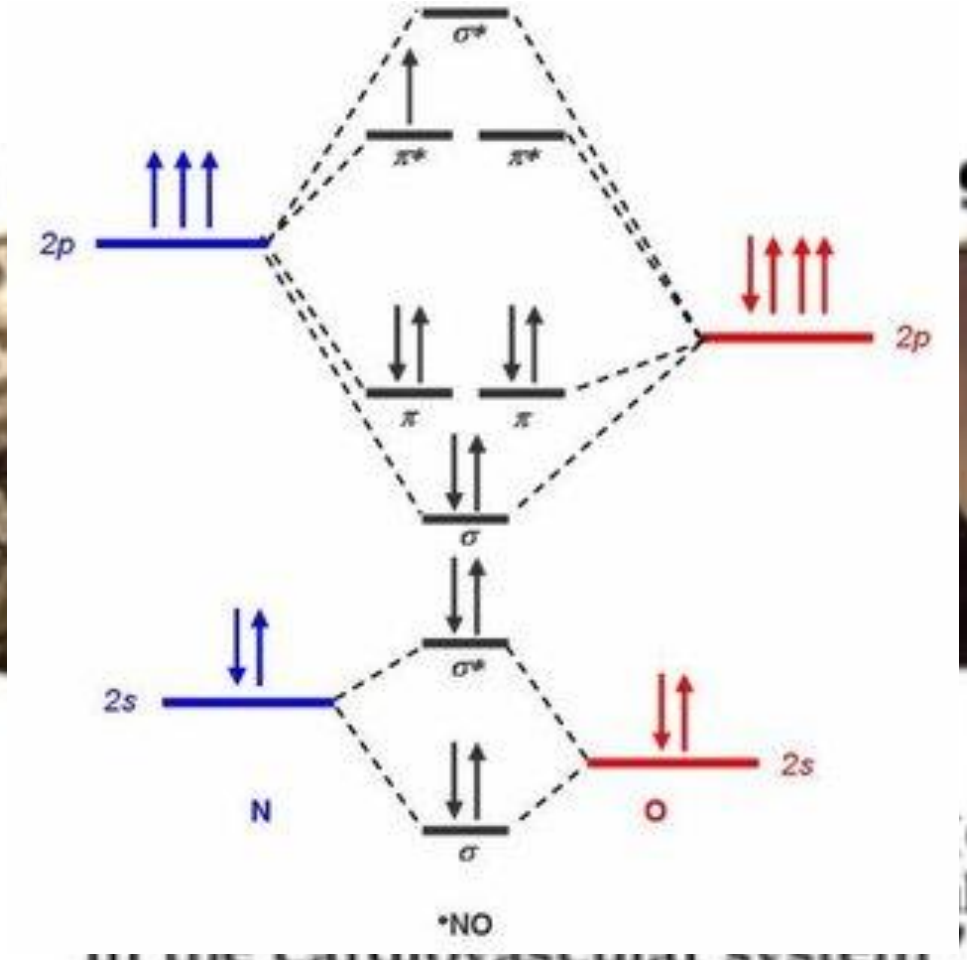


Abstract:
Nitric Oxide Synthases (NOS) are a family of oxidoreductases responsible for the biosynthesis of the free radical nitric oxide (NO). This is a very important signalling molecule involved in many different biological processes, both physiologic and pathologic.
In particular, the inhibition of the inducible NOS (iNOS) has been proposed as a targeted therapy in several diseases, including cancer, neurodegeneration and inflammatory bowel disease. In the past years our research group has disclosed different new potent and selective acetamidines as iNOS inhibitors, collecting evidence their usefulness as anticancer agents.
In the present work, starting from the observation that different chalcone-based compounds can modulate the iNOS expression levels, we have synthesised a set of acetamidin-chalcones and acetamidin-stilbenes and we evaluated them as inhibitors of the iNOS activity. Results obtained from these studies will be presented.

