Design and Synthesis of Sulindac New Derivitives as Possible Mutual Prodrug with Potential to Maximized Therapeutic Area

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Abstract

The urgent necessity today for development of anti cancer agent is crucial so highly dependent for searching for new anti neoplastic action ,the drug discovery process is costly and consume long time ,in my study focusing my efforts toward drug optimization process using sulindac (NSAID) which has a fantastic attractive area as anti cancer and anticancer in addition to it is anti inflammatory action .

The study describes design and synthesis of mutual pro-drug of sulindac in combination with thenatural anti oxidants (menthol ,thymol ,vanillin,guiacol) as a single integral pharmaceutical unit byan chloro acetyl chlorideas spacer to form an ester mutual prodrug with expected to improve the anti inflammatory ,anti cancer , antioxidant action of sulindac by the conjugation with natural anti oxidative integral moiety and minimized the ulcerogenic adverse effect of sulindacit is carboxylic acid functionality .The synthesis is conferred byH1NMR, FT-IR, CHN and physiochemical properties.

Keywords: *sulindac , antioxidants, anticancer, mutual prodrug.*

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) consider as growing nucleus for driving research to screening anti neoplastic agents with due it is wide therapeutic & clinical applications that coverage a significant population in diversity clinical area in the world wide.

The epidemiological studies mention & demonstrate the fantastic action of NSAIDs in the prevention & treatment of cancer in the therapeutic area of NSAIDs with therapeutic dosage regimen.

The sulindac is only NSAID has a marked anti cancer action and a novel immunological mechanism [1] as well as anti oxidant activity [2].

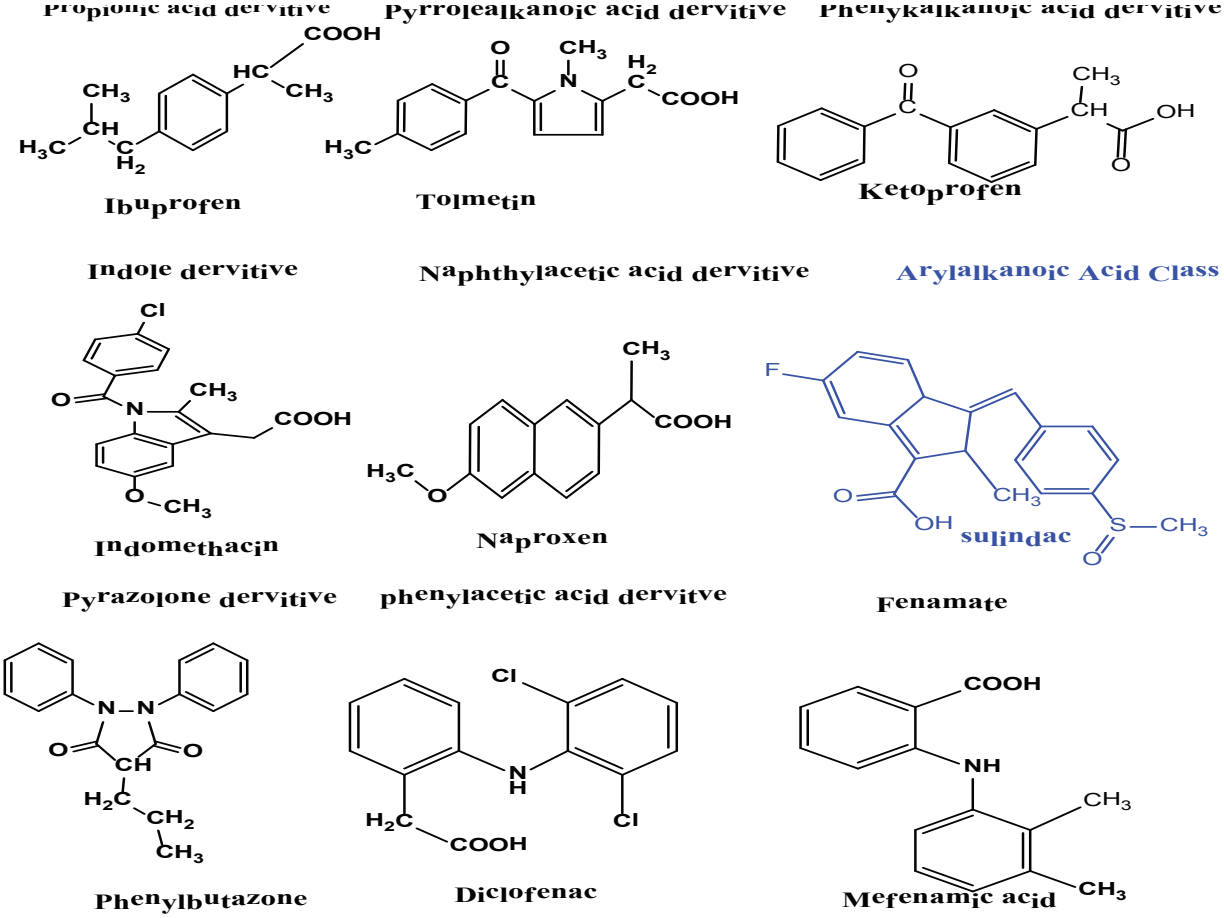
Today the human healthy life is limited to susceptibility of our vital organs and their cellular building units to natural environments and fresh natural bio resources .

