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Dedicated to Professor Valer Farcasan
on the occasion of his 95th anniversary

SELECTED MICHAEL ADDITIONS TO THIOPHENE-CONTAINING ANALOGUES OF CHALCONE

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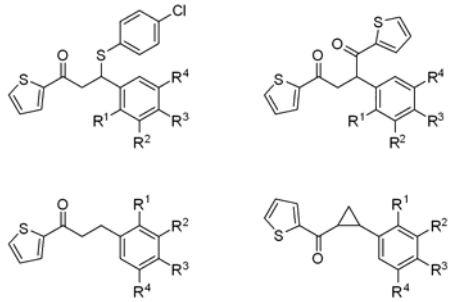
Using thiophene-containing analogues of chalcone as substrates, a series of Michael additions were investigated. Thia-Michael addition of 4-chlorothiophenol led to 1-(substituted aryl)-3-(4-chlorophenylmercapto)-1-(2-thienyl)-1-propanones, whereas catalytic hydrogenation over Pd/C yielded 1-(substituted aryl)-1-(2-thienyl)-1-propanones chemoselectively. The Stetter reaction of the aforementioned substrates with thiophene-2-carboxaldehyde afforded 2-(substituted aryl)-1,4-bis(2-thienyl)-1,4-butadiones, while 2-(substituted aryl)cycloprop-1-yl thiophen-2-yl ketones were obtained via the Corey-Chaykovsky reaction with dimethylsulfoxonium methylide.



INTRODUCTION

Our interest in the chemistry of the carbon atom α to the carbonyl function in alkyl aryl ketones has so far generated a number of publications dealing mostly with the aminomethylation of this particular class of ketones and the subsequent transformations of the synthesized ketonic Mannich bases (for example, one of the latest communication[1] in the series reports the generation of a structurally diverse library of compounds starting from 3-dimethylamino-1-(2-thienyl)-1-propanone hydrochloride). In addition, the involvement of the methyl group in 2-acetylthiophene in the Claisen condensation with a series of less common, bromo- and alkoxy-substituted benzaldehydes was examined,[2] and a few of the obtained thiophene-containing analogues of chalcone have been successfully cyclized to N^1-unsubstituted or N^1-substituted pyrazolines through reaction with hydrazines.[3] Furthermore, highly substituted cyclohexenones, useful as intermediates in the preparation of various fused heterocycles, have been synthesized through the base-catalyzed addition of ethyl acetoacetate to the previously reported thiophene-containing chalcone analogues.[4] Addition of bromine to thiophene-containing chalcone analogues has also been examined as a stage in a multi-step approach for the preparation of thiophene-containing isoxazoles.[5] To further explore the synthetic potential of these propenones in the preparation of different types of organic compounds, novel thiophene-containing analogues of chalcone have been obtained and subjected to addition of 4-chlorothiophenol, reduction to the

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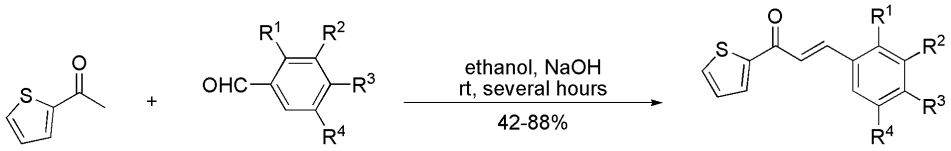
corresponding propanones, addition of thiophene-2-carboxaldehyde by means of the Stetter reaction, and cyclopropane ring formation using the Corey–Chaykovsky reaction.

RESULTS AND DISCUSSION

Chalcones and their heteroanalogues are known to participate in many chemical transformations, but additions of various nucleophiles to the conjugated double bond system and ring closure reactions are the most investigated types of chemical processes that these compounds could undergo.[6] The Michael reaction of a stabilized carbanion with α,β-unsaturated carbonyl compounds is one of the most important carbon–carbon bond-forming reaction in organic chemistry, and it has been widely used in organic synthesis. Replacement of the carbanion with heteroatom nucleophiles (such as amines, thiols, alcohols, phosphines, selenols, silanes) in the Michael reaction, and the subsequent formation of a carbon–heteroatom bond, unlocks this reaction's huge potential for the generation of carbonyl compounds β-substituted with heteroatoms. [7] In continuation of our work on the chemistry of thiophene-containing analogues of chalcone, several novel prop-2-en-1-ones derived from 2-acetylthiophene and various benzaldehydes **2**–**15** have been synthesized (Scheme 1). Benzaldehydes **2**–**11** were commercially available, whereas alkoxy-substituted benzaldehydes required for the preparation of several novel thiophene-containing analogues of chalcone (namely 2-benzyloxy-5-bromobenzaldehyde **12**, 4-(4-bromobenzyloxy) benzaldehyde **13** 4-(3,4-dichlorobenzyloxy)benzaldehyde **14** and 4-(3,4-dichlorobenzyloxy)-3 methoxybenzaldehyde **15**) were obtained through the *O*-alkylation of commercially available phenolic benzaldehydes with the corresponding benzyl halides. Subsequent Claisen condensation of benzaldehydes **2**–**15** with 2-acetylthiophene afforded the known chalcone analogues 3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **16**,[8] 3-(1,3-benzo[*d*]dioxol-5-yl)-1-(thiophen-2-yl)-2-propen-1-one **17**,[8] 3-(3,4,5-trimethoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **18**,[9] 3-(4-chlorophenyl)-1-(thiophen-2-yl)-2-propen-1-one **20**,[8] 3-(3-bromo-4-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **22**,[2] and 3-(4-benzyloxy-3-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **24**,[2] along with novel thiophene-containing analogues of chalcone **19**, **21**, **23** and **25**–**29**. The presence in the ^{1}H NMR spectra of these novel heterochalcones of doublets having a coupling constant of approximately 16 Hz that are associated with the protons of the carbon atoms of the newly formed carbon–carbon double bond provided confirmation of the prop-2-en-1-one structure for compounds **19**, **21**, **23** and **25**–**29**.

Addition of sulfur-containing nucleophiles to α,β-unsaturated carbonyl compounds (the thia-Michael addition) allows the creation of a novel carbon–sulfur bond, and, when applied to β-substituted-α,β-unsaturated carbonyl compound, provides direct access to optically active sulfides. The enantioselective version of the thia-Michael addition has found practical applications in the synthesis of biologically relevant compounds, such as 13-thiaprostaglandins,[10] antidepressant agent thiazesim,[11] GABA analogues,[12] or neuraminidase inhibitor (–)-oseltamivir.[13] Recently, the Michael reaction of thiophenol[14,15] and thioglycolic acid[16] with analogues of chalcone has been employed to generate a series of adducts that were evaluated

