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Triazole Inhibitors of *Cryptosporidium parvum* Inosine 5′-Monophosphate Dehydrogenase

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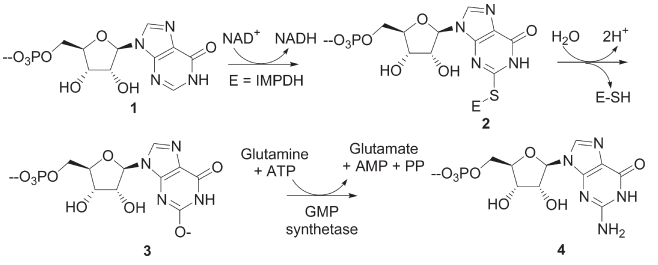
Cryptosporidium parvum is an important human pathogen and potential bioterrorism agent. This protozoan parasite cannot salvage guanine or guanosine and therefore relies on inosine 5′-monophosphate dehydrogenase (IMPDH) for biosynthesis of guanine nucleotides and hence for survival. Because *C. parvum* IMPDH is highly divergent from the host counterpart, selective inhibitors could potentially be used to treat cryptosporidiosis with minimal effects on its mammalian host. A series of 1,2,3-triazole containing ether *Cp*IMPDH inhibitors are described. A structure−activity relationship study revealed that a small alkyl group on the α-position of the ether was required, with the (*R*)-enantiomer significantly more active than the (*S*)-enantiomer. Electron-withdrawing groups in the 3- and/or 4-positions of the pendent phenyl ring were best, and conversion of the quinoline containing inhibitors to quinoline-*N*-oxides retained inhibitory activity both in the presence and absence of bovine serum albumin. The 1,2,3-triazole *Cp*IMPDH inhibitors provide new tools for elucidating the role of IMPDH in *C. parvum* and may serve as potential therapeutics for treating cryptosporidiosis.

Introduction

Inosine 5′-monophosphate dehydrogenase (IMPDH[a]) catalyzes the nicotinamide-adenine dinucleotide (NAD^+)-dependent oxidation of inosine 5′-monophosphate (IMP, **1**) to xanthosine 5′-monophosphate (XMP, **3**), the first committed and rate limiting step in the biosynthesis of guanosine monophosphate (GMP, **4**, Scheme 1).[1] IMPDH controls the guanine nucleotide pool and therefore plays an integral role in cellular proliferation.[2] Human IMPDH exists in two isoforms, IMPDH1 and IMPDH2, which have high (85%) sequence identity. Human IMPDH1 is most prevalent in leukocytes and lymphocytes, while IMPDH2 is found in greatest abundance in rapidly proliferating cells, including neoplastic cells.[3] IMPDH has emerged as an attractive therapeutic target for the treatment of various conditions[4] including cancer[5] and viral infections.[6] IMPDH inhibitors have also been used clinically as immunosuppressants, prompting further interest in utilizing this class of therapeutics for treating other autoimmune diseases.[7]

IMPDH may also be a target for antimicrobial chemotherapy, although its utility can be compromised if the microorganism can salvage guanine and/or xanthine. Prokaryotic and eukaryotic IMPDHs have divergent amino acid sequences and display significantly different kinetic properties, suggesting that it should be possible to develop selective inhibitors.[1,8] Prokaryotic IMPDHs are resistant to the known human IMPDH inhibitor mycophenolic acid, demonstrating that selective inhibition is possible. IMPDH is a promising target for the treatment of cryptosporidiosis, a major cause of diarrhea and malnutrition initiated by the protozoan parasites *Cryptosporidium parvum* and a related pathogenic species *Cryptosporidium hominis*.[9] These organisms can cause severe gastroenteritis and diarrhea, which can be life threatening in immunocompromised individuals. In addition, *C. parvum* is a potential bioterrorism agent. Interestingly, both *C. parvum* and *C. hominis* rely exclusively on the IMPDH-mediated pathway for guanine nucleotide synthesis by salvaging and converting adenosine to **1** and then subsequently to **4**.[10−12] *C. parvum* IMPDH (*Cp*IMPDH) appears to

Scheme 1. IMPDH Catalyzed Conversion of **1** to **3**, Which Is Further Processed to **4**



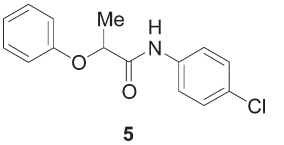


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Figure 1. *Cp*IMPDH inhibitor identified by HTS.

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[a] Abbreviations: *Cp*, *Cryptosporidium parvum*; BSA, bovine serum albumin; DCM, dichloromethane; DIBAL, diisobutylaluminum hydride; EDCI, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide; GMP, guanosine monophosphate; HTS, high throughput screening; IMP, inosine 5′-monophosphate; IMPDH, inosine 5′-monophosphate dehydrogenase; *m*-CPBA, *m*-chloroperoxybenzoic acid; NAD^+, nicotinamide-adenine dinucleotide; XMP, xanthosine 5′-monophosphate.

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have been obtained from an ε-proteobacterium by lateral gene transfer.[13] These observations suggest that selective inhibition of *Cp*IMPDH may provide an attractive means for parasite-specific inhibition, while minimizing potential side effects on the human (or other mammalian) host.

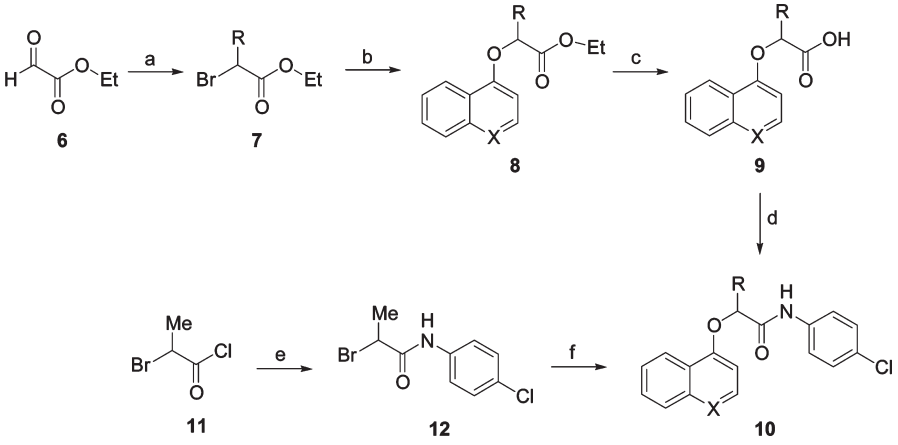
Our laboratories have been seeking to identify and optimize low molecular weight molecules capable of selectively inhibiting *Cp*IMPDH in order to provide lead compounds for therapeutic development to treat cryptosporidiosis.[14] During a high throughput screening (HTS) campaign, **5** was identified (Figure 1) as a moderately potent and very selective inhibitor of *Cp*IMPDH ($EC_{50} = 3.3 \pm 0.2\ \mu M$) with no detectable activity against the human enzyme ($EC_{50} \gg 50\ \mu M$).[15] The compound demonstrated uncompetitive inhibition with respect to **1** and noncompetitive (mixed) inhibition with respect to NAD^+. It was also shown to bind the nicotinamide subsite and to directly or indirectly impose on the ADP site.[15] Herein, we report a structure−activity relationship (SAR) study for this class of inhibitors, including a key structural change to the amide functional group.

