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Design, Synthesis, and Biological Evaluation of New Cinnamic Derivatives as Antituberculosis Agents

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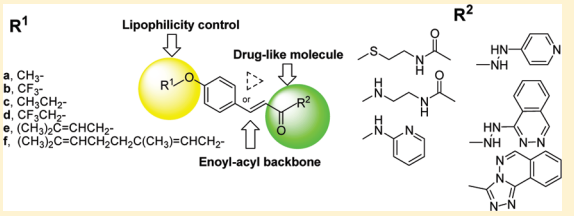
Supporting Information

ABSTRACT: Tuberculosis, HIV coinfection with TB, emergence of multidrug-resistant TB, and extensively drug-resistant TB are the major causes of death from infectious diseases worldwide. Because no new drug has been introduced in the last several decades, new classes of molecules as anti-TB drugs are urgently needed. Herein, we report the synthesis and structure−activity relationships of a series of thioester, amide, hydrazide, and triazolophthalazine derivatives of 4-alkoxy cinnamic acid. Many compounds exhibited submicromolar minimum inhibitory concentrations against *Mycobacterium tuberculosis* strain ($H_{37}Rv$). Interestingly, compound **13e**, a 4-isopentenyloxycinnamyl triazolophthalazine derivative, was found to be 100−1800 times more active than isoniazid (INH) when tested for its ability to inhibit the growth of INH-resistant *M. tuberculosis* strains. The results also revealed that **13e** does not interfere with mycolic acid biosynthesis, thereby pointing to a different mode of action and representing an attractive lead compound for the development of new anti-TB agents.



INTRODUCTION

Tuberculosis (TB) is a threat to worldwide public health. The high susceptibility of human immunodeficiency virus (HIV)-infected persons to the disease[1] and the emergence of multidrug-resistant (MDR) strains[2a−2c] have brought this infectious disease into the focus of scientific interest. This fact forced the scientific community to develop new antimycobacterial agents to treat *Mycobacterium tuberculosis* strains resistant to existing drugs and to shorten the duration of treatment to improve patient compliance. The lack of treatment observance is possibly the biggest cause of the occurrence and spread of MDR strains of *M. tuberculosis*.[3a,3b] However, after many trials,[3b,4] two regimens have emerged that involve two periods of treatment: first, a 2 month long treatment with a set of four drugs, mainly involving inhibitors of cell envelope component biosynthesis and particularly fatty acid biosynthesis inhibitors like isoniazid (INH). This is often followed by 4 months treatment of INH and rifampin. Hepatotoxicity, being a major side effect in some cases, forces a premature treatment termination.[5] Fluoroquinolones, considered to be good inhibitors of DNA-based processes, are still in the process of being established as a second line of anti-TB drugs.[6a] Studies for the treatment of MDR TB using the first antibiotic of the oxazolidinone class, linezolide,[6b] revealed some cases of peripheral neuropathy as a side effect.[6c] Although a number of classes of compounds have been reported[6a] with an effect on *M. tuberculosis*, treatment failure is too often a fact.[6d] Therefore, the urgency and the growing need for the new class of chemical compounds are well accepted.

In recent years, *trans*-cinnamic acid derivatives have attracted much attention due to their antioxidative,[7a] antitumor,[7b] and antimicrobial[7c,7d] properties. Piplartin (**1**),[7b] an alkaloid and a *trans*-cinnamic acid derivative, isolated from *Piper tuberculatum*, has been shown to have antitumor as well as antiproliferative activities. Recently, the synergistic activity[8] of *trans*-cinnamic acid in drug combinations with INH, rifamycin, and other known antimicrobial agents against *M. tuberculosis* has been exemplified. Importantly, superior intracellular and in vivo activity of a cinnamyl-rifamycin derivative (**2**) (Chart 1), in comparison with rifamycin,[9] was observed when tested against 20 susceptible and MDR *M. tuberculosis* strains. Significantly, *trans*-cinnamic acid was used to treat TB even before antimicrobial chemotherapy was used.[10]

We have reported in a preliminary communication[11] the synthesis and biological evaluation of various cinnamic thioesters and amides as potential enoyl-acyl carrier protein (enoyl-ACP) analogues. Importantly, (*E*)-*N*-(2-acetamidoethyl)-3-{4-[(*E*)-3,7-dimethylocta-2,6-dienyloxy]phenyl}propanamide (**8f**) was found to have an excellent in vitro activity (MIC = 0.1 μg/mL)

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Chart 1. Piplartin (1) and Cinnamyl-Rifamycin Derivative (2)

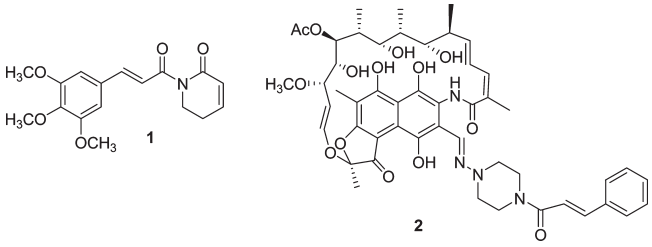
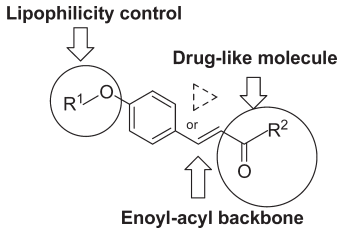


Chart 2. Illustration of Drug Design Strategy



against *M. tuberculosis*. In continuation of our ongoing research program, directed toward design and synthesis of cinnamoyl derivatives as anti-TB agents, we describe in this report the synthesis and biological evaluation of new and very potent drug candidates, an extended family of cinnamyl-thioesters, amides, hydrazides, and triazolo-phthalazides.

CHEMISTRY

To design new cinnamic acid-based drug candidates, we divided the projected molecules in three parts: the cinnamic acid part as enoyl-acyl backbone, 4-alkoxy substitution as lipophilicity control, following Lipinski's[12] rules, and attachment of druglike molecules to the acid functionality (Chart 2). Variations were accomplished with the choice of alkyl groups in alkoxy substitution and druglike molecules. Some cyclopropyl, isosteric to the double bond, derivatives that have been already synthesized[13] replacing the enoyl-acyl part were also evaluated to explore the possible importance of the double bond.

(*E*)-4-Hydroxycinnamic acid (**3**) and (*E*)-4-methoxycinnamic acid (**6a**) are commercially available. The carboxylic function of 4-hydroxycinnamic acid (**3**) was protected first to introduce different alkyl chains on the phenolic functionality and used as a common precursor of most of the amides, thioesters, hydrazides, and phthalazides obtained. Methyl-ester of (*E*)-4-hydroxy cinnamic acid[14] was prepared in excellent yield (95%) by refluxing it in methanol in the presence of a catalytic amount of concentrated H_2SO_4 and 4 Å molecular sieves. (*E*)-Methyl-4-hydroxycinnamate (**4**) was then subjected to alkylation by refluxing suitable alkyl halide (isopentenyl bromide, geranyl bromide, or ethyl iodide) in dry acetone in the presence of anhydrous K_2CO_3 and KI (used only in case of alkyl bromides) to give corresponding phenoxy ethers **5c**,**e**,**f** in good to excellent yields (70−95%). Because of the presence of a trifluoromethyl functionality, a similar reaction with 2,2,2-trifluoroethyl iodide resulted in a poor yield (38%) of (*E*)-methyl 4-trifluoroethoxycinnamate (**5d**). Therefore, we modified the reaction procedure, and **5d** was prepared from **4** using 2,2,2-trifluoroethyl iodide as the alkylating agent and NaH as the base in dimethyl sulfoxide (DMSO) in 52% yield. (*E*)-Methyl 4-trifluoromethoxycinnamate (**5b**) was obtained (89% yield) by Wadworth−Emmons coupling reaction between commercially available 4-trifluoromethoxybenzaldehyde (**4′**) and methyl diethylphosphonoacetate under basic conditions[15] (Scheme 1). The methyl-2(4-alkoxyphenyl)cinnamates **5b**−**f** were then saponified to the corresponding carboxylic acids **6b**−**f** using K_2CO_3 in refluxing aqueous methanol as reported in Scheme 1 (97−99% yields).

The acids **6a**,**e**,**f** were coupled with *N*-acetylcysteamine using 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC·HCl) in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) in dry dichloromethane (Scheme 2) to furnish acetamidoethyl 3-(4-alkoxyphenyl)prop-2-enethioate derivatives **7a**, **e**,**f** (67−78% yields). *N*-Acetylethylenediamine, a nitrogen variant of *N*-acetylcysteamine, was used as a coupling partner of the enoyl-acids **6a**,**e**,**f**. The (*E*)-*N*-(2-acetamidoethyl)-3-(4-alkoxyphenyl) prop-2-enamide derivatives **8a**,**e**,**f** were prepared in good yields (63−83%) under similar conditions as described for the synthesis of **7a**,**e**,**f**. We synthesized (*E*)-3-(4-alkoxyphenyl)-*N*-(pyridin-2-yl)prop-2-enamide derivatives **9a**,**e**,**f** (40−48% yields) using 2-aminopyridine, an aromatic amine as coupling partner, in the presence of EDC·HCl and DMAP in dichloromethane.

In view of the recent report on the cinnamyl-rifamycin derivative,[9] we decided to synthesize (2*E*)-3-(4-methoxyphenyl)-*N*-(3-oxo-1,2-oxazolidin-4-yl)prop-2-enamide (**10a**). To overcome the poor solubility of D-cycloserine, BSA (bis-trimethylsilylacetamide) was used in the coupling reaction between acid chloride, made from acid (**6a**), oxalyl chloride, and D-cycloserine in the presence of *N*-methylpyrrolidine in dichloromethane to afford amide **10a** in good yield (71%).[16] In spite of the fact that D-cycloserine was found to inhibit[6a] D-alanine racemase and D-alanine D-alanine ligase enzymes involved in bacterial cell wall biosynthesis, **10a** showed an extremely poor MIC (see biological results) against *M. tuberculosis*; thus, no further alkyl modification was pursued.

In continuation of our ongoing effort, we decided to explore the biological features of 4-alkoxycinnamyl hydrazides as attractive antituberculosis agents. INH, a frontline drug of TB and an inhibitor of mycolic acid biosynthesis, was chosen as the coupling partner of cinnamic acids. Coupling of acids **6a**−**f** with INH was carried out using *N*,*N*,*N*′,*N*′-tetra-methyl-*O*-(1*H*-benzotriazol-1-yl)-uronium hexafluorophosphate (HBTU) in the presence of diisopropylethylamine, in acetonitrile to afford the respective (*E*)-*N*′-[3-(4-alkoxyphenyl)propenoyl]isonicotinohydrazide derivatives (**11a**−**f**) in good yields (61−81%). We would like to mention that (*E*)-*N*′-[3-(4-methoxyphenyl)propenoyl]isonicotinohydrazide (**11a**) was found to be identical in all aspects as reported by Carvalho et al.[7d]

To explore the influence of other hydrazides, 1-hydrazinophthalazine hydrochloride, an antihypertensive drug[17a,17b] of moderate potency, was coupled with acids **6a**−**f** in the presence of EDC·HCl, *N*-hydroxybenzotriazole (HOBt), and triethylamine to afford (2*E*,*N*′,*E*)-3-(4-alkoxyphenyl)-*N*′-[phthalazin-1-(2*H*)-ylidiene]acrylohydrazides (**12a**−**f**) in good yields as reported in Scheme 3. In addition to the usual characterization, X-ray of **12e** confirms the structure (Chart 3).

However, in a different experimental condition, coupling of acids **6a**−**f** with 1-hydrazinophthalazine hydrochloride in acetonitrile under reflux for 48 h in the presence of EDC·HCl, HOBt, and triethylamine furnished the corresponding 3-(4-alkoxystyryl)-[1,2,4]triazolo[3,4-α]phthalazines (**13a**−**f**) in good yields (65−90%). The X-ray

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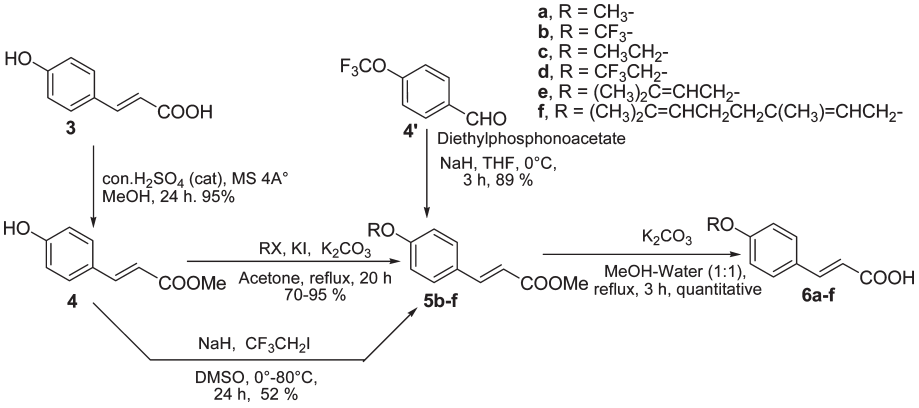
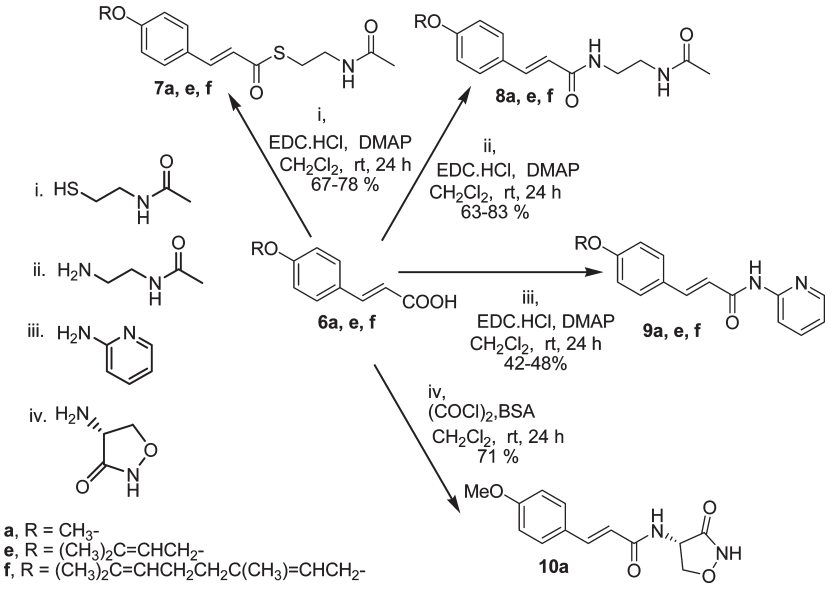
Scheme 1. Synthesis of Four Alkoxycinnamic Acids



Scheme 2. Synthesis of Thioester and Amide Derivatives



structure of the compound **13a** (Chart 4) confirmed the formation of the triazolophthalazine derivative as well as the styryl backbone of the entire series of compounds issued by a coupling−intramolecular cyclization−dehydration sequence. The present reaction conditions established for the synthesis of triazolo-phthalazine derivatives add to other different methodologies available in the literature.[18a−18d]

RESULTS AND DISCUSSION

All of the synthesized compounds were tested for their ability to inhibit (minimum inhibitory concentration; MIC) the growth of *M. tuberculosis* strain $H_{37}Rv$ in a colorimetric microassay based on the reduction of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Sigma] to formazan by metabolically active cells.[19,20]

A significant portion of the compounds was found highly active in inhibiting *M. tuberculosis* at a submicromolar level. Among compounds with *N*-acetylcysteamine frame, compound **7f** with a geranyl chain was found to be 150-fold more active (1.5 μM) than its methyl analogue (**7a**, 225 μM). A similar trend was observed when *N*-acetylethylenediamine was used as a druglike molecule. While amides **8a** and **8e** were found to be less active than their thioester counterparts, the derivative **8f** showed a very potent activity (0.24 μM) as well as cytotoxicity [IC_{50} = 28 μM; selectivity index (SI) = 116] (Table 1). The family of compounds with 2-aminopyridine, an aromatic amine, as a coupling partner also showed an increase in activity with an increase in lipophilicity as compound **9f** was found to have a better MIC (2.7 μM) in comparison to its methyl (**9a**; 248 μM) and isopentenyl (**9e**; 52 μM) analogues. Moreover, cytotoxicity (IC_{50} = 388 μM) and SI (144) of 2-aminopyridine derivative **9f** were encouraging. The D-cycloserine derivative (**10a**) was found to have poor activity (950 μM) as well as a poor lipophilic factor (<2); thus, no further derivative was made.