Keywords: Chalcone; inhibitors; nitric oxide synthases; synthesis; stilbene

Introduction





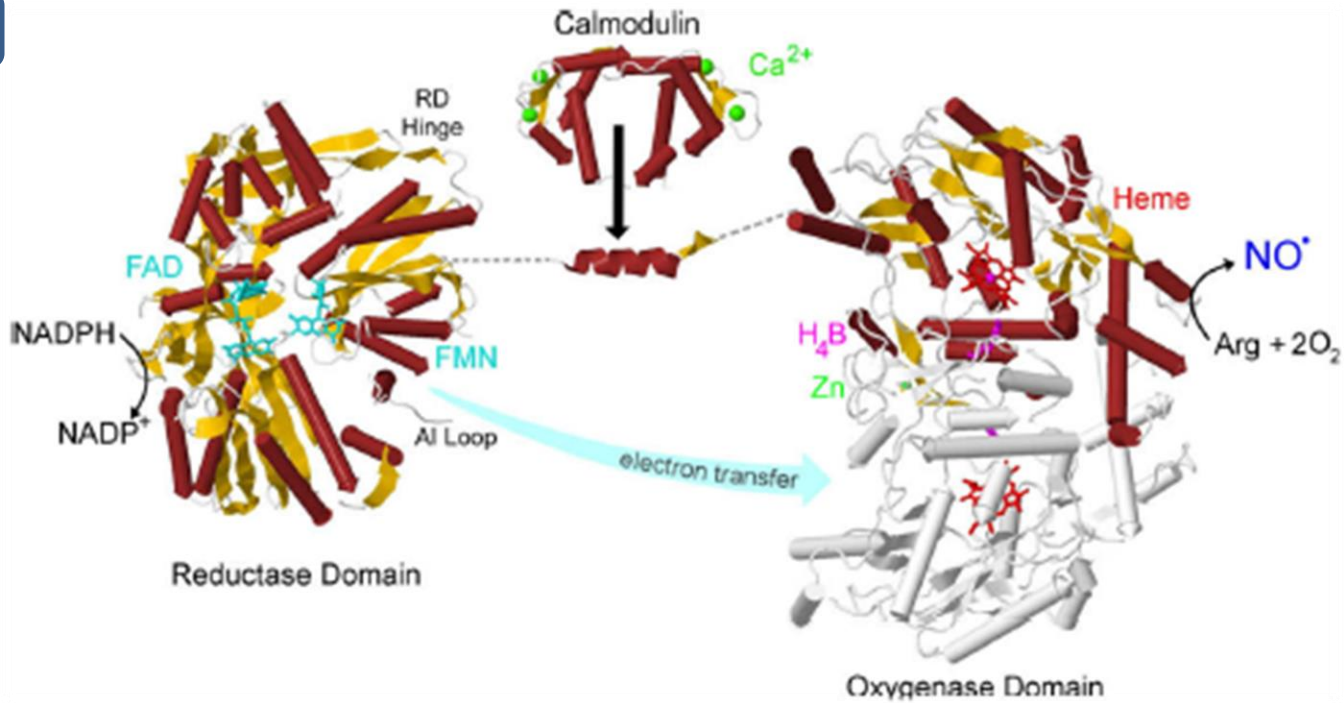
Introduction: Nitric Oxide is biosynthesed by Nitric Oxide Synthases

nNOS (NOS-1)

eNOS (NOS-3)