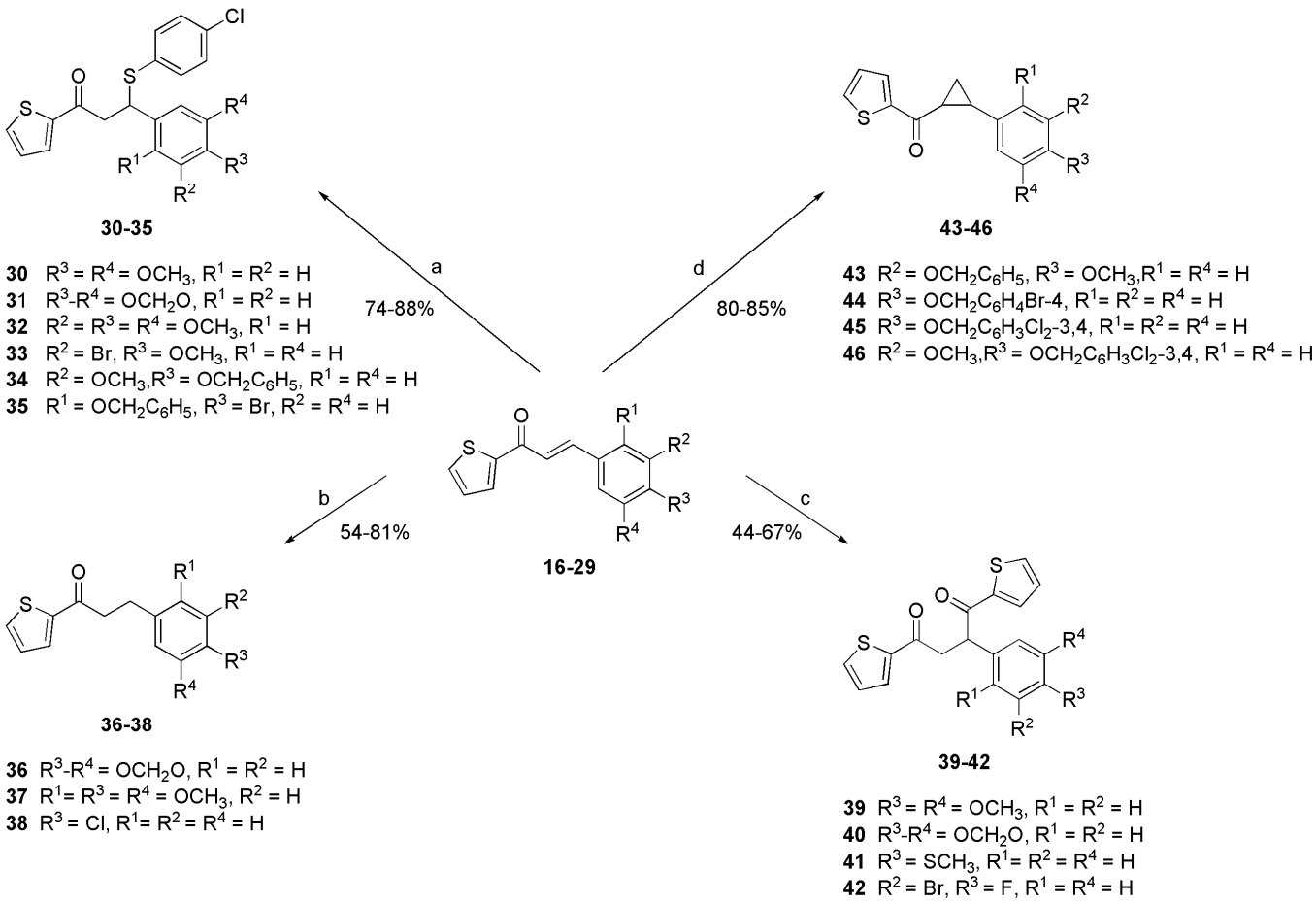


1 **2-15** **16-29**

2, **16** $R^3 = R^4 = OCH_3$, $R^1 = R^2 = H$
3, **17** R^3-$R^4 = OCH_2O$, $R^1 = R^2 = H$
4, **18** $R^2 = R^3 = R^4 = OCH_3$, $R^1 = H$
5, **19** $R^1 = R^3 = R^4 = OCH_3$, $R^2 = H$
6, **20** $R^3 = Cl$, $R^1 = R^2 = R^4 = H$
7, **21** $R^3 = SCH_3$, $R^1 = R^2 = R^4 = H$
8, 22 $R^2 = Br$, $R^3 = OCH_3$, $R^1 = R^4 = H$
9, **23** $R^2 = Br$, $R^3 = F$, $R^1 = R^4 = H$
10, **24** $R^2 = OCH_3$,$R^3 = OCH_2C_6H_5$, $R^1 = R^4 = H$
11, **25** $R^2 = OCH_2C_6H_5$, $R^3 = OCH_3$,$R^1 = R^4 = H$
12, **26** $R^1 = OCH_2C_6H_5$, $R^3 = Br$, $R^2 = R^4 = H$
13, **27** $R^3 = OCH_2C_6H_4Br$-4, $R^1 = R^2 = R^4 = H$
14, **28** $R^3 = OCH_2C_6H_3Cl_2$-3,4, $R^1 = R^2 = R^4 = H$
15, **29** $R^2 = OCH_3$,$R^3 = OCH_2C_6H_3Cl_2$-3,4, $R^1 = R^4 = H$

Scheme 1 – Claisen–Schmidt condensation of 2-acetylthiophene **1** with variously substituted benzaldehydes **2**–**15**.

against a panel of human pathogens (yeasts, gram-negative bacteria and gram-positive bacteria), and some of these candidates had significant antimicrobial activity against several of these microorganisms. Although a few of these 1,3-diaryl-3-phenylthio-1-propanones featured a 2-thienyl residue as the aryl at position 3 of the propanone moiety, none of them had a 2-thienyl residue as the aryl moiety at position 1. Therefore, with the view to broaden the structural variety of these 1,3-diaryl-3-(arylthio)-1-propanones, the Michael addition of 4-chlorothiophenol to selected chalcones having a 2-thienyl residue as the aryl moiety at position 1 of the prop-2-en-1-one moiety was explored in order to afford novel candidates **30**–**35** for antimicrobial screening (Scheme 2). Despite the fact that both potassium *tert*-butoxide[14] and iodine–CH_2Cl_2 system[15] have been previously shown to catalyze effectively this particular type of thia-Michael addition, we chose to investigate the use of a milder base as catalyst. In our hands, heating the reactants in refluxing ethanol in the presence of triethylamine yielded the desired adducts **30**–**35** in excellent yields. In addition, this synthetic methodology allows easy and fast separation of the reaction product (as compounds **30**–**35** crystallized from the reaction mixture upon cooling, and were isolated through filtration in high purity), whereas in previously reported approaches the isolation of the reaction products required neutralization of the catalyst prior to liquid extraction, which was often followed by column chromatography to finally yield the pure thia-Michael adducts. NMR analysis provided confirmation for the structure of 1,3-diaryl-3-(arylthio)-1-propanones **30**–**35** through the presence in their ^{1}H NMR spectra of signals centered around 4.8 ppm and associated with the



Scheme 2 – Michael additions to thiophene-containing analogues of chalcone **16**–**29**. a) 4-chlorothiophenol, triethylamine, ethanol, reflux, 2 h; b) H_2, Pd/C, ethanol (or methanol, or ethyl acetate), rt, 17–62 h; c) thiophene-2-carboxaldehyde, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, triethylamine, 2-propanol, reflux, 17 h; d) trimethylsulfoxonium iodide, NaH, dimethylsulfoxide, rt, 3 h.

proton of the methine group. These signals appear in the spectra either as a barely noticeable doublet of doublets (in the case of compounds **32** and **34**), but mostly as a triplet resulting from the superimposition of the doublet of doublets (for compounds **30**, **31**, **33** and **35**). In addition, the two doublets associated with the diastereotopic protons of the methylene group can be observed at approximately 3.45 ppm. In the ^{13}C NMR spectra of 3-mercaptopropan-1-ones **30**–**35**, the presence of two signals in the aliphatic region (around 45 and 48 ppm for the majority of the newly synthesized compounds), confirms the addition of 4-chlorothiophenol at the carbon–carbon double bond in chalcone analogues, and the subsequent transformation of these sp^2 carbon atoms into sp^3 carbon atoms in the methylene and methine groups in the propanone moiety of compounds **30**–**35**.