Gratifyingly, the series of INH derivatives (**11a**−**f**) were found to show extremely good activity range (0.3−2.3 μM). The derivative with a methyl chain (**11a**) was found to be the best in the series in terms of its activity (0.3 μM) as well as cytotoxicity (IC_{50} = 168 μM; 50 μg/mL) and SI (560). Importantly, the

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Scheme 3. Synthesis of 4-Alkoxycinnamic Hydrazides

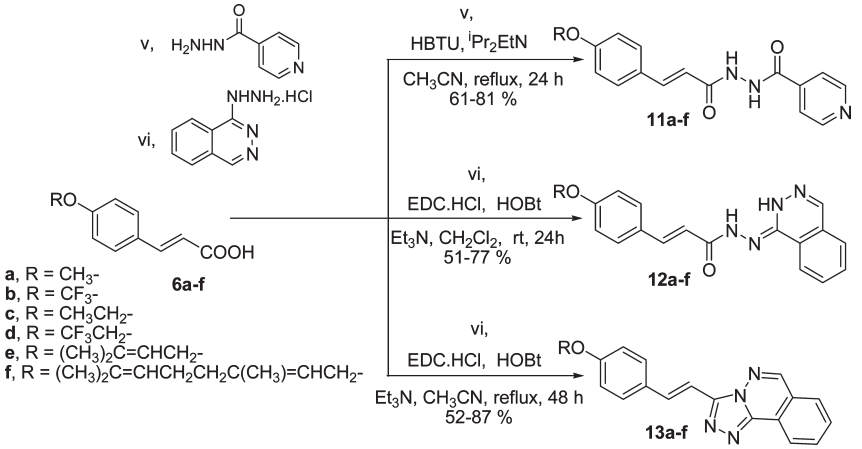


Chart 3. X-ray Structure of 12e

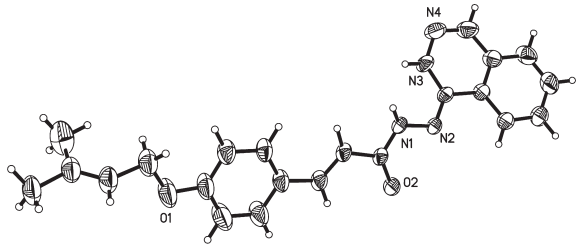
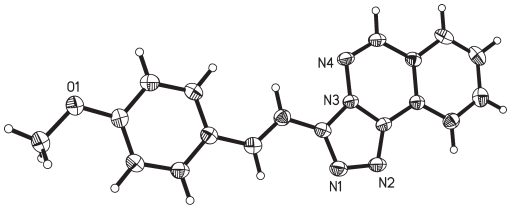


Chart 4. X-ray Structure of 13a



introduction of ethyl (**11c**), trifluoromethyl (**11b**), and/or trifluoroethyl (**11d**) alkyl chains as 4-alkoxy groups still showed good potency (1.3, 1.1, and 2.2 μM, respectively) and good lipophilicity (ClogP) values as antituberculosis agents. The isopentenyl and geranyl derivatives (**11e** and **11f**, respectively) showed a similar range of MIC results; **11e** was found to have a better potentiality as a drug candidate in view of its good cytotoxicity (IC_{50} = 256 μM; 90 μg/mL, SI = 111) profile. Significantly, TLC analysis[21] of methyl esters derivatives obtained after saponification of metabolically labeled *M. tuberculosis* with [1-^{14}C] acetate in the presence of synthesized molecules showed that **11e**, a representative of the series (**11a**−**f**), inhibits mycolic acid biosynthesis (Chart 5).

Concerning the family of 1-phthalazine (**12a**−**f**), MIC results were moderate, but the trend of cytotoxic behavior was not acceptable. Interestingly, the combination of isopentenyl chain as a 4-alkoxy substituent with triazolophthalazine (**13e**), a modified enoyl-acyl system obtained by the intramolecular cyclization−dehydration of the parent compound **12e**, showed excellent antitubercular potency (MIC = 1.4 μM), in comparison with other derivatives in the series, and more importantly, with good cytotoxicity (IC_{50} = 449 μM; 160 μg/mL) and SI (SI = 320).

To explore the importance of the enoyl-acyl backbone, with an approach to replace the double bond by isosteric cyclopropyl moiety, we also synthesized[13] 3-[2-(4-alkoxyphenyl)cyclopropyl]-[1,2,4]triazolo[3,4-α]phthalazine (**14a**−**f**; racemates; synthesis described elsewhere[13]), and their in vitro anti-TB potentiality have been evaluated (Table 2). Significantly, the MIC values of the compounds (**14a**−**f**) were found to be poor as compared to their olefinic analogues (**13a**−**f**). In regard to the difference in activities between the enoyl and the cyclopropyl series, a plausible explanation could be the respective Michael acceptor ability. Chew et al.[22] have recently showed that cinnamaldehydes can act as Michael acceptors and inhibit thioredoxin reductase through nucleophilic addition of glutathione cystine −SH residues. In our case, from a chemical point of view, the compounds having an electron-withdrawing group in the para-position of the aromatic ring should be more active to Michael addition. It should be a clear structure−activity relationship if this is the possible reason of their activity, that is, 4-OCF_3 derivatives are expected to show better inhibitory activities as compared to their 4-OCH_3 analogues. However, this is not the case as compound **11a** has a 4-fold better activity (0.3 μM) as compared to **11b** (1.1 μM), and similarly, **13a** (53 μM) exhibits approximately 15-fold better activity than **13b** (702 μM). In view of these results, we can suggest that the Michael addition is not the mode of action of these compounds.

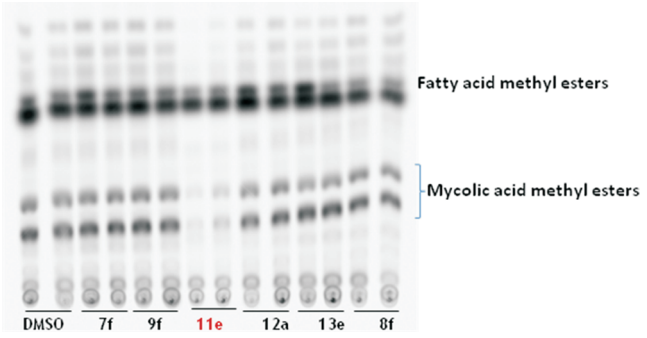
Because resistance to the current drugs remains a serious problem, resulting in the occurrence of MDR, which are resistant to the frontline INH and rifampicin drugs, and extensively drug-resistant (XDR), we decided to test our newly synthesized compounds on INH-resistant strains. As mutations in InhA[23] and *katG* represent the main modes of primary resistance to INH in TB patients,[24] we chose to evaluate the inhibitory activity of our compounds on two INH-resistant strains. MYC5165 is a *M. tuberculosis* strain mutated in InhA, whereas 1400 is mutated in *katG*. Two representative INH derivatives **11a,e** and the most active triazolophthalazine derivative **13e** were tested on MYC5165 and 1400. The inhibitory activities of **11a,e** were found to be following similar trends with values in the same log range as that of INH itself

Table 1. Structure and Activities of Cinnamic Derivatives

compd	R^1	R^2	$H_{37}Rv$ MIC (μM)	toxicity IC_{50}[a] (μM) (SI)[b]	CLogP[c]	PSA[d] (Å^2)
7a[11]	methyl	*N*-acetylcysteamine	225	197 (0.7)	1.65	80.32
7e[11]	isopentenyl	*N*-acetylcysteamine	48	84 (1)	3.46	80.32
7f[11]	geranyl	*N*-acetylcysteamine	1.5	34 (23)	5.75	80.32
8a[11]	methyl	*N*-acetylethylenediamine	>1908	858 (−)	1.08	67.43
8e[11]	isopentenyl	*N*-acetylethylenediamine	186	196 (1)	2.78	67.43
8f[11]	geranyl	*N*-acetylethylenediamine	0.24	28 (116)	4.81	67.43
9a[11]	methyl	2-aminopyridine	248	255 (1)	2.54	51.22
9e[11]	isopentenyl	2-aminopyridine	52	ND	4.62	51.22
9f[11]	geranyl	2-aminopyridine	2.7	388 (144)	6.64	51.22
10a	methyl	D-cycloserine	950	ND	1.24	76.66
11a	methyl	INH	0.3	168 (560)	1.87	80.32
11b	CF_3	INH	1.1	ND	2.98	80.32
11c	ethyl	INH	1.3	ND	2.40	80.32
11d	CF_3CH_2	INH	2.2	ND	2.66	80.32
11e	isopentenyl	INH	2.3	256 (111)	3.57	80.32
11f	geranyl	INH	1.9	43 (22)	5.60	80.32
12a	methyl	hydralazine	50	437 (8)	2.08	76.41
12b	CF_3	hydralazine	21	ND	3.19	76.41
12c	ethyl	hydralazine	12	ND	2.61	76.41
12d	CF_3CH_2	hydralazine	20	ND	2.87	76.41
12e	isopentenyl	hydralazine	21	26 (1)	3.78	76.41
12f	geranyl	hydralazine	72	56 (0.8)	5.81	76.41
13a	methyl	triazolophthalazine	53	695 (13)	3.20	52.31
13b	CF_3	triazolophthalazine	702	ND	4.31	52.31
13c	ethyl	triazolophthalazine	39	ND	3.73	52.31
13d	CF_3CH_2	triazolophthalazine	170	ND	4.00	52.31
13e	isopentenyl	triazolophthalazine	1.4	449 (320)	4.91	52.31
13f	geranyl	triazolophthalazine	19	259 (13)	6.94	52.31
INH			0.6	>3649 (>6081)	−0.66	50.94

[a] Fifty percent inhibitory concentration (cytotoxicity toward THP-1 cells). [b] Selectivity index: ratio of cytotoxicity to in vitro activity against *M. tuberculosis* (IC_{50}/Mtb MIC). [c] CLogP calculated using the ChemDraw Ultra, version 10.0, software by Cambridge Soft. ND, not done. [d] Polar surface area (PSA): Calculated using Calculator Plugin Marvin in www.chemaxon.com.

Chart 5. Radio Thin-Layer Chromatography Analysis of Mycolic Acids from *M. tuberculosis* Treated with Different Doses of Selected Compounds[a]

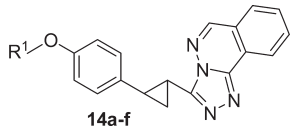


[a] For each compound: left, MIC; right, MIC/5.

as represented in Table 3, thus not allowing at the moment to propose these compounds as INH prodrugs or not.

Finally, to our great delight, compound **13e** showed 100-fold better in vitro activity against MYC5165 strain (**13e**; MIC = 0.2 μM) and 1800-fold better activity against 1400 strain (**13e**; MIC = 0.4 μM) as compared to INH (MIC = 18 and 729 μM, respectively). The importance of the isopentenyl side chain, cinnamic double bond, and triazolophthalazine part is evident from these biological results as none of the other triazolophthalazine derivatives (**13a**−**d**,**f**) are active enough. Furthermore, the

Table 2. Anti-TB Activities of Cyclopropyl Derivatives



14a-f

compd	R^1	$H_{37}Rv$ MIC (μM)	CLogP
14a	methyl-	395	2.63
14b	CF_3-	170	3.74
14c	ethyl	378	3.16
14d	CF_3CH_2-	1302	3.12
14e	isopentenyl-	21	4.33
14f	geranyl-	28	6.36

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Table 3. Anti-TB Activities against INH-Resistant *M. tuberculosis* Strains to INH

compd	MYC5165 MIC (μM)	1400 MIC (μM)
11a	16	320
11e	27	68
13e	0.2	0.4
INH	18	729
ciprofloxacine	5	5

radio thin-layer chromatography analysis (Chart 5) revealed that compound **13e** does not inhibit mycolic acid biosynthesis. This fact, in combination with its inhibitory efficacy against INH-resistant strains, suggests that compound **13e** may be considered as a good hit, in terms of MIC values, cytotoxicity profile (SI = 320), CLogP (4.91), and PSA (52.31 Å^2)[25] values with a mode of action to be discovered.