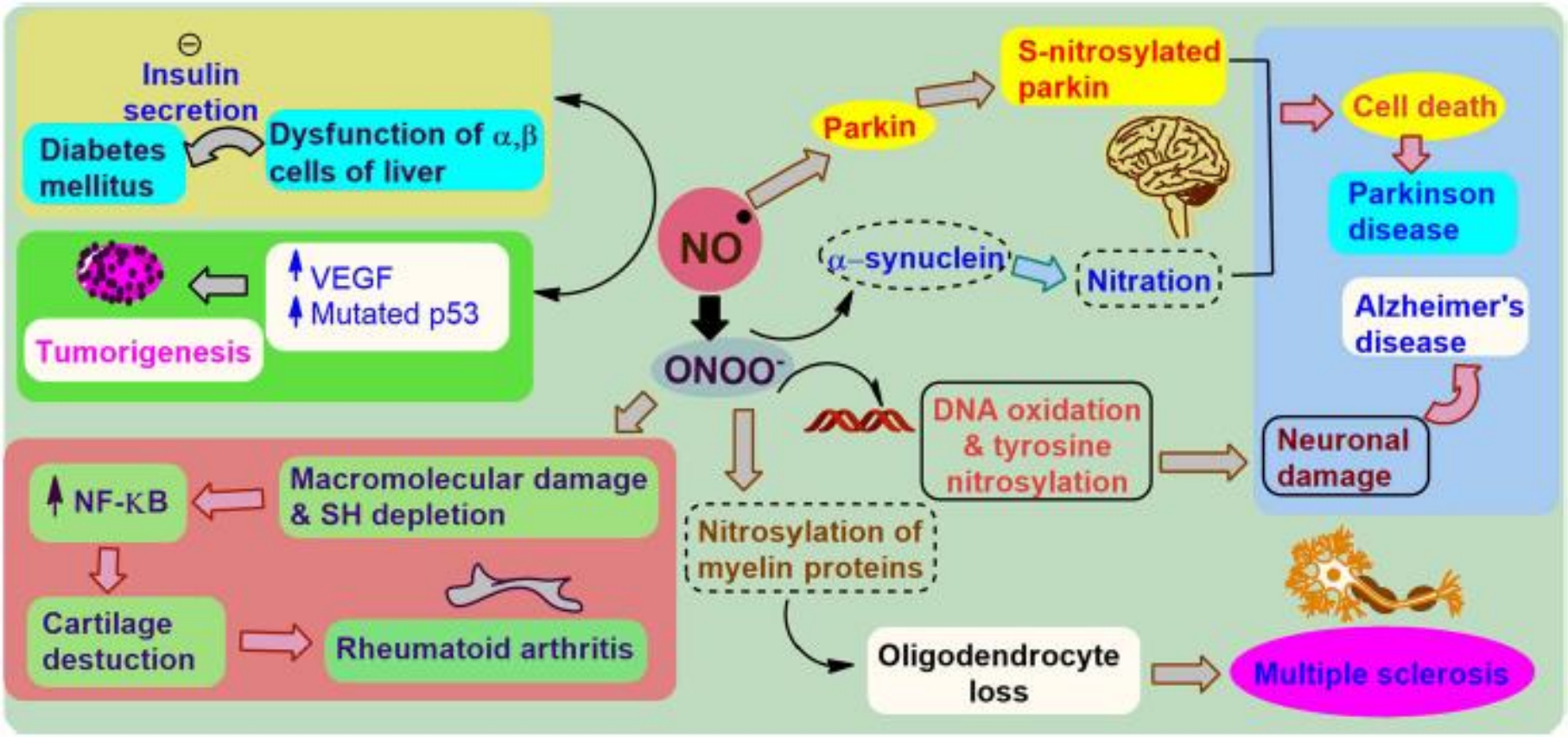
iNOS (NOS-2)

Constitutive



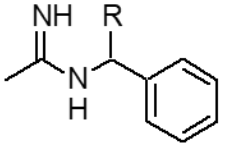
European Heart Journal, **2012**, *33*, 829–837

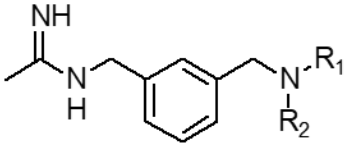
Introduction: Role of Nitric Oxide in different pathological conditions

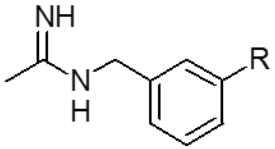


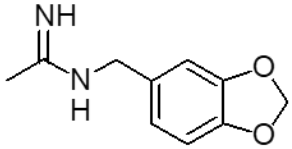
Med. Res. Rev. **2020**; *40*, 823-855.

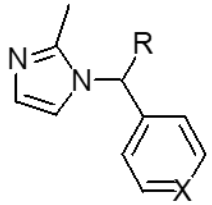
Introduction: Acetamidines as iNOS inhibitors











Maccallini, C et al. *J. Med. Chem.* **2009**, *52*, 1481–1485

Maccallini, C et al. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 6495–6499

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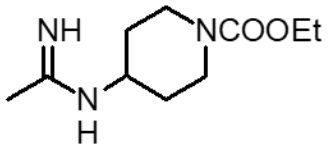
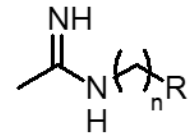
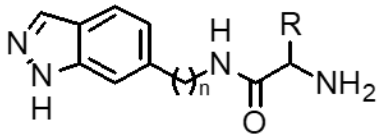
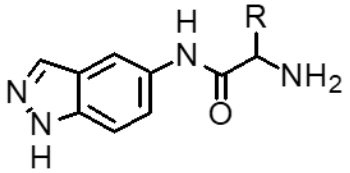
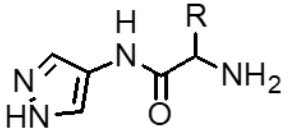


