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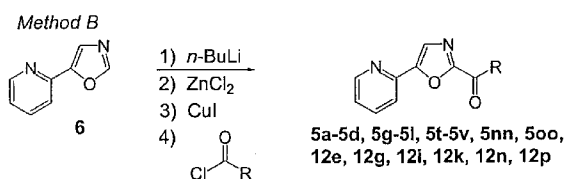
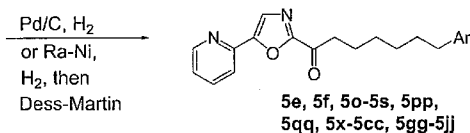
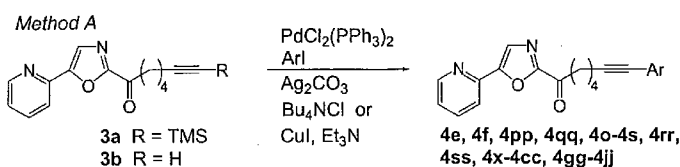
(71) Applicant and

(72) Inventor: **BOGER, Dale, L.** [US/US]; 2819 Via Posada,
La Jolla, California 92037 (US).(74) Agents: **STEFFEY, Charles, E.** et al.; Schwegman, Lund-
berg & Woessner, P.A., P.O. Box 2938, Minneapolis, Min-
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(54) Title: TRICYCLIC INHIBITORS OF FATTY ACID AMIDE HYDROLASE



(57) Abstract: A series of substituted oxazole compounds having an alpha keto side chain at the 2 position and an aromatic, heteroaromatic or heterocycle substituent at the 5 position are disclosed. These compounds exhibit inhibition of fatty acid amid hydrolase and are useful for treatment of malconditions involving that enzyme.

Figure 3

TRICYCLIC INHIBITORS OF FATTY ACID AMIDE HYDROLASE

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Field of the Invention:

The present invention related to certain oxazole compounds, pharmaceutical compositions containing them, and methods of using them for the treatment of disease states, disorders, and conditions mediated by fatty acid amide hydrolase (FAAH)

10 activity.

Background of the Invention:

The enzyme fatty acid amide hydrolase (FAAH) is the primary catabolic regulator of several bioactive lipid amides *in vivo*, including anandamide (**1a**) and oleamide (**1b**) (Bracey, M. H.; Hanson, M. A.; et al. *Science* **2002**, 298, 1793–1796; Cravatt, B. F.; Giang, D. K.; et al. *Nature* **1996**, 384, 83–87; Giang, D. K.; Cravatt, B. F. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, 94, 2238–2242; Patricelli, M. P.; Cravatt, B. F. *Vit. Hormones* **2001**, 62, 95–131). The central nervous system distribution of FAAH suggests that it degrades neuromodulating fatty acid amides at their sites of action and is intimately involved in their regulation (Egertova, M.; Cravatt, B. F.; et al. *Neuroscience* **2003**, 119, 481–496). Fatty acid amide hydrolase is currently the only characterized mammalian enzyme that is in the amidase signature family bearing an unusual catalytic Ser-Ser-Lys triad (Bracey, M. H.; Hanson, M. A.; et al. *Science* **2002**, 298, 1793–1796; Patricelli, M. P.; Cravatt, B. F. *Vit. Hormones* **2001**, 62, 95–131; Patricelli, M. P.; Cravatt, B. F. *Biochemistry* **1999**, 38, 14125–14130; Patricelli, M. P.; Cravatt, B. F. *J. Biol. Chem.* **2000**, 275, 19177–19184; Patricelli, M. P.; Lovato, M. A.; et al. *Biochemistry* **1999**, 38, 9804–9812). Recently, the crystal structure of FAAH cocrystallized with an irreversibly-bound arachidonyl fluorophosphonate confirmed its unusual catalytic triad and provided structural details of this enzyme (Bracey, M. H.; Hanson, M. A.; et al. *Science* **2002**, 298, 1793–1796).

Both anandamide (**1a**) (Dervane, W. A.; Hanus, L.; et al. *Science* **1992**, 258, 1946–1949) and oleamide (**1b**) (Boger, D. L.; Henriksen, S. J.; et al. *Curr. Pharm.*

Des. **1998**, *4*, 303–314; Cravatt, B. F.; Lerner, R. A.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 580–590; Cravatt, B. F.; et al. *Science* **1995**, *268*, 1506–1509) have emerged as prototypical members of the class of bioactive lipid amides (Boger, D. L.; Fecik, R. A.; et al. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2613–2616; Lang, W.; Qin, C.; et al. *J. Med. Chem.* **1999**, *42*, 896–902) that serve as chemical messengers (Figure 1). Anandamide (**1a**), the most recognizable member of the endogenous fatty acid ethanolamides (Schmid, H. H. O.; Schmid, P. C.; Natarajan, V. *Prog. Lipid Res.* **1990**, *29*, 1–43), binds and activates both the central type-1 (CB1) and peripheral type-2 (CB2) cannabinoid receptors. Anandamide (**1a**), and members of the cannabinoid family (Lambert, D. M.; Fowler, C. J. *J. Med. Chem.* **2005**, *48*, 5059–5087), have been implicated in the modulation of nociception (Calignano, A.; La Rana, G.; et al. *Nature* **1998**, *394*, 277–281; Cravatt, B. F.; Lichtman, A. H. *J. Neurobiol.* **2004**, *61*, 149–160; Walker, J. M.; Huang, S. M.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 12198–12203), feeding (Gomez, R.; Navarro, M.; et al. *J. Neurosci.* **2002**, *22*, 9612–9617; Williams, C. M.; Kirkham, T. C. *Physiol. Behav.* **2002**, *76*, 241–250), emesis, anxiety (Kathuria, S.; Gaetani, S.; et al. *Nat. Med.* **2003**, *9*, 76–81), cell proliferation (Melck, D.; Rueda, D.; et al. *FEBS Lett.* **1999**, *463*, 235–240; Yamaji, K.; Sarker, K. P.; et al. *Thromb. Haemostasis* **2003**, *89*, 875–884), inflammation (Massa, F.; Marsicano, G.; et al. *J. Clin. Invest.* **2004**, *113*, 1202–1209), memory (Mallet, P. E.; Beninger, R. J. *Psychopharmacology* **1998**, *140*, 11–19) and neuroprotection after brain injury (Panikashvili, D.; Simeonidou, C.; et al. *Nature* **2001**, *413*, 527–531). Thus, the cannabinoids have clinical relevance for analgesia, anxiety, epilepsy, cachexia, cancer, Alzheimer's disease as well as other neurodegenerative diseases (Axelrod, J.; Felder, C. C. *Neurochem. Res.* **1998**, *23*, 575–581; Di Marzo, V.; Bisogno, T.; et al. *Curr. Med. Chem.* **1999**, *6*, 721–744; Martin, B. R.; Mechoulam, R.; et al. *Life Sci.* **1999**, *65*, 573–595).

Oleamide (**1b**) was found to accumulate in the cerebrospinal fluid of animals under conditions of sleep deprivation and to induce physiological sleep in a dose dependent manner (Boger, D. L.; Henriksen, S. J.; et al. *Curr. Pharm. Des.* **1998**, *4*, 303–314; Cravatt, B. F.; et al. *Science* **1995**, *268*, 1506–1509). It modulates serotonergic systems (Cheer, J. F.; Cadogan, A.-K.; et al. *Neuropharmacology* **1999**, *38*, 533–541; Thomas, E. A.; Cravatt, B. F.; et al. *J. Neurochem.* **1999**, *72*, 2370–2378; Boger, D. L.; Patterson, J. E.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*,

4102–4107) and GABAergic transmission (Lees, G.; Dougalis, A. *Brain Res.* **2004**, 997, 1–14; Yost, C. S.; Hampson, A. J.; et al. *Anesth. Analg.* **1998**, 86, 1294–1299), decreases body temperature and locomotor activity (Huitrón-Reséndiz, S.; Gombart, L.; et al. *Exp. Neurol.* **2001**, 172, 235–243), and blocks glial gap junction cell-cell communication (Boger, D. L.; Patterson, J. E.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, 95, 4810–4815; Guan, X.; Cravatt, B. F.; et al. *J. Cell Biol.* **1997**, 139, 1785–1792). The dual inhibition of presynaptic Na⁺ channels and postsynaptic GABA_A receptors suggests oleamide (**1b**) may possess a mode of action common to drugs that are widely used for the treatment of anxiety, sleep disorders, and epilepsy and that it represents an endogenous ligand for such depressant drug sites in the mammalian brain. Oleamide (**1b**) decreases body temperature and locomotor activity (Huitrón-Reséndiz, S.; Gombart, L.; et al. *Exp. Neurol.* **2001**, 172, 235–243), and exhibits the characteristic *in vivo* analgesic and cannabinoid behavioral effects of anandamide (Cheer, J. F.; Cadogan, A.-K.; et al. *Neuropharmacology* **1999**, 38, 533–541; Mechoulam, R.; Fride, E.; et al. *Nature* **1997**, 389, 25–26), albeit without apparent cannabinoid receptor activation. It has been suggested that the cannabinoid behavioral effects of oleamide (**1b**) may be mediated through an as yet unknown distinct pharmacological target (Lees, G.; Dougalis, A. *Brain Res.* **2004**, 997, 1–14). Because oleamide (**1b**) may play an important role in sleep, it may provide opportunities for the development of sleep aids that induce physiological sleep lacking the side effects of the sedative-hypnotics (e.g., benzodiazepene class), which include rebound insomnia, anterograde amnesia and suicide abuse potential.

The pharmacological actions of anandamide (**1a**) and oleamide (**1b**) are terminated by FAAH (Figure 1) (Bracey, M. H.; Hanson, M. A.; et al. *Science* **2002**, 298, 1793–1796; Cravatt, B. F.; Giang, D. K.; et al. *Nature* **1996**, 384, 83–87; Giang, D. K.; Cravatt, B. F. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, 94, 2238–2242; Patricelli, M. P.; Cravatt, B. F. *Vit. Hormones* **2001**, 62, 95–131). Studies with FAAH knockout mice have not only shown that FAAH is a key regulator of fatty acid amide signaling *in vivo*, but that the animals exhibit a significantly augmented behavioral response (e.g., increased analgesia, hypomotility, catalepsy) to administered anandamide (**1a**) and oleamide (**1b**), that correlated with a CB1-dependent analgesic phenotype (Clement, A. B.; Hawkins, E. G.; et al. *J. Neurosci.* **2003**, 23, 3916–3923; Cravatt, B. F.; Demarest, K.; et al. *Proc. Natl. Acad. Sci.*

U.S.A. **2001**, *98*, 9371–9376; Cravatt, B. F.; Saghatelian, A.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 10821–10826; Lichtman, A. H.; Shelton, C. C.; et al. *Pain* **2004**, *109*, 319–327). As such, FAAH has emerged as an interesting new therapeutic target for a range of clinical disorders (Lambert, D. M.; Fowler, C. J. *J. Med. Chem.* **2005**, *48*, 5059–5087; Cravatt, B. F.; Lichtman, A. H. *Curr. Opin. Chem. Biol.* **2003**, *7*, 469–475).

Due to the potentially exciting therapeutic potential of inhibiting FAAH, there has been increasing interest in the development of potent inhibitors (Figure 2)

(Kathuria, S.; Gaetani, S.; et al. *Nat. Med.* **2003**, *9*, 76–81; Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856; Boger, D. L.; Sato, H.; et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 265–270; Boger, D. L.; Sato, H.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 5044–5049; De Petrocellis, L.; Melck, D.; et al. *Biochem. Biophys. Res. Commun.* **1997**, *231*, 82–88; Deutsch, D. G.; Omeir, R.; et al. *Biochem. Pharmacol.* **1997**, *53*, 255–260; Deutsch, D. G.; Lin, S.; et al. *Biochem. Biophys. Res. Commun.* **1997**, *231*, 217–221; Du, W.; Hardouin, C.; et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 103–106; Edgmond, W. S.; Greenberg, M. J.; et al. *J. Pharmacol. Exp. Ther.* **1998**, *286*, 184–190; Fernando, S. R.; Pertwee, R. G. *Br. J. Pharmacol.* **1997**, *121*, 1716–1720; Koutek, B.; Prestwich, G. D.; et al. *J. Biol. Chem.* **1994**, *269*, 22937–22940; Patricelli, M. P.; Patterson, J. P.; et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 613–618; Patterson, J. E.; Ollmann, I. R.; et al. *J. Am. Chem. Soc.* **1996**, *1996*, 5938–5945; Tarzia, G.; Duranti, A.; et al. *ChemMedChem* **2006**, *1*, 130–139; Tarzia, G.; Duranti, A.; et al. *J. Med. Chem.* **2003**, *46*, 2352–2360; Mor, M.; Rivara, S.; et al. *J. Med. Chem.* **2004**, *47*, 4998–5008; Muccioli, G. G.; Fazio, N.; et al. *J. Med. Chem.* **2006**, *49*, 417–425). These include the discovery that the endogenous sleep-inducing molecule 2-octyl γ -bromoacetoacetate is an effective FAAH inhibitor (Patricelli, M. P.; Patterson, J. P.; et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 613–618), a series of reversible inhibitors bearing an electrophilic ketone (Boger, D. L.; Sato, H.; et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 265–270; Koutek, B.; Prestwich, G. D.; et al. *J. Biol. Chem.* **1994**, *269*, 22937–22940; Patterson, J. E.; Ollmann, I. R.; et al. *J. Am. Chem. Soc.* **1996**, *1996*, 5938–5945) (e.g., trifluoromethyl ketone-based) that have not proven selective for FAAH over other mammalian serine hydrolases (Leung, D.; Du, W.; et al. *Bioorg. Med. Chem. Lett.*

2005, 15, 1423–1428) and a set of irreversible inhibitors (De Petrocellis, L.; Melck, D.; et al. *Biochem. Biophys. Res. Commun.* **1997**, 231, 82–88; Deutsch, D. G.; Omeir, R.; et al. *Biochem. Pharmacol.* **1997**, 53, 255–260; Deutsch, D. G.; Lin, S.; et al. *Biochem. Biophys. Res. Commun.* **1997**, 231, 217–221; Edgemond, W. S.;

5 Greenberg, M. J.; et al. *J. Pharmacol. Exp. Ther.* **1998**, 286, 184–190; Fernando, S. R.; Pertwee, R. G. *Br. J. Pharmacol.* **1997**, 121, 1716–1720) (e.g., fluorophosphonates and sulphonyl fluorides). Recently, two classes of inhibitors have been disclosed that provide significant opportunities for the development of an inhibitor with therapeutic potential. One class is the aryl carbamates (e.g., URB-597

10 **2a**; Figure 2) that acylate an active site catalytic serine and which were shown to exhibit anxiolytic activity and induce analgesia (Kathuria, S.; Gaetani, S.; et al. *Nat. Med.* **2003**, 9, 76–81; Tarzia, G.; Duranti, A.; et al. *ChemMedChem* **2006**, 1, 130–139; Tarzia, G.; Duranti, A.; et al. *J. Med. Chem.* **2003**, 46, 2352–2360; Mor, M.; Rivara, S.; et al. *J. Med. Chem.* **2004**, 47, 4998–5008; Hohmann, A. G.; Suplita, R.

15 L.; et al. *Nature* **2005**, 435, 1108–1112). However, the selectivity of such aryl carbamate inhibitors is low and recent studies illustrate that either no or minimal selectivity is achieved (e.g., other targets of URB-597 **2a** are carboxylesterase 6 and triacylglyceride hydrolase) (Alexander, J. P.; Cravatt, B. F. *Chem. Biol.* **2005**, 12, 1179–1187; Lichtman, A. H.; Leung, D.; et al. *J. Pharmacol. Exp. Ther.* **2004**, 311,

20 441–448; Alexander, J. P.; Cravatt, B. F. *J. Am. Chem. Soc.* **2006**, 128, 9699–9704). A second class is the α -ketoheterocycle-based inhibitors of which some are extraordinarily potent (e.g., OL-135 **2b**; Figure 2) (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856; Boger, D. L.; Sato, H.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, 97, 5044–5049; Du, W.; Hardouin, C.; et al. *Bioorg. Med. Chem. Lett.* **2005**, 15, 103–106; Leung, D.; Du, W.; et al. *Bioorg. Med. Chem. Lett.* **2005**,

25 15, 1423–1428; Boger, D. L.; Miyauchi, H.; et al. *Bioorg. Med. Chem. Lett.* **2001**, 11, 1517–1520). These competitive inhibitors bind to FAAH via reversible hemiketal formation with an active site serine, and are not only potent and extraordinarily selective for FAAH versus other mammalian serine hydrolases (Boger, D. L.;

30 Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856; Leung, D.; Du, W.; et al. *Bioorg. Med. Chem. Lett.* **2005**, 15, 1423–1428), but many are efficacious *in vivo* and promote analgesia (Lichtman, A. H.; Leung, D.; et al. *J. Pharmacol. Exp. Ther.* **2004**, 311, 441–448; Chang, L.; Luo, L.; et al. *Br. J. Pharmacol.* **2006**, 148, 102–113).

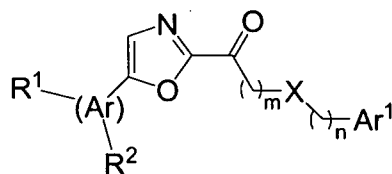
The present invention concerns the synthesis and evaluation of a systematic series of α -keto oxazole inhibitors having variations at the C2 acyl side chain along with results of the proteome-wide selectivity screening of the candidate inhibitors.

- 5 The screening protocol is described by Leung, D.; Hardouin, C.; et al. *Nature Biotech.* **2003**, *21*, 687–691.

Summary of the Invention:

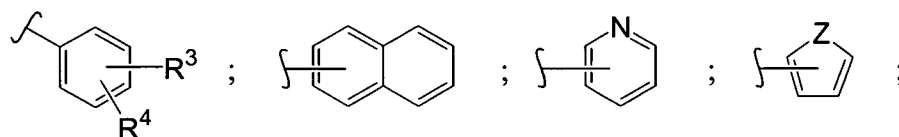
- The novel 2-keto-oxazole derivatives of the invention have FAAH-modulating
 10 activity. A series of derivatives was prepared and evaluated for FAAH inhibitory potency as well as FAAH selectivity versus competitive serine proteases (e.g., TGH, KIAA1363). Aryl substitutions along the acyl side chain resulted in effective
 inhibitors. A large series of phenyl substituents proved to be effective inhibitors with hydrophobic or electron-withdrawing *meta* substituents generally enhancing binding
 15 affinity to the greatest extent, for example, compound **5hh** (aryl = 3-Cl-Ph, K_i = 900 pM) displayed extremely potent activity. A systematic series of heteroatoms (O, NMe, S) and electron-withdrawing groups (SO, SO₂) positioned within the acyl side chain was investigated. The most tolerant position (position 6) along the acyl side
 chain provided effective inhibitors (see compound **12p**, X = S, K_i = 3 nM). A series of
 20 amides within the linking chain and hydroxyl substitutions on the chain were also explored. The activity of the compounds having amide placement at various positions along the side chain varied in potency. Hydroxyl substitution at positions 2 and 6
 provided highly effective inhibitors (**13a**, 2-position OH, K_i = 8 nM). Just as
 25 importantly, proteome-wide selectivity screening of the candidate inhibitors showed extraordinary selectivity for FAAH over all other serine hydrolases and proteases.

More particularly, in one general aspect, the invention relates to compounds of the following Formula (I), represented by following structure:



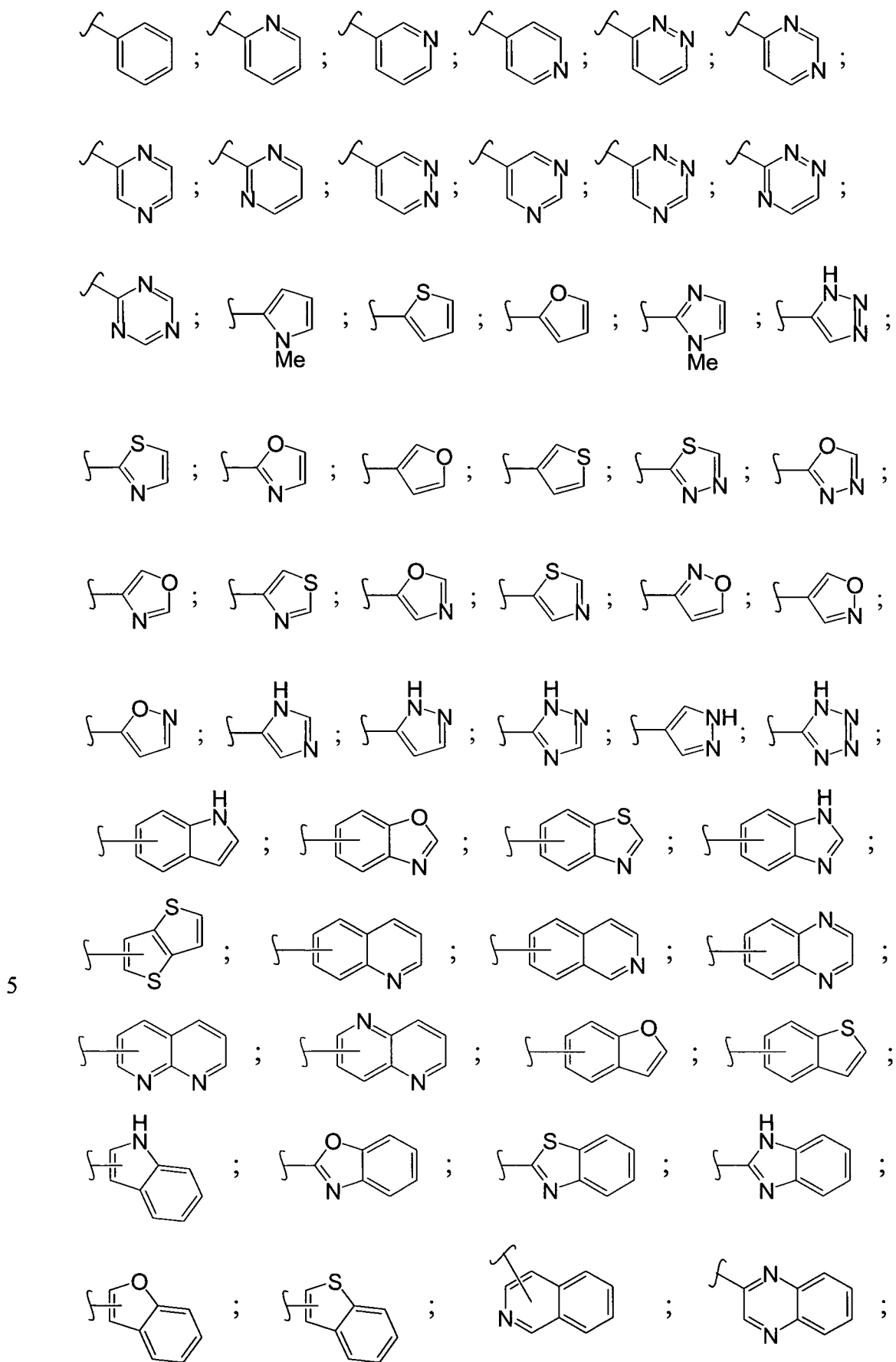
Formula (I).

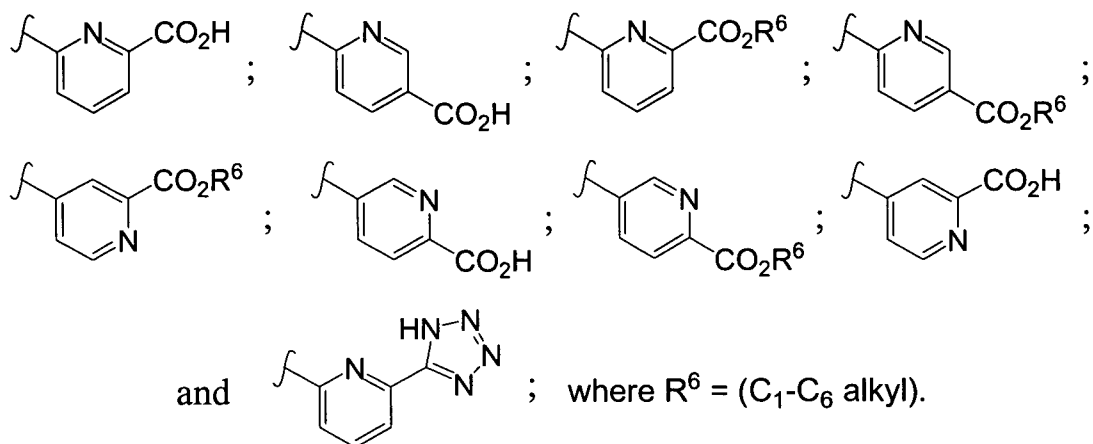
In Formula I, Ar is a 5- or 6-membered aryl or heteroaryl ring having a carbon as its point of attachment to the oxazole; R¹ is independently selected from the group consisting of -(C₁-C₆ alkyl), -(C₃-C₆ alkyl), -CF₃, -CN, -C(O)C₁-C₄ alkyl optionally substituted with one, two, or three fluoro substituents, -CO₂(C₁-C₄ alkyl), -CO₂H, -C(O)N(R^a)R^b, -OH, -O(C₁-C₆ alkyl), halo, -NO₂, -NR^aR^b, -N(R^a)C(O)R^b, -N(R^a)SO₂R^b, -SO₂N(R^a)R^b, -SR^a, -S(O)R^a, -SO₂R^a; where R^a and R^b are each independently selected from the group consisting of -H, -(C₁-C₆ alkyl), and -(C₃-C₆ cycloalkyl); and R² is independently selected from the group consisting of -(C₁-C₆ alkyl), -(C₃-C₆ alkyl), -CF₃, -CN, -C(O)C₁-C₄ alkyl optionally substituted with one, two, or three fluoro substituents, -CO₂(C₁-C₄ alkyl), -CO₂H, -C(O)N(R^c)R^d, -OH, -O(C₁-C₆ alkyl), -halo, -NO₂, -NR^cR^d, -N(R^c)C(O)R^d, -N(R^c)SO₂R^d, -SO₂N(R^c)R^d, -SR^c, -S(O)R^c, -SO₂R^c; where R^c and R^d are each independently selected from the group consisting of -H, -(C₁-C₆ alkyl), or -(C₃-C₆ cycloalkyl); and Ar¹ selected from the group consisting of the following radicals:



X is selected from the group of diradicals consisting of -CH₂-, -O-, -S-, -S(O)-, -S(O)₂-, -NR⁵-, -C≡C-, -CH(OH)-, -C(O)NH-; and R³ and R⁴ are independently selected from the group consisting -H, -NHBOC, -F, -Cl, -Br, -I, -NH₂, -NO₂, -O(C₁-C₆ alkyl), -S(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), -CF₃, -COOH, -CO₂(C₁-C₆ alkyl), -(C₁-C₆ alkyl); R⁵ is selected from the group consisting of -H, and -(C₁-C₆ alkyl); and Z is selected from the group of diradicals consisting of -O-, -S-, and -NR⁵-; and

m is an integer between 0 and 6; and n is an integer between 0 and 6. However, the following provisos apply: if m is 0, then n cannot be 0; and if X is -CH₂-, then Ar¹ cannot be phenyl. In a preferred embodiment, Ar is selected from the group consisting of phenyl, pyridyl, pyridazinyl, pyrimidinyl, pyrimidinedione, pyrazinyl, thiophenyl, furanyl, imidazolyl, oxazolyl, triazolyl and tetrazolyl. In other preferred embodiments, Ar is selected from the following group:





In yet other embodiments, R^1 is selected from the group consisting of $-CH_3$, $-CF_3$, $-CN$, $-C(O)CF_3$, $-CO_2CH_3$, $-CO_2H$, $-C(O)NH_2$, $-OH$, $-OCH_3$, $-F$, $-NO_2$, $-NH_2$, and $-SO_2NH_2$. Preferably, R^2 is $-H$.

Another aspect of the invention is directed to a process for inhibiting the catalytic activity of fatty acid amide hydrolase. The process comprises the step of contacting the fatty acid amide hydrolase with a solution having an inhibitory concentration of a compound of Formula I.

In preferred embodiments, the compound of Formula (I) is a compound specifically described or exemplified in the detailed description below.

In a further general aspect, the invention relates to pharmaceutical compositions each comprising: (a) an effective amount of an agent selected from compounds of Formula (I) and pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites thereof; and (b) a pharmaceutically acceptable excipient.

In another general aspect, the invention relates to pharmaceutical combinations of a compound of Formula I and another bioactive agent such as another FAAH inhibitor, as well as NSAIDs, Cox inhibitors and the like as described in detail in the following section.

In another general aspect, the invention relates to prodrugs and active metabolites of a compound of Formula I.

In another general aspect, the invention is directed to a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition mediated by FAAH activity, comprising administering to the subject in need of such treatment an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically active metabolite of such compound.

In certain preferred embodiments of the inventive method, the disease, disorder, or medical condition is selected from: anxiety, pain, sleep disorders, eating disorders, inflammation, multiple sclerosis and other movement disorders, HIV wasting syndrome, closed head injury, stroke, Alzheimer's disease, epilepsy, Tourette's syndrome, Niemann-Pick disease, Parkinson's disease, Huntington's chorea, optic neuritis, autoimmune uveitis, symptoms of drug withdrawal, nausea, emesis, sexual dysfunction, post-traumatic stress disorder, cerebral vasospasm, glaucoma, irritable bowel syndrome, inflammatory bowel disease, immunosuppression, gastroesophageal reflux disease, paralytic ileus, secretory diarrhea, gastric ulcer, rheumatoid arthritis, unwanted pregnancy, hypertension, cancer, hepatitis, allergic airway disease, auto-immune diabetes, intractable pruritis, and neuroinflammation.

Additional embodiments, features, and advantages of the invention will be apparent from the appended claims, which are incorporated into this summary by reference, as well as from the following detailed description.

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Brief Description of Drawings:

Figure 1 illustrates both anandamide (**1a**) and oleamide (**1b**) undergoing hydrolysis by fatty acid amide hydrolase (FAAH) to their respective carboxylic acids. Both have emerged as prototypical members of the class of bioactive lipid amides that serve as chemical messengers. The pharmacological actions of anandamide (**1a**) and oleamide (**1b**) are terminated by FAAH.

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Figure 2 shows the structures of URB-597 and OL-135 along with their respective activities. URB-597 is from one class comprising the aryl carbamates that acylate an active site catalytic serine and which were shown to exhibit anxiolytic activity and induce analgesia. OL-135 is an example of a ketoheterocycle-based inhibitor.

5

Figure 3 illustrates how the majority of the candidate inhibitors were prepared.

Figure 4 illustrates the methods used in the synthesis of the inhibitors that were not prepared by either Method A or B.

10

Figure 5 illustrates a collection of tables showing a systematic series of aryl replacements and phenyl substitutions for the terminal phenyl group of OL-135 (**2b**).

Figure 6 illustrates two tables where the linker chain contains an alkynyl group connecting the methylene portion to the aryl ring.

15

Figure 7 illustrates a series of tables showing the effects of substitution along the side chain.

Figure 8 illustrates a table showing a series of amides within the linking chain and hydroxyl substitutions on the chain was also explored.

20

Figure 9 illustrates is a table showing several additional side chain modifications that were examined and represent intermediates or byproducts derived from the synthesis of the preceding candidate inhibitors.

25

Figure 10 illustrates a short table listing the differing K_i 's between human FAAH and rat FAAH for some of the more potent compounds.

Figure 11 illustrates is a table showing the K_i with FAAH and the other columns are IC_{50} 's with FAAH, KIAA1363 and TGH.