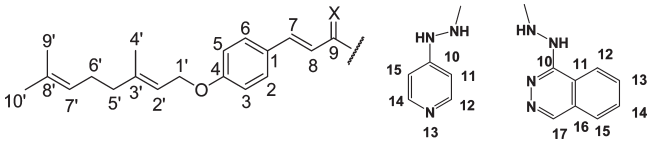
CONCLUSIONS

New cinnamic acid-based molecules were synthesized by simple, clean, and efficient synthetic protocols. Introduction of selective alkyl groups as lipophilicity control was achieved successfully. The importance of the double bond was also probed. Many of the synthesized molecules have encouraging antituberculosis activities (MIC) and cytotoxicity ranges toward THP-1 cells and possess satisfactory druggability (PSA = 50−80 Å^2). The compounds (*E*)-*N*-(pyridin-2-yl)-3-[4-{(*E*)-3,7-dimethylocta-2,6-dienyloxy}phenyl]prop-2-enamide (**9f**) and (*E*)-3-[4-(3-methylbut-2-enyloxy)styryl]-[1,2,4]triazolo[3,4-α]phthalazine (**13e**) were found to have good anti-TB activity, and both are compatible in terms of cytotoxycity and ClogP values. Moreover, the entire series of INH derivatives (**11a**−**f**) have good anti-TB activities. Importantly, the MIC value of **11a** against *M. tuberculosis* $H_{37}Rv$ strain is comparable to, if not even better than that of, INH, a frontline anti-TB drug. Compound **11e** was found to inhibit the biosynthesis of mycolic acids, as does INH. Further development of the INH derivatives is underway, in particular, biomimetic and enzymatic studies, to elucidate their mode of action. Finally and most importantly, compound **13e** does not inhibit mycolic acid biosynthesis but is extremely active against two INH-resistant strains. Thus, **13e** may be considered as a hit in terms of excellent antitubercular activity, lipophilicity, and PSA values. The comprehension of the mode of action of **13e** is one of the goals of the ongoing research program in our laboratories.

EXPERIMENTAL SECTION

Biology. *Inhibition of Mycobacterial Growth.* The susceptibility of *M. tuberculosis* strain $H_{37}Rv$ to all synthesized compounds was evaluated by determining the MIC. We used a colorimetric microassay based on the reduction of MTT (Sigma) to formazan by metabolically active cells.[19,20] Briefly, serial 2-fold dilutions of each drug solubilized in DMSO were prepared in 7H9 broth [Middlebrook 7H9 broth base (Difco)] using 96-well microtiter plates, and 100 μL of *M. tuberculosis* $H_{37}Rv$ suspension in 7H9 broth was added to each well. After 6 days of incubation, MTT was added (50 μL, 1 mg/mL). After 1 day of incubation, solubilization buffer was added to each well. The optical densities were measured at 570 nm. The MIC was determined as the lowest concentration of drug that inhibited bacterial growth (absorbance from untreated bacilli was taken as a control for growth). Reported MICs are an average of three individual measurements.

Chart 6. Enumeration of Molecules



Toxicity. Cytotoxicities (IC_{50}; 50% inhibitory concentration) toward THP-1 cells were determined for some relevant molecules by using the Graph Pad Prism 5.0 Software after measuring the extent of reduction of MTT following 72 h of exposure to compounds. Corresponding SIs have been calculated (IC_{50}/MIC).

Evaluation of the in Vivo Effects of Compounds on Mycolic Acid Biosynthesis[21]. The synthesized compounds were added at two concentrations (MIC and MIC/5) to broth cultures of *M. tuberculosis* in the exponential growth phase. After 8 h of incubation, [1-^{14}C]acetate (2 μCi, 13 μM) was added to follow the biosynthesis of lipid products. After 24 h, bacteria were treated with 40% KOH (w/v) in methoxyethanol (1:7) overnight at 100 °C. The suspensions were then acidified by addition of 20% H_2SO_4. Lipids, including mycolic acids, were then extracted with diethyl ether. The crude fatty acids were methylated, and methyl ester derivatives were analyzed by thin-layer chromatography on Silica Gel 60 (Macherey-Nagel) run in dichloromethane followed by phosphorimaging (Variable Mode Imager Typhoon TRIO, Amersham Biosciences).

Chemistry. Organic solvents were purified when necessary by standard methods[26] or were purchased from Aldrich. Melting points (mp) were obtained on a Buchi apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1725 infrared spectrophotometer, and the data are reported in inverse centimeters. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a Bruker AC-300 spectrometer. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS), and signals are given as follows: s, singlet; d, doublet; t, triplet; and m, multiplet. For better NMR data analysis, compounds were numerated as follow (Chart 6). Mass spectra were recorded on an R 10-10 C Nermag (70 eV) quadripolar spectrometer using desorption chemical ionization (DCI), electrospray (ES), or fast atomic bombardment (FAB) techniques. Analytical HPLC was carried out on Acquity Waters HPLC system with a Acquity BEH C18 1.7 μm, 21 mm × 50 mm column and PDA eλ Waters UV detector. The flow rate was 0.3 mL/min with gradient eluation over 6 min, from 70% CH_3CN-H_2O to 100% CH_3CN with 0.1% TFA. All of the compounds tested for the antitubercular activity were at least 95% pure as determined by HPLC (Supporting Information).

*(E)-Methyl-3-(4-hydroxyphenyl) Propenoate (**3**).* Compound **1** was synthesized by the reported procedure.[14]

*Preparation of (E)-Methyl-3-(4-alkoxyphenyl)prop-2-enoate (**5a**−**f**): General Procedure.* To compound **4** (0.5 g, 2.8 mmol, 1 equiv) in dry acetone (15 mL) was added KI (added only in the case of alkyl bromide; 0.6 g, 4.2 mmol, 1.5 equiv), K_2CO_3 (0.58 g, 4.2 mmol, 1.5 equiv), and alkyl halide (4.2 mmol, 1.5 equiv). The reaction mixture was refluxed for 20 h and then cooled to room temperature and filtrated. The filtrate was evaporated to dryness, and water (20 mL) was added into the residue and extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatography over silica gel (20% ethyl acetate in petroleum ether) to afford compound **5a**−**f** as white solids.

*(E)-Methyl-3-(4-ethoxyphenyl)prop-2-enoate (**5c**).* Compound **5c** was prepared from ester **4** according to procedure by using ethyl iodide. Solid (0.40 g, 70%); mp 57−58 °C. IR (KBr) ν cm^{-1}: 2977 (C−H), 1708 (C═O), 1604 (C═C arom.), 1513 (C═C arom.), 1254 (O−C ether). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.42 (t, 3H, J = 7.0 Hz,

$H_{2'}$), 3.79 (s, 3H, $-COOCH_3$, H_{10}), 4.06 (q, 2H, J = 7,0 Hz, $H_{1'}$), 6.30 (d, 1H, J = 16.0 Hz, H_8), 6.90 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.46 (d, 2H, J = 8.8 Hz, $H_{2,6}$), 7.64 (d, 1H, J = 16.0 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 14.7 (CH_3), 51.5 ($COOCH_3$, C_{10}), 63.6 (CH_2), 114.7 ($C_{3,5}$), 115.1 (C_8), 126.9 (C_1), 129.1 ($C_{2,6}$), 144.5 (C_7), 160.7 (C_4), 167.7 (C_9). MS (DCI, CH_4, pos.) m/z: 207.1 (MH^+).

*(E)-Methyl-3-[4-(3-methylbut-2-enyloxy)phenyl]prop-2-enoate (**5e**).* Compound **5e** was prepared from ester **4** according to the procedure by using 3,3-dimethylallyl bromide. White solid (0.59 g, 86%); mp 55−57 °C. IR (KBr, ν_{max}) cm^{-1}: 2945 (C−H), 1716 (C═O), 1635 (C═C arom.), 1513 (C═C arom.), 1251(O−C ether). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.69 (s, 3H, $H_{4'}$), 1.74 (s, 3H, $H_{5'}$), 3.73 (s, 3H, CH_3), 4.49 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.42 (th, 1H, J = 6.6 Hz, J = 1.5 Hz, $H_{2'}$), 6.24 (d, 1H, J = 15.9 Hz, H_8), 6.84 (d, 2H, J = 8.5 Hz, $H_{3,5}$), 7.41 (d, 2H, J = 8.5 Hz, $H_{2,6}$), 7.60 (d, 1H, J = 15.9 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 14.20 ($C_{4'}$), 39.51 ($C_{5'}$), 51.55 (C_{10}), 64 0.91 ($C_{1'}$), 114.89 ($C_{3,5}$), 115.14 (C_8), 119.22 ($C_{2'}$), 126.99 (C_1), 129.70 ($C_{2,6}$), 138.66 ($C_{3'}$), 144.60 (C_7), 160.74 (C_4), 167.80 (C_9). MS (DCI, NH_3, pos.) m/z: 264.2 (MNH_4^+), 264.2 (MNH_4^+).

*(E)-Methyl-3-{4-[(E)-3,7-dimethylocta-2,6-dienyloxy]phenyl}prop-2-enoate (**5f**).* Compound **5f** was prepared from ester **4** according to procedure for **5e** synthesis by using geranyl bromide. Solid (0.84 g, 95%); mp 72−75 °C. IR (KBr) ν cm^{-1}: 3168 (C═C−H ethyl.), 2942 (C−H), 2854 (C−H CH_3−O), 1720 (C═O), 1637 (C═C ethyl.), 1603 (C═C ethyl.), 1572 (C═C arom.), 1511 (C═C arom.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.60 (s, 3H, $CH_{9'}$), 1.67 (s, 3H, $H_{4'}$), 1.74 (s, 3H, $H_{10'}$), 2.10 (m, 4H, $H_{5'}$ and $H_{6'}$), 3.79 (s, 3H, CH_3), 4.57 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.07 (m, 1H, $H_{7'}$), 5.48 (t, 1H, = 6.5 Hz, $H_{2'}$), 6.31 (d, 1H, J = 15.9 Hz, H_8), 6.91 (d, 2H, J = 8.9 Hz, $H_{3,5}$), 7.47 (d, 2H, J = 8.9 Hz, $H_{2,6}$), 7.64 (d, 1H, J = 15.9 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 16.68 ($C_{9'}$), 25.67 ($C_{4'}$), 26.26 ($C_{6'}$), 39.17 ($C_{10'}$), 39.51 ($C_{5'}$), 51.53 (CH_3), 64 0.88 ($C_{1'}$), 110.03 (C_8), 115.11 ($C_{3,5}$), 118.84 ($C_{2'}$), 123.73 ($C_{7'}$), 126.97 (C_1), 129.69 ($C_{2,6}$), 131.83 ($C_{8'}$), 141.66 ($C_{3'}$), 144.61 (C_7), 160.16 (C_4), 167.78 (C_9). MS (APCI, MeOH, pos.) m/z: 315.25 (MH^+).

*Preparation of (E)-Methyl-3-[4-(trifluoromethoxy)phenyl]prop-2-enoate (**5b**).* A clean dry round-bottom flask (100 mL) with a stir bar was charged with NaH (60% dispersion in mineral oil, 950 mg, 23.7 mmol, 1.5 equiv) under argon. It was then washed with petroleum ether (5 mL × 2). Dry THF (40 mL) was added to the reaction flask and stirred at 0 °C for 15 min. Methyldiethylphosphonoacetate (3.5 mL, 19 mmol, 1.2 equiv) was added to the suspension over 10 min. It was then stirred at 0 °C for 30 min when a colorless solution resulted. A solution of 4-trifluoromethoxybenzaldehyde (2.3 mL, 15.8 mmol, 1 equiv) in dry tetrahydrofurane (12 mL) was slowly added to the reaction flask over 10 min. The reaction was then stirred at room temperature (25 °C) for 20 h and was monitored by TLC. A saturated aqueous NH_4Cl (2 mL) solution was then added to quench the reaction. Tetrahydrofurane was removed under reduced pressure, and water (30 mL) was added to the reaction mixture. It was then extracted with ethylacetate (60 mL × 3). The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (3% ethyl acetate in petroleum ether) to afford compound **5b** as a solid (3.3 g, 89%); mp 48−50 °C. IR (KBr) ν cm^{-1}: 2956 (C−H), 1713 (C═O), 1641 (C═C arom.), 1510 (C═C arom.), 1284 (C−O ether), 1161 (C−F), 990 (CH═CH ethylenic), 839 (C arom 1−4). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.81 (s, 3H, H_{10}), 6.41 (d, 1H, J = 16.0 Hz, H_8), 7.23 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.54 (d, J = 8.9 Hz, $H_{2,6}$), 7.66 (d, J = 16.0 Hz, H_7). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.62 (C_{10}), 118.59 (C_8), 120.17 (q, J = 258.1 Hz, CF_3), 120.97 ($C_{3,5}$), 129.29 ($C_{2,6}$), 132.80 (C_1), 142.89 (C_7), 150.21 (C_4), 166.89 (C_9). ^{19}F NMR ($CDCl_3$ 282 MHz) δ ppm: −57.79 (s, 3F, CF_3O−). HRMS (APCI, MH^+) calcd for $C_{11}H_{10}F_3O_3$, 247.0582; found, 247.0575.

*(E)-Methyl-3-[4-(2′,2′,2′-trifluoroethoxy)phenyl]prop-2-enoate (**5d**).* A clean dry round-bottom flask (50 mL) with a stir bar was charged with NaH (60% dispersion in mineral oil, 240 mg, 6 mmol, 1.2 equiv) under argon. Dry dimethylsulfoxide (4 mL) was added to the reaction flask and stirred at 0 °C for 15 min. A solution of phenol (**4**) (890 mg, 5 mmol, 1 equiv) in DMSO (2 mL) was added to the suspension slowly over 10 min (1 mL of DMSO was used for rinsing). It was then allowed to stir at 0 °C for 30 min when a dark yellow solution resulted. 2,2,2-Trifluoroethyl iodide (1.5 mL, 15 mmol, 3 equiv) was added to the reaction flask. The reaction was then stirred at 80 °C for 24 h and monitored by TLC (1/9 ethyl acetate/petroleum ether). A saturated aqueous NH_4Cl (2 mL) solution was added to quench the reaction. Water (20 mL) was added and then extracted with diethyl ether (30 mL × 3). The organic layer was dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (3% ethyl acetate in petroleum ether) to afford compound **5d** as a solid (0.68 g, 52%); mp 96−98 °C. IR (KBr) ν cm^{-1}: 2951 (C−H), 1708 (C═O), 1604 (C═C arom.), 1515 (C═C arom.), 1245 (C−O), 1170 (C−F), 974 (CH═CH), 830 (C arom. 1−4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 3.80 (s, 3H, H_{10}), 4.38 (q, 2H, J = 8.0 Hz, CH_2), 6.34 (d, 1H, J = 16.0 Hz, H_8), 6.95 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.50 (d, 2H, J = 8.5 Hz, $H_{2,6}$), 7.65 (d, 1H, J = 16.0 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 51.69 (C_{10}), 65.66 (q, J = 35.9 Hz, CH_2), 115.18 ($C_{2,6}$), 116.51 (C_8), 123.15 (q, J = 277.9 Hz, $C_{2'}$), 128.90 (C_1), 129.61 ($C_{3,5}$), 143.87 (C_7), 158.80 (C_4), 167.52 (C_9). ^{19}F NMR ($CDCl_3$ 282 MHz) δ ppm: −73,85 (t, 3F, J = 8 Hz). MS (DCI, CH_4, pos.) m/z: 261.07 (MH^+).