Results and Discussion

Chemistry. Various analogues of **5** that contain the amide functional group were prepared according to Scheme 2. Ethyl glyoxylate was allowed to react with *c*-PrMgBr to give a corresponding alcohol that was subsequently converted to bromide **7** (R = *c*-Pr) with carbon tetrabromide and triphenylphosphine. Various other bromide derivatives of **7** were commercially available. Treatment of **7** with 1-naphthol in the presence of base (K_2CO_3) gave ester **8** (X = CH). The ester was saponified with 3N sodium hydroxide in THF to give acid **9** (X = CH), which was subsequently converted to amide **10** (X = CH) with the aid of EDCI·HCl in anhydrous dichloromethane (DCM). In the case of a quinoline analogue of **10** (X = N), the acetyl chloride derivative **11** was first converted to amide **12**, which was treated with 4-hydroxyquinoline to give **10** (X = N).

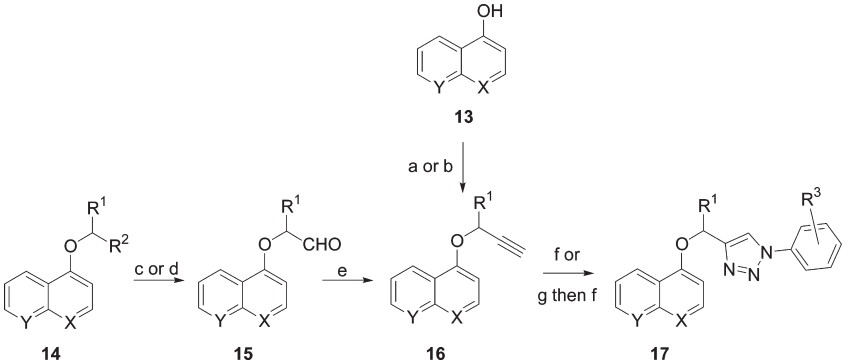
Analogues of **5** that replaced the amide functional group with a 1,2,3-triazole were prepared according to Scheme 3. The common intermediate in the synthesis of these derivatives was propargyl ether **16**. This intermediate was prepared using several different routes. In the first route (R^1 = Me or H), **13** was alkylated utilizing either a Mitsonobu reaction with a propargyl alcohol or by treatment with propargyl bromide in the presence of potassium carbonate. The route employing the Mitsonobu reaction also afforded enantiomerically enriched ethers starting with (*S*)- or (*R*)-but-3-yn-2-ol. When R^1 = *i*-Pr and $R^2 = CO_2H$, the acid **14** (prepared via Scheme 2) was reduced to the corresponding alcohol with

Scheme 2. General Procedure for the Synthesis of Amide Derivatives[a]



[a] Reagents and conditions: (a) (i) *c*-PrMgBr, THF, −20 °C, 2 h, (ii) Ph_3P, CBr_4, DCM, 0 °C, 2 h; (b) 1-naphthol, K_2CO_3, DMF, rt, 2 h; (c) 3 M NaOH, THF:H_2O (2:1), 80 °C, 6 h; (d) 4-chloroaniline, 0 °C, EDCI·HCl, DCM, rt, 12 h; (e) 4-chloroaniline, cat. DMAP, DCM, rt, 2 h; (f) 4-hydroxyquinoline, K_2CO_3, DMF, 0 °C, rt, 12 h.

Scheme 3. General Procedure for the Synthesis of 1,2,3-Triazole Derivatives[a]



[a] Reagents and conditions: X and Y = N, CH or CCl. (a) [R^1 = Me] MeCH(OH)C≡CH, 0 °C, Ph_3P, 10 min, DEAD, rt, 12 h; (b) [R^1 = H] $BrCH_2C{\equiv}CH$, K_2CO_3, DMF, rt, 12 h; (c) [R^1 = *i*-Pr, $R^2 = CO_2H$] (i) $LiAlH_4$, THF, 0 °C, 4 h, (ii) $(COCl)_2$, DMSO, DCM, Et_3N, −78 °C, 3 h; (d) [R^1 = Et, $R^2 = CO_2Et$] DIBAL, THF, −78 °C, 6 h; (e) (i) CBr_4, Ph_3P, DCM, 0 °C, 2 h, (ii) *n*-BuLi, THF, −78 °C, 2 h; (f) R^3PhN_3, CH_3CN, DIPEA, CuI, rt, 30 min; (g) *m*-CPBA, DCM, 0 °C, 12 h.

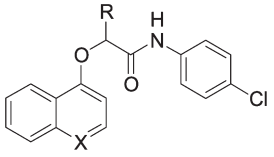
$LiAlH_4$ and then oxidized to aldehyde **15** under Swern conditions.[16] When R^1 = Et, R^2 = CO_2Et, the ester **14** (prepared via Scheme 2) was reduced directly to aldehyde **15** with DIBAL in THF at −78 °C. Aldehyde **15** was converted to the corresponding alkyne utilizing the two-step procedure described by Corey and Fuchs.[17] Ether **16** was converted to 1,2,3-triazole **17** in the presence of an aryl azide and CuI.[18] In the case of *N*-oxide derivatives, **16** (X or Y = N) was first treated with *m*-CPBA. The *N*-oxide of **16** was then converted to **17** (X or *Y* = N^+-O^-).

Biology. IC_{50} Determinations for *Cp*IMPDH Inhibition. Evaluation of *Cp*IMPDH inhibitory activity for the various prepared compounds was conducted utilizing an assay for the conversion of **1** to **3** by monitoring the production of NADH by fluorescence in the presence of varying inhibitor concentrations.[15] For all the compounds reported herein, the IC_{50} values were determined in three independent experiments. The average IC_{50} values and standard deviations are reported in Tables 1 and 2. It is commonly observed that antimicrobial or antiparasitic activity of compounds can be adversely affected by nonspecific binding to serum proteins, which sequesters the compounds preventing interaction with the target.[19] This in vitro effect can translate into poor efficacy in vivo due to low free fraction concentration of compound that can enter the pathogenic organism.[20] To characterize the nonspecific binding of inhibitors, IC_{50} values were also determined in the presence of 0.05% fatty acid free bovine serum albumin (BSA). In addition, none of the compounds displayed inhibitory activity against human IMPDH2 (< 10% at 5 μM).