Reduction of chalcones may lead to three major different types of products, namely allylic alcohols (obtained from the reduction of the carbonyl function), dihydrochalcones (resulting from the reduction of the double carbon–carbon bond), or the corresponding 1,3-diaryl-1-propanol, arising from the simultaneous reduction of carbonyl function and double carbon–carbon bond. Depending on the reaction conditions, reduction of chalcones may yield mixtures of the aforementioned reduction compounds, or it may proceed chemoselectively to produce one of these reduction compounds as the sole reaction product. Although substantial progress has been made lately into identifying the best reaction conditions, selective hydrogenation of chalcones and their analogues still remains a challenging issue. Despite recent advances in the development of novel methodologies for the selective reduction of the double carbon–carbon bond in chalcones using *N*,*N*-dimethylammine borane in the presence of palladium and nickel complexes,[17] hydrogen and rhodium-based catalysts in ionic liquids,[18] triethylsilane in the presence of $PdCl_2$,[19] ammonium formate in the presence of Pd/C[20] or Pd/hydroxyapatite,[21] Mg–$ZnCl_2$ system in water,[22] or Zn–acetic acid–ethanol system in the presence of CH_3COONH_4,[23] NH_4Cl,[24] or ultrasound,[25] classical catalytic hydrogenation with Pd/C represents a simple, yet valuable synthetic approach for the reduction of the ethylenic moiety in chalcone analogues. Hydrogenation of thiophene-containing analogues of chalcone **17**, **19** and **20** was attempted under different reaction conditions with a view to obtain good yields of dihydrochalcone (Scheme 2). Thus, chalcone analogue **17** was hydrogenated at room temperature and atmospheric pressure overnight, and because of the limited solubility of chalcone analogue **17** in ethanol, a large volume of solvent was required to ensure the dissolution of the substrate. TLC analysis of the reaction mixture showed that chalcone analogue **17** was still present after 16 h, and repeated attempts to find the appropriate solvent system for the separation of the product **36** from the unreacted **17** by flash column chromatography were not very successful, as both compounds had almost the same R_f values. In the end, the reaction mixture was carefully separated using hexanes–ethyl acetate (19:1, v/v), but the recovery of the dihydrochalcone **36** from the fractions containing the pure compound reached only 59% of the theoretical amount. In another attempt to push the hydrogenation forward and improve the yields, methanol and ethanol were used as co-solvents for the hydrogenation of chalcone analogue **19**, and the reaction time was extended to 36 h. Repeated ^1H NMR analysis of aliquots taken from the reaction mixture at different reaction times showed that the conversion of **19** into dihydrochalcone **37** reached a plateau at approximately 85–90%, and although the transformation was still incomplete at the end of the reaction time, separation of the reaction product from unreacted chalcone analogue using column chromatography was performed. Again, close elution of the compounds **19** and **37** under the best separation conditions limited the yield of pure dihydrochalcone **37** to 54%. However, when ethyl acetate was used as solvent in the hydrogenation of chalcone analogue **20**, and the reaction time was extended to 62 h, no evidence for the presence of unreacted **20** could be found in the ^1H NMR spectrum of an aliquot of the crude reaction mixture at the end of the reaction time. Even though dihydrochalcone **38** could be isolated in good purity after work-up, column chromatography of the residue was still undertaken, to finally afford the reaction product **38** in 81% yield. Because the presence of the other two potential by-products of chalcone hydrogenation, namely the allylic alcohol and the 1,3-diaryl-1-propanol, could not be evidenced in the analysis of ^1H NMR spectra of the crude reaction mixtures isolated in all the three cases, catalytic hydrogenation of these thiophene-containing analogues of chalcone in the presence of Pd appears to be selective. ^1H NMR spectra of

hydrochalcones **36-38** exhibited multiplets at approximately 3.0 and 3.2 ppm, which can be associated with the protons in the two newly formed methylene groups in the propanone bridge between the aromatic moieties, whereas the two novel peaks in their ^{13}C NMR spectra at approximately 30 ppm and 40 ppm were attributed to the aliphatic carbon atoms in the same two methylene groups.

1,4-Addition of aldehydes to α,β-unsaturated carbonyl compounds (such as chalcones and their analogues, α,β-unsaturated esters, or α,β-unsaturated nitriles) in the presence of a suitable nucleophile, developed in the 1970s by Stetter,[26] provides easy access to synthetically useful 1,4-dicarbonyl compounds, which would be otherwise challenging to obtain in a straightforward manner. 1,4-Dicarbonyl compounds obtained through the Stetter reaction are intermediates in the total synthesis of natural products,[27–29] or are valuable starting materials in the Paal-Knorr synthesis leading to monoheteroatomic five-membered ring systems[30] that possess interesting extended heterocyclic systems[31,32] or exhibit biological activities.[33,34] Thiophene-contaning analogues of chalcone **16**, **17**, **21** and **23** were reacted with thiophene-2-carboxaldehyde in refluxing 2-propanol in the presence of 0.2 equivalents of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride as catalyst overnight to afford the desired 1,2,4-trisubstituted-1,4-butanediones **39**–**42**, respectively, in good yields (Scheme 2). The structure of these novel 1,4-dicarbonyl compounds having two thiophene moieties has been established through the inspection of their ^{1}H NMR spectra, which showed two sets of double doublets at 3.2 and 4.0 ppm corresponding to the two diastereotopic protons of the methylene group, and double doublet at approximately 5.0 ppm, associated with the proton of the methine group. The presence of two individual thiophene rings in the structure of 1,4-butadiones **39**–**42** is clearly evidenced (at least for compounds **39** and **40**) by the presence of two distinct, slightly shifted sets of doublet of doublets having similar coupling constants at approximately 7.1, 7.6 and 7.8 ppm. ^{13}C NMR spectra of 1,4-butadiones **39**–**42** further confirmed the proposed structure through the presence of two peaks at 44 and 50 ppm, attributable to the carbon atoms of the methylene and methine groups in the butanedione linker between the two 2-thienyl moieties.

1,4-Addition of Corey-Chaykovsky's reagent to α,β-unsaturated carbonyl compounds is an important route for the synthesis of aroylcylopropanes,[35] which could be employed as intermediates in organic synthesis for facile access to heteroaromatic ring-fused cyclohexanones[36-39] or for the preparation of 1-butanones through reductive cleavage.[40] In a typical procedure, thiophene-contaning analogues of chalcone **25** and **27–29** with dimethylsulfoxonium methylide (previously generated *in situ* from trimethylsulfoxonium iodide and NaH) were stirred in DMSO at room temperature for 3 h to afford the desired 2-(substituted aryl)cycloprop-1-yl 2-thienyl ketones **43**–**46** (Scheme 2). All of these (2-thienoyl)cyclopropanes were isolated as crystalline solids in very good yields, and characterized by NMR spectroscopy. The cyclopropane structure for compounds **43**–**46** was confirmed by the presence of the ABCD spin system in the aliphatic region of their ^{1}H NMR spectra corresponding to the four magnetic non-equivalent protons in the unsymmetrically 1,2-disubstituted cyclopropane ring, and by the presence of three peaks at approximately 19, 29 and 30 ppm in the aliphatic region of their ^{13}C NMR spectra, that can be associated with the carbon atoms in the newly formed cyclopropane ring. Based on the comparison with previously published NMR data for aroylcyclopropanes having similar structures and obtained through a similar procedure,[41] the current results strongly suggest a *trans* orientation for the substituents in the cyclopropane ring.

