Bioorganic & Medicinal Chemistry 18 (2010) 4178–4186

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

A new class of potential anti-tuberculosis agents: Synthesis and preliminary evaluation of novel acrylic acid ethyl ester derivatives

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ARTICLE INFO

Article history:
Received 5 March 2010
Revised 2 May 2010
Accepted 4 May 2010
Available online 7 May 2010

Keywords:
Anti-tuberculosis
Mycobacterium smegmatis
Mycobacterium tuberculosis
Vinylthioether of acrylic acid ethyl ester
Vinylether of acrylic acid ethyl ester
Vinylamines of acrylic acid ethyl ester

ABSTRACT

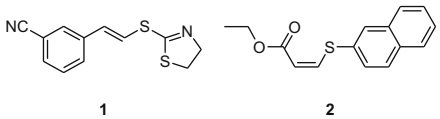
Novel acrylic acid ethyl ester derivatives were synthesized and evaluated as potential agents against *Mycobacterium* species. A versatile and efficient copper-catalyzed coupling process was developed and used to prepare a library of substituted acrylic acid ethyl ester analogs. Minimum inhibitory concentration assays indicated that two of these compounds **3** and **4** have greater in vitro activity against *Mycobacterium smegmatis* than rifampin, one of the current, first-line anti-mycobacterial chemotherapeutic agents. Moreover, members of this new class of compounds appear to exhibit a specific anti-mycobacterial effect and do not inhibit the growth of the other Gram-positive or Gram-negative species tested.

1. Introduction

Tuberculosis (TB) is an airborne infectious disease caused by species found in the *Mycobacterium tuberculosis* complex that includes *M. tuberculosis*. The World Health Organization (WHO) estimates that 9.27 million new cases of TB occurred in 2007.[1] The TB epidemic has been further complicated by the rapid spread of Human Immunodeficiency Virus (HIV) and the emergence of multidrug resistant (MDR) and extensively drug resistant (XDR) forms. Tuberculosis has again become a significant threat to global health.[1] Current first-line treatment of drug-sensitive tuberculosis infections consists of a four-drug regimen that includes rifampin, isoniazid, pyrazinamide, and ethambutol. When effective, this treatment requires a minimum of six months to completely eradicate the infection.[2] Due to the emergence of drug-resistant strains, there has been a rise in transmission rates, treatment failures, and mortality due to TB.[3,4] Consequently, the development of alternative chemotherapeutics for *M. tuberculosis* infections is needed.

Previously, members of a class of stilbene, phenoxystyrene, and phenothiostyrene analogs were reported to exhibit promising antibacterial activity against Gram-positive bacteria.[5] In addition to inhibition of the growth of a range of Gram-positive bacteria, phenothiostyrene **1** (Fig. 1) was found to also exhibit a minimum inhibitory concentration (MIC) of 64 μg/mL against *Mycobacterium smegmatis*, a safer surrogate of the clinically significant and more virulent *M. tuberculosis*.[6] In early efforts to increase the molecular diversity in the study of these antimicrobial structure–activity relationships (SAR), certain acrylic acid ethyl esters such as **2** were also synthesized, and this lead compound exhibited a promising MIC value of 64 μg/mL against *M. smegmatis*.[6]

Hence, a library of vinyl-substituted derivatives of acrylic acid ethyl esters (Schemes 1 and 2) was designed to evaluate the effect of structural changes on anti-mycobacterial activity. First, various thioacrylate analogs **3–12** were synthesized to determine the effects of electron-rich (**3**, **9**, **10**, and **11**), electron-deficient (**4–7**), and bulky (**6**, **8**, and **9**) substituents on the activity relative to **2**. Additional analogs **13–26** contained an oxygen atom in place of



1 2

Figure 1. Lead compounds.

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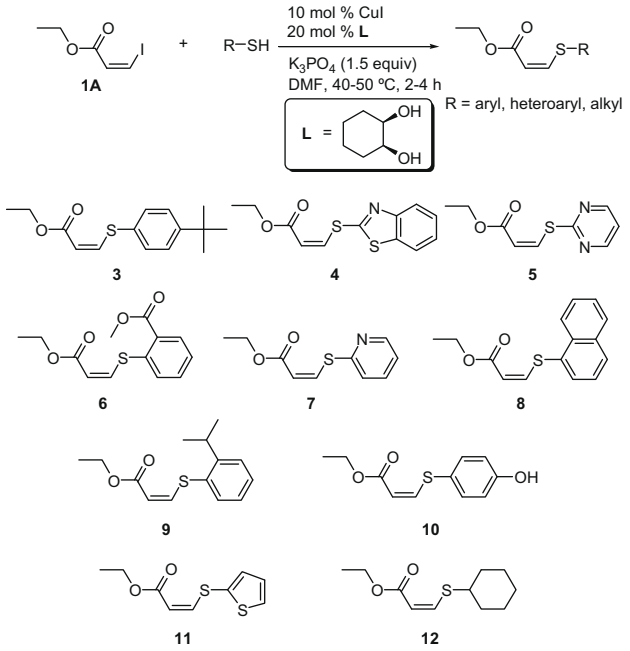
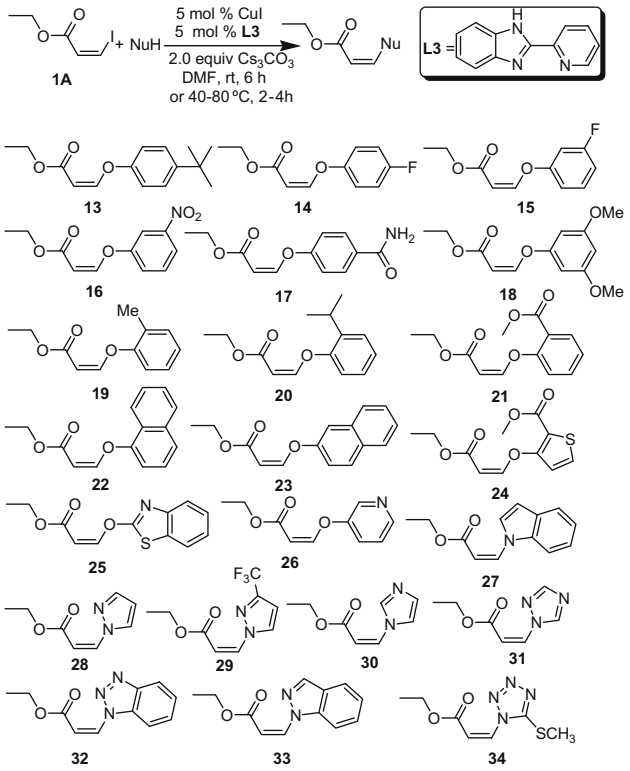
doi:10.1016/j.bmc.2010.05.016



Scheme 1. Synthesis of vinyl thioether derivatives of acrylic acid ethyl ester **1A**.



Scheme 2. Synthesis of vinyl ether and vinyl amine analogues of acrylic acid ethyl ester **1A**.

the sulfur functionality. This structural change altered the bond angle slightly, from ~105° for the C–S–C bond, to ~120° for the C–O–C bond, changing the overall conformation of the ethers with respect to the thioethers. This also permitted alteration of the electronic character adjacent to the double bond from sulfur to oxygen. Finally, a series of cyclic vinylamines **27–34** was prepared using the same methods, and various *N*-heterocycles were obtained such that the amine attached to the acrylate system resulted in slightly truncated molecules. Similar derivatives have been reported to possess anti-retroviral properties.[7] In all cases, use of the commercially available ethyl *cis*-3-iodo-acrylate **1A** enabled rapid generation of this library of substituted acrylates using a new copper-mediated coupling process.[8,9]

2. Results and discussion

2.1. Chemistry

The arylthioacrylate analogs **3–11** and the alkylthioacrylate **12** were synthesized by employing copper-catalyzed coupling processes that were developed recently (Scheme 1) with *cis*-1,2-hexanediol serving as the ligand.[8] This process involved a cross-coupling reaction between the ethyl *cis*-3-iodo-acrylate **1A** and the thiophenol or alkyl mercaptan. As shown in the sequence outlined in Scheme 1, this general copper-mediated coupling method was employed to construct all of the new substituted thioacrylate ester analogs.