Fusing an additional benzo-ring onto the phenyl ether of **5** resulted in a compound (**18**), demonstrating a 3-fold increase in *Cp*IMPDH inhibitory activity (Table 1). However, when the methyl group on the α-carbon of the amide was replaced with a phenyl (**19**), inhibitory activity was lost. An isopropyl group (**20**) was well tolerated, but surprisingly a cyclopropyl (**21**) was not. The naphthyl ether could also be replaced with a 4-quinolinyl ether, resulting in a compound (**22**) exhibiting an IC_{50} of 0.66 μM. The amide derivatives that demonstrated *Cp*IMPDH inhibitory activity were then evaluated for enzyme inhibitory activity in the presence BSA. The *Cp*IMPDH inhibitory activities of **18**, **20**, and **22** were only slightly decreased in the presence of BSA.

Early in the SAR study of **5**, attempts were made to find a bioisostere for the amide functional group.[21] Given the many reported successes with the use of 1,2,3-triazole in ligand design[20−24] including as a replacement for amide bonds, this heterocycle was incorporated into an analogue of **18**, resulting in **23**.[25−30] Gratifyingly, **23** demonstrated increased *Cp*IMPDH inhibitory activity with an IC_{50} of 130 nM (Table 2). However, the IC_{50} value increased significantly to

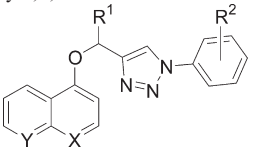
Table 1. IC_{50} Determinations for Inhibition of *Cp*IMPDH by Amide Derivatives



			IC_{50} (μM)[a,b]	
compd	R	X	(−) BSA[c]	(+) BSA
18	Me	CH	1.06 ± 0.1	1.64 ± 0.2
19	Ph	CH	> 5	ND[d]
20	*i*-Pr	CH	0.71 ± 0.1	0.83 ± 0.2
21	*c*-Pr	CH	> 5	ND
22	Me	N	0.66 ± 0.2	0.86 ± 0.2

[a] Positive control: **5**; IC_{50} = 3.3 ± 0.2 μM. [b] IC_{50} ± SD were determined from three independent experiments. [c] 0.05% Fatty acid free bovine serum albumin. [d] Not determined.

Table 2. IC_{50} Determinations for Inhibition of *Cp*IMPDH by 1,2,3-Triazole Derivatives



					IC_{50} (μM)[a,b]	
compd	R^1	R^2	X	Y	(−) BSA[c]	(+) BSA
23	Me	4-Cl	CH	CH	0.13 ± 0.03	0.78 ± 0.2
24	*i*-Pr	4-Cl	CH	CH	> 5	ND[d]
25	Me	2-Cl	CH	CH	> 5	ND
26	Me	4-Cl	CCl	CH	0.087 ± 0.03	3.9 ± 0.08
27	Me	4-Cl	N	CH	0.024 ± 0.008	0.23 ± 0.06
28	H	4-Cl	N	CH	0.44 ± 0.2	0.48 ± 0.2
29	Me	3,4-di-Cl	N	CH	0.020 ± 0.01	0.70 ± 0.2
30	Me	4-CN	N	CH	0.14 ± 0.03	0.34 ± 0.1
31	Me	3-Cl, 4-CN	N	CH	0.040 ± 0.002	1.4 ± 0.4
32	(*R*)-Me	3,4-di-Cl	N	CH	0.009 ± 0.006	0.65 ± 0.1
33	(*S*)-Me	3,4-di-Cl	N	CH	0.13 ± 0.03	0.88 ± 0.03
34	(*R*)-Me	3-Cl, 4-CN	N	CH	0.031 ± 0.009	1.1 ± 0.2
35	(*S*)-Me	3-Cl, 4-CN	N	CH	0.60 ± 0.05	2.3 ± 0.04
36	(*R*)-Me	4-Cl	CH	N	0.009 ± 0.001	0.030 ± 0.001
37	Me	4-Cl	N^+-O^-	CH	0.029 ± 0.01	0.050 ± 0.002
38	Me	3,4-di-Cl	N^+-O^-	CH	0.018 ± 0.003	0.042 ± 0.003
39	Me	4-Cl	CH	N^+-O^-	0.044 ± 0.002	0.059 ± 0.02
40	(*R*)-Me	4-Cl	N^+-O^-	CH	0.013 ± 0.005	0.050 ± 0.02
41	(*R*)-Me	4-Cl	CH	N^+-O^-	0.024 ± 0.005	0.052 ± 0.01

[a] Positive control: **5**; IC_{50} = 3.3 ± 0.2 μM. [b] IC_{50} ± SD were determined from three independent experiments. [c] 0.05% Fatty acid free bovine serum albumin. [d] Not determined.

780 nM in the presence of BSA. Also, unlike the amide series, replacing the methyl substituent with an isopropyl (**24**) in the 1,2,3-triazole series was not tolerated. In addition, moving the *para*-chloro group on the pendent phenyl to the *ortho*-position (**25**) was detrimental. However, adding a chlorine atom on the naphthyl ether (**26**) or replacing the naphthyl with a 4-quinolinyl (**27**) resulted in further increases in inhibitory activity, with IC_{50} values of 87 and 24 nM, respectively. Unfortunately, the inhibitory activity for both compounds was eroded in the presence of BSA. Given the potency of **27**, various other changes were made to this compound. For example, removing the methyl group (**28**) resulted in a significant loss of activity. Introduction of an additional chloride atom in the 3-position of the pendent phenyl (**29**) retained potent inhibitory activity. Introduction of 4-cyano (**30**) or 3-chloro-4-cyano (**31**) substituents on the pendent phenyl resulted in IC_{50} values of 140 and 40 nM, respectively. Next, the enantiomers of **29** were evaluated. The (*R*)-enantiomer (**32**), which demonstrated an IC_{50} of 9 nM, was significantly more potent (~14-fold) than the (*S*)-enantiomer (**33**). A similar finding was observed with the enantiomers **34** and **35**. The connectivity of the ether to the quinoline ring was changed to the 5-position (**36**) with retention of potent inhibitory activity. Interestingly, the inhibitory activity of this quinoline derivative was not as adversely affected as the other analogues by the presence of BSA. Finally, in an attempt to increase the polarity of the 1,2,3-triazole series with the goal of mitigating the effects of BSA on inhibitory activity, the *N*-oxide of **27** was evaluated. The IC_{50} value of **37** was 29 nM and in the presence of BSA only slightly increased to 50 nM. This 2-fold increase was less than seen with many of the non-*N*-oxide derivatives and was reminiscent of the results observed with the amide series. Several other *N*-oxide derivatives in the 1,2,3-triazole series, such as **38**−**41** also demonstrated potent inhibitory activity both in the presence and absence of BSA.

