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Pd/C-mediated synthesis of (*Z*)-3-alkylidenephthalides of potential pharmacological interest

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ABSTRACT

The coupling of *o*-bromobenzoic acid with terminal alkynes using 10% Pd/C–Et₃N–CuI–PPh₃ as a catalyst system leads to the synthesis of (*Z*)-3-alkylidenephthalides as the major product along with the traces of isocoumarin when the reaction was performed in 1,4-dioxane. The methodology afforded a range of compounds including (*Z*)-3-(4-(methylsulfonyl)benzylidene)isobenzofuran-1(3*H*)-one of potential pharmacological interest.

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Phthalides (e.g., **A**, Fig. 1) are an interesting class of oxygen heterocycles that possess a furan-2-(5*H*)-one framework and often found to be an integral part of many natural products including biologically active compounds.^{1a} The 3,4-diarylfuran-2(5*H*)-ones (**B**, Fig. 1) on the other hand have attracted particular interest in the discovery and development of anti-inflammatory agents targeting cyclooxygenase-2 (COX-2)^{1b-d} for example rofecoxib or Vio-xx[®] (**B**, Fig. 1; when $Ar^1 = C_6H_4SO_2CH_3-p$ and $Ar^2 = C_6H_5$). In pursuance of the identification of furan-2-(5*H*)-one based inhibitors² of cyclooxygenase (COX) for example 5-alkylidenefuranome^{2c} **C** (Fig. 1) we became interested to construct a library of small molecules based on 3-alkylidenephthalide **D** (Fig. 1) for their in vitro evaluation against COX. We therefore required a direct and convenient synthetic route to **D**.

Among the numerous methods known for the synthesis of 3alkylidenephthalides as major or minor products, the use of *o*-halobenzoic acids and terminal alkynes has been explored as the key starting materials.³ All these methodologies usually consist of two separate steps: for example (i) a Sonogashira type reaction followed by (ii) an intramolecular cyclization mediated by metal complexes,^{4–6} bases,⁷ or halogens.⁸ The first one-pot synthesis of 3-alkylidenephthalides following this coupling-cyclization strategy was reported by Castro et al.⁹ way back in 1966. The methodology however involved the use of a stoichiometric amount of copper acetylide, a large volume of environmentally harmful pyridine, and elevated temperature. Thus, a catalytic method was developed by Kundu et al. in 1993 which involved the use of PdCl₂(PPh₃)₂–Cul as a catalyst system and the methodology showed greater selectivity toward phthalides.¹⁰ In 2007, Zhou et al. reported the synthesis of phthalides via Pd/CNT-catalyzed reaction of terminal alkynes and *o*-iodobenzoic acid under copper and ligand-free conditions.¹¹ Subsequently, Li et al. reported the synthesis of phthalides via regioselective cyclization of *o*-alkynyl benzaldehydes in the presence of sodium chlorite under environmentally friendly oxidative conditions.¹² All these methods generally involved the use of expensive starting material (e.g., *o*-iodobenzoic acid) or Pd-catalyst or ligands. In 2005, during our



Figure 1. Phthalide (A), 3,4-diarylfuran-2(5*H*)-ones (B), 5-alkylidenefuranone (C), and 3-alkylidenephthalides (D).





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studies on the Pd/C mediated synthesis of isocoumarins^{4f} we observed that the use of Pd/C–CuI–PPh₃ as a catalyst system in the presence of Et₃N in 1,4-dioxane afforded 3-alkylidenephthalides as a major product instead of isocoumarin. In continuation of that study, we have examined the coupling of commercially available and inexpensive *o*-bromobenzoic acid (in place of *o*-iodobenzoic acid) with terminal alkynes under Pd/C–Cu catalysis in 1,4-dioxane. Once again, we observed that the reaction showed better selectivity toward phthalide. This prompted us to develop a Pd/C mediated general method for the synthesis of (*Z*)-3-alkylidenephthalides. Herein, we report our preliminary results. To the best of our knowledge, a similar one-pot and regioselective synthesis of (*Z*)-3-alkylidenephthalides (**3**) from *o*-bromobenzoic acid (**1**) and terminal alkynes (**2**) under Pd/C–Cu catalysis (Scheme 1) has not been reported earlier.