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Detailed Description of Invention and Its Embodiments:

The present invention concerns substituted oxazole compounds having an alpha keto side chain at the 2 position of oxazole and an aryl or heteroaryl substituent at the 5 position of the oxazole. A series of aryl variations along the alpha keto side chain provided effective inhibitors (e.g., **5c**, aryl = 1-naphthyl, $K_i = 2.6$ nM) and an extensive series of phenyl substituents were incorporated to provide effective inhibitors with hydrophobic or electron-withdrawing *meta* substituents most significantly enhancing binding affinity. For example compound **5hh** (aryl = 3-Cl-Ph, $K_i = 900$ pM) described below had extreme potency. Also, a series of heteroatom substitutions along the alpha keto side chain (O, NMe, S) and electron-withdrawing groups (SO, SO₂) were explored. It was discovered that these substitutions affected potency such that substitution β to the electrophilic carbonyl lowers potency. The most tolerant position (position 6 along the chain) provided effective inhibitors (**12p**, X = S, $K_i = 3$ nM). A series of amides within the linking chain and hydroxyl substitutions on the chain were also explored. Amide placement within the side chain led to variation in inhibitory potency whereas hydroxyl substitution at positions 2 and 6 provided effective inhibitors (**13d**, 2-position OH, $K_i = 8$ nM). Proteomic-wide screening of selected candidate inhibitors revealed that these new inhibitors are exquisitely selective for FAAH over all other mammalian serine proteases.

20

The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. For the sake of brevity, the disclosures of the publications cited in this specification are herein incorporated by reference.

25

As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

Unless otherwise indicated by the text of this application, the use of the single articles of speech, "a", "an" and "the" include both the singular form and the plural form of the nouns with which they are associated. For example the term "a compound of Formula I" includes each single compound of Formula I, multiple compounds of Formula I and the group of compounds delineated by Formula I such that this term

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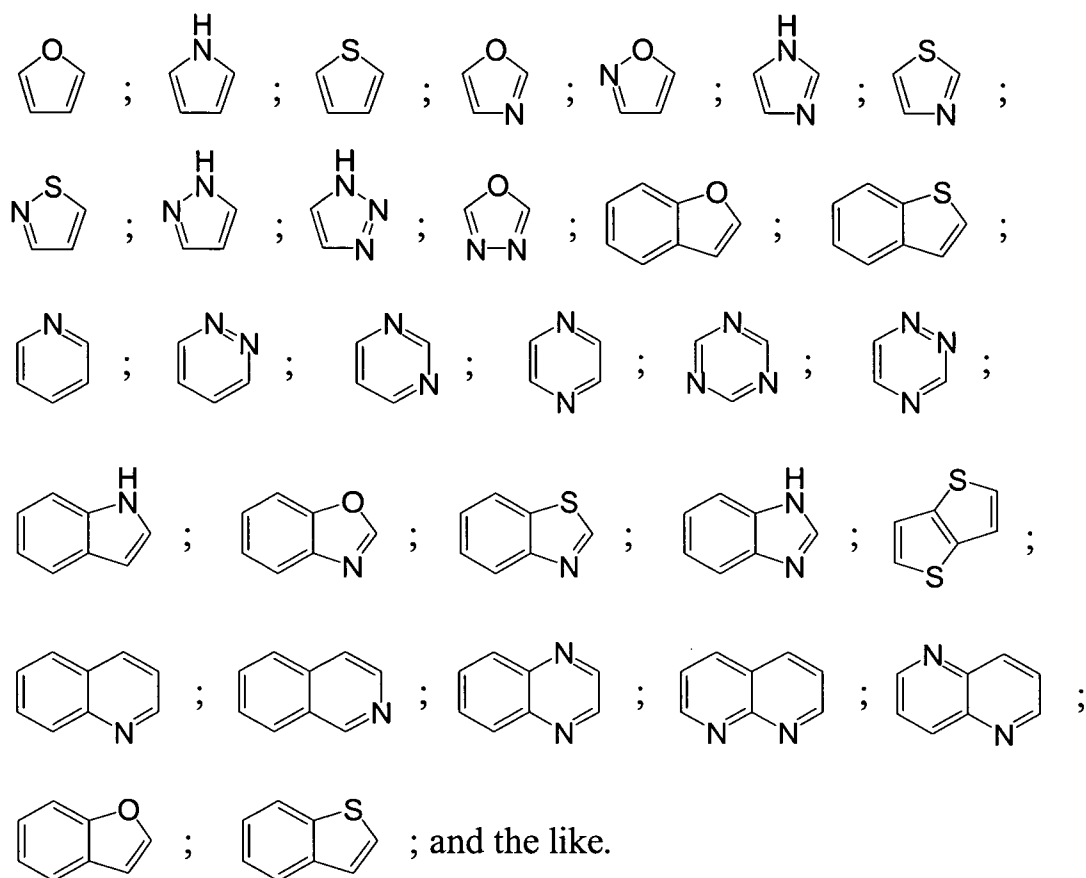
encompasses the phrases “compounds delineated by Formula I and “an individual compound delineated by Formula I.”

5 The term “alkyl” refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Exemplary alkyl groups include methyl (Me, which also may be structurally depicted by /), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like.

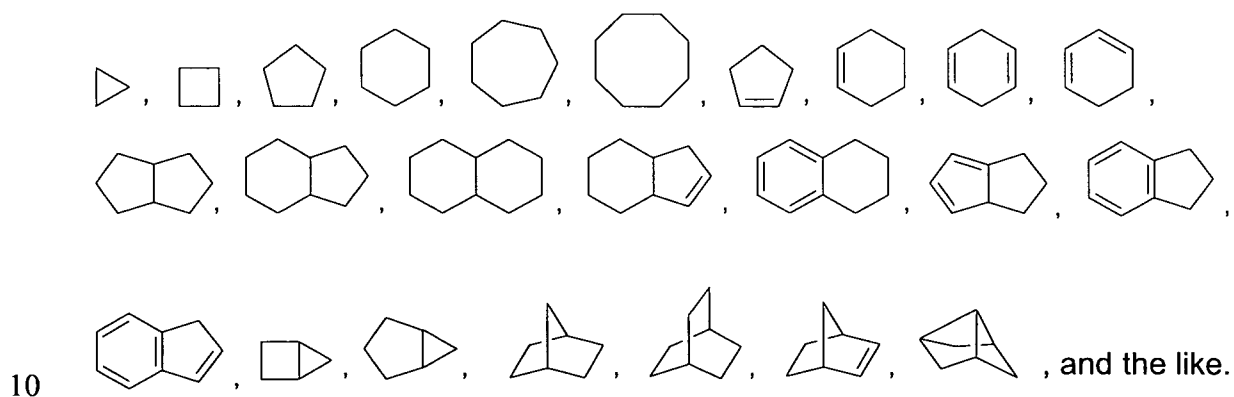
10 The term “aryl” refers to a monocyclic, fused bicyclic, or fused polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) having from 3 to 12 ring atoms per carbocycle. (Carbon atoms in aryl groups are sp^2 hybridized.) Illustrative examples of aryl groups include phenyl, naphthyl, anthracenyl, phenanthrenyl, and the like.

15

 The term “heteroaryl” refers to a monocyclic, fused bicyclic, or fused polycyclic aromatic heterocycle (ring structure having ring atoms selected from carbon atoms as well as nitrogen, oxygen, and sulfur heteroatoms) having from 3 to 12 ring atoms per heterocycle. Illustrative examples of heteroaryl groups include the
20 following moieties:



The term “cycloalkyl” refers to a saturated or partially saturated, monocyclic,
 fused polycyclic, or spiro polycyclic, carbocycle having from 3 to 12 ring atoms per
 5 carbocycle. Illustrative examples of cycloalkyl groups include the following
 moieties:



The term “halogen” represents chlorine, fluorine, bromine or iodine. The term
 “halo” represents chloro, fluoro, bromo or iodo.

The term “substituted” means that the specified group or moiety bears one or
 more substituents. The term “unsubstituted” means that the specified group bears no

substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents. Where the term "substituted" is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system.

5

Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof, are considered within the scope of the formula. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof.

Furthermore, certain structures may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers. Additionally, any formula given herein is intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, phosphorous, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{125}I , respectively. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H , ^{11}C , and ^{14}C are incorporated. Such isotopically labeled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or ^{11}C labeled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier

isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

When referring to any formula given herein, the selection of a particular moiety from a list of possible species for a specified variable is not intended to define the moiety for the variable appearing elsewhere. In other words, where a variable appears more than once, the choice of the species from a specified list is independent of the choice of the species for the same variable elsewhere in the formula.

In preferred embodiments of the invention, Ar is selected from the group consisting of phenyl, pyridyl, pyridazinyl, pyrimidinyl, pyrimidine-dione, pyrazinyl, thiophenyl, furanyl, imidazolyl, oxazolyl, and tetrazolyl.

The invention includes also pharmaceutically acceptable salts of the compounds represented by Formula (I), such as of those described above. Pharmaceutically acceptable salts of the specific compounds exemplified are especially preferred.

A "pharmaceutically acceptable salt" is intended to mean a salt of a free acid or base of a compound represented by Formula (I) that is not toxic, biologically intolerable, or otherwise biologically undesirable. *See*, generally, S.M. Berge, *et al.*, "Pharmaceutical Salts", J. Pharm. Sci., 1977, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*; Stahl, P.H., Wermuth, C.G., Eds.; Wiley-VCH and VHCA: Zurich, 2002. Preferred pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. A compound of Formula (I) may possess a sufficiently acidic group, a sufficiently basic group, or both types of functional groups, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts

include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the compound of Formula (I) contains a basic nitrogen, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an α -hydroxy acid, such as mandelic acid, citric acid, or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, or ethanesulfonic acid, or the like.

If the compound of Formula (I) is an acid, such as a carboxylic acid or sulfonic acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide, or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, carbonates, bicarbonates, primary, secondary, and tertiary amines, and cyclic amines, such as benzylamines, pyrrolidines, piperidine, morpholine, and

piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

The invention also relates to treatment methods employing pharmaceutically acceptable prodrugs of the compounds of Formula (I). The term "prodrug" means a precursor of a designated compound that, following administration to a subject, yields the compound *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the compound of Formula (I)). A "pharmaceutically acceptable prodrug" is a prodrug that is not toxic, biologically intolerable, or otherwise biologically unsuitable for administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Exemplary prodrugs include compounds having an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, covalently joined through an amide or ester bond to a free amino, hydroxy, or carboxylic acid group of a compound of Formula (I). Examples of amino acid residues include the twenty naturally occurring amino acids, commonly designated by three letter symbols, as well as 4-hydroxyproline, hydroxylysine, demosine, isodemossine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone.

Additional types of prodrugs may be produced, for instance, by derivatizing free carboxyl groups of structures of Formula (I) as amides or alkyl esters. Exemplary amides include those derived from ammonia, primary C₁₋₆alkyl amines and secondary di(C₁₋₆alkyl) amines. Secondary amines include 5- or 6-membered heterocycloalkyl or heteroaryl ring moieties. Preferred amides are derived from ammonia, C₁₋₃alkyl primary amines, and di(C₁₋₂alkyl)amines. Exemplary esters of the invention include C₁₋₇alkyl, C₅₋₇cycloalkyl, phenyl, and phenyl(C₁₋₆alkyl) esters. Preferred esters include methyl esters. Prodrugs may also be prepared by derivatizing free hydroxy groups using groups including hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, following procedures

such as those outlined in *Adv. Drug Delivery Rev.* **1996**, *19*, 115. Carbamate derivatives of hydroxy and amino groups may also yield prodrugs. Carbonate derivatives, sulfonate esters, and sulfate esters of hydroxy groups may also provide prodrugs. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers, wherein the acyl group may be an alkyl ester, optionally substituted with one or more ether, amine, or carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, is also useful to yield prodrugs. Prodrugs of this type may be prepared as described in *J. Med. Chem.* **1996**, *39*, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including ether, amine, and carboxylic acid functionalities.

Pharmaceutically active metabolites may also be used in the methods of the invention. A "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a compound of Formula (I) or salt thereof. Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini et al., *J. Med. Chem.* **1997**, *40*, 2011-2016; Shan et al., *J. Pharm. Sci.* **1997**, *86* (7), 765-767; Bagshawe, *Drug Dev. Res.* **1995**, *34*, 220-230; Bodor, *Adv. Drug Res.* **1984**, *13*, 224-331; Bundgaard, *Design of Prodrugs* (Elsevier Press, **1985**); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, **1991**).

The compounds of Formula (I) and their pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites (collectively, "agents") of the present invention are useful as FAAH inhibitors in the methods of the invention. The agents may be used in the inventive methods for the treatment or prevention of medical conditions, diseases, or disorders mediated through inhibition or modulation of FAAH, such as those described herein. Agents according to the invention may therefore be used as an analgesic, neuroprotectant, sedative, appetite stimulant, or contraceptive.

Exemplary medical conditions, diseases, and disorders include anxiety, pain, sleep disorders, eating disorders, inflammation, multiple sclerosis and other

movement disorders, HIV wasting syndrome, closed head injury, stroke, Alzheimer's disease, epilepsy, Tourette's syndrome, epilepsy, Niemann-Pick disease, Parkinson's disease, Huntington's chorea, optic neuritis, autoimmune uveitis, symptoms of drug withdrawal, nausea, emesis, sexual dysfunction, post-traumatic stress disorder, or
5 cerebral vasospasm.

Thus, the pharmaceutical agents may be used to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated through FAAH activity. The term "treat" or "treating" as used herein is intended to refer to administration of
10 an agent or composition of the invention to a subject for the purpose of effecting a therapeutic or prophylactic benefit through modulation of FAAH activity. Treating includes reversing, ameliorating, alleviating, inhibiting the progress of, lessening the severity of, or preventing a disease, disorder, or condition, or one or more symptoms of such disease, disorder or condition mediated through modulation of FAAH activity.
15 The term "subject" refers to a mammalian patient in need of such treatment, such as a human. "Modulators" include both inhibitors and activators, where "inhibitors" refer to compounds that decrease, prevent, inactivate, desensitize or down-regulate FAAH expression or activity, and "activators" are compounds that increase, activate, facilitate, sensitize, or up-regulate FAAH expression or activity.

20 Accordingly, the invention relates to methods of using the pharmaceutical agents described herein to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated through FAAH activity, such as: anxiety, pain, sleep disorders, eating disorders, inflammation, or movement disorders (e.g., multiple
25 sclerosis).

Symptoms or disease states are intended to be included within the scope of "medical conditions, disorders, or diseases." For example, pain may be associated with various diseases, disorders, or conditions, and may include various etiologies.
30 Illustrative types of pain treatable with a FAAH-modulating agent according to the invention include cancer pain, postoperative pain, GI tract pain, spinal cord injury pain, visceral hyperalgesia, thalamic pain, headache (including stress headache and migraine), low back pain, neck pain, musculoskeletal pain, peripheral neuropathic pain, central neuropathic pain, neurogenerative disorder related pain, and menstrual

pain. HIV wasting syndrome includes associated symptoms such as appetite loss and nausea. Parkinson's disease includes, for example, levodopa-induced dyskinesia. Treatment of multiple sclerosis may include treatment of symptoms such as spasticity, neurogenic pain, central pain, or bladder dysfunction. Symptoms of drug withdrawal
5 may be caused by, for example, addiction to opiates or nicotine. Nausea or emesis may be due to chemotherapy, postoperative, or opioid related causes. Treatment of sexual dysfunction may include improving libido or delaying ejaculation. Treatment of cancer may include treatment of glioma. Sleep disorders include, for example, sleep apnea, insomnia, and disorders calling for treatment with an agent having a
10 sedative or narcotic-type effect. Eating disorders include, for example, anorexia or appetite loss associated with a disease such as cancer or HIV infection/AIDS.

In a treatment method according to the invention, an effective amount of a pharmaceutical agent according to the invention is administered to a subject suffering
15 from or diagnosed as having such a disease, disorder, or condition. An "effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic or prophylactic benefit in patients in need of such treatment.

Effective amounts or doses of the agents of the present invention may be
20 ascertained by routine methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating
25 physician. An exemplary dose is in the range of from about 0.001 to about 200 mg of agent per kg of subject's body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

30

Once improvement of the patient's disease, disorder, or condition has occurred, the dose may be adjusted for preventative or maintenance treatment. For example, the dosage or the frequency of administration, or both, may be reduced as a function of the symptoms, to a level at which the desired therapeutic or prophylactic

effect is maintained. Of course, if symptoms have been alleviated to an appropriate level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

5 In addition, the agents of the invention may be used in combination with additional active compounds in the treatment of the above conditions. The additional compounds may be coadministered separately with an agent of Formula (I) or included with such an agent as an additional active ingredient in a pharmaceutical composition according to the invention. In an exemplary embodiment, additional
10 active compounds are those that are known or discovered to be effective in the treatment of conditions, disorders, or diseases mediated by FAAH activity, such as another FAAH modulator or a compound active against another target associated with the particular condition, disorder, or disease. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency
15 or effectiveness of an agent according to the invention), decrease one or more side effects, or decrease the required dose of the agent according to the invention. In one illustrative embodiment, a composition according to the invention may contain one or more additional active ingredients selected from opioids, NSAIDs (e.g., ibuprofen, cyclooxygenase-2 (COX-2) inhibitors, and naproxen), gabapentin, pregabalin,
20 tramadol, acetaminophen, and aspirin.

 The agents of the invention are used, alone or in combination with one or more other active ingredients, to formulate pharmaceutical compositions of the invention. A pharmaceutical composition of the invention comprises: (a) an effective
25 amount of a pharmaceutical agent in accordance with the invention; and (b) a pharmaceutically acceptable excipient.

 A "pharmaceutically acceptable excipient" refers to a substance that is not toxic, biologically intolerable, or otherwise biologically unsuitable for administration
30 to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of a pharmaceutical agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

Delivery forms of the pharmaceutical compositions containing one or more dosage units of the pharmaceutical agents may be prepared using suitable pharmaceutical excipients and compounding techniques now or later known or
5 available to those skilled in the art. The compositions may be administered in the inventive methods by oral, parenteral, rectal, topical, or ocular routes, or by inhalation.

The preparation may be in the form of tablets, capsules, sachets, dragees,
10 powders, granules, lozenges, powders for reconstitution, liquid preparations, or suppositories. Preferably, the compositions are formulated for intravenous infusion, topical administration, or oral administration.

For oral administration, the compounds of the invention can be provided in the
15 form of tablets or capsules, or as a solution, emulsion, or suspension. To prepare the oral compositions, the agents may be formulated to yield a dosage of, e.g., from about 0.05 to about 50 mg/kg daily, or from about 0.05 to about 20 mg/kg daily, or from about 0.1 to about 10 mg/kg daily.

20 Oral tablets may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose,
25 magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the
30 tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

Liquids for oral administration may be in the form of suspensions, solutions, emulsions or syrups or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

The agents of this invention may also be administered by non-oral routes. For example, the compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the agents of the invention may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms will be presented in unit-dose form such as ampules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses may range from about 1 to 1000 $\mu\text{g/kg/minute}$ of agent, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

For topical administration, the agents may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug to vehicle. Another

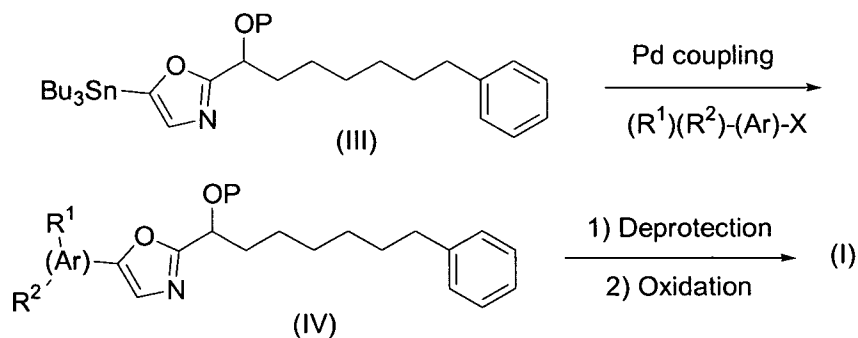
mode of administering the agents of the invention may utilize a patch formulation to affect transdermal delivery.

Agents may alternatively be administered in methods of this invention by inhalation, via the nasal or oral routes, e.g., in a spray formulation also containing a suitable carrier.

Chemistry

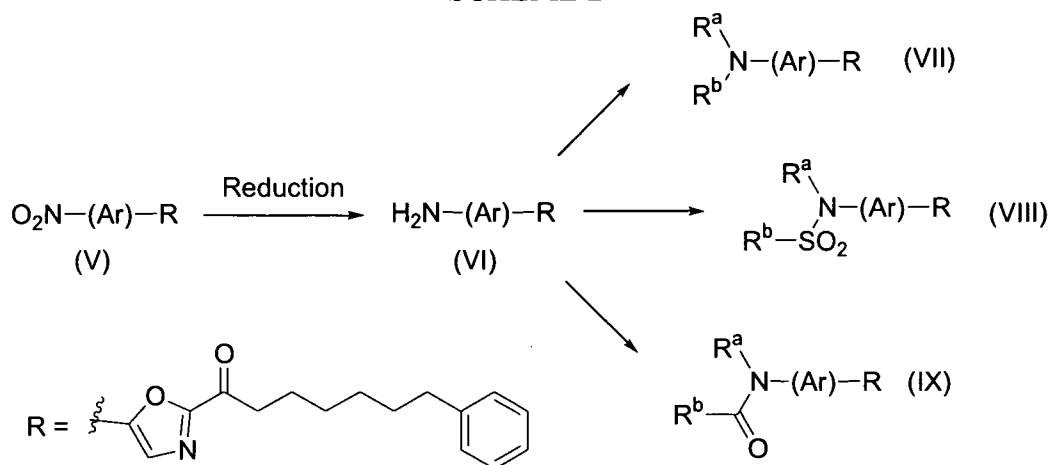
Exemplary agents useful in methods of the invention will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Unless otherwise specified, the variables are as defined above in reference to Formula (I). Figures 3 and 4 also illustrate these schemes.

SCHEME A



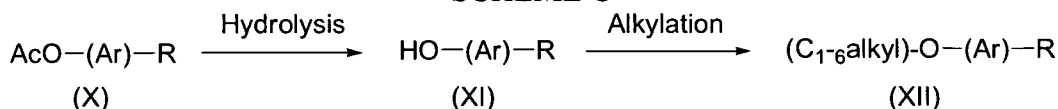
Referring to Scheme A, stannanes of formula (III), where P is a suitable hydroxyl protecting group, are prepared as previously described (Boger, *J. Med. Chem.* **2005**, 48, 1849). Stannanes (III) are coupled with various aryl or heteroaryl halides using Stille coupling procedures. Preferred conditions utilize $Pd(PPh_3)_4$ or $Pd(P(t-Bu)_3)_2$ as the catalyst. Compounds of formula (IV) are then deprotected (for example, where P is a silyl protecting group, with a silyl deprotecting agent such as TBAF) and oxidized to compounds of Formula (I) using oxidizing agents such as Dess-Martin periodinane or TPAP/NMO.

SCHEME B



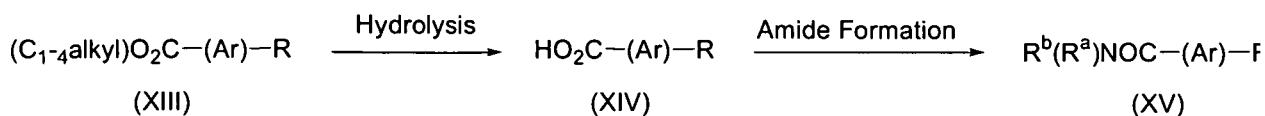
Referring to Scheme B, compounds of formula (V) may be obtained according to the methods shown in Scheme A. The nitro group may be reduced to an amino group (formula (VI)) using standard nitro reduction methods, such as exposure to SnCl_2 or by hydrogenation in the presence of a Pd catalyst. Amines (VI) may be alkylated via alkylation or reductive amination protocols to form amines (VII). Amines (VI) may be alternatively sulfonylated with the appropriately substituted sulfonyl chlorides to form compounds of formula (VIII). Reaction of amines (VI) with suitably substituted acid chlorides or via peptide coupling with appropriate acids (e.g. in the presence of HOAt/EDCI) generate amides (IX). Installation of the R^a substituent may be accomplished before (via alkylation or reductive amination) or after (via alkylation) the sulfonylation/acylation step. One skilled in the art will recognize that Formula (I) includes compounds of formulae (VI), (VII), (VIII), and (IX).

SCHEME C



Referring to Scheme C, acetates of formula (X), where R is defined as in Scheme B, may be obtained according to the methods shown in Scheme A. Deprotection of the acetate group, using, for example, a base such as LiOH or NaOMe, gives the corresponding alcohols (XI). These alcohols may in turn be converted to ethers of formula (XII) by treatment with an appropriate alkyl halide in the presence of a base, or with an appropriate alcohol under Mitsunobu conditions (for example, PPh_3/DEAD). One skilled in the art will recognize that Formula (I) includes compounds of formulae (XI) and (XII).

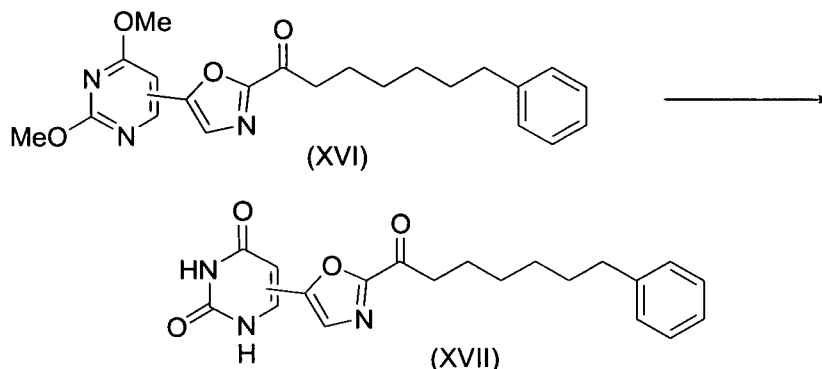
SCHEME D



- 5 Referring to Scheme D, esters of formula (XIII), where R is defined as in Scheme B, and prepared according to Scheme A, may be hydrolyzed to acids (XIV) using a base such as LiOH. Acids (XIV) may be converted to their corresponding amides (XV) by reaction with a suitable amine under peptide coupling conditions (e.g. HOAt/EDCI). One skilled in the art will recognize that Formula (I) includes
- 10 compounds of formulae (XIII), (XIV), and (XV).

One skilled in the art will recognize that transformations depicted for R¹ may analogously be performed for R².

SCHEME E



- 15 Referring to Scheme E, pyrimidines (XVI), prepared according to Scheme A, may be converted to uracils (XVII) by treatment of a demethylating agent such as TMSI. One skilled in the art will recognize that Formula (I) includes compounds of formulae (XVI) and (XVII).

- 20 The following examples are provided to further illustrate the invention and various preferred embodiments.

The majority of the candidate inhibitors were prepared by one of two methods (Figure 3). Sonogashira coupling (Method A) of **3a** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856) or **3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856) with a series of aryl iodides afforded inhibitors **4e**, **4f**, **4pp**, **4qq**, **4o–4s**, **4rr**, **4ss**, **4x–4cc**, **4gg–4jj** (Sonogashira, K.; Tohda, Y.; et al. *Tetrahedron Lett.* **1975**, *16*, 4467–4470). Hydrogenation of the alkyne provided

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inhibitors **5e**, **5f**, **5o–5s**, **5pp**, **5qq**, **5x–5cc**, **5gg–5jj**. Alternatively, direct acid chloride acylation (Method B) of a Zn/Cu-metalated 5-(pyridin-2-yl)oxazole (Saikachi, H.; Kitagawa, T.; et al. *Chem. Pharm. Bull.* **1969**, *27*, 793–796) (**6**) following the protocol of Anderson et al. (Harn, N. K.; Gramer, C. J.; et al. *Tetrahedron Lett.* **1995**, *36*, 9453–9456) yielded inhibitors **5a–5d**, **5g–5l**, **5t–5v**, **5nn**, **5oo**, **12e**, **12g**, **12i**, **12k**, **12n**, **12p**.

Figure 4 summarizes the synthesis of the inhibitors that were not prepared by either Method A or B. Oxazole **6** was lithiated at C2, converted to its C2-stannane upon treatment with Bu₃SnCl and subsequently treated with the corresponding acid chloride to afford **12a** and **12b** (Dondoni, A.; Fantin, G.; et al. *J. Org. Chem.* **1988**, *53*, 1748–1761; Dondoni, A.; Mastellari, A. R.; et al. *Synthesis* **1986**, 757–760). Compound **12f** was prepared by Michael addition of *N*-methyl-3-phenylpropylamine to enone **7**. Treatment of **8** with TiCl₄ followed by *N*-methyl-2-phenylethylamine provided **12h** (Pocar, D.; Stradi, R.; et al. *Tetrahedron* **1975**, *31*, 2427–2429; Yovell, J.; Hirsch, D.; et al. *J. Org. Chem.* **1977**, *42*, 850–855). Compounds **9j** and **9o** were transformed to a series of amino ketones upon treatment with the corresponding amine in the presence of K₂CO₃ in 2-butanone or by treatment with the neat amine. Esters **14a–14c** were readily converted to their corresponding amides **13a–13c**. α -Hydroxylation of OL-135 (**2b**) with the Davis reagent (Davis, F. A.; Vishwakarma, L. C.; et al. *J. Org. Chem.* **1984**, *49*, 3241–3243) afforded **13d**. Enolization of **10** with KHMDS and subsequent treatment with 5-phenylpentanal yielded **13e**. Inhibitors **5kk–5mm**, **12c**, **12d**, **12i**, **12m**, **12q** and **12r** were prepared by oxidation (*m*-CPBA) of the corresponding sulfides **5t–v**, **12b**, **12k**, and **12p**.

Enzyme Assay

Enzyme assays were performed at 20–23 °C with purified recombinant rat FAAH expressed in *E. coli* (Patricelli, M. P.; Lashuel, H. A.; et al. *Biochemistry* **1998**, *37*, 15177–15187) (unless indicated otherwise) or with solubilized COS-7 membrane extracts from cells transiently transfected with human FAAH cDNA (Giang, D. K.; Cravatt, B. F. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2238–2242) (where specifically indicated) in a buffer of 125 mM Tris/1 mM EDTA/0.2% glycerol/0.02% Triton X-100/0.4 mM Hepes, pH 9.0 buffer (Patricelli, M. P.; Patterson, J. P.; et al. *Bioorg.*

Med. Chem. Lett. **1998**, 8, 613–618). The initial rates of hydrolysis (≤ 10 –20% reaction) were monitored using enzyme concentrations at least three times below the measured K_i by following the breakdown of ^{14}C -oleamide and K_i 's (standard deviations are provided in Supporting Information tables) were established as described (Dixon plot) (Boger, D. L.; Sato, H.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, 97, 5044–5049). Lineweaver–Burk analysis previously established reversible, competitive inhibition (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856).

Substitution of C2 Side Chain Terminal Phenyl Group. A systematic series of aryl replacements and phenyl substitutions, aryl replacement derivatives (**5a–5f**), thiophene replacements **5a** and **5b**, 1-naphthyl substitution **5c**, 2-naphthyl derivative **5d** proved to be effective inhibitors. Incorporation of the more polar pyridine substituent **5e** and **5f** led to reductions in the K_i . Figure 5 illustrates this series.