The rapid explosive developmental revolution in different area of life(industrial , agricultural, nutritional etc)has been accomplished by the marked incidence of an auto immune disorders mainly rheumatoid arthritis which is one of major complicated disease limits human life [3,4].

On other hand, The generation of free radicals have been contributing etiology in Parkinson's disease, senile and drug-induced deafness, schizophrenia, arthritis, ,diabetes mellitus, aging process and Alzheimer's[5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) display promising anticancer activity in many patient with solid tumors involving colorectal cancer. Previous evidence referred to that sulindac sulfide (SS) can inhibit the growth of tumor cells through cyclooxygenase-2 (COX-2) based path way or other biomechanical ways.

Clearly, COX-2 independent mechanismincludeda low toxic criteria to support the clinical potential sulindac as a chemoprevention drug. However, the molecular mechanisms responsible for COX-2 independent pathway have not been completely elucidated.[6]



One of predicted mechanism says that carcinogenic cell obey a critical remodeling phase of intracellular Ca2+ homeostasis that rationalize to critical cancer hallmarks. Store-operated Ca2+ entry (SOCE), a Ca2+ entry pathway In addition, majority of carcinogenic cells generate the Warburg effect, a metabolic switch from mitochondrial metabolism to glycolysis that supplies survival advantages.

The selection of non-steroidal anti-inflammatory drugs depolarize mitochondria, inhibit mitochondrial Ca2+ uptake that promote SOC inactivation, leading to inhibition of both SOCE and carcinogenic cell proliferation. Thus, mitochondria sustain store-proceeds currents in colon neoplastic cells but not in non neoplastic normal colonic cells and this action is counteracted by selected NSAIDs supplying a pathway for cancer chemoprevention .[7]

The anti-inflammatory drugs Sulindac and Aspirin, displays significantly higher IC50 values in proliferation assays for AA cell lines compared to CA cell lines indicating the anti-inflammatory actions of these drugs by measuring the secretion of inflammatory cytokines and MAPKs activation in response to the pro-inflammatory cytokine TNF-alpha.[8]

Sulindac can reduce the number and size of precancerous colonic adenomas in patients with history adenomatous polyposis (FAP), but is not recommended for long-term as a cancer chemopreventive drug due to fatal toxicities related to cyclooxygenase (COX) inhibition[9].

Natural antioxidants are the most important molecules for centuries, it has been used in traditional medicine and has been shown to possess various pharmacological properties including antioxidant, free radical scavenging, anti-inflammatory, analgesic, antispasmodic, antibacterial, antifungal, antiseptic and antitumor activities.[10]

The pharmacological criteria of thymol is for example it has a multiple therapeutic actions against various metabolic and malignant diseases at both biochemical and molecular levels ,cardiovascular, rheumatological,neurological,gastrointestinal. It is promising therapeutic potential, molecular mechanisms and pharmacological properties as well as pharmacokinetic crtireia for the pharmaceutical development of thymol.[11][12]

Here we characterize the antineoplastic actions of a novel sulindac derivatives in conjugation with natural anti oxidants as mutual prodrug to combine the anti neoplastic action of sulindac with anti neoplastic anti oxidative power of the nature as a single synergistic integral therapeutic unit with minimal adverse effects

Materials and Methods

Experimental:

All reagents and anhydrous solvents were of analytical grade and supplied from (Sigma-Aldrich Germany ; BDH England ;ReidalDehean Germany). Melting points were determined by capillary tube method by melting point apparatus SMP30 Stuart(UK). Rf values were determined through using ascending thin layerchromatography method , on DC-Kartan SI Alumina 0.2 mm to ensure the purity and flow of the reaction, usingmethanol: chloroform (50:50) as mobile phase. Determination of FT-IR spectra done by FT-IR Shimatzu spectrophotometer, at facultyof pharmacy, kufa university, by using KBr discs. CHNmicroanalysis has been donein a centralbio-chemical libratoryfaculty of pharmacy-Kufa university, by using Euro EA 3000 elemental analyzer (Italy),HNMR).

