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DESIGN AND SYNTHESIS OF NEW DERIVATIVES OF KETOPROFEN LINKED TO NATURAL ANTIOXIDANTS (THYMOL, MENTHOL & GUAIACOL) AS POSSIBLE MUTUAL PRODRUGS

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) represent one of the most widely used classes of drugs. They are used primarily for the treatment of osteoarthritis, rheumatoid arthritis and other inflammatory disorders. However, the use of NSAIDs is limited due to possibility of inducing erosions and ulcers in the gastrointestinal tract. Recently, it has been well established that generation of various reactive oxygen species (ROS) locally plays a significant role in the formation of gastric ulceration associated with NSAID therapy. Therefore, in the present study NSAIDs (ketoprofen) have been conjugated with different antioxidants (thymol, menthol and guaiacol) having anti ulcerogenic activity. The objective was to obtain Ketoprfen–antioxidant derivatives as possible mutual prodrug that includes: Ketoprofen-thymol (Compound I), Ketoprofen-menthol (Compound II) and Ketoprofen - guaiacol (Compound III). The mutual prodrug of NSAID and antioxidant was designated to generate the complementary pharmacological action as a single chemical entity with improved anti-inflammatory action and reduced ulcerogenic adverse effect. The synthesis is conferred by FT-IR, CHNS and physiochemical properties.

KEYWORDS: Ketoprofen, Thymol, Menthol, Guaiacol, Mutual prodrug.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of chronic inflammatory diseases, such as arthritis. Prolonged administration of these drugs

exhibit several undesired side effects; the most important are gastro-intestinal irritation and ulceration which still represent an unsolved therapeutic problem. The development of a gastrointestinal tract (GIT) safe anti-inflammatory therapy for the treatment of disease of joints presents a unique challenge.[1] It is well accepted fact that the GI side effect of acidic NSAIDs is a result of two different mechanisms.[2-4] The first mechanism involves a local action comprising of a direct contact effect and an indirect effect on the gastric mucosa and the second mechanism is based on the generalized systemic action occurring after absorption and can be manifested even after intravenous dosing.[4, 5] During recent years, it has been well established that generation of reactive oxygen species (ROS) plays a significant role in the formation of gastric mucosal lesions associated with NSAIDs therapy. Based on these observations, it has been suggested that co administration of antioxidants and NSAIDs in pharmaceutical dosage forms may possibly decrease the risk of NSAIDs induced GI ulcerogenicity.[6]