Substitution involving the terminal phenyl ring of the alpha acyl side chain provided effective inhibition and the complete range of *ortho*, *meta*, or *para* substituents provided effective FAAH inhibitors (**5g–5oo**; Figure 5). However, the carboxylic acid derivatives (**5dd–ff**) that are deprotonated under the assay conditions did not display strong binding. Typically, hydrophobic or electron-withdrawing substituents enhanced the binding affinity of the inhibitors more significantly than polar or electron-donating substituents. However, and with a couple of notable exceptions, each substituent enhanced binding affinity indicative of additional favorable binding contacts within the active site. Although this may not be surprising for the hydrophobic substituents (CH_3 , CF_3 , F, Cl, $\text{SCH}_3 \geq \text{OCH}_3$, H), it is especially interesting that polar substituents (CO_2CH_3 , NO_2 , SO_2CH_3 , NH_2) can be tolerated in this hydrophobic pocket and that some even enhance inhibitory potency. This appears to be especially true of the *m*-position where even the methylsulfone **5ll** produced an inhibitor of significant potency. whereas the corresponding *o*- and *p*-methylsulfone derivatives (**5kk** and **5mm**, respectively) were approximately 10-fold less effective. The potency of such derivatives typically ranged from 5–0.9 nM (K_i), displayed a variable and weak preference for the site of attachment, and the most potent members typically were the *m*-substituted derivatives. Significantly, **5hh** (R = Cl) broke the nanomolar potency barrier providing a K_i of 900 pM. Accordingly, this region

provides a rich area where substituents or modifications can be introduced to enhance inhibitor potency, impact features contributing to or improving *in vivo* properties, and substantially enhance selectivity. The invention, therefore encompasses all hydrophobic as well as hydrophilic and ionic substitution at these positions.

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Extending an alkyl *m*- or *p*-substituent revealed that **5nn** (*p*-substituent) displayed significant potency whereas **5oo** (*m*-substituent) was less effective.

Finally, the alkyne precursors **4** to series **5** inhibitors prepared by the Shonogashira coupling (Method A) were also examined for FAAH inhibition and the results are summarized in Figure 6. It was observed that there was a loss in activity with the alkynes compared to their corresponding alkane derivatives (Figure 5) suggesting that this restriction places the terminal aryl ring in a less favorable area in the FAAH active site.

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Substitution along the side chain. A systematic series of heteroatoms and electron-withdrawing substituents positioned within the alpha keto side chain was also investigated (Figure 7). Placing a heteroatom or electron-withdrawing substituent at the 2-position of the side chain (**12a–12d**) β to the electrophilic carbonyl resulted in a loss in potency despite their inductive electron-withdrawing character that would be expected to enhance the electrophilic character of the carbonyl. Only the least electronegative atom of the series (X = S, **12b**) displayed significant potency and the most electronegative functionality (X = SO₂, **12d**) resulted in a significant loss in potency. A rough trend in the *K_i* is observed as heteroatoms move along the chain where heteroatoms at each end of the chain (2- and 6-positions) are better tolerated than in the middle (3–5 positions). At each location, the substitutions exhibited a well-defined trend of CH₂ ≥ S > O > NMe > SO > SO₂, which reflects the hydrophobic character of this region of FAAH active site. Introduction of a sulfur provided inhibitors that displayed significant potency (**12b**, 2-position; **12p**, 6-position, **12k**, 5-position). Other heteroatoms caused reduction in potency as the above delineated trend indicates. At the most tolerant position (position 6), the magnitude of these effects for sulfur, oxygen, and NMe are dampened with each providing effective inhibitors.

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A series of amides within the linking chain and hydroxyl substitutions on the chain was also explored (Figure 8). Amide placement in the side chain led to a loss in inhibitory potency. Consistent with expectations, **13a**, but not **13b** or **13c**, exists as the stable *N*-acyl hemiaminal and this is reflected in its lower ability to inhibit FAAH. Consistent with the previous series of inhibitors (Figure 7), a well-defined trend in K_i is observed as the hydroxyl substitution moves along the side chain where the hydroxyl group at each end of the side chain was better tolerated than those in the middle of the side chain. Within this series, only **13f** (50%, CDCl_3) and **13g** (50%, CDCl_3) exist in equilibrium with their internal hemiketal. Thus, even though **13f** has a lower potency than other compounds of this series, it will prove useful to examine in vivo where the electrophilic carbonyl would potentially be less prone to metabolic reduction due to the reversible hemiketal formation.

Several additional side chain modifications were examined and represent intermediates or byproducts derived from the synthesis of the preceding candidate inhibitors. The results of their examination are summarized in Figure 9 and highlight several features. Shortening of the side chain and removal of the phenyl group of OL-135 (**2b**) with a small series of methyl esters (**14a–14c**) led to a significant progressive decrease in potency. The cyclopropyl and cyclopentyl derivatives **14d** and **14e** lacking the extended chain and phenyl group similarly resulted in a loss of activity. Interestingly, and in contrast, the simple α -chloroketone **14f** was still a submicromolar inhibitor of FAAH although it lacked nearly all of the α keto side chain. Presumably this result reflects that inhibitor's increased electrophilic carbonyl reactivity which significantly increases its potency over the known inactive methyl ketone (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856). Placement of a ketone beta to the electrophilic carbonyl (**14g**) led to a significant loss of inhibitory potency. In this instance, the electrophilic C2 carbonyl of **14g** is enolized (>95%, CDCl_3) and unreactive toward nucleophilic attack.

Finally two alcohol derivatives were examined, e.g., **14h** and **14i**, and both resulted in a substantial loss in inhibitory potency with **14h** exhibiting a greater loss in activity relative to its corresponding ketone **13d**.

Although inhibitory potency among the compounds of the invention varies, other factors such as lack of side effects, selectivity for the FAAH relative to other enzymes, bioavailability, ability to cross biological barriers such as the gut-blood barrier, the blood-cell barrier and the blood-brain barrier, among others, are important for development of an effective pharmaceutical compound. Consequently, lower potency does not mean that an individual compound of Formula I lacks pharmaceutical interest. For example, while pyridine substitution for phenyl on the alpha keto side chain led to lower potency, the selectivity for FAAH was increased as discussed below. Nevertheless, unless otherwise indicated by selectivity or other experimental factors described herein, the compounds of Formula I having higher inhibitory K_i 's are preferred according to the invention.

Inhibition of Recombinant Human FAAH. Rat and human FAAH are very homologous (84% sequence identity), exhibit near identical substrate selectivities and inhibitor sensitivities in studies disclosed to date (Boger, D. L.; Sato, H.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 5044–5049), and embody an identical amidase signature sequence suggesting the observations made with rat FAAH would be analogous to those made with the human enzyme. Consequently, the inhibitors of the present inventive series were examined against the human enzyme and consistent with previous observations (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856; Romero, F. A.; Du, W.; et al. *J. Med. Chem.* **2006**, *submitted*) were found to exhibit the same relative and absolute potencies (Figure 10).

Selectivity Screening. Early assessments of α -ketoheterocycle inhibitors of FAAH against possible competitive enzymes (e.g., phospholipase A2, ceramidase) revealed no inhibition. Consequently a method for proteomic-wide screening capable of globally profiling all mammalian serine hydrolases was developed (Leung, D.; Hardouin, C.; et al. *Nature Biotech.* **2003**, *21*, 687–691) and studies have shown that the α -ketoheterocycle class of inhibitors generally are exquisitely selective for FAAH (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856; Leung, D.; Du, W.; et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1423–1428; Lichtman, A. H.; Leung, D.; et al. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 441–448). However, two

enzymes did emerge as potential competitive targets: triacylglycerol hydrolase (TGH) and an uncharacterized membrane-associated hydrolase that lacks known substrates or function (KIAA1363). In this screen, IC_{50} values are typically higher than the measured K_i values, but the relative potency, the magnitude of binding affinity differences and the rank order binding determined in the assay parallels that established by standard substrate assays.

Summarized in Figure 11 are the results of the selectivity screening of selected candidate inhibitors. In general, the inhibitors were very selective for FAAH over TGH and KIAA1361. The pyridyl replacements (**5e**, **5f**) of the terminal phenyl group of the alpha keto side chain proved very selective for FAAH over KIAA1363, but only moderately selective for FAAH over TGH. Substitution on the terminal phenyl ring of **2b** also provided selective inhibitors and this was relatively independent of the substitution position (*o*-, *m*-, or *p*-) and whether it was electron-donating or electron-withdrawing (**5j–5l** vs. **5gg–5ii**).

The following experimental description of individual compounds of Formula I further illustrates the present invention. These examples and their corresponding biological activities provide further information about the present invention. However, the invention is fully characterized in the foregoing Summary and the following claims. The examples are not meant to act as limitations of the invention. Additional embodiments and examples will be readily apparent to the practitioner based upon the foregoing Summary, synthetic schemes and the examples provided below.

Experimental

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-chlorophenyl)heptane (5hh). A solution of hept-6-ynoic acid (1.90 g, 14.8 mmol) in anhydrous THF (90 mL) at -78°C was treated with *n*-BuLi (2.3 M in hexanes, 14.5 mL, 33.3 mmol). After stirring for 2 min, TMSCl (5.8 mL, 46.0 mmol) was added. The reaction mixture was allowed to warm slowly to 25°C and was stirred for 1 h. The reaction was quenched with the addition of aqueous 2 N HCl and extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 , filtered and concentrated. Column chromatography (SiO_2 , 4×6 cm,

20% EtOAc–hexanes) afforded 7-(trimethylsilyl)hept-6-ynoic acid (2.7 g, 13.6 mmol, 92%) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 2.40 (t, 2H, $J = 7.4$ Hz), 2.24 (t, 2H, $J = 7.3$ Hz), 1.78–1.72 (m, 2H), 1.62–1.56 (m, 2H), 0.15 (s, 9H).

5 A solution of 5-(2-pyridyl)oxazole (Saikachi, H.; Kitagawa, T.; et al. *Chem. Pharm. Bull.* **1969**, 27, 793–796) (600 mg, 4.11 mmol) in anhydrous THF (15 mL) at -78°C was treated dropwise with a solution of *n*-BuLi (2.2 M in hexanes, 2.4 mL, 4.52 mmol,) under N_2 and the resulting solution was stirred at -78°C for 20 min. A solution of ZnCl_2 (0.5 M in THF, 18 mL, 8.22 mmol,) was added, and the mixture
10 was warmed to 0°C . After stirring at 0°C for 45 min, CuI (850 mg, 4.46 mmol) was added to the mixture. After the mixture was stirred at 0°C for 10 min, a solution of 7-(trimethylsilyl)hept-6-ynoyl chloride (1.2 equiv; prepared from 7-(trimethylsilyl)hept-6-ynoic acid and oxalyl chloride) in anhydrous THF (9 mL) was added dropwise, and the mixture was stirred at 0°C for an additional 1 h. The reaction mixture was diluted
15 with a 1:1 mixture of hexanes and EtOAc (60 mL) and washed with 15% aqueous NH_4OH (2×30 mL), water (30 mL) and saturated aqueous NaCl (30 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and evaporated. Column chromatography (SiO_2 , 4×6 cm, 30% EtOAc–hexanes) afforded 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a**, 875 mg, 2.68 mmol, 74%) as a
20 tan oil: ^1H NMR (CDCl_3 , 400 MHz) δ 8.68 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.6, 1.8$ Hz), 7.34–7.31 (m, 1H), 3.15 (t, 2H, $J = 7.3$ Hz), 2.30 (t, 2H, $J = 7.2$ Hz), 1.94–1.86 (m, 2H), 1.68–1.60 (m, 2H), 0.14 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 187.9, 157.2, 153.2, 150.0, 146.1, 137.0, 126.8, 124.1, 120.3, 106.6, 84.8, 38.4, 27.9, 22.9, 19.6, 0.0; IR (film) ν_{max} 2955, 2867, 2173, 1699, 1603, 1576, 1504, 1469, 1426,
25 1383, 1249, 1152, 1118, 1083, 1024, 929, 842, 784, 760 cm^{-1} ; ESI-TOF m/z 327.1530 ($\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2\text{Si} + \text{H}^+$ requires 327.1523).

A solution of 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a**, 570 mg, 1.75 mmol, 1 equiv) in anhydrous THF (6 mL) at 0°C was treated with a
30 solution of Bu_4NF in THF (1 M, 2.1 mL, 2.1 mmol). After stirring for 35 min at 0°C , the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered and evaporated. Column chromatography (SiO_2 , 2.5×3 cm, 30% EtOAc–hexanes) afforded 1-oxo-1-[5-(2-

pyridyl)oxazol-2-yl]-hept-6-yne (**3b**, 340 mg, 1.36 mmol, 77%) as a tan solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, J = 7.6, 1.8 Hz), 7.34–7.31 (m, 1H), 3.15 (t, 2H, J = 7.3 Hz), 2.27 (td, 2H, J = 7.2, 2.7 Hz), 1.96 (t, 2H, J = 2.7 Hz), 1.94–1.88 (m, 2H), 1.68–1.62 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 187.9, 157.2, 153.2, 150.1, 146.2, 137.1, 126.8, 124.1, 120.3, 83.8, 68.7, 38.4, 27.7, 22.9, 18.2; IR (film) ν_{max} 2938, 2867, 2115, 1698, 1603, 1575, 1505, 1470, 1426, 1385, 1283, 1245, 1127, 1086, 1024, 991, 962, 853, 785, 743 cm^{-1} ; ESI-TOF m/z 255.1135 ($\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2 + \text{H}^+$ requires 255.1128).

10 A solution of 1-chloro-3-iodobenzene (49 mg, 0.205 mmol) in anhydrous THF (0.5 mL) was treated with $\text{PdCl}_2(\text{PPh}_3)_2$ (7 mg, 0.01 mmol). After stirring for 5 min at 25 °C, Et_3N (0.2 mL, 0.603 mmol) and CuI (10 mg, 0.053 mmol) were added. The suspension was stirred for 35 min and 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b**, 30 mg, 0.067 mmol) was added. After stirring for 14 h at 25 °C, the reaction mixture was filtered through Celite and concentrated. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-chlorophenyl)hept-6-yne (**4hh**, 24 mg, 0.066 mmol, 56%) as a yellow solid: mp 50–51 °C; ^1H NMR (CDCl_3 , 500 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, J = 7.7, 1.8 Hz), 7.38 (m, 1H), 7.34–7.31 (m, 1H), 7.27–7.18 (m, 3H), 3.20 (t, 2H, J = 7.4 Hz), 2.49 (t 2H, J = 7.0 Hz), 2.00–1.95 (m, 2H), 1.77–1.71 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 187.9, 157.2, 153.3, 150.1, 146.2, 137.1, 133.9, 131.4, 129.6, 129.3, 127.8, 126.8, 125.5, 124.1, 120.3, 90.9, 79.8, 38.5, 27.8, 23.1, 19.1; IR (film) ν_{max} 3061, 2932, 2865, 2230, 1703, 1592, 1575, 1558, 1505, 1471, 1426, 1385, 1283, 1243, 1152, 1081, 1065, 1023, 990, 962, 930, 880, 784, 740, 683 cm^{-1} ; ESI-TOF m/z 365.1058 ($\text{C}_{21}\text{H}_{17}\text{ClN}_2\text{O}_4 + \text{H}^+$ requires 365.1051).

A solution of the oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-chlorophenyl)hept-6-yne (**4hh**, 15 mg, 0.041 mmol) in anhydrous THF (1 mL) was treated with a catalytic amount of Raney nickel (washed before use with THF). The reaction mixture was purged with H_2 and stirred at 25 °C overnight. The suspension was filtered through Celite and concentrated. The crude product was dissolved in anhydrous CH_2Cl_2 (2 mL) and treated with Dess–Martin reagent (29 mg, 0.068 mmol). After stirring for 3 h at 25 °C, the reaction mixture was quenched with saturated aqueous Na_2CO_3 and

saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$. After stirring for 15 min, the mixture was extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 , filtered and concentrated. PTLC (SiO_2 , 40% EtOAc–hexanes) afforded the title compound (**5hh**, 10 mg, 0.027 mmol, 67%) as a white solid: mp 91–92 °C; ^1H NMR (CDCl_3 , 600 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.8, 1.4$ Hz), 7.34–7.31 (m, 1H), 7.21–7.14 (m, 3H), 7.04 (d, 1H, $J = 7.5$ Hz), 3.11 (t, 2H, $J = 7.4$ Hz), 2.59 (t, 2H, $J = 7.4$ Hz), 1.81–1.76 (m, 2H), 1.65–1.60 (m, 2H), 1.46–1.36 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.4, 157.3, 153.2, 150.1, 146.3, 144.7, 137.1, 133.9, 129.5, 128.5, 126.8, 126.6, 124.1, 120.4, 39.0, 35.5, 31.0, 28.9, 28.8, 23.8; IR (film) ν_{max} 2930, 2856, 1698, 1601, 1575, 1505, 1470, 1426, 1385, 1285, 1081, 1035, 990, 962, 935, 783, 741, 696 cm^{-1} ; ESI–TOF m/z 369.1363 ($\text{C}_{21}\text{H}_{21}\text{ClN}_2\text{O}_2 + \text{H}^+$ requires 369.1364).

General Procedure A. A solution of the aldehyde (1 equiv) and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (**S1**, 1.05 equiv) in anhydrous THF (20 mL/4.46 mmol of aldehyde) at –78 °C was treated with a suspension of *t*-BuOK (1.4 equiv) in anhydrous THF (8 mL). The reaction mixture was allowed to warm at 0 °C and was stirred for 20 h. The reaction mixture was concentrated, diluted with aqueous 4 N NaOH and extracted with EtOAc. The aqueous phase was treated with aqueous 4 N HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (SiO_2) afforded the corresponding unsaturated acid. The mixture of isomers (1 equiv) in EtOAc (10 mL) was treated with 10% Pd/C (0.2 equiv) and purged with H_2 . After stirring for 24 h at 25 °C, the reaction mixture was filtered through Celite and concentrated to afford the product.

General Procedure B. A solution of 5-(2-pyridyl)oxazole (1.0 equiv) in anhydrous THF (3 mL/0.34 mmol) at –78 °C was treated dropwise with a solution of *n*-BuLi in hexanes (2.5 M, 1.2 equiv) under N_2 and the resulting solution was stirred at –78 °C for 35 min. A solution of ZnCl_2 in THF (0.5 M, 2 equiv) was added to the mixture and the mixture was allowed to warm to 0 °C. After stirring at 0 °C for 45 min, CuI (1.2 equiv) was added to the mixture. After the mixture was stirred at 0 °C for 15 min, a solution of the acid chloride (1.2 equiv; prepared from the corresponding carboxylic acid and oxalyl chloride) in anhydrous THF (2 mL) was added dropwise, and the mixture was stirred for an additional 1 h. The reaction mixture was quenched with

addition of saturated aqueous NaHCO_3 and extracted with EtOAc. The organic layer was filtered through Celite, dried over anhydrous Na_2SO_4 , filtered and evaporated to yield the crude product, which was purified by flash chromatography (SiO_2).

- 5 **General Procedure C.** A solution of 5-(2-pyridyl)oxazole (1.0 equiv) in anhydrous THF (5.0 mL/0.51 mmol) at -78°C was treated dropwise with a solution of *n*-BuLi in hexanes (2.5 M, 1.1 equiv) under N_2 and the resulting solution was stirred at -78°C for 20 min. A solution of ZnCl_2 in THF (0.5 M, 2.0 equiv) was added to the mixture, and the mixture was warmed to 0°C . After stirring at 0°C for 45 min, CuI (1.0 equiv)
10 was added to the mixture. After the mixture was stirred at 0°C for 10 min, a solution of the acid chloride (1.2 equiv; prepared from the corresponding carboxylic acid and oxalyl chloride) in anhydrous THF (3.0 mL) was added dropwise, and the mixture was stirred at 0°C for an additional 1 h. The reaction mixture was diluted with a 1:1 mixture of hexanes and EtOAc (60 mL) and washed with 15% aqueous NH_4OH ($2 \times$
15 30 mL), water (30 mL) and saturated aqueous NaCl (30 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and evaporated. Column chromatography (SiO_2) afforded the product.

- 20 **General Procedure D.** A solution of the alkyne (1.0 equiv) in anhydrous THF (0.5 mL/0.12 mmol of alkyne) was treated with the aryl iodide (1.5 equiv), Ag_2CO_3 (0.7 equiv), Bu_4NCl (1.8 equiv) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.10 equiv). After stirring for 22 h at 90°C , the reaction was quenched with aqueous saturated NaCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 , filtered and concentrated. Chromatography (SiO_2) afforded the product.

- 25 **General Procedure E.** A solution of the aryl iodide (1.6 equiv) in anhydrous THF (0.6 mL/0.19 mmol of alkyne) was treated with $\text{PdCl}_2(\text{PPh}_3)_2$ (0.07 equiv). After stirring for 5 min at 25°C , Et_3N (9 equiv) and CuI (0.35 equiv) were added. The suspension was stirred for 35 min and 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne
30 (3b (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856), 1 equiv) was added. After stirring for 14 h at 25°C , the reaction mixture was filtered through Celite and concentrated. Flash chromatography (SiO_2) afforded the product.

General Procedure F. A solution of the alkyne (1 equiv) in EtOAc (0.5 mL/0.027 mmol of alkyne) was treated with 10% Pd/C (0.2 equiv). The reaction mixture was purged with H₂ and stirred overnight at 25 °C. The suspension was filtered through Celite and concentrated.

5

General Procedure G. A solution of the alkyne (1 equiv) in anhydrous THF (1 mL/0.038 mmol of alkyne) was treated with a catalytic amount of Raney nickel (washed before use with THF). The reaction mixture was purged with H₂ and stirred at 25 °C overnight. The suspension was filtered through Celite and concentrated. The crude product was dissolved with anhydrous CH₂Cl₂ (2 mL) and treated with Dess–Martin reagent (1.5 equiv). After stirring for 3 h at 25 °C, the reaction mixture was quenched with saturated aqueous Na₂CO₃ and saturated aqueous Na₂S₂O₃. After stirring for 15 min, the mixture was extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered and concentrated. Chromatography (SiO₂) afforded the product.

10

15

General Procedure H. A solution of the sulfide (1.0 equiv) in anhydrous CH₂Cl₂ (0.7 mL/0.050 mmol of sulfide) at 0 °C was treated with *m*-CPBA (2.2 equiv). After 1 h, the reaction mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The organic layer was dried on Na₂SO₄, filtered and concentrated. Chromatography (SiO₂) afforded the product.

20

General Procedure I. A solution of the alkyne (1 equiv) in a mixture of THF/MeOH (1 mL, 1/1; for 0.12 mmol of alkyne) was treated with 10% Pd/C (0.2 equiv). The suspension was purged under H₂ and stirred for 20 h at 25 °C. 10% Pd/C (0.2 equiv) was added again and the reaction mixture was stirred for an additional 20 h at 25 °C. Chromatography (SiO₂) afforded the product.

25

General Procedure J. A solution of the carbamate (1 equiv) in CH₂Cl₂ (0.2 mL/0.045 mmol of carbamate) at 0 °C was treated with 0.2 mL of TFA. After stirring for 1 h at 0 °C, the reaction mixture was concentrated, diluted with aqueous saturated NaHCO₃ and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered and concentrated. Chromatography (SiO₂) afforded the product.

30

General Procedure K. A solution of the acid (1 equiv; prepared by hydrogenation of the 4-hydroxycinnamic acid) in anhydrous DMF (16 mL/4.2 mmol of acid) at 0 °C was treated with Bu₄NI (0.01 equiv) and a suspension of NaH (60% in mineral oil, 2.7 equiv) in anhydrous DMF (10 mL). After stirring for 10 min, benzyl bromide (1.3 equiv) was added dropwise. The reaction mixture was allowed to warm at 25 °C and was stirred overnight. The reaction was quenched with aqueous 10% HCl and extracted with EtOAc. The organic layer was washed with saturated aqueous NH₄Cl, dried and concentrated. Column chromatography (SiO₂) afforded the product.

General Procedure L. The methyl ester (1 equiv) was dissolved in THF (0.15 mL/0.033 mmol) and LiOH (1.1 equiv) was added. The reaction mixture was stirred at room temperature overnight, diluted with H₂O and acidified to pH 2 with aqueous 1 N HCl. The acidic aqueous phase was extracted with EtOAc and the organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated. Preparative thin layer chromatography (SiO₂) afforded the pure acids.

General Procedure M. A solution of the sulfide (1 equiv) in anhydrous CH₂Cl₂ (0.1 M) was cooled to 0 °C and treated with *m*-CPBA (1.0 or 1.5 equiv). The suspension was stirred for 2 h and quenched with saturated aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. PTLC (66% EtOAc–hexanes, SiO₂) afforded in the order of elution the sulfones and the sulfoxides in good combined yields.

General Procedure N. The methyl ester (1.0 equiv) was dissolved in 1:1 THF:H₂O (4 mL/0.62 mmol of methyl ester) and LiOH (1.0 equiv) was added. After stirring at room temperature for 6 h, the reaction mixture was concentrated and the residue dried under high vacuum. The dried lithium carboxylate salt was dissolved in anhydrous DMF (5 mL) and HATU (1.0 equiv) was added. The reaction mixture was stirred for 10 min before adding a solution containing the requisite amine (1.1 equiv) and *i*-Pr₂NEt (2.1 equiv) in anhydrous DMF (2 mL). After stirring at room temperature for 1 h, the DMF was removed *in vacuo* and the residue taken up into EtOAc. The organic layer was washed successively with aqueous 0.1 N HCl, 0.1 N NaOH and H₂O, and then dried over anhydrous Na₂SO₄ and concentrated. The crude amides were purified using PTLC (SiO₂).

General Procedure O. The TIPS ether (1 equiv) was dissolved in anhydrous THF (0.5 mL/0.12 mmol of TIPS ether) under Ar and cooled to 0 °C. Bu₄NF (1.0 M solution in THF, 1.3 equiv) was added dropwise and the reaction mixture stirred for 5 30 min. The ice bath was removed and the reaction mixture was allowed to stir for 3 h at room temperature. The THF was removed under a stream of N₂ and the residue taken up into Et₂O and washed with water. The organic phase was dried over anhydrous Na₂SO₄ and concentrated. PTLC (SiO₂) afforded the alcohol.

10 **General Procedure P.** A solution of the alcohol (1 equiv) in anhydrous CH₂Cl₂ (0.2 M) at 0 °C was treated with PCC (1.5 equiv) and the mixture was stirred for 45 min. The reaction mixture was allowed to warm at 25 °C and stirred for 3 h. The suspension was filtered through Celite and concentrated. Column chromatography (SiO₂) afforded the aldehyde.

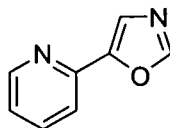
15 **General Procedure Q.** A solution of the aldehyde (1 equiv) in anhydrous THF (65 mL/20.0 mmol of aldehyde) at 0 °C was treated with the Grignard reagent (1.2 equiv). After stirring for 30 min, the reaction mixture was quenched with saturated aqueous NH₄Cl. The organic layer was extracted with EtOAc, dried over Na₂SO₄, filtered and 20 concentrated. Column chromatography (EtOAc–hexanes) afforded the alcohol. A solution of the alcohol (1 equiv) in anhydrous THF at 0 °C was treated with NaH (1.2 equiv). After 15 min, TIPS–OTf (1.2 equiv) was added dropwise and the reaction mixture was allowed to warm to 25 °C. After 1 h, the reaction was quenched with saturated aqueous NH₄Cl. The organic phase was extracted with EtOAc, dried over 25 Na₂SO₄, filtered and concentrated. Column chromatography (SiO₂) afforded the TIPS protected alcohol.

General Procedure R. A solution of the benzyl protected alcohol (1 equiv) in EtOAc (0.22 M) was treated with 10% Pd/C (0.2 equiv). The reaction mixture was purged 30 with H₂ and stirred overnight at 25 °C. The suspension was filtered through Celite, concentrated and purified by column chromatography (SiO₂) to afford the alcohol.

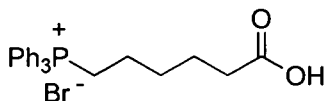
General Procedure S. A solution of the alcohol (1 equiv) in anhydrous DMF (0.14 M) was treated with PDC (3 equiv). After stirring at 25 °C for 20 h, the reaction

mixture was quenched with saturated aqueous NH_4Cl . The organic layer was extracted with CH_2Cl_2 , dried over Na_2SO_4 , filtered and concentrated. Column chromatography (SiO_2) afforded the carboxylic acid.

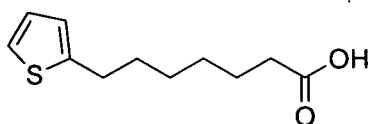
5



2-Oxazol-5-yl-pyridine (6) (Saikachi, H.; Kitagawa, T.; et al. *Chem. Pharm. Bull.* 1969, 27, 793–796). A solution of 2-pyridinecarboxaldehyde (2.3 g, 21.3 mmol) in anhydrous MeOH (70 mL) was treated with tosylmethyl isocyanide (4.4 g, 22.6 mmol) and K_2CO_3 (3.4 g, 24.4 mmol). After 2 h at reflux, the mixture was concentrated, diluted with saturated aqueous NaHCO_3 and extracted with CH_2Cl_2 . The organic layers were combined, dried (Na_2SO_4) and concentrated. Chromatography (SiO_2 , 40–50% EtOAc–hexanes gradient elution) provided **6** as a tan oil (3.10 g, 97%): ^1H NMR (CDCl_3 , 400 MHz) δ 8.55–8.53 (m, 1H), 7.90 (s, 1H), 7.66 (td, J = 7.8, 1.8 Hz, 1H), 7.62 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.14 (ddd, J = 7.8, 4.9, 1.2 Hz, 1H).



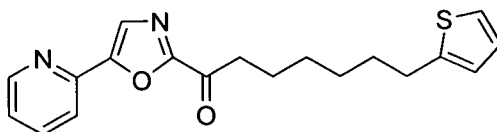
6-(Triphenylphosphonium bromide)-hexanoic acid (S1, ($\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$)). A solution of 6-bromohexanoic acid (3.9 g, 20.0 mmol, 1 equiv) in anhydrous acetonitrile (16 mL) was treated with triphenylphosphine (6.3 g, 24.0 mmol, 1.2 equiv) and warmed at reflux for 20 h. The reaction mixture was concentrated and the crude product was purified by column chromatography (SiO_2 , 5.5×8 cm, 50–100% EtOAc–hexanes gradient and then 5% MeOH– CH_2Cl_2) to afford **S1** (8.7 g, 19.0 mmol, 95%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 7.78–7.67 (m, 15H), 3.58 (m, 2H), 2.33 (m, 2H), 1.63 (m, 4H).



7-(Thien-2-yl)heptanoic acid (S2). The title compound was prepared from thiophene-2-carboxaldehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (**S1**) following general procedure A. Column chromatography (SiO_2 , 3.5×7 cm, 30% EtOAc–hexanes)

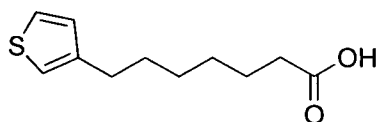
afforded **S2** (440 mg, 2.1 mmol, 47%, 2 steps) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 7.24 (dd, 1H, $J = 4.8, 3.1$ Hz), 6.94–6.92 (m, 2H), 2.63 (t, 2H, $J = 7.7$ Hz), 2.36 (t, 2H, $J = 7.3$ Hz), 1.68–1.61 (m, 4H), 1.42–1.33 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 180.2, 145.5, 128.0, 126.6, 123.9, 34.0, 30.4, 30.0, 28.6 (2C), 24.4.