Conclusions

An SAR study of the α-phenoxide anilide derivative **5** that was previously shown to be a moderately potent and very selective inhibitor of *C. parvum* IMPDH,[15] an essential enzyme to this important human pathogenic protozoan parasite and potential bioterrorism agent, was undertaken. Initially, the amide was retained and addition of a fused ring onto the phenyl ether, resulting in 1-naphthyl or 4-quinolinyl ethers, was shown to increase *Cp*IMPDH inhibitory activity. The active amide analogues retained inhibitory activity in the presence of BSA. Replacement of the amide with the bioisostere 1,2,3-triazole resulted in increased *Cp*IMPDH inhibitory activity, but activity was eroded in the presence of BSA. Further increases in *Cp*IMPDH inhibitory activity were accomplished with various electron-withdrawing groups in the 3- and/or 4-positions, but not the 2-position, of the pendent phenyl ring. Also, a small alkyl group (i.e., methyl) was required on the α-position of the ether with the (*R*)-enantiomers demonstrating significantly more activity than the (*S*)-enantiomers. Finally, conversion of the quinolines to quinoline-*N*-oxides retained potent inhibitory activity both in the presence and absence of BSA. The 1,2,3-triazole *Cp*IMPDH inhibitors described herein can serve as new tools for elucidating the role of IMPDH in *C. parvum* and related organisms. These inhibitors could also serve as potential lead compounds for therapeutic development for the treatment of cryptosporidiosis.

Experimental Section

Chemistry Material and Methods. Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without further purification. All reactions were performed under nitrogen atmosphere unless otherwise noted. The NMR spectra were obtained using a 400 or 500 MHz spectrometer. All ^1H NMR spectra are reported in δ units ppm and are referenced to tetramethylsilane (TMS) if conducted in $CDCl_3$ or to the central line of the quintet at 2.49 ppm for samples in DMSO-d_6. All chemical shift values are also reported with multiplicity, coupling constants, and proton count. All ^{13}C NMR spectra are reported in δ units ppm and are referenced to the central line of the triplet at 77.23 ppm if conducted in $CDCl_3$ or to the central line of the septet at 39.5 ppm for samples in DMSO-d_6. Coupling constants (J values) are reported in hertz. Column chromatography was carried out on SILICYCLE SiliaFlash silica gel F60 (40−63 μm, mesh 230−400). High-resolution mass spectra were obtained using a SX-102A mass spectrometer (JEOL USA, Inc., Peabody, MA), a LCT mass spectrometer (Micromass Inc., Beverly, MA), or a Q-tof Ultima API mass spectrometer. All melting points were taken in glass capillary tubes on a Mel-Temp apparatus and are uncorrected. All test compounds had a purity ≥95% as determined by either elemental analysis or high performance liquid chromatography (HPLC) analysis, unless otherwise noted. The elemental composition of compounds agreed to within ±0.4% of the calculated values. Chemical and enantiomeric purities were determined using high performance liquid chromatography (HPLC) analysis on a Hewlett-Packard 1100 series instrument equipped with a quaternary pump and a Daicel Chiralpak AD column (250 × 4.6 mm). UV absorption was monitored at $\lambda = 254$ nm. The injection volume was 1 μL. HPLC gradient was 50% *n*-hexane and 50% *i*-propanol with a flow rate of 1.0 mL/min. In some cases, chemical purity was determined using a Agilent 1100 HPLC instrument equipped with a quaternary pump and a Zorbax SB-C8 column (30 mm × 4.6 mm, 3.5 μm). UV absorption was monitored at $\lambda = 254$ nm. The injection volume was 5 μL. HPLC gradient went from 5% acetonitrile and 95% water to 95% acetonitrile and 5% water (both solvents contain 0.1% trifluoroacetic acid) over 1.9 min with a total run time of 2.5 min and a flow rate of 3.0 mL/min.

Synthesis of Ethyl α-Bromocyclopropaneacetate (7, R = *c*-Pr). A flame-dried two-neck round-bottom flask fitted with a reflux condenser and nitrogen inlet was charged with anhydrous THF, freshly activated Mg (120 mg, 4.95 mmol), and a catalytic amount of iodine. A small portion of cyclopropyl bromide dissolved in THF was added. After initiation of reflux, the reaction mixture was cooled to −20 °C and the remaining cyclopropyl bromide (500 mg, 4.13 mmol) was gradually added. After 30 min, a freshly distilled solution of glyoxalate **9** (549 mg, 5.37 mmol) in THF was added over a 10 min period and the resulting solution was stirred at −20 °C for 2 h before being quenched with a small amount of water. After 10 min, the reaction mixture was further diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by column chromatography eluting with ethyl acetate/*n*-hexane (a gradient of 10−20%) to furnish ethyl α-hydroxycyclopropaneacetate (422 mg, 71%) as a viscous oil. The oil (350 mg, 2.43 mmol) was dissolved in anhydrous DCM and cooled to 0 °C. Then Ph_3P (2.04 g, 7.78 mmol) was added followed by CBr_4 (1.20 g, 3.64 mmol). The reaction mixture was stirred at 0 °C for 2 h and then concentrated in vacuo. The Ph_3PO was precipitated by addition of *n*-hexane and removed by filtration. The crude reaction mixture was purified by flash column chromatography eluting with ethyl acetate/*n*-hexane (1:9) to furnish ethyl α-bromocyclopropaneacetate (**7**, R = *c*-Pr): (311 mg, 62% yield).

General Procedure for the Synthesis of 2-(1-Naphthalenyloxy)-acetic Acids (9). Exemplified for 2-Cyclopropyl-2-(1-naphthalenyloxy)acetic Acid (9, R = *c*-Pr). To a solution of 1-naphthol (170 mg, 1.18 mmol) in anhydrous DMF (10 mL) was added K_2CO_3 (510 mg, 3.53 mmol) and ethyl α-bromocyclopropaneacetate (295 mg, 1.41 mmol). The mixture was stirred at room temperature for 2 h and then diluted with water (50 mL) and then extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography using a mixture of ethyl acetate/*n*-hexane (1:9) to furnish ethyl 2-cyclopropyl-2-(1-naphthalenyloxy)acetate (**8**, R = *c*-Pr, 296 mg, 93%) as a white solid. The ester (250 mg, 0.92 mmol) was dissolved in 20 mL THF:H_2O (2:1), and then 3 N NaOH (111 mg, 2.77 mmol) was added. The reaction was heated at 80 °C for 6 h. After cooling, the reaction mixture was quenched with 1N HCl to a pH ∼7 and then extracted with chloroform. The organic extract was dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography eluting with a mixture of ethyl acetate/*n*-hexane (2:1) to furnish 2-cyclopropyl-2-(1-naphthalenyloxy)acetic acid (**9**, R = *c*-Pr) (136 mg, 61%) as a white solid.