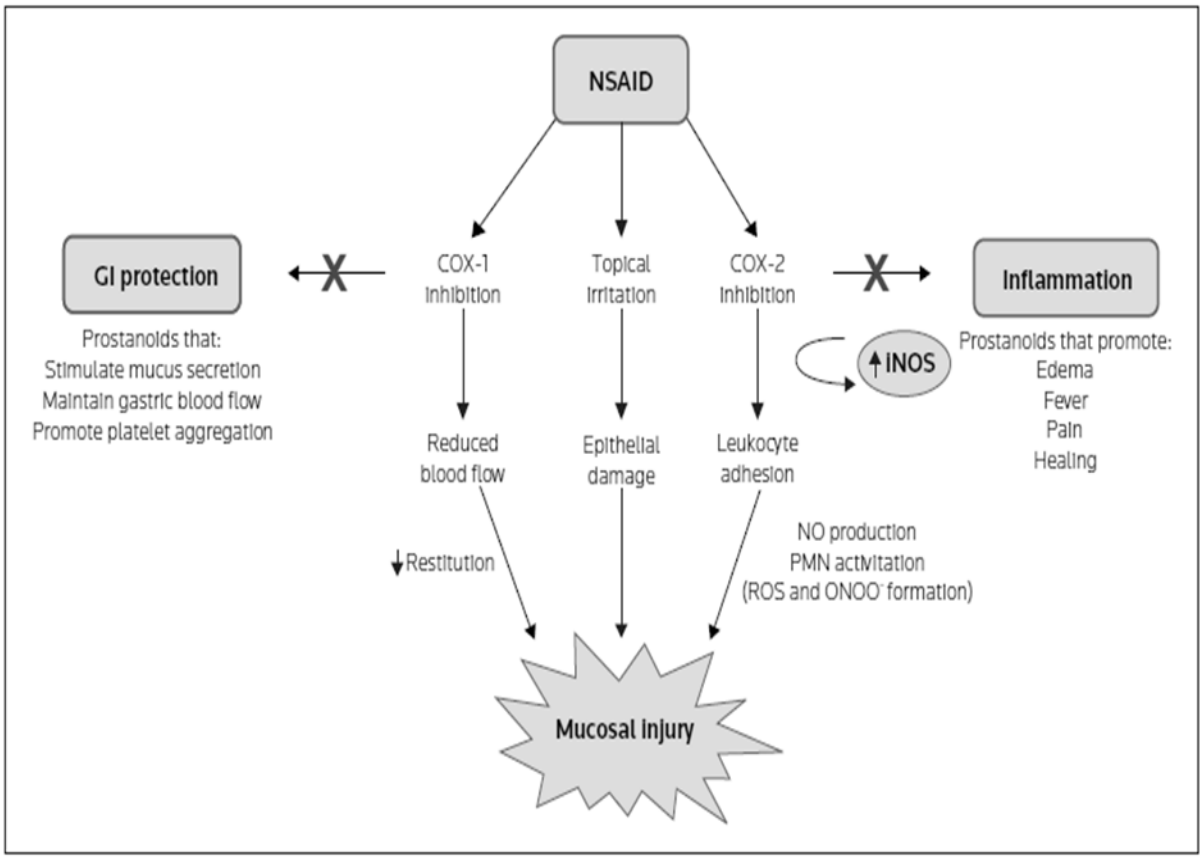


Figure 1: Mechanism of NSAIDs induced gastric ulceration.[7]

Combinations of antioxidant and anti-inflammatory drugs, such as polyphenols and NSAIDs have been proposed in the treatment of different neurodegenerative diseases. However, both polyphenols and NSAIDs gave rise to some problems when used in clinical setting. Due to

their scarce bioavailability, only a negligible amount of polyphenols reaches brain tissue and the concentrations achieved are much lower than those efficacious in vitro.[8] Guaiacol and thymol had the greatest oxygen radical-scavenging ability. This may be in part because both compounds are phenols. It has been reported that phenolic compounds exhibit antioxidant activity, which is correlated with health benefits.[9] Phenolic antioxidants with one or more phenolic ring and methoxy groups in their structure showed high inhibitory effect (they possess potent antioxidant, anti-mutagenic and anti-carcinogenic activities). One of the underlying major mechanisms is their action on cellular enzymatic pathways. They were tested on human polymorphonuclear leuckocyte 5-lipooxygenase (PMNL 5-LO) activity and observed that the formation of leukotrienes was significantly inhibited in a concentration-dependent manner.[10] Menthol also induced cytotoxicity in human gastric cancer cells by inhibiting the gene expression of topoisomerases. Menthol generates the chemo preventive effect by two directions:[11] by detoxifying antioxidant enzymes system and inhibition of anti-inflammatory and anti-cell growth signaling pathways culminating in apoptosis and/or cell cycle arrest. Ketoprofen is a propionic acid derivative that inhibits both cyclooxygenase (non-selectively) and lipoxygenase. Concurrent administration of probenecid elevates ketoprofen levels and prolongs its plasma half-life. The effectiveness of ketoprofen at dosages of 100–300 mg/d is equivalent to that of other NSAIDs in the treatment of rheumatoid arthritis, osteoarthritis, gout, dysmenorrhea, and other painful conditions. In spite of its dual effect on prostaglandins and leukotrienes, ketoprofen is not superior to other NSAIDs. Its major adverse effects are on the gastrointestinal tract.[12] The objective of this study was to obtain Ketoprfen derivatives as possible mutual prodrug with complementary pharmacological action as a single chemical entity with improved anti-inflammatory action and reduced ulcerogenic adverse effect.