It was found that the specific protocol used to prepare the thioethers, in which the ligand was *cis*-cyclohexanediol, did not prove efficient in the coupling of substituted phenols with vinyl iodides. Thus, a more efficient copper catalytic system involving the new ligand, 2-pyridin-2-yl-1*H*-benzoimidazole (**L3**), was developed (Scheme 2).[9–12] This modified approach provided ready access to the substituted phenoxyacrylates **13–26**. In addition, when this same ligand was used in the cross coupling of various *N*-heterocycles with *cis*-3-iodo-acrylate, **1A**, this process afforded substituted vinylamines **27–34**, illustrating the versatility and usefulness of this new catalytic coupling system (Scheme 2).

2.2. Biology

Antimicrobial activity determined using standard minimum inhibitory concentration (MIC) assays indicated measurable anti-mycobacterial activity in 53% of the compounds tested (Table 1). Two agents (**29** and **31**) were insoluble (in DMSO) and were not assayed. Relative to rifampin, six analogs (**2**, **5**, **6**, **10**, **16**, and **22**) showed similar activity, while two analogs (**3** and **4**) had activity that surpassed that of the positive control. Both of these compounds demonstrated enhanced activity as compared to the other thioacrylate analogs. Of these two, the agent containing an electron-deficient group (**4**) demonstrated twice the potency of rifampin, whereas the compound with the electron-rich substituent (**3**) demonstrated a four-fold increase in potency over rifampin. To further assess the anti-mycobacterial potential of these two most potent agents, they also were tested against *M. tuberculosis* (Table 2). A green fluorescent protein (GFP)-based assay was used to measure the efficacy of **3** and **4** in the inhibition of the growth of *M. tuberculosis*.[13] In those assays, both isoniazid and rifampin were employed as the positive controls, and these had respective MIC values of 0.25 μg/mL and <0.03 μg/mL. The MIC values of **3** and **4** were both found to be 25 μg/mL. Finally, **3** and **4** were each assayed against five additional *Mycobacterium* strains: *Mycobacterium fortuitum, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium avium,* and *Mycobacterium intracellulare*. In this series, the respective MIC values for **3** were 4, 16, 8, 64, and 128 μg/mL; and the respective MIC values for **4** were 16, 8, 8, 64, and 16 μg/mL.

Beyond these anti-mycobacterial activities, the entire series of compounds showed essentially no activity against either the Gram positive (*Staphylococcus aureus*, *Bacillus cereus*) or Gram-negative (*Escherichia coli*) bacteria investigated (Table 1). Indeed, only the nitro compound **16** showed activity beyond the *M. smegmatis* assays, with an MIC of 64 μg/mL against *S. aureus*.

Table 1
Minimum inhibitory concentration (MIC) values for acrylic acid ethyl ester analogs (μg/mL)

Compd	*M. smegmatis*	*S. aureus* ATCC 29213	*B. cereus*	*E. coli* ATCC 29522
1	64	>128	>128	>128
2	64	128	>128	>128
3	16	>128	>128	>128
4	32	>128	>128	>128
5	64	>128	>128	>128
6	64	>128	>128	>128
7	128	>128	>128	>128
8	128	>128	>128	>128
9	>128	>128	>128	>128
10	64	128	128	>128
11	128	>128	>128	>128
12	>128	>128	>128	>128
13	128	>128	>128	>128
14	>128	>128	>128	>128
15	>128	>128	>128	>128
16	64	64	>128	>128
17	>128	>128	>128	>128
18	128	>128	>128	>128
19	>128	>128	>128	>128
20	>128	>128	>128	>128
21	>128	>128	>128	>128
22	64	>128	>128	>128
23	128	>128	>128	>128
24	>128	>128	>128	>128
25	128	>128	>128	>128
26	>128	>128	>128	>128
27	>128	>128	>128	>128
28	>128	>128	>128	>128
29	ND[b]	ND[b]	ND[b]	ND[b]
30	>128	>128	>128	>128
31	ND[b]	ND[b]	ND[b]	ND[b]
32	>128	>128	>128	>128
33	>128	>128	>128	>128
34	128	>128	>128	>128
Rifampin[a]	64	ND[b]	ND[b]	ND[b]

[a] Positive control.
[b] ND = not determined.

Table 2
MIC values for **3** and **4** against *Mycobacterium* strains (μg/mL)

Compd	*M. tuberculosis*	*M. fortuitum*	*M. kansasii*	*M. chelonae*	*M. avium*	*M. intracellulare*
3	25	4	16	8	64	128
4	25	16	8	8	64	16
Isoniazid[a]	0.25	ND[b]	ND[b]	ND[b]	ND[b]	ND[b]
Rifampin[a]	<0.03	ND[b]	ND[b]	ND[b]	ND[b]	ND[b]

[a] Positive control.
[b] ND = not determined in our assays.

Furthermore, the cytotoxicities of the two most active analogs to ward putative host cells were assessed using a tryptan exclusion assay employing murine J774A.1 cells.[14] In this assay, the IC_{50} values obtained for **3** and **4** were 150 μg/mL and 200 μg/mL, respectively.

3. Conclusion

A series of acrylic acid ethyl esters with vinyl thioether, ether, and cyclic amine substituents were prepared using a new copper-mediated coupling process. These compounds were designed to establish early structure-activity relationships among this class of compounds, which have shown promising anti-mycobacterial activity. Of particular importance is these small molecules appear to be highly selective for the inhibition of the growth of mycobacteria while not affecting any of the other types of microorganisms tested. Of the 33 new compounds prepared, eight inhibited the growth of *M. smegmatis* at concentrations equivalent to, or better than, the primary anti-mycobacterial agent currently used to treat clinical TB infections, rifampin. Aryl vinyl thioethers **3** and **4** exhibited the strongest anti-*M. smegmatis* activity, and these were therefore assayed against the more virulent strain, *M. tuberculosis*, demonstrating MIC values of 25 μg/mL each, indicating that, in this assay, these new lead compounds are not as potent as the existing drugs isoniazid and rifampin. However, these two compounds also possessed generally good in vitro inhibitory activities against the five other less common *Mycobacterium* species tested and did not effect any other types of cells. This activity may signify a new mechanism of action for these readily available small molecules.

With respect to these nascent SAR studies, it was clear from examination of the initial lead structures **1** and **2** that a planar molecule with lipophilic substituents in ring B likely would be more active. In keeping with this hypothesis, the series of thio substituted acrylate esters **3**–**12** were prepared and evaluated against *M. smegmatis* and found to be much more active than the analogous oxygen or nitrogen substituted analogs (compare the activities of **2**, **3**, and **4** with **13**, **23**, and **25**, and also note that none of the nitrogen based acrylate esters demonstrated activity at the concentrations tested). Because the electron density of the sulfur atom is similar to carbon, it is tempting to speculate that the lipophilic character at that position is important, but more examples will need to be evaluated before a reliable conclusion can be reached. Further, examination of the aromatic moiety in the most active analogues **2**, **3**, **4**, **5**, **6**, and **10** indicates that both lipophilic aromatic rings and more polar aromatic rings demonstrate activity. Importantly, all of these compounds showed activity only against *Mycobacterium* species (seven different strains) and not against other Gram-positive or Gram-negative bacteria. This suggests a novel, *Mycobacterium*-selective mechanism of action for **2**, **3**, **4**, **5**, **6**, and **10**, which indicates that these acrylic esters warrant further study.