General Procedure for theSynthesis of *N*-(4-Chlorophenyl)-2-(1-naphthalenyloxy)acetamides (10, X = CH). Exemplified for *N*-(4-Chlorophenyl)-2-cyclopropyl-2-(1-naphthalenyloxy)acetamide (21). To a solution of 2-cyclopropyl-2-(1-naphthalenyloxy)acetic acid (120 mg, 0.49 mmol) and 4-chloroaniline (44.0 μL, 0.49 mmol) in anhydrous DCM (10 mL) under N_2 cooled at 0 °C was added EDCI·HCl (187.9 mg, 0.98 mmol) portion wise. The resulting solution was stirred at room temperature for 12 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 100 mL). The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using ethyl acetate/*n*-hexane (a gradient of 5−10%) to furnish **21** (148 mg, 86%) as a white solid; mp 204−206 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65−0.78 (m, 4H), 1.52 (m, 1H), 4.41 (d, *J* = 6.4 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 6.0 Hz, 3H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.61−7.70 (m, 3H), 7.97 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 2.70, 3.16, 14.42, 82.72, 108.01, 115.68, 121.47, 122.03, 122.96, 127.64, 128.43, 129.28, 129.63, 130.07, 132.96, 135.61, 152.83, 169.27. ESI-HRMS for $C_{21}H_{17}ClNO_2$ $(M - H)^+$ calcd 350.0948; found 350.0956.

***N*-(4-Chlorophenyl)-2-(1-naphthalenyloxy)propanamide (18).** Melting point 146−148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.79 (d, *J* = 6.8 Hz, 3H), 4.98 (q, *J* = 6.8, 13.2 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.56 (dd, *J* = 7.8, 12.5 Hz, 3H), 7.86 (m, 1H), 8.24−8.32 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.08, 76.26, 107.41, 121.42, 121.54, 122.47, 125.91, 126.04, 126.16, 127.03, 128.14, 129.26, 129.95, 134.93, 135.75, 152.61, 170.58. Anal. ($C_{19}H_{16}ClNO_2$) C, H, N.

***N*-(4-Chlorophenyl)-α-(1-naphthalenyloxy)benzeneacetamide (19).** Yield 92%; mp 176−178 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.86 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 7.26−7.61 (m, 11H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.87 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 8.44 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 81.09, 107.87, 121.41, 121.47, 122.58, 125.66, 126.01, 126.27, 126.61, 127.02, 128.25, 129.12, 129.15, 129.27, 130.06, 134.94, 135.71, 135.98, 152.34, 168.11. Anal. ($C_{24}H_{18}ClNO_2$) C, H, N.

***N*-(4-Chlorophenyl)-3-methyl-2-(1-naphthalenyloxy)butanamide (20).** Yield 91%; mp 150−152 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (dd, *J* = 6.8, 22.8 Hz, 6H), 2.54 (m, 1H), 4.68 (d, *J* = 4.4 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 7.25 (m, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.54−7.60 (m, 2H), 7.86 (m, 1H), 8.01 (s, 1H), 8.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.47, 19.54, 32.48, 84.51, 106.81, 121.53, 122.20, 125.71, 126.12, 127.04, 128.15, 129.21, 129.97, 134.92, 135.57, 153.52, 169.68. Anal. ($C_{21}H_{20}ClNO_2$) C, H, N.

Synthesis of 2-Bromo-*N*-(4-chlorophenyl)propanamide (12). To a solution of 4-chloroaniline (400 mg, 3.13 mmol) in anhydrous DCM at room temperature under a nitrogen atmosphere was added slowly 2-bromopropanoyl chloride (474 μL, 4.7 mmol). The reaction mixture was stirred at room temperature for 2 h and then diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give 2-bromo-*N*-(4-chlorophenyl)propanamide, which was used without further purifications.

Synthesis *N*-(4-Chlorophenyl)-2-[[4-quinolinyl]oxy]propanamide (22). To a solution of 4-hydroxyquinoline (100 mg, 0.69 mmol) in anhydrous DMF under a nitrogen atmosphere was added K_2CO_3 (286 mg, 2.10 mmol) and a solution of 2-bromo-*N*-(4-chlorophenyl)propanamide (218 mg, 0.83 mmol) in DMF. The reaction mixture was stirred for 12 h at room temperature before being diluted with water (50 mL) and extracted with chloroform (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash chromatography using ethyl acetate/*n*-hexane (1:9) to furnish **22** (207 mg, 92% yield) as a white solid; mp 170−172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83 (d, *J* = 6.4 Hz, 3H), 5.06 (q, *J* = 6.8, 13.6 Hz, 1H), 6.76 (d, *J* = 5.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.76 (d, *J* = 5.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.72, 75.83, 102.05, 122.27, 121.32, 121.58, 126.61, 129.34, 129.60, 130.34, 130.51, 135.40, 149.74, 151.48, 159.47, 169.20. ESI-HRMS for $C_{18}H_{16}N_2O_2Cl$ $(M + H)^+$ calcd 327.0900; found 327.0901.

General Procedure for the Preparation of Propargyl Ether 16 via the Mitsonobu Reaction. Exemplified for 1-[(1-Methyl-2-propyn-1-yl)oxy]naphthalene (16, R^1 = Me, X = Y = CH). To a solution of 1-naphthol (200 mg, 1.38 mmol) and but-3-yn-2-ol (146 mg, 2.07 mmol) in anhydrous DCM (10 mL) under a nitrogen atmosphere and at 0 °C was added Ph_3P (435 mg, 1.66 mmol) portion wise. The reaction mixture was stirred for 10 min. and then DEAD (360 mg, 2.07 mmol) (70% solution in toluene) was slowly added. The resulting reaction solution was stirred at the room temperature for 24 h and then diluted with water (50 mL) and extracted with chloroform (3 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and the residue was purified by flash column chromatography using ethyl acetate/*n*-hexane (a gradient of 5−10%) to furnish 1-[(1-methyl-2-propyn-1-yl)oxy]naphthalene (176 mg, 65%) as a viscous oil.