EXPERIMENTAL

Materials and methods

Melting points were taken on a Mel-Temp II apparatus and are uncorrected. Elemental analysis was conducted in-house, on a PerkinElmer 2400 Series II CHNS/O system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals owing to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to deuteriochloroform (δ = 77.16 ppm) or d_6-dimethyl sulfoxide (δ = 39.52 ppm). The chemical reagents were obtained from Sigma–Aldrich and were used without prior purification.

The alkoxy-substituted benzaldehydes **12**–**15** required for the synthesis of novel thiophene-containing chalcone analogues have been prepared through *O*-alkylation of commercially available phenolic benzaldehydes, as described below.

2-Benzyloxy-5-bromobenzaldehyde (**12**)

To a solution of KOH (660 mg, 10 mmol, 85% purity) in ethanol (8 mL) was added 5-bromo-2-hydroxybenzaldehyde (2.01 g, 10 mmol), followed by benzyl chloride (1.27 g,

10 mmol). The mixture was refluxed for 2 h, then it was cooled to room temperature and further refrigerated at 2–4 °C for 2 h. The solid was filtered and washed sequentially with cold ethanol (5 mL), 5% aq. KOH (15 mL) and water (2× 15 mL). The crude material was recrystallized from ethanol to afford colorless crystals (1.95 g, 67%), mp 69–70 °C. The reported melting point for same compound, previously obtained through *O*-benzylation of 5-bromosalicylaldehyde (using DMF as a solvent, and either NaH[42] or K_2CO_3[43] as base) was 67.5–69.5 °C[42] and 70–71 °C,[43] respectively.

4-(4-Bromobenzyloxy)benzaldehyde (**13**)

A mixture of 4-hydroxybenzaldehyde (1.22 g, 10 mmol), 4-bromobenzyl bromide (2.5 g, 10 mmol) and anhydrous K_2CO_3 (2.76 g, 20 mmol) in 2-butanone (25 mL) was refluxed for 6 h. The solvent was removed under reduced pressure to give a residue that was partitioned between water (50 mL) and ethyl acetate (30 mL). The organic phase was washed successively with dilute KOH, water and brine, and then the solvent was evaporated under reduced pressure. The residue was recrystallized from a small volume of ethanol to give the aldehyde (1.95 g, 67%) as a light yellow solid, mp 88–89 °C (lit.[44] mp 91 °C).

4-(3,4-Dichlorobenzyloxy)benzaldehyde (**14**)

4-Hydroxybenzaldehyde (1.22 g, 10 mmol) and 3,4-dichlorobenzyl chloride (1.96 g, 10 mmol) were reacted in 2-butanone (30 mL) using the synthetic procedure described for 4-(4-bromobenzyloxy)benzaldehyde **13** to yield the title compound as off-white crystals (1.97 g, 70%). The ^{1}H NMR spectrum of **14** was identical to the one reported in the literature.[45]

4-(3,4-Dichlorobenzyloxy)-3-methoxybenzaldehyde (**15**)

Vanillin (1.52 g, 10 mmol) and 3,4-dichlorobenzyl chloride (1.96 g, 10 mmol) were reacted in ethanol (20 mL) using the synthetic procedure described for 2-benzyloxy-5-bromobenzaldehyde **12** to afford the title compound as colorless crystals (1.96 g, 63%), mp 113–114 °C (ethanol). The same compound, prepared through *O*-methylation of 4-(3,4-dichlorobenzyloxy)-3-hydroxybenzaldehyde, had mp 113 °C.[46]

Synthesis of thiophene-containing chalcone analogues – General procedure

To a solution of the aldehyde (5 mmol) in ethanol (minimum volume required to solve the aldehyde at room temperature) was added 2-acetylthiophene (630 mg, 5 mmol) followed by 3–4 drops of 10% aq. NaOH. The mixture was stirred at room temperature overnight, then it was refrigerated for 2 h. The solid was filtered, washed with cold ethanol (5 mL), and recrystallized from the appropriate solvent.

1-(Thiophen-2-yl)-3-(2,4,5-trimethoxyphenyl)-2-propen-1-one (**19**)

This compound was obtained from 2-acetylthiophene and 2,4,5-trimethoxybenzaldehyde **5** as yellow crystals (885 mg, 58%), mp 136–137 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 6.52 (s, 1H), 7.11 (s, 1H), 7.16 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.38 (d, *J* = 16.0 Hz, 1H), 7.64 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.84 (dd, *J* = 1.2 and 4.0 Hz, 1H), 8.11 (d, *J* = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.2, 56.5, 56.8, 97.1, 112.0, 115.5, 120.1, 128.2, 131.4, 133.2, 139.6, 143.4, 146.2, 152.7, 155.0, 182.7; *Anal*. Calcd. for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30. Found: C, 63.41; H, 5.10.

3-(4-Methylthiophenyl)-1-(thiophen-2-yl)-2-propen-1-one (**21**)

This compound was obtained from 2-acetylthiophene and 4-(methylthio)benzaldehyde **7** as bright yellow crystals (730 mg, 56%), mp 86–87 °C (ethanol) (lit.[47] mp 80–82 °C); ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H), 7.18 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 15.6 Hz, 1H), 7.67 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.81 (d, *J* = 15.6 Hz, 1H), 7.86 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 15.3, 120.8, 126.2, 128.3, 129.0, 131.4, 131.8, 133.8, 142.6, 143.7, 145.8, 182.1; *Anal*. Calcd. for $C_{14}H_{12}OS_2$: C, 64.58; H, 4.65. Found: C, 64.33; H, 4.87.

3-(3-Bromo-4-fluorophenyl)-1-(thiophen-2-yl)-2-propen-1-one (**23**)

This compound was obtained from 2-acetylthiophene and 3-bromo-4-fluorobenzaldehyde **9** as colorless crystals (980 mg, 63%), mp 143–144 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 7.13–7.22 (m, 2H), 7.33 (d, *J* = 15.6 Hz, 1H), 7.52–7.57 (m, 1H), 7.70 (dd, *J* = 1.2 and 5.2 Hz, 1H), 7.73 (d, *J* = 15.2 Hz, 1H), 7.85 (dd, *J* = 2.0 and 6.4 Hz, 1H), 7.87 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 110.1 (d, *J* = 21.6 Hz), 117.2 (d, *J* = 22.7 Hz), 122.6 (d, *J* = 2.0 Hz), 128.5, 129.5 (d, *J* = 7.5 Hz) 132.2, 132.6 (d, *J* = 4.0 Hz), 133.3, 134.4, 141.3, 145.4, 160.3 (d, *J* = 251.1 Hz), 181.6; *Anal*. Calcd. for $C_{13}H_8BrFOS$: C, 50.18; H, 2.59. Found: C, 49.98; H, 2.82.