MATERIALS AND METHODS

Materials

All reagents and anhydrous solvents were of analar type and generally used as received from the commercial suppliers (Merck, Germany, Reidel De-Haen, Germany, Sigma-Aldrich, Germany and BDH, England). Ketoprofen was supplied by Wuxihexia chemicals Company, China. Guaiacol was supplied by Sigma USA, Menthol was supplied by BDH, England and Thymol was supplied by Fluka, Switzerland.

Synthesis of Target Compounds

0.5 g of Ketoprofen (2 mmol) was dissolved in dry chloroform (25 ml) and 0.412 g of N,N-dicyclohexylcarbodiimide (DCC) (2 mmol) were added with continuous stirring on magnetic stirrer. The reaction mixture was stirred at 0^{o}C for 1 hour. Then 20 mg dimethylaminopyridine (DMAP) and 2 mmol antioxidants (0.3gm thymol or 0.33 menthol or 0.248gm=0.22ml guiacol) were added. The reaction mixture was stirred at room temperature for 24 hour in dark. The precipitated N, N-dicyclohexylurea (DCU) was removed by filtration. The organic layer was washed twice using 10 ml hydrochloric acid (0.5 N) and then using 10 ml sodium bicarbonate (5% w/v). The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure to produce a semi solid product. The resulting semisolid product was re-crystallized from ethanol to produce target compounds (I-III).[13]

Analysis of Compound

Melting points were determined by capillary method on Electrical melting point apparatus SMP30 Stuart, England. To check the purity and progress of reactions, ascending thin layer chromatography (TLC) was run on DC-Kartan SI alumina (0.2 mm) plates. The identification of compounds was done using a U.V. detector and the chromatograms were eluted with Dichloromethane:Methanol (8:2). IR spectra were recorded on a FTIR-spectrophotometer Shimadzu as KBr disks. CHNS microanalysis was done using a Euro EA 3000 elemental analyzer (Italy).

RESULTS AND DISCUSSION

The objective was to obtain Ketoprfen–antioxidant derivatives as possible mutual prodrug that includes: Ketoprofen-thymol (Compound I), Ketoprofen-menthol (Compound II) and Ketoprofen - guaiacol (Compound III). The synthesis scheme is presented in figure 2. The general routes outlined in the schemes were used to synthesize all compounds described here.