To establish an optimum reaction condition for the Pd/C-Cu mediated synthesis of phthalides, we chose to examine the coupling reaction of o-bromobenzoic acid (1) with phenyl acetylene (2a) in the presence of 10% Pd/C (0.03 equiv), PPh₃ (0.12 equiv), Cul (0.06 equiv), and Et₃N (5 equiv) under various conditions. The results obtained are summarized in Table 1. The reaction was initially carried out in 1,4-dioxane for 12 h when the desired product that is (Z)-3-benzylideneisobenzofuran-1(3H)-one (3a) was isolated in 65% yield (entry 1, Table 1) along with a trace amount of 3-phenyl isocoumarin. The increase of reaction time did not improve the product yield further (entry 2, Table 1). The reaction was performed in the presence of 0.03 equiv of 10% Pd/C. The use of a lower or higher quantity of Pd/C did not improve the product yield (entries 3 and 4, Table 1) whereas its omission decreased the product yield significantly (entry 5, Table 1). The omission of Cul, or PPh₃, or Et₃N also decreased the yield of **3a** (entries 6–8, Table 1). The use of other solvents such as EtOH and DMF was examined and found to afford the corresponding isocoumarin as a major product (entries 9 and 10, Table 1). To test the recyclability of Pd/C used, the catalyst was recovered and reused for additional three runs (after completion of the first reaction the Pd/C was filtered off. washed with water, acetone, and EtOAc, dried at 100 °C, and reused in the next run along with fresh CuI and PPh₃ in every repeated run) when the product **3a** was isolated in 62%, 59%, and 55% yield respectively. Since best result for the synthesis of phthalide was achieved by using 1,4-dioxane as a solvent all the subsequent studies were carried out using this solvent.

To investigate the scope and generality of the present Pd/C–Cu mediated coupling-cyclization reaction leading to phthalide, a range of commercially available terminal alkynes (**2**) were coupled with *o*-bromobenzoic acid (**1**) under the optimized reaction conditions^{13a} presented in entry 1 of Table 1. The results are summarized in Table 2. A variety of phthalides containing alkylidene, hydroxyalkylidene and arylidene substituents at C-3 were prepared in moderate to good yields by using this methodology. The yields were generally good when aryl (entries 1 and 6–10, Table 2) or highly substituted alkyl acetylene (entry 5, Table 2) was employed. The other terminal alkynes except the trimethylsilyl acetylene (**20**) provided the desired products in acceptable yields. In the case of **20**, the product isolated was found to be a desilylated one for example **30** (entry 15, Table 2) as indicated by the NMR



Scheme 1. Pd/C-Cu mediated synthesis of (Z)-3-alkylidenephthalides.

Table 1

Effect of reaction conditions on Pd/C-mediated coupling-cyclization of o-bromobenzoic acid (1) with phenyl acetylene $(2a)^a$



Entry	Solvent	10% Pd/C	Time (h)	%Yield ^b
1	1,4-Dioxane	0.03	12	65
2	1,4-Dioxane	0.03	24	67
3	1,4-Dioxane	0.01	12	44
4	1,4-Dioxane	0.05	12	63
5	1,4-Dioxane	_	12	29 ^c
6	1,4-Dioxane	0.03	12	12 ^d
7	1,4-Dioxane	0.03	12	27 ^e
8	1,4-Dioxane	0.03	12	0 ^f
9	EtOH	0.03	12	10 ^g
10	DMF	0.03	12	11 ^g

 a All the reactions were carried out by using 1 (1.49 mmol), 2a (0.28 mmol), 10% Pd/C (0.044 mmol), PPh₃ (0.17 mmol), CuI (0.088 mmol), and Et_3N (7.45 mmol) under a nitrogen atmosphere.

