P. Bindu,[a,b] Shravan Reddy Naini,[a] K. Shanmukha Rao,[a] P. K. Dubey,[b] and Sarbani Pal[a]*

[a]Department of Chemistry, MNR Degree and PG College, Kukatpally, Hyderabad 500072, India
[b]JNT University, Kukatpally, Hyderabad 500072, India
*E-mail: sarbani277@yahoo.com

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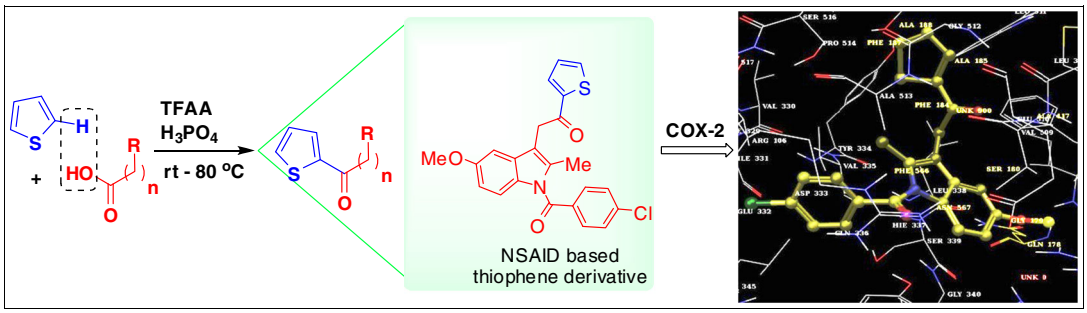

A number of aliphatic and aromatic carboxylic acids were reacted with thiophene in the presence of trifluoroacetic anhydride and H_3PO_4 to give a variety of acylated thiophenes in good to excellent yields. The methodology was used to prepare known nonsteroidal anti-inflammatory drug-based novel compounds of potential pharmacological significances. Molecular modeling studies were carried out by using nonsteroidal anti-inflammatory drug-based thiophene derivatives to assess their cyclooxygenase inhibiting potential *in silico*. On the basis of docking studies followed by subsequent *in vitro* assay, indomethacin-based thiophene derivative was identified as a novel cyclooxygenase-2 inhibitor with balanced selectivity.

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INTRODUCTION

Thiophene derivatives possessing a –COAr group at C-2 are of particular interest because of their valuable pharmacological properties. For example, (*RS*)-2-[4-(2-thienylcarbonyl) phenyl]propanoic acid (**A**, Figure 1) or suprofen, an nonsteroidal anti-inflammatory drug (NSAID) marketed under the trade name of Profenal, is presently used to prevent miosis during and after ophthalmic surgery [1]. Similarly, [2,3-dichloro-4-(2-thienylcarbonyl)phenoxy]acetic acid (**B**, Figure 1) or tienilic acid that belongs to this class is a diuretic drug that possesses uric acid-lowering (uricosuric) properties and was formerly marketed for the treatment of hypertension [2]. Because of their medicinal value, we became interested to synthesize a library of thiophene derivatives **C** (Figure 1) related to **A** and **B** for their potential pharmacological applications. An impressive number of methods have been reported for the synthesis of 2-aroyl thiophenes. Some of these include the reaction of the following: (a) thiophene with benzoic anhydride [3–8], (trichloromethyl)benzene [9], *t*-butylbenzoate [10], pyridin-2-yl benzoate [11], (1*H*-imidazol-1-yl)(phenyl) methanone [12], or $PhCO_2POF_2$ [13]; (b) thiophene-2-boronic acid with benzoic anhydride [14–17]; (c) 2-iodothiophene with carbon monoxide and phenyl boronic acid or PhLi [18–20]; (d) tributyl(thiophen-2-yl)stannane with Ph_2TeCl_2 [21] or Ph_2IBF_4 and carbon monoxide [22]; (e) thiophen-2-boronic acid with benzoyl chloride [23]; (f) thiophene-2-carbonyl chloride with phenyl boronic acid [24,25], Ph_3Bi [26], or Ph_4BiNa [27]; (g) thiophene-2-carbonyl fluoride with Ph_2Zn [28]; (h) 2-bromothiophene [29,30] or thiophen-2-ylmagnesium bromide [31] or trimethyl(thiophen-2-yl)stannane [32] or dithiophen-2-ylmercury [33] with benzoyl chloride; (i) thiophen-2-aldehyde with iodobenzene [34]; and (j) 1-methyl-3-(*N*-methylthiophene-2-carboxamido)-1*H*-imidazol-3-ium iodide with PhMgBr [35]. Most of these methods, however, require the use of a transition metal or other catalyst and cumbersome preparation of unstable or moisture-sensitive starting materials or special reagents. Some of these catalysts are either expensive or not readily available and therefore not suitable for use in large scale synthesis. Moreover, in many cases, these methodologies were found to be specific for the syntheses of a particular compound and therefore are not general in nature. Nevertheless, the simplest and widely used method for the preparation of 2-aroyl thiophenes is Friedel–Crafts acylation reaction between thiophene and benzoyl chloride [36–40] and $AlCl_3$ being the main catalyst, although the use of other catalysts, for example, $SnCl_4$, $ZnCl_2$, $Yb(OTf)_3$, $(TMP)_2CuCl$, P_2O_5, $TiCl_4$, silica gel, iron silicate, and iodine, has also been explored. This methodology is also associated with several drawbacks such as requirement of stoichiometric amount of environmentally harmful $AlCl_3$ and moisture-sensitive acid chloride. Although the direct use of benzoic acid in place of benzoyl chloride has been explored in the presence of various catalysts [13,41,42], these methodologies however were not developed as general methods for the preparation of compounds represented by **C** (Figure 1). Thus

