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Note

Synthesis of novel α-arylpropionic acids and their derivatives

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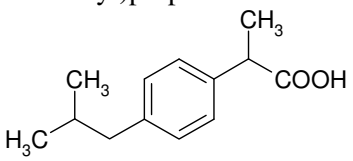
A series of 2-(6*H*-benzo[c]chromen-3-yl)propionic acids have been synthesized and evaluated for COX-2 inhibitor activity.

Keywords: α-arylpropionic acids, COX-2 inhibitor activity

Non-steriodal anti-inflammtory drugs (NSAIDs) are used extensively to ameliorate the symptoms of inflammation and pain, particularly those associated with rheumatoid arthritis[1]. The primary mode of action of carboxylic acid NSAIDs, of which aspirin is the prototype, is the inhibition of prostaglandin biosynthesis by obstructing the action of cyclooxygenase in the arachidonic acid cascade[2]. However, their usage is limited by the side-effects produced by them, thereby searching new molecular entities[3]. Among the NSAIDs, those of the 2-arylpropionic acid class[4] are probably the most prominent, and are represented by ibuprofen **1**, naproxen, ketoprofen, fenoprofen, and flurbiprofen. In view of these observations, it was considered of interest to synthesize some new 2-(6*H*-benzo[c]chromen-3-yl)propionic acids **6** and evaluate their COX-2 inhibitor activity.



Ibuprofen **1**

Results and Discussion

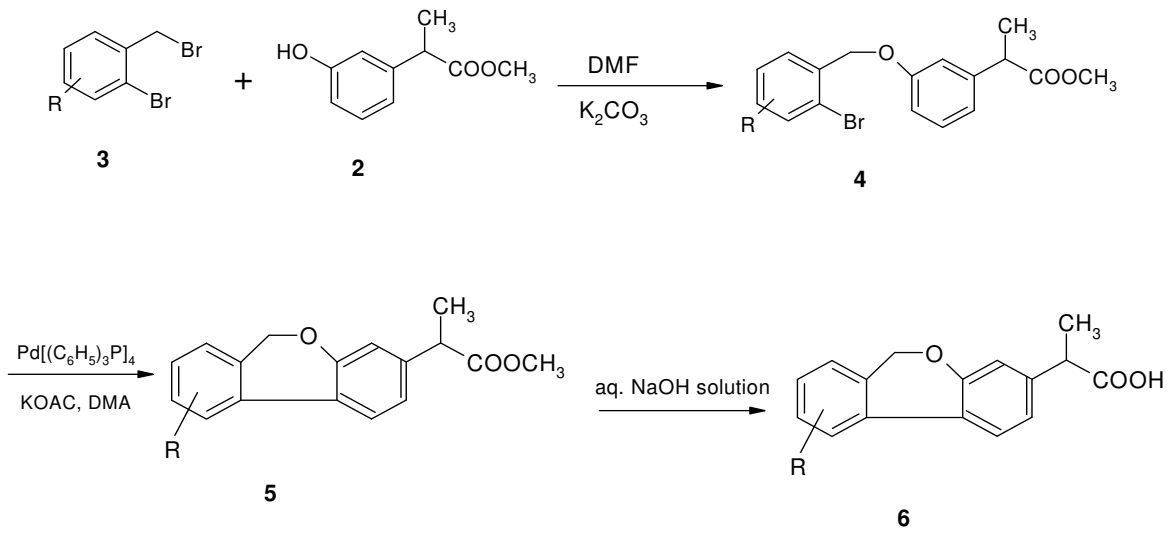
Methyl-2-(3-hydroxyphenyl)propionate **2** required as starting material in the present work and the same is produced according to the procedure described in the literature[5]. Reaction of **2** with substituted 2-bromobenzyl bromide **3** in the presence of K_2CO_3 in dimethyl formamide at 70-75°C gave **4** in excellent yields. Compound **4** was cyclised to 2-(6*H*-benzo[c]-chromen-3-yl) propionic acid methyl ester **5** using tetrakis(triphenyl phosphine) palladium (0) (refs 6-11) as a catalyst in the presence of potassium acetate in dimethyl acetamide at 65-70°C. Hydrolysis of representative **5** in aq. methanolic NaOH furnished the corresponding acids **6 (Scheme I)**. All other compounds are prepared similarly **(Table I)**. Compounds **6a-d** were fully characterized. The ^1H and ^{13}C NMR data is depicted in **Table II**.

Methyl 2-(3-hydroxyphenyl)propionate **2** on condensation with 1,2-dibromo benzene **7** using copper powder as a catalyst (Ullmann reaction) in the presence of potassium carbonate at 150-155°C gave **8**. The product obtained **8** under Heck reaction conditions gave **9**. The cyclic ether compound **13** was hydrolyzed with aq. NaOH solution gave compound **10** in good to excellent yields **(Scheme II)**.