3-(3-Benzyloxy-4-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one (**25**)

This compound was obtained from 2-acetylthiophene and 3-benzyloxy-4-methoxybenzaldehyde **11** as light yellow crystals (1.19 g, 68%), mp 130–131 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.93 (s, 3H), 5.21 (s, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.12–7.27 (m, 4H), 7.29–7.54 (m, 5H), 7.66 (dd, *J* = 1.2 and 5.2 Hz, 1H), 7.75 (d, *J* = 15.6 Hz, 1H), 7.82 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.2, 71.4, 111.8, 113.5, 123.7, 127.5, 127.7, 128.2, 128.3, 128.8, 131.6, 133.7, 136.9, 144.2, 145.9, 148.5, 152.3, 182.1; *Anal*. Calcd. for $C_{21}H_{18}O_3S$: C, 71.98; H, 5.18. Found: C, 71.73; H, 4.98.

3-(2-Benzyloxy-5-bromophenyl)-1-(thiophen-2-yl)-2-propen-1-one (**26**)

This compound was obtained from 2-acetylthiophene and 2-benzyloxy-5-bromobenzaldehyde **12** as light yellow crystals (1.76 g, 88%), mp 149–150 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 5.15 (s, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 7.08 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.36–7.50 (m, 6H), 7.51 (dd, *J* = 1.2 and 4.0 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.64 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.97 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 71.1, 113.5, 114.5, 124.4, 126.2, 128.0, 128.2, 128.5, 129.0, 132.0, 133.1, 133.9, 134.0, 136.1, 138.3, 145.9, 157.3, 182.4; *Anal*. Calcd. for $C_{20}H_{15}BrO_2S$: C, 60.16; H, 3.79. Found: C, 60.34; H, 3.66.

3-(4-(4-Bromobenzyloxy)phenyl)-1-(thiophen-2-yl)-2-propen-1-one (**27**)

This compound was obtained from 2-acetylthiophene and 4-(4-bromobenzyloxy)benzaldehyde **13** as off-white crystals (1.44 g, 72%), mp 143–144 °C (ethanol); ^{1}H NMR (d_6-DMSO): δ 5.17 (s, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.30 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.69 (d, J = 15.6 Hz, 1H), 7.75 (d, J = 15.6 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 8.03 (dd, *J* = 0.8 and 3.6 Hz, 1H), 8.29 (dd, *J* = 0.8 and 4.0 Hz, 1H); ^{13}C NMR (d_6-DMSO): δ 68.5, 115.2, 119.6, 120.9, 127.4, 128.7, 129.7, 130.6, 131.3, 133.0, 134.9, 136.1, 142.8, 145.6, 160.2, 181.4; *Anal*. Calcd. for $C_{20}H_{15}BrO_2S$: C, 60.16; H, 3.79. Found: C, 59.96; H, 3.96.

3-(4-(3,4-Dichlorobenzyloxy)phenyl)-1-(thiophen-2-yl)-2-propen-1-one (**28**)

This compound was obtained from 2-acetylthiophene and 4-(3,4-dichlorobenzyloxy)benzaldehyde **14** as light yellow crystals (1.38 g, 71%), mp 179–180 °C (ethanol–acetone); ^{1}H NMR (d_6-DMSO): δ 5.21 (s, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.31 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.46 (dd, *J* = 1.8 and

8.0 Hz, 1H), 7.63–7.79 (m, 4H), 7.86 (d, *J* = 8.4 Hz, 2H), 8.03 (d, *J* = 4.8 Hz, 1H), 8.29 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (d_6-DMSO): δ 67.8, 115.2, 119.7, 127.6, 127.9, 128.8, 129.5, 130.5, 130.7, 130.8, 131.1, 133.2, 135.2, 137.9, 142.9, 145.7, 160.0, 181.5. *Anal*. Calcd. for $C_{20}H_{14}Cl_2O_2S$: C, 61.70; H, 3.62. Found: C, 61.94; H, 3.88.

3-(4-(3,4-Dichlorobenzyloxy)-3-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one (**29**)

This compound was obtained from 2-acetylthiophene and 4-(3,4-dichlorobenzyloxy)-3-methoxybenzaldehyde **15** as yellow crystals (880 mg, 42%), mp 171–172 °C (ethanol–acetone); ^{1}H NMR ($CDCl_3$): δ 3.96 (s, 3H), 5.13 (s, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 7.16–7.21 (m, 3H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 15.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 1.2 and 5.2 Hz, 1H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.86 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.2, 69.7, 111.2, 113.8, 120.2, 122.8, 126.6, 128.3, 128.8, 129.3, 130.8, 131.7, 132.3, 133.0, 133.8, 137.0, 144.1, 145.8, 150.0, 150.1, 182.1; *Anal*. Calcd. for $C_{21}H_{16}Cl_2O_3S$: C, 60.15; H, 3.85. Found: C, 59.97; H, 4.02.

Addition of 4-chlorothiophenol to thiophene-containing chalcone analogues – General procedure

To a mixture of the corresponding thiophene-containing chalcone analogue (2 mmol) in ethanol (15 to 40 mL, depending on the solubility of the heterochalcone at reflux temperature), 4-chlorothiophenol (289 mg, 2 mmol) and triethylamine (3 drops) were added, and the mixture was heated at reflux temperature for 2 h. The solution was then refrigerated to give a solid that was filtered and recrystallized from the appropriate solvent.

3-(4-Chlorophenylthio)-3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)propan-1-one (**30**)

This compound was obtained from 3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **16** as colorless crystals (735 mg, 88%), mp 105–106 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.45 (dd, *J* = 7.6 and 11.6 Hz, 2H), 3.80 (s, 6H), 4.82 (t, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 6.78–6.81 (m, 2H), 7.07 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.15–7.24 (m, 4H), 7.61 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.65 (dd, *J* = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 45.2, 48.5, 55.7, 55.8, 110.7, 110.8, 119.8, 128.1, 128.9, 132.1, 132.5, 132.9, 133.8, 134.1, 134.2, 143.9, 148.2, 148.7, 189.6; *Anal*. Calcd. for $C_{21}H_{19}ClO_3S_2$: C, 60.20; H, 4.57. Found: C, 59.89; H, 4.44.

3-(1,3-Benzo[d]dioxol-5-yl)-3-(4-chlorophenylthio)-1-(thiophen-2-yl) propan-1-one (**31**)

This compound was obtained from 3-(1,3-benzo[*d*]dioxol-5-yl)-1-(thiophen-2-yl)-2-propen-1-one **17** as colorless crystals (645 mg, 80%), mp 102–103 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.43 (dd, *J* = 7.6 and 11.6 Hz, 2H), 4.81 (t. *J* = 7.2 Hz, 1H), 5.88 (s, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.70 (dd, *J* = 1.6 and 8.0 Hz, 1H), 6.86 (d, *J* = 1.6 Hz, 1H), 7.08 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.15–7.24 (m, 4H), 7.60 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.64 (dd, *J* = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 45.3, 48.4, 101.0, 107.8, 108.0, 121.2, 128.1, 128.9, 132.1, 132.5, 133.7, 134.0, 134.2, 134.3, 143.8, 146.8, 147.7, 189.4; *Anal*. Calcd. for $C_{20}H_{15}ClO_3S_2$: C, 59.62; H, 3.75. Found: C, 59.89; H, 3.64.