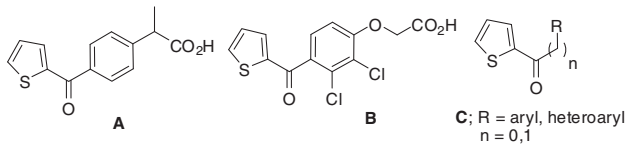


Figure 1. Thiophene-based drugs suprofen (**A**), tienilic acid (**B**), and the proposed library (**C**).

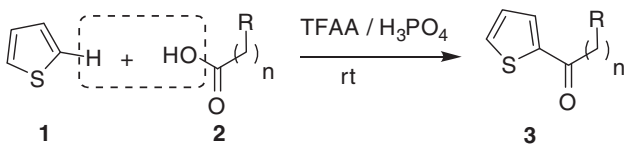
a direct, general, and convenient method was required to prepare **C** that could eventually help us to build a diversity-based compound library. Herein, we report a new, one-pot, and simple synthesis of thiophene-based compound **3** (**C** in Figure 1) directly from thiophene (**1**) and various carboxylic acids (**2**) via a C–C bond-forming reaction (Scheme 1).

RESULTS AND DISCUSSION

Chemistry. The use of TFAA/H_3PO_4 as an efficient catalyst system for C–C bond forming reaction between a carboxylic acid and arenes has been studied earlier [43–45]. Accordingly, we have reported TFAA/H_3PO_4-mediated smooth C-acylation of arenes and heteroarenes [46,47]. However, exploring this methodology for the preparation of compound **3** and related studies have not been reported earlier. We anticipated that this methodology could be developed as a general route for accessing thiophene-based compound library represented by **C**.

Benzoic acid **2a** (**2**; R = Ph, $n = 0$, Scheme 1) was initially chosen as an acid partner to establish the optimized reaction conditions for the present C-acylation of thipohene (**1**). Results of this study are summarized in Table 1. Thus, the acid **2a** (1.0 mol) was reacted with thiophene **1** (1.0 mol) in the presence of commercially available 85% H_3PO_4 (1.0 mol) and TFAA (4.0 mol) at room temperature. The yield of the product, that is, 2-benzoyl thiophene **3a** (**3**; R = Ph, $n = 0$, Scheme 1), was examined at different interval of time and was found to be 51, 70, and 92% after 5, 15, and 120 min, respectively (entries 1–3, Table 1). Further increase in time did not improve the product yield. The use of lower quantity of TFAA and H_3PO_4 was also examined and found to be less productive as the progress of the reaction was slow and the product yield was decreased significantly. The isolated product **3a** was well characterized by NMR, IR, and MS and compared with the reported data. Having established the optimum reaction condition, we then decided to examine the reaction of **1** with other carboxylic acids (**2b–2l**).

Scheme 1. Preparation of thiophene derivatives from thiophene and carboxylic acids.