General Procedure for the Preparation of Propargyl Ether 16 via the Corey−Fuchs Reaction. Exemplified for the Synthesis of 1-(1-Methylethyl)-2-propyn-1-yl]oxy]naphthalene (16, R^1 = *i*-Pr, X = Y = CH). A solution of **14** (R^1 = *i*-Pr, R^2 = CO_2H, X = Y = CH, 880 mg, 3.27 mmol) in anhydrous THF was cooled to 0 °C, and then $LiAlH_4$ (311 mg, 8.18 mmol) was added. The reaction mixture was stirred for 5 h at 0 °C and then quenched with water (50 mL). The mixture was stirred until the organic and aqueous layers separated. The mixture was extracted with chloroform (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography using ethyl acetate/*n*-hexane (2:1) to give alcohol **14** (R^1 = *i*-Pr, R^2 = CH_2OH, X = Y = CH, 466 mg, 62%) as a thick viscous oil.

A flame-dried two-neck round-bottom flask containing oxalyl chloride (370 μL, 4.34 mmol) in anhydrous DCM was cooled at −78 °C under a nitrogen atmosphere. Next, anhydrous DMSO (679 mg, 8.7 mmol) was added dropwise via a syringe. The resulting solution was allowed to stir at −78 °C for 10 min, and then alcohol **14** (R^1 = *i*-Pr, R^2 = CH_2OH, X = Y = CH, 400 mg, 1.74 mmol) dissolved in anhydrous DCM was added gradually via a syringe. The resulting reaction mixture was allowed to stir for 1 h at −78 °C and then quenched with triethylamine (1.95 mL, 13.9 mmol) before being allowed to

warm to room temperature. The reaction mixture was extracted with DCM (3 × 50 mL), washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give aldehyde **15** (R^1 = *i*-Pr, X = Y = CH), which was used without further purification.

A solution of **15** (R^1 = *i*-Pr, X = Y = CH, 360 mg, 1.58 mmol) in DCM (10 mL) was cooled at 0 °C, and then Ph_3P (1.24 g, 4.74 mmol) and CBr_4 (785 mg, 2.37 mmol) were sequentially added. The resulting mixture was stirred at room temp for 2 h. The reaction mixture was concentrated in vacuo, and the Ph_3PO was precipitated by addition of *n*-hexane and removed by filtration. The filtrate was concentrated and the residue purified using a filter column (ethyl acetate/*n*-hexane as eluent). The resulting material (360 mg, 1.58 mmol) was dissolved in anhydrous THF and cooled to −78 °C. Next, *n*-BuLi (121 mg, 1.90 mmol) was gradually added, and the resulting solution stirred for 2 h at −78 °C. The mixture was quenched with water (50 mL), allowed to stir at room temperature for 30 min, and then extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography eluting with ethyl acetate/*n*-hexane (5:95) to furnish 1-(1-methylethyl)-2-propyn-1-yl]oxy]naphthalene (**16**, R^1 = *i*-Pr, X = Y = CH, 282 mg, 72%) as a white solid.

General Procedure for the Preparation of 1*H*-1,2,3-Triazoles 17. Exemplified for 1-(4-Chlorophenyl)-4-(2-methyl-1-(1-naphthalenyloxy)propyl)-1*H*-1,2,3-triazole (24). A single-neck round-bottom flask under an argon atmosphere was charged with **16** (R^1 = *i*-Pr, X = Y = CH, 114 mg, 0.51 mmol), anhydrous acetonitrile (5 mL), 1-azido-4-chlorobenzene (78.3 mg, 0.51 mmol), and DIPEA (254 μL, 1.53 mmol). The reaction mixture was allowed to stir at room temperature for 10 min, and then finely powdered CuI (194.2 mg, 1.02 mmol) was added portion wise. After 30 min of stirring at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl, diluted with water (50 mL), and extracted with chloroform (3 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography using ethyl acetate/*n*-hexane (a gradient of 10−20%) to furnish **24** (167 mg, 87%) as a gelatinous solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16, 1.20 (dd, *J* = 6.5, 22.0 Hz, 6H), 2.47−2.53 (m, 1H), 5.55 (d, *J* = 5.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.25 (m, 1H), 7.37−7.43(m, 3H), 7.49 (m, 2H), 7.61 (d, *J* = 9.0 Hz, 2H), 7.79 (m, 2H), 8.38 (m, 1H). ESI-HRMS for $C_{22}H_{21}ClN_3O$ $(M + H)^+$ calcd 378.1373; found 378.1383.

1-(4-Chlorophenyl)-4-(1-(naphthalene-1-yloxy)ethyl)-1*H*-1,2,3-triazole (23). Melting point 98−100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91 (d, *J* = 6.0 Hz, 3H) 5.90 (q, *J* = 6.8, 12.8 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 7.26 (s, 1H), 7.31 (t, *J* = 8.8 Hz, 1H), 7.41−7.51 (m, 5H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.80 (m, 1H), 7.88 (s, 1H), 8.34 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.56, 69.90, 107.02, 119.08, 120.98, 121.87, 122.19, 125.53, 126.07, 126.14, 126.66, 127.80, 130.07, 134.73, 134.82, 135.64, 151.38, 153.21. ESI-HRMS for $C_{20}H_{17}ClN_3O$ $(M + H)^+$ calcd 350.1060; found 350.1074.

1-(2,6-Dichlorophenyl)-4-(1-(naphthalen-1-yloxy)ethyl)-1*H*-1,2,3-triazole (25). Yield 86%; gelatinous solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.98 (d, *J* = 6.0 Hz, 3H), 5.92 (q, *J* = 6.5, 13.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.37−7.49 (m, 6H), 7.79 (m, 1H) 8.32 (m, 1H). ESI-HRMS for $C_{20}H_{16}Cl_2N_3O$ $(M + H)^+$ calcd 384.0670; found 384.0672.

4-(1-(4-Chloronaphthalen-1-yloxy)ethyl)-1-(4-chlorophenyl)-1*H*-1,2,3-triazole (26). yield 84%; gelatinous solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (d, *J* = 6.5 Hz, 3H), 5.86 (q, *J* = 6.5, 13.5 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.56 (t, *J* = 8.5 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 3H), 7.87 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.36 (d, *J* = 8.5 Hz, 1H). ESI-HRMS for $C_{20}H_{16}Cl_2N_3O$ $(M + H)^+$ calcd 384.0670; found 384.0684.

4-(1-(1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)quinoline (27). Yield 91%; mp 128−130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (d, *J* = 6.4 Hz, 3H), 5.97 (q, *J* = 6.4, 12.8 Hz, 1H), 6.89 (d, *J* = 5.2 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.91 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 8.70 (d, *J* = 4.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.21, 70.05, 102.42, 119.17, 121.92, 121.99, 125.93, 129.23, 130.06, 130.14, 134.98, 135.48, 149.59, 150.01, 151.51, 160.17. ESI-HRMS for $C_{19}H_{16}ClN_4O$ $(M + H)^+$ calcd 351.1013; found 351.1002. Purity as determined by HPLC analysis was 94.7%.