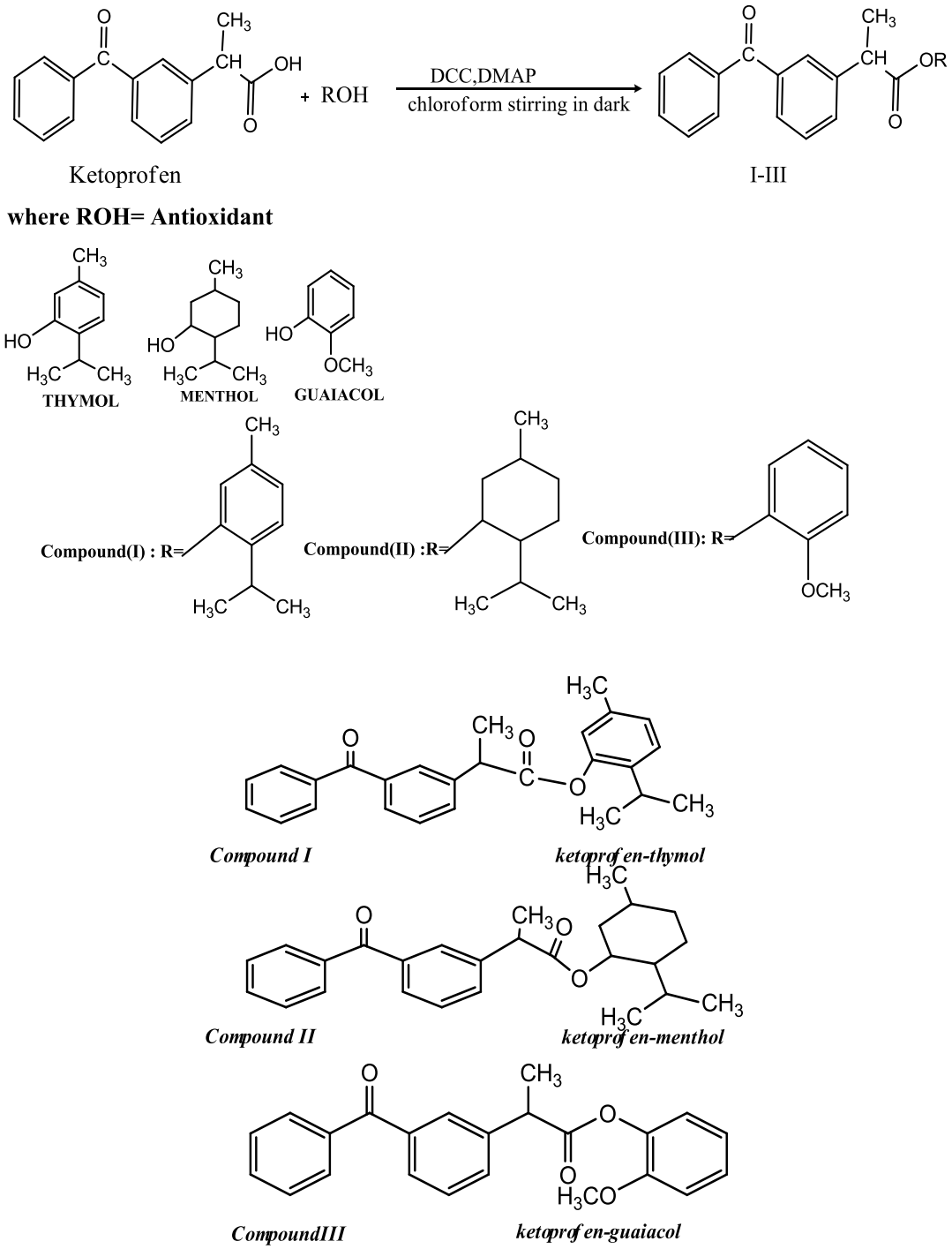


Figure 2: The scheme for synthesis of target compounds and their structures.

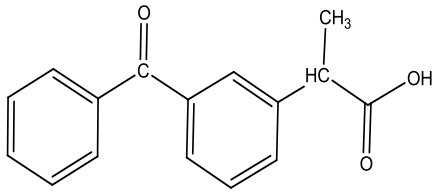
After synthesis the compounds were analyzed and the percent yield, physical appearance, melting point and TLC results were listed in table 1. The calculated elemental analysis for compound I was C, 80.8; H, 6.7 and founded elemental analysis was C, 80.2; H, 6.3. The calculated elemental analysis for compound II: was C, 79.56; H, 8.22 and founded elemental analysis was C, 79.44; H, 79.1. The calculated elemental analysis for compound III was C,