Chemical synthesis:

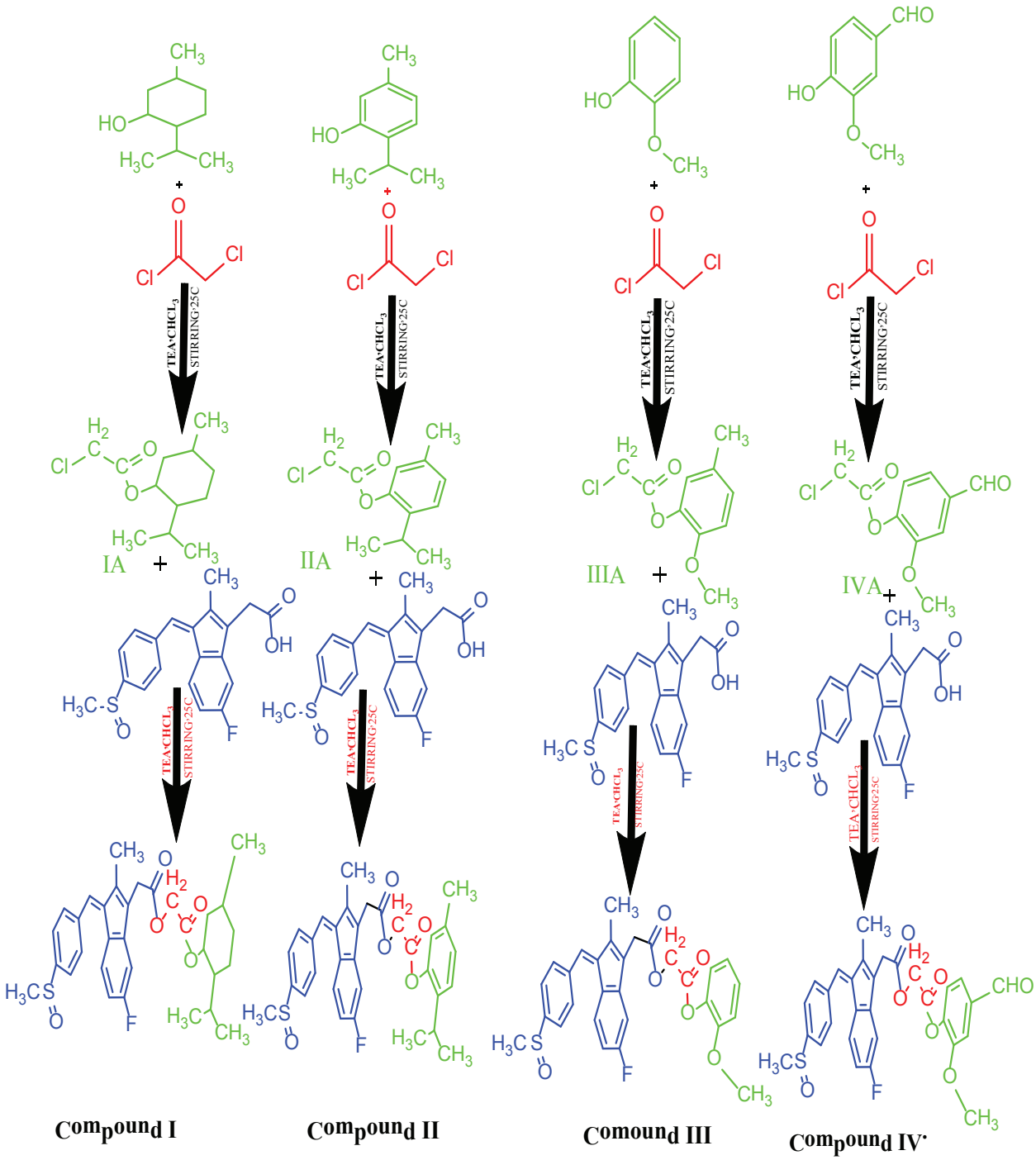
Chemistry:

1-Coupling reaction of antioxidants with chloroacetylchrolide:

Antioxidant(menthol or thymolorguiacol or vanilline) (10mmol) from each antioxidant coupling separately, was dissolved in chloroform (40 ml), then TEA (1.4 ml, 10mmol) wasadded. The reaction mixture was stirred on ice bath,chloroacetylchloride (0.78 ml, 10mmol in 10 ml $CHCl_3$) wasadded drop wise with continuous stirring over a period of one hour, followed by refluxing of the mixture for threehours. Then, the solvent was evaporated under reduced pressure and the recrystallized fromethanol, to provide compounds (IA , IIA,IIIA and IVA) respectively[13]. The percent yield, physical appearance, and Rf values were given in table(1), and FT-IR spectrum was given in table 2.

2-Coupling reaction of sulindac with compounds (IA , IIA,IIIA and IVA).