4-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)quinoline (28). Yield 89%; mp 230−232 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.50 (s, 2H), 6.34 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.57−7.65 (m, 4H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.77 (s, 1H), 8.46 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.81, 111.20, 115.77, 120.21, 121.92, 124.28, 127.49, 127.58, 130.24, 132.75, 135.29, 139.87, 143.11, 143.93, 178.46. ESI-HRMS for $C_{18}H_{14}ClN_4O$ $(M + H)^+$ calcd 337.0856; found 337.0847.

4-(1-(1-(3,4-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)quinoline (29). Yield 89%; mp 62−64 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (d, *J* = 6.4 Hz, 3H), 5.97 (q, *J* = 6.4, 12.8 Hz, 1H), 6.87 (d, *J* = 5.6 Hz, 1H), 7.26 (s, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.57 (s, 2H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.85 (s, 1H), 7.91 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.70 (d, *J* = 4.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.21, 69.96, 102.37, 119.13, 119.69, 121.72, 121.97, 122.50, 125.98, 129.26, 130.10, 131.68, 133.35, 134.23, 135.98, 149.61, 150.28, 151.50, 160.10. Anal. ($C_{19}H_{14}Cl_2N_4O$) C, H, N.

4-(4-(1-(Quinolin-4-yloxy)ethyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile (30). Yield 87%; mp 176−178 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (d, *J* = 6.8 Hz, 3H), 5.98 (q, *J* = 6.0, 12.8 Hz, 1H), 6.87 (d, *J* = 4.8 Hz, 1H), 7.26 (s, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 8.03 (m, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.70 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.16, 69.90, 102.35, 112.86, 117.78, 118.98, 120.82, 121.94, 126.02, 129.25, 130.15, 134.11, 139.74, 149.59, 150.55, 151.45, 160.07. ESI-HRMS for $C_{20}H_{16}N_5O$ $(M + H)^+$ calcd 342.1355; found 342.1355.

2-Chloro-4-(4-(1-(quinolin-4-yloxy)ethyl)-1*H*-1,2,3-triazol-1-yl)-benzonitrile (31). Yield 85%; mp 194−196 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (d, *J* = 6.8 Hz, 3H), 5.98 (q, *J* = 6.0, 12.8 Hz, 1H), 6.84 (d, *J* = 4.8 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.72 (t, *J* = 8.0 Hz, 1H), 7.79 (q, *J* = 8.4, 15.2 Hz, 2H), 7.97 (s, 1H), 8.00 (s, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 8.69 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.14, 69.81, 102.29, 113.53, 115.12, 118.60, 119.02, 121.51, 121.65, 121.91, 126.06, 129.27, 130.18, 135.53, 138.93, 140.24, 149.60, 150.82, 151.43, 159.98. ESI-HRMS for $C_{20}H_{15}ClN_5O$ $(M + H)^+$ calcd 376.0965; found 376.0975.

(*R*)-4-(1-(1-(3,4-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)-quinoline (32). Yield 91%; mp 62−64 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (d, *J* = 6.8 Hz, 3H), 5.97 (q, *J* = 6.4, 12.8 Hz, 1H), 6.87 (d, *J* = 5.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.58 (s, 2H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.85 (s, 1H), 7.91 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.70 (bs, 1H). ESI-HRMS for $C_{19}H_{15}N_4OCl_2$ $(M + H)^+$ calcd 385.0623; found 385.0605.

(*S*)-4-(1-(1-(3,4-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)-quinoline (33). Yield 89%; mp 64−66 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (d, *J* = 6.8 Hz, 3H), 5.98 (q, *J* = 6.8, 12.8 Hz, 1H), 6.88 (d, *J* = 4.8 Hz, 1H), 7.54 (t, *J* = 6.4 Hz, 1H), 7.58 (d, *J* = 1.2 Hz, 2H), 7.72 (m, 1H), 7.85 (m, 1H), 7.91 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.70 (d, *J* = 5.6 Hz, 1H). ESI-HRMS for $C_{19}H_{15}N_4OCl_2$ $(M + H)^+$ calcd 385.0623; found 385.0628.

(*R*)-2-Chloro-4-(4-(1-(quinolin-4-yloxy)ethyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile (34). Yield 92%; mp 176−178 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (d, *J* = 6.0 Hz, 3H), 5.98 (q, *J* = 6.0, 12.8 Hz, 1H), 6.84 (d, *J* = 5.6 Hz, 1H) 7.55 (t, *J* = 7.2 Hz, 1H), 7.71−7.83 (m, 3H), 7.97 (m, 2H), 8.04 (d, *J* = 8.4 Hz, 1H),

8.28 (d, J = 8.8 Hz, 1H), 8.70 (d, J = 5.2 Hz, 1H). ESI-HRMS for $C_{20}H_{15}N_5OCl$ $(M + H)^+$ calcd 376.0965; found 376.0964.

(*S*)-2-Chloro-4-(4-(1-(quinolin-4-yloxy)ethyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile (35). Yield 91%; mp 176−178 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (d, J = 6.8 Hz, 3H), 5.98 (q, J = 6.0, 12.8 Hz, 1H), 6.84 (d, J = 5.6 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.71−7.82 (m, 3H), 7.98 (m, 2H), 8.04 (d, J = 8.0 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.70 (d, J = 4.8 Hz, 1H). ESI-HRMS for $C_{20}H_{15}N_5OCl$ $(M + H)^+$ calcd 376.0965; found 376.0974.

(*R*)-5-(1-(1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)-quinoline (36). Yield 82%; mp 94−96 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.92 (d, J = 6.4 Hz, 3H), 5.89 (q, J = 6.0, 12.8 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 7.40 (dd, J = 3.6, 8.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.55 (t, J = 8.4 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.8 Hz, 1H), 7.88 (s, 1H), 8.65 (d, J = 8.0 Hz, 1H), 8.91 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.36, 70.17, 107.39, 119.10, 120.52, 121.40, 121.87, 122.32, 129.56, 130.10, 131.00, 134.85, 135.56, 149.36, 150.76, 150.95, 152.95. ESI-HRMS for $C_{19}H_{16}N_4OCl$ $(M + H)^+$ calcd 351.1013; found 351.1002.