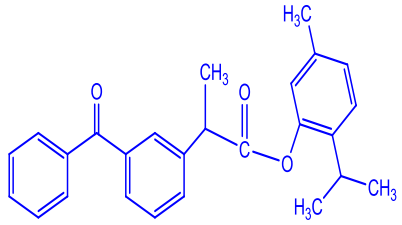
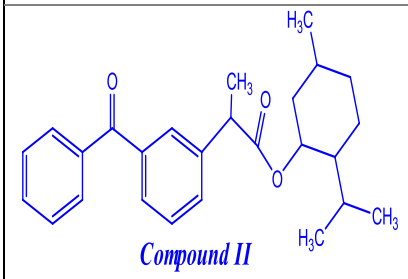
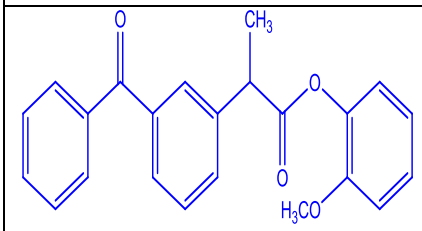
76.65; H, 5.59 and founded elemental analysis was C, 75.77; H, 5.21. The observed elemental analysis was nearly same to the calculated elemental analysis. The FT-IR spectra are shown table 2.

Table 1: The percent yield, physical appearance, melting point and R_f values of the target products.

Compounds	Chemical formula	Molecular weight	Description	% yield	Melting point ^oC	R_f value
Ketoprofen	$C_{16}H_{14}O_3$	254	White crystals	…	94	0.93
Compound I	$C_{26}H_{26}O_3$	386	Faint yellow semisolid sub.	69	--	0.66
Compound II	$C_{26}H_{32}O_3$	392	Colorless oily substance	72	--	0.83
Compound III	$C_{23}H_{20}O4$	360	Yellow oily substance	65	--	0.75

Table 2: IR characteristic bands of the synthesized compounds.

Compounds	*Bands (cm^{-1})*	*Interpretation*
 Ketoprofen	*2500-3200*	*Broad (O-H) stretching vibration of carboxylic acid*
	3055	*(C-H)stretching of aromatic*
	2978,2937	*asy.&sym.(C-H) stretching vibration of CH_2 &CH_3*
	1697	*(C=O) stretching vibration of acid*
	1654	*(C=O) stretching vibration of ketone*
	1598,1444	*(C=C) stretching vibration of aromatic overlapping with O-H bending .*
	1417,1284	*(C-H) bend of CH_3 & CH_2*
	1228	*(C-O) stretching vibration of acid(C-O-C) stretching*
	968,717	*Aromatic out of plane (C–H) & (C=C) bending.*

 *Compound I* [2-isopropyl-5-methylphenyl 2-(3-benzoylphenyl)propanoate]	*3029* *2931,2852* *1734* *1658* *1579,1450* *1284* *1207* *1180,721*	*(C-H)stretching vibration of aromatic asymmetrical and symmetrical (C-H) stretching vibration of CH_2 &CH_3 (C=O) stretching vibration of ester (C=O) stretching vibration of ketone (C=C) stretching vibration of aromatic (C-H) bending of CH_3 & CH_2 (C-O) stretching vibration of ester (C-O-C) stretching vibration Aromatic out of plane(C–H)&(C=C)bending.*
 *Compound II* *[2-isopropyl-5-methylcyclohexyl 2-(3-benzoylphenyl)propanoate]*	*3029* *2951,2852* *1736* *1662* *16271597, 1448* *1246* *1180,1078, 821*	*(C-H)stretching vibration of aromatic asymmetrical & symmetrical (C-H) stretching vibration of CH_2 &CH_3 (C=O) stretching vibration of ester (C=O) of stretching vibration ketone (C=C) stretching vibration of aromatic combined (C-H) bending of CH_3 & CH_2 (C-O) stretching vibration of ester Aromatic out of plane(C–H)&(C=C)bending*
 *CompoundIII* *[2-methoxyphenyl 2-(3-benzoylphenyl)propanoate]*	*3027* *2931,2852* *1743* *1627* *1575,1452, 1298* *1261* *1207* *1091,746*	*(C-H) stretching of aromatic asym.&sym.(C-H) stretching vibration of CH_3&CH_2.* *(C=O) stretching vibration of ester, (C=O) stretching vibration of ketone (C=C) stretching vibration of aromatic (C-H) bend of CH_2 & CH_3 (C-O) stretching vibration of ester asymmetric (C–O–C) stretching vibration. Aromatic out of plane (C–H)&(C=C) bending.*

