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Effective Approach to 4,5-Diaryl-3(*2H*)-Furanones – a Promising Inhibitors for Cyclooxygenase-2

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***Abstract*—It is well known that coxibs effect on the arachidonic acid cascade that leads to undesirable side effects of these drugs. 3(*2H*)-furanones turned out to be very promising inhibitors of COX-2 with a low risk of gastro-intestinal (GI) and cardiovascular complications. We proposed a new approach to biologically active 4,5-diaryl substituted 3(*2H*)-furanones which can be used as a relatively cheap and safe anti-inflammatory drugs (NSAIDs) for prolonged use. Our approach allows to obtain 3(*2H*)-furanones in total yield of 22% at six stages that is notably higher than using previously reported methods.**

Keywords—3(2H)-furanones; NSAIDs; COX-2; coxibs;

I. INTRODUCTION

Anti-inflammatory action of some species is well known since Greek physician Hippocrates who prescribed extract from willow bark and leaves for treatment of fever and inflammation. In the 17th century the active component of willow bark was isolated and identified as salicylic acid [1]. Acetylsalicylic acid (aspirin) proved to be a very efficient non-steroidal anti-inflammatory drug (NSAID) [2, 3]. But unfortunately long-term use of traditional NSAIDs (aspirin, ibuprofen, naproxen et. al) usually leads to serious side effects as gastric peptic ulcer bleeding (PUB) and blood thinning [4-7]. There was a hypothesis that aspirin poisoning had contributed substantially to the fatalities during flu pandemic (1918 – 1920) [8-9]. The origin of side effects started becoming clear after John Vane discovery of the mechanism of action of NSAIDs. He revealed relationship between aspirin and synthesis of prostaglandins that earned him the Nobel Prize in Physiology and Medicine in 1982 [10-13]. Later in 90's Needleman and co-workers reported the existence of second inducible isoform of the enzyme COX [14-16]. Thus, it was found that at least two isoforms of COX exist: COX-1 is a constitutive enzyme that is responsible for a normal functioning of kidney and stomach, COX-2 is an inducible enzyme which expression in normal functioning body is highly restricted but dramatically upregulated under inflammation. COX-2 involved in biosynthesis of pro-inflammatory prostaglandins, therefore inhibition of COX-2 is responsible for anti-inflammatory properties of NSAIDS [17-18], while inhibition of COX-1 is highly undesirable and leads to gastric ulceration and renal failure [19-22].

The whole picture of involvement of the COX-1 and COX-2 in prostaglandins synthesis is illustrated in Fig. 1. Eicosanoids are known as an important group of biologically active compounds which are formed *via* arachidonic acid cascade by three different routes – cyclooxygenase (COX), cytochrome P-450 or lipoxygenase (LOX) pathways [23]. Traditional NSAIDs inhibit both isoforms of COX enzyme decreasing the levels of PGs such as PGE2 and PGI2 produced by COX-1 pathway which are known to exhibit cytoprotective effects on the GI mucosa [24]. The discovery of the second isoform of COX enzyme allowed to design inhibitors with higher affinity for COX-2 than for COX-1 and with reduced adverse effects as compared to traditional NSAIDs.