*Representative Procedure: (E)-3-[4-(3-Methylbut-2-enyloxy)phenyl]-prop-2-enoic Acid (**6e**).* To compound **5e** (0.5 g, 2.03 mmol, 1 equiv) in MeOH (10 mL) was added K_2CO_3 (1.4 g, 10.1 mmol, 5 equiv) dissolved in H_2O (10 mL). The reaction mixture was refluxed for 3 h, and then, MeOH was removed under reduced pressure. It was then cooled at 0 °C and acidified to pH 2 with HCl (1M). The mixture was extracted with diethyl ether (30 mL × 3). The combined organic layer was washed with brine (30 mL), dried with Na_2SO_4, and evaporated in vacuo to give **6e** as white solid (0.37 g, 91%); mp 148−150 °C. IR (KBr) ν cm^{-1}: 3268 (N−H), 3168 (C═C−H), 2942 (C−H), 2854 (C−H, CH_3−O), 1720 (C═O), 1637 (C═C), 1603 (C═C), 1572 (C═C arom.), 1511 (C═C arom.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.69 (s, 3H, $H_{4'}$), 1.74 (s, 3H, $H_{5'}$), 4.49 (d, 2H, J = 5 Hz, $H_{1'}$), 5.42 (t, 1H, = 5 Hz, $H_{2'}$), 6.25 (d, 1H, J = 15.6 Hz, H_8), 6.86 (d, 2H, J = 8.5 Hz, $H_{3,5}$), 7.43 (d, 2H, J = 8.5 Hz, $H_{2,6}$), 7.67 (d, 1H, J = 15.6 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 18.24 ($C_{4'}$), 25.83 ($C_{5'}$), 64 0.96 ($C_{1'}$), 114.20 (C_8), 114.97 ($C_{3,5}$), 119.16 ($C_{2'}$), 126.69 (C_1), 130.11 ($C_{2,6}$), 138.75 ($C_{3'}$), 146.80 (C_7), 161.11 (C_4), 172.90 (C_9). HRMS (DCI, CH_4, pos.) m/z: calcd for $C_{14}H_{17}O_3$ (MH^+), 233.1178; obtained, 233.1180.

*(E)-3-[4-(Trifluoromethoxy)phenyl]prop-2-enoic Acid (**6b**).* Compound **6b** was prepared from ester **5b** according to procedure used for **6e** synthesis. Solid (0.47 g, quantitative); mp 180−182 °C. IR (KBr) ν cm^{-1}: 3462(OH), 1686 (C═O), 1629 (C═C arom.), 1510 (C═C arom.), 1268 (C−O ether), 1216 (C−F), 931 (CH═CH), 832 (C arom. 1−4). ^{1}H NMR (acetone-d_6, 300 MHz) δ ppm: 6.57 (d, 1H, J = 16.1 Hz, H_8), 7.39 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.7 (d, 1H, J = 16.1 Hz, H_7), 7.84 (d, 2H, J = 8.6 Hz, $H_{2,6}$). ^{13}C NMR (acetone-d_6, 75 MHz) δ ppm: 121.83 (C_8), 122.59 (q, J = 256.2 Hz, CF_3), 123.42 ($C_{3,5}$), 132.10 ($C_{2,6}$), 135.94 (C_1), 144.89 (C_7), 152.20 (C_4), 166.78 (C_9). ^{19}F NMR (acetone-d_6, 282 MHz) δ ppm: −58.52 (s, 3F, CF_3O−). HRMS: calcd for $C_{10}H_8F_3O_3$ (MH^+), 233.0426; found, 233.0427.

*(E)-3-(4-Ethoxyphenyl)prop-2-enoic Acid (**6c**).* Compound **6c** was prepared from ester **5c** according to procedure used for **6e** synthesis. Solid (0.40 g, quantitative); mp 184−185 °C. IR (KBr) ν cm^{-1}: 3431 (OH), 2980 (C−H), 1679 (C═O), 1600 (C═C arom.), 1510 (C═C arom.), 1248 (C−O). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.43 (t, 3H, J = 7.0 Hz, $H_{2'}$), 4.8 (q, 2H, J = 7.0 Hz, $H_{1'}$), 6.1 (d, 1H, J = 15. Hz, H_8), 6.90 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.49 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.74 (d, 1H, J = 15.9 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 14.73 ($C_{2'}$), 63.68

($C_{1'}$), 114.44 (C_8), 114.88 ($C_{3,5}$), 126.62 (C_1), 130.14 ($C_{2,6}$), 146.84 (C_7), 161.19 (C_4), 172.41 (C_9). HRMS (DCI, CH_4, pos.) m/z: calcd for $C_{11}H_{13}O_3$ (MH^+), 193.0865; obtained, 193.0870.

*(E)-3-[4-(2′,2′,2′-Trifluoroethoxy)phenyl]prop-2-enoic Acid (**6d**).* Compound **6d** was prepared from ester **5d** according to procedure used for **6e** synthesis. Solid (0.50 g, quantitative); mp 205−207 °C. IR (KBr) ν cm^{-1}: 3436 (OH), 2921 (C−H), 1683 (C═O), 1603(C═C arom.), 1511 (C═C arom.), 1294 (C−O ether), 1174 (C−F), 973 (CH═CH), 830 (C arom. 1−4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 4.57 (q, 2H, J = 8.5 Hz, $H_{1'}$), 6.37 (d, 1H, J = 16.0 Hz, H_8), 7.04 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.57 (d, 2H, J = 8.5 Hz, $H_{2,6}$), 7.61 (d, 1H, J = 16.0 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 66.45 (q, J = 35.2 Hz, CH_2), 116.56 ($C_{3,5}$), 118.17 (C_8), 125.28 (q, J = 277.0 Hz, CF_3), 130.21 (C_1), 131.28 ($C_{2,6}$), 145.22 (C_7), 160.32 (C_4), 168.41 (C_9). ^{19}F NMR: (acetone-d_6, 282 MHz) δ ppm: −74.65 (t, 3F, J = 8.5 Hz, CF_3). HRMS: calcd for $C_{11}H_{11}F_3O_3$ (MH^+), 247.0583; found, 247.0582.

*(E)-3-{4-[(E)-3,7-Dimethylocta-2,6-dienyloxy]phenyl}prop-2-enoic Acid (**6f**).* Compound **6f** was prepared from ester **5f** according to procedure used for **6e** synthesis. Solid (0.49 g, 71%); mp 115−117 °C. IR (KBr) ν cm^{-1}: 3429 (O−H), 2968 (C═CH), 2925 (C−H), 2856 (C−H), 1671 (C═O), 1626 (C═C), 1602 (C═C), 1573 (C═C arom.), 1512 (C═C arom.), 1246 (C−O ether), 991 (CH═CH trans), 827 (C arom 1−4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.54 (s, 3H, $H_{9'}$), 1.61 (s, 3H, $H_{4'}$), 1.64 (s, 3H, $H_{10'}$), 2.04 (m, 4H, $H_{5',6'}$), 4.51 (d, 2H, J = 6.9 Hz, $H_{1'}$), 5.03 (m, 1H, $H_{7'}$), 5.41 (t, 1H, J = 6.9 Hz, $H_{2'}$), 6.25 (d, 1H, J = 15.9 Hz, H_8), 6.85 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.42 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.66 (d, 1H, J = 15.9 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 16.71 ($C_{4'}$), 17.71 ($C_{9'}$), 25.68 ($C_{10'}$), 26.26 ($C_{6'}$), 39.53 ($C_{5'}$), 65.05 ($C_{1'}$), 114.47 (C_8), 115.11 ($C_{3,5}$), 118.97 ($C_{2'}$), 123.73 ($C_{7'}$), 126.66 (C_1), 130.08 ($C_{2,6}$), 131.83 ($C_{8'}$), 141.77 ($C_{3'}$), 146.79 (C_7), 161.13 (C_4), 172.32 (C_9). MS (DCI, NH_3, pos.) m/z: 301 (MH^+), 318 (MNH_4^+).

*Representative Procedure: Preparation of (E)-S-2-Acetamidoethyl 3-[4-(3-Methylbut-2-enyloxy)phenyl]prop-2-enethioate (**7e**).* A clean dry round-bottom flask (25 mL) with a magnetic stir bar was charged with carboxylic acid **6e** (0.46 g, 2 mmol, 1 equiv), *N*-acetylcysteamine (0.24 g, 2 mmol, 1 equiv), DMAP (0.26 g, 2.2 mmol, 1.1 equiv), and EDC·HCl (0.42 g, 2.2 mmol, 1.1 equiv) under argon. Dry dichloromethane (15 mL) was added to it and stirred at room temperature for 24 h. TLC was monitored in ethylacetate. Dichloromethane was removed under reduced pressure. Ethylacetate (60 mL) was added to the crude yellow mass, and the solution was thoroughly washed with water (30 mL × 3). The organic layer was then dried over $MgSO_4$. Removal of the solvent gave a crude yellowish mass. It was the purified over silica gel (70−200 mesh) using 80% ethylacetate in petroleum ether to afford **7e** as sticky solid (0.52 g, 78%,). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.76 (s, 3H, $H_{4'}$), 1.81 (s, 3H, $H_{5'}$), 1.99 (s, 3H, H_{13}), 3.16 (t, 2H, J = 6.4 Hz, H_{10}), 3.50 (td, 2H, J = 6.4 Hz, HC_{11}), 4.51 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.42 (th, 1H, J = 6.6 Hz, J = 1.5 Hz, $H_{2'}$), 5.99 (s, 1H, NH), 6.54 (d, 1H, J = 15.9 Hz, H_8), 6.85 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.43 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.53 (d, 1H, J = 15.9 Hz, H_7). ^{13}C NMR ($CDCl_3$, 300 MHz) δ ppm: 18.23 (s, 1C, $C_{4'}$), 23.22 (C_{13}), 25.82 ($C_{5'}$), 28.67 (C_{10}), 39.92 (C_{11}), 64.85 ($C_{1'}$), 115.17 ($C_{3,5}$), 119.07 ($C_{2'}$), 122.10 (C_8), 126.35 (C_1), 130.27 ($C_{2,6}$), 141.15 (C_7), 161.24 (C_4), 170.46 (C_{12}), 190.00 (C_9). MS (DCI, NH_3, pos.) m/z: 334.3 (MH^+), 351.3 (MNH_4^+). HPLC purity: 100%.

*(E)-S-2-Acetamidoethyl 3-(4-Methoxyphenyl)prop-2-enethioate (**7a**).* Compound **7a** was prepared from acid **6a** according to procedure used for **7e** synthesis. White solid (0.43 g, 77%); mp 96−97 °C. IR (KBr) ν cm^{-1}: 3268 (NH), 3168 (CH), 1640 (CO), 1548 (C═C arom.), 979 (HC═CH). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.91 (s, 3H, C_{13}), 3.15 (t, 2H, J = 6.4 Hz, CH_2S), 3.50 (q, 2H, J = 5.9 Hz, H_{10}), 3.85 (s, 3H, C_{13}), 6.61 (d, 1H, J = 15.7 Hz, H_8), 6.91 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.50 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.59 (d, 1H, J = 15.7 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 23.4 (C_{13}), 28.5 (C_{10}), 40.0 (C_{11}), 55.5 ($C_{1'}$), 114.5 ($C_{3,5}$), 122.2 (C_7), 126.5 (C_1), 130.24 ($C_{2,6}$), 141.20 (C_8), 160.0 (C_4), 165.6 (C_{12}), 188.0 (C_9). EI MS (m/z): 279 (M^+), 161 (M^+ − Cys), 133 (M^+ − Cys−CO). Anal. calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 5.28. Observed: C, 57.01; H, 5.66; N, 4.79).

*(E)-S-2-Acetamidoethyl 3-{4-[(E)-3,7-Dimethylocta-2,6-dienyloxy]-phenyl}prop-2-enethioate (**7f**).* Compound **7f** was prepared from acid **6f** according to procedure used for **7e** synthesis. Sticky solid (0.54 g, 67%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.53 (s, 3H, $H_{9'}$), 1.60 (s, 3H, $H_{4'}$), 1.67 (s, 3H, $H_{10'}$), 1.91 (s, 3H, C_{13}), 2.03 (m, 4H, $H_{5',6'}$), 3.08 (t, 2H, J = 6.4 Hz, CH_2S), 3.42 (q, 2H, J = 6.4 Hz, H_{10}), 4.50 (d, 2H, J = 6.5 Hz, $H_{1'}$), 5.01 (m, 1H, $H_{7'}$), 5.40 (tt, J = 6.6 Hz, J = 1.0 Hz, 1H, $H_{2'}$), 6.0 (bs, 1H, NH), 6.54 (d, 1H, J = 15.7 Hz, H_8), 6.85 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.42 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.52 (d, 1H, J = 15.7 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 16.6 ($C_{4'}$), 17.6 ($C_{9'}$), 23.1 ($C_{10'}$), 25.6 (C_{13}), 26.2 ($C_{6'}$), 28.4 (C_{10}), 39.4 ($C_{5'}$), 39.8 (C_{11}), 65.0 ($C_{1'}$), 114.9 ($C_{3,5}$), 118.9 ($C_{2'}$), 122.0 ($C_{7'}$), 122.2 (C_7),126.3 (C_1), 130.2 ($C_{2,6}$), 131.8 ($C_{8'}$), 141.2 (C_8), 141.7 ($C_{3'}$), 161.2 (C_4), 170.8 (C_{12}), 190.03 (C_9). MS (DCI, NH_3, pos.) m/z: 402.0 (MH^+), 420.0 ($M + NH_4^+$). HPLC purity: 100%.