In general, these promising results suggest that small ligands such as **3** and **4** could potentially be developed into viable alternatives to current front line therapies used in the treatment of TB and other less common infections caused by *Mycobacterium* species. Furthermore, it appears that an appropriately substituted acrylic acid ethyl ester scaffold could serve as a promising launch point for the development of new chemotherapeutic agents with utility in treating *Mycobacterium* infections. These small molecules are much easier to synthesize than those agents employed in front-line therapy including rifampin. Further refinement and a continuation of these SAR studies are now underway.

4. Experimental

4.1. Chemistry

Copper(I) iodide (99.99% purity), 1,2-cyclohexanediol (**L**, 99% purity) and DMF (anhydrous, 99.8% purity) were purchased from Aldrich Chemical Co. and employed as is. Analytically pure ligand **L3** was prepared and characterized as previously reported.[9] All sulfides, phenols, and amines were used as received from Aldrich or Alfa Aesar without further purification. Potassium phosphate was purchased from Alfa Aesar (97% purity). Caesium carbonate (99% purity) was purchased from Aldrich Chemical Co. Silica gel (Dynamic Adsorbents, 230–400 mesh) for flash chromatography was utilized to purify the analogues. The ^{1}H and ^{13}C NMR data were obtained on a Bruker Spectrospin 300 MHz and GE500 MHz instruments, with chemical shifts reported relative to TMS. Some yields were determined by HPLC analysis on a Hewlett Packard 1100 Series instrument equipped with a silica column (ISCO, 5 μm packing, 4.6 × 250 mm). The HRMS and GC/MS spectral data were performed by the Laboratory for Biological Mass Spectrometry, Texas A&M University, College Station, TX 77843 and by the Laboratory

for Mass Spectrometry, University of Kansas, Lawrence, KS 66045–7582, USA.

4.1.1. Procedure for the preparation of ligand L3 (2-pyridin-2-yl-1*H*-benzoimidazole, L3)[9,12]

The pyridine-2-carboxaldehyde (2.0 equiv) in dry methanol (0.5 M) was added dropwise to a suspension of anhydrous Na_2SO_4 (1.5 equiv) and *o*-phenylenediamine (1.0 equiv) in dry methanol (0.5 M) under argon at rt. The reaction mixture that resulted was stirred at rt for 5 h. The reaction mixture was then filtered through a sintered glass funnel, and the filtrate was concentrated in vacuo. The crude material was suspended in hot, dry CH_3CN and allowed to cool to rt to precipitate the ligand, **L3**. The precipitate was then recrystallized from CH_3OH to afford pure L3 (84% yield). The spectral data obtained for **L3** were in excellent agreement with that reported in the literature.[9,12] ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.1 (1H, s, NH), δ 8.73 (1H, m, HAr) δ 8.34 (1H, d, J = 8.1 Hz, HAr), δ 7.99 (1H, dt, J = 7.7, 1.7 Hz, HAr), δ 7.70–7.72 (1H, m, HAr), δ7.52–7.57 (1H, m, HAr), δ 7.51 (1H, dddd J = 7.5, 4.9, 1.0 Hz, HAr), δ 7.18–7.27 (2H, m, HAr) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 150.8, 149.4 148.5, 143.9, 137.5, 134.9, 124.7, 123.2, 121.9, 121.4, 119.3, 112.1 ppm. White solid, mp 222.9 °C (lit.: 224.0 °C)[9] CHN: calcd for $C_{12}H_9N_3$; C, 73.82; H, 4.65; N, 21.52. Found: C, 73.46; H, 4.66; N 21.34.

4.1.2. General procedure (A) for the Cu-catalyzed cross coupling of vinyl iodides (1A) with thiols

An oven dried round bottom flask which contained a magnetic stir bar was sealed with a rubber septum. This flask was evacuated and backfilled with argon and the sequence was repeated three times while cooling to rt. The round bottom flask was then charged with anhydrous potassium phosphate (1.5 equiv), copper (I) iodide (10 mol%), *cis*-1,2-cyclohexanediol **L** (20 mol%) and dry DMF (2 mL). The solution that resulted was stirred for 5–10 min at rt. The reaction mixture took on a light green color within 3–5 min. The reaction vessel was then evacuated and backfilled with argon one more time before adding the thiol and the vinyl iodide. The appropriate thiol (1.2 equiv) was added to the reaction mixture through a rubber septum, and the mixture was stirred for another 5 min at rt. The vinyl iodide (1.0 equiv) of choice was added to the resulting reaction mixture through a rubber septum in a minimum amount of dry DMF. The contents of the reaction mixture were heated to 30–60 °C for 0.5–4 h, depending on the substrate. The reaction mixture was then cooled to rt and filtered through a pad of silica gel to remove any insoluble residue. The pad of silica gel was washed with ethyl acetate (100 mL). The combined filtrate was washed with brine (4 x 50 mL) and dried (Na_2SO_4), after which it was concentrated *in vacuo* on a rotatory evaporator. The concentrated crude oil was purified by flash column chromatography on silica gel using the eluent (2–10%) ethyl acetate and hexane (depending on the substrate) to obtain the analytically pure target ligand (84–98%).

4.1.3. General procedure (B) for the Cu-catalyzed cross coupling of vinyl iodides (1A) with phenols and cyclic amines

An oven dried round bottom flask which contained a magnetic stir bar was sealed with a rubber septum and then evacuated and backfilled with argon (the sequence was repeated three times) while cooling to rt. The round bottom flask was then charged with anhydrous cesium carbonate (2.0 equiv), copper (I) iodide (5 mol%), **L3** (5 mol%) and DMF (2 mL). The resulting solution was stirred for 5–10 min at rt. The reaction mixture took on a light green color within 3–5 min. The reaction vessel was evacuated and backfilled with argon one more time before adding the phenol or amine, and the vinyl iodide. The appropriate phenol or cyclic amine (1.5 equiv) was added to the reaction mixture through a rubber septum, and the mixture was allowed to stir for an additional 5 min at rt. Vinyl iodide **1A** (1.0 equiv), in a minimal amount of dry DMF, was added to the reaction mixture through a rubber septum. The contents of the reaction flask were heated from rt to 40 °C for 0.5–6 h, depending on the substrate. The reaction mixture was then cooled to rt and filtered through a pad of silica gel to remove any insoluble residue. The pad of silica gel was washed with ethyl acetate and hexane (40:60) (100 mL). The combined filtrates were washed with brine (5 x 50 mL) and dried (Na_2SO_4), after which it was concentrated *in vacuo* on a rotatory evaporator. The concentrated crude oil was purified by flash column chromatography on silica gel, using the eluent (2–20%) ethyl acetate and hexane (depending on the substrate) to obtain the pure target compound (81–98%).

4.1.4. Preparation of (*Z*)-3-(naphthalen-2-ylthio)-acrylic acid ethyl ester (2)

General procedure **A** was followed (2 h). Ethyl *cis*-3-iodo-acrylate (90 mg, 0.40 mmol), 2-naphthalenethiol (84.9 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis*-1,2-cyclohexanediol **L** (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain the thioether **2** as a pale yellow oil. Column chromatography (solvent 10% EtOAc in hexane) provided pure **2** (98 mg, 95% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (1H, s, HAr), δ 7.93–7.81 (3H, m, HAr), δ 7.58–7.50 (3H, m, HAr), δ 7.41 (1H, d, J = 10.0 Hz, HC(S)=CH), δ 5.99–5.96 (1H, d, J = 10 Hz, HC=CH-S), δ 4.35–4.28 (2H, q, J = 7.2 Hz, H_2C-CH_3), δ 1.27 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}CNMR:166.6, 149.4, 133.4, 133.2, 132.5, 130.7, 129.3, 127.6, 126.6, 125.4, 113.2, 60.3, 14.2. HRMS (ESI) $(M+H)^+$, calcd for $C_{15}H_{15}O_2S$ 259.0793; found 259.0789.