5

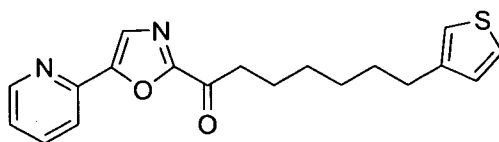


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-thienyl)heptane (5a). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 7-(thien-2-yl)heptanoic (**S2**) following general procedure B. PTLC (SiO_2 , 40% EtOAc–hexanes) afforded **5a** (18 mg, 0.05 mmol, 16%) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.67 (m, 1H), 7.88–7.85 (m, 2H), 7.82 (td, 1H, $J = 7.8, 1.8$ Hz), 7.34–7.31 (m, 1H), 7.10 (dd, 1H, $J = 5.2, 1.1$ Hz), 6.91 (dd, 1H, $J = 5.2, 3.3$ Hz), 6.79–6.77 (m, 1H), 3.12 (t, 2H, $J = 7.3$ Hz), 2.84 (t, 2H, $J = 7.7$ Hz), 1.80 (m, 2H), 1.71 (m, 2H), 1.47–1.41 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.5, 157.3, 153.3, 150.1, 146.3, 145.5, 137.1, 126.8, 126.6, 124.1, 124.0, 122.8, 120.4, 39.0, 31.5, 29.8, 28.8, 28.7, 23.9; IR (film) ν_{max} 2929, 2854, 1700, 1602, 1576, 1502, 1468, 1425, 1382, 1282, 1236, 1118, 1081, 1040, 989, 962, 849, 784, 694 cm^{-1} ; ESI–TOF m/z 341.1324 ($\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{S} + \text{H}^+$ requires 341.1318).

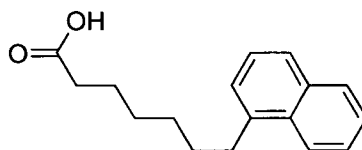
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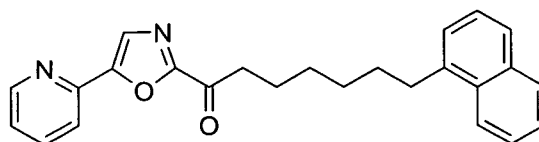
7-(Thien-3-yl)heptanoic acid (S3). The title compound was prepared from 3-thiophenecarboxaldehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (**S1**) following general procedure A. No further purification was required to yield **S3** (430 mg, 2.0 mmol, 46%, 2 steps) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 7.24 (dd, 1H, $J = 4.8, 3.1$ Hz), 6.94–6.92 (m, 2H), 2.63 (t, 2H, $J = 7.7$ Hz), 2.36 (t, 2H, $J = 7.3$ Hz), 1.68–1.61 (m, 4H), 1.42–1.33 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 183.3, 142.9, 128.2, 125.1, 119.8, 34.0, 30.3, 30.1, 28.8 (2C), 24.5.



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-thienyl)heptane (5b). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-(thien-3-yl)heptanoic (S3) acid using general procedure B. PTLC (SiO₂, 40% EtOAc–hexanes) afforded **5b** (42 mg, 0.12 mmol, 26%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.67 (m, 1H), 7.88 (s, 1H), 7.87–7.85 (m, 2H), 7.80 (td, 1H, *J* = 7.8, 1.8 Hz), 7.35–7.31 (m, 1H), 7.23 (dd, 1H, *J* = 4.9, 3.1 Hz), 7.01–6.99 (m, 2H), 3.11 (t, 2H, *J* = 7.3 Hz), 2.64 (t, 2H, *J* = 7.7 Hz), 1.79 (m, 2H), 1.65 (m, 2H), 1.48–1.37 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.4, 157.3, 153.2, 150.1, 146.2, 142.9, 137.1, 128.2, 126.8, 125.1, 124.1, 120.3, 119.8, 39.0, 30.3, 30.1, 28.9 (2C), 23.9; IR (film) ν_{max} 2929, 2855, 1699, 1602, 1576, 1502, 1468, 1425, 1382, 1282, 1151, 1118, 1081, 1036, 989, 962, 852, 783 cm⁻¹; ESI-TOF *m/z* 341.1316 (C₁₉H₂₀N₂O₂S + H⁺ requires 341.1318).



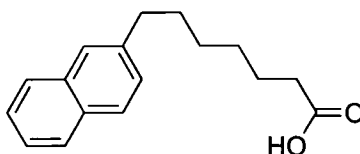
7-(1-Naphthyl)heptanoic acid (S4). The title compound was prepared from 1-naphthaldehyde and BrPh₃P(CH₂)₅CO₂H (S1) following general procedure A. No further purification was required to yield **S4** (260 mg, 1.01 mmol, 33%, 2 steps) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.04 (d, 1H, *J* = 8.0 Hz), 7.86 (d, 1H, *J* = 8.0 Hz), 7.71 (d, 1H, *J* = 8.0 Hz), 7.53–7.46 (m, 2H), 7.40 (t, 1H, *J* = 7.7 Hz), 7.32 (d, 1H, *J* = 6.6 Hz), 3.08 (t, 2H, *J* = 7.3 Hz), 2.37 (t, 2H, *J* = 7.3 Hz), 1.80–1.74 (m, 2H), 1.70–1.64 (m, 2H), 1.50–1.43 (m, 4H).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(1-naphthyl)heptane (5c). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-(naphthalen-1-yl)heptanoic acid (S4) using general procedure B. PTLC (SiO₂, 40% EtOAc–hexanes) afforded **5c** (33 mg, 0.085 mmol, 21%) as a yellow oil: ¹H NMR (CDCl₃, 500 MHz) δ 8.67 (m, 1H), 8.04 (d, 1H, *J* = 8.5 Hz), 7.89 (s, 1H), 7.87–7.80 (m, 3H), 7.70 (d, 1H, *J* = 8.1 Hz), 7.53–7.45 (m, 2H), 7.40 (t, 1H, *J* = 7.5 Hz), 7.34–7.30 (m, 1H), 3.13 (t, 2H, *J* = 7.4 Hz), 3.08 (t, 2H, *J* = 7.7 Hz), 1.84–1.75 (m, 4H), 1.53–1.47 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 188.4, 157.3, 153.2, 150.1, 146.2, 138.7, 137.0, 133.8, 131.8,

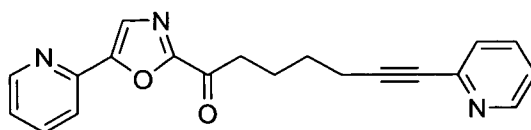
128.7, 126.8, 126.4, 125.8, 125.6, 125.5, 125.3, 124.1, 123.8, 120.3, 39.0, 32.9, 30.6, 29.4, 29.0, 23.9; IR (film) $\nu_{\max}$ 3054, 2931, 2856, 1699, 1602, 1575, 1558, 1505, 1470, 1426, 1385, 1283, 1238, 1151, 1118, 1081, 1029, 990, 963, 936, 852, 782, 740, 712, 694 cm^{-1} ; ESI-TOF m/z 385.1916 ($\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_2 + \text{H}^+$ requires 385.1916).

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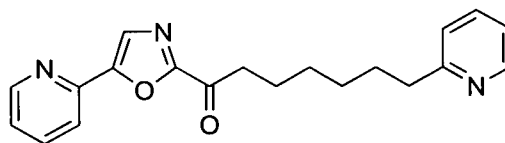


7-(2-Naphthyl)heptanoic acid (S5). This material was prepared from 2-naphthaldehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (S1) following general procedure A. No further purification was required to yield S5 (310 mg, 1.21 mmol, 34%, 2 steps) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 7.89–7.84 (m, 3H), 7.69 (s, 1H), 7.54–7.47 (m, 2H), 7.41 (dd, 1H, $J = 8.4, 1.8$ Hz), 2.79 (t, 2H, $J = 7.3$ Hz), 2.39 (t, 2H, $J = 7.3$ Hz), 1.75–1.66 (m, 4H), 1.43–1.40 (m, 4H).

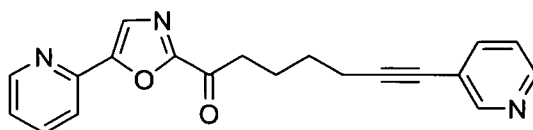
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-naphthyl)heptane (5d). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-(2-naphthyl)heptanoic acid (S5) using general procedure B. PTLC (SiO_2 , 40% EtOAc–hexanes) afforded 5d (33 mg, 0.085 mmol, 21%) as a yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (m, 1H), 7.88–7.75 (m, 6H), 7.60 (s, 1H), 7.47–7.39 (m, 2H), 7.35–7.30 (m, 2H), 3.12 (t, 2H, $J = 7.3$ Hz), 2.78 (t, 2H, $J = 7.3$ Hz), 1.82–1.72 (m, 4H), 1.47–1.43 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.4, 163.9, 157.3, 153.2, 150.0, 146.2, 140.1, 137.0, 133.5, 131.8, 127.7, 127.5, 127.3, 126.8, 126.2, 125.7, 124.9, 124.0, 120.3, 39.0, 35.9, 31.0, 28.9 (2C), 23.8; IR (film) $\nu_{\max}$ 3054, 2930, 2855, 1700, 1652, 1602, 1575, 1558, 1505, 1471, 1426, 1385, 1300, 1283, 1239, 1153, 1122, 1082, 1037, 990, 963, 852, 817, 784, 742 cm^{-1} ; ESI-TOF m/z 385.1913 ($\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_2 + \text{H}^+$ requires 385.1916).



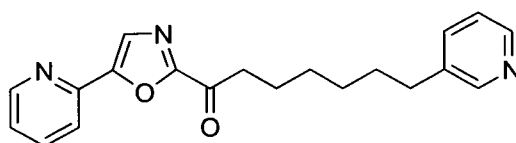
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-pyridyl)hept-6-yne (4e). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b**) (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and 2-iodopyridine following general procedure E. PTLC (SiO₂, 50% EtOAc–hexanes + 1% Et₃N) afforded **4e** (21 mg, 0.06 mmol, 54%) as a pale yellow oil: ¹H NMR (CDCl₃, 600 MHz) δ 8.67 (app d, 1H, *J* = 4.4 Hz), 8.53 (d, 1H, *J* = 4.9 Hz), 7.88–7.85 (m, 2H), 7.81 (td, 1H, *J* = 7.5, 1.3 Hz), 7.60 (td, 1H, *J* = 7.9, 1.7 Hz), 7.37 (d, 1H, *J* = 7.9 Hz), 7.32 (dd, 1H, *J* = 7.0, 4.9 Hz), 7.17 (dd, 1H, *J* = 7.4, 4.9 Hz), 3.19 (t, 2H, *J* = 7.2 Hz), 2.53 (t, 2H, *J* = 7.0 Hz), 2.01–1.95 (m, 2H), 1.80–1.74 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 187.9, 157.2, 153.2, 150.0, 149.7, 146.2, 143.6, 137.0, 136.0, 126.8 (2C), 124.1, 122.3, 120.3, 90.1, 80.7, 38.4, 27.6, 23.1, 19.1; IR (film) ν_{max} 2928, 2231, 1699, 1602, 1582, 1506, 1465, 1429, 1386, 1283, 1151, 1084, 1023, 989, 962, 782 cm⁻¹; ESI–TOF *m/z* 332.1396 (C₂₀H₁₇N₃O₂ + H⁺ requires 332.1393).



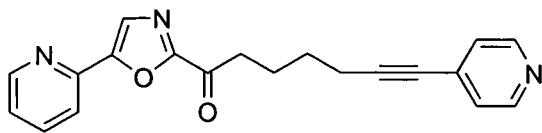
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-pyridyl)heptane (5e). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-pyridyl)hept-6-yne (**4e**) following general procedure F. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **5e** (7 mg, 0.021 mmol, 78%) as a pale yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.67 (app d, 1H, *J* = 4.4 Hz), 8.52 (d, 1H, *J* = 4.4 Hz), 7.87–7.83 (m, 2H), 7.81 (td, 1H, *J* = 7.7, 1.5 Hz), 7.59 (td, 1H, *J* = 7.7, 1.8 Hz), 7.33–7.30 (m, 1H), 7.14 (d, 2H, *J* = 7.7 Hz), 7.10 (dd, 1H, *J* = 6.4, 4.9 Hz), 3.11 (t, 2H, *J* = 7.3 Hz), 2.79 (t, 2H, *J* = 7.7 Hz), 1.82–1.73 (m, 4H), 1.49–1.41 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.5, 162.2, 157.3, 153.2, 150.1, 149.1, 146.3, 137.1, 136.3, 126.8, 124.1, 122.7, 120.9, 120.4, 39.0, 38.2, 29.6, 29.0, 28.9, 23.9; IR (film) ν_{max} 2930, 2856, 1699, 1501, 1470, 1425, 1283, 1119, 991, 962, 785 cm⁻¹; ESI–TOF *m/z* 336.1703 (C₂₀H₂₁N₃O₂ + H⁺ requires 336.1706).



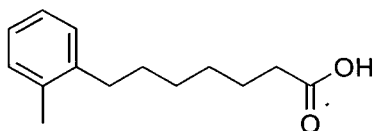
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-pyridyl)hept-6-yne (4f). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856)) and 3-iodopyridine following general procedure E. PTLC (SiO₂, 50% EtOAc–hexanes + 1% Et₃N) afforded **4f** (20 mg, 0.06 mmol, 50%) as a pale yellow solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.66 (app d, 1H, *J* = 4.7 Hz), 8.62 (br s, 1H), 8.48 (br s, 1H), 7.87–7.85 (m, 2H), 7.81 (td, 1H, *J* = 7.6, 1.5 Hz), 7.66 (d, 1H, *J* = 7.9 Hz), 7.33–7.30 (m, 1H), 7.20 (dd, 1H, *J* = 7.8, 4.9 Hz), 3.19 (t, 2H, *J* = 7.3 Hz), 2.51 (t, 2H, *J* = 7.0 Hz), 2.00–1.93 (m, 2H), 1.78–1.70 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 187.9, 157.2, 153.3, 152.2, 150.1, 147.9, 146.2, 138.5, 137.1, 126.8, 124.1, 122.9, 120.9, 120.4, 93.2, 77.8, 38.4, 27.8, 23.1, 19.2; IR (film) ν_{max} 2932, 2233, 1699, 1602, 1573, 1503, 1469, 1425, 1407, 1386, 1283, 1119, 1083, 1023, 989, 962, 785, 707 cm⁻¹; ESI–TOF *m/z* 332.1403 (C₂₀H₁₇N₃O₂ + H⁺ requires 332.1393).



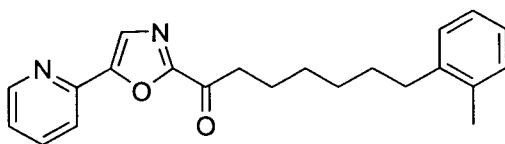
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-pyridyl)heptane (5f). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-pyridyl)hept-6-yne (**4f**) following general procedure F. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **5f** (9.5 mg, 0.021 mmol, 95%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.67–8.65 (m, 1H), 8.45–8.42 (m, 1H), 7.88–7.83 (m, 2H), 7.81 (td, 1H, *J* = 7.7, 1.8 Hz), 7.50 (d, 1H, *J* = 7.7 Hz), 7.33–7.30 (m, 1H), 7.21 (dd, 1H, *J* = 7.7, 4.8 Hz), 3.11 (t, 2H, *J* = 7.3 Hz), 2.62 (t, 2H, *J* = 7.7 Hz), 1.81–1.75 (m, 2H), 1.68–1.62 (m, 2H), 1.47–1.37 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.4, 157.3, 153.3, 150.1, 149.6, 147.0, 146.2, 137.8, 137.1, 136.0, 126.8, 124.1, 123.3, 120.4, 39.0, 32.9, 30.9, 28.8 (2C), 23.8; IR (film) ν_{max} 2929, 2856, 1698, 1602, 1575, 1503, 1469, 1425, 1382, 1283, 1119, 1027, 990, 963, 785, 713 cm⁻¹; ESI–TOF *m/z* 336.1706 (C₂₀H₂₁N₃O₂ + H⁺ requires 336.1706).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-pyridyl)hept-6-yne (4pp). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and 4-iodopyridine following general procedure D. PTLC (SiO₂, 50% EtOAc–hexanes + 1% Et₃N) afforded **4pp** (31 mg, 0.09 mmol, 79%) as a yellow solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.68–8.66 (m, 1H), 8.54 (br s, 2H), 7.88–7.85 (m, 2H), 7.81 (td, 1H, *J* = 7.9, 1.8 Hz), 7.34–7.30 (m, 1H), 7.25 (d, 2H, *J* = 3.8 Hz), 3.19 (t, 2H, *J* = 7.3 Hz), 2.51 (t, 2H, *J* = 7.0 Hz), 2.00–1.92 (m, 2H), 1.78–1.71 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 187.8, 157.2, 153.3, 150.1, 149.5, 146.1, 137.1, 132.0, 128.4, 126.8, 126.0, 124.1, 120.3, 95.0, 78.8, 38.4, 27.6, 23.0, 19.2; IR (film) ν_{max} 2939, 2231, 1699, 1593, 1505, 1470, 1425, 1283, 1239, 1214, 1152, 1118, 1082, 1024, 990, 962, 824, 786, 695 cm⁻¹; ESI–TOF *m/z* 332.1396 (C₂₀H₁₇N₃O₂ + H⁺ requires 332.1393).



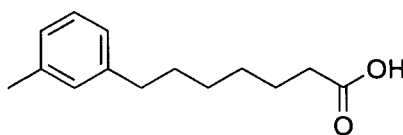
7-(*o*-Tolyl)heptanoic acid (S6). The title compound was prepared from *o*-tolualdehyde and BrPh₃P(CH₂)₅CO₂H (**S1**) following general procedure A. No further purification was required to yield **S6** (365 mg, 1.66 mmol, 45%, 2 steps) as a tan oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.13–7.11 (m, 4H), 2.60 (t, 2H, *J* = 7.6 Hz), 2.37 (t, 2H, *J* = 7.4 Hz), 2.32 (s, 3H), 1.68–1.57 (m, 4H), 1.43–1.40 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 180.0, 140.8, 135.8, 130.1, 128.7, 125.8, 125.7, 34.0, 33.2, 30.0, 29.2, 28.9, 24.6, 19.3.



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(*o*-tolyl)heptane (5g). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 7-(*o*-tolyl)heptanoic acid (**S6**) using general procedure B. Column chromatography (SiO₂, 2.5 × 6.5 cm, 20% EtOAc–hexanes) followed by PTLC (SiO₂, 50% EtOAc–hexanes) afforded **5g** (65 mg, 0.19

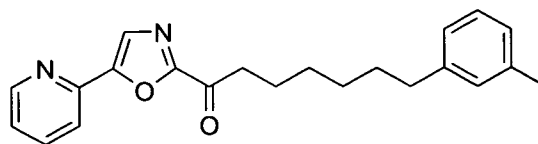
mmol, 39%) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.68 (app d, 1H, $J = 4.8$ Hz), 7.89–7.87 (m, 2H), 7.82 (td, 1H, $J = 7.7, 1.5$ Hz), 7.34–7.31 (m, 1H), 7.14–7.08 (m, 4H), 3.13 (t, 2H, $J = 7.3$ Hz), 2.60 (t, 2H, $J = 7.7$ Hz), 2.31 (s, 3H), 1.84–1.78 (m, 2H), 1.63–1.57 (m, 2H), 1.47–1.44 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.4, 157.5, 153.2, 150.0, 146.2, 137.0, 135.7, 130.0, 128.7, 126.8, 125.8, 125.6, 124.0, 120.3, 39.0, 34.9, 33.1, 30.0, 29.3, 29.0, 23.9, 19.2; IR (film) ν_{max} 2931, 2857, 1699, 1602, 1575, 1558, 1505, 1470, 1426, 1381, 1237, 1151, 1118, 1082, 1033, 990, 963, 936, 851, 785, 741 cm^{-1} ; ESI-TOF m/z 349.1926 ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3 + \text{H}^+$ requires 349.1916).

10



7-(*m*-Tolyl)heptanoic acid (S7). The title compound was prepared from *m*-tolualdehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (S1) following general procedure A. No further purification was required to yield S7 (315 mg, 1.43 mmol, 37%, 2 steps) as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.17 (t, 1H, $J = 3.8$ Hz), 7.01–6.99 (m, 3H), 2.58 (t, 2H, $J = 7.6$ Hz), 2.38 (t, 2H, $J = 7.4$ Hz), 2.35 (s, 3H), 1.70–1.59 (m, 4H), 1.40–1.36 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 180.1, 142.6, 137.6, 129.2, 128.1, 126.3, 125.4, 35.8, 34.1, 31.3, 28.9, 24.6, 21.4.

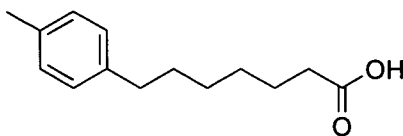
20



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(*m*-tolyl)heptane (5h). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-(*m*-tolyl)heptanoic acid (S7) using general procedure B. Column chromatography (SiO_2 , 2.5×4.5 cm, 20% EtOAc–hexanes) followed by PTLC (SiO_2 , 50% EtOAc–hexanes) afforded 5h (60 mg, 0.17 mmol, 36%) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.68 (app d, 1H, $J = 4.4$ Hz), 7.89–7.87 (m, 2H), 7.82 (td, 1H, $J = 7.7, 1.5$ Hz), 7.34–7.31 (m, 1H), 7.17 (t, 1H, $J = 7.4$ Hz), 7.00–6.96 (m, 3H), 3.12 (t, 2H, $J = 7.3$ Hz), 2.59 (t, 2H, $J = 7.7$ Hz), 2.33 (s, 3H), 1.84–1.76 (m, 2H), 1.67–1.61 (m, 2H), 1.47–1.37 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.4, 157.3, 153.1, 150.0, 146.2, 142.5, 137.6, 137.0, 129.1, 128.0,

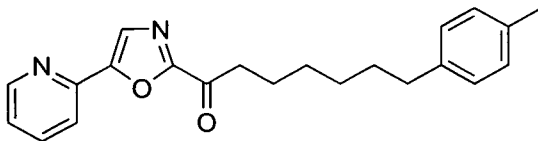
126.8, 126.2, 125.3, 124.0, 120.3, 39.0, 35.7, 31.2, 28.9 (2C), 23.8, 21.3; IR (film) $\nu_{\max}$ 2930, 2856, 1700, 1605, 1575, 1505, 1470, 1426, 1382, 1283, 1151, 1118, 1082, 1037, 990, 963, 936, 851, 784, 740, 700 cm^{-1} ; ESI-TOF m/z 349.1910 ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3 + \text{H}^+$ requires 349.1916).

5



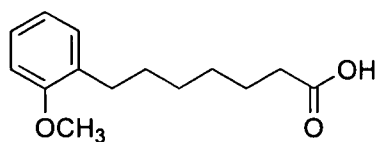
7-(*p*-Tolyl)heptanoic acid (S8). The title compound was prepared from *p*-tolualdehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (**S1**) following general procedure A. No further purification was required to yield **S8** (285 mg, 1.30 mmol, 32%, 2 steps) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 7.11–7.06 (m, 4H), 2.58 (t, 2H, $J = 7.6$ Hz), 2.37 (t, 2H, $J = 7.4$ Hz), 2.34 (s, 3H), 1.68–1.60 (m, 4H), 1.39–1.36 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 179.8, 139.5, 135.0, 128.9, 128.2, 35.4, 33.9, 31.4, 28.9, 28.8, 24.6, 21.0.

15

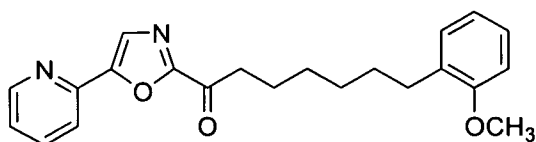


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(*p*-tolyl)heptane (5i). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 7-(*p*-tolyl)heptanoic acid (**S8**) using general procedure B. Column chromatography (SiO_2 , 2.5×5 cm, 20% EtOAc–hexanes) followed by PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **5i** (58 mg, 0.17 mmol, 35%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.68 (m, 1H), 7.89–7.85 (m, 2H), 7.82 (t, 1H, $J = 7.4$ Hz), 7.34–7.31 (m, 1H), 7.06 (s, 4H), 3.11 (t, 2H, $J = 7.3$ Hz), 2.58 (t, 2H, $J = 7.3$ Hz), 2.32 (s, 3H), 1.83–1.75 (m, 2H), 1.67–1.61 (m, 2H), 1.46–1.37 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.5, 157.3, 150.1, 146.3, 139.5, 137.6, 137.1, 135.0, 128.9, 128.2, 126.8, 124.1, 120.4, 39.1, 35.4, 31.4, 28.9 (2C), 23.9, 21.0; IR (film) $\nu_{\max}$ 2921, 2849, 1698, 1604, 1575, 1558, 1515, 1471, 1427, 1404, 1386, 1260, 1235, 1129, 1094, 1078, 1035, 990, 961, 933, 809, 784, 742 cm^{-1} ; ESI-TOF m/z 349.1912 ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3 + \text{H}^+$ requires 349.1916).

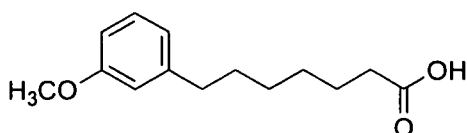
25



7-(2-Methoxyphenyl)heptanoic acid (S10). The title compound was prepared from *o*-anisaldehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (**S1**) following general procedure A. No further purification was needed to afford **S10** (370 mg, 1.30 mmol, 59%, 2 steps) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 7.20–7.13 (m, 2H), 6.91–6.85 (m, 2H), 3.83 (s, 3H), 2.62 (t, 2H, $J = 7.4$ Hz), 2.37 (t, 2H, $J = 7.6$ Hz), 1.66–1.60 (m, 4H), 1.40–1.37 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 180.4, 157.4, 131.0, 129.7, 126.8, 120.3, 110.2, 55.2, 34.1, 30.0, 29.5, 29.1, 28.9, 24.6.

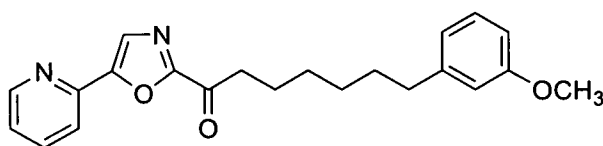


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-methoxyphenyl)heptane (5j). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 7-(2-methoxyphenyl)heptanoic acid (**S10**) using general procedure B. Column chromatography (SiO_2 , 2.5×6 cm, 15–25% EtOAc–hexanes gradient) followed by PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **5j** (65 mg, 0.18 mmol, 37%) as a pale yellow solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.67 (app d, 1H, $J = 4.4$ Hz), 7.89–7.86 (m, 2H), 7.81 (td, 1H, $J = 7.4, 1.8$ Hz), 7.34–7.30 (m, 1H), 7.19–7.11 (m, 2H), 6.88 (t, 1H, $J = 7.4$ Hz), 6.84 (d, 1H, $J = 8.2$ Hz), 3.82 (s, 3H), 3.12 (t, 2H, $J = 7.4$ Hz), 2.61 (t, 2H, $J = 7.6$ Hz), 1.83–1.75 (m, 2H), 1.64–1.56 (m, 2H), 1.49–1.40 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.5, 157.3, 153.1, 150.0, 146.2, 137.0, 131.0, 129.7, 126.8, 126.7, 124.0, 120.3, 120.2, 55.1, 39.1, 30.0, 29.5, 29.2, 28.9, 23.9; IR (film) ν_{max} 3053, 2931, 2856, 1699, 1601, 1575, 1494, 1455, 1427, 1382, 1288, 1242, 1177, 1151, 1119, 1082, 1049, 1029, 990, 963, 936, 851, 785, 753 cm^{-1} ; ESI-TOF m/z 365.1877 ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3 + \text{H}^+$ requires 365.1865).

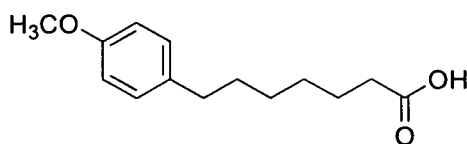


7-(3-Methoxyphenyl)heptanoic acid (S11). The title compound was prepared from *m*-anisaldehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (**S1**) following general procedure A. No

further purification was needed to afford **S11** (415 mg, 1.76 mmol, 67%, 2 steps) as a colorless oil: ^1H NMR (CDCl_3 , 500 MHz) δ 7.22–7.15 (m, 1H), 6.77 (d, 1H, $J = 7.6$ Hz), 6.75–6.72 (m, 2H), 3.80 (s, 3H), 2.59 (t, 2H, $J = 7.7$ Hz), 2.37 (t, 2H, $J = 7.4$ Hz), 1.68–1.60 (m, 4H), 1.40–1.36 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 180.5, 159.5, 144.3, 129.1, 120.8, 114.1, 110.8, 55.0, 35.8, 34.0, 31.1, 28.8 (2C), 24.5.

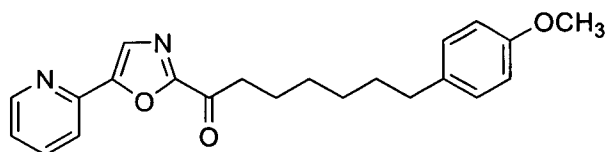


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-methoxyphenyl)heptane (5k). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 7-(3-methoxyphenyl)heptanoic acid (**S11**) using procedure B. Column chromatography (SiO_2 , 2×6 cm, 10–25% EtOAc–hexanes gradient) followed by PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **5k** (80 mg, 0.22 mmol, 46%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (d, 1H, $J = 4.7$ Hz), 7.89–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.6, 1.6$ Hz), 7.34–7.30 (m, 1H), 7.21–7.17 (m, 1H), 6.77 (d, 1H, $J = 7.6$ Hz), 6.72–6.70 (m, 3H), 3.80 (s, 3H), 3.11 (t, 2H, $J = 7.4$ Hz), 2.59 (t, 2H, $J = 7.6$ Hz), 1.83–1.75 (m, 2H), 1.67–1.60 (m, 2H), 1.47–1.40 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.5, 157.3, 153.1, 150.0, 146.2, 137.0, 131.0, 129.7, 126.8, 126.7, 124.0, 120.3, 120.2, 55.1, 39.1, 30.0, 29.5, 29.2, 28.9, 23.9; IR (film) ν_{max} 3052, 2932, 2855, 1699, 1601, 1505, 1471, 1455, 1427, 1283, 1259, 1152, 1118, 1082, 1045, 990, 963, 936, 851, 784, 740, 696 cm^{-1} ; ESI–TOF m/z 365.1868 ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3 + \text{H}^+$ requires 365.1865).

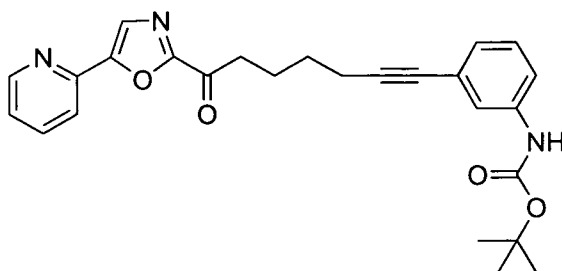


7-(4-Methoxyphenyl)heptanoic acid (S12). The title compound was prepared from *p*-anisaldehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (**S1**) following general procedure A. No further purification was required to yield **S12** (471 mg, 2.0 mmol, 75%, 2 steps) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 7.09 (d, 2H, $J = 8.4$ Hz), 6.83 (d, 2H, $J = 8.4$ Hz), 3.80 (s, 3H), 2.56 (t, 2H, $J = 7.3$ Hz), 2.36 (t, 2H, $J = 7.3$ Hz), 1.68–1.58 (m,

4H), 1.39–1.36 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 180.4, 157.5, 134.7, 129.2, 113.5, 55.0, 34.9, 34.0, 31.4, 28.8 (2C), 24.6.