Biological activity

All the compounds (**6a-d** and **10**) were tested for cyclooxygenase-2 inhibitory activity. The method of Copeland *et al.*[12] was followed to determine the IC_{50} values. The enzyme activity was measured using chromogenic assay based on oxidation of N,N,N^1,N^1-tetramethylparaphenylenediamine (TMPD) during the reduction of prostaglandin G_2 to prostaglandin H_2 by COX-1 and COX-2 enzymes. COX-1 enzyme is from ram seminal vesicles (microsomal fraction) and COX-2 is recombinant human enzyme purified from SF_9 cells (microsomal fraction) were used in the assay.

The compounds were dissolved in DMSO and the stock solution was diluted to the required assay concentration. The assay mixture consists of tris buffer (*p*H 8.0), EDTA solution and hematin as co-factor, the enzyme and the drug of assay



Scheme I

Table I—Characterization data of compounds **4a-d** and **5a-d***

S.No	Starting material	Reactant used	Product obtained	Yield (%)	m.p. °C
1	**2**	**3** (R = H)	**4a** (R = H)	81	Liquid
2	**2**	**3** (R = 5-Cl)	**4b** (R = 5-Cl)	85	Liquid
3	**2**	**3** (R = 5-NO_2)	**4c** (R = 5-NO_2)	92	99-100
4	**2**	**3** (R = 6-NO_2)	**4d** (R = 6-NO_2)	46	Liquid
5	**4a**	$Pd[(C_6H_5)_3P]_4$ KOAC, DMA	**5a** (R = H)	53	Liquid
6	**4b**	$Pd[(C_6H_5)_3P]_4$ KOAC, DMA	**5b** (R = 8-Cl)	56	Liquid
7	**4c**	$Pd[(C_6H_5)_3P]_4$ KOAC, DMA	**5c** (R = 8-NO_2)	63	107-109
8	**4d**	$Pd[(C_6H_5)_3P]_4$ KOAC, DMA	**5d** (R = 7-NO_2)	50	Liquid

*All the compounds showed satisfactory IR spectra

concentration in DMSO. The assay mixture was preincubated at 25°C and then TMPD in ethanol was added. The enzyme activity was measured by estimating the initial velocity during the first 25 seconds by measuring the absorbance at 603 nm. IC_{50} values were calculated from four parameter least squares non-linear regression analysis of the log dose vs percentage inhibition plot. The compounds **6a** and **10** reported in **Table III**, exhibited significant inhibition activity compared to other compounds prepared (**6b-d**). Compounds **6a** and **10** showed COX-2 inhibition compared to ibuprofen and (s)-naproxen.

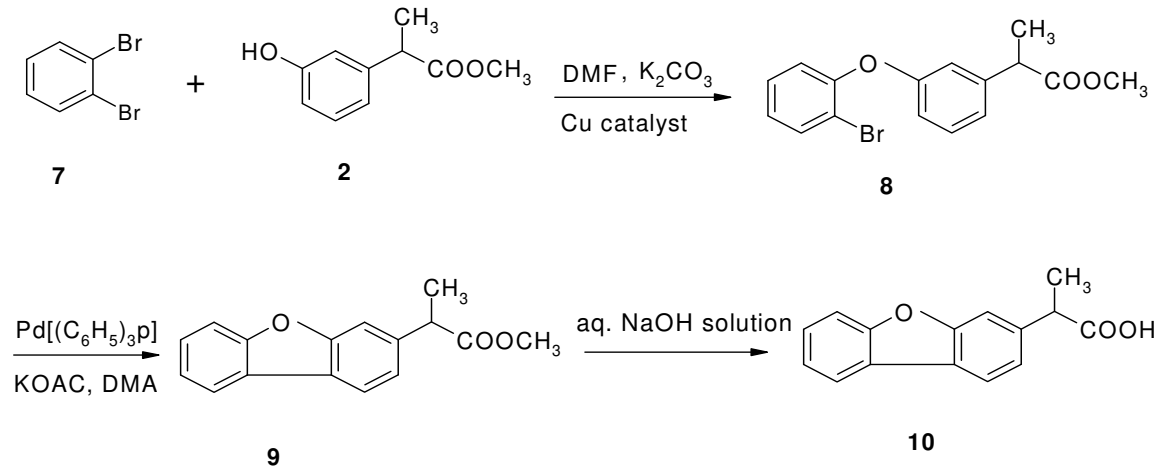
COX-1 activity of these compounds is under investigation. Further work is in progress to study SAR of these molecules

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel-GF 254 (Merck) coated plates. IR spectra were recorded using a Perkin-Elmer model-2000 instrument, ^1H NMR spectra were recorded on a Brucker 400 MHz instrument with TMS as internal standard (chemical shifts in δ, ppm) and Mass spectra have been recorded on API 4000 Model.