*Representative Procedure: Preparation of (E)-N-(2-Acetamidoethyl)-3-[4-(3-methylbut-2-enyloxy)phenyl]prop-2-enamide (**8e**).* A clean dry round-bottom flask (10 mL) with a magnetic stir bar was charged with carboxylic acid **6e** (0.05 g, 0.28 mmol, 1 equiv), *N*-acetylethylenediamine (0.043 g, 0.42 mmol, 1.5 equiv), DMAP (0.037 g, 0.31 mmol, 1.1 equiv), and EDC·HCl (0.06 g, 0.31 mmol, 1.1 equiv) under argon. Dry dichloromethane (4 mL) was added to it and stirred at room temperature for 24 h. TLC was monitored in dichloromethane/methanol (95/5). Dichloromethane was removed under reduced pressure. Ethylacetate (60 mL) was added to the crude yellow mass, and the solution was thoroughly washed with water (30 mL × 3). The organic layer was then dried over $MgSO_4$. Removal of the solvent gave a crude yellowish mass. It was purified over silica gel (70−200 mesh) using 10% methanol in ethylacetate to afford **8e** as a white solid (0.055 g, 63%); mp 177−179 °C. IR (KBr) ν cm^{-1}: 3289 (N−H), 3091 (C═C−H), 1654 (C═O), 1620 (C═C), 1605 (C═C arom.), 1561,1511 (C═C arom.), 1228 (O−C arom), 972 (CH═CH), 824 (arom 1−4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.76 (s, 3H, $H_{4'}$), 1.81 (s, 3H, $H_{5'}$), 2.01 (s, 3H, H_{13}), 3.49 (m, 4H, CH_2N), 4.54 (d, 2H, $H_{1'}$), 5.5 (t, 1H, J = $H_{2'}$), 6.32 (d, 1H, J = 15.6 Hz, H_8), 6.63 (m, 2H, NH), 6.90 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.45 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.58 (d, 1H, J = 15.6 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 18.22 (C_{13}), 23.24 ($C_{4'}$), 25.83 ($C_{5'}$), 40.33 ($C_{10\text{ or }11}$), 40.35 ($C_{11\text{ or }10}$), 64.88 ($C_{1'}$), 114.95 ($C_{3,5}$), 117.86 ($C_{2'}$), 119.25 (C_8), 127.23 (C_1), 129.41 ($C_{2,6}$), 138.63 ($C_{3'}$), 140.93 (C_7), 160.33 (C_4), 167.57 (C_9), 171.61 (C_{12}). HRMS calcd for $C_{18}H_{24}N_2O_3$ ($M + Na$)$^+$, 339.1685; found, 339.1696. HPLC purity: 97%.

*(E)-N-(2-Acetamidoethyl)-3-(4-methoxyphenyl)prop-2-enamide (**8a**).* Compound **8a** was prepared from acid **6a** according to procedure for **8e** synthesis. White solid (0.046 g, 62%); mp 190−192 °C. IR (KBr) ν cm^{-1}: 3290 (N−H), 3084 (C═C−H), 1652 (C═O), 1619 (C═C), 1559 (C═C arom.), 1227 (O−C arom), 975 (CH═CH). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 2.02 (s, 3H, H_{13}), 3.50 (m, 4H, $H_{10,11}$), 3.85 (s, 3H, MeO−), 6.31 (d, 1H, J = 15.6 Hz, H_8), 6.50 (m, 2H, NH), 6.90 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.46 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.59 (d, 1H, J = 15.6 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 23.2 (C_{13}), 40.3 (C_{10}), 40.4 (C_{11}), 55.36 (CH_3), 114.2 ($C_{3,5}$), 117.9 (C_8), 127.3 (C_1), 129.4 ($C_{2,6}$), 140.9 (C_7), 161.0 (C_4), 167.5 (C_9), 171.6 (C_{12}). HRMS calcd for $C_{14}H_{19}N_2O_3$ (MH^+), 263.1396; found, 263.1422. HPLC purity: 95%.

*(E)-N-(2-Acetamidoethyl)-3-{4-[(E)-3,7-dimethylocta-2,6-dienyloxy]-phenyl}prop-2-enamide (**8f**).* Compound **8f** was prepared from acid **6f** according to the procedure for **8e** synthesis. White solid (0.089 g, 83%); mp 155−157 °C. IR (KBr) ν cm^{-1}: 3287 (N−H), 3087(C═C−H), 2924 (C−H), 2856 (C−H), 1651 (C═O), 1623 (C═C), 1562 (C═C arom.), 1229 (O−C arom.), 974 (CH═CH). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.36 (s, 3H, $H_{4'}$), 1.43 (s, 3H, $H_{9'}$), 1.48 (s, 3H, $H_{10'}$), 1.72 (s, 3H, H_{13}), 1.85 (m, 4H, $H_{5',6'}$), 3.20 (t, 2H, J = 5.1 Hz, H_{10}), 3.25 (t, 2H, J = 5.1 Hz, H_{11}), 4.28 (d, 2H, J = 6.5 Hz, $H_{1'}$), 4.83 (t, 1H, J = 6.2

Hz, $H_{7'}$), 5.22 (t, 1H, J = 6.2 Hz, $H_{2'}$), 6.14 (d, 1H, J = 15.6 Hz, H_8), 6.59 (d, 2H, J = 8.5 Hz, $H_{3,5}$), 6.98 (t, 2H, J = 4.9 Hz, NH), 7.08 (t, 2H, J = 4.8 Hz, NH), 7.15 (d, 2H, J = 8.5 Hz, $H_{2,6}$), 7.31 (d, 1H, J = 15.6 Hz, H_7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 16.67 ($C_{4'}$), 17.70 ($C_{9'}$), 23.16 ($C_{10'}$), 25.68 (C_{13}), 26.26 ($C_{6'}$), 39.52 ($C_{5'}$), 40.01 ($C_{10,11}$), 64.95 ($C_{1'}$), 114.96 ($C_{3,5}$), 118.18 (C_8), 119.05 ($C_{2'}$), 123.72 ($C_{7'}$), 127.24 (C_1), 129.36 ($C_{2,6}$), 131.82 ($C_{8'}$), 140.62 (C_7), 141.58 ($C_{3'}$), 160.29 (C_4), 167.65 (C_9), 171.67 (C_{12}). HRMS calcd for $C_{23}H_{32}N_2O_3$ $(M + Na)^+$, 407.2311; found, 407.2283. HPLC purity: 97%.

*(E)-N-(Pyridin-2-yl)-3-[4-(3-methylbut-2-enyloxy)phenyl]prop-2-enamide (**9e**).* A clean dry round-bottom flask (25 mL) with a magnetic stir bar was charged with carboxylic acid **6e** (0.46 g, 2 mmol, 1 equiv), 2-aminopyridine (0.23 g, 2.4 mmol, 1.2 equiv), DMAP (0.26 g, 2.2 mmol, 1.1 equiv), and EDC·HCl (0.42 g, 2.2 mmol, 1.1 equiv) under argon. Dry dichloromethane (15 mL) was added to it and stirred at room temperature for 24 h. TLC was monitored in ethylacetate. Dichloromethane was removed under reduced pressure. Ethylacetate (60 mL) was added to the crude yellow mass, and the solution was thoroughly washed with water (30 mL × 3). The organic layer was then dried over $MgSO_4$. Removal of the solvent gave a crude yellowish mass. It was the purified over silica gel (70−200 mesh) using 80% ethylacetate in petroleum ether to afford **9e** as a white solid (0.26 g, 42%); mp 130−132 °C). IR (KBr) ν cm^{-1}: 3431 (NH), 3190 (HC═CH), 3007 (C−H), 1693 (C═O), 1630 (C═N), 1605 (C═C arom.), 1582 (C═C arom.), 1516 (C═C arom.), 1260 (C−O), 987 (CH═CH), 823 (C arom.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.68 (s, 3H, $H_{4'}$), 1.73 (s, 3H, $H_{5'}$), 4.48 (d, 2H, J = 6.8 Hz, $H_{1'}$), 5.42 (t, 1H, J = 6.8 Hz, $H_{2'}$), 6.52 (d, 1H, J = 15.6 Hz, H_8), 6.82 (m, 1H, H_{11}), 6.84 (d, 2H, J = 8.5 Hz, $H_{3,5}$), 7.13 (t, 1H, J = 7.3 Hz, H_{13}), 7.42 (d, 2H, J = 8.5 Hz, $H_{2,6}$), 7.68 (d, 1H, J = 15.6 Hz, H_7), 7.89 (t, 1H, J = 7.3 Hz, H_{14}), 8.14 (d, 1H, J = 2.0 Hz, H_{11}), 9.80 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 14.19 ($C_{4'}$), 25.82 ($C_{5'}$), 64.92 ($C_{1'}$), 114.65 (C_{11}), 115.04 ($C_{3,5}$), 117.91 ($C_{2'}$), 119.21 (C_8), 119.58 (C_{13}), 127.61 (C_1), 129.73 ($C_{2,6}$), 138.67 ($C_{3'}$), 138.79 (C_{12}), 142.88 (C_7), 147.23 (C_{14}), 151.95 (C_{10}), 160.69 (C_4), 164.79 (C_9). HRMS calcd for $C_{19}H_{21}N_2O_2$ (MH^+), 309.1603; found, 309.1591. HPLC purity: 95%.

*(E)-N-(Pyridin-2-yl))-3-(4-mehoxyphenyl)prop-2-enamide (**9a**).* Compound **9a** was prepared from acid **6a** according to procedure used for **9e** synthesis (0.37 g, 73%). White solid; mp 93−95 °C. IR (KBr) ν cm^{-1}: 3432 (NH), 3194 (HC═CH), 3008 (C−H), 1693 (C═O), 1630 (C═N), 1605 (C═C arom.), 1582 (C═C arom.), 1516 (C═C arom.), 1260 (C−O), 988 (CH═CH), 824 (C arom.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 3.83 (s, 3H, $H_{1'}$), 6.50 (d, 1H, J = 15.5 Hz, H_8), 6.88 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.10 (dd, 1H, J = 7.3 Hz, J = 5.0 Hz, H_{13}), 7.45 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.75 (d, 1H, J = 15.5 Hz, H_7), 7.75 (m, 1H, H_{12}), 8.30 (d, 1H, J = 4.9 Hz, H_{14}), 8.40 (d, 1H, J = 8.4 Hz, H_{11}), 9.28 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 55.3 ($C_{1'}$), 114.3 (C_{11}), 114.6 ($C_{3,5}$), 118.1 (C_8), 119.6 (C_{13}), 127.2 (C_1), 129.7 ($C_{2,6}$), 138.5 (C_{12}), 142.6 (C_7), 147.6 (C_{14}), 152.0 (C_{10}), 161.3 (C_4), 164.6 (C_9). HRMS calcd for $C_{15}H_{15}N_2O_2$ (MH^+), 255.1134; found, 255.1141. HPLC purity: 95%.

*(E)-N-(Pyridin-2-yl)-3-{4-[(E)-3,7-dimethylocta-2,6-dienyloxy]phenyl}-prop-2-enamide (**9f**).* Compound **9f** was prepared from acid **6f** according to procedure used for **9e** synthesis (0.72 g, 48%). White solid; mp 98−100 °C. IR (KBr) ν cm^{-1}: 3426 (NH), 3187 (HC═CH), 3008 (C−H), 1697 (C═O), 1634 (C═N), 1604 (C═C arom.), 1579 (C═C arom.), 1514 (C═C arom.), 1261 (C−O), 981 (CH═CH), 827(C arom.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.38 (s, 3H, $H_{4'}$), 1.45 (s, 3H, $H_{9'}$), 1.51 (s, 3H, $H_{10'}$), 1.87 (m, 4H, $H_{5',6'}$), 4.34 (d, 2H, J = 6.5 Hz, $H_{1'}$), 4.87 (t, 1H, J = 6.6 Hz, $H_{7'}$), 5.25 (t, 1H, J = 6.5 Hz, $H_{2'}$), 6.25 (d, 1H, J = 15.5 Hz, H_8), 6.66 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 6.83 (dd, 1H, J = 7.2 Hz, J' = 5.5 Hz, H_{13}), 7.21 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.52 (d, 1H, J = 15.5 Hz, H_7), 7.53 (m, 1H, H_{12}), 8.10 (d, 1H, J = 4.5 Hz, H_{14}), 8.20 (d, 1H, J = 8.4 Hz, H_{11}), 9.22 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 16.71 ($C_{4'}$), 17.72 ($C_{9'}$), 25.70 ($C_{10'}$), 26.27 ($C_{6'}$), 39.53 ($C_{5'}$), 65.01 ($C_{1'}$), 114.77 (C_{11}), 115.07 ($C_{3,5}$), 118.04 (C_8), 119.07 ($C_{2'}$), 119.53 (C_{13}), 123.73 ($C_{7'}$), 127.11 (C_1), 129.66 ($C_{2,6}$), 131.87 ($C_{8'}$), 138.58 (C_{12}), 141.65 ($C_{3'}$), 142.70 (C_7), 147.60 (C_{14}), 152.89 (C_{10}), 161.64 (C_4), 164.87 (C_9). HRMS calcd for $C_{24}H_{28}N_2O_2$ (MH^+), 377.2253; found, 377.2229. HPLC purity: 95%.

*(E)-N-(3-Oxo-1,2-oxazolidin-4-yl)-3-(4-methoxyphenyl)prop-2-enamide (**10a**).* A clean dry round-bottom flask (10 mL) was charged with *p*-methoxycinnamic acid (0.06 g, 0.34 mmol, 1 equiv) and oxalyl chloride (3 mL) at 0 °C and sealed with anhydrous calcium chloride guard tube. The reaction mixture was stirred at room temperature for 2 h, and then, excess oxalyl chloride was removed in vacuo to give corresponding acyl chloride quantitatively.

In another round-bottom flask (25 mL) D-cycloserine (0.035 g, 0.34 mmol, 1 equiv) in dry dichloromethane (5 mL), *N*-methylpyrrolidine (NMP) (1 mL, 9.6 mmol, 30 equiv) and bis-(trimethylsilyl)acetamide (BSA) (0.17 g, 0.85 mmol, 2.5 equiv) were stirred under N_2 at room temperature for 1 h. The reaction mixture was cooled to 0 °C. Then, pyridine (0.07 mL g, 6.8 mmol, 20 equiv) and acyl chloride dissolved in dichloromethane (2 mL) were added to the reaction flask. The reaction mixture was then stirred at room temperature for 12 h. Volatiles were removed under reduced pressure. The residue dissolved in ethylacetate (15 mL) and washed with dilute aqueous HCl (pH ca. 2, 3 × 5 mL) and brine. The organic layer was dried over anhydrous Na_2SO_4 and then evaporated in vacuo. The resulting brown solid was triturated with 10% ethylacetate in hexanes, filtered, and dried to afford compound **10a** as a solid (0.063 g, 71%); mp 198−200 °C. $[\alpha]_D$ + 4.3; C = 0.01 g/cm^3. IR (KBr) ν cm^{-1}: 3254 (N−H), 3058 (C−H), 1708 (C═O), 1651 (C═O), 1623 (C═C), 1604 (C═C arom.), 1512 (C═C arom.), 1256 (C−O ether), 972 (CH═CH), 826 (C arom. 1−4). ^{1}H NMR (MeOD-d_4, 300 MHz) δ ppm: 3.80 (s, 3H, CH_3), 4.11 (dd, 1H, J = 9.9 Hz, J = 8.6 Hz, H_{11}), 4.66 (t, 1H, J = 8.5 Hz, H_{10}), 5.03 (dd, 1H, J = 9.9 Hz, J' = 8.6 Hz, H_{11}), 6.50 (d, 1H, J = 15.7 Hz, H_8), 6.92 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.50 (d, 2H, J = 8.6 Hz, $H_{2,6}$), 7.53 (d, 1H, J = 15.7 Hz, H_7). ^{13}C NMR (MeOD-d_4, 75 MHz) δ ppm: 51.93 (C_{10}), 54.45 ($C_{1'}$), 72.92 (C_{11}), 113.98 ($C_{3,5}$), 116.86 (C_8), 127.22 (C_1), 129.24 ($C_{2,6}$), 141.33 (C_7), 161.40 (C_4), 167.89 (C_9), 170.56 (C_{12}). HRMS calcd for $C_{13}H_{15}N_2O_4$ (MH^+), 263.1066; found, 263.1072. HPLC purity: 96%.