^b Isolated yields.

^c The reaction was carried out without Pd/C.

^d The reaction was carried out without Cul.

^e The reaction was carried out without PPh₃.

^f The reaction was carried out without Et₃N.

^g 3-Phenyl isocoumarin was isolated as a major product.

data (Fig. 2). While phthalides were isolated as major products in all these cases, the formation of 10-20% of corresponding isocoumarins was also observed depending on the nature of terminal alkynes used. The dimerization of terminal alkynes as a side reaction was also observed in some of the cases. We also tested the coupling reaction of the terminal alkyne 2a with a highly substituted bromobenzoic acid for example 2,3-bis(benzyloxy)-5-bromoterephthalic acid prepared according to a similar procedure described in the literature.^{13b} However, the reaction did not afford the desired phthalide^{13c} and debrominated product of the bromobenzoic acid used was isolated. Notably, its iodo analogue afforded the corresponding phthalide when treated with propargyl alcohol in the presence of (PPh₃)₄Pd, ZnCl₂ and Et₃N.^{13b} The use of the relatively less substituted bromobenzoic acid for example 2-bromo-5-methoxybenzoic acid afforded the desired product that is (Z)-3-benzylidene-6-methoxyisobenzofuran-1(3H)-one (51% yield) on coupling with terminal alkyne 2a. Based on the spectral data of the compounds synthesized¹⁴ and comparing them with those reported in the literature^{4a} all the compounds synthesized were found to possess the exocyclic double bond with Z-geometry. Thus the present approach to 3-alkylidenephthalides appears to be a regio and stereoselective process.

A plausible mechanism for the present Pd/C–Cu mediated synthesis of phthalides via coupling-cyclization strategy is shown in Scheme 2. The reaction appears to proceed via in situ generation of 2-(1-alknyl)benzoic acid from the coupling of *o*-bromobenzoic acid (**1**) with a terminal alkyne (**2**) in the presence of 10% Pd/C, PPh₃, and CuI, which in turn undergoes 5-*endo-dig* cyclization that gives the five membered (*Z*)-3-alkylidenephthalides. Initially, a minor portion of the bound palladium (Pd/C) generates an active Pd(0) species via a Pd leaching process into the solution.¹⁵ On interactions with phosphine ligands the leached Pd affords a dissolved Pd(0)–PPh₃ complex which being the active species actually catalyzes the C–C bond forming reaction in solution. It is evident that the catalytic cycle therefore works in solution rather than on the surface. An oxidative addition of the active Pd(0) species with triethylammonium salt of *o*-bromobenzoic acid **1** gives the

Table 2

Pd/C-mediated preparation of (Z)-3-alkylidenephthalides^a



(continued on next page)

Table 2 (continued)



^a All the reactions were carried out by using 1 (1.49 mmol), 2 (0.28 mmol), 10% Pd/C (0.044 mmol), PPh₃ (0.17 mmol), Cul (0.088 mmol), and Et₃N (7.45 mmol) under a nitrogen atmosphere at 80 °C for 12-24 h.

^b Identified by ¹HNMR, IR, mass.

^c Isolated yield.

organo-Pd(II) species X. The reaction then follows (i) trans organometallation of **X** with copper acetylide generated in situ from CuI and terminal alkyne followed by (ii) reductive elimination of Pd(0) to give the 2-(1-alknyl)benzoic acid salt Y and then (iii) Et_3NH^+ (conjugate acid) mediated 5-exo-dig ring closure of Y in an intramolecular fashion^{4a,7a} to give the five-membered ring product (**3**). At the end of the reaction re-precipitation of Pd occurs on the surface of the charcoal. It is worthy to note that the 6-endodig cyclization leading to isocoumarin is more favored when 1 was reacted with terminal alkynes in ethanol.^{4f}

We have shown that (Z)-3-alkylidenephthalides can be accessed directly via a one-pot Pd/C-Cu mediated coupling of o-bromobenzoic acid with terminal alkynes in 1,4-dioxane. Some of these compounds showed biological activities¹⁶ when tested in vitro¹⁷