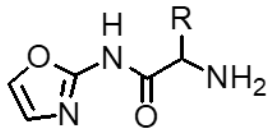


Maccallini , C. et al. *Med. Chem.*, **2012**, *8*, 991-995









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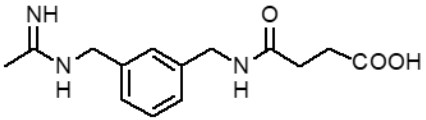
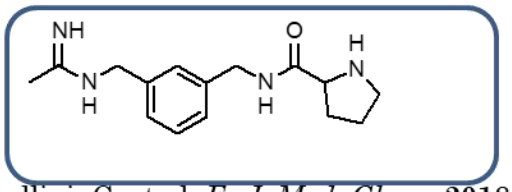
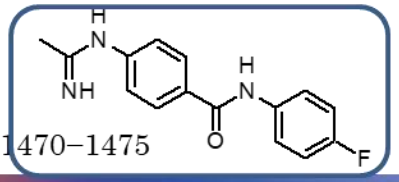


Maccallini, C. et al. *ACS Med. Chem. Lett.* **2015**, *6*, 635–640

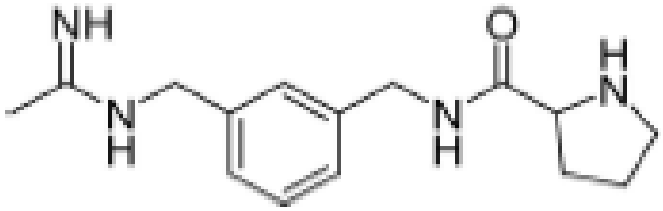


Maccallini, C. et al. *E. J. Med. Chem.* **2018**, *152*, 53–64

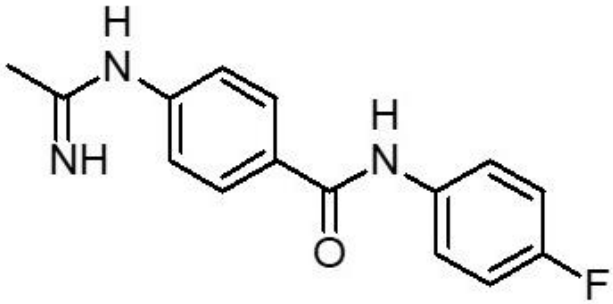


Maccallini, C. et al. *ACS Med. Chem. Lett.* **2020**, *11*, 1470–1475

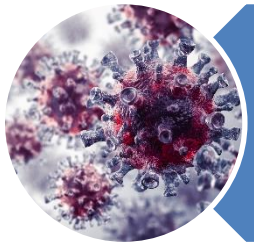
Introduction: CM544 and FAB1020 bioactivity



CM544
iNOS IC_{50}: 58 nM
Selectivity eNOS/iNOS=4569

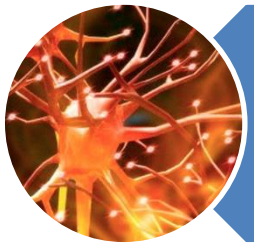


FAB1020
iNOS IC_{50}: 11 nM
Selectivity eNOS/iNOS>900



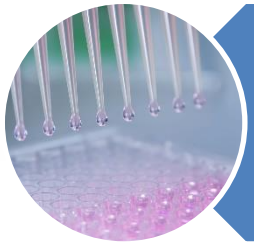
Antiglioma activity

E. J. Med. Chem. **2018**, *152*, 53
Int. J. Mol. Sci. **2019**, *20*, 495
ACS Med. Chem. Lett. **2020**, *11*, 1470



Neuroprotective

Molecules **2020**, *25*, 2646



Immunomodulatory

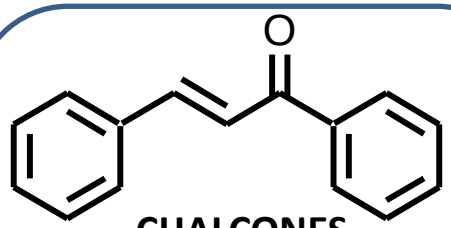
Molecules **2021**, *26(15)*, 4419

Introduction: chalcones and stilbenes, privileged structures in medicinal chemistry