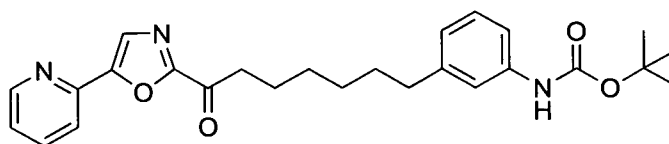


- 5 **1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-methoxyphenyl)heptane (5I).** The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-(4-methoxyphenyl)heptanoic acid (S12) using general procedure B. Column chromatography (SiO_2 , 2×6 cm, 10–25% EtOAc–hexanes gradient) followed by PTLTC (SiO_2 , 50% EtOAc–hexanes) afforded **5I** (55 mg, 0.15 mmol, 32%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (app d, 1H, $J = 4.1$ Hz), 7.88–7.86 (m, 2H), 7.81 (td, 1H, $J = 7.4, 1.8$ Hz), 7.34–7.30 (m, 1H), 7.08 (d, 2H, $J = 8.5$ Hz), 6.81 (d, 2H, $J = 8.7$ Hz), 3.78 (s, 3H), 3.11 (t, 2H, $J = 7.4$ Hz), 2.59 (t, 2H, $J = 7.4$ Hz), 1.82–1.75 (m, 2H), 1.64–1.57 (m, 2H), 1.44–1.37 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.4, 157.5, 157.3, 153.2, 150.1, 146.2, 137.1, 134.7, 129.2, 126.8, 124.1, 120.3, 113.6, 55.2, 39.0, 34.9, 31.4, 28.9, 28.8, 23.9; IR (film) ν_{max} 2926, 2851, 1696, 1652, 1506, 1470, 1456, 1428, 1236, 1035, 984, 961, 927 cm^{-1} ; ESI–TOF m/z 365.1852 ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3 + \text{H}^+$ requires 365.1865).

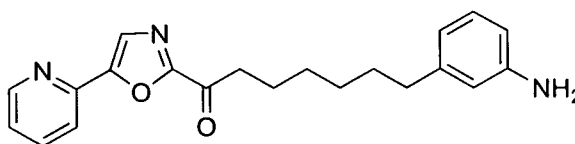


- 20 **1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(tert-butyloxycarbonyl)aminophenyl)hept-6-yne (4o).** The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and iodo-3-(tert-butyloxycarbonyl)aminobenzene following general procedure E. Column chromatography (SiO_2 , 2.5×3.5 cm, 25–50% EtOAc–hexanes gradient) afforded **4o** (28 mg, 0.063 mmol, 40%) as a yellow oil: ^1H NMR (CDCl_3 , 600 MHz) δ 8.67 (app d, 1H, $J = 4.8$ Hz), 7.89 (s, 1H), 7.87 (d, 1H, $J = 7.9$ Hz), 7.82 (td, 1H, $J = 7.8, 1.8$

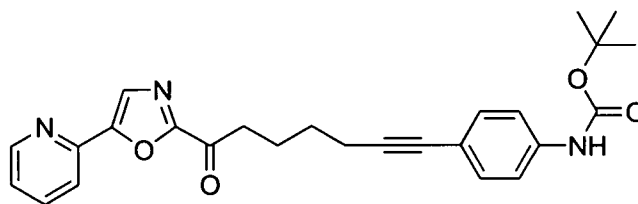
Hz), 7.39 (br s, 1H), 7.33–7.29 (m, 2H), 7.18 (t, 1H, $J = 7.9$ Hz), 7.06 (d, 1H, $J = 7.4$ Hz), 6.48 (br s, 1H), 3.19 (t, 2H, $J = 7.3$ Hz), 2.47 (t, 2H, $J = 7.0$ Hz), 1.99–1.94 (m, 2H), 1.75–1.70 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 188.0, 163.1, 157.3, 153.2, 152.6, 150.1, 146.2, 138.2, 137.1, 128.8, 126.8, 126.2, 124.5, 124.1, 121.3, 120.4, 117.8, 89.6, 80.8, 38.5, 29.6, 28.3, 28.0, 23.1, 19.1; IR (film) ν_{max} 3344, 3054, 2930, 2230, 1731, 1698, 1605, 1584, 1538, 1470, 1427, 1367, 1276, 1236, 1160, 1050, 991, 962, 851, 785, 740, 690 cm^{-1} .



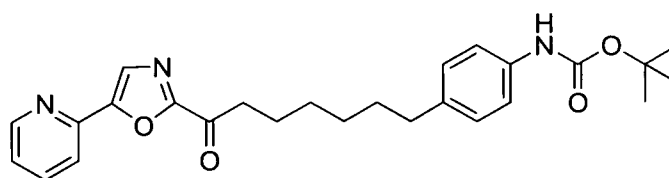
10 **1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(*tert*-butyloxycarbonyl)aminophenyl)heptane (5o).** The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(*tert*-butyloxycarbonyl)aminophenyl)hept-6-yne (4o) following procedure I. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **5o** (9 mg, 0.020 mmol, 55%) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.68 (app d, 1H, $J = 4.0$ Hz), 7.89–7.87 (m, 2H), 7.82 (td, 1H, $J = 7.5, 1.7$ Hz), 7.34–7.31 (m, 1H), 7.23 (br s, 1H), 7.18 (t, 1H, $J = 7.9$ Hz), 7.14–7.12 (m, 1H), 6.85 (d, 1H, $J = 7.3$ Hz), 6.48 (br s, 1H), 3.11 (t, 2H, $J = 7.3$ Hz), 2.58 (t, 2H, $J = 7.7$ Hz), 1.81–1.75 (m, 2H), 1.66–1.59 (m, 2H), 1.52 (s, 9H), 1.45–1.35 (m, 4H).



20 **1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-aminophenyl)heptane (5m).** The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(*tert*-butyloxycarbonyl)aminophenyl)heptane (5o) following procedure J. PTLC (SiO_2 , pretreated with 1% Et_3N –hexanes, 20% EtOAc–hexanes) afforded **5m** (2 mg, 0.0057 mmol, 67%) as a tan film: ^1H NMR (CDCl_3 , 400 MHz) δ 8.77 (m, 1H), 7.99–7.95 (m, 3H), 7.48–7.45 (m, 1H), 7.26–7.12 (m, 4H), 3.08 (t, 2H, $J = 7.3$ Hz), 2.58 (t, 2H, $J = 7.3$ Hz), 1.79–1.72 (m, 2H), 1.63–1.56 (m, 2H), 1.40–1.28 (m, 4H); ESI-TOF m/z 350.1865 ($\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2 + \text{H}^+$ requires 350.1863).



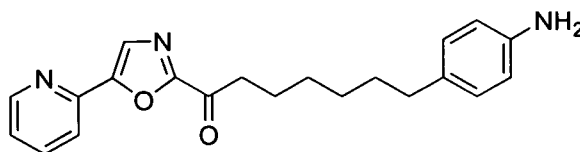
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(tert-butyloxycarbonyl)aminophenyl)hept-6-yne (4p). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and iodo-(4-tert-butyloxycarbonyl)aminobenzene following general procedure E. Column chromatography (SiO₂, 3 × 5 cm, 10–40% EtOAc–hexanes gradient) afforded **4p** (70 mg, 0.157 mmol, 67%) as a yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.67 (d, 1H, *J* = 4.4 Hz), 7.88 (s, 1H), 7.85 (d, 1H, *J* = 7.7 Hz), 7.81 (td, 1H, *J* = 7.7, 1.8 Hz), 7.33–7.26 (m, 5H), 6.55 (s, 1H), 3.19 (t, 2H, *J* = 7.5 Hz), 2.47 (t, 2H, *J* = 7.0 Hz), 2.00–1.97 (m, 2H), 1.95–1.93 (m, 2H), 1.51 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.0, 157.2, 153.2, 152.4, 150.0, 146.1, 137.8, 137.1, 132.2, 126.8, 124.1, 120.3, 118.1, 117.9, 88.5, 80.7, 80.6, 38.5, 28.2, 28.0, 23.1, 19.1; IR (film) ν_{max} 3332, 2932, 2271, 1732, 1699, 1588, 1520, 1505, 1471, 1456, 1427, 1367, 1312, 1232, 1159, 1052, 1027, 838, 784, 738 cm⁻¹; ESI–TOF *m/z* 446.2073 (C₂₆H₂₇N₃O₄ + H⁺ requires 446.2074).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(tert-butyloxycarbonyl)aminophenyl)heptane (5p). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(tert-butyloxycarbonyl)aminophenyl)hept-6-yne (**4p**) following general procedure I. Column chromatography (SiO₂, 2.5 × 4.5 cm, 20–40% EtOAc–hexanes gradient) afforded **5p** (49 mg, 0.109 mmol, 87%) as a pale yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.67 (app d, 1H, *J* = 4.8 Hz), 7.89–7.86 (m, 2H), 7.82 (t, 1H, *J* = 7.7 Hz), 7.34–7.31 (m, 1H), 7.25 (d, 2H, *J* = 8.4 Hz), 7.09 (d, 2H, *J* = 8.4 Hz), 6.45 (s, 1H), 3.11 (t, 2H, *J* = 7.7 Hz), 2.55 (t, 2H, *J* = 7.7 Hz), 1.81–1.75 (m, 2H), 1.63–1.57 (m, 2H), 1.51 (s, 9H), 1.43–1.37 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.5, 157.3, 153.1, 152.9, 150.0, 146.2, 137.4, 137.2, 135.9, 128.8, 126.9, 124.1, 120.4,

118.6, 80.2, 39.0, 35.1, 31.3, 28.9, 28.8, 28.3, 23.9; IR (film) $\nu_{\max}$ 3343, 2931, 2856, 2252, 1732, 1694, 1593, 1470, 1427, 1366, 1366, 1311, 1237, 1159, 1051, 991, 963, 910, 836, 784, 727 cm^{-1} ; ESI-TOF m/z 472.2205 ($\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_4 + \text{Na}^+$ requires 472.2207).

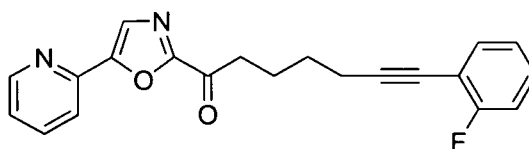
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1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-aminophenyl)heptane (5n). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(*tert*-butyloxycarbonyl)aminophenyl)heptane (**5p**) following general procedure J.

- 10 Chromatography (SiO_2 pretreated with 1% Et_3N -hexanes, 20% EtOAc-hexanes) afforded **5n** (10 mg, 0.029 mmol, 66%) as a tan solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (app d, 1H, $J = 3.8$ Hz), 7.89–7.86 (m, 2H), 7.82 (t, 1H, $J = 7.6$ Hz), 7.34–7.31 (m, 3H), 6.97 (d, 2H, $J = 7.9$ Hz), 6.65 (d, 2H, $J = 7.7$ Hz), 3.11 (t, 2H, $J = 7.3$ Hz), 2.51 (t, 2H, $J = 7.6$ Hz), 1.80–1.75 (m, 2H), 1.61–1.56 (m, 2H), 1.43–1.36 (m, 4H);
- 15 ^{13}C NMR (CDCl_3 , 150 MHz) δ 188.5, 157.4, 153.2, 150.1, 149.9, 146.3, 137.1, 136.9, 129.2, 126.8, 124.1, 120.4, 39.1, 35.0, 31.5, 29.7, 28.9, 23.9; IR (film) $\nu_{\max}$ 3372, 3053, 2930, 2856, 1699, 1615, 1576, 1516, 1471, 1426, 1373, 1265, 1194, 1152, 1122, 964, 785, 741 cm^{-1} ; ESI-TOF m/z 350.1871 ($\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2 + \text{H}^+$ requires 350.1863).

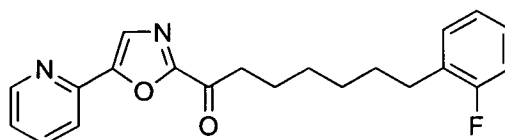
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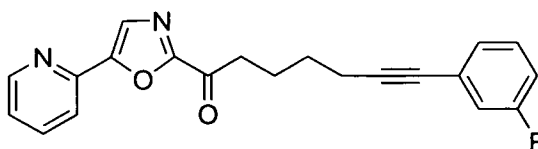
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-fluorophenyl)hept-6-yne (4q). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856)) and 1-fluoro-2-iodobenzene following general procedure D. PTLC (SiO_2 , 50% EtOAc-hexanes) afforded **4q** (20 mg, 0.057 mmol, 38%) as a yellow oil:

25 ^1H NMR (CDCl_3 , 400 MHz) δ 8.68–8.66 (m, 1H), 7.88–7.85 (m, 2H), 7.81 (td, 1H, $J = 7.7, 1.8$ Hz), 7.38 (t, 1H, $J = 7.0$ Hz), 7.33–7.30 (m, 1H), 7.26–7.20 (m, 1H), 7.06–7.00 (m, 2H), 3.20 (t, 2H, $J = 7.4$ Hz), 2.53 (t, 2H, $J = 7.0$ Hz), 2.02–1.95 (m, 2H),

1.79–1.72 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.0, 162.7 (d, $J = 248.7$ Hz), 157.3, 153.3, 150.1, 146.2, 137.1, 133.5, 129.1 (d, $J = 7.6$ Hz), 126.8, 124.1, 123.7 (d, $J = 3.0$ Hz), 120.4, 115.2 (d, $J = 21.2$ Hz), 112.2 (d, $J = 16.7$ Hz), 94.9 (d, $J = 4.6$ Hz), 74.4, 38.5, 27.9, 23.0, 19.4; IR (film) ν_{max} 2931, 2233, 1705, 1603, 1575, 1558, 1505, 1492, 1471, 1455, 1425, 1385, 1255, 1214, 1104, 1024, 785, 759 cm^{-1} ; ESI-TOF m/z 349.1343 ($\text{C}_{21}\text{H}_{17}\text{FN}_2\text{O}_4 + \text{H}^+$ requires 349.1347).

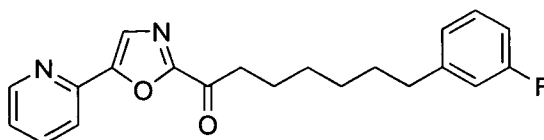


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-fluorophenyl)heptane (5q). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-fluorophenyl)hept-6-yne (**4q**) following general procedure F. No further purification was required to yield **5q** (9 mg, 0.025 mmol, 90%) as a pale yellow solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.69–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.7$, 1.8 Hz), 7.34–7.31 (m, 1H), 7.19–7.13 (m, 2H), 7.05 (td, 1H, $J = 7.5$, 1.2 Hz), 7.01–6.97 (m, 1H), 3.12 (t, 2H, $J = 7.4$ Hz), 2.65 (t, 2H, $J = 7.7$ Hz), 1.82–1.76 (m, 2H), 1.67–1.60 (m, 2H), 1.49–1.38 (m, 4H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 188.5, 161.1 (d, $J = 242.7$ Hz), 157.4, 153.2, 150.1, 146.3, 137.1, 130.6 (d, $J = 5.7$ Hz), 129.4 (d, $J = 16.0$ Hz), 127.3 (d, $J = 32.0$ Hz), 126.8, 124.1, 123.8 (d, $J = 3.4$ Hz), 120.4, 115.1 (d, $J = 21.8$ Hz), 39.1, 29.9, 29.0, 28.9, 28.8, 23.9; IR (film) ν_{max} 2930, 2858, 1699, 1652, 1602, 1575, 1558, 1506, 1490, 1470, 1456, 1425, 1385, 1282, 1228, 1181, 1151, 1036 cm^{-1} ; ESI-TOF m/z 353.1664 ($\text{C}_{21}\text{H}_{21}\text{FN}_2\text{O}_2 + \text{H}^+$ requires 353.1665).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-fluorophenyl)hept-6-yne (4r). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and 1-fluoro-3-iodobenzene following general procedure D. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **4r** (22 mg, 0.063 mmol, 52%) as a yellow solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.68–8.66 (m, 1H), 7.88–7.86 (m, 2H), 7.81 (td,

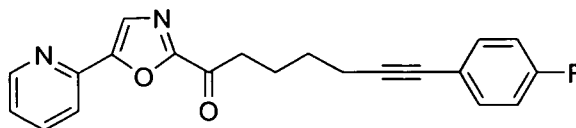
1H, $J = 7.8, 1.8$ Hz), 7.34–7.31 (m, 1H), 7.25–7.20 (m, 1H), 7.18–7.15 (m, 1H), 7.10–7.06 (m, 1H), 3.19 (t, 2H, $J = 7.3$ Hz), 2.49 (t, 2H, $J = 7.0$ Hz), 2.00–1.94 (m, 2H), 1.77–1.70 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.0, 162.3 (d, $J = 244.2$ Hz), 157.2, 153.3, 150.1, 146.2, 137.1, 129.6 (d, $J = 8.6$ Hz), 127.4 (d, $J = 2.9$ Hz), 126.8, 125.6 (d, $J = 9.6$ Hz), 124.1, 120.4, 118.3 (d, $J = 22.9$ Hz), 114.8 (d, $J = 21.0$ Hz), 90.6, 80.0, 38.5, 27.9, 23.1, 19.1; IR (film) ν_{max} 2931, 2222, 1699, 1609, 1579, 1505, 1470, 1426, 1280, 1171, 1151, 1082, 1024, 870, 784 cm^{-1} ; ESI-TOF m/z 349.1348 ($\text{C}_{21}\text{H}_{17}\text{FN}_2\text{O}_4 + \text{H}^+$ requires 349.1347).



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1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-fluorophenyl)heptane (5r). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-fluorophenyl)hept-6-yne (4r) following general procedure F. No further purification was required to yield **5r** (9 mg, 0.025 mmol, 90%) as a yellow oil: ^1H NMR (CDCl_3 , 600 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.6, 1.8$ Hz), 7.34–7.31 (m, 1H), 7.24–7.20 (m, 1H), 6.94 (d, 1H, $J = 7.9$ Hz), 6.89–6.84 (m, 2H), 3.11 (t, 2H, $J = 7.6$ Hz), 2.61 (t, 2H, $J = 7.9$ Hz), 1.81–1.76 (m, 2H), 1.66–1.61 (m, 2H), 1.47–1.36 (m, 4H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 188.4, 162.9 (d, $J = 243.8$ Hz), 157.4, 153.3, 150.1, 146.3, 145.2 (d, $J = 6.9$ Hz), 137.1, 129.5 (d, $J = 8.0$ Hz), 126.8, 124.1, 120.0 (d, $J = 2.3$ Hz), 115.1 (d, $J = 20.6$ Hz), 112.4 (d, $J = 20.6$ Hz), 39.0, 35.6, 30.9, 28.9, 28.8, 23.9; IR (film) ν_{max} 2930, 2856, 1699, 1615, 1589, 1506, 1470, 1425, 1251, 1139, 1037, 962, 787, 742, 692 cm^{-1} ; ESI-TOF m/z 353.1663 ($\text{C}_{21}\text{H}_{21}\text{FN}_2\text{O}_2 + \text{H}^+$ requires 353.1665).

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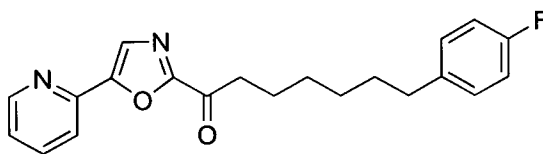


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1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-fluorophenyl)hept-6-yne (4s). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (3a (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856)) and 1-fluoro-4-iodobenzene following general procedure D. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **4s** (16 mg, 0.046 mmol, 30%) as a pale yellow

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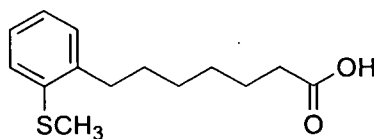
solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.68–8.66 (m, 1H), 7.88–7.85 (m, 2H), 7.81 (td, 1H, $J = 7.7, 1.8$ Hz), 7.38–7.31 (m, 3H), 6.95 (t, 2H, $J = 8.8$ Hz), 3.19 (t, 2H, $J = 7.3$ Hz), 2.47 (t, 2H, $J = 7.0$ Hz), 2.01–1.93 (m, 2H), 1.76–1.69 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.0, 162.5 (d, $J = 247.2$ Hz), 157.3, 153.3, 150.1, 146.2, 137.1, 133.3 (d, $J = 7.6$ Hz), 126.8, 124.2, 120.4, 119.9, 115.3 (d, $J = 22.8$ Hz), 89.1, 80.0, 38.5, 28.0, 23.1, 19.1; IR (film) ν_{max} 2940, 2357, 1699, 1652, 1601, 1558, 1506, 1470, 1424, 1219, 1156, 1093, 838, 785 cm^{-1} ; ESI-TOF m/z 349.1343 ($\text{C}_{21}\text{H}_{17}\text{FN}_2\text{O}_4 + \text{H}^+$ requires 349.1347).



10

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-fluorophenyl)heptane (5s). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-fluorophenyl)hept-6-yne (4s) following general procedure F. No further purification was required to yield 5s (9 mg, 0.025 mmol, 90%) as a white solid: ^1H NMR (CDCl_3 , 600 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.9, 1.8$ Hz), 7.34–7.31 (m, 1H), 7.13–7.10 (m, 2H), 6.97–6.93 (m, 2H), 3.11 (t, 2H, $J = 7.4$ Hz), 2.58 (t, 2H, $J = 7.9$ Hz), 1.82–1.76 (m, 2H), 1.64–1.58 (m, 2H), 1.46–1.36 (m, 4H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 188.4, 161.1 (d, $J = 246.0$ Hz), 157.4, 153.2, 150.1, 146.3, 138.2 (d, $J = 2.3$ Hz), 137.1, 129.6 (d, $J = 8.0$ Hz), 126.8, 124.1, 120.4, 114.9 (d, $J = 20.6$ Hz), 39.0, 35.0, 31.3, 28.9, 28.8, 23.9; IR (film) ν_{max} 2924, 2855, 1703, 1601, 1510, 1463, 1422, 1216, 1160, 1117, 1079, 962, 934, 831, 790, 744, 694 cm^{-1} ; ESI-TOF m/z 353.1662 ($\text{C}_{21}\text{H}_{21}\text{FN}_2\text{O}_2 + \text{H}^+$ requires 353.1665).

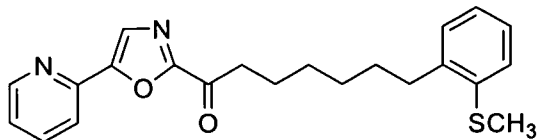
20



7-(2-(Methylthio)phenyl)heptanoic acid (S13). The title compound was prepared from 2-methylthiobenzaldehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (S1) following general procedure A. No further purification was required to yield S13 (600 mg, 2.40 mmol, 38%, 2 steps) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 7.20 (d, 2H, $J = 3.7$ Hz), 7.15 (d, 1H, $J = 7.3$ Hz), 7.12–7.08 (m, 1H), 2.71 (t, 2H, $J = 7.7$ Hz), 2.47 (s,

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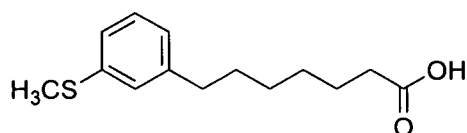
3H), 2.37 (t, 2H, $J = 7.7$ Hz), 1.68–1.63 (m, 4H), 1.43–1.40 (m, 4H); ^{13}C NMR (CDCl₃, 125 MHz) δ 180.3, 140.3, 137.0, 128.9, 126.5, 125.3, 124.7, 34.0, 33.5, 29.6, 29.1, 28.8, 24.6, 15.6.



5

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(methylthio)phenyl)heptane (5t). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-(2-(methylthio)phenyl)heptanoic acid (S13) using general procedure B. Column chromatography (SiO₂, 2.5 × 6 cm, 20% EtOAc–hexanes) afforded **5t** (240 mg, 0.66 mmol, 79%) as a yellow oil: ^1H NMR (CDCl₃, 400 MHz) δ 8.69–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.81 (td, 1H, $J = 7.7, 1.8$ Hz), 7.34–7.30 (m, 1H), 7.19 (d, 1H, $J = 3.3$ Hz), 7.14 (d, 1H, $J = 7.3$ Hz), 7.11–7.07 (m, 1H), 3.13 (t, 2H, $J = 7.3$ Hz), 2.71 (t, 2H, $J = 7.9$ Hz), 2.46 (s, 3H), 1.84–1.77 (m, 2H), 1.68–1.62 (m, 2H), 1.47–1.44 (m, 4H); ^{13}C NMR (CDCl₃, 100 MHz) δ 188.5, 157.3, 153.2, 150.1, 146.2, 140.3, 137.1, 128.9, 126.8, 126.4, 125.2, 124.7, 124.1, 120.3, 39.1, 33.5, 29.6, 29.2, 28.9, 23.9, 15.6; IR (film) ν_{max} 3055, 2926, 2856, 1704, 1602, 1557, 1505, 1471, 1427, 1385, 1283, 1119, 1045, 990, 963, 935, 850, 784, 742 cm⁻¹; ESI–TOF m/z 381.1631 (C₂₂H₂₄N₂O₂S + H⁺ requires 381.1631).

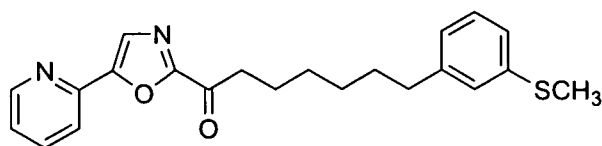
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7-(3-(Methylthio)phenyl)heptanoic acid (S14). The title compound was prepared from 3-methylthiobenzaldehyde and BrPh₃P(CH₂)₅CO₂H (S1) following general procedure A. No further purification was required to yield **S14** (300 mg, 1.19 mmol, 31%, 2 steps) as a yellow oil: ^1H NMR (CDCl₃, 500 MHz) δ 7.23–7.19 (m, 1H), 7.10–7.08 (m, 2H), 6.96 (d, 1H, $J = 8.0$ Hz), 2.59 (t, 2H, $J = 7.8$ Hz), 2.49 (s, 3H), 2.37 (t, 2H, $J = 7.3$ Hz), 1.69–1.60 (m, 4H), 1.40–1.37 (m, 4H); ^{13}C NMR (CDCl₃, 125 MHz) δ 180.3, 143.3, 138.1, 128.7, 126.6, 125.3, 123.8, 35.8, 34.0, 31.1, 28.8 (2C), 24.5, 15.8.

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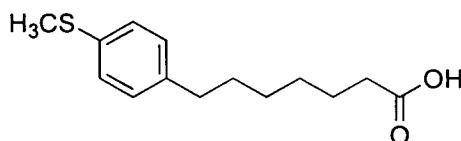


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(methylthio)phenyl)heptane (5u). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-(3-

(methylthio)phenyl)heptanoic acid (S14) using general procedure B. Column

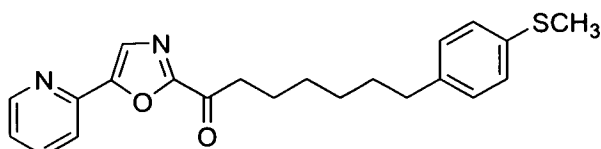
5 chromatography (SiO₂, 2 × 5 cm, 10–20% EtOAc–hexanes gradient) afforded **5u** (80 mg, 0.21 mmol, 56%) as a yellow oil: ¹H NMR (CDCl₃, 500 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.8, 1.8 Hz), 7.33–7.30 (m, 1H), 7.20 (t, 1H, *J* = 7.4 Hz), 7.08–7.06 (m, 2H), 6.95 (d, 1H, *J* = 7.7 Hz), 3.11 (t, 2H, *J* = 7.4 Hz), 2.58 (t, 2H, *J* = 7.7 Hz), 2.48 (s, 3H), 1.82–1.76 (m, 2H), 1.66–1.60 (m, 2H), 1.47–1.36 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.4, 157.3, 153.2, 150.1, 146.2, 143.2, 138.0, 137.0, 128.6, 126.8, 126.5, 125.2, 124.1, 123.8, 120.3, 39.0, 35.7, 31.1, 28.9, 28.8, 15.8, 16.4; IR (film) *v*_{max} 2928, 2855, 1699, 1591, 1574, 1558, 1506, 1471, 1424, 1152, 1118, 1086, 990, 963, 936, 783, 741, 697 cm⁻¹; ESI-TOF *m/z* 381.1637 (C₂₂H₂₄N₂O₂S + H⁺ requires 381.1631).

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7-(4-(Methylthio)phenyl)heptanoic acid (S15). The title compound was prepared from 4-methylthiobenzaldehyde and BrPh₃P(CH₂)₅CO₂H (S1) following general procedure A. No further purification was required to yield **S15** (400 mg, 1.59 mmol,

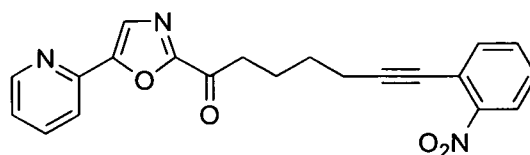
20 25%, 2 steps) as a white solid: ¹H NMR (CDCl₃, 600 MHz) δ 7.21 (d, 2H, *J* = 7.9 Hz), 7.11 (d, 2H, *J* = 7.9 Hz), 2.58 (t, 2H, *J* = 7.6 Hz), 2.48 (s, 3H), 2.37 (t, 2H, *J* = 7.4 Hz), 1.68–1.58 (m, 4H), 1.39–1.35 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 180.1, 139.8, 134.5, 128.9, 127.1, 35.2, 34.0, 31.2, 28.8 (2C), 24.5, 16.3.



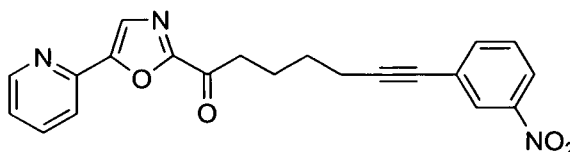
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1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(methylthio)phenyl)heptane (5v). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-(4-(methylthio)phenyl)heptanoic acid (S15) using general procedure B. Column chromatography (SiO₂, 3 × 8 cm, 20% EtOAc–hexanes) afforded **5v** (195 mg, 0.51

mmol, 76%) as a yellow oil: ^1H NMR (CDCl_3 , 500 MHz) δ 8.68–8.66 (m, 1H), 7.88–7.85 (m, 2H), 7.81 (td, 1H, $J = 7.7, 1.8$ Hz), 7.33–7.30 (m, 1H), 7.19 (d, 2H, $J = 8.1$ Hz), 7.10 (d, 2H, $J = 8.1$ Hz), 3.11 (t, 2H, $J = 7.3$ Hz), 2.57 (t, 2H, $J = 7.7$ Hz), 2.46 (s, 3H), 1.81–1.75 (m, 2H), 1.64–1.58 (m, 2H), 1.47–1.35 (m, 4H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 188.4, 157.3, 153.2, 150.1, 146.3, 139.8, 137.1, 134.9, 128.9, 127.1, 124.1, 120.4, 39.0, 35.2, 31.2, 28.9, 28.8, 23.9, 16.4; IR (film) ν_{max} 3097, 2927, 2855, 1694, 1603, 1557, 1505, 1495, 1471, 1429, 1236, 1124, 1093, 962, 935, 786, 743, 697 cm^{-1} ; ESI-TOF m/z 381.1635 ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2\text{S} + \text{H}^+$ requires 381.1631).

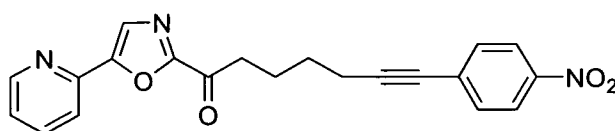


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-nitrophenyl)hept-6-yne (4rr). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and 1-iodo-2-nitrobenzene following general procedure E. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **4rr** (39 mg, 0.104 mmol, 59%) as a yellow solid: ^1H NMR (CDCl_3 , 600 MHz) δ 8.67–8.65 (m, 1H), 7.95 (d, 1H, $J = 7.7$ Hz), 7.86 (s, 1H), 7.85 (d, 1H, $J = 7.4$ Hz), 7.80 (td, 1H, $J = 7.8, 1.8$ Hz), 7.58 (dd, 1H, $J = 7.8, 1.3$ Hz), 7.51 (td, 1H, $J = 7.4, 1.3$ Hz), 7.39 (td, 1H, $J = 7.4, 1.3$ Hz), 7.33–7.30 (m, 1H), 3.20 (t, 2H, $J = 7.3$ Hz), 2.56 (t, 2H, $J = 7.0$ Hz), 2.02–1.97 (m, 2H), 1.80–1.74 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 187.9, 157.3, 153.2, 150.1, 150.0, 146.2, 137.1, 134.8, 132.5, 127.9, 126.8, 124.3, 124.1, 120.4, 119.1, 98.4, 76.4, 38.5, 27.6, 23.0, 19.6; IR (film) ν_{max} 2931, 2231, 1705, 1607, 1568, 1520, 1505, 1470, 1425, 1343, 1287, 1152, 1084, 1023, 990, 963, 852, 785, 745, 694 cm^{-1} ; ESI-TOF m/z 376.1298 ($\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_4 + \text{H}^+$ requires 376.1292).