A number of carboxylic acids were reacted with thiophene to give a variety of thiophene derivatives possessing an acyl group at the C-2 position of the thiophene ring (entries 4–13, Table 1). Whereas 2.0 h was found to be optimum for benzoic acid (entry 3, Table 1), the reaction time, however, varied depending on the nature of acids used. For example, aromatic acids containing electron-donating groups (e.g., Me, Cl, or OMe) on the benzene ring required relatively shorter reaction time (entries 4–7 and 9, Table 1) than those containing electron-withdrawing groups (e.g., NO_2, entry 8, Table 1). The use of simple aliphatic acids was also found to be effective, and the reaction was completed within 1.5 h (entries 10 and 11, Table 1). All the thiophene derivatives synthesized were isolated in good to excellent yields, and formation of no side products were detected during the acylation process. To expand the generality and scope of this process, we examined the reaction of thiophene with few highly functionalized carboxylic acids, for example, ibuprofen, indomethacin, and mefenamic acid (entries 12–14, Table 1). Although the reaction proceeded smoothly at room temperature, it took longer time to give the desired product in good yield. However, the reaction was completed within 2.0 h when carried out at 80°C, and the corresponding thiophene based products (**3j–3l**) were isolated in 78–90% yields. The ^{1}H NMR spectrum of compound **3k** is shown in Figure 2. Notably, all these acids used are well-known NSAIDs and have been in patient's use for the treatment of diseases related to pain and inflammation. Thus, the novel thiophene derivatives prepared from these acids are not only expected to have potential medicinal value but also might play important role as precursors in the synthesis of various thiophene-based bioactive molecules.

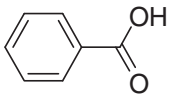
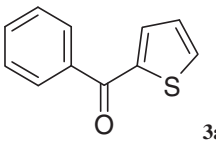
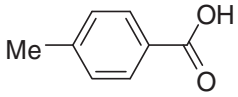
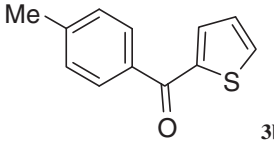
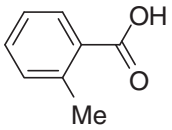
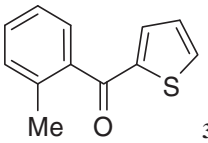
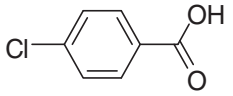
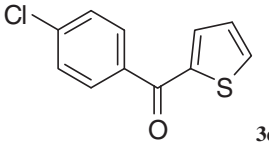
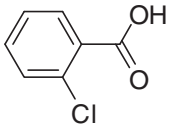
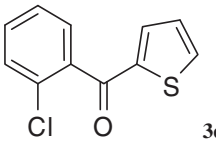
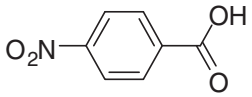
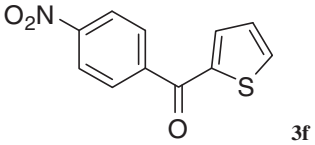
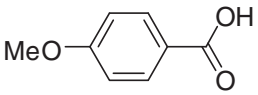
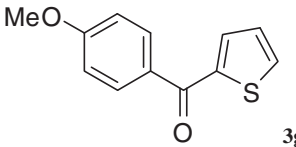
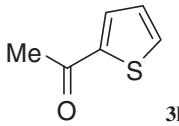
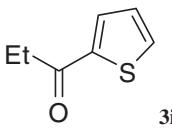
A probable mechanism for TFAA/H_3PO_4-mediated reaction of carboxylic acids with thiophene is shown in Scheme 2 [43–45]. Thus, phosphoric acid that plays the role of a covalent catalyst leads to the generation of acyl bis(trifluoroacetyl)phosphate **T-2** from the acylation precursor acyl trifluoroacetate **T-1** generated *in situ* [43]. The acyl bis(trifluoroacetyl)phosphate **T-2** then acetylates the (hetero)arene ring in the presence of phosphoric acid to afford the products **3**. Thiophene being an electron-rich heterocyclic ring facilitates the acylation step greatly after activation of **T-2** by phosphoric acid as a proton source. It is worthy to mention that excess of TFAA and TFA (trifluoroacetic acid generated during the reaction) can be removed by distillation during a large scale synthesis [48] of compound **3**, and the recovered TFA can be converted back to TFAA via dehydration, thereby eliminating the acid waste.