Scheme 2. Probable mechanism of Pd/C-mediated synthesis of (Z)-3-alkylidenephthalides (3).

against the cyclooxygenase (COX) enzyme. Compound **3j** was converted to the corresponding sulfone derivative that is (Z)-3-(4-(methylsulfonyl)benzylidene)isobenzofuran-1(3*H*)-one (**4**) in the

presence of oxone (2KHSO₅·KHSO₄·K₂SO₄) in 1:2 acetone–H₂O at room temperature in 87% yield. Notably, the methanesulfonyl group is usually known to confer optimal COX inhibitory activity

when present at the C-4 position of an appropriate aryl ring.¹⁸ Accordingly, compound **4** showed 80% and 16% inhibition of COX-2 and COX-1, respectively, when tested at 10 μ M in vitro with the reference compound indomethacin showing 97 and 100% inhibiton of COX-2 and 1 at 10 μ M. Compound **4** also showed good interactions with COX-2 when docked into this protein in silico (see SI).¹⁹ Overall, the COX inhibiting potential of the present class of phthalide has not been explored earlier and our preliminary studies indicate that 3-alkylidenephthalide can be a useful template for the identification of potential inhibitors of COX.

In conclusion, we have described Pd/C-Cu mediated general, one-pot and direct synthesis of (Z)-3-alkylidenephthalides via the coupling-cyclization reaction of *o*-bromobenzoic acid with a range of terminal alkynes under mild conditions. The scope and limitations of the methodology are presented. The methodology involved the use of readily available and relatively inexpensive starting material (o-bromobenzoic acid is cheaper than o-iodobenzoic acid) and catalyst [Pd/C is cheaper than Pd(PPh₃)Cl₂, Pd(PPh₃)₄, and Pd(OAc)₂ etc.]. The methodology afforded a range of compounds (Z)-3-(4-(methylsulfonyl)benzylidene)isobenzofuranincluding 1(3*H*)-one of potential pharmacological interest. In spite of some demerits the described methodology permits an easy access to 3alkylidenephthalides for synthetic and medicinal uses. Further application of this methodology for the synthesis of more complex molecules is under active investigation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version of this article, at http://dx.doi.org/10.1016/j.tetlet.2013.03.121.