*Representative Procedure: Preparation of (E)-N′-{3-[4-(3-Methylbut-2-enyloxy)phenyl]propenoyl}isonicotinohydrazide (**11e**).* A clean round-bottom flask (25 mL) was charged with **6e** (0.2 g, 0.86 mmol, 1 equiv), HBTU (0.49 g, 1.29 mmol, 1.5 equiv), and INH (0.18 g, 1.29 mmol, 1.5 equiv) in dry DMF (10 mL). Diisopropylethylamine (0.3 mL, 1.72 mmol, 2 equiv) was added to it, and the reaction mixture was stirred at room temperature for 24 h. Dimethylformamide was removed under vacuum, and brine (20 mL) was added to the residue. The aqueous phase was extracted with ethyl acetate (40 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a yellow residue that was purified over silica gel using 5% methanol in dichloromethane to afford compound **11e**. White solid (0.206 g, 68%); mp 176−178 °C. IR (KBr) ν cm^{-1}: 3242 (N−H), 3019 (C═C−H), 1679 (C═O), 1634 (C═C), 1605 (C═C), 1587 (C═C arom.), 1495 (C═C arom.), 1176 (O−C), 1466 (CH_2), 981 (CH═CH), 837 (C arom 1−4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.77 (bs, 3H, $H_{4'}$), 1.82 (bs, 3H, $H_{5'}$), 4.55 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.49 (t, 1H, J = 6.6 Hz, J' = 1.3 Hz, $H_{2'}$), 6.51 (d, 1H, J = 15.6 Hz, H_8), 6.88 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.40 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.66 (d, 1H, J = 15.6 Hz, H_7), 7.71 (d, 2H, J = 5.6 Hz, $H_{12,15}$), 8.73 (d, 2H, J = 5.6 Hz, $H_{13,14}$), 9.59 (bs, 1H, NH), 10.34 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 18.11 ($C_{4'}$), 25.62 ($C_{5'}$), 65.04 ($C_{1'}$), 114.12 ($'C_8$), 115.17 ($C_{3,5}$), 119.34 ($C_{12,15}$), 121.0 ($C_{2'}$), 126.88 (C_1), 129.66 ($C_{2,6}$), 138.33 ($C_{3'}$), 138.57 (C_{11}), 143.27 (C_7), 150.61 ($C_{13,14}$), 160.96 (C_4), 162.36 (C_{10}), 163,93 (C_9). HRMS calcd for $C_{20}H_{22}N_3O_3$ (MH^+), 352.1685; found, 352.1661. HPLC purity: 95%.

*(E)-N′-[3-(4-Methoxyphenyl)propenoyl]isonicotinohydrazide (**11a**).* Compound **11a** was prepared from acid **6a** according to procedure used

for **11e** synthesis. White solid (0.95 g, 74%); mp 242−245 °C. IR (KBr) ν cm^{-1}: 3208 (N−H), 3028 (C═C−H), 2837 (C−H), 1688 (C═O), 1630 (C═C), 1587 (C═C arom.), 1498 (C═C arom.), 1254 (O−C), 981 (CH═CH), 826 (C arom. 1−4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 3.80 (s, 3H, $H_{1'}$), 6.62 (d, 1H, J = 16.2 Hz, H_8), 7.0 (d, 2H, J = 8.5 Hz, $H_{2,6}$), 7.55 (d, 1H, J = 16.2 Hz, H_7), 7.58 (d, 2H, J = 8.5 Hz, $H_{3,5}$), 7.81 (d, 2H, J = 4.2 Hz, $H_{12,15}$), 8.70 (d, 2H, J = 4.2 Hz, $H_{13,14}$), 10.24 (s, 1H, NH), 10.83 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 55.77 ($C_{1'}$), 114.93 ($C_{3,5}$), 117.09 (C_8), 121.81 ($C_{12,15}$), 127.54 (C_1), 129.90 ($C_{2,6}$), 139.93 (C_{11}), 140.74 (C_7), 150.89 ($C_{13,14}$), 161.16 (C_4), 164.38 (C_{10}), 165.10 (C_9). HRMS calcd for $C_{16}H_{15}N_3O_3$ (MH^+), 298.1192; found, 298.1212. HPLC purity: 95%.

*(E)-N′-[3-(4-Trifluoromethoxyphenyl)propenoyl]isonicotinohydrazide (**11b**).* Compound **11b** was prepared from acid **6b** according to procedure used for **11e** synthesis. White solid (0.24 g, 81%); mp 196−198 °C. IR (KBr) ν cm^{-1}: 3197 (NH), 3018 (C═CH), 1638 (C═O), 1587 (C═C arom.), 1554 (C═C arom.), 1271 (C−O), 1218 (C−F), 971 (CH═CH), 843 (C arom. 1−4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 6.79 (d, 1H, J = 15.9 Hz, H_8), 7.43 (d, 2H, J = 8.3 Hz, $H_{3,5}$), 7.63 (d, 1H, J = 15.9 Hz, H_7), 7.78 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.82 (d, 2H, J = 5.9 Hz, $H_{12,15}$), 8.78 (d, 2H, J = 5.8 Hz, $H_{13,14}$), 10.43 (m, 1H, NH), 10.83 (m, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 120.46 (q, J = 255.0 Hz, CF_3), 120.90 (C_8), 121.81 ($C_{12,15}$), 121.86 ($C_{3,5}$), 130.17 ($C_{2,6}$), 134.29 (C_1), 139.40 (C_7), 139.84 (C_{11}), 149.54 (C_4), 150.88 ($C_{13,14}$), 164.35 (C_{10}), 164.48 (C_9). ^{19}F NMR (DMSO-d_6, 282 MHz) δ ppm: −56.76 (s, 3F, CF_3O−). HRMS calcd for $C_{16}H_{13}F_3N_3O_3$ (MH^+), 352.0928; found, 352.9022. HPLC purity: 98%.

*(E)-N′-[3-(4-Ethoxyphenyl)propenoyl]isonicotinohydrazide (**11c**).* Compound **11c** was prepared from acid **6c** according to procedure used for **11e** synthesis. White solid (0.19 g, 65%); mp 215−217 °C. IR (KBr) ν cm^{-1}: 3277 (NH), 3028 (C═CH), 1662 (C═O), 1628 (C═CH), 1604 (C═C arom.), 1513 (C═C arom.), 1260 (C−O). ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 1.40 (t, 3H, J = 6.9 Hz, $H_{2'}$), 4.13 (q, 2H, J = 6.9 Hz, $H_{1'}$), 6.66 (d, 1H, J = 15.8 Hz, H_8), 7.04 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.59 (d, 1H, J = 15.4 Hz, H_7), 7.63 (d, 2H, J = 8.6 Hz, $H_{2,6}$), 7.87 (d, 2H, J = 6.1 Hz, $H_{12,15}$), 8.84 (d, 2H, J = 6.0 Hz, $H_{13,14}$), 10.29 (s, 1H, NH), 10.89 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 14.11 ($C_{2'}$), 62.78 ($C_{1'}$), 114.40 ($C_{3,5}$), 116.04 (C_8), 120.87 ($C_{12,15}$), 126.44 (C_1), 128.96 ($C_{2,6}$), 138.98 (C_{11}), 139.81 (C_7), 149.96 ($C_{13,14}$), 159.50 (C_4), 163.42 (C_{10}), 164.15 (C_9). HRMS calcd for $C_{17}H_{18}N_3O_3$ (MH^+), 312.1353; found, 312.1348. HPLC purity: 95%.

*(E)-N′-[3-(4-(2′,2′,2′-Trifluoroethoxyphenyl]propenoyl]isonicotinohydrazide (**11d**).* Compound **11d** was prepared from acid **6d** according to procedure used for **11e** synthesis. White solid (0.23 g, 74%); mp 208−210 °C. IR (KBr) ν cm^{-1}: 3225 (NH), 3027 (C═CH), 2854 (C−H), 1635 (C═O), 1604 (C═C arom.) (C═C arom.), 1243 (C−O), 1172 (C−F). ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 4.83 (q, 2H, J = 8.9 Hz, $H_{1'}$), 6.66 (d, 1H, J = 15.8 Hz, H_8), 7.13 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.56 (d, 1H, J = 15.8 Hz, H_7), 7.63 (d, 2H, J = 8.8 Hz, $H_{2,6}$), 7.81 (d, 2H, J = 6.1 Hz, $H_{12,15}$), 8.78 (d, 2H, J = 6.0 Hz, $H_{13,14}$). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 65.04 (q, J = 34.5 Hz, $C_{1'}$), 115.81 ($C_{3,5}$), 118.12 (C_8), 118.89 ($C_{12,15}$), 124.41 (q, 1C, J = 276 Hz, $C_{2'}$), 129.09 (C_1), 129.93 ($C_{2,6}$), 139.91 (C_{11}), 140.30 (C_7), 150.89 ($C_{13,14}$), 158.60 (C_4), 164.36 (C_{10}), 164,93 (C_9). ^{19}F NMR (DMSO-d_6, 282 MHz) δ ppm: −72,48 (t, 3F, J = 8.8 Hz, CF_3−). HRMS calcd for $C_{17}H_{15}F_3N_3O_3$ (MH^+), 366.1050; found, 366.1066. HPLC purity: 95%.

*(E)-N′-[3-{4-[(E)-3,7-Dimethylocta-2,6-dienyloxy]phenyl}propenoyl]-isonicotinohydrazide (**11f**).* Compound **11f** was prepared from acid **6f** according to procedure used for **11e** synthesis. White solid (0.22 g, 61%); mp 110−112 °C. IR (KBr) ν cm^{-1}: 3249 (NH), 2969 (C═CH), 2923 (C−H), 1678 (C═CH), 1646 (C═O), 1604 (C═C arom.), 1513 (C═C arom.), 1236 (C−O), 997 (CH═CH), 844 (C arom. 1−4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.60 (s, 3H, $H_{9'}$), 1.67 (s, 3H, $H_{10'}$), 1.73 (s, 3H, $H_{4'}$), 2.10 (m, 4H, $H_{5',6'}$), 4.53 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.07 (t, 1H, J = 6.7 Hz, $H_{7'}$), 5.46 (t, 1H, J = 6.6 Hz, $H_{2'}$), 6.54 (d, 1H, J = 15.7 Hz, H_8), 6.83 (d, 2H, J = 8.0 Hz, $H_{3,5}$), 7.35 (d, 2H, J = 8.0 Hz, $H_{2,6}$), 7.57 (d, 1H, J = 15.4 Hz, H_7), 7.71 (d, 2H, J = 4.6 Hz, $H_{12,15}$), 8.64 (d, 2H, J = 4.3 Hz, H_{13-14}), 10.17 (s, 1H, NH), 11.04 (m, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 16.72 ($C_{9'}$), 17.73 ($C_{10'}$), 25.71 ($C_{4'}$), 26.30 ($C_{6'}$), 39,55 ($C_{5'}$), 65.0 ($C_{1'}$), 114.36 (C_8), 115.02 ($C_{3,5}$), 118.7 ($C_{7'}$), 121.37 ($C_{2'}$), 123.73 ($C_{12,15}$), 126.86 (C_1), 129.72 ($C_{2,6}$), 131.86 ($C_{8'}$), 138.67 ($C_{3'}$), 141.72 (C_{11}), 143.03 (C_7), 150.30 ($C_{13,14}$), 160.79 (C_4), 163.41 (C_{10}), 165.19 (C_9). HRMS calcd for $C_{25}H_{30}N_3O_3$ (MH^+), 420.2296; found, 420.2287. HPLC purity: 95%.

*(2E,N′,E)-3-[4-(3-Methylbut-2-enyloxy)phenyl]-N′-(phthalazin-1-(2H)-ylidiene)acrylo Hydrazide (**12e**).* A clean dry round-bottom flask (10 mL) with a magnetic stir bar was charged with carboxylic acid (**6e**, 0.64 g, 1.7 mmol, 1 mmol), 1-hydrazinophthalazine hydrochloride (0.5 g, 2.53 mmol, 1.5 equiv), HOBt (0.27 g, 2 mmol, 1.2 equiv), and EDC·HCl (0.48 g, 2.53 mmol, 1.5 equiv) under argon. Dry dichloromethane (15 mL) was added to it and stirred. Triethylamine (0.47 mL, 3.4 mmol, 2 equiv) was added to the reaction mixture and stirred at room temperature for 24 h, then poured into aqueous saturated NH_4Cl solution, extracted with dichloromethane (60 mL × 3), and was thoroughly washed with water (30 mL × 3). The organic layer was then dried over $MgSO_4$. Removal of the solvent gave a crude yellowish mass that was filtered off to afford **12e**. Yellow solid (0.5 g, 77%); mp 175−177 °C. IR (KBr) ν cm^{-1}: 3205 (NH), 2980 (C═CH), 2921 (C−H), 1644 (C═O), 1604 (C═C), 1572 (C═C arom.), 1547 (C═C arom.), 1222 (C−O), 984 (CH═CH), 827 (C arom. 1−4). ^{1}H NMR (DMSO-d_6, + few drops of CF_3COOD, 300 MHz) δ ppm: 1.70 (s, 3H, $H_{4'}$), 1.72 (s, 3H, $H_{5'}$), 4.56 (d, 2H, J = 6.7 Hz, $H_{1'}$), 5.42 (t, 1H, J = 6.6 Hz, $H_{2'}$), 6.68 (d, 1H, J = 15.9 Hz, H_8), 670 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.60 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.62 (d, 1H, J = 15.8 Hz, H_7), 8.19 (td, 1H, J = 7.1 Hz, J' = 1.7 Hz, H_{13}), 822 (dd, 1H, J = 7.6 Hz, J' = 1.8 Hz, H_{12}), 8.28 (td, 1H, J = 7.4 Hz, J' = 1.7 Hz, H_{14}), 8.73 (d, 1H, J = 7.6 Hz, H_{15}), 9.14 (s, 1H, H_{17}). ^{13}C NMR (DMSO-d_6, + few drops of CF_3COOD, 75 MHz) δ ppm: 18.14 ($C_{4'}$), 25.57 ($C_{5'}$), 64.89 ($C_{1'}$), 115.53 ($C_{3,5}$), 116.40 (C_8), 117.33 (C_{11}), 119.93 ($C_{2'}$), 124.66 (C_{15}), 127.14 (C_1), 128.13 (C_{16}), 129.18 (C_{12}), 129.98 ($C_{2,6}$), 134.96 (C_{13}), 136.78 (C_{14}), 137.88 ($C_{3'}$), 141.72 (C_7), 145.88 (C_{17}), 152.61 (C_4), 160.71 (C_{10}), 166.04 (C_9). HRMS calcd for $C_{22}H_{23}N_4O_2$ (MH^+), 375.1836; found, 375.1821. HPLC purity: 95%.

