

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

International University of Africa

Graduate College

**Pharmacological Investigations and LD₅₀
Determination of New Amide Prodrug of
Ibuprofen**

*A thesis submitted to the department of pharmacology and toxicology,
faculty of pharmacy, for the fulfillment of requirement for the degree of M.
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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿يَرْفَعُ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ
أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ
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DEDICATION

I dedicate this work

To my lovely mother WAFI for always encourage
and for staying on my side.

To my lovely father ELMUTASIM for his
unconditional support

To my sisters and brothers who have never left my
side and are very special

To my big family, friends and colleges who supported
me throughout the process

Finally, this work is dedicated to all those who believe
in the richness of learning.

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BIOGRAPHICAL SKETCH

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LIST OF ABBREVIATIONS

AA	Arachidonic acid
COX	Cyclooxygenase enzyme
CV	Cardiovascular
EC₅₀	Half maximum effective concentration that indicate the potency
E_{max}	maximum possible effect of the agonist that indicate the efficacy
Fig	Figure
GI	Gastrointestinal
IL	Interleukin
IFN-γ	Interferon- γ
LD₅₀	The median lethal dose value
LPC	Lyso phosphatidylcholine
NSAIDs	Non-steroidal anti-inflammatory drugs
OECD	Organization for Economic Co-operation and development
pA₂	Negative logarithm of antagonist concentration that reduces an agonist effect to E _{max} /2, indicate the affinity
PAF	Platelet-activating factor
pA_x	-Log of antagonist conc.
PD₂	-log (EC ₅₀)
PGs	Prostaglandins
ROS	Reactive oxygen species
TAI-Pd	Tilal amide Ibuprofen prodrug
TG	Test guidelines
Th	T-helper cells
TNF-α	Tumor necrosis factor-alpha
UDP	Up-and-down procedure

ENGLISH ABSTRACT

Background: Inflammation is a complex process occurs within the damaged tissue. The severity of the side effects of NSAIDs, which used for inflammation management, encourage researchers to develop new medications with high safety. Literature survey revealed that masking the carboxyl group of NSAIDs improves the therapeutic efficacy and safety.

Aims: The study aimed to investigate anti-inflammatory activity of **TAI-Pd**. In addition, to determine other pharmacological action, possible mechanism(s) of action and pharmacodynamics interactions using isolated rabbit intestine. Moreover, determination of LD₅₀.

Methodology: The carrageenan-induced paw edema and the inhibition of protein denaturation were used for the anti-inflammatory activity investigation. A full dose-response curves for **TAI-Pd** and the standard agonists (Ach, 5-HT and BaCl₂) were constructed in cumulative manner, in absence and presence of standard antagonists (atropine and cyproheptadine). Also the possible pharmacodynamic interactions were determined for the standard agonists by constructing dose-response curves in the presence of **TAI-Pd** mixed with each of them in 50: 50 ratio (as agonist), and in high and low dose (as antagonist). In order to determine LD₅₀ *in vivo*, the OECD test guideline 425 protocol used.

Results: The results of the carrageenan-induced paw edema *in vivo* revealed that **TAI-Pd** exhibited potent anti-inflammatory effect compared to Ibuprofen, maximum at 4 hours, with % of inhibition of edema [23.25± 2.594]

for TAI-Pd at dose 35mg/kg and $[19.75 \pm 3.95]$ for standard Ibuprofen at dose 70mg/kg, and the inhibition of protein denaturation confirmed this findings.

The effect on isolated rabbit intestine revealed that **TAI-Pd** displayed dose dependant contracting effect, that blocked partially by atropine and cyprohepatadine. **TAI-Pd** potentiate the effect of Ach, while it possesses a neglectable effect on the 5-HT when administered in combination and decreases the agonistic effect of BaCl₂. This derivative exhibited a cyprohepatadine like effect on 5-HT when added as antagonist. The LD₅₀ of **TAI-Pd** is 2000mg/kg.

Conclusion: **TAI-Pd** exhibited potent anti-inflammatory activity when compared to Ibuprofen. **TAI-Pd** produces partial contracting effect on isolated rabbit intestine in vitro. **TAI-Pd** represent a better toxicological profile compared with standard Ibuprofen.