References and notes

- (a) For a review, see: Lin, G.; Chan, S. S.-K.; Chung, H.-S.; Li, S.-L. Chemistry and Biological Activities of Naturally Occurring Phthalides In Studies in Natural Products Chemistry; Rahman, A., Ed.; Elsevier: Amsterdam, 2005; Vol. 32, pp 611–669; (b) Riendeau, D.; Percival, M. D.; Boyce, S.; Brideau, C.; Charlson, S.; Cromlish, W.; Ethier, D.; Evans, J.; Falgueyret, J.-P.; Ford-Hutchinson, A. W.; Gordon, R.; Greig, G.; Gresser, M.; Guay, J.; Kargman, S.; Leger, S.; Mancini, J. A.; O'Neil, G.; Ouellet, M.; Rodger, I. W.; Therien, M.; Wang, Z.; Webb, J. K.; Wong, E.; Xu, L.; Young, R. N.; Zamboni, R.; Prasit, P.; Chan, C.-C. B. J. Pharmacol. 1997, 121, 105; (c) Li, C.-S.; Black, W. C.; Brideau, C.; Chan, C.-C.; Charlson, S.; Cromlish, W. A.; Claveau, D.; Gauthier, J. Y.; Gordon, R.; Greig, G.; Grimm, E.; Guay, J.; Lau, C. K.; Riendeau, D.; Therien, M.; Visco, M. D.; Wong, E.; Xu, L.; Prasit, P. Bioorg. Med. Chem. Lett. 1999, 9, 3181; (d) Leblanc, Y.; Roy, P.; Boyce, S.; Brideau, C.; Chan, C.-C.; Charlson, S.; Gordon, R.; Grimm, E.; Guay, J.; Leger, S.; Li, C. S.; Riendeau, D.; Visco, D.; Wang, Z.; Webb, J.; Xu, L. J.; Prasit, P. Bioorg Med. Chem. Lett. 1999, 9, 2207.
- (a) Pal, M.; Rao, Y. K.; Rajagopalan, R.; Misra, P.; Kumar, P. M.; Rao, C. S. World Patent WO 01/90097, Nov 29, 2001; *Chem. Abstr.* 2002, *136*, 5893.; (b) Pattabiraman, V. R.; Padakanti, P. S.; Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. R. Synlett 2002, 947; (c) Padakanti, S.; Veeramaneni, V. R.; Pattabiraman, V. R.; Pal, M.; Yeleswarapu, K. R. *Tetrathedron Lett.* 2002, *43*, 8715; (d) Pal, M.; Rao, V. V.; Srinivas, P.; Murali, N.; Akhila, V.; Premkumar, M.; Rao, C. S.; Misra, P.; Ramesh, M.; Rao, Y. K. *Indian J. Chem.* 2003, *42B*, 593; (e) Pal, M.; Veeramaneni, V. R.; Nagaballi, M.; Kalleda, S. R.; Misra, P.; Casturi, S. R.; Yeleswarapu, K. R. Bioorg, Med. Chem. Lett. 2003, *13*, 1639.
- (a) Villemin, D.; Goussu, D. *Heterocycles* 1989, 29, 1255; (b) Yao, T.; Larock, R. C. J. Org. Chem. 2003, 68, 5936; (c) Larock, R. C.; Doty, M. J.; Han, X. J. Org. Chem. 1999, 64, 8770; (d) Batu, G.; Stevenson, R. J. Org. Chem. 1980, 45, 1532; (e) Kotora, M.; Negishi, E. Synthesis 1997, 121; (f) Sashida, H.; Kawamukai, A. Synthesis 1999, 1145; (g) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. J. Am. Chem. Soc. 1984, 106, 5274.
- Catalyzed by Pd, see: (a) Kundu, N. G.; Pal, M.; Nandi, B. J. Chem. Soc., Perkin Trans. 1 1998, 561; (b) Liao, H.-Y.; Cheng, C.-H. J. Org. Chem. 1995, 60, 3711; (c) Sashida, H.; Kawamukai, A. Synthesis 1999, 7, 1145; (d) Rossi, R.; Bellina, F.;

Biagetti, M.; Catanese, A.; Mannina, L. *Tetrahedron Lett.* **2000**, *41*, 5281; (e) Kirsh, G.; Hesse, S.; Comel, A. *Curr. Org. Synth.* **2004**, *1*, 47; (f) Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. J. Org. Chem. **2005**, *70*, 4778.