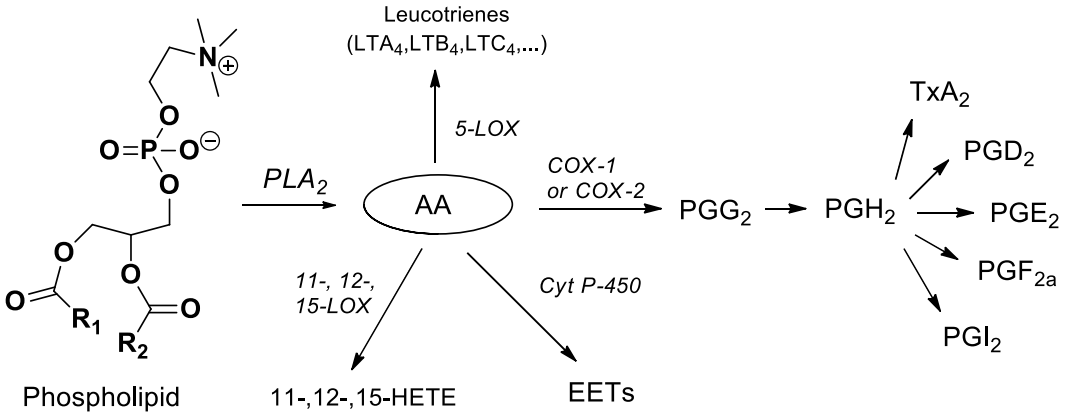


Fig. 1. Arachidonic acid (AA) cascade. Prostaglandin synthesis *via* COX-pathway. Synthesis of leucotriens and hydroperoxyeicosatetraenoic acids (HPETEs) via LOX pathways. Synthesis of epoxyeicosatrienonic acids (EETs) *via* cytochrome P-450.

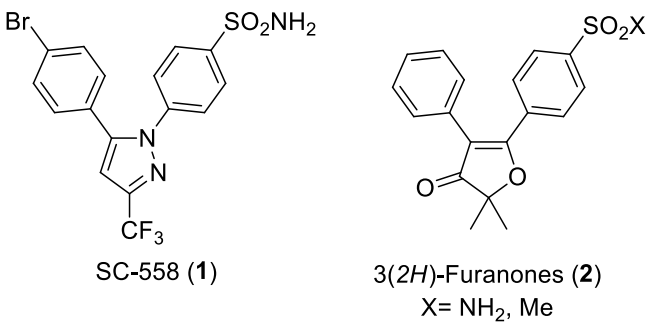
Since 1999, when the first selective COX-2 inhibitor celecoxib [25] was launched by Pfizer, lots of research studies aimed at finding selective COX-2 were made [26-29]. Unfortunately in 2004 one of the selective COX-2 inhibitors (rofecoxib) was withdrawn from the market due to an increased risk of cardiovascular events associated with the drug [30]. Since then discussion has surrounded the cardiovascular safety of selective COX-2 inhibitors [31]. Since arachidonic acid cascade is responsible for the synthesis biologically active eicosanoids *via* several different pathways, blocking the COX-2 pathway can critically effect on the whole synthesis of eicosanoids.

There are several theories about origin of cardiovascular risk associated with long-term use of selective COX-2 inhibitors. First of all distinction between COX-1 and COX-2 enzymes as "constitutive" and "inducible" forms turned to be oversimplified [32]. It was found recently that COX-2 is constitutively expressed in some tissues [33-34], exhibits a protective role in asthma [35] and may play an important role in some body functions [36-37]. COX-1 plays role in nociception [38]. As that takes place, complete inhibition of COX-2 could lead to infringement of the functions of a body [39].

Second origin comes from the difference in the COX-2 and COX-1 pathways. COX-1 enzyme is responsible for the formation of proaggregatory thromboxane A2 (TxA2) which causes vasoconstriction and stimulates platelet aggregation. The COX-2 catalyzes synthesis of antiaggregatory PGI2 [40]. Coxibs cause decreasing in level of PGI2, while the level of TxA2 keeps constant. Thus, selective COX-2 inhibitors lead to changing in natural balance between TxA2 and PGI2 that could increase a thrombotic cardiovascular event. Since the coxibs effect not only on the COX-pathway in arachidonic acid cascade but also indirectly on LOX and Cyp P-450 pathways, one can suggest that there is no clear relation between specificity of selective COX-2 inhibitors and risk of cardiovascular events what was confirmed by recent studies [41].