Table II — Spectral data of compounds **6a-d** and **10**

S.No	Starting material	Reactant used	Product obtained	Yield %	^{1}H and ^{13}C NMR data
1	**5a**	Aq.NaOH solution	**6a**	85	^{1}H NMR ($CDCl_3$) δ, 1.37 (d, 3H, -CH_3), 3.68 (q, 1H, -CH), 5.11 (s, 2H, -CH_2). 6.8 - 7.8 (m, 7H, aromatic protons), 12.3 (s, 1H, -COOH) ^{13}C NMR ($CDCl_3$) δ, 18.35, 44.49, 67.67, 116, 121.1, 121.4, 121.9, 123.68, 124.95, 127.78, 128.53, 129.29, 131, 143, 154.32, 175.16
2	**5b** (R = 8-Cl)	Aq.NaOH solution	**6b** (R = 8-Cl)	87	^{1}H NMR ($CDCl_3$) δ, 1.38 (d, 3H, -CH_3), 3.67 (q, 1H, -CH), 5.11 (s, 2H, -COOH), 6.88-7.8 (m, 6H, aromatic protons), 12.38 (s, 1H, -COOH) ^{13}C NMR ($CDCl_3$) δ, 18.29, 44.48, 67.01, 116, 120.2, 121.6, 123.79, 124.9, 128.28, 128.35, 132.16, 133.14, 143.45, 154.13, 175.06
3	**5c** (R = 8-NO_2)	Aq.NaOH solution	**6c** (R = 8-NO_2)	83	^{1}H NMR ($CDCl_3$) δ, 1.36 (d, 3H, -CH_3), 3.68 (q, 1H, -CH), 5.28 (s, 2H, -CH_2), 6.9-8.2 (m, 6H, aromatic protons), 12.3 (s, 1H, -COOH)
4	**5d** (R = 7-NO_2)	Aq.NaOH solution	**6d** (R = 7-NO_2)	85	^{1}H NMR ($CDCl_3$) δ, 1.42 (d, 3H, -CH_3), 3.73 (q, 1H, -CH), 5.29 (s, 2H, -CH_2), 6.8-8.3 (m, 6H, aromatic protons), 12.4 (s, 1H, -COOH)
5	**9**	Aq.NaOH solution	**10**	90	^{1}H NMR ($CDCl_3$) δ, 1.45 (d, 3H, -CH_3), 3.88 (q, 1H, -CH), 7.3-8.1 (m, 7H, aromatic protons), 11.2 (s, 1H, -COOH) ^{13}C NMR ($CDCl_3$) δ, 18.79, 45.04, 110.59, 111.63, 120.94, 121.02, 122.29, 123.11, 123.45, 127.39, 141.42, 155.7, 175.3



Scheme II

Table III — Inhibitory studies of cyclooxygenase-2

Sample	IC_{50} value for cyclooxygenase-2 (μM)
Compound **6a**	5
Compound **6b**	49
Compound **6c**	55
Compound **6d**	49
Compound **10**	15
Ibuprofen	1.53
(S)-Naproxen	2.0-28.4

Preparation of methyl 2-[3-(2-bromobenzyloxy)phenyl]propionate (General procedure): A mixture of **2** (2.0 g, 0.011 mole), dimethylformamide (8 mL), 2-bromobenzyl bromide (**3**) (3.0 g, 0.012 mole), and potassium carbonate (3.0 g, 0.021 mole) was stirred at 65-70°C for 5-6 hr. At the end of this period, the reaction mixture was cooled to RT and poured into water (50 mL). The mixture was extracted with ethyl acetate (2 × 25 mL) and the ethyl acetate extract was distilled off under reduced pressure to

obtain **4** as crude product. The crude product was purified using column chromatography to yield pure **4**. Yield = 3.1 g (81% molar). ^{1}H NMR spectrum ($CDCl_3$/TMS): δ 1.48 (d, 3H, -CH_3), 3.67 (s, 3H, -OCH_3), 3.71 (q, 1H, -CH), 5.11 (s, 2H, benzylic CH_2), 6.8-7.5 (m, 8H, aromatic protons).