Docking studies and pharmacology. Having prepared NSAID-based thiophene derivatives **3j–3l**, we decided to assess their potential for cyclooxygenase (COX)-inhibiting properties *in silico*. COX, which catalyzes the first step of biosynthesis of prostanoids, exists in two isoforms, that is, a constitutive form called COX-1 responsible for

physiological production of prostaglandins and an inducible form, known as COX-2, which is involved in the processes of inflammation [49]. Classical NSAIDs such as **2j–2l** are nonselective inhibitors of COX, and their long-term use leads to the side effects particularly ulceration. Thus, a number of selective COX-2 inhibitors were developed, and few were launched in the market, for example, celecoxib and rofecoxib [50]. However, the

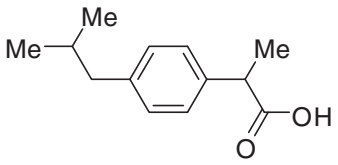
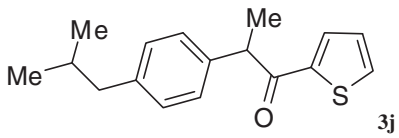
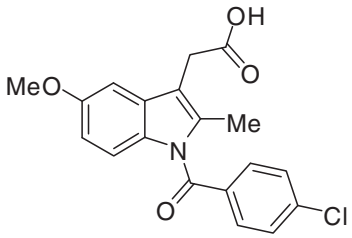
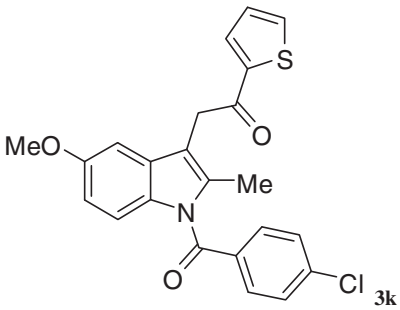
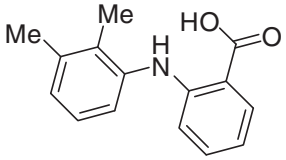
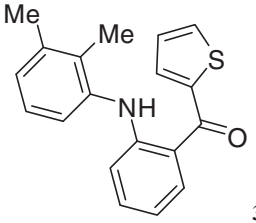
Table 1

TFAA/H_3PO_4-mediated synthesis of thiophene derivatives (**3**) from thiophene (**1**) and various carboxylic acids (**2**).[a]

Entry	Carboxylic acid (**2**)	Time (h)	Product (**3**)	% Yield[b]
1	 **2a**	5 min	 **3a**	51
2	**2a**	15 min	**3a**	70
3	**2a**	2.0	**3a**	92
4	 **2b**	2.0	 **3b**	93
5	 **2c**	2.0	 **3c**	80
6	 **2d**	2.0	 **3d**	87
7	 **2e**	2.0	 **3e**	81
8	 **2f**	2.5	 **3f**	79
9	 **2g**	1.5	 **3g**	85
10	$MeCO_2H$ **2h**	1.5	 **3h**	94
11	$EtCO_2H$ **2i**	1.5	 **3i**	89

(*Continued*)

Table 1
(Continued)

Entry	Carboxylic acid (**2**)	Time (h)	Product (**3**)	% Yield[b]
12	 **2j**	2.0	 **3j**	83[c]
13	 **2k**	2.0	 **3k**	90[c]
14	 **2l**	2.0	 **3l**	78[c]

[a]All the reactions were carried out using thiophene **1** (1.0 mol), acid **2** (1.0 mol), 85% H_3PO_4 (1.0 mol), and TFAA (4.0 mol) at room temperature.
[b]Isolated yield.
[c]The reaction was carried out at 80°C.

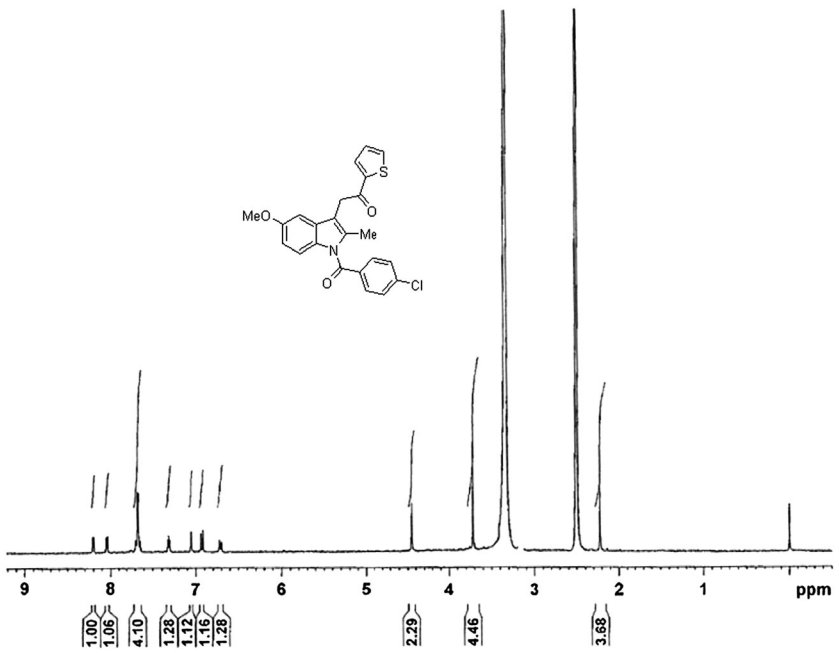
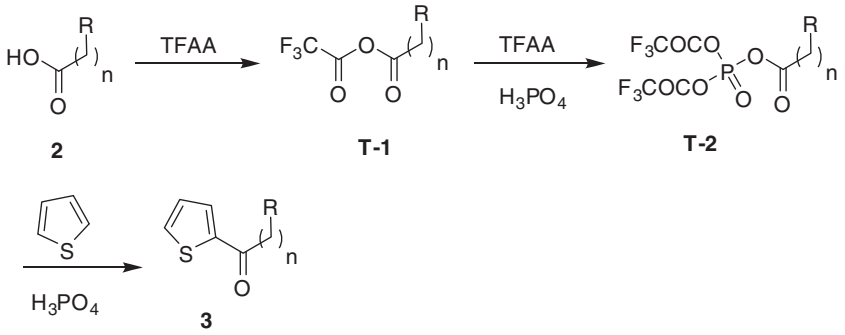