Due to the fact that both traditional NSAIDs and selective COX-2 inhibitors cause undesirable side effects, there is a big need to develop anti-inflammatory drugs with decreased GI side effects and low risk of cardiovascular events such as myocardial infarction and stroke. NSAIDs containing NO-donor groups (NO-NSAIDs) are good alternatives to traditional NSAIDs and exhibits reduced GI and cardiovascular side effects since NO was known to protect the GI mucosa [42-43]. However, long-term treatment with NO-NSAIDs can cause "nitrate tolerance" and decrease the efficiency of drugs [44]. In addition, dual COX/5-LOX inhibitors [45] and anti-TNF-therapy [46] studies were performed but it seems that there is still no universal drugs for treatment the pains of inflammatory genesis.

Nevertheless, COX-2 inhibitors are of greater interest especially due to their potential use for treatment and prevention of cancer [47-48]. Also for patients with high risk of GI events, COX-2 inhibitors are highly recommended [49]. Thus, a development of a new efficient and safe selective COX-2 inhibitors are of a great interest.



Scheme 1. Selective inhibitors of COX-2.

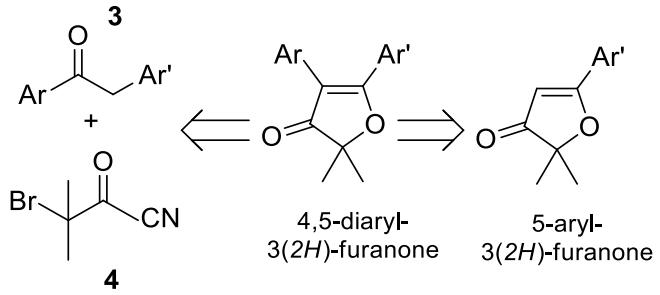
In this paper a new and effective approach to promising inhibitors of COX-2 3(2H)-furanones (Scheme 1) is described and discussed. Previous studies by S. Shin and co-workers showed that 5-aryl-2,2-dialkyl-4-phenyl-3(2H)-furanone derivatives have a IC_{50} comparable to that of rofecoxib [50]. We proposed a more convenient approach to these structures allowing to avoid some drawbacks that were presented in the previous studies and in addition to obtain 3(2H)-furanones in a higher total yield.

II. Results and Discussion

Crucial structural differences between shapes of active zones of COX-1 and COX-2 have been exploited to design selective COX-2 inhibitors. Due to replacement of isoleucine at position 523 and isoleucine at position 434 on smaller in volume valine leads to creation of a secondary pocket which is accessible in the COX-2 active site [51]. Scaffold of *cis*-1,2-diaryl-alkene type turned to be a perfect for selective inhibition of COX-2 [52-53]. The scaffold of COX-2 inhibitors is critical not only for their selectivity but also to their *in vivo* profiles that could be responsible for side effects [50].

Based on the structures of both isoforms of COX enzyme, one can predict structural elements which are responsible for biological activity of the designed drugs. First element is *cis*-1,2-diaryl-alkene scaffold as it was mentioned earlier. The main part of coxibs is heterocycle containing 1,2-diaryl fragment. The crystal structure of coxib **1** (SC-558) showed an important role that SO_2X group plays in biological activity of selective inhibitors of COX-2, namely aryl group containing SO2X group inserts into the COX-2 secondary 'pocket', where it interact with amino acid residues (His90, Arg513, Phe518, Gln192) [51]. Structure-activity relationship (SAR) confirmed that SO_2Me or SO_2NH_2 groups in *para*-position of phenyl ring are essential for optimal activity of coxibs [54].

3(2H)-furanones have similar to typical coxibs scaffold – heterocyclic core containing 1,2-diaryl fragment. S. Shin and co-workers performed numerous studies of the *in vitro* and *in vivo* activity of different substituted 3(2H)-furanones [50]. The obtained compounds were characterized by a high value of COX-2 selectivity (up to 6667-fold COX-2 selectivity over COX-1) with IC_{50} (COX-2) values down to 0.003 μg/mL. *In vivo* studies [50] showed that 3(2H)-furanone scaffold turned out to be a good choice for oral bioavailability, also several



Scheme 2. Previously proposed approaches for synthesis of 3(2H)-furanones .