4.1.5. Preparation of (*Z*)-3-(4-*tert*-butyl-phenylsulfanyl)-acrylic acid ethyl ester (3)

General procedure (**A**) was followed (2 h). Ethyl *cis*-3-iodo-acrylate **1A** (90 mg, 0.40 mmol), 4-tert-butylbenzenethiol (87.8 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis*-1,2-cyclohexanediol **L** (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain thioether **3** as a colorless oil. Column chromatography (solvent 3–5% EtOAc in hexane) provided pure **3** (103.6 mg, 98% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ7.46–7.39 (4H, m, HAr), δ 7.28 (1H, d, J = 10.1 Hz, HC(S)=CH), δ 5.90 (1H, d, J = 10.1 Hz, HC=CH-S), δ 4.27 (2H, q, J = 7.1 Hz, H_2C-CH_3), δ 1.37–1.32 (12H, m, H_3C-CH_2 & $(H_3C)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 151.5, 150.4, 132.7, 131.0, 126.3, 112.9, 60.2, 34.5, 31.1, 14.3. HRMS (ESI) $(M+H)^+$, calcd for $C_{15}H_{21}O_2S$ 265.1262; found 265.1259.

4.1.6. Preparation of (*Z*)- 3-(benzothiazol-2-ylsulfanyl)-acrylic acid ethyl ester (4)

General procedure (**A**) was followed (4 h). Ethyl *cis*-3-iodo-acrylate **1A** (90 mg, 0.40 mmol), benzothiazole-2-thiol (88.6 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis*-1,2-cyclohexanediol **L** (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain the thioether **4** as a colorless oil. Column chromatography (solvent 10% EtOAc in hexane) provided pure **4** (101 mg, 95% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, d, J = 10.0 Hz, HC(S)=CH), δ 7.96 (1H, d, J = 8.2 Hz, HAr), δ 7.82 (1H, d, J = 7.8 Hz, HAr), δ 7.51 (1H, t, J = 7.6 Hz, HAr), δ 7.37 (1H, t, J = 7.5 Hz, HAr), δ 6.19 (1H, d, J = 10.0 Hz, HC=CH-S), δ 4.30 (2H, q, J = 7.2 Hz, J = 21.4 Hz, H_2C-CH_3), δ 1.36 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 164.2, 152.6, 140.6, 135.4, 126.3, 124.9, 122.1, 121.2, 115.6, 60.8, 14.2. HRMS (ESI) $(M+H)^+$, calcd for $C_{12}H_{12}NO_2S_2$ 266.0309; found 266.0311.

4.1.7. Preparation of (*Z*)-3-(pyrimidin-2-ylsulfanyl)-acrylic acid ethyl ester (5)

General procedure (**A**) was followed (4 h). Ethyl *cis*-3-iodo-acrylate **1A** (90 mg, 0.40 mmol), 2-pyrimidinethiol (59.4 mg,

0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis* 1,2-cyclohexanediol **L** (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain the thioether **5** as a colorless oil. Column chromatography (solvent, 3–5% EtOAc in hexane) provided pure **5** (78.2 mg, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64–8.61 (2H, m, HAr), δ 8.53 (1H, d, J = 10.4 Hz, HC(S)=CH), δ 7.12 (1H, t, J = 4.8 Hz, HAr), δ 6.11 (1H, d, J = 10.4 Hz, HC=CH-S), δ 4.28 (2H, q, J = 7.1 Hz, H_2C-CH_3), δ 1.34 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 166.4, 157.7, 141.4, 117.9, 114.9, 60.5, 14.2. HRMS (ESI) $(M+Li)^+$, calcd for $C_9H_{10}N_2O_2SLi$ 217.0623; found 217.0621.

4.1.8. Preparation of (*Z*)-2-(2-ethoxycarbonyl-vinylsulfanyl)-benzoic acid methyl ester (6)

General procedure (**A**) was followed (2 h). Ethyl *cis*-3-iodo-acrylate **1A** (90 mg, 0.40 mmol), 2-mercapto-benzoic acid methyl ester (89.2 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis* 1,2-cyclohexanediol **L** (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain thioether **6** as a colorless solid. Column chromatography (solvent 2–3% EtOAc in hexane) provided pure **6** (99 mg, 93% yield)**:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (1H, d, J = 7.8 Hz, HAr), δ 7.59–7.49 (2H, m, HAr), δ 7.38 (1H, t, J = 7.5 Hz, HAr), δ 7.26 (1H, d, J = 10.2 Hz, HC(S)=CH), δ 5.97 (1H, d, J = 10.2 Hz, HC=CH-S), δ 4.27 (2H, q, J = 7.2 Hz, J = 21.4 Hz, H_2C-CH_3), δ 3.94 (3H, s, H_3C-O), δ 1.35 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 166.2, 148.5, 137.8, 132.1, 130.5, 127.5, 114.4, 60.3, 52.3, 14.3. HRMS (ESI) $(M+Li)^+$, calcd for $C_{13}H_{14}O_4SLi$ 273.0773; found 273.0769.

4.1.9. Preparation of (*Z*)-3-(pyridin-2-ylsulfanyl)-acrylic acid ethyl ester (7)

General procedure (**A**) was followed (4 h). Ethyl *cis*-3-iodo-acrylate (**1A**) (90 mg, 0.40 mmol), pyridine-2-thiol (58.9 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis* 1,2-cyclohexanediol **L** (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain the thioether **7** as a colorless solid. Column chromatography (solvent 10% EtOAc in hexane) provided pure **7** (81 mg, 97% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (2H, d, J = 10.2 Hz, HAr), δ 7.60 (1H, t, J = 7.7 Hz, HAr), δ 7.34–7.28 (1H, m, HC(S)=CH), δ 7.16–7.12 (1H, m, HAr), δ 6.11 (1H, d, J = 10.2 Hz, HC=CH-S), δ 4.27 (2H, q, J = 7.2 Hz, J = 21.4 Hz, H_2C-CH_3), δ 1.34 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 155.2, 149.5, 141.8, 136.7, 123.2, 121.2, 113.8, 60.3, 14.2. HRMS (ESI) $(M+H)^+$, calcd for $C_{10}H_{12}NO_2S$ 210.0589; found 210.0591.

4.1.10. Preparation of (*Z*)-3-(naphthalen-1-ylthio)-acrylic acid ethyl ester (8)

General procedure (**A**) was followed (2 h). Ethyl *cis*-3-iodo-acrylate **1A** (90 mg, 0.40 mmol), 1-naphthalenethiol (84.9 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis* 1,2-cyclohexanediol (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain the thioether **8** as a colorless solid. Column chromatography (solvent 10% EtOAc in hexane) provided pure **8** (96 mg, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (1H, d, J = 8 Hz, HAr), δ 7.92 (2H, d, J = 8.4 Hz, HAr), δ 7.81 (1H, d, J = 6.9 Hz, HAr), δ 7.62–7.54 (2H, m, HAr), δ 7.51–7.46 (1H, m, HAr), δ 7.15 (1H, d, J = 10 Hz, HC(S)=CH), δ 5.94 (1H, d, J = 10 Hz, HC=CH-S), δ 4.31 (2H, q, J = 7.1 Hz, H_2C-CH_3), δ 1.34 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}CNMR:166.6, 150.7, 134.1, 133.3, 132.1, 129.8, 128.5, 127.0, 126.4, 125.5, 113.2, 60.2, 14.3. HRMS (ESI) $(M+H)^+$, calcd for $C_{15}H_{15}O_2S$ 258.0715; found 258.0789.