The direct effects of NSAIDs are attributed to the local inhibition of prostaglandin (PG) synthesis in the GI tract. The indirect effect can be attributed to a combination of an ion-trapping mechanism of NSAIDs in mucosal cells and back diffusion of H^+ ions from the lumen into the mucosa. Topical irritation by the free carboxylic group of the NSAIDs is

considered an important factor in establishing superficial stomach erosion, particularly in the corpus region of the stomach.[2-5] The systemic effects are manifested due to inhibition of synthesis of gastric PGs like PGI2 and PGE2. NSAIDs inhibit the conversion of arachidonic acid into prostaglandins and thromboxanes by acting on a cyclooxygenase enzyme (COX) which catalyzes this conversion. Prostaglandins perform a central role in physiological processes such as pain, fever, homeostasis and immunity.[14, 15] Reduction of prostaglandins diminishes these effects and COX-inhibitors are therefore believed to be analgesic, anti-inflammatory and antipyretic. When prostaglandins are synthesized, a number of potentially harmful substances are produced as well. These substances include organic free radicals, peroxides, and activated oxygen compounds.[16] They activate environmental carcinogens and stimulate metastasis.[17] Inhibition of prostaglandin synthesis by NSAIDs was therefore hypothesized to be preventative for the development of cancer.[18, 19] Derivatization of the carboxylate moiety in NSAIDs would eliminate their ability to inhibit COX-1 without significantly affecting their COX-2 inhibitory properties. Because many NSAIDs contain a carboxylic acid group, this represents a general strategy for the conversion of nonselective NSAIDs into selective COX-2 inhibitors. The rationale behind designing new compound as possible mutual prodrug is to achieve temporary blockade of the free carboxylic group present in the ketoprofen till their systemic absorption. Furthermore, there are potential advantages in giving antioxidant drugs of natural origin (thymol, menthol and guaiacol) as good therapeutic agents for treating free radical mediated diseases like NSAID induced peptic ulcers. Such agents are named as mutual prodrugs that are designed with the aim of improving physiochemical properties.[20, 21] In comparison to physical mixture of NSAID and natural antioxidant, the reduction in ulcer index is superior due to the polar nature of antioxidant that lead to low bioavailability of antioxidants. Such agents might deliver complementary pharmacological activities in the form of a single chemical entity.

CONCLUSION

In the present study, the combined derivatives of NSAID (ketoprofen) and natural antioxidants (thymol, menthol and guaiacol) have been designed and synthesized. They are considered as possible mutual prodrugs to abolish ulcerogenic adverse effect of ketoprofen and enhanced oral bioavailability of highly polar natural antioxidants to improve therapeutic anti-inflammatory action.