*(2E,N′,E)-3-(4-Methoxyphenyl)-N′-[phthalazin-1-(2H)-ylidiene]acrylohydrazide (**12a**).* Compound **12a** was prepared from acid **6a** according to procedure used for **12e** synthesis. Yellow solid (0.42 g, 78%); mp 194−196 °C. IR (KBr) ν cm^{-1}: 3199 (NH), 3072 (C═CH), 2996 (C−H), 1643 (C═O), 1604 (C═C arom.), 1546 (C═C arom.), 1259 (C−O), 982 (CH═CH), 828 (C arom. 1−4). ^{1}H NMR (DMSO-d_6, + few drops of CF_3COOD, 300 MHz) δ ppm: 3.72 (s, 3H, $C_{1'}$), 6.61 (d, 2H, J = 15.9 Hz, H_8), 6.93 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.55 (d, 2H, J = 9.0 Hz, $H_{3,5}$), 7.56 (d, 1H, J = 15.1 Hz, H_7), 8.13 (td, 1H, J = 7.8 Hz, J' = 1.7 Hz, H_{13}), 8.18 (td, 1H, J = 7.5 Hz, J' = 2.2 Hz, H_{14}), 8.22 (dd, 1H, J = 7.4 Hz, J' = 2.2 Hz, H_{12}), 8.62 (dd, 1H, J = 7.7 Hz, J' = 1.7 Hz, H_{15}), 9.08 (s, 1H, H_{17}). ^{13}C NMR (DMSO-d_6, + few drops of CF_3COOD, 75 MHz) δ ppm: 55.61 ($C_{1'}$), 114.96 ($C_{3,5}$), 116.54 (C_8), 118.63 (C_{11}), 124.61 (C_{15}), 127.29 (C_1), 128.14 (C_{16}), 129.26 (C_{12}), 130.07 ($C_{2,6}$), 135.06 (C_{13}), 136.86 (C_{14}), 141.70 (C_7), 145.93 (C_{17}), 152.65 (C_4), 161.47 (C_{10}), 166.07 (C_9). HRMS calcd for $C_{18}H16N_4O_2$ (MH^+), 321.1351; found, 321.1370. HPLC purity: 95%.

*(2E,N′,E)-3-(4-Trifluoromethoxyphenyl)-N′-[phthalazin-1-(2H)-ylidiene]acrylohydrazide (**12b**).* Compound **12b** was prepared from acid **6b** according to procedure used for **12e** synthesis. Yellow solid (0.41 g, 65%); mp 210−212 °C. IR (KBr) ν cm^{-1}: 3204 (NH), 3070 (C═CH), 1658 (C═O), 1572 (C═C arom.), 1548 (C═C arom.), 1266 (C−O), 1218 (C−F), 986 (CH═CH), 841 (C arom. 1−4). ^{1}H NMR (DMSO-d_6, + few drops of CF_3COOD, 300 MHz) δ ppm: 6.87 (d, 1H, J = 15.9 Hz, H_8), 7.42 (d, 2H, J = 8.3 Hz, $H_{3,5}$), 7.72 (d, 1H, J = 15.9 Hz, H_7), 7.82 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 8.21 (t_d, 1H, J = 7.1 Hz, J' = 1.4 Hz, H_{13}), 8.25 (d, 1H, J = 7.2 Hz, H_{12}), 8.30 (t_d, 1H, J = 7.3 Hz, J' = 1.4 Hz, H_{14}), 8.71

(d, 1H, J = 7.7 Hz, H_{15}), 9.71 (s, 1H, H_{17}). ^{13}C NMR (DMSO-d_6, + few drops of CF_3COOD, 75 MHz) δ ppm: 118.10 (C_{11}), 119.91 (C_8), 119.95 (q, 1C, J = 255 Hz, CF_3), 121.27 ($C_{3,5}$), 124.11 (C_{15}), 127.11 (C_1), 128.75 (C_{12}), 129.10 ($C_{2,6}$), 133.47 (C_{16}), 134.56 (C_{13}), 136.31 (C_{14}), 139.65 (C_7), 145.44 (C_{17}), 149.35 (C_4), 152.11 (C_{10}), 164.96 (C_9). ^{19}F NMR (DMSO-d_6, + few drops of CF_3COOD, 282 MHz) δ ppm: −57.71 (s, 3F). HRMS calcd for $C_{18}H_{14}F_3N_4O_2$ (MH^+), 375.1059; found, 375.1069. HPLC purity: 95%.

*(2E,N′,E)-3-(4-Ethoxyphenyl)-N′-[phthalazin-1-(2H)-ylidiene]acrylohydrazide (**12c**).* Compound **12c** was prepared from acid **6c** according to procedure used for **12e** synthesis. Yellow solid (0.32 g, 55%); mp 225−227 °C. IR (KBr) ν cm^{-1}: 3204 (NH), 3073 (C═CH), 2979 (C−H), 1643 (C═O), 1604 (C═C arom.), 1571 (C═C arom.), 1510 (C═C arom.), 1259 (C−O). ^{1}H NMR (DMSO-d_6, + few drops of CF_3COOD, 300 MHz) δ ppm: 1.24 (t, 3H, J = 6.9 Hz, $H_{2'}$), 3.98 (q, 2H, J = 6.9 Hz, $H_{1'}$), 6.58 (d, 1H, J = 15.9 Hz, H_8), 6.90 (d, 2H, J = 8.6 Hz, $H_{3,5}$), 7.52 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.55 (d, 1H, J = 15.7 Hz, H_7), 8.11 (td, 1H, J = 7.1 Hz, J' = 1.6 Hz, H_{13}), 8.14 (dd, 1H, J = 7.5 Hz, J' = 1.7 Hz, H_{12}), 8.20 (td, 1H, J = 7.3 Hz, J' = 1.6 Hz, H_{14}), 8.61 (d, 1H, J = 7.6 Hz, H_{15}), 9.05 (s, 1H, H_{17}). ^{13}C NMR (DMSO-d_6, + few drops of CF_3COOD, 75 MHz) δ ppm: 14.29 ($C_{2'}$), 63.15 ($C_{1'}$), 114.82 ($C_{3,5}$), 115.79 (C_8), 118.07 (C_{11}), 124.02 (C_{15}), 126.54 (C_1), 127.61 (C_{16}), 128.75 (C_{12}), 129.55 ($C_{2,6}$), 134.55 (C_{13}), 136.36 (C_{14}), 141.22 (C_7), 145.44 (C_{17}), 152.11 (C_4), 160.24 (C_{10}), 165.49 (C_9). HRMS calcd for $C_{19}H_{19}N_4O_2$ $(M + H)^+$, 335.1512; found, 335.1508. HPLC purity: 95%.

*(2E,N′,E)-3-[4-(2′,2′,2′-Ttrifluoroethoxy)phenyl]-N′-[phthalazin-1-(2H)-ylidiene]acrylo Hydrazide (**12d**).* Compound **12d** was prepared from acid **6d** according to procedure used for **12e** synthesis. Yellow solid (0.43 g, 66%); mp 254−256 °C. IR (KBr) ν cm^{-1}: 3152 (NH), 3049 (C−H), 1650 (C═O), 1605 (C═C arom.), 1550 (C═C arom.), 1246 (C−O), 1174 (C−F). ^{1}H NMR (DMSO-d_6, + few drops of CF_3COOD, 300 MHz) δ ppm: 4.80 (q, 2H, J = 8.8 Hz, CH_2), 6.71 (d, 1H, J = 15.9 Hz, H_8), 7.12 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.61 (d, 1H, J = 15.2 Hz, H_7), 7.65 (d, 2H, J = 8.3 Hz, $H_{2,6}$), 8.20 (td, 1H, J = 7.0 Hz, J' = 1.4 Hz, H_{13}), 8.23 (dd, 1H, J = 6.9 Hz, J' = 1.8 Hz, H_{12}), 8.29 (td, 1H, J = 7.3 Hz, J' = 1.7 Hz, H_{14}), 8.72 (d, 1H, J = 7.7 Hz, H_{15}), 9.15 (s, 1H, H_{17}). ^{13}C NMR (DMSO-d_6, + few drops of CF_3COOD, 75 MHz) δ ppm: 65.05 (q, J = 30.6 Hz, CH_2), 115.84 ($C_{3,5}$), 117.59 (C_8), 118.63 (C_{11}), 124.33 (q, J = 278.0 Hz, CF_3), 124.69 (C_{15}), 128.13 (C_1), 128.81 (C_{16}), 129.29 (C_{12}), 130.01($C_{2,6}$), 135.10 (C_{13}), 136.89 (C_{14}), 141.10 (C_7), 145.90 (C_{17}), 152.59 (C_4), 158.83 (C_{10}), 165.81 (C_9). ^{19}F NMR (DMSO-d_6, + few drops of CF_3COOD, 282 MHz) δ ppm: −72,68 (t, 3F, J = 8,8 Hz). HRMS calcd for $C_{19}H_{16}F_3N_4O_2$ (MH^+), 389.1228; found, 389.1225. HPLC purity: 95%.

*(2E,N′,E)-3-{4-(E)-[3,7-Dimethylocta-2,6-dienyloxy]phenyl}-N′-[phthalazin-1-(2H)-ylidiene]acrylo Hydrazide (**12f**).* Compound **12f** was prepared from acid **6f** according to procedure used for **12e** synthesis. Yellow solid (0.38 g, 51%); mp 164−166 °C. IR (KBr) ν cm^{-1}: 3204 (NH); 2968 (C═CH), 2920 (C−H), 1649 (C═O), 1604 (C═C), 1573 (C═C arom.), 1547 (C═C arom.), 1221 (C−O), 984 (CH═CH), 825 (C arom.). ^{1}H NMR (DMSO-d_6, + few drops of CF_3COOD, 300 MHz) δ ppm: 1.56 (s, 3H, $H_{9'}$), 1.62 (s, 3H, $H_{10'}$), 1.72 (s, 3H, $H_{4'}$), 2.05 (m, 4H, $H_{5',6'}$), 4.61 (d, 2H, J = 6.2 Hz, $H_{1'}$), 5.07 (t, 1H, J = 6.6 Hz, $H_{7'}$), 5.44 (t, 1H, J = 6.3 Hz, $H_{2'}$), 6.67 (d, 1H, J = 15.8 Hz, H_8), 7,02 (d, 2H, J = 8.5 Hz, $H_{3,5}$), 7.63 (d, 2H, J = 8.9 Hz, $H_{2,6}$), 7.64 (d, 1H, J = 15.3 Hz, H_7), 8.24 (t, 1H, J = 7.0 Hz, H_{13}), 8.27 (d, 1H, J = 6.6 Hz, H_{12}), 8.32 (t, 1H, J = 7.2 Hz, H_{14}), 8.69 (d, 1H, J = 7.1 Hz, H_{15}), 9.18 (s, 1H, H_{17}). ^{13}C NMR (DMSO-d_6, + few drops of CF_3COOD, 75 MHz) δ ppm: 16.75 ($C_{9'}$), 17.92 ($C_{10'}$), 25.85 ($C_{4'}$), 26.24 ($C_{6'}$), 39.32 ($C_{5'}$), 65.02 ($C_{1'}$), 115.67 ($C_{3,5}$), 116.40 (C_8), 118.65 (C_{11}), 119.85 ($C_{2'}$), 124.18 (C_{15}), 124.59 ($C_{7'}$), 127.16 (C_1), 128.16 (C_{16}), 129.34 (C_{12}), 130.08 ($C_{2,6}$), 131.48 ($C_{8'}$), 135.15 (C_{13}), 136.94 (C_{14}), 141.06 ($C_{3'}$), 141.75 (C_7), 145.98 (C_{17}), 152.66 (C_4), 160.70 (C10), 166.05 (C_9). HRMS calcd for $C_{27}H_{31}N_4O_2$ (MH^+), 443.2460; found, 443.2447. HPLC purity: 95%.

*(E)-3-[4-(3-Methylbut-2-enyloxy)styryl]-[1,2,4]triazolo[3,4-α]phthalazine (**13e**).* A clean dry round-bottom flask (25 mL) with a magnetic stir bar was charged with carboxylic acid (**6e**, 0.46 g, 1.3 mmol, 1 equiv), 1-hydrazinophthalazine hydrochloride (0.25 g, 1.3 mmol, 1 equiv), HOBt (0.25 g, 1,3 mmol, 1 equiv), and EDC·HCl (0.25 g, 1.3 mmol, 1 equiv) under argon. Dry acetonotrile (10 mL) was added to it and stirred. Triethylamine (0.24 mL, 1.72 mmol, 1.1 equiv) was added to the reaction mixture and refluxed for 48 h. TLC was monitored in ethylacetate. Acetonitrile was removed under reduced pressure. Ethylacetate (40 mL) was added to the crude yellow mass, and the solution was thoroughly washed with water (30 mL × 3). The organic layer was then dried over $MgSO_4$. Removal of the solvent gave a crude yellowish mass. It was then purified over silica gel (70−200 mesh) using 80% ethylacetate in petroleum ether to afford **13e**. Yellow solid (0.25 g, 52%); mp 170−172 °C. IR (KBr) ν cm^{-1}: 2964 (C═C−H), 1638 (C═C), 1603 (C═C arom.), 1515 (C═C arom.), 1246 (O−C), 966 (CH═CH trans), 834 (C arom. 1−4). ^{1}H NMR ($CDCl_3$ 300 MHz) δ ppm: 1.77 (bs, 3H, $H_{4'}$), 1.81 (bs, 3H, $H_{5'}$), 4.56 (d, 2H, J = 6.7 Hz, $H_{1'}$), 5.51 (t, 1H, J = 6.8 Hz, $H_{2'}$), 6.96 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.37 (d, 1H, J = 16.5 Hz, H_8), 7.60 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.81 (td, 1H, J = 6.8 Hz, J' = 1.0 Hz, H_{13}), 7.94 (d, 1H, J = 7.6 Hz, H_{12}), 7.96 (td, 1H, J = 7.3 Hz, J' = 1.2 Hz, H_{14}), 8.11 (d, 1H, J = 16.5 Hz, H_7), 8.67 (s, 1H, H_{17}), 8.70 (d, 1H, J = 7.8 Hz, H_{15}). ^{13}C NMR ($CDCl_3$ 75 MHz) δ ppm: 18.25 ($C_{4'}$), 25.85 ($C_{5'}$), 64.90 ($C_{1'}$), 108.03 (C_8), 115.04 ($C_{3,5}$), 119.40 ($C_{2'}$), 123.14 (C_{11}), 123.42 (C_{15}), 123.54 (C_{16}), 128.08 (C_{12}), 128.68 (C_1), 128.82 ($C_{2,6}$), 130.90 (C_{13}), 134.18 (C_{14}), 136.17 (C_7), 138.58 ($C_{3'}$), 142.71 (C_9), 147.54 (C_{17}), 149.04 (C_{10}), 159.89 (C_4). HRMS calcd for $C_{22}H_{20}N_4O$ (MH^+), 357.1715; found, 357.1748. HPLC purity: 95%.