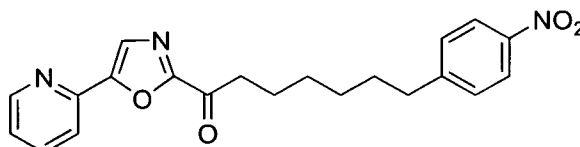


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-nitrophenyl)hept-6-yne (4ss). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and 1-iodo-3-nitrobenzene following general procedure E. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **4ss** (48 mg, 0.128 mmol, 71%) as a tan solid: ^1H NMR (CDCl_3 , 600 MHz) δ

8.67–8.65 (m, 1H), 8.22 (s, 1H), 8.11–8.09 (m, 1H), 7.88 (s, 1H), 7.86 (dd, 1H, $J = 7.8, 1.3$ Hz), 7.83–7.80 (m, 1H), 7.68 (dd, 1H, $J = 7.8, 1.2$ Hz), 7.44 (t, 1H, $J = 7.8$ Hz), 7.34–7.31 (m, 1H), 3.21 (t, 2H, $J = 7.5$ Hz), 2.52 (t, 2H, $J = 7.0$ Hz), 2.01–1.96 (m, 2H), 1.78–1.73 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 187.9, 157.2, 153.3, 150.1, 148.0, 146.2, 137.3, 137.1, 129.1, 126.8, 126.3, 125.6, 124.1, 122.3, 120.4, 92.6, 79.0, 38.4, 27.7, 23.1, 19.1; IR (film) ν_{max} 2933, 2232, 1699, 1602, 1575, 1558, 1532, 1506, 1471, 1425, 1349, 1282, 1082, 1024, 990, 963, 785, 737, 675 cm^{-1} ; ESI-TOF m/z 376.1295 ($\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_4 + \text{H}^+$ requires 376.1292).

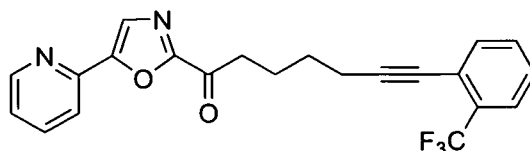


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-nitrophenyl)hept-6-yne (4w). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and 1-iodo-4-nitrobenzene following general procedure E. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **4w** (10 mg, 0.027 mmol, 67%) as a tan solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.68–8.66 (m, 1H), 8.13 (d, 2H, $J = 8.8$ Hz), 7.87–7.85 (m, 2H), 7.81 (td, 1H, $J = 7.7, 1.8$ Hz), 7.51 (d, 2H, $J = 8.8$ Hz), 7.34–7.31 (m, 1H), 3.21 (t, 2H, $J = 7.4$ Hz), 2.54 (t, 2H, $J = 7.0$ Hz), 2.01–1.95 (m, 2H), 1.79–1.73 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 187.8, 157.2, 153.3, 150.1, 146.6, 146.1, 137.1, 132.2, 130.6, 126.8, 124.1, 124.2, 123.4, 120.3, 95.7, 79.7, 38.4, 27.6, 23.0, 19.3; IR (film) ν_{max} 2943, 2231, 1704, 1593, 1515, 1467, 1425, 1342, 1284, 1107, 1082, 1025, 989, 963, 933, 854, 790, 750, 691 cm^{-1} ; ESI-TOF m/z 376.1300 ($\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_4 + \text{H}^+$ requires 376.1292).



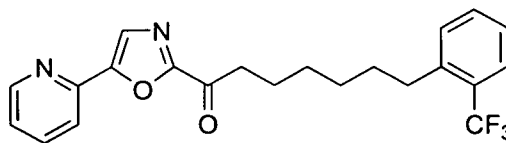
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-nitrophenyl)heptane (5w). A solution of 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-nitrophenyl)hept-6-yne (**4w**, 10 mg, 0.027 mmol) in THF/*t*-BuOH (1/1, 0.8 mL) was treated with 0.05 equiv of Wilkinson's catalyst ($\text{Rh}(\text{PPh}_3)_3\text{Cl}$). The solution was purged with H_2 and stirred for 20 h at 25 °C. The reaction mixture was filtered through Celite and concentrated. PTLC (SiO_2 , 50% EtOAc–hexanes + 1% Et_3N) afforded **5w** (6 mg, 0.015 mmol, 79%) as a tan solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.69–8.67 (m, 1H), 8.14 (d, 2H, $J = 8.8$ Hz), 7.89–7.86

(m, 2H), 7.82 (td, 1H, $J = 7.8, 1.8$ Hz), 7.35–7.31 (m, 3H), 3.12 (t, 2H, $J = 7.3$ Hz), 2.72 (t, 2H, $J = 7.7$ Hz), 1.81–1.75 (m, 2H), 1.71–1.64 (m, 2H), 1.49–1.39 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.3, 157.3, 153.3, 150.5, 150.1, 146.2, 137.1, 135.0, 129.1, 127.7, 124.2, 123.6, 120.4, 38.9, 35.7, 30.7, 28.8 (2C), 23.8; IR (film) ν_{max} 2926, 2857, 1705, 1601, 1557, 1515, 1466, 1424, 1344, 797 cm^{-1} ; ESI-TOF m/z 380.1614 ($\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_2 + \text{H}^+$ requires 380.1610).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(trifluoromethyl)phenyl)hept-6-yne (4x).

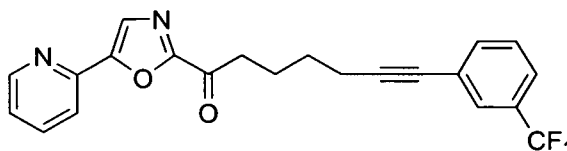
The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856)) and 2-iodo-trifluoromethylbenzene following general procedure D. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **4x** (13 mg, 0.032 mmol, 28%) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.67 (app d, 1H, $J = 4.8$ Hz), 7.88–7.85 (m, 2H), 7.81 (td, 1H, $J = 7.4, 1.5$ Hz), 7.60 (d, 1H, $J = 7.7$ Hz), 7.53 (d, 1H, $J = 7.7$ Hz), 7.44 (t, 1H, $J = 7.5$ Hz), 7.36–7.31 (m, 2H), 3.20 (t, 2H, $J = 7.4$ Hz), 2.54 (t, 2H, $J = 7.0$ Hz), 2.02–1.96 (m, 2H), 1.79–1.72 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.0, 157.3, 153.3, 150.1, 146.2, 137.1, 133.9, 131.4 (d, $J = 30.5$ Hz), 131.2, 127.2, 126.9, 125.6 (q, $J = 4.8$ Hz), 124.1, 123.6 (d, $J = 271.9$ Hz), 122.2 (d, $J = 1.9$ Hz), 120.4, 95.7, 77.3, 38.5, 27.3, 22.9, 19.3; IR (film) ν_{max} 2929, 2864, 2234, 1703, 1603, 1575, 1504, 1490, 1469, 1426, 1318, 1169, 1133, 1111, 1062, 1033, 963, 844, 784, 766 cm^{-1} ; ESI-TOF m/z 399.1326 ($\text{C}_{22}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2 + \text{H}^+$ requires 399.1320).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(trifluoromethyl)phenyl)heptane (5x).

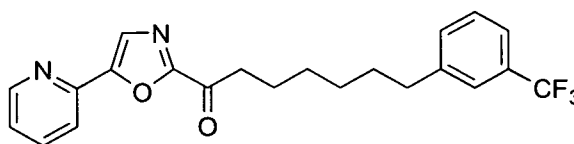
The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(trifluoromethyl)phenyl)hept-6-yne (**4x**) following general procedure F. No further purification was required to yield **5x** (8 mg, 0.02 mmol, 80%) as a yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 8.69–8.67 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.9, 1.8$ Hz), 7.44–7.31 (m, 5H), 3.12 (t, 2H, $J = 7.3$ Hz), 2.67 (t, 2H, $J = 7.6$ Hz),

1.83–1.76 (m, 2H), 1.70–1.62 (m, 2H), 1.47–1.37 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.4, 157.3, 153.3, 150.1, 146.3, 143.8, 137.1, 131.8, 130.5 (d, $J = 31.5$ Hz), 128.6, 126.8, 125.0 (q, $J = 3.8$ Hz), 124.1, 122.5 (t, $J = 3.8$ Hz), 120.4, 39.0, 35.7, 31.1, 28.9 (2C), 23.8; IR (film) ν_{max} 2929, 2857, 1699, 1606, 1575, 1505, 1470, 1426, 1313, 1165, 1119, 1059, 1034, 963, 784, 769, 741 cm^{-1} ; ESI-TOF m/z 403.1629 ($\text{C}_{22}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_2 + \text{H}^+$ requires 403.1628).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(trifluoromethyl)phenyl)hept-6-yne (4y).

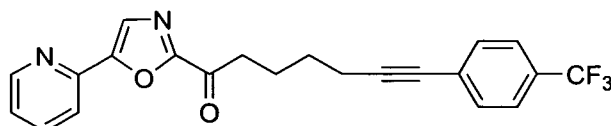
The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (3a) and 3-iodo-trifluoromethylbenzene following general procedure D. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **4y** (31 mg, 0.078 mmol, 64%) as a yellow solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.67 (app d, 1H, $J = 4.4$ Hz), 7.89–7.86 (m, 2H), 7.81 (td, 1H, $J = 7.7, 1.5$ Hz), 7.65 (s, 1H), 7.55 (d, 1H, $J = 7.7$ Hz), 7.50 (d, 1H, $J = 8.1$ Hz), 7.39 (t, 1H, $J = 7.7$ Hz), 7.34–7.31 (m, 1H), 3.21 (t, 2H, $J = 7.4$ Hz), 2.51 (t, 2H, $J = 7.0$ Hz), 2.01–1.95 (m, 2H), 1.78–1.72 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.0, 157.2, 153.3, 150.1, 146.2, 137.1, 134.6, 128.6, 128.3 (q, $J = 4.5$ Hz), 126.8, 125.1, 124.1, 124.0, 122.3, 120.4, 91.4, 79.7, 38.5, 27.8, 23.1, 19.1; IR (film) ν_{max} 2934, 2866, 2233, 1699, 1603, 1576, 1504, 1469, 1426, 1335, 1237, 1166, 1127, 1072, 1024, 801, 784, 696 cm^{-1} ; ESI-TOF m/z 399.1323 ($\text{C}_{22}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2 + \text{H}^+$ requires 399.1320).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(trifluoromethyl)phenyl)heptane (5y).

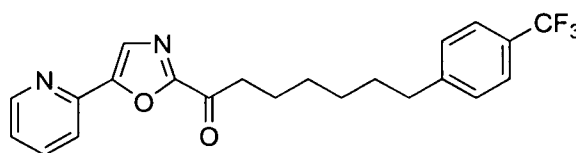
The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(trifluoromethyl)phenyl)hept-6-yne (**4y**) following general procedure F. No further purification was required to yield **5y** (7 mg, 0.017 mmol, 89%) as a pale yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 8.69–8.67 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.9, 1.8$ Hz), 7.44–7.31 (m, 5H), 3.12 (t, 2H, $J = 7.3$ Hz), 2.67 (t, 2H, $J = 7.6$ Hz), 1.83–1.76 (m, 2H), 1.70–1.62 (m, 2H), 1.47–1.37 (m, 4H); ^{13}C NMR (CDCl_3 , 125

MHz) δ 188.4, 157.3, 153.3, 150.1, 146.3, 143.8, 137.1, 131.8, 130.5 (d, $J = 31.5$ Hz), 128.6, 126.8, 125.0 (q, $J = 3.8$ Hz), 124.1, 122.5 (t, $J = 3.8$ Hz), 120.4, 39.0, 35.7, 31.1, 28.9 (2C), 23.8; IR (film) $\nu_{\max}$ 2929, 2859, 1699, 1603, 1576, 1505, 1469, 1426, 1329, 1163, 1122, 1074, 784, 702 cm^{-1} ; ESI-TOF m/z 403.1641 ($\text{C}_{22}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_2 + \text{H}^+$ requires 403.1628).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(trifluoromethyl)phenyl)hept-6-yne (4z).

The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856)) and 4-iodo-trifluoromethylbenzene following general procedure D. PTLTC (SiO_2 , 50% EtOAc–hexanes) afforded **4z** (28 mg, 0.070 mmol, 60%) as a yellow solid: ^1H NMR (CDCl_3 , 500 MHz) δ 8.67 (app d, 1H, $J = 4.4$ Hz), 7.88–7.85 (m, 2H), 7.81 (td, 1H, $J = 7.7, 1.8$ Hz), 7.52 (d, 2H, $J = 8.4$ Hz), 7.48 (d, 2H, $J = 8.1$ Hz), 7.34–7.31 (m, 1H), 3.20 (t, 2H, $J = 7.4$ Hz), 2.51 (t, 2H, $J = 7.0$ Hz), 2.01–1.95 (m, 2H), 1.78–1.71 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.0, 157.2, 153.3, 150.1, 146.2, 137.1, 131.7, 129.2 (d, $J = 33.3$ Hz), 127.7, 126.8, 125.1 (q, $J = 3.1$ Hz), 124.1, 124.0 (d, $J = 270.0$ Hz), 120.4, 91.4, 79.7, 38.5, 27.8, 23.1, 19.1; IR (film) $\nu_{\max}$ 2934, 2866, 2232, 1698, 1614, 1577, 1503, 1469, 1426, 1323, 1166, 1125, 1067, 1017, 963, 843, 784 cm^{-1} ; ESI-TOF m/z 399.1326 ($\text{C}_{22}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2 + \text{H}^+$ requires 399.1320).

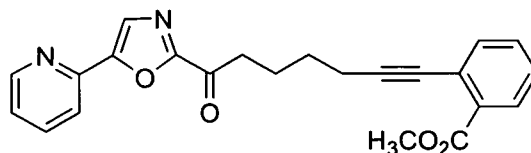


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(trifluoromethyl)phenyl)heptane (5z).

The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(trifluoromethyl)phenyl)hept-6-yne (**4z**) following general procedure F. No further purification was required to yield **5z** (12 mg, 0.03 mmol, 93%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.81 (td, 1H, $J = 7.7, 1.8$ Hz), 7.52 (d, 2H, $J = 8.2$ Hz), 7.34–7.31 (m, 1H), 7.28 (d, 2H, $J = 8.0$ Hz), 3.12 (t, 2H, $J = 7.3$ Hz), 2.67 (t, 2H, $J = 7.6$ Hz), 1.83–1.75 (m, 2H), 1.69–1.62 (m, 2H), 1.48–1.39 (m, 4H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 188.4, 157.3, 153.3, 150.1,

146.7, 137.1, 128.6, 128.1, 127.9, 126.8, 125.1 (q, $J = 3.4$ Hz), 124.1, 120.4, 39.0, 35.6, 30.9, 28.9 (2C), 23.8; IR (film) $\nu_{\max}$ 3104, 2933, 2855, 1698, 1604, 1503, 1468, 1428, 1385, 1327, 1237, 1162, 1109, 1068, 962, 845, 821, 783 cm^{-1} ; ESI-TOF m/z 403.1640 ($\text{C}_{22}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_2 + \text{H}^+$ requires 403.1628).

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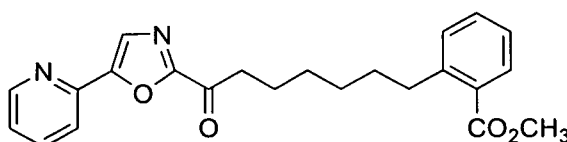


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(methoxycarbonyl)phenyl)hept-6-yne

(4aa). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**,

10 48, 1849–1856)) and methyl 2-iodobenzoate following general procedure D. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **4aa** (10 mg, 0.026 mmol, 29%) as a yellow oil: ^1H NMR (CDCl_3 , 500 MHz) δ 8.67 (app d, 1H, $J = 4.8$ Hz), 7.89–7.85 (m, 3H), 7.81 (td, 1H, $J = 7.4$, 1.5 Hz), 7.51 (d, 1H, $J = 7.7$ Hz), 7.42 (td, 1H, $J = 7.4$, 1.3 Hz), 7.33–7.28 (m, 2H), 3.91 (s, 3H), 3.21 (t, 2H, $J = 7.4$ Hz), 2.57 (t, 2H, $J = 7.0$ Hz), 2.04–1.97 (m, 2H), 1.79–1.75 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.1, 166.9, 157.3, 153.2, 150.1, 146.2, 137.1, 134.3, 131.8, 131.5, 130.1, 127.2, 126.8, 124.2, 124.1, 120.4, 95.0, 79.7, 52.1, 38.6, 28.0, 23.1, 19.6; IR (film) $\nu_{\max}$ 2948, 2313, 1728, 1693, 1600, 1503, 1468, 1426, 1294, 1251, 1129, 1083, 785, 760 cm^{-1} ; ESI-TOF m/z 389.1507 ($\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4 + \text{H}^+$ requires 389.1496).

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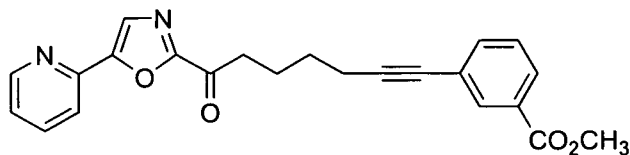


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(methoxycarbonyl)phenyl)heptane (5aa).

The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(methoxycarbonyl)phenyl)hept-6-yne (**4aa**) following general procedure F. No further

25 purification was required to yield **5aa** (4 mg, 0.010 mmol, 57%) as a colorless film: ^1H NMR (CDCl_3 , 500 MHz) δ 8.68 (app d, 1H $J = 4.8$ Hz), 7.89 (s, 1H), 7.87–7.84 (m, 2H), 7.82 (td, 1H, $J = 7.6$, 1.8 Hz), 7.41 (td, 1H, $J = 7.7$, 1.5 Hz), 7.34–7.31 (m, 1H), 7.26–7.22 (m, 2H), 3.90 (s, 3H), 3.12 (t, 2H, $J = 7.3$ Hz), 2.95 (t, 2H, $J = 7.7$ Hz), 1.81–1.76 (m, 2H), 1.63–1.57 (m, 2H), 1.48–1.43 (m, 4H); ^{13}C NMR (CDCl_3 , 30 125 MHz) δ 188.5, 169.9, 153.0, 144.0, 137.9, 134.7, 133.3, 127.1, 120.7, 118.6,

117.6, 116.3, 113.2, 45.4, 41.5, 39.1, 37.3, 37.0, 32.8; IR (film) $\nu_{\max}$ 2927, 2855, 1722, 1699, 1602, 1575, 1504, 1469, 1426, 1259, 1094, 963, 785, 753, 711 cm^{-1} ; ESI-TOF m/z 393.1813 ($\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_4 + \text{H}^+$ requires 393.1809).



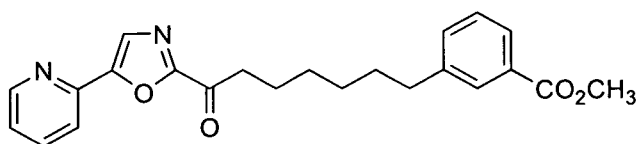
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1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(methoxycarbonyl)phenyl)hept-6-yne

(4bb). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and methyl 3-iodobenzoate following general procedure D. PTLC

10 (SiO₂, 50% EtOAc–hexanes) afforded **4bb** (12 mg, 0.031 mmol, 34%) as a pale yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.67 (app d, 1H, J = 4.8 Hz), 8.06 (d, 1H, J = 1.5 Hz), 7.92 (dt, 1H, J = 9.1, 1.4 Hz), 7.89–7.85 (m, 2H), 7.81 (td, 1H, J = 7.7, 1.8 Hz), 7.56 (dt, 1H, J = 7.7, 1.4 Hz), 7.35 (t, 1H, J = 7.7 Hz), 7.33–7.30 (m, 1H), 3.91 (s, 3H), 3.20 (t, 2H, J = 7.7 Hz), 2.50 (t, 2H, J = 7.3 Hz), 2.02–1.96 (m, 2H),
15 1.78–1.72 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 188.0, 166.5, 157.3, 153.2, 150.0, 146.2, 137.2, 135.8, 132.7, 130.2, 128.6, 128.3, 126.9, 124.3, 124.2, 120.4, 90.6, 80.1, 52.2, 38.5, 27.9, 23.1, 19.2; IR (film) $\nu_{\max}$ 2949, 2353, 1722, 1698, 1601, 1573, 1503, 1469, 1426, 1298, 1230, 1107, 1083, 1024, 785, 755 cm^{-1} ; ESI-TOF m/z 389.1510 ($\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4 + \text{H}^+$ requires 389.1496).

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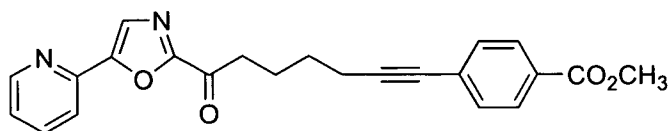


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(methoxycarbonyl)phenyl)heptane (5bb).

The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(methoxycarbonyl)phenyl)hept-6-yne (**4bb**) following general procedure F. PTLC

25 (SiO₂, 50% EtOAc–hexanes) afforded **5bb** (6 mg, 0.015 mmol, 79%) as a pale yellow film: ¹H NMR (CDCl₃, 500 MHz) δ 8.68 (app d, 1H, J = 4.8 Hz), 7.89 (s, 1H), 7.87–7.84 (m, 3H), 7.82 (td, 1H, J = 7.7, 1.5 Hz), 7.40–7.31 (m, 3H), 3.92 (s, 3H), 3.12 (t, 2H, J = 7.4 Hz), 2.66 (t, 2H, J = 7.7 Hz), 1.82–1.76 (m, 2H), 1.70–1.63 (m, 2H), 1.47–1.39 (m, 4H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.5, 169.8, 153.0, 150.1, 143.0,
30 137.1, 133.1, 130.1, 129.5, 128.3, 127.0, 126.8, 120.4, 52.1, 39.0, 35.6, 31.1, 29.7,

28.9, 23.9; IR (film) $\nu_{\max}$ 2927, 2855, 1716, 1699, 1602, 1575, 1505, 1470, 1425, 1283, 1201, 1108, 1035, 785, 752 cm^{-1} ; ESI-TOF m/z 393.1816 ($\text{C}_{23}\text{H}_{24}\text{N}_2\text{O} + \text{H}^+$ requires 393.1809).

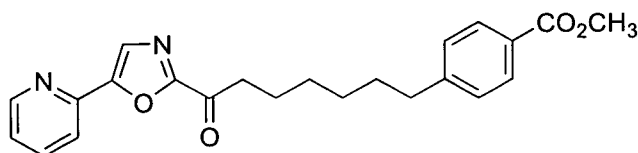


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1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(methoxycarbonyl)phenyl)hept-6-yne

(**4cc**). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(trimethylsilyl)hept-6-yne (**3a** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856)) and methyl 4-iodobenzoate following general procedure D. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **4cc** (12 mg, 0.031 mmol, 34%) as a pale yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.68 (br s, 1H), 7.94 (d, 1H, J = 8.4 Hz), 7.88–7.80 (m, 3H), 7.44 (d, 1H, J = 8.4 Hz), 7.33 (m, 1H), 3.91 (s, 3H), 3.21 (t, 2H, J = 7.4 Hz), 2.50 (t, 2H, J = 7.0 Hz), 2.02–1.96 (m, 2H), 1.78–1.72 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 188.0, 166.6, 157.3, 153.2, 150.0, 146.2, 137.1, 131.5, 129.4, 128.8, 128.6, 126.9, 124.1, 120.4, 93.0, 80.6, 52.1, 38.5, 27.8, 23.1, 19.3; IR (film) $\nu_{\max}$ 3097, 2949, 2224, 1715, 1691, 1604, 1573, 1501, 1470, 1427, 1277, 1177, 1109, 1019, 963, 856, 784, 769 cm^{-1} ; ESI-TOF m/z 389.1495 ($\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4 + \text{H}^+$ requires 389.1496).

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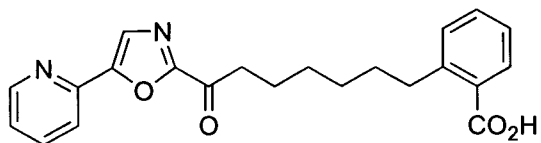
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(methoxycarbonyl)phenyl)heptane (5cc).

The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(methoxycarbonyl)phenyl)hept-6-yne (**4cc**) following general procedure F. No further purification was required to yield **5cc** (7 mg, 0.018 mmol, 88%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.68–8.66 (m, 1H), 7.95 (d, 2H, J = 8.5 Hz), 7.89 (s, 1H), 7.86 (m, 1H), 7.82 (td, 1H, J = 7.8, 1.8 Hz), 7.34–7.31 (m, 1H), 7.24 (d, 2H, J = 8.5 Hz), 3.90 (s, 3H), 3.11 (t, 2H, J = 7.3 Hz), 2.67 (t, 2H, J = 7.6 Hz), 1.82–1.75 (m, 2H), 1.69–1.62 (m, 2H), 1.47–1.38 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.4, 167.1, 157.3, 153.2, 150.1, 148.2, 146.2, 137.1, 129.6, 128.4, 127.6, 126.8, 124.1, 120.4, 51.9, 39.0, 35.8, 30.9, 28.9 (2C), 23.8; IR (film) $\nu_{\max}$ 2928, 2855, 1716, 1694,

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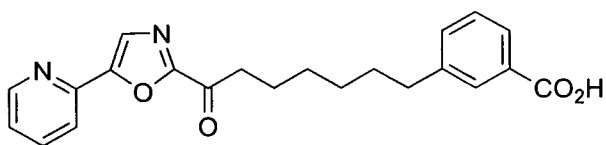
1602, 1502, 1469, 1432, 1383, 1281, 1180, 1112, 1037, 989, 962, 937, 791, 759 cm^{-1} ;
ESI-TOF m/z 393.1808 ($\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_4 + \text{H}^+$ requires 393.1809).



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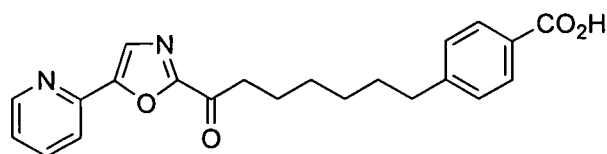
2-(7-Oxo-7-(5-(pyridin-2-yl)oxazol-2-yl)heptyl)benzoic acid (5dd). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(methoxycarbonyl)phenyl)heptane (**5aa**) following general procedure L. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **5dd** (8 mg, 21%) as a white solid: ^1H NMR (CDCl_3 , 600 MHz) δ 8.72 (br s), 8.01 (app d, $J = 8.4$ Hz, 1H), 7.81–7.91 (m, 3H), 7.44 (app t, $J = 7.8$ Hz, 1H), 7.34 (app s, 1H), 7.25–7.27 (m, 3H), 3.12 (t, $J = 7.2$ Hz, 2H), 3.02 (t, $J = 7.8$ Hz, 2H), 1.79–1.81 (m, 2H), 1.64–1.67 (m, 2H), 1.43–1.50 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.6, 171.1, 157.4, 153.0, 150.0, 146.0, 145.4, 137.4, 132.5, 131.4, 131.1, 128.4, 127.0, 125.8, 124.3, 120.6, 39.1, 34.3, 31.3, 29.0, 28.6, 23.9;
ESI-TOF m/z 379.1659 ($\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4 + \text{H}^+$ requires 379.1652).

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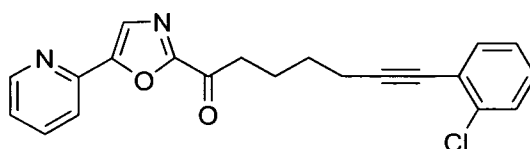


3-(7-Oxo-7-(5-(pyridin-2-yl)oxazol-2-yl)heptyl)benzoic acid (5ee). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(methoxycarbonyl)phenyl)heptane (**5bb**) following general procedure L. PTLC (SiO_2 , 50% EtOAc–hexanes) afforded **5ee** (5 mg, 15%) as a white solid: ^1H NMR (CDCl_3 , 600 MHz) δ 8.72 (app d, $J = 4.2$ Hz, 1H), 7.86–7.93 (m, 4H), 7.83 (t, $J = 5.0$ Hz, 1H), 7.36–7.42 (m, 2H), 7.34 (app t, $J = 6.0$ Hz, 1H), 3.13 (t, $J = 7.8$ Hz, 2H), 2.69 (t, $J = 7.8$ Hz, 2H), 1.80 (quint, $J = 7.2$ Hz, 2H), 1.68 (quint, $J = 7.2$ Hz, 2H), 1.38–1.49 (m, 4H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.4, 170.6, 157.4, 153.0, 150.1, 146.1, 143.0, 137.3, 133.8, 130.1, 129.3, 128.4, 127.6, 127.0, 124.2, 120.6, 39.0, 35.4, 31.0, 28.7, 28.5, 23.8; ESI-TOF m/z 379.1654 ($\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4 + \text{H}^+$ requires 379.1652).

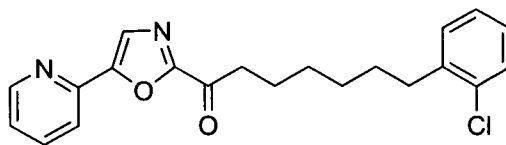
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25



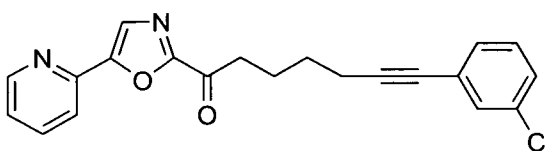
- 4-(7-Oxo-7-(5-(pyridin-2-yl)oxazol-2-yl)heptyl)benzoic acid (5ff).** The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(methoxycarbonyl)-phenyl)heptane (**5cc**) following general procedure L. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **5ff** (6 mg, 33%) as a white solid: ¹H NMR (CDCl₃, 600 MHz) δ 8.69 (app d, *J* = 4.2 Hz, 1H), 8.02 (app d, *J* = 7.8 Hz, 2H), 7.87–7.90 (m, 2H), 7.82 (app t, *J* = 7.8 Hz, 1H), 7.33 (app t, *J* = 5.4 Hz, 1H), 7.26–7.28 (m, 2H), 3.11 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.8 Hz, 2H), 1.79 (quint, *J* = 7.2 Hz, 2H), 1.67 (quint, *J* = 7.8 Hz, 2H), 1.41–1.47 (m, 4H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.4, 171.1, 157.4, 153.2, 150.1, 149.1, 146.2, 137.2, 130.3, 128.5, 126.9, 125.9, 124.2, 120.5, 39.0, 36.0, 30.8, 28.9, 23.9; ESI–TOF *m/z* 379.1652 (C₂₂H₂₂N₂O₄ + H⁺ requires 379.1652).