4.1.11. Preparation of (*Z*)-3-(2-Isopropyl-phenylsulfanyl)-acrylic acid ethyl ester (9)

General procedure (**A**) was followed (2 h). Ethyl *cis*-3-iodo-acrylate **1A** (90 mg, 0.40 mmol), 2-isopropyl-benzenethiol (80.7 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis* 1,2-cyclohexanediol, **L** (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain the thioether **9** as a colorless oil. Column chromatography solvent (2–3% EtOAc in hexane) provided pure **9** (98 mg, 98% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (1H, d, J = 7.6 Hz, HAr), δ 7.37–7.35 (2H, m, HAr), δ 7.25–7.21 (1H, m, HAr), δ 7.16 (1H, d, J = 10.0 Hz, HC(S)=CH), δ 5.91 (1H, d, J = 10.0 Hz, HC=CH-S), δ 4.28 (2H, q, J = 7.0 Hz, J = 21.4 Hz, H_2C-CH_3), δ 3.63–3.58 (1H, m, HC-$(CH_3)_2$), δ 1.35 (3H, t, J = 7.1 Hz, H_3C-CH_2), δ 1.25 (6H, d, J = 6.8 Hz, H_3C-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 150.9, 150.2, 134.4, 133.2, 129.1, 126.7, 125.9, 113.0, 60.1, 30.5, 23.5, 14.3. HRMS (ESI) $(M+Li)^+$, calcd for $C_{14}H_{18}O_2SLi$ 257.1188; found 257.1190.

4.1.12. Preparation of (*Z*)-3-(4-hydroxy-phenylsulfanyl)-acrylic acid ethyl ester (10)

The general procedure (**A**) was followed (2 h). Ethyl *cis*-3-iodo-acrylate **1A** (90 mg, 0.40 mmol), 4-hydroxythiophenol (66.9 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis*-1,2-cyclohexanediol (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain the thioether **10** as a colorless semi-solid. Column chromatography solvent (15% EtOAc in hexane) provided pure **10** (81 mg, 91% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.48 (2H, d, J = 7.7 Hz, HAr), δ 7.20–7.17 (1H, d, J = 10 Hz, HC(S)=CH), δ 6.91–6.87 (2H, d, J = 7.7 Hz, HAr),δ 5.88–5.84 (1H, d, J = 10 Hz, HC=CH-S), δ 4.30–4.25 (2H, q, J = 7.1 Hz, H_2C-CH_3), δ 1.33 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}CNMR: 1665, 155.3, 146.1, 130.9, 130.6, 127.3, 117.2, 116.3, 113.7, 61.4, 14.8. HRMS (ESI) $(M-1)^-$ calcd for $C_{11}H_{12}O_3S$ 223.0507; found 223.0429.

4.1.13. Preparation of (*Z*)-3-(thiophen-2-ylthio)-acrylic acid ethyl ester (11)

The general procedure (**A**) was followed (2 h). Ethyl *cis*-3-iodo-acrylate **1A** (90 mg, 0.40 mmol), cyclohexanethiol (61.6 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis* 1,2-cyclohexanediol, **L** (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain thioether **11** as a colorless oil. Column chromatography solvent (3–5% EtOAc in hexane) provided pure **11** (81 mg, 94% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (1H, d, J = 17.6 Hz, HC(S)=CH), δ 5.84 (1H, d, J = 10.2 Hz, HC=CH-S), δ 4.21 (2H, q, J = 7.0 Hz, J = 21.4 Hz, H_2C-CH_3), δ 2.88–2.81 (5H, m, HCy), δ 2.06–1.38 (5H, m, HCy), δ 1.30 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 148.2, 112.5, 59.9, 47.5, 33.5, 25.7, 25.3, 14.3. HRMS (ESI) $(M+H)^+$, calcd for $C_9H_{11}O_2S_2$ 215.0122; found 215.0127.

4.1.14. Preparation of (*Z*)-3-cyclohexylsulfanyl-acrylic acid ethyl ester (12)

The general procedure (**A**) was followed (2 h). Ethyl *cis*-3-iodo-acrylate **1A** (90 mg, 0.40 mmol), cyclohexanethiol (61.6 mg, 0.53 mmol), CuI (7.6 mg, 0.040 mmol), *cis* 1,2-cyclohexanediol, **L** (8.2 mg, 0.080 mmol), K_3PO_4 (127 mg, 0.60 mmol) and DMF (2.0 mL) were stirred at 40–50 °C to obtain the thioether **12** as a colorless oil. Column chromatography solvent (3–5% EtOAc in hexane) provided pure **12** (81 mg, 94% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (1H, d, J = 17.6 Hz, HC(S)=CH), δ 5.84 (1H, d, J = 10.2 Hz, HC=CH-S), δ 4.21 (2H, q, J = 7.0 Hz, J = 21.4 Hz, H_2C-CH_3), δ 2.88–2.81 (5H, m, HCy), δ 2.06–1.38 (5H, m, HCy), δ 1.30 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 148.2, 112.5, 59.9, 47.5, 33.5, 25.7, 25.3, 14.3. HRMS (ESI) $(M+H)^+$, calcd for $C_{11}H_{18}O_2S$ 215.1106; found 215.1107.

4.1.15. Preparation of (*Z*)- 3-(4-*tert*-butyl-phenoxy)-acrylic acid ethyl ester (13)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodo-acrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3

(67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), 4-*tert*-butylphenol (99.1 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **13** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **13** (101.6 mg, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (1H, d, J = 12.2 Hz, H(O)C=CH), δ 7.43–7.38 (2H, m, HAr), δ 7.04–6.99 (2H, m, HAr), δ 5.54 (1H, d, J = 12.2 Hz, HC=C(O)H), δ 4.21 (2H, q, J = 3.6 Hz, J = 10.7 Hz, H_2C-CH_3); δ 1.34 (9H, s, H_3C-C-), δ 1.30 (3H, t, J = 7.1 Hz, H_3C–CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 158.5, 152.6, 147.2, 126.5, 117.4, 101.6, 60.1, 35.3, 32.6, 15.5. HRMS (ESI) $(M+H)^+$, calcd for $C_{15}H_{21}O_3$ 249.1491; found 249.1502.

4.1.16. Preparation of (*Z*)-3-(4-fluoro-phenoxy)-acrylic acid ethyl ester (14)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), 4-fluorophenol (74.0 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **14** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **14** (77.8 mg, 84% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (1H, d, J = 12.2 Hz, HC(O)=CH), δ 7.12–7.02 (4H, m, HAr), δ 5.52 (1H, d, J = 12.2 Hz, HC=CH–O), δ 4.21 (2H, q, J = 3.6 Hz, J = 10.7 Hz, H_2C–CH_3), δ 1.30 (3H, t, J = 7.1 Hz, H_3C–CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 159.2, 119.7, 119.6, 116.6, 116.3, 102.1, 60.0, 14.2. HRMS (EI), calcd for $C_{11}H_{11}O_3$ 210.0692; found 210.0690.

4.1.17. Preparation of (*Z*)-3-(3-fluorophenoxy)-acrylic acid ethyl ester (15)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), 3-fluorophenol (74.0 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **15** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **15** (72.1 mg, 78% yield): ^{1}H NMR (300 MHz, $CDCl_3$): 7.79 (1H, d, J = 12 Hz, HC(O)=CH), δ 7.37–7.29 (1H, m, HAr), δ 6.95–6.80 (3H, m, HAr), δ 5.64 (1H, d, J = 12 Hz, HC=CH(O)), δ 4.23 (2H, q, J = 7.1 Hz, J = 14.2 Hz, H_2CCH_3), δ 1.28 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 165.9, 157.8, 130.8, 113.4, 111.9, 106.1, 103.1, 60.1, 14.2. HRMS (ESI) $(M+H)^+$, calcd for $C_{11}H_{12}FO_3$ 211.0770; found 211.0767.

