Synthesis, physicochemical characterization and biological evaluation of newly synthesized N-hydroxyurea and hydroxamic acid derivatives as potential dual inhibitors of cyclooxygenase-2 and 5-lipoxygenase enzymes

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INTRODUCTION

Prolonged production of inflammatory mediators derived from arachidonic acid through the enzymes cyclooxygenase (COX) and lipoxygenase (LOX) are responsible for various inflammatory diseases.

It was showed that inhibition of any of these pathways could potentiate the other one, so inhibition of both pathways represents a rational approach to the design and development of more effective and safer anti-inflammatory drugs.

The aim of the study was synthesis, physico-chemical characterization, investigation of antioxidant, COX-2 and 5-LOX inhibitory activity of N-hydroxyurea and hydroxamic acid derivatives.

METHODS

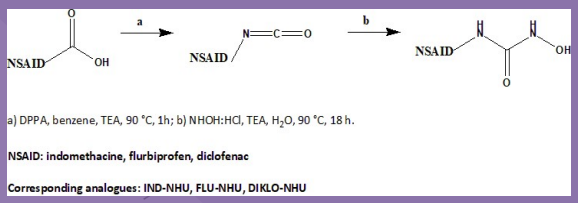
* Compounds **IND-NHU**, **FLU-NHU**, **DIKLO-NHU**, **IBU-Ac** and **NAP-Ac**, designed as potential dual COX-2 and 5-LOX inhibitors based on SAR study, were synthesized according to literary procedures (1, 2).

* Physico-chemical characterization of newly synthesized compounds included determination of the melting points and spectroscopic techniques (ATR-FTIR, 1H-NMR, 13C-NMR, MS/MS)).

* Investigation of antioxidant properties was performed according to literature procedures (3). Effects of various concentrations of newly synthesized compounds on oxidative stress parameters (TOS, TAS, PAB and SHG) were observed and oxy scores were calculated.

* COX-2 and 5-LOX inhibitory activity was tested using a fluorimetric COX-2 and 5-LOX inhibitor screening kits (4, 5).

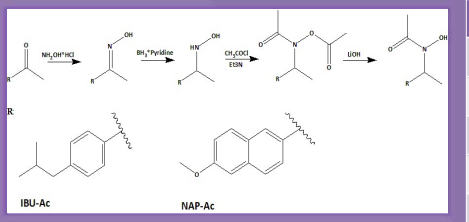
SYNTHESIS



a) DPPA, benzene, TEA, 90 °C, 1h; b) NHOH:HCl, TEA, H_2O, 90 °C, 18 h.

NSAID: indomethacine, flurbiprofen, diclofenac

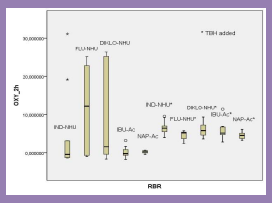
Corresponding analogues: IND-NHU, FLU-NHU, DIKLO-NHU

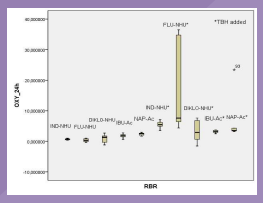


ID	Yield
IND-NHU	21 %
FLU-NHU	35.5 %
DIKLO-NHU	23.6 %
IBU-Ac	33 %
NAP-Ac	16 %

BIOLOGICAL EVALUATION

* Antioxidant properties of newly synthesized compounds before and after addition of prooxidant TBH (terc-butylhydroperoxide) and after 2h (OKSI2) and 24h (OKSI24) incubation:





* In vitro COX-2 and 5-LOX activity:

Compounds	IND-NHU	FLU-NHU	DIKLO-NHU	IBU-Ac	NAP-Ac	Celecoxib[b]	Zileuton[c]
COX-2 * IC_{50} [μM] [a]	10	/	/	/	/	0.45	/
5-LOX IC_{50} [μM] [a]	12.65	1.93	0.91	1.05	1.27	/	0.53

[a] In vitro test compound concentration required to produce 50% inhibition of enzime
[b] Selective COX-2 inhibitor, inhibitor control
[c] 5-LOX inhibitor, inhibitor control
*** investigation of COX-2 inhibitory activity of remaining compounds is in progress**

* Low values of oxidative stress parameters and oxy scores indicate good antioxidative potency of synthesized compounds.
* According to the enzyme inhibition results, **IND-NHU** represents dual COX-2 and 5-LOX inhibitor.

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[5] https://cdn.mybiosource.com/tds/protocol_manuals/800000-9999999/MBS846911.pdf

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