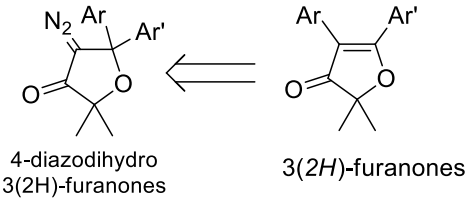
3(2H)-furanones turned out to be highly potent against Adjuvant-induced arthritis.

The problem associated with 3(2H)-furanones is to develop a convenient approach to 4,5-diaryl substituted 3(2H)-furanones. Looking through the known ways to 3(2H)-furanones one can note that the majority of approaches gives rise to 5-aryl-3(2H)-furanones containing H-substituent at the 4th position. Replacement of H atom for Ar group was made by S. Shin and co-workers by the sequence of bromination and Suzuki reaction. In this approach bromine (very toxic, dangerous for the environment) and $Pd(PPh_3)_4$ (cytotoxic effect [55]) were used.

Another approach has been suggested based on a one-pot synthesis starting from compounds **3** and **4** (Scheme 2). In spite of a formal simplicity this way is very expensive and cannot be applied in industry.

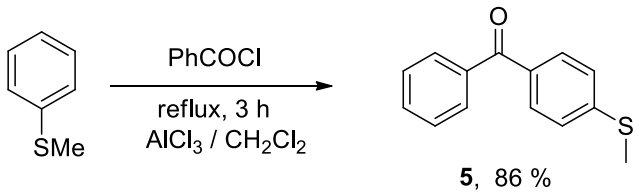
Since there is no general and convenient way to 4,5-diaryl-3(2H)-furanones we proposed a new approach for the synthesis of these promising coxibs based on decomposition reaction of 4-diazo-2,2-dialkyl-5,5-diaryldihydro-3(2H)-furanones (Scheme 3).

Our approach consists of 6 steps that gives rise to 3(2H)-furanones in the total yield of 22% and allows to avoid usage of bromine and Pd-catalyst. Purification of the products by column chromatography is required only at the final step of the synthesis.



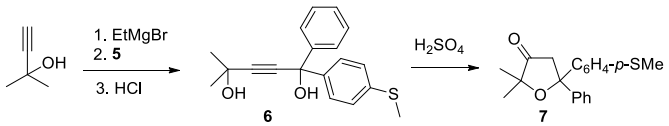
Scheme 3. Proposed approach for the synthesis of 3(2H)-furanones.

The first step of the synthesis is Friedel-Crafts reaction between thioanisole and benzoyl chloride in DCM catalyzed by anhydrous aluminium chloride to furnish the 80 – 90% yield of ketone **5** (Scheme 4). Second step consists of nucleophilic addition of the Grignard reagent derived from 2-methyl-but-3-yn-2-ol to ketone **5** to produce diol **6** in 85-90% yield (Scheme 5).



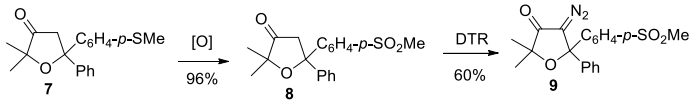
Scheme 4. First step of suggested method – Friedel-Crafts acylation.

At the third step diol **6** was transformed into corresponding monoketone **7** by intramolecular cyclization which requires 2 hours refluxing in ethanol (Scheme 5). The target 2,2-diaryl-5,5-diaryldihydrofuran-3(2H)-one formed during the process precipitates from the reaction mixture under cooling (yield 60-90%).



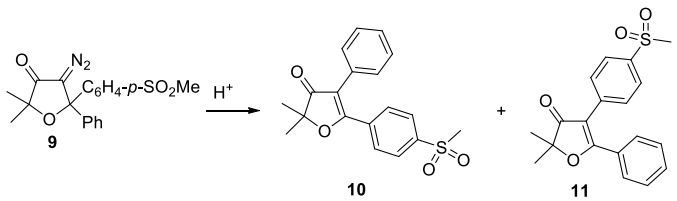
Scheme 5. Intramolecular cyclisation followed by Grignard reaction .