Figure 2. ^{1}H NMR (400 MHz) spectrum of compound **3k** in DMSO-d_6.

Scheme 2. Probable mechanism for TFAA/H_3PO_4-mediated reaction of carboxylic acids with thiophene.



withdrawal of rofecoxib in 2004 followed by valdecoxib in 2005 has raised several safety-related questions including the one that inhibitors possessing high selectivity towards COX-2 have any real benefits. Nevertheless, our effort was directed towards the identification of potential inhibitors possessing balanced selectivity. Accordingly, compounds **3j–3l** were docked in both COX-1 and COX-2 proteins, and their interactions along with binding energies were analyzed. On the basis of the binding energy data presented in Table 2, it was evident that all the compounds interacted well with both the COX isoforms. However, compound **3k** showed better affinity towards COX-2 in comparison with **3j** and **3l**, although it interacted with COX-1 as well. Thus, **3k** was predicted to be COX-2 selective, whereas **3j** and **3l** appeared to be nonselective inhibitors of COX isozymes.

Table 2

Binding energy of compounds **3j–3l** after docking with COX-1 and COX-2.

	Binding energy (kcal/mol)	
Compound	COX-1	COX-2
3j	−10.42	−9.35
3k	−8.48	−11.08
3l	−11.31	−10.61

The interaction of **3k** with COX-1 and COX-2 is shown in Figures 3 and 4, respectively. Its interaction with COX-1 was mainly contributed by a hydrogen bonding between the indole C═O group with the –NH group of the Arg120 residue of COX-1. In contrast, no such H-bonding was observed when **3k** was docked with COX-2 protein, and the overall interaction was mainly contributed by hydrophobic and van der Waals type of interactions.

Prompted by this observation, compound **3k** was tested against human COX-2 (expressed in *sf9* insect cells using baculovirus) and COX-1 (ram seminal vesicles) enzymes *in vitro* [51]. At the concentration of 30 μ*M*, this compound showed fourfold selectivity for COX-2 (80% inhibition) over COX-1 (20% inhibition). The moderate COX-2 selectivity shown by **3k** could be beneficial as this might lead to the identification of COX-2 inhibitors with better safety profile. Nevertheless, the present study indicated that a new class of thiophene-based inhibitor could be generated

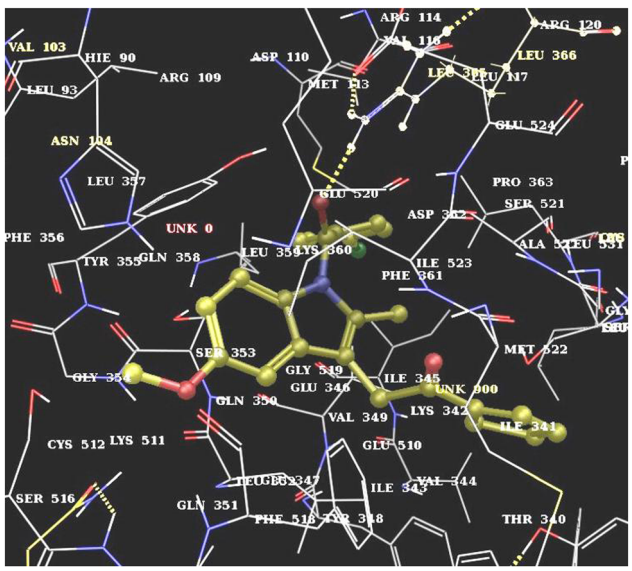


Figure 3. Docking of **3k** with the COX-1 protein (color figure can be viewed in the online issue, which is available at www.interscience.wiley.com).