4.1.18. Preparation of (*Z*)-3-(3-nitrophenoxy)-acrylic acid ethyl ester (16)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), 3-nitrophenol (91.8 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **16** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **16** (67.8 mg, 65% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10–8.07 (1H, m HAr), 7.96 (1H, t, J = 2.2 Hz, HAr), 7.82 (1H, d, J = 12 Hz, HC(O)=CH), δ 7.59 (1H, t, J = 8.2 Hz, HAr), δ 7.46–7.42 (1H, m HAr), δ 5.71 (1H, d, J = 12 Hz, HC=CH(O)), δ 4.28 (2H, q, J = 7.1 Hz, J = 14.2 Hz, H_2CCH_3), δ 1.32 (3H, t, J = 7.1 Hz, H_3C–CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 156.8, 156.0, 153.1, 130.7, 123.9, 119.6, 113.0, 104.5, 60.4, 14.2.

4.1.19. Preparation of (*Z*)-3-(4-carbamoylphenoxy)-acrylic acid ethyl ester (17)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), 4-hydroxybenzamide (90.51 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **17** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **17** (94 mg, 91% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90–7.85 (2H, m, HAr), δ 7.84 (1H, d, J = 12.2 Hz, HC(O)=CH), δ 7.20–7.13 (2H, m, HAr), δ 5.70 (1H, d, J = 12.2 Hz, HC=CH(O)), δ 4.23 (2H, m, H_2CCH_3) δ 1.31 (3H, m, H_3C–CH_2). HRMS (ESI) $(M+H)^+$, calcd for $C_{12}H_{14}NO_4$ 236.0923; found 236.0926.

4.1.20. (*Z*)-3-(3,5-Dimethoxy-phenoxy)-acrylic acid ethyl ester (18)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), 3,5-dimethoxyphenol (101.8 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **18** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **18** (108.8 mg, 98% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (1H, d, J = 12.2 Hz, HC(O)=CH), δ 6.30 (1H, t, J = 2.2 Hz, HAr), δ 6.25–6.24 (2H, m, HAr), δ 5.59 (1H, d, J = 12.2 Hz, HC=CH–O), δ 4.22 (2H, q, J = 3.6 Hz, J = 10.7 Hz, H_2C–CH_3), δ 3.80 (6H, s, H_3CO), δ 1.31 (3H, t, J = 7.1 Hz, H_3C–CH_2).^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 161.6, 158.4, 157.5, 102.3, 96.9, 96.5, 60.0, 55.4, 14.2. HRMS (EI), calcd for $C_{13}H_{16}O_5$ 252.0998; found 252.1007.

4.1.21. Preparation of (*Z*)-(3)-(*o*-tolyloxy)-acrylic acid ethyl ester (19)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), *o*-cresol (71.4 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **19** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **19** (84 mg, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (1H, d, J = 12 Hz, HC(O)=CH), δ 7.25–7.20 (2H, m HAr), δ 7.15–7.10 (1H, m HAr), δ 7.02 (1H, d, J = 9 Hz), δ 5.40 (1H, d, J = 12 Hz, HC=CH(O)), δ 4.23 (2H, q, J = 6.0 Hz, J = 14.1 Hz, H_2CCH_3), δ 2.26 (1H, s, CH_3), δ 1.29 (3H, t, J = 6.9 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 159.9, 153.6, 131.4, 128.8, 127.2, 125.2, 118.4, 100.9, 59.9, 15.7, 14.2. HRMS (ESI) $(M+Li)^+$, calcd for $C_{12}H_{14}O_3Li$ 213.1103; found 213.1106.

4.1.22. Preparation of (*Z*)-3-(2-isopropyl-phenoxy)-acrylic acid ethyl ester (20)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), 2-isopropylphenol (89.9 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **20** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **20** (97.9 mg, 95% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (1H, d, J = 12.3 Hz, HC(O)=CH), δ 7.34–7.30 (1H, m, HAr), δ 7.26–7.16 (2H, m, HAr), δ 7.02–6.99 (1H, m, HAr), δ 5.46 (1H, d, J = 12.3 Hz, HC=CH–O), δ 4.20 (2H, q, J = 3.6 Hz, J = 10.7 Hz, H_2C–CH_3), δ 3.22 (1H, hep, $HC(CH_3)_2$), δ 1.35–1.23 (9H, m, H_3C–CH_2 and $(H_3C)_2CH$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 160.3, 152.9, 139.2, 127.0, 125.5, 118.5, 101.2, 59.9, 27.0, 22.8, 14.2. HRMS (ESI) $(M+H)^+$, calcd for $C_{14}H_{19}O_3$ 235.1334; found 235.1334.

4.1.23. Preparation of (*Z*)-3-(2-methylbenzoate)-acrylic acid ethyl ester (21)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), methyl salicylate (100.4 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **21** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **21** (82.6 mg, 75% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (1H, dd, J = 1.7 Hz, J = 7.8 Hz, HAr), 7.76 (1H, d, J = 12 Hz, HC(O)=CH), δ 7.57 (1H, dt,

J = 1.7 Hz, J = 7.8 Hz, HAr), δ 7.30 (1H, m, HAr), δ 7.09 (1H, d, J = 8 Hz, HAr), δ 5.46 (1H, d, J = 12 Hz, HC═CH(O)), δ 4.23 (2H, q, J = 7.1 Hz, J = 14.2 Hz, H_2CCH_3), δ 3.91 (3H, s, OCH_3), δ 1.31 (3H, t, J = 6.9 Hz, $H_3C–CH_2$). HRMS (ESI) $(M+H)^+$, calcd for $C_{13}H_{15}O_5$ 251.0919; found 251.0917.

4.1.24. Preparation of (*Z*)-3-(naphtalen-1-yloxy)-acrylic acid ethyl ester (22)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), naphthalene-1-ol (95.2 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **22** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **22** (102.3 mg, 96% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12–8.09 (1H, m HAr) δ 7.97 (1H, d, J = 12.2 Hz, HC(O)═CH), δ 7.92–7.87 (1H, m HAr), δ 7.73–7.70 (1H, m HAr, δ 7.63–7.56 (2H, m HAr), δ 7.46 (1H, t, J = 7.8 Hz, HAr), δ 7.17–7.15 (1H, m HAr), δ 5.65 (1H, d, J = 12.2 Hz, HC═CH(O)), δ 4.25 (2H, q, J = 6.0 Hz, J = 15.4 Hz, H_2CCH_3) δ 1.31 (3H, t, J = 7.1 Hz, $H_3C–CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 159.6, 151.7, 134.6, 127.7, 126.8, 126.4, 125.7, 125.4, 125.0, 121.3, 112.7, 102.4, 60.0, 14.2. HRMS (ESI) $(M+H)^+$, calcd for $C_{15}H_{15}O_3$ 243.1021; found 243.1013.

4.1.25. Preparation of (*Z*)-3-(naphtalen-2-yloxy)-acrylic acid ethyl ester (23)

The general procedure **(B)** was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), naphthalene-2-ol (95.2 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **23** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **23** (99 mg, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (1H, d, J = 12 Hz, HC(O)═CH), δ 7.89–7.80 (3H, m HAr), δ 7.56–7.45 (3H, m HAr), δ 7.28 (1H, d, J_1 = 9 Hz, J_2 = 3 Hz, HAr), δ 5.67 (1H, d, J = 12 Hz, HC═CH(O)), δ 4.25 (2H, q, J = 6.0 Hz, J = 14.4 Hz, H_2CCH_3) δ 1.32 (3H, t, J = 7.2 Hz, $H_3C–CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 158.7, 153.4, 133.8, 130.7, 130.1, 127.7, 127.2, 126.8, 125.3, 118.5, 113.5, 102.5, 60.0, 14.2. HRMS (ESI) $(M+H)^+$, calcd for $C_{15}H_{15}O_3$ 243.1021; found 243.1025.