Further, at the fourth step monoketone **7** without any additional purification was oxidized to sulfon **8** by hydrogen peroxide (Scheme 6). Reaction completed within 2 h to give 96% of the desired product. The obtained 2,2-dimethyl-5-(4-(methylsulsonyl)phenyl)-5-phenyldihydrofuran-3(2H)-one was purified by recrystallization from a mixture of CCl_4 and $CHCl_3$.



Scheme 6. Sequence of reactions leading to the diazo ketone **9**.

The fifth step was transformation of monoketone **8** into diazoketone **9** by diazo transfer reaction that was carried out in benzene solution at r. t. using arylsulfonyl azide as a source of diazofunction (Scheme 6). The reaction gives rise to 4-diazo-2,2-dimethyl-5-(4-(methylsulfonyl)phenyl)-5-phenyldihydro-furan-3(2H)-one in 60 to 75% yield after recrystallization from a mixture of CCl_4 and $CHCl_3$.



Scheme 7. Acid-catalysed decomposition of diazo ketone **9**.

Acid-catalyzed decomposition of diazoketone **9** led to corresponding 3(2H)-furanones **10** and **11** (6.1:1) with excellent yield up to 95% (Scheme 7). Silica gel chromatography of this mixture afforded corresponding 3(2H)-furanones which were recrystallized from ethanol.

It should be emphasized that in fact both isomers could serve as a selective COX-2 inhibitors, but 3(2H)-furanone **11** has never been synthesized before and needs further *in vivo* and *in vitro* studies.

The developed by us approach was tested using 16 different diazo compounds. In all cases corresponding 3(2H)-furanones were obtained in good to very good total yields. Thus we elaborated a general way for the synthesis of different coxibs with 3(2H)-furanone scaffold.

III. CONCLUSIONS

We successfully developed a new and convenient 6-steps approach for the synthesis of 4,5-diaryl-3(2H)-furanones, promising COX-2 inhibitors, with total yield 22%. Moreover, the cost of all reagents is approximately 6 times less than in the alternative method [50].

Expanding the synthetic potential of the proposed approach is primarily concerned with the synthesis of another coxibs having 3(2H)-furanone scaffold with halogen, cycloalkyl fragments in the structure.

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REFERENCES

[1] E. Stone, “An Account of the Success of the Bark of the Willow in the Cure of Agues. In a Letter to the Right Honourable George Earl of Macclesfield, President of R. S. from the Rev. Mr. Edmund Stone, of Chipping-Norton in Oxfordshire,” Phil. Trans., vol. 53, pp. 195-200, 1763.

[2] W. Sneader, “The discovery of aspirin: A reappraisal,” BMJ, vol. 321, pp. 1591-1594, 2000.

[3] J.R. Vane, “The fight against rheumatism: from willow bark to COX-1 sparing drugs,” J. Physiol. Pharmacol., vol. 51, pp. 573-586, 2000.

[4] R. Tamblyn, L. Berkson, W.D. Dauphinee, D. Grad, A. Huang, L. Isaac, P. McLeod, L. Snell, “Unnecessary Prescribing of NSAIDs and the Management of NSAID-Related Gastropathy in Medical Practice,” Ann. Intern. Med., vol. 127, pp. 429-438, 1997.

[5] S. Macdonald, “Aspirin use to be banned in under 16 year olds,” BMG, vol. 325, p. 988, 2002.

[6] W.L. Smith, D.L. DeWitt, “Prostaglandin endoperoxide H synthases-1 and -2,” Adv. Immunol., vol. 62, pp. 167-215, 1996.

[7] M. Pariet, L. Churchill, G. Engelhardt, “New Targets in Inflammation: Inhibitors of COX-2 or Adhesion Molecules,” N. Bazan, J. Botting, J. Vane Eds. Kluwer Academic: London, pp 23-38, 1996.