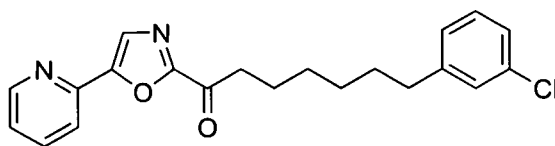
- 1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-chlorophenyl)hept-6-yne (4gg).** The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856)) and 1-chloro-2-iodobenzene following general procedure E. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **4gg** (27 mg, 0.074 mmol, 63%) as a yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.7, 1.8 Hz), 7.44–7.42 (m, 1H), 7.37–7.31 (m, 2H), 7.21–7.15 (m, 2H), 3.21 (t, 2H, *J* = 7.4 Hz), 2.56 (t, 2H, *J* = 7.0 Hz), 2.05–1.99 (m, 2H), 1.80–1.74 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.0, 157.3, 153.2, 150.1, 146.2, 137.1, 135.7, 133.2, 129.1, 128.5, 126.8, 126.3, 124.1, 123.6, 120.4, 95.2, 78.0, 38.5, 27.9, 23.0, 19.3; IR (film) ν_{max} 3055, 2931, 2865, 2232, 1699, 1602, 1575, 1558, 1505, 1471, 1429, 1385, 1283, 1152, 1118, 1083, 1065, 1032, 990, 962, 784, 756 cm^{−1}; ESI–TOF *m/z* 365.1053 (C₂₁H₁₇ClN₂O₄ + H⁺ requires 365.1051).



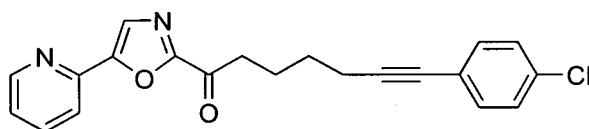
- 1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-chlorophenyl)heptane (5gg).** The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-chlorophenyl)hept-6-yne (**4gg**) following general procedure G. PTLC (SiO₂, 43% EtOAc–hexanes) afforded **5gg** (11 mg, 0.030 mmol, 78%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.7, 1.5 Hz), 7.34–7.31 (m, 2H), 7.22–7.15 (m, 2H), 7.12 (td, 1H, *J* = 7.3, 1.8 Hz), 3.12 (t, 2H, *J* = 7.4 Hz), 2.73 (t, 2H, *J* = 7.8 Hz), 1.83–1.77 (m, 2H), 1.67–1.61 (m, 2H), 1.50–1.40 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.5, 157.3, 153.2, 150.1, 146.3, 140.2, 137.1, 133.8, 130.3, 129.4, 127.1, 126.8, 126.6, 124.1, 120.4, 39.1, 33.5, 29.5, 29.1, 28.9, 23.9; IR (film) ν_{max} 3056, 2929, 2857, 1694, 1602, 1575, 1505, 1470, 1425, 1382, 1283, 1151, 1118, 1081, 1050, 989, 962, 935, 784, 752 cm^{−1}; ESI–TOF *m/z* 369.1366 (C₂₁H₂₁ClN₂O₂ + H⁺ requires 369.1364).



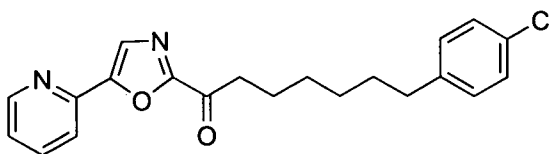
- 1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-chlorophenyl)hept-6-yne (4hh).** The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and 1-chloro-3-iodobenzene following general procedure E. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **4hh** (24 mg, 0.066 mmol, 56%) as a yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.7, 1.8 Hz), 7.38 (m, 1H), 7.34–7.31 (m, 1H), 7.27–7.18 (m, 3H), 3.20 (t, 2H, *J* = 7.4 Hz), 2.49 (t, 2H, *J* = 7.0 Hz), 2.00–1.95 (m, 2H), 1.77–1.71 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 187.9, 157.2, 153.3, 150.1, 146.2, 137.1, 133.9, 131.4, 129.6, 129.3, 127.8, 126.8, 125.5, 124.1, 120.3, 90.9, 79.8, 38.5, 27.8, 23.1, 19.1; IR (film) ν_{max} 3061, 2932, 2865, 2230, 1703, 1592, 1575, 1558, 1505, 1471, 1426, 1385, 1283, 1243, 1152, 1081, 1065, 1023, 990, 962, 930, 880, 784, 740, 683 cm^{−1}; ESI–TOF *m/z* 365.1058 (C₂₁H₁₇ClN₂O₄ + H⁺ requires 365.1051).



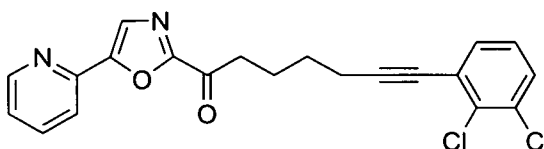
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-chlorophenyl)heptane (5hh). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-chlorophenyl)hept-6-yne (**4hh**) following general procedure G. PTLC (SiO₂, 40% EtOAc–hexanes) afforded **5hh** (10 mg, 0.027 mmol, 67%) as a white solid: ¹H NMR (CDCl₃, 600 MHz) δ 8.68–8.66 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.8, 1.4 Hz), 7.34–7.31 (m, 1H), 7.21–7.14 (m, 3H), 7.04 (d, 1H, *J* = 7.5 Hz), 3.11 (t, 2H, *J* = 7.4 Hz), 2.59 (t, 2H, *J* = 7.4 Hz), 1.81–1.76 (m, 2H), 1.65–1.60 (m, 2H), 1.46–1.36 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.4, 157.3, 153.2, 150.1, 146.3, 144.7, 137.1, 133.9, 129.5, 128.5, 126.8, 126.6, 124.1, 120.4, 39.0, 35.5, 31.0, 28.9, 28.8, 23.8; IR (film) ν_{max} 2930, 2856, 1698, 1601, 1575, 1505, 1470, 1426, 1385, 1285, 1081, 1035, 990, 962, 935, 783, 741, 696 cm^{−1}; ESI-TOF *m/z* 369.1363 (C₂₁H₂₁ClN₂O₂ + H⁺ requires 369.1364).



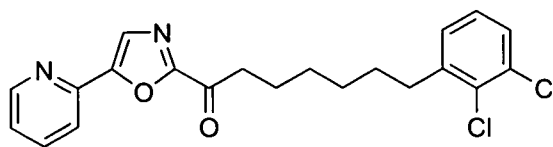
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-chlorophenyl)hept-6-yne (4ii). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and 1-chloro-4-iodobenzene following general procedure E. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **4ii** (21 mg, 0.058 mmol, 50%) as a yellow solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.68 (app d, 1H, *J* = 4.7 Hz), 7.88–7.86 (m, 2H), 7.81 (td, 1H, *J* = 7.7, 1.7 Hz), 7.34–7.30 (m, 3H), 7.23 (d, 2H, *J* = 12.3 Hz), 3.20 (t, 2H, *J* = 7.4 Hz), 2.48 (t, 2H, *J* = 7.0 Hz), 2.01–1.93 (m, 2H), 1.77–1.69 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.0, 157.2, 153.3, 150.1, 146.2, 137.1, 133.4, 132.7, 128.4, 126.8, 124.1, 122.3, 120.3, 90.6, 80.0, 38.5, 27.9, 23.1, 19.2; IR (film) ν_{max} 3097, 2941, 2350, 1698, 1604, 1488, 1471, 1426, 1285, 1243, 1193, 1088, 1025, 1012, 959, 933, 824, 785 cm^{−1}; ESI-TOF *m/z* 365.1049 (C₂₁H₁₇ClN₂O₄ + H⁺ requires 365.1051).



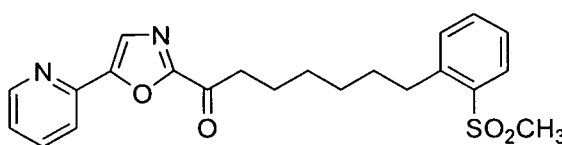
- 1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-chlorophenyl)heptane (5ii).** The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-chlorophenyl)hept-6-yne (**4ii**) following general procedure G. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **5ii** (6 mg, 0.016 mmol, 60%) as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.69–8.67 (m, 1H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.8, 1.8 Hz), 7.34–7.31 (m, 2H), 7.24 (d, 2H, *J* = 8.2 Hz), 7.09 (d, 2H, *J* = 8.2 Hz), 3.11 (t, 2H, *J* = 7.3 Hz), 2.58 (t, 2H, *J* = 7.7 Hz), 1.82–1.75 (m, 2H), 1.65–1.57 (m, 2H), 1.47–1.35 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.4, 157.3, 153.3, 150.1, 146.3, 141.0, 137.1, 131.2, 129.7, 128.3, 126.8, 124.1, 120.4, 39.0, 35.1, 31.1, 28.9, 28.8, 23.8; IR (film) ν_{max} 2933, 2858, 1698, 1602, 1574, 1505, 1470, 1426, 1094, 817, 787, 741, 693 cm⁻¹; ESI–TOF *m/z* 369.1367 (C₂₁H₂₁ClN₂O₂ + H⁺ requires 369.1364).



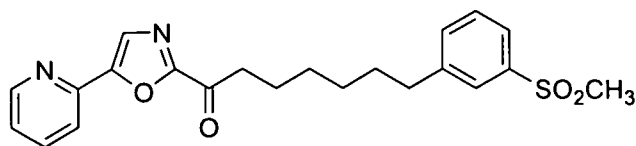
- 1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2,3-dichlorophenyl)hept-6-yne (4jj).** The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-hept-6-yne (**3b** (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, *48*, 1849–1856)) and 1,2-dichloro-3-iodobenzene following general procedure E. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **4jj** (59 mg, 0.148 mmol, 63%) as a yellow solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.67 (app d, 1H, *J* = 4.4 Hz), 7.88–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.8, 1.8 Hz), 7.36–7.31 (m, 3H), 7.10 (t, 1H, *J* = 7.9 Hz), 3.21 (t, 2H, *J* = 7.3 Hz), 2.57 (t, 2H, *J* = 7.0 Hz), 2.05–1.97 (m, 2H), 1.81–1.73 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 187.9, 157.2, 153.3, 150.1, 146.2, 137.1, 134.1, 133.0, 131.4, 129.4, 126.8, 125.7, 124.1, 120.3, 96.2, 77.8, 38.4, 27.7, 23.0, 19.6; IR (film) ν_{max} 2931, 2864, 2232, 1708, 1604, 1579, 1503, 1469, 1426, 1408, 1383, 1238, 1191, 1154, 1084, 1024, 991, 963, 913, 783, 741 cm⁻¹; ESI–TOF *m/z* 399.0668 (C₂₁H₁₆Cl₂N₂O₂ + H⁺ requires 399.0662).



1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2,3-dichlorophenyl)heptane (5jj). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2,3-dichlorophenyl)hept-6-yne (**4jj**) following general procedure G. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **5jj** (8 mg, 0.020 mmol, 36%) as a pale yellow solid: ¹H NMR (CDCl₃, 600 MHz) δ 8.68 (app d, 1H, *J* = 4.4 Hz), 7.89–7.87 (m, 2H), 7.82 (td, 1H, *J* = 7.8, 1.8 Hz), 7.34–7.29 (m, 2H), 7.12–7.10 (m, 2H), 3.13 (t, 2H, *J* = 7.4 Hz), 2.77 (t, 2H, *J* = 7.8 Hz), 1.83–1.78 (m, 2H), 1.67–1.62 (m, 2H), 1.49–1.42 (m, 4H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.4, 157.3, 153.3, 150.1, 146.3, 142.6, 137.1, 133.0, 132.1, 128.4, 128.0, 127.0, 126.8, 124.1, 120.4, 39.0, 34.5, 29.3, 29.0, 28.9, 23.9; IR (film) ν_{max} 2928, 2857, 1698, 1602, 1575, 1504, 1469, 1426, 1382, 1282, 1237, 1186, 1152, 1118, 1081, 1044, 990, 963, 936, 853, 783, 740 cm⁻¹; ESI–TOF *m/z* 403.0964 (C₂₁H₂₀Cl₂N₂O₂ + H⁺ requires 403.0975).

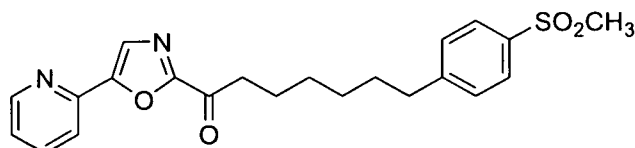


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(methylsulfonyl)phenyl)heptane (5kk). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(2-(methylthio)phenyl)heptane (**5t**) following procedure H. PTLC (SiO₂, 33% EtOAc–hexanes) afforded **5kk** (17 mg, 0.041 mmol, 83%) as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.68 (app d, 1H, *J* = 4.4 Hz), 8.02 (dd, 1H, *J* = 7.9, 1.2 Hz), 7.89–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.7, 1.8 Hz), 7.55 (td, 1H, *J* = 7.6, 1.2 Hz), 7.39–7.31 (m, 3H), 3.12 (t, 2H, *J* = 7.3 Hz), 3.08 (s, 3H), 3.02 (t, 2H, *J* = 7.9 Hz), 1.84–1.69 (m, 4H), 1.54–1.44 (m, 4H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.4, 157.3, 153.1, 150.0, 146.1, 142.6, 138.3, 137.2, 133.6, 131.6, 129.4, 126.9, 126.6, 124.2, 120.4, 44.7, 39.0, 32.9, 31.8, 29.4, 28.8, 23.7; IR (film) ν_{max} 2931, 2857, 1699, 1602, 1575, 1505, 1470, 1427, 1306, 1247, 1151, 1082, 962, 914, 785, 753 cm⁻¹; ESI–TOF *m/z* 413.1524 (C₂₂H₂₄N₂O₄S + H⁺ requires 413.1529).

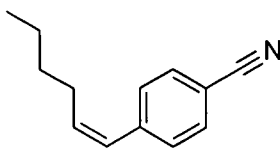


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(methylsulfonyl)phenyl)heptane (5II). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-(methylthio)phenyl)heptane (**5u**) following procedure H. PTLC (SiO₂, 50% EtOAc–
 5 hexanes) afforded **5II** (18 mg, 0.043 mmol, 64%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.69 (app d, 1H, *J* = 4.7 Hz), 7.90 (s, 1H), 7.88 (d, 1H, *J* = 8.0 Hz), 7.83 (td, 1H, *J* = 7.7, 1.8 Hz), 7.78–7.76 (m, 2H), 7.49–7.47 (m, 2H), 7.35–7.32 (m, 1H), 7.19 (d, 2H, *J* = 8.1 Hz), 7.10 (d, 2H, *J* = 8.1 Hz), 3.12 (t, 2H, *J* = 7.3 Hz), 3.07 (s, 3H), 2.71 (t, 2H, *J* = 7.7 Hz), 1.83–1.77 (m, 2H), 1.71–1.65 (m, 2H), 1.48–1.39 (m,
 10 4H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.3, 157.3, 153.0, 150.0, 146.0, 144.4, 140.4, 137.3, 133.8, 129.2, 126.9 (2C), 124.7, 124.2, 120.5, 44.5, 38.9, 35.6, 30.9, 28.8 (2C), 23.7; IR (film) ν_{max} 2930, 2857, 1699, 1602, 1575, 1558, 1505, 1470, 1455, 1428, 1300, 1251, 1144, 1085, 963, 914, 786, 758, 697 cm⁻¹; ESI–TOF *m/z* 413.1529 (C₂₂H₂₄N₂O₄S + H⁺ requires 413.1529).

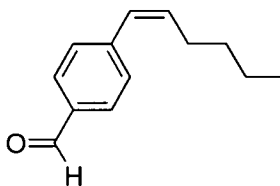
15



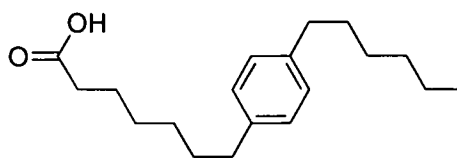
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(methylsulfonyl)phenyl)heptane (5mm). The title compound was prepared from 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-(methylthio)phenyl)heptane (**5v**) following procedure H. PTLC (SiO₂, 40% EtOAc–
 20 hexanes) afforded **5mm** (20 mg, 0.049 mmol, 68%) as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.68 (app d, 1H, *J* = 4.7 Hz), 7.89–7.86 (m, 2H), 7.84 (d, 2H, *J* = 8.2 Hz), 7.82 (td, 1H, *J* = 7.7, 1.8 Hz), 7.37 (d, 2H, *J* = 8.2 Hz), 7.35–7.31 (m, 1H), 3.12 (t, 2H, *J* = 7.3 Hz), 3.05 (s, 3H), 2.71 (t, 2H, *J* = 7.3 Hz), 1.82–1.75 (m, 2H), 1.70–1.63 (m, 2H), 1.48–1.39 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 188.3, 157.3,
 25 153.1, 150.0, 149.2, 146.1, 137.8, 137.2, 129.3, 127.4, 126.8, 124.2, 120.4, 44.5, 38.9, 35.7, 30.8, 28.8 (2C), 23.7; IR (film) ν_{max} 2930, 2856, 1699, 1651, 1600, 1575, 1505, 1470, 1427, 1304, 1148, 1090, 962, 787 cm⁻¹; ESI–TOF *m/z* 413.1516 (C₂₂H₂₄N₂O₄S + H⁺ requires 413.1529).



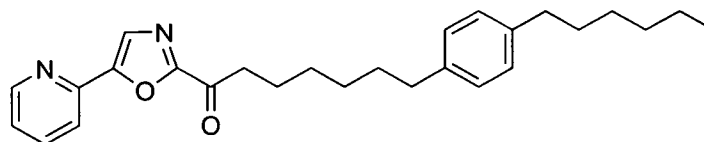
4-((Z)-Hex-1-enyl)benzonitrile (S16). A suspension of $\text{BrPh}_3\text{P}(\text{CH}_2)_4\text{CH}_3$ (4.69 g, 11.3 mmol, 1.6 equiv) in anhydrous THF (40 mL) at -78°C was treated with *n*-BuLi (2.5 M in hexanes, 4.3 mL, 10.8 mmol, 1.5 equiv) and the mixture was stirred for 5 min. The reaction mixture was allowed to warm slowly at 25°C and was then cooled to -78°C . A solution of 4-cyanobenzaldehyde (920 mg, 7.0 mmol, 1.0 equiv) in anhydrous THF (35 mL) was added dropwise over 1 h and the reaction was quenched with the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated. Chromatography (SiO₂, 0–5% EtOAc–hexanes) afforded **S16** (1.20 g, 92%) as a pale yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.60 (d, 2H, $J = 8.3$ Hz), 7.34 (d, 2H, $J = 8.0$ Hz), 6.37 (d, 1H, $J = 13.2$ Hz), 5.83–5.79 (m, 1H), 2.32–2.27 (m, 2H), 1.47–1.31 (m, 4H), 0.89 (t, 3H, $J = 7.4$ Hz).



4-((Z)-Hex-1-enyl)benzaldehyde (S17). A solution of 4-((Z)-hex-1-enyl)benzonitrile (**S16**, 625 mg, 3.38 mmol) in anhydrous toluene (20 mL) at 0°C was treated with DIBAL-H (1 M in toluene, 4.8 mL, 4.8 mmol, 1.4 equiv) and stirred for 15 min. The reaction mixture was quenched with the addition of aqueous 1 N HCl and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated. Chromatography (SiO₂, 0–5% EtOAc–hexanes) afforded **S17** (540 mg, 85%) as a pale yellow oil: ^1H NMR (CDCl_3 , 500 MHz) δ 10.0 (s, 1H), 7.85 (d, 2H, $J = 8.1$ Hz), 7.43 (d, 2H, $J = 8.1$ Hz), 6.44 (d, 1H, $J = 13.2$ Hz), 5.96–5.80 (m, 1H), 2.38–2.33 (m, 2H), 1.51–1.33 (m, 4H), 0.90 (t, 3H, $J = 7.0$ Hz).

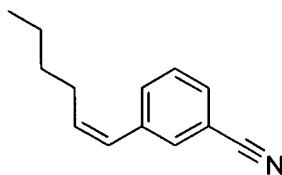


7-(4-Hexylphenyl)heptanoic acid (S18). A solution of 4-((*Z*)-hex-1-enyl)benzaldehyde (**S17**, 400 mg, 2.13 mmol) and $\text{BrPh}_3\text{P}(\text{CH}_2)_5\text{CO}_2\text{H}$ (2.40 g, 5.25 mmol, 2.4 equiv) in anhydrous THF (10 mL) at -78°C was treated with a suspension of *t*-BuOK (1.4 equiv) in anhydrous THF (8 mL). After 1 h, the reaction mixture was allowed to warm at 0°C and was stirred for 16 h. The reaction was quenched with the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated. Chromatography (SiO_2 , 25–40% EtOAc–hexanes) afforded the diene (480 mg, 1.68 mmol, 79%). The material (400 mg, 1.40 mmol) was dissolved in EtOH (15 mL) and was treated with 10% Pd/C (120 mg). The suspension was purged with H_2 and was stirred overnight at 25°C . The reaction mixture was filtered through Celite and concentrated. Chromatography (SiO_2 , 25% EtOAc–hexanes) afforded **S18** (540 mg, 2.87 mmol, 85%) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 7.17 (s, 4H), 2.66 (t, 4H, $J = 7.7$ Hz), 2.44 (t, 2H, $J = 7.3$ Hz), 1.75–1.67 (m, 6H), 1.46–1.39 (m, 12H), 0.97 (t, 3H, $J = 7.0$ Hz).

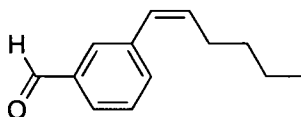


1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(4-hexylphenyl)heptane (5nn). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 7-(4-hexylphenyl)heptanoic acid (**S18**) using general procedure B. Column chromatography (SiO_2 , 2.5×7 cm, 20–50% Et_2O –hexanes gradient) afforded **5nn** (95 mg, 0.22 mmol, 61%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.68 (app d, 1H, $J = 4.1$ Hz), 7.90–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.9, 1.7$ Hz), 7.34–7.31 (m, 1H), 7.09 (s, 4H), 3.12 (t, 2H, $J = 7.2$ Hz), 2.58 (t, 2H, $J = 7.3$ Hz), 2.56 (t, 2H, $J = 7.3$ Hz), 1.83–1.75 (m, 2H), 1.67–1.56 (m, 4H), 1.45–1.39 (m, 4H), 1.35–1.29 (m, 6H), 0.88 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.5, 157.3, 153.1, 150.1, 146.2, 140.1, 139.8, 137.1, 128.2, 128.1, 126.9, 124.1, 120.4, 39.1, 35.5, 35.4, 31.7, 31.5, 31.3, 29.0 (2C), 23.9, 22.6, 14.1; IR (film) ν_{max} 2927, 2855, 1699, 1603, 1576, 1504,

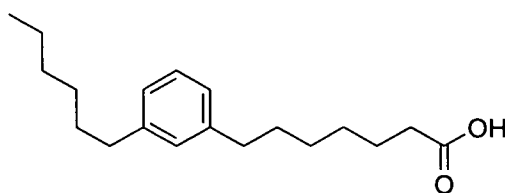
1468, 1425, 1380, 1151, 1117, 1035, 989, 963, 784 cm^{-1} ; ESI-TOF m/z 441.2510 ($\text{M} + \text{Na}^+$, $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_2$ requires 441.2512).



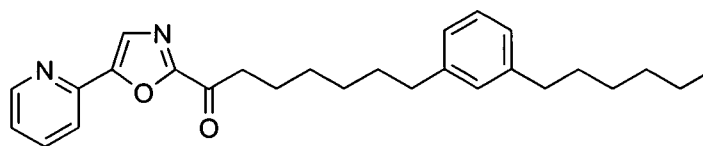
- 5 **3-((Z)-Hex-1-enyl)benzonitrile (S19).** The title compound was prepared from 3-cyanobenzaldehyde and $\text{BrPh}_3\text{P}(\text{CH}_2)_4\text{CH}_3$ following the procedure described for 4-((Z)-hex-1-enyl)benzonitrile (S16). Chromatography (SiO_2 , 0–5% EtOAc–hexanes) afforded **S19** (1.20 g, 6.48 mmol, 86%) as a pale yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.61–7.34 (m, 4H), 6.37 (d, 1H, $J = 11.7$ Hz), 5.83–5.76 (m, 1H), 2.32–2.26 (m, 2H), 1.48–1.32 (m, 4H), 0.90 (t, 3H, $J = 7.3$ Hz).
- 10



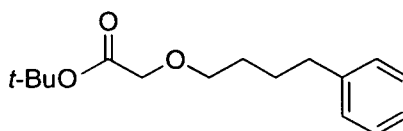
- 3-((Z)-Hex-1-enyl)benzaldehyde (S20).** The title compound was prepared from 3-((Z)-hex-1-enyl)benzonitrile (S19) following the procedure described for 4-((Z)-hex-1-enyl)benzaldehyde (S17). Chromatography (SiO_2 , 0–5% EtOAc–hexanes) afforded **S20** (270 mg, 53%) as a pale yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 10.0 (s, 1H), 7.78–7.74 (m, 2H), 7.55–7.48 (m, 2H), 6.45 (d, 1H, $J = 11.7$ Hz), 5.82–5.75 (m, 1H), 2.37–2.31 (m, 2H), 1.50–1.33 (m, 4H), 0.90 (t, 3H, $J = 7.1$ Hz).
- 15



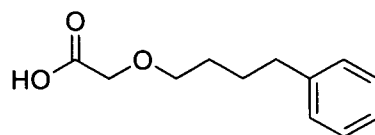
- 20 **7-(3-Hexylphenyl)heptanoic acid (S21).** The title compound was prepared from 3-((Z)-hex-1-enyl)benzaldehyde (S20) following the procedure described for 7-(4-hexylphenyl)heptanoic acid (S18). Chromatography (SiO_2 , 0–5% EtOAc–hexanes) afforded **S21** (300 mg, 78%) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 7.19 (t, 1H, $J = 7.6$ Hz), 7.01–6.98 (m, 3H), 7.01–6.98 (m, 3H), 2.58 (t, 4H, $J = 7.7$ Hz), 2.37 (t, 2H, $J = 7.4$ Hz), 1.66–1.59 (m, 6H), 1.39–1.31 (m, 12H), 0.89 (t, 3H, $J = 7.0$ Hz).
- 25



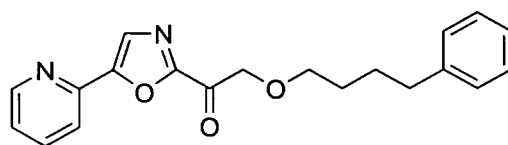
1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-(3-hexylphenyl)heptane (500). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-(3-hexylphenyl)heptanoic acid (S21) using general procedure B. Column chromatography (SiO₂, 2.5 × 7 cm, 20–50% Et₂O–hexanes gradient) afforded **500** (85 mg, 0.20 mmol, 51%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.68 (app d, *J* = 4.4 Hz, 1H), 7.90 (s, 1H), 7.88 (d, 1H, *J* = 8.0 Hz), 7.82 (td, 1H, *J* = 7.8, 1.8 Hz), 7.34–7.31 (m, 1H), 7.18 (t, 1H, *J* = 7.9 Hz), 7.00–6.96 (m, 3H), 3.12 (t, 2H, *J* = 7.3 Hz), 2.60–2.56 (m, 4H), 1.82–1.76 (m, 2H), 1.67–1.57 (m, 4H), 1.47–1.30 (m, 10H), 0.88 (t, 3H, *J* = 6.4 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 188.5, 157.4, 153.1, 150.0, 146.2, 142.9, 142.6, 137.2, 128.5, 128.1, 127.0, 125.7, 125.6, 124.1, 120.4, 39.1, 36.0, 35.9, 31.7, 31.5, 31.3, 29.1, 29.0, 23.9, 22.6, 14.1; IR (film) ν_{max} 2928, 2855, 1699, 1673, 1604, 1576, 1505, 1468, 1425, 1361, 1261, 1082, 1023, 785 cm⁻¹; ESI-TOF *m/z* 419.2695 (M + H⁺, C₂₇H₃₄N₂O₂ requires 419.2693).



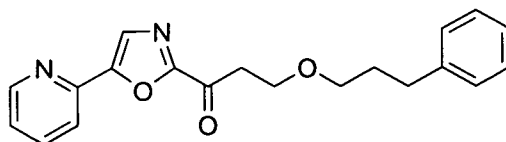
tert-Butyl 2-(4-phenylbutoxy)acetate (S52). A solution of 1-phenyl-4-butanol (900 mg, 6.0 mmol) in toluene (25 mL) was treated with *tert*-butyl 2-bromoacetate (2.7 mL, 18.3 mmol), *tert*-butylammonium bromide (100 mg, 0.27 mmol) and aqueous 50% NaOH (10 mL). After stirring at 25 °C for 30 h, the reaction mixture was quenched with aqueous 1 N HCl and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. Column chromatography (SiO₂, 4 × 6 cm, 0–2% EtOAc–hexanes gradient) afforded **S52** (1.50 g, 5.68 mmol, 95%) as a yellow oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.29–7.26 (m, 2H), 7.20–7.16 (m, 3H), 3.95 (s, 2H), 3.54 (t, 2H, *J* = 6.3 Hz), 2.65 (t, 2H, *J* = 7.4 Hz), 1.75–1.65 (m, 4H), 1.49 (s, 3H).



2-(4-Phenylbutoxy)acetic acid (S53). A solution of *tert*-butyl 2-(4-phenylbutoxy)acetate (**S52**, 1.40 g, 5.30 mmol) in anhydrous CH₂Cl₂ (40 mL) was treated with TFA (18 mL) and was stirred at 25 °C for 3 h. The reaction mixture was concentrated, treated with aqueous 1 N HCl and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. Column chromatography (SiO₂, 4 × 5 cm, 30% EtOAc–hexanes) afforded **S53** (1.01 g, 4.86 mmol, 92%) as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 7.30–7.26 (m, 2H), 7.19–7.16 (m, 3H), 4.12 (s, 2H), 3.58 (t, 2H, *J* = 6.2 Hz), 2.65 (t, 2H, *J* = 7.4 Hz), 1.75–1.66 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 175.6, 142.1, 128.3, 128.2, 125.7, 71.8, 67.6, 35.5, 28.9, 27.6.

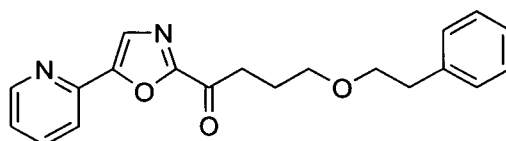


2-(4-Phenylbutoxy)-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (12a). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 2-(4-phenylbutoxy)acetic acid (**S53**) following general procedure B. PTLC (SiO₂, 50% EtOAc–hexanes) afforded **12a** (4 mg, 0.012 mmol, 1.2%) as a pale yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 8.68 (d, 1H, *J* = 4.4 Hz), 7.89–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.8, 1.8 Hz), 7.34–7.31 (m, 2H), 7.22–7.18 (m, 5H), 4.90 (s, 2H), 3.65 (t, 2H, *J* = 6.3 Hz), 2.66 (t, 2H, *J* = 7.7 Hz), 1.77–1.69 (m, 4H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.4, 157.3, 153.3, 150.1, 146.1, 137.2, 128.4, 128.3, 128.2, 126.8, 125.7, 124.3, 120.5, 73.1, 72.0, 35.6, 29.1, 27.8; IR (film) ν_{max} 2925, 2859, 1712, 1603, 1573, 1502, 1469, 1426, 1282, 1150, 1020, 961, 784, 743, 700 cm⁻¹; ESI–TOF *m/z* 337.1550 (C₂₀H₂₀N₂O₃ + H⁺ requires 337.1547).