3-(4-Chlorophenylthio)-1-(thiophen-2-yl)-3-(3,4,5-trimethoxyphenyl)propan-1-one (**32**)

This compound was obtained from 3-(3,4,5-trimethoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **18** as colorless crystals (725 mg, 81%), mp 117–118 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.47 (dd, *J* = 7.6 and 11.2 Hz, 2H), 3.78 (s, 6H), 3.79 (s, 3H), 4.82 (dd, *J* = 7.6 Hz, 1H), 6.50 (s, 2H), 7.11 (dd, *J* = 3.6 and 4.8 Hz, 1H), 7.18–7.29 (m, 4H), 7.64 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.67 (dd, *J* = 1.2 and 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 45.5, 49.3, 56.2, 61.0, 104.9, 128.3, 129.2, 132.3, 132.7, 134.1, 134.4, 136.3, 137.5, 144.1, 153.3, 189.7; *Anal*. Calcd. for $C_{22}H_{21}ClO_4S_2$: C, 58.85; H, 4.71. Found: C, 58.69; H, 4.79.

3-(3-Bromo-4-methoxyphenyl)-3-(4-chlorophenylthio)-1-(thiophen-2-yl)propan-1-one (**33**)

This compound was obtained from 3-(3-bromo-4-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **22** as colorless crystals (765 mg, 82%), mp 128–129 °C (acetone); ^{1}H NMR ($CDCl_3$): δ 3.44 (dd, *J* = 7.2 and 10.4 Hz, 2H), 3.82 (s, 3H), 4.79 (t, *J* = 7.2 Hz, 1H), 6.71–6.75 (m, 1H), 7.07–7.24 (m, 6H), 7.49–7.68 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 45.1, 47.5, 56.1, 111.4, 111.5, 128.0, 128.2, 129.0, 132.1, 132.2, 132.3, 134.0, 134.2, 134.3, 143.7, 155.0, 189.2; *Anal*. Calcd. for $C_{20}H_{16}BrClO_2S_2$: C, 51.35; H, 3.45. Found: C, 51.21; H, 3.49.

3-(4-Benzyloxy-3-methoxyphenyl)-3-(4-chlorophenylthio)-1-(thiophen-2-yl)propan-1-one (**34**)

This compound was from 3-(4-benzyloxy-3-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **24** obtained as colorless crystals (730 mg, 74%), mp 100–101 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.47 (dd, *J* = 7.2 and 10.0 Hz, 2H), 3.83 (s, 3H), 4.83 (dd, *J* = 6.8 Hz, 1H), 5.10 (s, 2H), 6.73–6.77 (m, 2H), 6.84 (s, 1H), 7.10 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.15–7.24 (m, 4H), 7.27–7.44 (m, 5H), 7.63 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.66 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 45.4, 48.7, 56.1, 71.1, 111.6, 113.8, 119.9, 127.4, 128.0, 128.3, 128.6, 129.1, 132.3, 132.7, 133.7, 134.0, 134.3, 134.5, 137.1, 144.1, 147.7, 149.6, 189.7; *Anal*. Calcd. for $C_{27}H_{23}ClO_3S_2$: C, 65.51; H, 4.68. Found: C, 65.86; H, 4.74.

3-(2-Benzyloxy-5-bromophenyl)-3-(4-chlorophenylthio)-1-(thiophen-2-yl)propan-1-one (**35**)

This compound was obtained from 3-(2-benzyloxy-5-bromophenyl)-1-(thiophen-2-yl)-2-propen-1-one **26** as colorless crystals (805 mg, 74%), mp 119–120 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 3.50 (dd, *J* = 7.2 and 10.8 Hz, 2H), 5.00 (d, *J* = 11.6 Hz, 2H), 5.09 (d, *J* = 11.6 Hz, 2H), 5.27 (t, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 7.06 (dd, *J* = 3.8 and 5.0 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.27 (dd, *J* = 2.4 and 8.4 Hz, 1H), 7.32–7.44 (m, 6H), 7.60 (dd, *J* = 1.0 and 3.8 Hz, 1H), 7.62 (dd, *J* = 1.0 and 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 43.0, 44.6, 70.8, 113.3, 114.2, 127.5, 128.3, 128.8, 129.1, 131.2, 131.4, 132.0, 132.3, 132.9, 134.0, 134.2, 134.4, 136.6, 144.1, 155.0, 189.5; *Anal*. Calcd. for $C_{26}H_{20}BrClO_2S_2$: C, 57.41; H, 3.71. Found: C, 57.17; H, 3.86.

Catalytic reduction of thiophene-containing chalcone analogues

3-(1,3-Benzo[d]dioxol-5-yl)-1-(thiophen-2-yl)propan-1-one (**36**)

To a solution of 3-(1,3-benzo[*d*]dioxol-5-yl)-1-(thiophen-2-yl)-2-propen-1-one **17** (516 mg, 2 mmol) in ethanol (70 mL), palladium on carbon (150 mg, 10 wt.% loading, 50% water wet) was added, then the mixture was stirred at room temperature under hydrogen atmosphere (1 atm, balloon) overnight. The mixture was filtered through Celite, the solvent was removed under reduced pressure, and the resulting oil was subjected to flash column chromatography (silicagel, hexanes–ethyl acetate 19:1, v/v) to give the title compound as yellowish solid (308 mg, 59%), mp 46–47 °C, R_f = 0.36 (hexanes–ethyl acetate 9:1, v/v); ^{1}H NMR ($CDCl_3$): δ 2.95–3.02 (m, 2H), 3.15–3.22 (m, 2H), 5.92 (s, 2H), 6.66–6.71 (m, 1H), 6.71–6.76 (m, 2H), 7.11 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.62 (dd, *J* = 1.2

and 4.8 Hz, 1H), 7.69 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 30.3, 41.5, 101.0, 108.4, 109.0, 121.3, 128.2, 131.9, 133.7, 134.9, 144.3, 146.0, 147.8, 192.2; *Anal*. Calcd. for $C_{14}H_{12}O_3S$: C, 64.60; H, 4.65. Found: C, 64.41; H, 4.52.

1-(Thiophen-2-yl)-3-(2,4,5-trimethoxyphenyl)propan-1-one (**37**)

To a solution of 1-(thiophen-2-yl)-3-(2,4,5-trimethoxyphenyl)-2-propen-1-one **19** (608 mg, 2 mmol) in a mixture of ethanol (35 mL) and methanol (10 mL), palladium on carbon (80 mg, 10 wt.% loading, 50% water wet) was added. The mixture was stirred at room temperature under hydrogen atmosphere (1 atm, balloon) for 36 h, then it was filtered through Celite and the solvent was removed under reduced pressure. The resulting oil was subjected to flash column chromatography (silicagel, hexanes–ethyl acetate 14:1, v/v) to give the title compound as off-white solid (330 mg, 54%), mp 94–95 °C, R_f = 0.31 (hexanes–ethyl acetate 4:1, v/v); ^{1}H NMR ($CDCl_3$): δ 2.94–3.02 (m, 2H), 3.11–3.19 (m, 2H), 3.81 (s, 6H), 3.87 (s, 3H), 6.51 (s, 1H), 6.75 (s, 1H), 7.09 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.60 (dd, *J* = 0.8 and 4.8 Hz, 1H), 7.68 (dd, *J* = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 25.8, 40.2, 56.3, 56.4, 56.8, 97.8, 114.6, 120.8, 128.1, 132.0, 133.5, 142.9, 144.6, 148.2, 151.6, 193.2; *Anal*. Calcd. for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92. Found: C, 62.83; H, 5.78.