[8] K.M. Starko, “Salicylates and Pandemic Influenza Mortality,” Clinical Infectious Diseases, vol. 49, pp.1405-1410, 2009.

[9] A. Noymer, D. Carreon, N. Johnson, “Questioning the salicylates and influenza pandemic mortality hypothesis in 1918–1919,” Clinical Infectious Diseases, vol. 50, pp. 1203-1204, 2010.

[10] S. Moncada, S.H. Ferreira, J.R. Vane, “Inhibition of prostaglandin biosynthesis as the mechanism of analgesia of aspirin-like drugs in the dog knee joint,” Eur. J. Pharm., vol. 31, pp. 250-260, 1975.

[11] S. Moncada, S.H. Ferreira, J.R. Vane, “Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-like Drugs,” Nature: New biology, vol. 231, pp. 232-235, 1971.

[12] S. Moncada, S.H. Ferreira, J.R. Vane, “Indomethacin and Aspirin abolish Prostaglandin Release from the Spleen,” Nature: New biology, vol. 231, pp. 237-239, 1971.

[13] S. Moncada, S.H. Ferreira, J.R. Vane, “Some effects of inhibiting endogenous prostaglandin formation on the responses of the cat spleen,” British Journal of Pharmacology, vol. 47, pp. 48-58, 1973.

[14] J.L. Masferrer, B.S. Zweifel, K. Seibert, P. Needleman, “Selective regulation of cellular cyclooxygenase by dexamethasone and endotoxin in mice,” J. Clin. Invest., vol. 86, pp. 1375-1379, 1990.

[15] X.L. Xie, J.G. Chipman, D.L. Robertson, R.L. Erikson, D.L. Simmons, “Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing,” Proc. Natl. Acad. Sci. USA, vol. 88, pp. 2692-2696, 1991.

[16] D.A. Kujubu, H.R. Herschman, “Dexamethasone inhibits mitogen induction of the TIS10 prostaglandin synthase/ceclooxygenase gene,” J. Biol. Chem., vol. 267, pp. 7991-7994, 1992.

[17] J.R. Vane, R.M. Botting, “Antiinflammatory drugs and their mechanism of action,” Inflammation Res., vol. 47, pp. 78-87, 1998.

[18] M. Katori, M. Majima, “Possible background mechanisms of the effectiveness of COX-2 inhibitors in treatment of rheumatoid arthritis,” Inflammation Res., vol. 47, pp. 107-111, 1998.

[19] D.L. Dewitt, “COX-2 Inhibitors: The super new aspirins,” Mol. Pharmacol., vol. 4**,** pp. 625–631, 1999.

[20] L.J. Marnett, A.S. Kalgutkar, “Design of selective inhibitors of COX-2 as non-ulcerogenic antiinflammatory agents,” Curr. Opin. Chem. Biol. 2, pp. 482–490, 1998.

[21] C.J. Hawkey, “COX-2 Inhibitors,” Lancet, vol 353, pp. 307–314, 1999.

[22] J.R. Vane, R. Botting, “Clinical Significance and Potential of Selective COX-2 Inhibition.” William Harvey Press, London, 1998.

[23] G.J. Cross, J.R. Falck, E.R. Gross, M. Isbel, J. Moore, K. Nithipatikom, “Cytochrome *P450* and arachidonic acid metabolites: Role in myocardial ischemia/reperfusion injury revisited,” Cardiovascular Research, vol. 68, pp. 18-25, 2005.

[24] T.A. Miller, “Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms,” Am. J. Physiol., vol. 245, pp. 601-623, 1983.

[25] T.D. Penning, J.J. Talley, S.R. Bertenshaw et. al., “Synthesis and Biological Evaluation of the 1.5 Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of (4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide (SC-58634, Celecoxib),” Journal of Medicinal Chemistry, vol. 40, pp. 1347-1365, 1997.