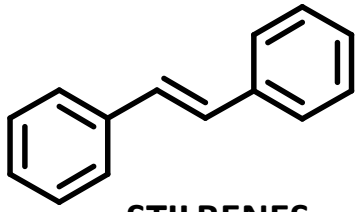
Antimicrobial

Antifungal

Antiparasitic



CHALCONES



STILBENES

Natural

Synthesised

Antidiabetic

↓ Blood glucose level

↑ Insuline secretion

↓ lipogenesis

Anti-inflammatory

↓ COX

↓ PGE2

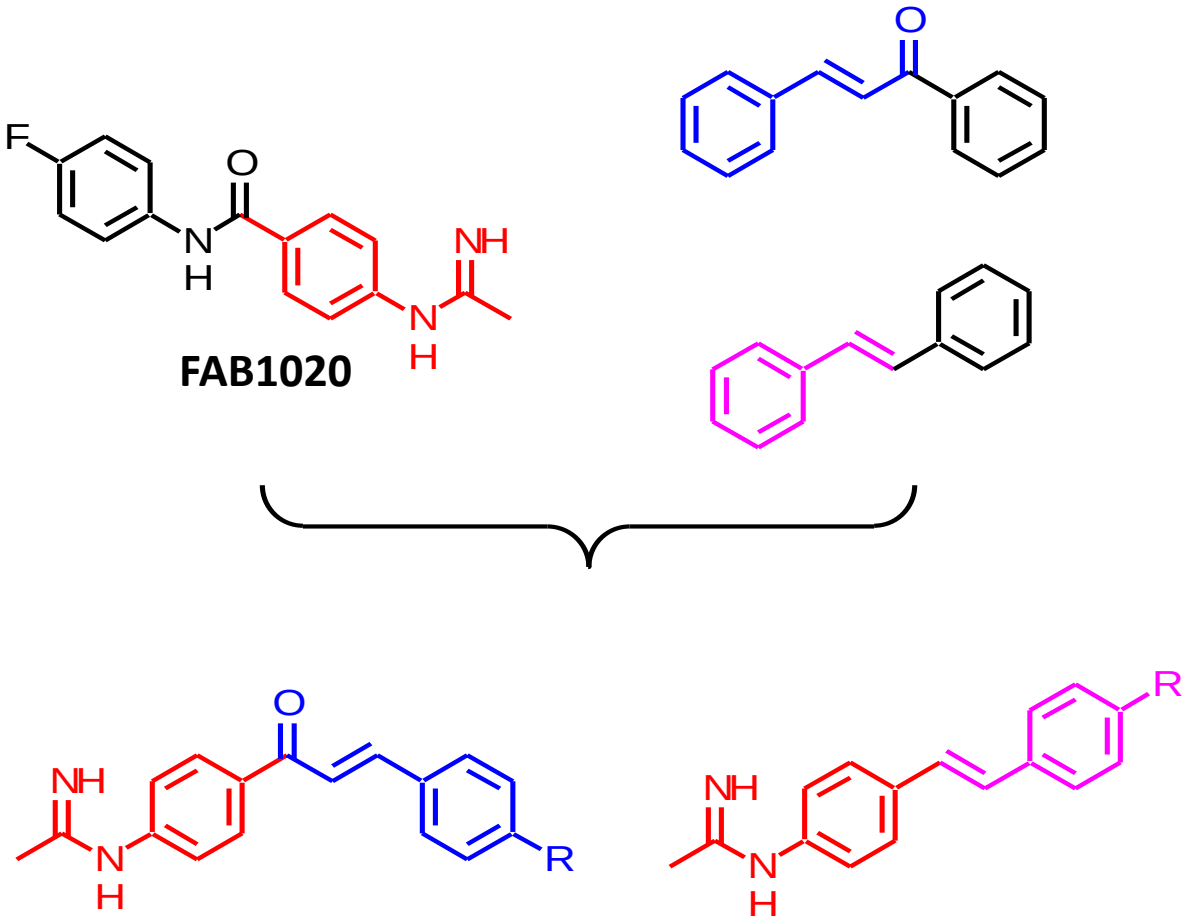
↓ TNF-a

Antiproliferative

↓ Cell proliferation

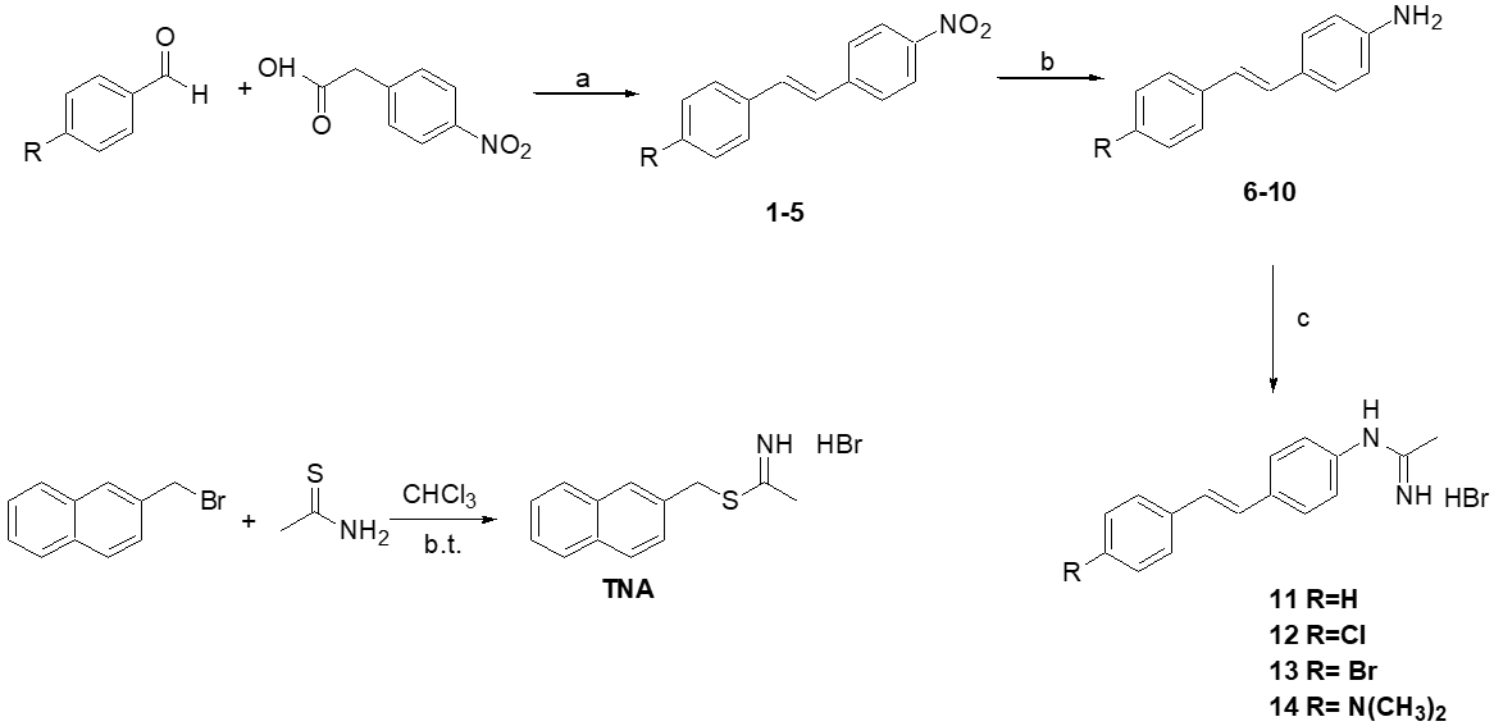
Front. Pharmacol. **2021**; 11:592654
ChemMedChem **2017**; 12:558

AIM of the WORK:



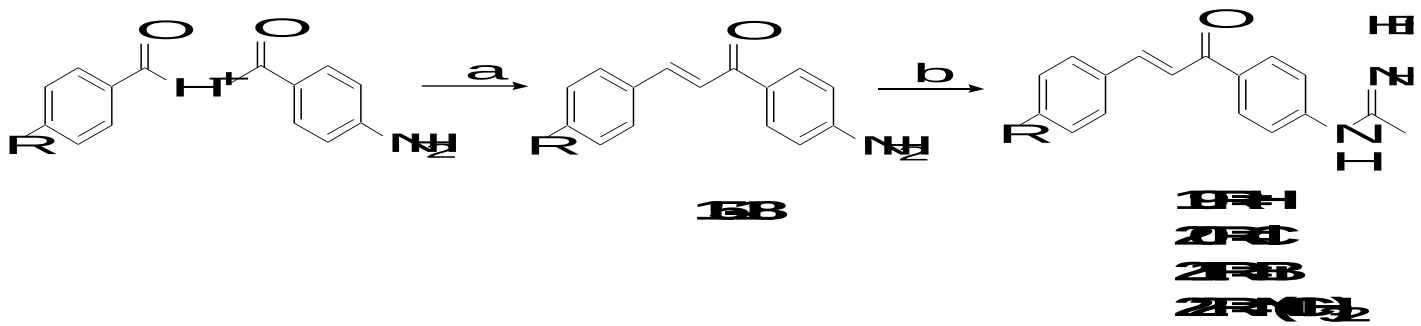
New chalcone and stilbene based acetamidines

Synthesis: Stilbene derivatives



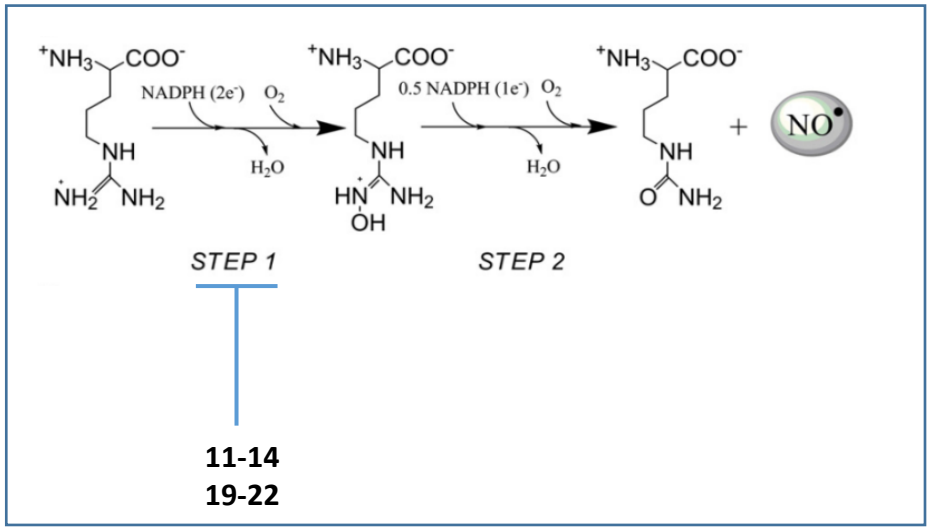
Scheme 1. Reaction conditions. a) EtOH, b.t, 24 h. b) $SnCl_2$, HCl, EtOH, b.t., 3 h. c) TNA, EtOH, b.t, 24h

Synthesis: Chalcone derivatives



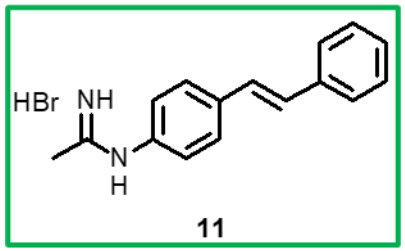
Scheme 2. Reaction conditions. a) NaOH, EtOH, from 0 °C to r.t., 24 h. b) TNA, EtOH, b.t, 24h

Biological evaluation of Stilbene and Chalcone derivatives



iNOS and eNOS %inhibition @ 1μM

Compound	iNOS	eNOS
11	32	*inactive*
12	*12*	n.d.
13	*inactive*	n.d.
14	64	*inactive*
19	82	*inactive*
20	*9*	n.d.
21	14	n.d.
22	n.d.	n.d.