3-(4-Chlorophenyl)-1-(thiophen-2-yl)propan-1-one (**38**)

To a solution of 3-(4-chlorophenyl)-1-(thiophen-2-yl)-2-propen-1-one **20** (497 mg, 2 mmol) in ethyl acetate (15 mL), palladium on carbon (75 mg, 10 wt.% loading) was added. The mixture was stirred at room temperature under hydrogen atmosphere (1 atm, balloon) for 62 h. After filtration through Celite, the solvent was removed under reduced pressure, and the resulting oil was subjected to flash column chromatography (silicagel, hexanes–ethyl acetate 9:1, v/v) to give the title compound as colorless solid (405 mg, 81%), mp 48–49 °C, R_f = 0.41 (hexanes–ethyl acetate 1:1, v/v); ^{1}H NMR ($CDCl_3$): δ 3.04 (t, *J* = 7.6 Hz, 2H), 3.21 (t, *J* = 7.6 Hz, 2H), 7.11 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.63 (dd, *J* = 0.8 and 4.8 Hz, 1H), 7.68 (dd, *J* = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 29.8, 41.0, 128.3, 128.8, 130.0, 132.0, 132.1, 133.8, 139.6, 144.2, 191.9; *Anal*. Calcd. for $C_{13}H_{11}ClOS$: C, 62.27; H, 4.42. Found: C, 62.11; H, 4.24.

Addition of thiophene-2-carboxaldehyde to thiophene-containing chalcone analogues (Stetter reaction) – General procedure

A mixture of thiophene-contaning analogue of chalcone (2 mmol), thiophene-2-carboxaldehyde (224 mg, 2 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (114 mg, 0.4 mmol) and triethylamine (121 mg, 1.2 mmol) in 2-propanol (7 mL) was refluxed overnight. The mixture was cooled and worked-up as described in each case.

2-(3,4-Dimethoxyphenyl)-1,4-bis(thiophen-2-yl)butan-1,4-dione (**39**)

This compound was obtained from 3-(3,4-dimethoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **16** by following the general procedure. The solvent was then removed with a pipette, and the sticky residue was recrystallized from methanol to afford colorless crystals (340 mg, 44%), mp 195–196 °C; ^{1}H NMR ($CDCl_3$): δ 3.26 (dd, *J* = 4.4 and 17.6 Hz, 1H), 3.83 (s, 3H), 3.87 (s, 3H), 4.04 (dd, *J* = 9.6 and 17.6 Hz, 1H), 5.07 (dd, *J* = 4.4 and 9.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.93 (dd, *J* = 2.0 and 8.0 Hz, 1H), 7.06 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.11 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.57 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.61 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.77 (dd, *J* = 1.2 and 4.0 Hz, 1H), 7.79 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 43.8, 49.8, 56.0, 56.1, 111.0, 111.7, 120.7, 128.2, 128.3, 131.1, 132.4, 133.0, 133.8, 133.9, 143.3, 143.8, 148.6, 149.5, 191.0, 191.7; *Anal*. Calcd. for $C_{20}H_{18}O_4S_2$: C, 62.15; H, 4.69. Found: C, 61.96; H, 4.93.

2-(1,3-Benzo[d]dioxol-5-yl)-1,4-bis(thiophen-2-yl)butan-1,4-dione (**40**)

This compound was obtained from 3-(1,3-benzo[*d*]dioxol-5-yl)-1-(thiophen-2-yl)-2-propen-1-one **17** by following the general procedure. The solvent was then removed with a pipette, and the sticky residue was recrystallized from ethanol to afford greyish crystals (460 mg, 62%), mp 151–152 °C; ^{1}H NMR ($CDCl_3$): δ 3.24 (dd, *J* = 4.4 and 17.2 Hz, 1H), 4.01 (dd, *J* = 9.2 and 17.2 Hz, 1H), 5.04 (dd, *J* = 4.4 and 9.2 Hz, 1H), 5.91 (dd, *J* = 1.2 and 6.0 Hz, 2H), 6.72–6.77 (m, 1H), 6.83–6.89 (m, 2H), 7.06 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.11 (dd, *J* = 4.0 and 5.2 Hz, 1H), 7.57 (dd, *J* = 1.2 and 5.2 Hz, 1H), 7.61 (dd, *J* = 1.2 and 5.2 Hz, 1H), 7.76 (dd, *J* = 1.2 and 4.0 Hz, 1H), 7.79 (dd, *J* = 1.2 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 43.8, 49.8, 101.3, 108.5, 108.9, 121.8, 128.2, 132.3, 133.0, 133.8, 133.9, 143.3, 143.7, 147.2, 148.3, 190.8, 191.5; *Anal*. Calcd. for $C_{19}H_{14}O_4S_2$: C, 61.60; H, 3.81. Found: C, 61.79; H, 3.97.

2-(4-(Methylthio)phenyl)-1,4-bis(thiophen-2-yl)butan-1,4-dione (**41**)

This compound was obtained from 3-(4-methylthiophenyl)-1-(thiophen-2-yl)-2-propen-1-one **21** by following the general procedure. The solid residue was then filtered and recrystallized from methanol to afford tan crystals (500 mg, 67%), mp 146–147 °C; ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 3.25 (dd, *J* = 4.4 and 17.6 Hz, 1H), 4.04 (dd, *J* = 9.4 and 17.6 Hz, 1H), 5.09 (dd, *J* = 4.4 and 9.4 Hz, 1H), 7.06 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.11 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.57 (dd, *J* = 1.2 and 4.8 Hz, 1H), 7.62 (dd, *J* =1.2 and 4.8 Hz, 1H), 7.74–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 15.8, 43.6, 49.6, 127.3, 128.3, 128.8, 132.4, 133.0, 133.9, 135.4, 138.1, 143.3, 143.7, 190.8, 191.5; *Anal*. Calcd. for $C_{19}H_{16}O_2S_3$: C, 61.26; H, 4.33. Found: C, 61.05; H, 4.46.

2-(3-Bromo-4-fluorophenyl)-1,4-bis(thiophen-2-yl)butan-1,4-dione (**42**)

This compound was obtained from 3-(3-bromo-4-fluorophenyl)-1-(thiophen-2-yl)-2-propen-1-one **23** by following the general procedure. The solid residue was then filtered and recrystallized from ethanol to afford off-white crystals (535 mg, 63%), mp 135–136 °C; ^{1}H NMR ($CDCl_3$): δ 3.27 (dd, *J* = 4.8 and 17.6 Hz, 1H), 4.02 (dd, *J* = 9.2 and 17.6 Hz, 1H), 5.09 (dd, *J* = 4.6 and 9.2 Hz, 1H), 7.03–7.15 (m, 3H), 7.30–7.36 (m, 1H), 7.58–7.65 (m, 3H), 7.77 (dd, *J* = 1.0 and 3.8 Hz, 1H), 7.79 (dd, *J* = 0.8 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 43.7, 48.9, 109.8 (d, *J* = 21.1 Hz), 117.2 (d, *J* = 22.2 Hz), 128.3, 128.4, 129.0 (d, *J* = 7.2 Hz), 132.5, 133.2, 134.2, 134.5, 136.0 (d, *J* = 3.6 Hz), 142.9, 143.4, 158.7 (d, *J* = 246.5 Hz), 190.3, 191.0; *Anal*. Calcd. for $C_{18}H_{12}BrFO_2S_2$: C, 51.07; H, 2.86. Found: C, 51.28; H, 3.04.