*(E)-3-(4-Methoxystyryl)-[1,2,4]triazolo[3,4-α]phthalazine (**13a**).* Compound **13a** was prepared from acid **6a** according to procedure used for **13e** synthesis. Yellow solid (0.24 g, 58%); mp 193−195 °C. IR (KBr) ν cm^{-1}: 3028 (C═C−H), 2837 (C−H), 1642 (C═C), 1604 (C═C arom.), 1517 (C═C arom.), 1255 (O−C arom), 1246 (O−C), 983 (CH═CH), 821 (C arom. 1−4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 3.84 (s, 3H, $H_{1'}$), 6.92 (d, 2H, J = 8.7 Hz, $H_{3,5}$), 7.33 (d, 1H, J = 16.6 Hz, H_8), 7.58 (d, 2H, J = 8.8 Hz, $H_{2,6}$), 7.79 (td, 1H, J = 7.4 Hz, J' = 0.6 Hz, H_{13}), 7.82 (d, 1H, J = 7.6 Hz, H_{12}), 7.95 (td, 1H, J = 7.0 Hz, J' = 0.7 Hz, H_{14}), 8.06 (d, 1H, J = 16.6 Hz, H_7), 8.65 (d, 1H, J = 7.4 Hz, H_{15}), 8.65 (s, 1H, H_{17}). ^{13}C NMR ($CDCl_3$ 75 MHz) δ ppm: 55.42 ($C_{1'}$), 108.22 (C_8), 114.25 ($C_{3,5}$), 123.05 (C_{11}), 123.28 (C_{15}), 123.51 (C_{16}), 128.11 (C_{12}), 128.72 (C_1), 128.80 ($C_{2,6}$), 130.85 (C_{13}), 134.13 (C_{14}), 135.73 (C_7), 142.75 (C_9), 147.50 (C_{17}), 148.90 (C_{10}), 160.40 (C_4). HRMS calcd for $C_{18}H_{15}N_4O$ (MH^+), 303.1256; found, 303.1246. HPLC purity: 97%.

*(E)-3-(4-Trifluoromethoxystyryl)-[1,2,4]triazolo[3,4-α]phthalazine (**13b**).* Compound **13b** was prepared from acid **6b** according to procedure used for **13e** synthesis. Yellow solid (0.40 g, 87%); mp 190−192 °C. IR (KBr) ν cm^{-1}: 3043 (C−H), 1628 (C═C), 1603 (C═C arom.), 1512 (C═C arom.), 1301 (C−F), 1219 (C−O), 988 (CH═CH), 839 (C arom. 1−4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 7.34 (d, 2H, J = 8.0 Hz, $H_{3,5}$), 7.53 (d, 1H, J = 16.6 Hz, H_8), 7.88 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.91 (td, 1H, J = 7.4 Hz, J' = 1.2 Hz, H_{13}), 8.0 (d, 1H, J = 16.6 Hz, H_7), 8.04 (td, 1H, J = 7.4 Hz, J' = 1.2 Hz, H_{14}), 8.21 (d, 1H, J = 7.6 Hz, H_{12}), 8.51 (d, 1H, J = 7.4 Hz, H_{15}), 9.11 (s, 1H, H_{17}). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 112.85 (C_8), 120.57 (q, J = 255.7 Hz, CF_3), 121.70 ($C_{3,5}$), 122.61 (C_{15}), 123.22 (C_{11}), 123.53 (C_{16}), 129.52 (C_{12}), 129.55 ($C_{2,6}$), 131.51 (C_{13}), 133.48 (C_7), 134.49 (C_{14}), 135.53 (C_1), 143.01 (C_9), 148.01 (C_{10}), 148.96 (C_{17}), 149.05 (C_4). ^{19}F NMR (DMSO-d_6, 282 MHz) δ ppm: −56,67 (s, 3F, F_1). HRMS calcd for $C_{18}H_{12}F_3N_4O$ (MH^+), 357.0951; found, 357.0963. HPLC purity: 97%.

*(E)-3-(4-Ethoxystyryl)-[1,2,4]triazolo[3,4-α]phthalazine (**13c**).* Compound **13c** was prepared from acid **6c** according to procedure used for **13e** synthesis. Yellow solid (0.76 g, 58%); mp 195−197 °C. IR (KBr) ν cm^{-1}: 2975 (C−H), 1624 (C═C ethyl.), 1605 (C═C arom.), 1516 (C═C arom.), 1252 (C−O). ^{1}H NMR ($CDCl_3$ 300 MHz) δ ppm: 1.46 (t, 3H,

J = 7.0 Hz, CH_3), 4.08 (q, 2H, J = 7.0 Hz, CH_2), 6.94 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.36 (d, 1H, J = 16.5 Hz, H_8), 7.60 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.81 (td, 1H, J = 7.0 Hz, J' = 1.2 Hz, H_{13}), 7.94 (d, 1H, J = 7.5 Hz, H_{12}), 7.96 (td, 1H, J = 6.7 Hz, J' = 1.3 Hz, H_{14}), 8.10 (d, 1H, J = 16.6 Hz, H_7), 8.66 (s, 1H, H_{17}), 8.68 (d, 1H, J = 8.9 Hz, H_{15}). ^{13}C NMR ($CDCl_3$ 75 MHz) δ ppm: 14.84 (CH_3), 63.59 (CH_2), 108.28 (C_8), 114.80 ($C_{3,5}$), 123.07 (C_{11}), 123.27 (C_{15}), 123.69 (C_{16}), 128.04 (C_{12}), 128.70 (C_1), 128.77 ($C_{2,6}$), 130.71 (C_{13}), 134.03 (C_{14}), 135.74 (C_7), 142.73 (C_9), 147.36 (C_{17}), 149.04 (C_{10}), 159.87 (C_4). HRMS calcd for $C_{19}H_{17}N_4O$ (MH^+), 317.1407; found, 317.1402. HPLC purity: 95%.

*(E)-3-(4-(2′,2′,2′-Trifluoroethoxy)styryl)-[1,2,4]triazolo[3,4-α]phthalazine (**13d**).* Compound **13d** was prepared from acid **6d** according to procedure used for **13e** synthesis. Yellow solid (0.29 g, 60%); mp 245−247 °C. IR (KBr) ν cm^{-1}: 2925 (C−H), 1640 (C═C), 1626 (C═C), 1605 (C═C arom.), 1605 (C═C arom.), 1519 (C═C arom.), 1242 (C−O), 1176 (C−F). ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 4.90 (q, 2H, J = 8.9 Hz, CH_2), 7.19 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.52 (d, 1H, J = 166 Hz, H_8), 784 (d, 2H, J = 8.8 Hz, $H_{2,6}$), 8.0 (td,1H, J = 7.5 Hz, J' = 12 Hz, H_{13}), 8.05 (d, 1H, J = 16.6 Hz, H_7), 8.13 (td, 1H, J = 7.4 Hz, J' = 1.3 Hz, H_{14}), 8.30 (d, 1H, J = 7.5 Hz, H_{12}), 8.59 (d, 1H, J = 7.9 Hz, H_{15}), 9.21 (s, 1H, H_{17}). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 65.10 (q, 1C, J = 34.2 Hz, CF_3), 110.04 (C_8), 115.80 ($C_{3,5}$), 122.63 (C_{15}), 123.30 (C_{11}), 123.55 (C_{16}), 124.94 (q, J = 277.9 Hz, CH_2), 129.39 ($C_{2,6}$), 129.60 (C_{12}), 130.35 (C_1), 131.53 (C_{13}), 134.57 (C_7), 134.92 (C_{14}), 142.92 (C_9), 148.44 (C_{10}), 148.91 (C_{17}), 148.07 (C_4). ^{19}F NMR (acetone-d_6, 282 MHz) δ ppm: 74.04 (t, 3F, J = 8.7 Hz). HRMS calcd for $C_{19}H_{14}F_3N_4O$ (MH^+), 371.1134; found, 371.1120. HPLC purity: 95%.

*3-(4-((E)-3,7-Dimethylocta-2,6-dienyloxy)styryl)-[1,2,4]triazolo-[3,4-α]phthalazine (**13f**).* Compound **13f** was prepared from acid **6f** according to procedure used for **13e** synthesis. Yellow solid (109 mg, 61%); mp 150−152 °C. IR (KBr) ν cm^{-1}: 2969 (C═C−H), 2912 (C−H), 2853 (C−H), 1638 (C═C), 1626 (C═C), 1604 (C═C arom.), 1519 (C═C arom.), 1249 (C−O), 968 (CH═CH), 822 (C arom 1−4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.61 (s, 3H, $H_{9'}$), 1.68 (s, 3H, $H_{10'}$), 1.76 (s, 3H, $H_{4'}$), 2.11 (m, 4H, $H_{5',6'}$), 4.59 (d, 2H, J = 6.6 Hz, $H_{1'}$), 5.09 (t, 1H, J = 6.6 Hz, $H_{7'}$), 5.51 (t, 1H, J = 6.6 Hz, $H_{2'}$), 6.95 (d, 2H, J = 8.8 Hz, $H_{3,5}$), 7.36 (d, 1H, J = 16.5 Hz, H_8), 7.59 (d, 2H, J = 8.7 Hz, $H_{2,6}$), 7.80 (td, 1H, J = 6.8 Hz, J' = 1.1 Hz, H_{13}), 7.93 (d, 1H, J = 7.6 Hz, H_{12}), 7.95 (td, 1H, J = 7.2 Hz, J' = 1.2 Hz, H_{14}), 8.10 (d, 1H, J = 16.5 Hz, H_7), 8.65 (s, 1H, H_{17}), 8.68 (d, 1H, J = 7.8 Hz, H_{15}). ^{13}C NMR ($CDCl_3$ 75 MHz) δ ppm: 16.71 ($C_{9'}$), 17.72 ($C_{10'}$), 25.70 ($C_{4'}$), 26.29 ($C_{6'}$), 39.55 ($C_{5'}$), 64.99 ($C_{1'}$), 108.34 (C_8), 115.03 ($C_{3,5}$), 119.24 ($C_{2'}$), 123.03 (C_{11}), 123.22 (C_{15}), 123.70 (C_{16}), 123.77 ($C_{7'}$), 128.0 (C_{12}), 128.69 (C_1), 128.76 ($C_{2,6}$), 130.64 (C_{13}), 131.97 ($C_{8'}$), 133.97 (C_{14}), 135.63 (C_7), 141.49 ($C_{3'}$), 142.72 (C_9), 147.29 (C_{17}), 149.03 (C_{10}), 159.79 (C_4). HRMS calcd for $C_{27}H_{28}N_4O$ (MH^+), 425.2341; found, 425.2364. HPLC purity: 95%.

X Ray Data. All data for all structures represented in this paper were collected at low temperatures using an oil-coated shock-cooled crystal on a Bruker-AXS APEX II diffractometer with Mo Kα radiation (λ = 0.71073 Å). The structure were solved by direct methods (SHELXS-97),[27] and all nonhydrogen atoms were refined anisotropically using the full-matrix least-squares method on F^2 (1.043; SHELXL-97, Program for Crystal Structure Refinement). CCDC 765509 (**12e**) and CCDC 765510 (**13a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom. Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

*Crystal Data for **10e**.* $C_{23}H_{25}N_4O_{2.50}S_{0.50}$, M = 413.50, monoclinic, space group $P2_1/c$, a = 17.9818(6) Å, b = 16.2296(6) Å, c = 8.0706(3) Å, β = 97.541(2), V = 2334.93(15) Å^3, Z = 4, T = 193(2) K, 26329 reflections collected (3547 independent, R_{int} = 0.0615), 334 parameters, R_1 [$I > 2\sigma(I)$] = 0.0637 and wR_2 [all data] = 0.1932, largest diff. peak and hole: 0.451 and −0.237 e.Å^{-3}.

*Crystal Data for **11a**.* $C_{18}H_{14}N_4O$, M = 302.33, monoclinic, space group $P2_1/n$, a = 7.9162(1) Å, b = 12.8303(2) Å, c = 14.6672(3) Å, β = 104.344(1), V = 1443.27(4) Å^3, Z = 4, T = 173(2) K, 21211 reflections collected (3557 independent, R_{int} = 0.0391), 209 parameters, R_1 [$I > 2\sigma(I)$] = 0.0392 and wR_2 [all data] = 0.1034, largest diff. peak and hole: 0.245 and −0.198 e.Å^{-3}.

■ ASSOCIATED CONTENT

Supporting Information. HPLC purity analysis data for target compounds and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

TB, tuberculosis; HIV, human immunodeficiency virus; MDR, multidrug-resistant; XDR, extensively drug-resistant; MIC, minimum inhibitory concentration; INH, isoniazid; ACP, acyl carrier protein; DMAP, 4-*N*,*N*-dimethylaminopyridine; BSA, bis-trimethylsilylacetamide; EDC·HCl, 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride; HOBt, *N*-hydroxybenzotriazole; HBTU, *N*,*N*,*N*′,*N*′-tetra-methyl-*O*-(1*H*-benzotriazol-1-yl)-uronium hexafluorophosphate; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; SI, selectivity index; PSA, polar surface area

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