- Catalyzed by Ag, see: (a) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* 1995, 41, 2587; (b) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* 2000, 56, 2533.
- Catalyzed by other metal complexes, see: (a) Sakamoto, T.; Anaka, M.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2754; (b) Menashe, N.; Shvo, Y. *Heterocycles* **1993**, *35*, 611; (c) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. J. Org. *Chem.* **1966**, *31*, 4071.
- (a) Kanazawa, C.; Terada, M. *Tetrahedron Lett.* 2007, *48*, 933; (b) Uchiyama, M.;
 Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T.
 Org. Lett. 2006, *8*, 5517; (c) Terada, M.; Kanazawa, C.; Yamanaka, M.
 Heterocycles 2007, *74*, 819.
- Promoted by halogen, see: (a) Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023; (b) Oliver, M. A.; Gandour, R. D. J. Org. *Chem.* **1984**, *49*, 558; (c) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857.
- 9. Castro, C. E.; Gaughan, E. J.; Owsley, D. C. J. Org. Chem. 1966, 31, 4071.
- 10. Kundu, N. G.; Pal, M. J. Chem. Soc. Chem. Commun. 1993, 86. see also Ref. 4a.
- 11. Zhou, L.; Jiang, H. F. Tetrahedron Lett. 2007, 48, 8449.
- 12. Li, J.; Chin, E.; Lui, A. S.; Chen, L. Tetrahedron Lett. 2010, 51, 5937.
- 13. (a) General procedure for the preparation of compound 3: A mixture of 1 (1.49 mmol), 10% Pd/C (0.044 mmol), PPh₃ (0.17 mmol), Cul (0.088 mmol), and Et₃N (7.45 mmol) in 1.4-dioxane (5 mL) was stirred at 25 °C for 30 min under nitrogen atmosphere. The acetylenic compound 2 (0.28 mmol) was added slowly with stirring. The mixture was then stirred at 80 °C for 12–24 h. The mixture was then cooled to room temperature, diluted with ethylacetate (20 mL), and filtered through Celite. The filtrate was collected and concentrated. The residue was purified by column chromatography (petroleum ether/ethylacetate) to afford the desired product.; (b) Waters, S. P.; Kozlowski, M. C. Tetrahedron Lett. 2001, 42, 3567; (c) We thank one of the reviewers for raising this concern.
- 14. Spectral data of selected compounds: (Z)-3-pentylideneisobenzofuran-1(3H)-one (**3b**): ¹H NMR (400 MHz, CDCl₃): δ 7.89–7.49 (4H, m), 5.63 (1H, t, *J* = 8.0 Hz), 2.47 (2H, t, J = 7.2 Hz), 1.52–1.50 (2H, m), 1.42–1.40 (2H, m), 0.93 (3H, t); IR (KBr) v_{max} 1716, 1656, 1055 cm⁻¹; EI-MS: m/z 203 (M+1, 100%); (Z)-3hexylideneisobenzofuran-1(3H)-one (3c): ¹H NMR (400 MHz, CDCl₃): δ 7.88-7.45 (4H, m), 5.64 (1H, t, J = 8.0 Hz), 2.47 (2H, q), 1.37-1.35 (2H, m), 1.34-1.30 (4H, m), 0.90 (3H, t); IR (KBr) v_{max} 1717, 1656, 1050 cm⁻¹; EI-MS: m/z 216.9 (M+1, 100%); (Z)-3-(3-hydroxypropylidene)isobenzofuran-1(3H)-one (3d): ¹H NMR (400 MHz, CDCl₃): δ 8.19 (1H, d, J = 7.6 Hz), 7.66–7.60 (1H, m), 7.57–7.50 (1H, m), 7.45–7.40 (1H, m), 7.30 (1H, d, J = 8.0 Hz), 6.36 (1H, s), 3.71 (2H, t, J = 6.4 Hz), 2.50 (2H, t, J = 6.4 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 162.8, 154.7, 137.2, 134.3, 129.3, 128.5, 127.6, 125.0, 104.7, 66.5, 23.4; IR (KBr) v_{max} 3395, 2922, 1717, 1655, 1050 cm⁻¹; El-MS: m/z 190.9 (M+1, 100%); 3-(2-hydroxy-heptylidene)-3H-isobenzofuran-1-one (**3m**): ¹H NMR (400 MHz, CDCl₃): δ 7.89 (1H, d, J = 7.6 Hz), 7.71–7.65 (2H, m), 7.55–7.52 (1H, m), 5.62 (1H, d, J = 8.3 Hz), 4.90-4.88 (1H, m), 1.92 (1H, br), 1.73-1.69 (2H, m), 1.62-1.58 (2H, m), 1.33-1.30 (4H, m), 0.86 (3H, t, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 