[26] R.G. Kurumbail, A.M. Stevens, J.K. Gierse, J.J. McDonald, R.A. Slegeman, J.Y. Park, D.I. Gildehaus, J.M. Miyashiro, T.D. Penning, K. Siebert, P.C. Isakson, W.C. Stallings, “Structural basis of selective inhibition of COX-2 by anti-inflamatory agents,” Nature, vol. 384, pp. 644-648, 1996.

[27] Y. Leblanc, W.C. Black, C.C. Chan, S. Charleson, D. Delorme, D. Denis, J.Y. Gautheir et al., “Synthesis and biological evaluation of both enantiomers of L-761000 as inhibitors of cyclooxygenase-1 and 2,” Bioorg. Med. Chem. Lett., vol. 6, pp. 731-736, 1996.

[28] K.M. Woods, R.W. McCroskey, M.R. Michaelides, “Heterocyclic compounds as COX-2 inhibitors,” World Patent WO989330, 4March 1997.

[29] T. Klein, R.M. Nusing, J. Pfeilschifetr, V. Ulrich, “Selective inhibition of COX-2,” Biochem. Pharmacol., vol. 48, pp. 1605-1610, 1994.

[30] R.S. Bresalier, R.S. Sandler, H. Quan, J.A. Bolognese, B. Oxenius, K. Horgan et al., “Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial,” N. Engl. J. Med., vol. 352, pp. 1092-1102, 2005.

[31] P. McGettigan, D. Henry, “Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2,” JAMA, vol. 296, pp. 1633-1644, 2006.

[32] G.A. FitzGerald, C. Patrono, “The coxibs, selective inhibitors of cyclooxygenase-2,” N. Engl. J. Med., vol. 345, pp. 433-442, 2001.

[33] D. Maslinska, A. Kaliszek, J. Opertowska, J. Toborowicz, K. Deregowsli, D. Szukiewicz, “Constitutive expression of cyclooxygenase-2 (COX-2) in developing brain. A. Choroid plexus in human fetuses,” Folia Neuropathol, vol. 37, pp. 287-291, 1999.

[34] M. Komhoff, J.L. Wang, H.F. Cheng, R. Langenbach, J.A. McKanna, R.C. Harris et al., “Cyclooxygenase-2-selective inhibitors impair glomerulogenesis and renal cortical development,” Kidney Int., vol. 57, pp. 414-422, 2000.

[35] M.G. Belvisi, M. Saunders, M. Yacoub, J.A. Mitchell, “Expression of cyclooxygenase-2 in human airway smooth muscle is associated with profound reductions in cell growth,” Br. J. Pharmacol., vol. 125, pp. 1102-1108, 1998.

[36] M. Katori, M. Majima, “Cyclooxygenase-2: its rich diversity of roles and possible application of its selective inhibitors,” Inflamm. Res., vol.49, pp. 367-392, 200.

[37] A.M. Simon, M.B. Manigrasso, J.P. O’Connor, “Cyclooxygenase-2 function is essential for bone fracture healing,” J. Bone. Miner. Res., vol. 17, pp. 963-976, 2002.

[38] L.R. Ballou, R.M. Botting, S. Goorha, J. Zhang, J.R. Vane, “Nociception in cyclooxygenase isozyme-deficent mice,” Proc. Natl. Acad. Sci. USA, vol. 97, pp. 10272-10276, 200.

[39] S.G. Morham, R. Langenbach, C.D. Loftin, H.F. Tiano, N. Vouloumanos, J.C. Jennette, J.F. Mahler, K.D. Kluckman, A. Leford, C.A. Lee, D. Smithies, “Prostaglandin Synthase-2 Gene Disruption Causes Severe Renal Pathology in the Mouse,” Cell, vol. 83, pp. 473-482, 1995.