المستخلص

خلفية الدراسة : الالتهاب هو عملية معقدة تحدث داخل الأنسجة المصابة. نسبة لخطورة الآثار الجانبية لمضادات الالتهاب غير الستيرويدية التي تستخدم عادة لعلاج الالتهاب، تشجع الباحثون للبحث عن علاج أكثر أمانا للالتهاب. اثبتت الدراسات السابقة ان إخفاء مجموعة الكربوكسيل الداخلة في تكوين مضادات الالتهاب غير الستيرويدية يؤدي الى تحسين الفعالية العلاجية ومأمونية الدواء.

الأهداف: تهدف هذه الدراسة إلى التحقق من الخصائص الدوائية للمركب الجديد **TAI-Pd** (مشتق الايبوبروفين) ، بالتأكد من فعاليته كمضاد للالتهابات ، كما تهدف ايضا لالقاء الضوء على أثر هذا المركب و آلية عمله إضافة إلى التداخلات الفارماكوديناميكيه له إلى جانب تحديد الجرعه المميته لنصف الحيوانات المجربة (LD_{50})

منهجية إجراء الدراسة: استخدمت تجربتا التورم الناجم عن الكاراجينان في مخلب الجرز ، و تثبيط تمسخ البروتين، للتأكد من فعالية المركب كمضاد للالتهاب.

تم بناء منحنى الجرعة والاستجابة التراكمي لكل من **TAI-Pd** والعقاقير القياسية المناهضة (الأسيتل كولين و السيروتونين وكلوريد الباريوم) ، منفردة و فى وجود جرعة منخفضة و اخرى في وجود جرعه عالية من الشالات القياسية (الأترابين والسيبروهيبتادين). كما تم دراسة التفاعلات الفارماكوديناميكيه المحتملة للعقاقير القياسية المناهضة مع **TAI-Pd**، ببناء منحنى الجرعة والاستجابة للمركب مختلطا مع كل واحد منهم بنسبة 50:50 (كمناهض)، وباضافته قبل كل منهم بجرعتين عالية و منخفضة (كشال).

من أجل تحديد الجرعة المميته لنصف الحيوانات المجربة، استخدم بروتوكول 425.

نتائج الدراسة: كشفت نتائج التورم الناجم عن الكاراجينان في المخلب ، أن **TAI-Pd** لديه تأثير قوي كمضاد للالتهابات مقارنة مع الايبوبروفين ، حيث يبلغ ذروته في 4 ساعات من الحقن، مع % تثبيط تورم قدرها $[2.594 \pm 23.25]$ ل **TAI-Pd** في جرعة 35 ملغ/ كغ و $[3.95 \pm 19.75]$ للايبوبروفين القياسي في جرعة 70 ملغ/ كغ. نتيجة تثبيط تمسخ البروتين في المختبر، جاءت مؤكدة للتأثير القوي ل **TAI-Pd** كمضاد للالتهابات.

اظهر المركب **TAI-Pd** انقباضا يتناسب والجرعة على الأمعاء الدقيقة المعزولة للأرنب ، و أثبتت الدراسة عن إمكانية قفله جزئيا بالاتروبين و السيبروهيبتادين . و لقد اظهر المركب تأثيرا تازريا مع

الأستيل كولين و مثبطا لكوريد الباريوم عند اضافته مناهضا ومن غير اثر على الفعالية القصوى للسيروتونين عندما اضيف له كمناهض و اثرا مشابها للسيبروهيبتادين عند اضافته كشال. بلغت الجرعة المميئة لنصف الحيوانات المجربة لمركب **TAI-PD** قيمة 2000ملغ/كغ. **الخلاصة:** اظهر المركب تأثيرا قويا كمضاد للالتهابات مقارنة بالايوبروفين، كما اظهر القدرة على القيام بأثر انقباضي في عضلات الأمعاء الدقيقة الملساء المعزولة للأرنب. يتمتع **TAI-Pd** بمأمونيه اكثر من التي يمتلكها عقار الايوبروفين.