Addition of a sulfur ylide to thiophene-containing chalcone analogues (Corey–Chaykovsky reaction) – General procedure

A mixture of trimethylsulfoxonium iodide (242 mg, 1.1 mmol) and sodium hydride (50 mg, 60% dispersion in mineral oil, washed with hexanes, 1.25 mmol) in dry dimethylsulfoxide (4 mL) was stirred at room temperature for 30 min, then the solution of a thiophene-containing chalcone

analogue (1 mmol) in dry dimethylsulfoxide (3–5 mL, depending on the solubility of the chalcone analogue) was added dropwise. The mixture was further stirred at room temperature for 3 h, then it was carefully diluted with water (30 mL), neutralized with 5% HCl, and worked-up as described in each case.

(2-(3-Benzyloxy-4-methoxyphenyl)cyclopropyl)-(thiophen-2-yl)-methanone (**43**)

This compound was obtained from 3-(3-benzyloxy-4-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **25** by following the general procedure. The mixture was then partitioned between water (70 mL) and ethyl acetate (10 mL), and then the aqueous phase was extracted again with ethyl acetate (10 mL). The combined organic phase was washed with water (2× 10 mL), dried over anhydrous Na_2SO_4, then the solvent was removed under reduced pressure to yield a residue that was recrystallized from ethanol to give yellowish crystals (290 mg, 80%), mp 111–112 °C; ^{1}H NMR ($CDCl_3$): δ 1.38–1.47 (m, 1H), 1.79–1.87 (m, 1H), 2.55–2.67 (m, 2H), 3.88 (s, 3H), 5.15 (s, 2H), 6.69–6.77 (m, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 3.8 and 5.0 Hz, 1H), 7.28–7.41 (m, 3H), 7.42–7.47 (m, 2H), 7.64 (dd, *J* = 1.0 and 5.0 Hz, 1H), 7.72 (dd, *J* = 1.0 and 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.8, 29.5, 30.0, 56.3, 71.4, 112.2, 113.3, 119.3, 127.5, 128.0, 128.3, 128.7, 131.8, 132.9, 133.6, 137.3, 145.0, 148.3, 148.9, 191.0; *Anal*. Calcd. for $C_{20}H_{20}O_3S$: C, 72.50; H, 5.53. Found: C, 72.29; H, 5.35.

(2-(4-(4-Bromobenzyloxy)phenyl)cyclopropyl)-(thiophen-2-yl)-methanone (**44**)

This compound was obtained from 3-(4-(4-bromobenzyloxy)phenyl)-1-(thiophen-2-yl)-2-propen-1-one **27** by following the general procedure. The resulting solid was then filtered and recrystallized from ethanol to give colorless crystals (340 mg, 82%), mp 135–136 °C; ^{1}H NMR ($CDCl_3$): δ 1.45–1.54 (m, 1H), 1.83–1.92 (m, 1H), 2.65–2.74 (m, 2H), 5.01 (s, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.14 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.64 (dd, *J* = 1.0 and 4.8 Hz, 1H), 7.79 (dd, *J* = 1.0 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.9, 29.2, 30.0, 69.5, 115.1, 122.0, 127.7, 128.3, 129.2, 131.9, 133.0, 133.6, 136.2, 145.0, 157.5, 191.1; *Anal*. Calcd. for $C_{21}H_{17}BrO_2S$: C, 61.02; H, 4.15. Found: C, 61.21; H, 4.00.

(2-(4-(3,4-Dichlorobenzyloxy)phenyl)cyclopropyl)-(thiophen-2-yl)-methanone (**45**)

This compound was obtained from 3-(4-(3,4-dichlorobenzyloxy)phenyl)-1-(thiophen-2-yl)-2-propen-1-one **28** by following the general procedure. The mixture was then partitioned between water (70 mL) and ethyl acetate (10 mL), and then the aqueous phase was extracted again with ethyl acetate (10 mL). The combined organic phase was washed with water (2× 10 mL), dried over anhydrous Na_2SO_4, then the solvent was removed under reduced pressure to yield a residue that was recrystallized from ethanol to give off-white crystals (335 mg, 83%), mp 126–127 °C; ^{1}H NMR ($CDCl_3$): δ 1.45–1.54 (m, 1H), 1.83–1.92 (m, 1H), 2.65–2.73 (m, 2H), 5.00 (s, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.13 (dd, *J* = 3.6 and 4.8 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 1.0 and 4.8 Hz, 1H), 7.79 (dd, *J* = 1.0 and 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.9, 29.1, 30.0, 68.8, 115.1, 126.6, 127.8, 128.3, 129.3, 130.7, 131.8, 132.1, 132.9, 133.3, 133.6, 137.4, 145.0, 157.2, 191.1; *Anal*. Calcd. for $C_{21}H_{16}Cl_2O_2S$: C, 62.54; H, 4.00. Found: C, 62.37; H, 4.16.

(2-(4-(3,4-Dichlorobenzyloxy)-3-methoxyphenyl)cyclopropyl)-(thiophen-2-yl)-methanone (**46**)

This compound was obtained from 3-(4-(3,4-dichlorobenzyloxy)-3-methoxyphenyl)-1-(thiophen-2-yl)-2-propen-1-one **29** by following the general procedure. The mixture was then partitioned between water (70 mL) and ethyl acetate (10 mL), and then the aqueous phase was extracted again with ethyl acetate (10 mL). The combined organic phase was washed with water (2× 10 mL), dried over anhydrous Na_2SO_4, then the solvent was removed under reduced pressure to give a residue that was recrystallized from ethanol to afford off-white crystals (365 mg, 85%), mp 115–116 °C; ^{1}H NMR ($CDCl_3$): δ 1.47–1.56 (m, 1H), 1.82–1.91 (m, 1H), 2.65–2.74 (m, 2H), 3.97 (s, 3H), 5.06 (s, 2H), 6.64 (dd, *J* = 2.0 and 8.4 Hz, 1H), 6.73–6.81 (m, 2H), 7.14 (dd, *J* = 4.0 and 4.8 Hz, 1H), 7.26 (dd, *J* = 1.8 and 8.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.65 (dd, *J* = 1.0 and 4.8 Hz, 1H), 7.80 (dd, *J* = 1.0 and 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.8, 29.5, 30.1, 56.1, 70.1, 111.1, 114.8, 118.1, 126.6, 128.3, 129.3, 130.7, 131.9, 132.0, 132.8, 133.7, 134.3, 137.7, 145.0, 146.6, 149.9, 191.0; *Anal*. Calcd. for $C_{22}H_{18}Cl_2O_3S$: C, 60.98; H, 4.19. Found: C, 61.22; H, 4.03.

CONCLUSIONS

Out of the numerous reactions in which chalcone analogues can act as substrates, the thia-Michael addition of 4-chlorothiophenol, the catalytic reduction using hydrogen in the presence of Pd/C, the Stetter reaction with thiophene-2-carboxaldehyde, and the Corey-Chaykovsky cyclopropanation using dimethylsulfoxonium methylide have been successfully employed in the generation of the corresponding adducts starting from several novel thiophene-containing chalcone analogues. The structure of these newly synthesized, hitherto unknown 3-(4-chlorophenylmercapto)-1-propanones, 1,3-diaryl-1-propanones, 1,2,4-triaryl-1,4-butanediones and 1-(2-thienoyl)-2-arylcyclopropanes has been established using NMR spectroscopy. The adducts reported in this study are useful as intermediates in the preparation of a variety of thiophene-containing chemical entities, or could present interesting biological properties.

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