166.4, 145.3, 139.0, 134.4, 130.1, 125.2, 124.2, 120.1, 110.7, 66.8, 37.1, 31.5, 24.8, 22.4, 14.0; IR (KBr) v_{max} 3415, 3055, 2930, 1787, 1685, 1470, 1275 cm⁻¹; El-MS: *m*/2 247.0 (M+1, 100%); 3-(5-hydroxy-pentylidene)-3H-isobenzofuran-1-one (**3n**): ¹H NMR (400 MHz, CDCl₃): δ 7.89 (1H, d, *J* = 7.7 Hz), 7.66–7.61 (1H, m), 7.43–7.41 (1H, m), 7.32 (1H, d, *J* = 7.6 Hz), 6.26 (1H, s), 3.64 (2H, t, *J* = 6.0 Hz), 2.83 (2H, t, $\begin{array}{l} 13.7, 52.6 (111, 4, 5-7, 512), 52.6 (111, 5), 55.6 (211, 4, 5-6, 512), 52.6 (211, 4, 5) \\ 57.2 (121, 167-156, 614), m); \\ 134.0, 129.3, 128.6, 127.8, 125.2, 103.6, 66.4, 34.0, 26.5, 23.0; IR (KBr) \\ v_{max} \\ 3433, 2927, 1717, 1652, 1203, 1050 \ cm^{-1}; \ El-MS: \ m/z \ 218.9 \ (M+1, 100\%); \ 3-6, 52.6 \ M-1, 100\% \\ 34.0, 120.6 \ M-1, 100\% \\ 34.0, 100\% \\ 34.$ methylene-3H-isobenzofuran-1-one (**3o**): ¹HNMR (400 MHz, CDCl₃): δ 7.92 (1H, d, J = 8.0 Hz), 7.72 (2H, d, J = 4.0 Hz), 7.62–7.57 (m, 1H), 5.24 (2H, dd, J = 3.0, 6.2 Hz,); ¹³C NMR (100 MHz, CDCl₃): δ 166.8, 151.8, 139.0, 134.4, 130.4, 125.2, 125.1, 120.6, 91.2; IR (KBr) v_{max} 2925, 1784, 1735, 1663, 1474, 1272, 1007, 955 cm⁻¹; EI-MS: *m/z* 147 (M+1, 100%).
- The leaching of Pd in a Pd/C-mediated coupling reaction has been investigated and confirmed earlier, see: (a) Chen, J.-S.; Vasiliev, A. N.; Panarello, A. P.; Khinast, J. G. *Appl. Catal. A* **2007**, 325, 76; (b) Rambabu, D.; Bhavani, S.; Nalivela, K. S.; Rao, M. V. B.; Pal, M. *Tetrahedron Lett.* **2013**, *54*, 1169.
- 16. The compounds were tested against recombinant human COX-2 (expressed in sf9 insect cells using baculovirus) and COX-1 (Ram Seminal vesicles) enzyme in vitro (% inhibition was recorded @10 μ M concentration of the drug). For the procedure, see Ref. 17.
- Brideau, C.; Kargman, S.; Liu, S.; Dallob, A. L.; Ehrich, E. W.; Rodger, I. W.; Chan, C.-C. Inflamm. Res. **1996**, 45, 68.
- Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1619.
- 19. The docking procedure: the molecular docking simulation was performed with Chemical Computing Group's Molecular Operating Environment (MOE) software 2008.10 Version, 'DOCK' application Module. The COX-2 protein (PDB code 3LN1) used as the receptor for docking studies was retrieved from PDB and protonated (addition of H atoms) with protonation 3D application in MOE. Connolly Molecular surface was generated around the ligand site of the protein, Gasteiger Partial charges were added to the protein and finally the energy was minimized to relieve bad crystallographic contacts. 'Active site finder' function of the MOE software was used to denote potential docking pockets within the protein crystal structure. Compound **4** was placed in the

active site pocket of the protein by the 'Triangle Matcher' Method, which generates poses by aligning the ligand triplet of atoms with the triplet of alpha spheres in cavities of tight atomic packing and Dock scoring was done with London dG method and then finally retaining and scoring the best 10 poses of the molecule. The preparation of the Ligands for Docking Simulation involved

the Energy minimization with Molecular Mechanics Force-field MMFF94x (Merck Molecular Force Field 94x) and then the molecule was subjected to conformational search in MOE using the Conformations Stochastic search module to find the lowest energy conformers.