4.1.26. Preparation of (*Z*)-3-(3-methylthiophene-2-carboxylate)-acrylic acid ethyl ester (24)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), methyl 3-hydroxy-2-thiophenecarboxylate (104.4 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **24** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **24** (92.4 mg, 82% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (1H, d, J = 12 Hz, HC(O)═CH), δ 7.51 (1H, d, J = 5.4 Hz, HAr), δ 6.92 (1H, d, J = 5.4 Hz, HAr), δ 5.58 (1H, d, J = 12 Hz, HC═CH(O)), δ 4.24 (2H, q, J = 7.1 Hz, J = 14.2 Hz, H_2CCH_3), δ 3.88 (3H, s, OCH_3), δ 1.29 (3H, t, J = 6.9 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 159.2, 158.1, 144.0, 137.4, 130.6, 120.8, 102.3, 60.1, 52.0, 14.2. HRMS (ESI) $(M+H)^+$, calcd for $C_{11}H_{13}O_5S$ 257.0484; found 257.0481.

4.1.27. Preparation of (*Z*)-3-(benzothiazol-2-yloxy)-acrylic acid ethyl ester (25)

The general procedure (**B**) was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), benzothiazol-2-ol (99.8 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **25** as a colorless oil. Column chromatography on silica gel (10% EtOAc in hexane) provided pure **25** (100.9 mg, 92% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (1H, d, J = 14.3 Hz, HC(O)═CH), δ 7.48–7.36 (3H, m, HAr), δ 7.31–7.26 (1H, m, HAr), δ 6.95 (1H, d, J = 14.3 Hz, HC═CH–O), δ 4.30 (2H, q, J = 3.6 Hz, J = 10.7 Hz, $H_2C–CH_3$), δ 1.36 (3H, t, J = 7.2 Hz, $H_3C–CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 167.1, 134.8, 133.5, 126.8, 124.7, 122.9, 122.0, 111.5, 110.4, 60.7, 14.2. HRMS (ESI) $(M+H)^+$, calcd for $C_{12}H_{12}NO_3S$ 250.0538; Found 250.0540.

4.1.28. Preparation of (*Z*)-3-(pyridin-3-yloxy)-acrylic acid ethyl ester (26)

The general procedure (**B**)was followed (2 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol) CuI (4.2 mg, 0.022 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (4.3 mg, 0.022 mmol), pyridine-3-ol (62.8 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the ether **26** as a colorless oil. Column chromatography solvent (15% EtOAc in hexane) provided pure **26** (73.0 mg, 86% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (2H, m, HAr), δ 7.78 (1H, d, J = 12.2 Hz, HC(O)═CH), δ 7.46–7.41 (1H, m, HAr), δ 7.37–7.33 (1H, m, HAr), δ 5.62 (1H, d, J = 12.2 Hz, HC═CH–O), δ 4.22 (2H, q, J = 3.6 Hz, J = 10.7 Hz, $H_2C–CH_3$), δ 1.30 (3H, t, J = 7.1 Hz, $H_3C–CH_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 157.8, 152.2, 146.2, 140.7, 125.1, 124.2, 103.6, 60.2, 14.2 ppm. HRMS (ESI) $(M+H)^+$, calcd for $C_{10}H_{12}NO_3$ 194.0817; found 194.0819.

4.1.29. Preparation of (*Z*)-3-(1*H*-indol-1-yl)-acrylic acid ethyl ester (27)

The general procedure (**B**) was followed (4 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (2.1 mg, 0.011 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (2.15 mg, 0.011 mmol), indole (77.3 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the vinyl amine **27** as an off-white solid. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **27** (71 mg, 75% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (1H, d, J = 14 Hz, HC(O)═CH), δ 7.64 (d, 1H, J = 3.3 Hz, HAr), δ 7.61 (1H, m, HAr), δ 7.41 (1H, d, J = 3.5 Hz, HAr), δ 7.35 (1H, m, HAr), 7.25 (1H, m, HAr), δ 6.75 (1H, d, J = 3.5 Hz, HAr), δ 6.00 (1H, d, J = 14 Hz, HC═CH(O)), δ 4.31 (2H, q, J = 7.1 Hz, H_2CCH_3), δ 1.37 (3H, t, J = 7.1 Hz, $H_3C–CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 137.0, 136.0, 129.7, 123.8, 123.4, 122.3, 121.4, 109.9, 108.6, 100.5, 103.2, 60.2, 14.3. Elemental Anal. Calcd for $C_{13}H_{13}NO_2$?0.27 H_2O: C, 70.95; H, 6.20; N, 6.36. Found: C, 70.95; H, 6.10; N, 6.32.

4.1.30. Preparation of (*Z*)-3-(1*H*-pyrazol-1-yl)-acrylic acid ethyl ester (28)

The general procedure (**B**) was followed (4 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (2.1 mg, 0.011 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (2.15 mg, 0.011 mmol), 1*H*-pyrazole (45 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the vinyl amine **28** as a white solid. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **28** (67.3 mg, 92% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (1H, d, J = 13.9 Hz, HC(O)═CH), δ 7.74 (1H, br, HAr), δ 7.68 (1H, d, J = 2.5 Hz, HAr), δ 6.46 (1H, m, HAr), δ 6.39 (1H, d, J = 13.9 Hz, HC═CH(O)), δ 4.29 (2H, q, J = 7.1 Hz, H_2CCH_3), δ 1.32 (3H, t, J = 7.1 Hz, H_3C-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 143.3, 139.4, 129.8, 108.9, 105.7, 60.5, 14.1. HRMS (EI), calcd for $C_8H_{10}N_2O_2$ 166.0742; found 166.0716.

4.1.31. Preparation of (*Z*)-3-[3-(trifluoromethyl]-1*H*-pyrazol-1-yl)-acrylic acid ethyl ester (29)

The general procedure (**B**) was followed (4 h). Ethyl *cis*-3-iodoacrylate **1A** (100 mg, 0.44 mmol), CuI (2.1 mg, 0.011 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (2.15 mg, 0.011 mmol), 3-(trifluoromethyl)-1*H*-pyrazole (89.8 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the vinyl amine **29** as a white solid. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **29** (99 mg, 96% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99

(1H, d, J = 14 Hz, HC(O)═CH), δ 7.74 (1H, d, J = 1.6 Hz, HAr), δ 7.70 (1H, d, J = 2.5 Hz, HAr), δ 6.53 (1H, d, J = 14 Hz, HC═CH(O)), δ 4.29 (2H, q, J = 7.1 Hz, H_2CCH_3), δ 1.34 (3H, t, J = 7.1 Hz, H_3C–CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 138.5, 131.1, 122.2, 118.5, 109.1, 106.8, 60.8, 14.1. HRMS (EI), calcd for $C_9H_9F_3N_2O_2$ 234.0616; found 234.0608.

4.1.32. Preparation of (*Z*)-3-(1*H*-imidazol-1-yl)-acrylic acid ethyl ester (30)

The general procedure (**B**) was followed (4 h). Ethyl *cis*-3-iodo-acrylate **1A** (100 mg, 0.44 mmol), CuI (2.1 mg, 0.011 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (2.15 mg, 0.011 mmol), 1*H*-imidazole (45 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the vinyl amine **30** as a colorless oil. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **30** (29 mg, 40% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (1H, d, J = 14.2 Hz, HC(O)═CH), δ 7.81 (1H, s, HAr), δ 7.26 (1H, s, HAr), δ 7.20 (1H, s, HAr), δ 6.10 (1H, d, J = 14.2 Hz, HC═CH(O)), δ 4.30 (2H, q, J = 7.1 Hz, H_2CCH_3), δ 1.33 (3H, t, J = 7.1 Hz, H_3C–CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 137.7, 136.2, 131.6, 116.1, 107.1, 60.8, 14.1. HRMS (EI), calcd for $C_8H_{10}N_2O_2$ 166.0742; found 166.0769.