4-(1-(1-(4-Chlorophenyl)-1H-1,2,3-triazol-4-yl)ethoxy)quinoline 1-Oxide (37). Yield 88%; mp 158−160 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.85 (d, J = 6.8 Hz, 3H), 6.09 (q, J = 6.0, 12.8 Hz, 1H), 7.20 (d, J = 6.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.74 (t, J = 7.6 Hz, 1H), 7.86 (t, J = 8.4 Hz, 1H), 7.95 (d, J = 9.2 Hz, 2H), 8.25 (d, J = 8.8 Hz, 1H), 8.50 (dd, J = 6.4, 12.0 Hz, 2H), 9.06 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 20.58, 69.53, 103.30, 119.27, 121.56, 121.82, 122.67, 122.80, 128.14, 129.87, 130.79, 133.06, 135.32, 135.48, 140.72, 148.38, 150.38. ESI-HRMS for $C_{19}H_{16}N_4O_2Cl$ $(M + H)^+$ calcd 367.0962; found 367.0948.

4-(1-(1-(3,4-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)-quinoline 1-Oxide (38). Yield 92%; mp 216−218 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.85 (d, J = 6.0 Hz, 3H), 6.09 (q, J = 6.0, 12.8 Hz, 1H), 7.19 (d, J = 6.4 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.86 (m, 2H), 7.98 (d, J = 9.2 Hz, 1H), 8.26 (m, 2H), 8.50 (dd, J = 7.2, 12.0 Hz, 2H), 9.12 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 20.58, 69.47, 103.33, 119.28, 120.16, 121.74, 121.85, 122.67, 122.78, 128.15, 130.76, 131.09, 131.81, 132.33, 135.39, 136.03, 140.71, 148.53, 150.21. ESI-HRMS for $C_{19}H_{15}N_4O_2Cl_2$ $(M + H)^+$ calcd 401.0571; found 401.0566.

5-(1-(1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)quinoline 1-Oxide (39). Yield 81%; mp 165−167 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93 (d, J = 6.0 Hz, 3H), 5.90 (q, J = 6.8 12.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H) 7.26 (t, J = 6.0 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.60 (t, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.91 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H) 8.29 (d, J = 9.2 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.27, 70.58, 109.66, 112.34, 119.20, 120.13, 121.03, 121.91, 123.94, 130.26, 130.73, 135.01, 135.49, 136.33, 142.76, 150.15, 153.56. ESI-HRMS for $C_{19}H_{16}N_4O_2Cl$ $(M + H)^+$ calcd 367.0962; found 367.0977. Purity as determined by HPLC analysis was 94.3%.

(*R*)-4-(1-(1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)-quinoline 1-Oxide (40). Yield 91%; mp 172−174 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (d, J = 8.8 Hz, 3H), 5.92 (q, J = 6.0, 12.8 Hz, 1H), 6.88 (d, J = 6.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 3H), 7.80 (t, J = 7.2 Hz, 1H), 7.96 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.39 (d, J = 6.8 Hz, 1H), 8.73 (d, J = 8.4 Hz, 1H). ESI-HRMS for $C_{19}H_{16}N_4O_2Cl$ $(M + H)^+$ calcd 367.0962; found 367.0948.

(*R*)-5-(1-(1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)-quinoline 1-Oxide (41). Yield 88%; mp 184−186 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93 (d, J = 6.0 Hz, 3H), 5.90 (q, J = 6.4, 12.8 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.28 (m, 3H), 7.48 (d, J = 9.2 Hz, 2H), 7.61 (t, J = 8.4 Hz, 1H), 7.65 (d, J = 9.2 Hz, 2H), 7.91 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 9.2 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H). ESI-HRMS for $C_{19}H_{16}N_4O_2Cl$ $(M + H)^+$ calcd 367.0962; found 367.0947.

General Procedure for the Preparation of Propargyl Ether Quinoline *N*-Oxides. Exemplified for (*R*)-5-(But-3-yn-2-yloxy)quinoline 1-Oxide (16, R^1 = (*R*)-Me, X = N^+-O^-, Y = CH). To a 0 °C solution of **16** (R^1 = (*R*)-Me, X = N, Y = CH, 120 mg, 0.61 mmol) in anhydrous DCM under a nitrogen atmosphere was added *m*-chloroperbenzoic acid (163 mg, 0.73 mmol, 77%). The reaction mixture was stirred at room temperature for 2 h, concentrated in vacuo, and purified by flash column chromatography eluting with methanol/chloroform (a gradient of 5−10%) to furnish (*R*)-5-(but-3-yn-2-yloxy)quinoline 1-oxide (**16**, R^1 = (*R*)-Me, X = N^+-O^-, Y = CH, 120 mg, 93%) as a white solid; mp 156−158 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82 (d, J = 6.8 Hz, 3H), 2.54 (s, 1H), 5.05 (q, J = 6.8, 13.6 Hz, 1H), 7.20 (d, 1H, J = 8.0 Hz, 1H) 7.26 (t, J = 8.0 Hz, 3H), 7.68 (t, J = 9.2 Hz, 1H), 8.15 (d, J = 9.2 Hz, 1H), 8.35 (d, J = 8.8 Hz, 1H), 8.54 (d, J = 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.32, 64.68, 75.09, 81.96, 109.52, 112.49, 120.09, 121.28, 123.85, 130.57, 136.32, 142.64, 153.36. ESI-HRMS for $C_{13}H_{12}NO_2$ $(M + H)^+$ calcd 214.0868; found 214.0875.

Evaluation of *Cp*IMPDH Inhibition. Determination of IC_{50} Values. Inhibition of recombinant *Cp*IMPDH, purified from *E. coli*,[12] was assessed by monitoring the production of NADH by fluorescence at varying inhibitor concentrations (25 pM to 5 μM). IMPDH was incubated with inhibitor for 5 min at room temperature prior to addition of substrates. The following conditions were used: 50 mM Tris-HCl, pH 8.0, 100 mM KCl, 3 mM EDTA, 1 mM dithiothreitol (assay buffer) at 25 °C, 10 nM *Cp*IMPDH, 300 μM NAD, and 150 μM **1**. To characterize the nonspecific binding of inhibitors, assays were also carried out in the presence of 0.05% BSA (fatty acid free). IC_{50} values were calculated for each inhibitor according to eq 1 using the SigmaPlot program (SPSS, Inc.):

$$v_i = v_o/(1+[I]/IC_{50}) \quad (1)$$

where v_i is initial velocity in the presence of inhibitor (I) and v_o is the initial velocity in the absence of inhibitor. Inhibition at each inhibitor concentration was measured in quadruplicate and averaged; this value was used as v_i. The IC_{50} values were determined three times; the average and standard deviations are reported.

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Supporting Information Available: Detailed information for combustion analyses, HPLC methods and purity assessments, including % ee determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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