Preparation of 2-(6*H*-benzo[*c*]chromen-3-yl)propionic acid methyl ester (General procedure): To a solution of **4** (2.0 g, 0.005 mole), dimethyl acetamide (8 mL) and potassium acetate (0.7 g, 0.007 mole) was added tetrakis(triphenylphosphine)palladium (0) (0.4 g, 0.00034 mole) under nitrogen. The reaction mass was stirred at 100°C for 5-6 hr. At the end of this period, the reaction mass was cooled to RT and poured into water (30 mL). The mixture was extracted with ethyl acetate (2 × 20 mL) and the ethyl acetate extracts were distilled off under reduced pressure to obtain crude **5** as residual mass. The crude product was purified by using column chromtography to yield pure **5**. Yield = 0.8 g (53% molar). ^{1}H NMR spectrum ($CDCl_3$/TMS): δ 1.49 (d, 3H, -CH_3), 3.68 (s, 3H, -OCH_3), 3.72 (q, 1H, -CH), 5.10 (s, 3H, benzylic CH_2), 6.9-7.6 (m, 7H, aromatic protons).

Preparation of 2-(6*H*-benzo[*c*]chromen-3-yl)propionic acid (General procedure): A mixture of **5** (1.0 g, 0.0037 mole), methanol (6.0 mL) and aq. NaOH (40%, 2.0 mL) was stirred at reflux temperature for 2-3 hr. At the end of this period, the reaction mass was cooled to RT, poured into water (15 mL) and washed with toluene (2 × 10 mL). The lower aqueous layer was adjusted for its acidic *p*H with conc. HCl (30%, 3.0 mL), the separated solid was filtered, washed with water and dried to obtain pure **6** as crystalline solid. Yield = 0.8 g, (85% molar). m.p: 109-111°C. IR (KBr): 3054 cm^{-1} (br, w, OH), 1720 cm^{-1} (sharp, s, C=O); ^{1}H NMR ($CDCl_3$): δ 1.5 (d, 3H, -CH_3), 3.72 (q , 1H, -CH), 5.11 (s, 2H, benzylic CH_2), 6.89-7.5 (m, 7H, aromatic protons), 8.05 (s, 1H, -COOH); ^{13}C NMR ($CDCl_3$): δ 14.02, 45.21, 69.2, 113.2, 114.5, 121.94, 122.2, 125.17, 127.3, 128.1, 129.5, 132.4, 137.6, 141.31, 158.5, 180.5; MS (*m/z*): 255 (M+1)

Preparation 2-[*m*-(2-bromophenoxy)phenyl]-propionic acid methyl ester 8: A mixture of **2** (10.0 g, 0.055 mole), 1,2-dibromobenzene **(7)** (39.2 g, 0.166 mole), potassium carbonate (19.16 g, 0.138 mole) and copper powder (2.0 g) was stirred at 160-165°C for 3 hr. After this period, the reaction mixture was cooled to RT and toluene (100 mL) was added. The mixture was filtered and washed with toluene (2 × 25 mL). The toluene filtrate was distilled off under reduced pressure to obtain **8** as crude residue, which was purified by column chromatography to obtain pure **8.** Yield = 54 %; ^{1}H NMR spectrum ($CDCl_3$): δ 1.48 (d, 3H, -CH_3), 3.67 (s, 3H, -OCH_3), 3.71 (q, 1H, -CH), 6.83-7.6 (m, 8H, aromatic protons); ^{13}C NMR ($CDCl_3$): δ 18.43, 45.18, 52.02, 114.7, 116.6, 117.5, 120.3, 122.4, 124.9, 128.6, 129.6, 133.7, 142.5, 153.5, 156.9, 174.5.

Preparation of 2-dibenzofuran-3-yl-propionic acid methyl ester 9: This compound was prepared from **8** according to the procedure described for **5**, yield 83%, ^{1}H NMR spectrum ($CDCl_3$ /TMS): δ 1.58 (d, 3H, -CH_3), 3.68 (s, 3H, -OCH_3), 3.88 (q, 1H,-CH), 7.2-7.9 (m, 7H, aromatic protons); ^{13}C NMR ($CDCl_3$ / TMS): δ 18.72, 45.5, 51.97, 110.5, 111.49, 120.4, 120.8, 122.2, 122.6, 123.1, 123.8, 126.9, 129.7, 139.9, 156.3, 174.6.

Preparation of 2-dibenzofuran-3-yl-propionic acid 10: This compound was prepared from **9** according to the procedure described for **6**, yield 91%. ^{1}H NMR spectrum ($CDCl_3$): δ 1.45 (d, 3H, -CH_3), 3.88 (q, 1H, -CH), 7.3-8.1 (m, 7H, aromatic protons), 11.2 (s, 1H, -COOH); ^{13}C NMR ($CDCl_3$): δ 18.79, 45.04, 110.5, 111.6, 120.9, 121.02, 122.2, 122.7, 123.1, 123.4, 127.3, 141.4, 155.7, 175.36; MS (*m/z*): 241 (M+1).

Conclusion

The compounds **6a** and **10** exhibited significant COX-2 inhibition activity. Further work is planned in this area with the help of structural activity studies.

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