4.1.33. Preparation of (*Z*)-3-(1*H*-1,2,4-triazol-1-yl)-acrylic acid ethyl ester (31)

The general procedure (**B**) was followed (4 h). Ethyl *cis*-3-iodo-acrylate **1A** (100 mg, 0.44 mmol), CuI (2.1 mg, 0.011 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (2.15 mg, 0.011 mmol), 1H-1,2,4-triazole (45.6 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the vinyl amine **31** as a white solid. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **31** (68.4 mg, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (s, 1H, HAr), 8.08 (s, 1H, HAr), 8.03 (1H, d, J = 13.8 Hz, HC(O)═CH), δ 6.63 (1H, d, J = 13.8 Hz, HC═CH(O)), δ 4.31 (2H, q, J = 7.1 Hz, H_2CCH_3), δ 1.35 (3H, t, J = 7.1 Hz, H_3C–CH_2).^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 153.5, 144.5, 134.9, 110.4, 61.0, 14.1. HRMS (EI), calcd for $C_7H_9N_3O_2$ 167.0694; found 167.0666.

4.1.34. Preparation of (*Z*)-3-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-acrylic acid ethyl ester (32)

The general procedure (**B**) was followed (4 h). Ethyl *cis*-3-iodo-acrylate **1A** (100 mg, 0.44 mmol), CuI (2.1 mg, 0.011 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (2.15 mg, 0.011 mmol), 1*H*-1,2,3-benzotriazole (78.6 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the vinyl amine **32** as a white crystalline solid. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **32** (90.8 mg, 95% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (1H, d, J = 14.3 Hz, HC(O)═CH), δ 8.17 (d, 1H, J = 8.3 Hz, HAr), δ 7.77 (1H, d, J = 8.3 Hz, HAr), δ 7.66 (1H, t, J = 7.4 Hz, HAr), δ 7.50 (1H, t, J = 7.4 Hz, HAr), δ 6.79 (1H, d, J = 14.3 Hz, HC═CH(O)), δ 4.36 (2H, q, J = 7.1 Hz, H_2CCH_3), δ 1.39 (3H, t, J = 7.1 Hz, H_3C–CH_2). ^{3}C NMR (75 MHz, $CDCl_3$): δ 165.8, 146.5, 135.0, 131.4, 129.2, 125.3, 120.7, 110.0, 108.1, 60.9, 14.1. HRMS (EI), calcd for $C_{11}H_{11}N_3O_2$ 217.0851; found 217.0832.

4.1.35. Preparation of (*Z*)-3-(1*H*-indazol-1-yl)-acrylic acid ethyl ester (33)

The general procedure (**B**) was followed (4 h). Ethyl *cis*-3-iodo-acrylate **1A** (100 mg, 0.44 mmol), CuI (2.1 mg, 0.011 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (2.15 mg, 0.011 mmol), 1*H*-indazole (78 mg, 0.66 mmol) and DMF (2.0 mL) were stirred at 40 °C to obtain the vinyl amine **33** as a white solid. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **33** (90.4 mg, 95% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, d, J = 13.7 Hz, HC(O)═CH), δ 8.22 (s, 1H, HAr), δ 7.79 (1H, d, J = 8 Hz, HAr), δ 7.69 (1H, d, J = 8.4 Hz, HAr), δ 7.54 (1H, t, J = 7.5 Hz, HAr), δ 7.32 (1H, t, J = 7.5 Hz, HAr), δ 6.55 (1H, d, J = 13.7 Hz, HC═CH(O)), δ 4.32 (2H, q, J = 7.1 Hz, H_2CCH_3), δ 1.37 (3H, t, J = 7.1 Hz, H_3C–CH_2).^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 139.5, 138.9, 136.5, 128.2, 125.5, 123.1, 121.5, 109.5, 103.2, 60.3, 14.1. Elemental Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.51; H, 5.65; N, 12.85.

4.1.36. Preparation of (*Z*)-3-(5-(methylthio)-1*H*-tetrazol-1-yl)-acrylic acid ethyl ester (34)

The general procedure (**B**) was followed (40–50 °C, 2–4 h). Ethyl *cis*-3-iodo-acrylate **1A** (100 mg, 0.44 mmol), CuI (2.1 mg, 0.011 mmol), Cs_2CO_3 (67.5 mg, 0.80 mmol), **L3** (2.15 mg, 0.011 mmol), 5-(methylsulfanyl)-1*H*-tetraazole (76.6 mg, 0.66 mmol) and DMF (2.0 mL) were employed to obtain the vinyl amine **34** (34 mg, 0.158 mmol, 36% yield) as a yellowish semi solid. Column chromatography on silica gel (5% EtOAc in hexane) provided pure **34** (spectral data matches that previously reported for compound **34**[9]): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (1H, d, J = 14.1 Hz, HC(O)═CH), δ 6.77 (1H, d, J = 14.1 Hz, HC═CH(O)), δ 4.34 (2H, q, J = 7.1 Hz, H_2CCH_3), δ 1.37 (3H, t, J = 7.1 Hz, H_3C-CH_2). HRMS (EI), calcd for $C_7H_{10}N_4O_2S$ 214.0524; found 214.0515.

4.2. Biology

All anti-*Mycobacterium* activity evaluations (except for the anti-*M. tuberculosis* assays) were performed using minimum inhibitory concentration assays in Middlebrook 7H9 broth with 10% OADC. The *Mycobacterium* cultures were grown statically for seven days in Middlebrook 7H9 broth with 10% OADC at 35 °C. Microtiter plates were incubated for 48 h at 35 °C and scored as either growth or no growth. Rifampin was used as the positive control. All other antimicrobial activity evaluations were performed using minimum inhibitory concentration assays in Cation-adjusted Mueller–Hinton–Broth.[15] Cultures were grown statically overnight on tryptic soy agar medium, incubated at 35 °C. Cultures included *S. aureus* ATCC 29213, *B. cereus,* and *E. coli* ATCC 29522. Microtiter plates were incubated for 18–24 h at 35 °C and scored as either growth or no growth. Tetracycline controls were included that correlated with established MIC values.[15]

The anti-*M. tuberculosis* activity evaluations were performed using a green fluorescent protein (GFP)-based assay to measure the efficacy of **3** and **4** against *M. tuberculosis*. Briefly, a *gfp* gene was cloned into the high copy number pHIGH plasmid, creating pHIGH22.[13] The pHIGH22 plasmid was transferred into *M. tuberculosis* H37Rv. Early logarithmic cultures of *M. tuberculosis* H37Rv/pHIGH22 were diluted in 96-well microtiter plates to an $O.D._{\cdot 600}$ of 0.025 in Middlebrook 7H9 medium. Test compounds were resuspended in DMSO to concentrations of 20 μg/ml and serially diluted twofold. Fluorescence was measured in a FLUOstar Omega microplate reader (BMG Labtech, San Francisco, CA) after seven days of growth at 37 °C. If the drug killed the bacteria, the fluorescence emitted from the plasmid would be extinguished in a manner similar to that described in a previous study using luciferase rather than GFP.[16] Both isoniazid (INH) and rifampin (RIF) were used as the positive controls.[13]

A tryptan exclusion assay employing murine J774A.1 (ATCC) monocyte cell lines was employed to assess the cytotoxicity of selected compounds. Briefly, monocytes were seeded at 1×10^6/well in a 24-well tissue culture plate with RPMI 1640 medium (Invitrogen). The next day, twofold dilutions of the test drug in PBS were added to each well with RPMI 1640 medium. On the following day, the spent medium was removed by aspiration, and a trypan blue solution was added to each well. After 10 min elapsed, the trypan blue solution was removed by aspiration, and an equal volume of PBS was added. Three fields of cells were counted per well. The number of dead (blue) and live (clear) cells was determined. An IC_{50} value was calculated for each well with 50% dead cells.

Acknowledgments

We wish to acknowledge financial assistance from the Research Growth Initiative of the University of Wisconsin-Milwaukee (J.M.C.) and a UW-System Applied Research Grant (A.M.).

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