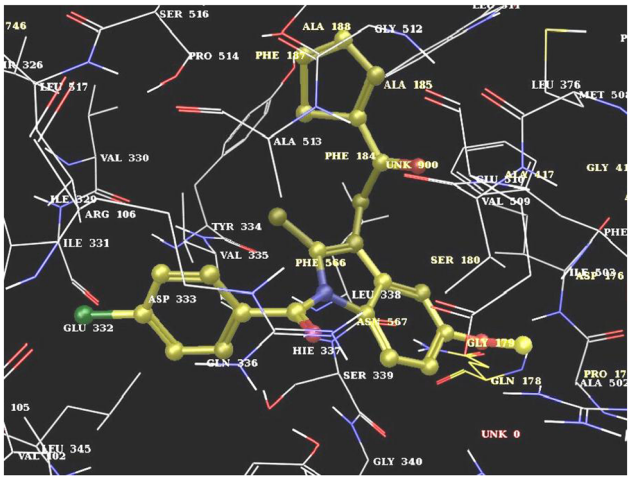


Figure 4. Docking of **3k** with the COX-2 protein (color figure can be viewed in the online issue, which is available at www.interscience.wiley.com).

via C-2 acylation of thiophene ring, and their COX inhibiting properties as well as COX-2 selectivity could be modulated via proper modifications in the acyl group. Moreover, because of the absence of carboxylic acid moiety, these compounds may exhibit favorable pharmacological properties than the parent NSAIDs.

CONCLUSIONS

In conclusion, a direct and facile synthesis of thiophene derivatives has been achieved via TFAA/H_3PO_4-mediated C-2 acylation of thiophene ring with the use of both aliphatic and aromatic carboxylic acids. The present one-pot method being simple and straightforward is easy to handle and does not involve the use of unstable/moisture-sensitive acid chlorides or expensive reagents/catalysts. The generality and scope of this methodology has been demonstrated in synthesizing novel acylated thiophenes derived from well-known NSAIDs. The methodology is expected to be superior to the classical Friedel–Crafts acylation technique and other multistep synthesis and therefore would find application for the preparation of thiophene-based library of compounds with desired diversity. Molecular modeling studies were carried out using NSAID-based thiophene derivatives synthesized to assess their COX-inhibiting potential *in silico*. On the basis of docking studies followed by subsequent *in vitro* assay, indomethacin-based thiophene derivative was identified as a novel COX-2 inhibitor with balanced selectivity. Overall, this is the first report on synthesis, docking studies, and *in vitro* pharmacological evaluation of NSAID-based thiophene derivatives that may show favorable pharmacological properties than the parent NSAIDs.

EXPERIMENTAL

Chemistry. Melting points were all determined by open glass capillary method on a Sisco melting point apparatus (Thana, Maharashtra, India) and are uncorrected. IR spectra were recorded on a PerkinElmer spectrometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400-MHz spectrometer using $CDCl_3$ as a solvent with tetramethylsilane as internal reference (TMS, $\delta = 0.00$). Elemental analyses were performed using Varian 3LV analyzer series CHN analyzer. Mass spectra were recorded on a Jeol JMCD-300 instrument. All solvents used were commercially available and distilled before use. All reactions were monitored by TLC on precoated silica gel plates (60 F 254; Merck). Column chromatography was performed on a 100–200 mesh silica gel (SRL, India) with the use of 10- to 20-fold excess (by weight) of the crude product. The organic extracts were dried over anhydrous Na_2SO_4. Ibuprofen, indomethacin, and mefenamic acid and all the carboxylic acids used are commercially available.

General method for the preparation of compound 3. To a mixture commercially available acid **2** (4.42 mmol) in TFAA (2.5 mL, 17.7 mmol), thiophene **1** (4.42 mmol) was added dropwise followed by 85% H_3PO_4 (4.42 mmol) with vigorous stirring at room temperature. The mixture was then stirred according to the conditions (e.g., temperature and time) indicated in Table 1. After completion of the reaction, the mixture was poured into ice-cold water (50 mL) with vigorous stirring. The mixture was filtered when solid was separated. The residue was washed with petroleum ether (2×5 mL), dried, and purified by column chromatography on silica gel (EtOAc/petroleum ether as eluting solvent) to give the desired product. In case of liquid product, the mixture was extracted with EtOAc (3×20 mL). The organic layers were collected, combined, washed with cold water (2×25 mL), dried, and purified by column chromatography on silica gel (EtOAc/petroleum ether as eluting solvent) to give the desired product.