[40] B.F. McAdam, F. Catella-Lawson, I.A. Mardini, S. Kapoor, J.A. Lawson, G.A. FitzGerald, “Systematic biosynthesis of prostacyclin by cyclooxygenase (COX-2): the human pharmacology of a selective inhibitor of COX-2, Proc. Natl. Acad. Sci. USA, vol. 96, pp. 272-277, 1999.

[41] S. Trelle, S. Reichenbach, S. Wandel, P. Hildebrand, B. Tschannen, P.M. Villiger, M. Egger, P. Juni, “Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis,” BMG, vol. 342, pp. 7086-7097, 2011.

[42] A.G. Herman, S. Moncada, “Therapeutic potential of nitric oxide donors in the prevention and treatment of atherosclerosis,” Eur. Heart J., vol. 26, pp. 1945-1955, 2005.

[43] J.L. Wallace, L.J. Ignarro, S. Fiorucci, “Potential cardioprotective actions of NO-releasing aspirin,” Nat. Rev. Drug. Disc, vol. 1, pp. 375—382, 2002.

[44] T. Csont, P. Ferdinandy, “Cardioprotective effects of glyceryl trinitrate: beyond vascular nitrate tolerance,” Pharmacol. Ther., vol. 48, pp. 4061-4076, 2005.

[45] C. Charlier, C. Michaux, “Dual inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) as a new strategy to provide safer non-steroidal anti-inflammatory drugs,” Eur. J. Med. Chem., vol. 38, pp. 645-659, 2003.

[46] M.A. Palladino, F.R. Bahjat, E.A. Theodarakis and L.L. Moldaver, “Anti-TNF-α-therapies: the next generation,” Nat. Rev. Drug Disc., vol. 2, pp. 736-746, 2003.

[47] J.R. Brown, R.N. DuBois, “COX-2: a molecular target for colorectal cancer prevention,” JCO, vol. 23, pp. 2840-285, 2005.

[48] L.W.C. Chow, W.T.Y. Loo, M. Toi, “Current directions for COX-2 inhbition in breast cancer,” Biomed. & Pharm., vol. 59, pp. 281-284, 2005.

[49] S. Gadzhanova, J. Ilomaki, E.E. Roughead, “COX-2 inhibitor and non-selective NSAID use in those at increased risk of NSAId-related adverse events,” Drugs Aging, vol. 30, pp. 23-30, 2013.

[50] S.S. Shin, Y. Byun, K.M. Lim, J.K. Choi, K.-W. Lee, J.H. Moh, J.K. Kim, Y.S. Jeong, J.Y. Kim, Y.H. Choi, H.-J. Koh, Y.-H. Park, Y.I. Oh, M.-S. Noh, S. Chung, “In Vitro Structure-Activity Relationship and in Vivo Studies for a Novel Class of Cyclooxygenase-2 Inhibitors: 5-Aryl-2,2-dialkyl-4-phenyl-3(2H)-furanone Derivatives,” J. Med. Chem., vol. 47, pp. 792-804, 2004.

[51] P.N. Praveen Rao, E.E. Knaus, “Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond,” J. Pharm. Pharmaceut. Sci., vol. 11, pp. 81-110, 2008.

[52] P. Prasit, D. Riendeau, “Selective cyclooxygenase-2 inhibitors,” Ann. Rep. Med. Chem., vol. 32, pp. 211-220, 1997.

[53] X.D. Leval, F. Julemont, J. Delarge, V. Sanna, B. Pirotte, J.-M. Dogne, “Advances in the field of COX-2 inhibition,” Expert. Opin. Ther. Patents, vol. 12, pp. 969-989, 2002.

[54] J.J. Talley, “Selective inhibitors of cyclooxygenase-2 (COX-2),” Prog. Med. Chem. Res., vol. 36, pp. 201-234, 1999.

[55] J. Bunger, J. Stork, K. Stalder, “Cyto- and genotoxic effects of coordination complexes of platinum, palladium and rhodium in vitro,” Int. Arch. Occup. Environ. Health, vol. 69, pp. 33-38, 1996.