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REFERENCES

1. Halen PK, Murumkar PR. Prodrug Designing of NSAIDs. Mini-Reviews in Medicinal Chemistry, 2009; 9(1): 125.
2. Allan HP, Fletcher M. Mechanism of NSAID induced gastro-entero pathy. Drugs, 1990; 40: 1-11.
3. Schoen R.T. Vender RJ. Mechanism of non-steroidal anti-inflammatory drug-induced gastric damage. Am. J. Med., 1989; 86: 449-58.
4. Mitchell JA, Warner TD. Cyclo-oxygenase-2: pharmacology, physiology, biochemistry and relevance to NSAID therapy. Br. J. Pharmacol. 1999; 128: 1121-32.
5. Wallace JL, Cirino G. The Development of Gastrointestinal-Sparing Nonsteroidal Anti-Inflammatory Drugs. Trends Pharma-col. Sci. 1994; 15: 405-6.
6. Fasiel M, Ashour H, Mobarak A. Design, synthesis &preliminary pharmacological evaluation of mutual prodrug of Non-Steroidal Anti-inflammatory Drug Coupling with Natural Antioxidants Via Glycine. AJPS, 2013; 13(1): 155-66.
7. Muscara MN, Vergnolle N, Lovren F, Triggle CR, Elliott SN, Asfaha S, Wallace JL. Selective cyclo-oxygenase-2 inhibition with celecoxib elevates blood pressure and promotes leukocyte adherence. Br J Pharmacol, 2000; 129(7): 1423-30.
8. Brambilla D, Mancuso C, Scuderi MR, Bosco P. Review Open Access The role of antioxidant supplement in immune system, neoplastic, and neurodegenerative disorders: a point of view for an assessment of the risk/benefit profile. Nutrition Journal, 2008; 1475: 7-29.
9. Zheng W, Wang SY. Antioxidant Activity and Phenolic Compounds in Selected Herbs. Journal of Agricultural and Food Chemistry, 2001; 49(11): 5165- 70.
10. Elmastas M, Turkekul I, Ozturk L, Gulcin I, Isildak O, Aboul-Enein HY. The antioxidant activity of two wild edible mushrooms (Morchella vulgaris and Morchella esculanta). Comb Chem High Tec., 2006; 9: 443–8.
11. Pan MH, Ho CT. Chemo preventive effects of natural dietary compounds on cancer development. Chem. Soc. Rev., 2008; 37: 2558–74.
12. Katzung BG. Basic and clinical pharmacology. 9th Ed. McGraw-Hill, New York, 2007; 809-815.

13. Shah K, Shrivastava SK, Mishra P. Evaluation of mefenamic acid mutual prodrugs. Med Chem Res., 2013; 22(1): 70-7.
14. Wallace JL, Keenan CM, Granger DN. Gastric ulceration induced by nonsteroidal anti-inflammatory drugs is a neutrophil-dependent process. Am. J. Physiol. Gastrointest. Liver Physiol., 1990; 259: G462-7.
15. Al-Turki DA, Abou-Zeid LA, Shehata IA, Al-Omer MA. Therapeutic and toxic effects of new NSAIDs and related compounds: A Review and Prospective Study. International Journal of Pharmacology, 2010; 6: 813-25.
16. Bertagnolli MM. The potential of non-steroidal anti-inflammatory drugs (NSAIDs) for colorectal cancer prevention. J. Surg. Oncol., 2003; 84(3): 113-9.
17. Lichtenberger LM. Where is the evidence that cyclooxygenase inhibition is the primary cause of non-steroidal anti-inflammatory drug (NSAID)-induced gastrointestinal injury? Topical injury revisited. Biochem. Pharmacol., 2001; 61(6): 631-7.
18. Siemes LE, Visser JWW, Coebergh A, Hofman1 AG, Uitterlinden BH, Stricker CH. Protective effect of NSAIDs on cancer and influence of COX-2 C-765G genotype. The Netherlands Current Cancer Drug Targets, 2008; 8: 753-64.
19. Kalgutkar AS, Crews BC, Rowlinson SW, Marnett AB, Kozak KR, Remmel RP, MarnettPnasu LJ. Biochemically based design of cyclooxygenase-2 (COX-2) inhibitors: Facile conversion of non-steroidal anti-inflammatory drugs to potent and highly selective COX-2 inhibitors. PNAS, 2000; 97(2): 925–30.
20. Manon B and Sharma PD. Design, synthesis and evaluation of diclofenac –anti oxidant mutual prodrug as safer NSAIDs. Indian journal of chemistry. 2009; 48B: 1279-87.
21. Madhukar M, Sawraj S, Sharma PD. Design, synthesis and evaluation of mutual prodrug of 4-biphenylacetic acid and quercetin tetramethyl ether (BPA-QTME) as gastrosparing NSAID. Eu J Med Chem, 2010; 45: 2591–6.