Phenyl(thiophen-2-yl)methanone (3a). Light brown solid; mp 54–55°C (petroleum ether, lit. [52] 54–55°C); MS *m/z* 140 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 3097, 3050, 1626, 1594, 1575; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, 2H, $J = 8.8$ Hz), 7.73–7.72 (m, 1H), 7.64–7.40 (3H, m), 7.24 (d, $J = 3.4$ Hz, 1H), 6.60 (dd, 1H, $J = 3.4$ and 1.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 187.6, 143.8, 138.5, 134.2, 133.5, 131.9, 128.9, 128.2, 127.6.

(Thiophen-2-yl)(p-tolyl)methanone (3b). Off-white solid; mp 70–71°C (ethanol, lit. [53] 72–75°C); MS *m/z* 203 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 3026, 2913, 1627, 1603, 1569; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, $J = 7.7$ Hz, 2H), 7.69 (d, $J = 4.8$ Hz, 1H), 7.64 (d, $J = 4.0$ Hz, 1H), 7.29 (d, $J = 8$ Hz, 2H), 7.15 (dd, $J = 4.8$ and 4.0 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 187.4, 144.1, 142.9, 136.0, 133.3, 129.3, 128.9, 127.7, 127.6, 21.4.

(Thiophen-2-yl)(o-tolyl)methanone (3c). Light yellow solid; mp 145–146°C (ethanol, lit. [41] 145–147°C); MS *m/z* 203 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 3026, 2913, 1627, 1603, 1569; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.1 (d, $J = 5.9$ Hz, 1H), 7.45–7.37 (m, 3H), 7.30–2.23 (m, 2H), 7.11 (dd, $J = 4.8$ Hz, 4.0 Hz, 1H); 2.44 (s, 3H).

(4-Chlorophenyl)(thiophen-2-yl)methanone (3d). Off white solid; mp 98–100°C (ethanol, lit. [52] 99–100°C); MS *m/z* 223 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 1629, 1586; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, $J = 8.4$ Hz, 2H); 7.75 (dd, $J = 4.9$ Hz, 1.1 Hz, 1H); 7.63 (dd, 1H, $J = 3.7$ Hz, 1.1 Hz); 7.48 (d, $J = 8.4$ Hz, 2H); 7.18 (dd, $J = 4.9$ Hz, 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 186.4, 143.3, 138.7, 136.7, 134.2, 133.9, 130.4, 128.6, 127.7.

(2-Chlorophenyl)(thiophen-2-yl)methanone (3e). Light brown oil [54]; MS *m/z* 223 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 1629, 1586; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (dd, 1H, $J = 4.9$ Hz, 1.1 Hz, 1H); 7.49–7.34 (m, 5H); 7.12 (dd, $J = 4.7$ Hz, 4.0 Hz, 1H).

(4-Nitrophenyl)(thiophen-2-yl)methanone (3f). Pale yellow solid; mp 172–173°C (EtOH, lit. [55] 173–174°C); MS *m/z* 233 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 1629, 1590, 1510; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, 2H, $J = 8.7$ Hz), 8.20 (d, 1H, $J = 4.2$ Hz), 8.0 (d, 2H, $J = 8.6$ Hz), 7.73 (d, 1H, $J = 2.80$ Hz), 7.30 (t, 1H, $J = 3.9$ Hz).

(4-Methoxyphenyl)(thiophen-2-yl)methanone (3g). Light brown solid; mp 65–66°C (ethanol, lit. [56] 69–72°C) MS *m/z* 219 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 3109, 3009, 2969, 1628, 1601; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, $J = 8.8$ Hz, 2H), 7.68 (d, $J = 5.1$ Hz, 1H), 7.64 (d, $J = 3.7$ Hz, 1H), 7.16 (dd, $J = 4.7$ and 3.7 Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 2H), 3.90 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) 186.3, 163.2, 143.9, 133.4, 132.8, 131.4, 131.1, 127.5, 113.8, 55.3.

1-(Thiophen-2-yl)ethanone (3h). Light brown gum [57]; MS *m/z* 126 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 1660; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.69 (dd, 1H, $J = 5.0$ and 1.4 Hz), 7.63 (dd,

1H, $J = 3.5$ and 1.4 Hz), 7.12 (dd, 1H, $J = 5.0$ and 3.5 Hz), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 190.7, 144.5, 132.6, 128.2, 133.8, 26.8.