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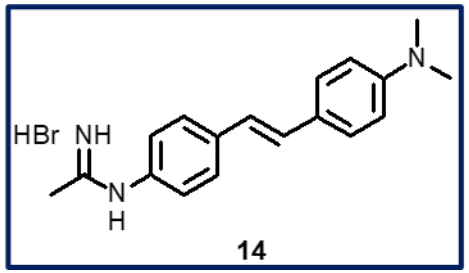

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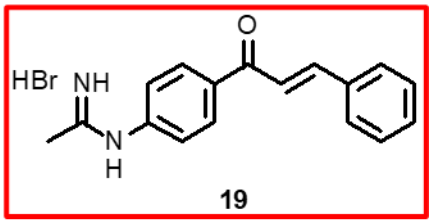

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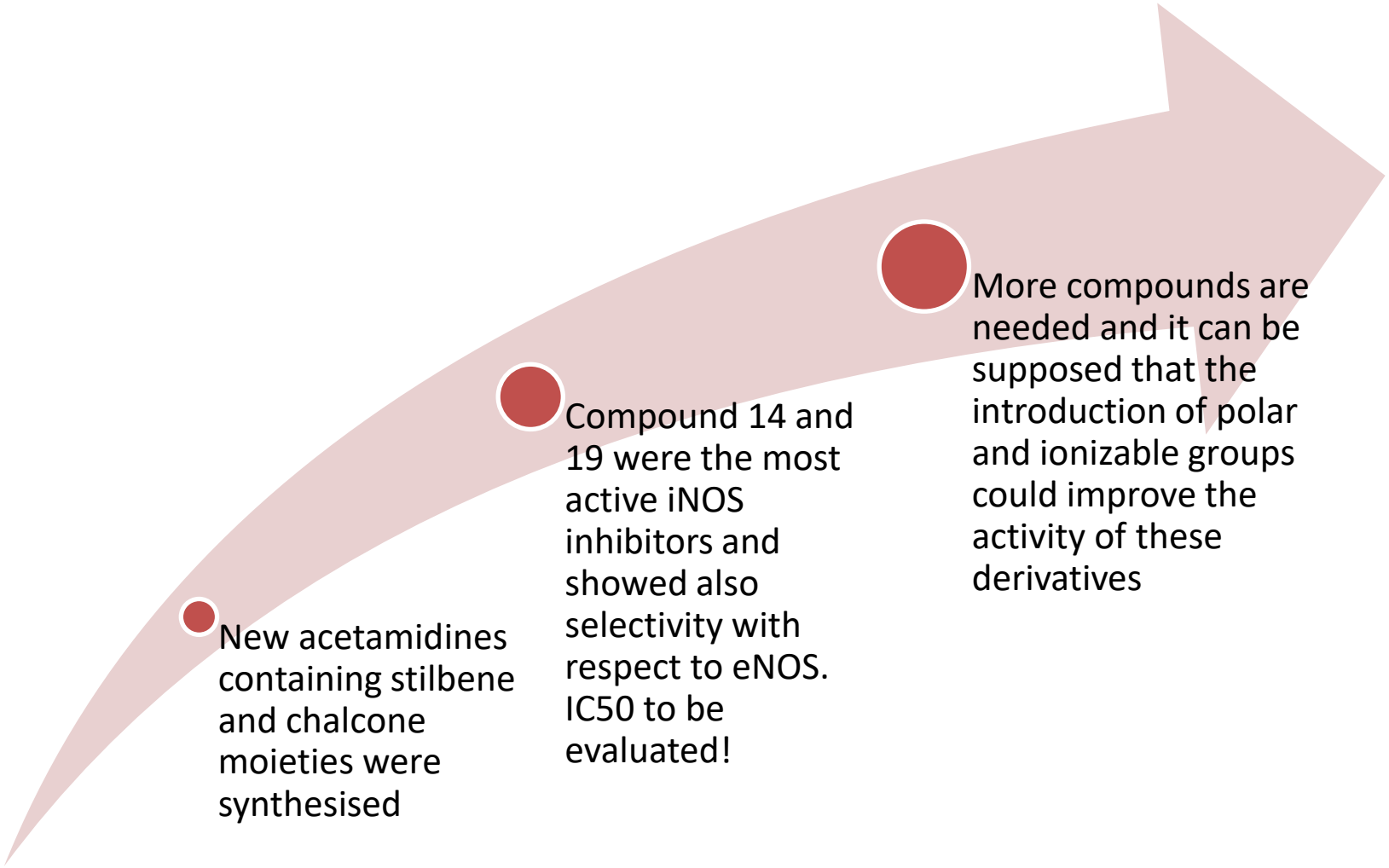
Conclusions and Perspectives



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