A mixture of each compound(IA or IIAor IIIA or IVA) (8mmol), and sulindac (8mmol), were dissolved in chloroform (40 ml), thenTEA (1.1ml, 8mmol), was added. The reaction mixture was stirred at room temperature overnight. The solventwas evaporated under reduced pressure ; the residue was triturated with acetone and recrystallized from methanol.[13,14,15] The percent yield,physical appearance, and Rf values were given in table 1, and FT-IR spectrum was given in table 2. All steps of the synthesis of all compounds are presented in following scheme .



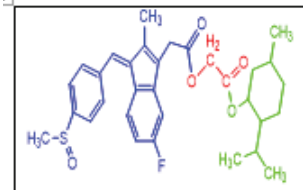
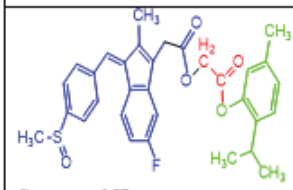
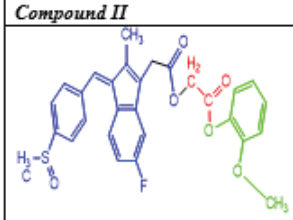
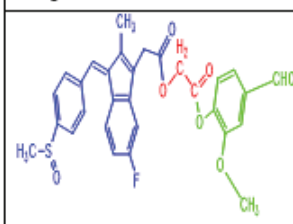
Reasult and Disscusion

Mutual new an ester derivatives of sulindac with natural antioxidants (menthol ,thymol ,vanillin ,guiacol) were synthesized by the scheme thatshown above. They were studied to physico-chemical characterization, the data are shown in Table 1, and theirstructures were confirmed by the FT-IR spectroscopy, thus confirmed the formation of double an ester bonds in the synthesized new derivatives of sulindac with the natual antioxidant as united molecule with combined therapeutic action

Table (1) the physiochemical properties of the synthesized compounds:

Synthesized compounds	chemical formula	Molecular weight	Description	% yield	Melting point oC	Rf value
CompoundIA	C12H21ClO2	232	Yellow oil	88	……	0.55
Compound.IIA	C12H15ClO2	226	Orange oil	95	.....	0.46
Compound IIIA	C10H9ClO4	229	Yellow oil	90	……	0.86
Compound IVA	C10H11ClO3	214	Red oil	95	…….	0.76
Compound I	C32H37FO5S	523	Yellow crystal	90	133-135	0.86
Compound II	C32H31FO5S	547	Yellow crystal	88	78-80	0.52
Compound III	C29H25FO6S	520	Orange crystal	80	144-146	0.83
CompoundIV	C30H25FO7S	549	Orange crystal	66	115-117	0.36

1H-NMRand C,H,N MICRO ANYLAYSIS

 ***Compound I***	*(6H,CH3,1.1ppm),(3H,CH3,2.5 ppm),(3H,CH3,0.9ppm),(2H,CH2,3.6ppm),(3H, CH3,2.9ppm),(1H,CH,2.9ppm),(1,CH,3ppm).* **Calculated: C, 69.54; H, 6.75** **actual: C, 69.2; H, 6.2**
 ***Compound II***	*(6H,CH3,1.3 PPM),(3H,CH3,1.1PPM),(3H,CH3,2.1PPM)(2H,CH2,3. 1PPM),(3H,CH3,2.8PPM).* **Calculated:** C, 70.31; H, 5.72 Actual: C, 70.2; H, 5.71
 ***Compound III***	*(6H,CH3,1.3 PPM),(3H,CH3,1.1PPM),(3H,CH3,2.1PPM)(2H,CH2,3. 1PPM),(3H,CH3,2.9PPM)* **Calculated:** C, 66.91; H, 4.84 Actual: C, 66.3; H, 4.54
 ***Compound IV***	*(6H,CH3,1.3 PPM),(3H,CH3,1.1PPM),(3H,CH3,2.1PPM)(2H,CH2,3. 1PPM),(3H,CH3,2.9PPM),(1H,CH.9.8PPM)* **Calculated:** C, 65.68; H, 4.59 Actual: C, 67.68; H, 4.77

Conclusions:

The synthesis of the designed compounds of sulindac and natural antioxidants(menthol , thymol ,guiacol , vanilline) (as a single unithas been successfully achieved by chloroacetylchloride as arm between sulindac and natural moiety.

The Purity and structural formulas of the synthesized compounds were confirmed by melting points determination, R_f values, FT-IR spectroscopy(C.H.N) microanalysis and H^1 NMR .

Competing Interests: The authors confirm that there is no conflicts of interest.

Funding: The author did not receive any external funding for this work.

Ethical Clearance: this study did not involve the testing on human or laboratory animal .

Recommendations:

1-Full kinetic studies of final compounds .

2-Study of the cell line to evaluate anti neo plastic activity.

3-Determination of COX-2 selectivity of the tested compounds by assessing COX-2:COX-1 inhibitory ratio using human whole blood assay.

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