1-(Thiophen-2-yl)propan-1-one (3i). Light brown oil [41]; MS *m/z* 140 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 1665; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.72 (dd, 1H, $J = 3.8$ and 1.2 Hz), 7.66 (dd, 1H, $J = 5.0$ and 1.2 Hz), 7.12 (dd, 1H, $J = 5.0$ and 3.8 Hz), 2.89 (q, $J = 7.2$ Hz, 2H), 1.35 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 193.7, 144.1, 133.6, 131.2, 128.3, 32.52, 8.51.

2-(4-Isobutylphenyl)-1-(thiophen-2-yl)propan-1-one (3j). MS *m/z* 273 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 1659; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, 1H, $J = 3.7$ Hz); 7.55 (d, 1H, $J = 4.8$ Hz); 7.22 (d, 2H, $J = 8.1$ Hz); 7.08–7.02 (m, 3H); 4.47 (q, 1H, $J = 7.0$ Hz); 2.41 (d, 2H, $J = 7.3$ Hz); 1.81–1.79 (m, 1H); 1.52 (d, 3H, $J = 7.0$ Hz); 0.87 (d, 6H, $J = 6.6$ Hz); elemental analysis found C, 74.66; H, 7.31; Calcd for $C_{17}H_{20}SO$; C, 74.96; H, 7.40.

***2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H*-indol-3-yl)-1-(thiophen-2-yl)ethanone (3k).** MS *m/z* 423 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 1659; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.2 (d, 1H, $J = 8.3$ Hz), 8.1 (d, 1H, $J = 8.3$ Hz), 7.75–7.65 (m, 4H), 7.62–7.60 (m, 1H), 7.18 (s, 1H), 6.92 (d, 1H, $J = 8.3$ Hz), 6.73 (d, 1H, $J = 8.3$ Hz), 4.45 (s, 2H), 3.73 (s, 3H), 2.20 (s, 3H); elemental analysis found C, 65.36; H, 4.32; N 3.19; Calcd for $C_{23}H_{18}ClNSO_3$; C, 65.17; H, 4.28; N, 3.30.

(2-(2,3-Dimethylphenylamino)phenyl)(thiophen-2-yl)methanone (3l). MS *m/z* 308 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 1629, 1586; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7·92 (dd, 1H, $J = 7.9$ and 1.2 Hz); 7.46–6.92 (m, 9H); 6.38 (d, 1H, $J = 8.6$ Hz); 2.3 (s, 3H); 2.1 (s, 3H); elemental analysis found C, 74.45; H, 5.35; Calcd for $C_{19}H_{17}$ NSO; C, 74.23; H, 5.57.

Docking procedure. In the present molecular docking studies, we have performed the energy minimization and conformational search with the MacroModel application in the Schrodinger package. Compounds **3j–3l** were energy minimized for flexibility of the molecules, and then conformational search was followed. We have used OPLS_2005 force field and water as implicit solvent. The Polak–Ribier conjugate gradient method of minimization with 500 iterations was followed with a threshold gradient on 0.05 kJ/mol. The conformational search conducted was based on Montecarlo multiple minimum torsional sampling. The ligands were then finally prepared with LigPrep application.

The COX-1 (3N8X) and COX-2 (3LN1) crystal structures were retrieved from the protein data bank and refined with the Protein Preparation Wizard application in which the hydrogens were added and missing side chains and loops were filled with Prime application. Water molecules were deleted except those within the distance of 5A from the het(hetroatom) groups. Finally, the protein was optimized and minimized using OPLS_2005 force filed. Grid-based docking was performed in the present study.

Pharmacology.

***In vitro* biochemical assays (spectrophotometric assay of COX-1 and COX-2).** Microsomal fraction of ram seminal vesicles were used as a source of COX-1 enzyme and microsomes from *sf9* cells infected with baculovirus containing human COX-2 cDNA were used as a source of COX-2 enzyme. Enzyme activity was measured using a chromogenic assay based on oxidation of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine (TMPD) during the reduction of PGG_2 to PGH_2 as per the procedure described by Copeland *et al*. [51] with some modifications. The assay mixture (1000 μL) contained 100-m*M* Tris pH 8.0, 3-mM EDTA, 15-μ*M* hematin, 150 units enzyme, and 8% DMSO. The mixture was pre-incubated at 25°C for 15 min before initiation of enzymatic reaction in the presence of compound/vehicle. The reaction was initiated by the addition of 100-μ*M* arachidonic acid and 120-μ*M* TMPD. The enzyme activity was measured by estimation of the initial velocity of TMPD oxidation over the first 25 s of the reaction followed from an increase in absorbance at 603 n*M*.

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