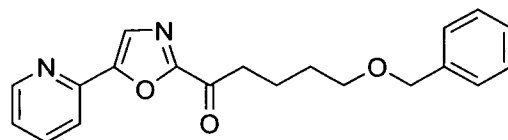
3-(3-Phenylpropoxy)-1-(5-(pyridin-2-yl)oxazol-2-yl)propan-1-one (12e). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 3-(3-phenylpropoxy)propanoic acid (Shaikh, A. A.; Thaker, K. *Indian Journal of*

Chemistry **1967**, 5, 585–586) using general procedure B. Column chromatography (SiO₂, 0–2% MeOH–CH₂Cl₂) followed by PTLC (1% MeOH–CH₂Cl₂) afforded **12e** (65 mg, 17%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.57 (app d, *J* = 4.8 Hz, 1H), 7.81 (s, 1H), 7.78–7.68 (m, 2H), 7.24–7.05 (m, 6H), 3.81 (t, *J* = 6.4 Hz, 2H),
 5 3.38 (t, *J* = 6.4 Hz, 2H), 3.30 (t, *J* = 6.4 Hz, 2H), 2.55 (t, *J* = 6.6 Hz, 2H), 1.78 (quint, *J* = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 186.2, 157.2, 153.3, 150.0, 146.1, 141.8, 137.0, 128.4, 128.2, 126.9, 125.6, 124.1, 120.3, 70.1, 65.4, 39.4, 32.1, 31.0; ESI–TOF *m/z* 337.1540 (C₂₀H₂₀N₂O₃ + H⁺ requires 337.1547).

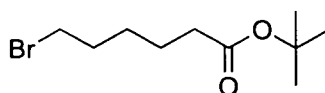


10 **4-Phenethoxy-1-(5-(pyridin-2-yl)oxazol-2-yl)butan-1-one (12g).** 4-Bromobutanoic acid (9.76 g, 58.4 mmol) and concentrated H₂SO₄ (3 drops) were dissolved in CH₂Cl₂ (20 mL) and the mixture was cooled to –78 °C. Isobutylene was bubbled into the solution until the volume doubled. The reaction mixture was stirred for 3 days at room
 15 temperature before it was cooled to –78 °C and N₂ was bubbled into the reaction mixture to remove excess isobutylene. The reaction mixture was diluted with CH₂Cl₂ and washed with aqueous 2 N KOH and saturated aqueous NaCl, and concentrated to yield *tert*-butyl 4-bromobutanoate (4.13 g, 32%) which required no further
 20 purification. *tert*-Butyl 4-bromobutanoate (2.29 g, 10.2 mmol) was dissolved in acetone (40 mL) and NaI (3.08 g, 20.5 mmol) was added. The reaction mixture was warmed to reflux for 3 h under an Ar atmosphere. The acetone was removed *in vacuo* and the resulting residue was dissolved in EtOAc. The solution was washed with saturated aqueous NaCl, dried over Na₂SO₄ and concentrated to yield *tert*-butyl 4-iodobutanoate (2.29 g, 83%) which required no further purification. To a solution of
 25 *tert*-butyl 4-iodobutanoate (1.30 g, 4.82 mmol) and phenethyl alcohol (2.94 g, 24.1 mmol) in benzene (10 mL) was added aqueous 50% NaOH (6 mL) and Bu₄HSO₄ (1.64 g, 4.82 mmol). The reaction mixture was stirred vigorously at room temperature for 3 h. The reaction mixture was diluted with ether and water. The aqueous layer was extracted with ether and the combined organic layers were washed with saturated
 30 aqueous NaCl, dried over Na₂SO₄ and concentrated to yield the crude ester. Column chromatography (20% EtOAc–hexanes) afforded *tert*-butyl 4-phenethoxybutanoate (332 mg, 26%). *tert*-Butyl 4-phenethoxybutanoate (332 mg, 1.26 mmol) was

dissolved in TFA (5 mL) and the reaction mixture was stirred at room temperature for 45 min. The solution was concentrated and the resulting residue was dissolved in ether and washed with aqueous 2 N KOH. The aqueous layer was acidified with concentrated HCl and extracted with ether. The combined organic layers were washed with saturated aqueous NaCl, dried over Na₂SO₄ and concentrated to yield the crude acid. Column chromatography (SiO₂, 10% EtOAc–hexanes) afforded 4-phenethoxybutanoic acid (210 mg, 80%). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 4-phenethoxybutanoic acid using general procedure B. PTLC (1% MeOH–CH₂Cl₂) afforded **12g** (40 mg, 23%) as colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 8.67 (app d, *J* = 4.8 Hz, 1H), 7.89 (s, 1H), 7.88–7.78 (m, 2H), 7.33–7.16 (m, 6H), 3.60 (t, *J* = 7.2 Hz, 2H), 3.54 (t, *J* = 6.0 Hz, 2H), 3.19 (t, *J* = 7.2 Hz), 2.82 (t, *J* = 7.2 Hz, 2H), 2.07 (quint, *J* = 6.4 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 188.0, 157.4, 153.1, 150.1, 146.3, 138.9, 137.0, 128.8, 128.2, 126.8, 126.1, 124.0, 120.3, 71.7, 69.6, 36.2, 36.0, 24.2; ESI–TOF *m/z* 337.1542 (C₂₀H₂₀N₂O₃ + H⁺ requires 337.1547).

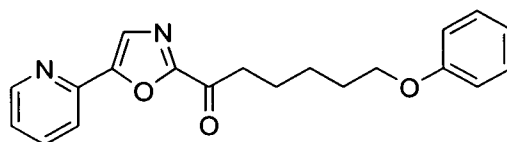


5-(Benzyloxy)-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (12i). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 5-(benzyloxy)pentanoic acid (Lerner, L. L.; Neeland, E. G.; et al. *Can. J. Chem.* **1992**, *70*, 1427–1445) using general procedure B. Column chromatography (SiO₂, 3 × 7 cm, 10–50% EtOAc–hexanes gradient) followed by PTLC (50% EtOAc–hexanes) afforded **12i** (67 mg, 19%) as a pale white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.66 (app d, *J* = 4.4 Hz, 1H), 7.87 (s, 1H), 7.86–7.76 (m, 2H), 7.34–7.23 (m, 6H), 4.50 (s, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 3.15 (t, *J* = 7.6 Hz, 2H), 1.94–1.86 (m, 2H), 1.76–1.71 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 188.1, 157.2, 153.1, 150.0, 146.2, 138.4, 137.0, 128.3, 127.5, 127.4, 126.8, 124.0, 120.3, 72.8, 69.8, 38.7, 29.0, 20.6; ESI–TOF *m/z* 337.1540 (C₂₀H₂₀N₂O₃ + H⁺ requires 337.1547).



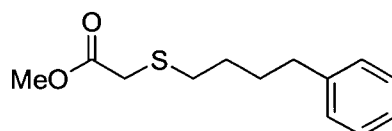
tert-Butyl 6-bromohexanoate (S54). 6-Bromohexanoic acid (6.0 g, 0.03 mmol) and concentrated H₂SO₄ (1 drop) was dissolved in a mixture of CHCl₃:1,4-dioxane (3:1,

30 mL) and the mixture was cooled to $-78\text{ }^{\circ}\text{C}$. Isobutylene was bubbled into the solution until the volume doubled. The reaction mixture was stirred for 30 days at room temperature before it was cooled to $-78\text{ }^{\circ}\text{C}$ and N_2 was bubbled into the reaction mixture to remove excess isobutylene. The reaction mixture was diluted with CH_2Cl_2 and washed with aqueous 2 N KOH and saturated aqueous NaCl, and concentrated to yield **S54** (5.2 g, 68%) which required no further purification: ^1H NMR (CDCl_3 , 500 MHz) δ 3.41 (t, 2H, $J = 6.6\text{ Hz}$), 2.23 (t, 2H, $J = 7.3\text{ Hz}$), 1.90–1.85 (m, 2H), 1.65–1.59 (m, 2H), 1.50–1.45 (m, 11H).

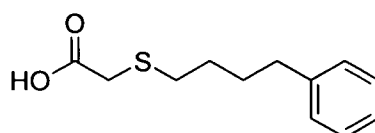


6-Phenoxy-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (12n). *tert*-Butyl 6-bromohexanoate (**S54**, 1.03 g, 4.09 mmol) was dissolved in acetone (30 mL) and NaI (1.23 g, 8.19 mmol) was added. The reaction mixture was warmed at reflux for 3 h under an Ar atmosphere. The acetone was removed *in vacuo* and the resulting residue was dissolved in EtOAc. The solution was washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated to yield *tert*-butyl 6-iodohexanoate (1.16 g, 94%) which required no further purification. *tert*-Butyl 6-iodohexanoate (1.16 g, 3.86 mmol) and phenol (726 mg, 7.72 mmol) were dissolved in DMF (20 mL) and K_2CO_3 (2.67 g, 19.3 mmol) was added. The reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the resulting residue was dissolved in ether. The solution was washed with aqueous 2 N KOH and saturated aqueous NaCl, dried over Na_2SO_4 and concentrated to yield *tert*-butyl 6-phenoxyhexanoate (953 mg, 93%) as a light yellow crystalline solid that required no further purification. *tert*-Butyl 6-phenoxyhexanoate (871 mg, 3.30 mmol) was dissolved in TFA (10 mL) and the reaction mixture was stirred at room temperature for 45 min. The solution was concentrated and the resulting residue was dissolved in ether and washed with aqueous 2 N KOH. The aqueous layer was acidified with concentrated HCl and extracted with ether. The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated to yield the crude acid. Column chromatography (SiO_2 , 10–100% EtOAc–hexanes) afforded 6-phenoxyhexanoic acid (634 mg, 92%). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 6-phenoxyhexanoic acid using general procedure B. Column

chromatography (SiO₂, 10–50% EtOAc–hexanes gradient) followed by PTLC (1% MeOH–CH₂Cl₂) afforded **12n** (93 mg, 27%) as colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 8.57 (app d, *J* = 4.8 Hz, 1H), 7.79 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.71 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.23–7.16 (m, 3H), 6.85–6.79 (m, 3H), 3.88 (t, *J* = 6.4 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 1.81–1.72 (m, 4H), 1.54–1.47 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 188.1, 158.9, 157.2, 153.2, 150.0, 146.1, 137.00, 129.3, 126.8, 124.0, 120.4, 120.3, 114.3, 67.3, 38.9, 28.9, 25.6, 23.6; ESI–TOF *m/z* 337.1540 (C₂₀H₂₀N₂O₃ + H⁺ requires 337.1547).

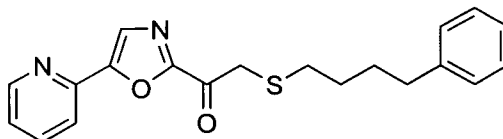


Methyl 2-(4-phenylbutylthio)acetate (S55). A solution of 1-phenyl-4-butanol (1.05 g, 7.0 mmol) in anhydrous CH₂Cl₂ (20 mL) was treated with CBr₄ (2.55 g, 7.6 mmol) and was stirred for 5 min at 25 °C. PPh₃ (2.02 g, 7.7 mmol) in anhydrous CH₂Cl₂ (6 mL) was added dropwise and was stirred for 1 h at 25 °C. The reaction mixture was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. Column chromatography (SiO₂, 5.5 × 9 cm, 3% EtOAc–hexanes) afforded 1-phenyl-4-bromobutane (1.41 g, 6.65 mmol, 95%) as a pale yellow oil. A solution of 1-phenyl-4-bromobutane (1.30 g, 6.13 mmol) in a mixture of acetone/DMSO (4/1, 20 mL) was treated with K₂CO₃ (2.57 g, 18.6 mmol) and methyl thioglycolate (0.66 mL, 7.4 mmol). After stirring for 30 h at 25 °C, the reaction mixture was quenched with an aqueous 1 N HCl solution and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. Column chromatography (SiO₂, 4 × 10 cm, 25% EtOAc–hexanes) afforded **S55** (1.31 g, 5.50 mmol, 90%) as a yellow oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.37–7.34 (m, 2H), 7.28–7.24 (m, 3H), 3.81 (s, 3H), 3.29 (s, 2H), 2.70–2.75 (m, 4H), 1.85–1.69 (m, 4H).

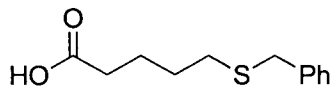


2-(4-Phenylbutylthio)acetic acid (S56). A solution of methyl 2-(4-phenylbutylthio)acetate (**S55**, 715 mg, 3.0 mmol) in a mixture of THF/MeOH (1/1, 6 mL) was treated with aqueous 1 N NaOH (2 mL) and was stirred overnight at 25 °C.

The reaction mixture was concentrated, treated with aqueous 1 N HCl and extracted with CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to afford **S56** (630 mg, 2.81 mmol, 94%) as a pale yellow oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.30–7.28 (m, 2H), 7.21–7.18 (m, 3H), 3.24 (s, 2H), 2.70 (t, 2H, *J* = 7.7 Hz), 1.78–1.65 (m, 4H).

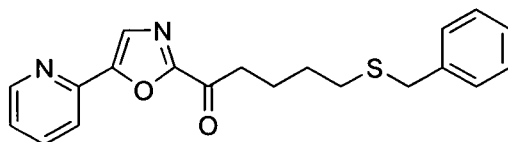


2-(4-Phenylbutylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (12b). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 2-(4-phenylbutylthio)acetic acid (**S56**) using general procedure B. PTLC (SiO₂, 40% EtOAc–hexanes) afforded **12b** (10 mg, 0.028 mmol, 6%) as a tan oil: ¹H NMR (CDCl₃, 500 MHz) δ 8.73 (d, 1H, *J* = 3.7 Hz), 8.34 (d, 1H, *J* = 9.2 Hz), 7.85–7.81 (m, 1H), 7.37–7.34 (m, 1H), 7.19–7.10 (m, 4H), 4.82 (s, 2H), 3.29 (t, 2H, *J* = 8.8 Hz), 2.60 (t, 2H, *J* = 8.8 Hz), 1.76–1.62 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 169.7, 159.2, 152.8, 150.2, 149.8, 141.9, 136.4, 128.3 (2C), 127.8, 125.8, 124.8, 124.6, 47.9, 35.2, 31.6, 30.1, 29.8; ESI–TOF *m/z* 353.1322 (C₂₀H₂₀N₂O₂S + H⁺ requires 353.1318).

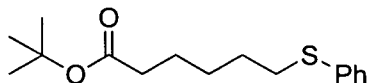


5-(Benzylthio)pentanoic acid (S57). A solution of α-mercaptotoluene (9.3 g, 75 mmol) and 5-bromovaleric acid (4.5 g, 24.8 mmol) in 30 mL of absolute EtOH was treated with a 4 N aqueous solution of NaOH (30 mL) and was warmed at reflux for 44 h. The mixture was concentrated, treated with 15 mL of aqueous 4 N NaOH and 50 mL of aqueous 1 N K₃FeCN₆. After stirring for 30 min at 25 °C, the mixture was extracted with Et₂O. The aqueous solution was treated with aqueous 6 N HCl and stirred for 10 min. The precipitate was collected by filtration, washed with H₂O and dried. The solid was recrystallized in hexane to give **S57** as white crystals (1.72 g, 7.7 mmol). The mother liquor and washings were concentrated and column chromatography (SiO₂, 4.5 × 10 cm, 10–25% EtOAc–hexanes gradient) afforded additional amounts of **S57** (1.17 g, 5.2 mmol, 52% combined yields) as a pale yellow solid: ¹H NMR (CDCl₃, 400 MHz) δ 7.32–7.30 (m, 4H), 7.26–7.23 (m, 1H), 3.71 (s, 2H), 2.43 (t, 2H, *J* = 7.3 Hz), 2.34 (t, 2H, *J* = 7.3 Hz), 1.74–1.57 (m, 4H); ¹³C NMR

(CDCl₃, 100 MHz) δ 179.8, 138.4, 128.8 (2C), 128.4 (2C), 126.9, 36.2, 33.5, 30.7, 28.4, 23.7.

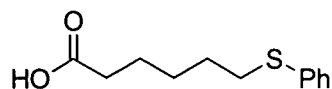


- 5 **5-(Benzylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (12k).** The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 5-(benzylthio)pentanoic acid (**S57**) using general procedure B. Column chromatography (SiO₂, 3.5 × 8 cm, 25% EtOAc–hexanes) followed by PTLC (25% acetone–petroleum ether) afforded **12k** (62 mg, 0.18 mmol, 9%) as a pale yellow solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.68 (app d, 1H, *J* = 4.4 Hz), 7.89–7.86 (m, 2H), 7.89–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.7, 1.8 Hz), 7.34–7.30 (m, 5H), 7.25–7.22 (m, 1H), 3.72 (s, 2H), 3.11 (t, 2H, *J* = 7.3 Hz), 2.47 (t, 2H, *J* = 7.3 Hz), 1.89–1.81 (m, 2H), 1.71–1.64 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 187.8, 157.1, 153.1, 150.0, 146.1, 138.3, 137.0, 128.7 (2C), 128.3 (2C), 126.8, 126.7, 124.0, 120.3, 38.4, 36.1, 30.7, 28.4, 22.9; IR (film) $\nu_{\max}$ 3059, 3027, 2925, 2856, 1791, 1703, 1694, 1602, 1575, 1504, 1469, 1454, 1425, 1383, 1283, 1238, 1152, 1118, 1072, 1018, 990, 962, 851, 784, 702 cm⁻¹; ESI–TOF *m/z* 353.1319 (C₂₀H₂₀N₂O₂S + H⁺ requires 353.1318).

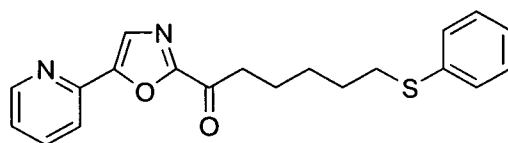


- 20 **tert-Butyl 6-(phenylthio)hexanoate (S58).** A solution of thiophenol (700 μ L, 6.8 mmol) in anhydrous benzene (20 mL) was treated with DBU (920 μ L, 6.2 mmol). After 5 min, *tert*-butyl 6-bromohexanoate (**S54**, 1.5 g, 6.0 mmol) was added and the reaction mixture was stirred overnight at 25 °C. The suspension was filtered through Celite and concentrated. The crude material was washed with aqueous 2 N KOH and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered and concentrated. Column chromatography (SiO₂, 10 × 4.5 cm, 5% EtOAc–hexanes) afforded **S58** (1.62 g, 5.8 mmol, 96%) as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 7.34–7.26 (m, 4H), 7.19–7.14 (m, 1H), 2.92 (t, 2H, *J* = 7.3 Hz), 2.21 (t, 2H, *J* = 7.5 Hz), 1.71–1.57 (m, 4H), 1.50–1.45 (m, 2H), 1.44 (s, 9H).

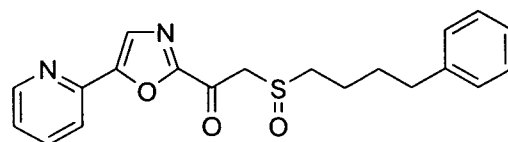
30



6-(Phenylthio)hexanoic acid (S59). A solution of *tert*-butyl 6-(phenylthio)hexanoate (S58, 1.16 g, 4.1 mmol) in 3 mL of anhydrous CH₂Cl₂ was treated with TFA (2 mL). After stirring for 2 h at 25 °C, the reaction mixture was treated with a saturated aqueous NaCl. The organic layer was extracted with CH₂Cl₂, dried over Na₂SO₄, filtered and concentrated to afford S59 (870 mg, 3.9 mmol, 94%) which required no further purification: ¹H NMR (CDCl₃, 400 MHz) δ 7.34–7.28 (m, 4H), 7.20–7.18 (m, 1H), 2.93 (t, 2H, *J* = 7.2 Hz), 2.37 (t, 2H, *J* = 7.4 Hz), 1.72–1.62 (m, 4H), 1.54–1.47 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 179.8, 136.6, 129.0 (2C), 128.8 (2C), 125.8, 33.8, 33.4, 28.7, 28.1, 24.1.

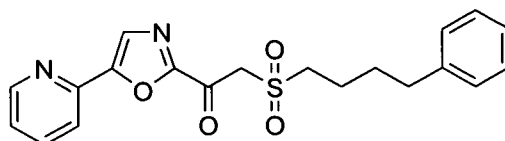


6-(Phenylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (12p). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 6-(phenylthio)hexanoic acid (S59) using general procedure B. Column chromatography (SiO₂, 4.5 × 9 cm, 15–20% EtOAc–hexanes gradient) afforded 12p (182 mg, 0.52 mmol, 22%) as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.68–8.66 (m, 1H), 7.88–7.86 (m, 2H), 7.82 (td, 1H, *J* = 7.7, 1.8 Hz), 7.34–7.25 (m, 5H), 7.19–7.14 (m, 1H), 3.12 (t, 2H, *J* = 7.3 Hz), 2.94 (t, 2H, *J* = 7.2 Hz), 1.85–1.77 (m, 2H), 1.76–1.68 (m, 2H), 1.59–1.51 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 188.1, 157.2, 153.3, 150.1, 146.2, 137.1, 136.6, 128.9 (2C), 128.8 (2C), 126.8, 125.7, 124.1, 120.3, 38.8, 33.2, 28.8, 28.2, 23.4; IR (film) ν_{max} 3055, 2931, 2858, 1699, 1602, 1575, 1504, 1480, 1425, 1382, 1283, 1235, 1152, 1118, 1085, 1025, 990, 962, 934, 784, 739, 691; ESI–TOF *m/z* 353.1321 (C₂₀H₂₀N₂O₂S + H⁺ requires 353.1318).



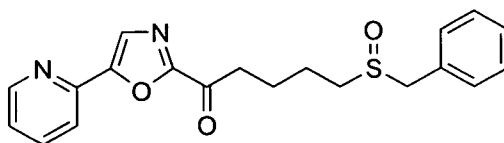
2-(4-Phenylbutylsulfinyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (12c). Oxidation of 2-(4-phenylbutylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (12b) with *m*-CPBA (1.0 equiv) using general procedure M provided 2-(4-phenylbutylsulfonyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (12c, 3 mg, 25%) and 12d (4 mg, 34%) as a white

solid: ^1H NMR (CDCl_3 , 600 MHz) δ 8.68 (app d, $J = 4.2$ Hz, 1H), 7.95 (s, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 7.84 (dt, $J = 7.5$, 1.2 Hz, 1H), 7.35 (app dd, $J = 6.6$, 5.4 Hz, 1H), 7.29–7.26 (m, 2H), 7.20–7.17 (m, 3H), 4.47 (q, $J = 13.2$ Hz, 2H), 3.01–2.91 (m, 2H), 2.69 (t, $J = 7.8$ Hz, 2H), 1.92–1.77 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 178.9, 157.9, 157.0, 150.2, 145.7, 141.4, 137.2, 128.4, 128.3, 127.6, 125.9, 124.5, 120.7, 59.3, 53.1, 35.3, 30.4, 22.0; ESI-TOF m/z 369.1261 ($\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{S} + \text{H}^+$ requires 369.1267).

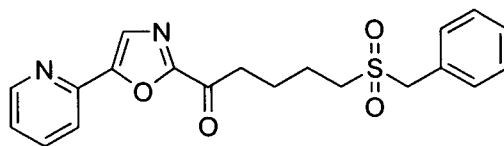


10 **2-(4-Phenylbutylsulfonyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (12d).**

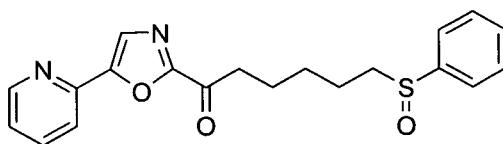
Oxidation of 2-(4-phenylbutylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (**12b**) with *m*-CPBA (1.0 equiv) using general procedure M provided **12c** (3 mg, 25%) and 2-(4-phenylbutylsulfinyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (**12d**, 4 mg, 34%) as a white solid: ^1H NMR (CDCl_3 , 600 MHz) δ 8.70 (app d, $J = 3.6$ Hz, 1H), 7.98 (s, 1H), 7.88, (d, $J = 7.8$ Hz, 1H), 7.85 (t, $J = 7.8$ Hz, 1H), 7.37 (app t, $J = 5.4$ Hz, 1H), 7.30–7.26 (m, 2H), 7.21–7.18 (m, 3H), 4.77 (s, 2H), 3.31 (t, $J = 7.8$ Hz, 2H), 2.69 (t, $J = 7.2$ Hz, 2H), 1.99–1.94 (m, 2H), 1.85–1.80 (m, 2H); ESI-TOF m/z 385.1208 ($\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S} + \text{H}^+$ requires 385.1216).



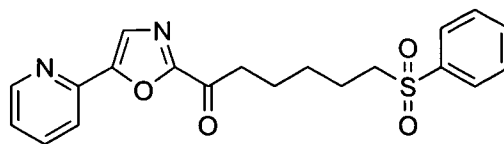
20 **5-(Benzylsulfinyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (12l).** Oxidation of 5-(benzylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (**12k**) with *m*-CPBA (1.0 equiv) using general procedure M provided 5-(Benzylsulfinyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (**12l**, 10 mg, 45%) and **12m** (10 mg, 48%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.68–8.66 (m, 1H), 7.88–7.86 (m, 2H), 7.82 (td, 1H, $J = 7.7$, 1.6 Hz), 7.41–7.28 (m, 6H), 4.05 (d, 1H, $J = 12.9$ Hz), 3.96 (d, 1H, $J = 12.9$ Hz), 3.16 (app t, 2H, $J = 6.6$ Hz), 2.63 (app t, 2H, $J = 7.0$ Hz), 1.95–1.84 (m, 4H); IR (film) ν_{max} 3057, 2922, 2852, 1704, 1694, 1603, 1575, 1505, 1470, 1455, 1426, 1386, 1284, 1153, 1119, 1074, 1028, 962, 936, 786, 739, 700 cm^{-1} ; ESI-TOF m/z 369.1268 ($\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{S} + \text{H}^+$ requires 369.1267).



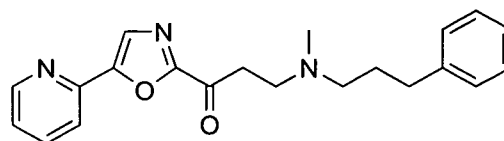
- 5-(Benzylsulfonyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (12m).** Oxidation of 5-(benzylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (**12k**) with *m*-CPBA (1.5 equiv) using the general procedure M provided **12l** (7 mg, 27%) and 5-(benzylsulfonyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (**12m**, 19 mg, 72%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.69–8.66 (m, 1H), 7.88–7.85 (m, 2H), 7.82 (td, 1H, $J = 7.7, 1.8$ Hz), 7.43–7.39 (m, 5H), 7.35–7.31 (m, 1H), 4.24 (s, 2H), 3.14 (t, 2H, $J = 6.7$ Hz), 2.89 (t, 2H, $J = 7.5$ Hz), 1.96–1.85 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 187.2, 157.0, 153.4, 150.1, 146.1, 137.1, 130.5 (2C), 129.1 (2C), 129.0, 128.0, 126.9, 124.2, 120.4, 59.5, 50.6, 38.1, 22.5, 21.3; IR (film) ν_{max} 2933, 1699, 1601, 1575, 1505, 1469, 1456, 1426, 1282, 1118, 1029, 961, 934, 784, 739, 696 cm^{-1} ; ESI-TOF m/z 385.1211 ($\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S} + \text{H}^+$ requires 385.1216).



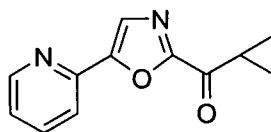
- 6-(Phenylsulfinyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (12q).** Oxidation of 6-(phenylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (**12p**) with *m*-CPBA (1.0 equiv) using general procedure M provided 6-(phenylsulfinyl)-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (**12q**, 10 mg, 26%) and **12r** (27 mg, 73%) as a pale yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 8.65 (app d, 1H, $J = 4.7$ Hz), 7.86–7.82 (m, 2H), 7.80 (td, 1H, $J = 7.7, 1.7$ Hz), 7.62–7.59 (m, 2H), 7.53–7.46 (m, 3H), 7.33–7.29 (m, 1H), 3.10 (t, 2H, $J = 7.1$ Hz), 2.81 (t, 2H, $J = 7.5$ Hz), 1.86–1.45 (m, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 187.9, 157.1, 153.3, 150.1, 146.1, 143.7, 137.1, 130.9, 129.2 (2C), 126.8, 124.1, 123.9 (2C), 120.3, 56.8, 38.6, 28.0, 23.3, 21.8; IR (film) ν_{max} 3057, 2938, 2865, 1704, 1694, 1602, 1575, 1505, 1471, 1427, 1284, 1154, 1087, 1030, 962, 933, 787, 744, 692 cm^{-1} ; ESI-TOF m/z 369.1271 ($\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{S} + \text{H}^+$ requires 369.1267).



6-(Phenylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (12r). Oxidation of 6-(phenylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (**12p**) with *m*-CPBA (1.5 equiv) using general procedure M provided **12q** (8 mg, 20%) and 6-(phenylthio)-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (**12r**, 31 mg, 79%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67–8.65 (m, 1H), 7.92–7.89 (m, 2H), 7.86–7.83 (m, 2H), 7.80 (td, 1H, $J = 7.7, 1.7$ Hz), 7.67–7.63 (m, 1H), 7.59–7.54 (m, 2H), 7.33–7.30 (m, 1H), 3.13–3.06 (m, 4H), 1.82–1.71 (m, 4H), 1.52–1.44 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 187.7, 157.1, 153.3, 150.1, 146.1, 139.0, 137.1, 133.7, 129.3 (2C), 128.0 (2C), 126.8, 124.2, 120.4, 56.0, 38.5, 27.7, 23.2, 22.5; IR (film) ν_{max} 3062, 2937, 2870, 1699, 1603, 1575, 1505, 1470, 1426, 1385, 1303, 1148, 1086, 1026, 963, 914, 786, 729, 690 cm^{-1} ; ESI-TOF m/z 385.1221 ($\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S} + \text{H}^+$ requires 385.1216).

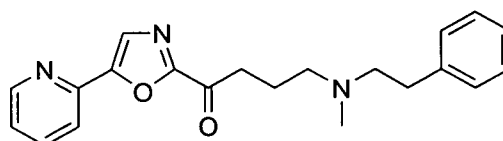


3-(Methyl(3-phenylpropyl)amino)-1-(5-(pyridin-2-yl)oxazol-2-yl)propan-1-one (12f). 1-(5-(Pyridin-2-yl)oxazol-2-yl)prop-2-en-1-one was prepared from 5-(pyridin-2-yl)oxazole (**6**) and 3-bromopropionyl chloride using general procedure B. 1-(5-(pyridin-2-yl)oxazol-2-yl)prop-2-en-1-one (34 mg, 0.17 mmol) was dissolved in anhydrous CH_2Cl_2 (0.4 mL) under Ar and *N*-methyl-3-phenylpropylamine (38 mg, 0.255 mmol) was added dropwise. After 20 min, the reaction mixture was loaded onto a PTLC plate and eluted with 3% Et_3N in EtOAc. The crude product was subjected to further PTLC (1st, 1% MeOH- CH_2Cl_2 ; 2nd, 3% Et_3N -EtOAc) to yield **12f** (4 mg, 7%) as a colorless oil: ^1H NMR (CDCl_3 , 500 MHz) δ 8.67 (ddd, $J = 5.0, 1.5, 1.0$ Hz, 1H), 7.89 (s, 1H), 7.87–7.78 (m, 2H), 7.32 (ddd, $J = 7.4, 4.8, 1.5$ Hz, 1H), 7.26–7.23 (m, 2H), 7.20–7.14 (m, 3H), 3.28 (t, $J = 7.0$ Hz, 2H), 2.94 (t, $J = 7.0$ Hz, 2H), 2.59 (t, $J = 7.5$ Hz, 2H), 2.44 (t, $J = 7.0$ Hz, 2H), 2.30 (s, 3H), 1.76–1.82 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.4, 158.2, 157.3, 150.1, 146.3, 142.2, 137.1, 128.4, 128.3, 126.9, 125.7, 124.1, 120.4, 56.8, 52.3, 41.9, 36.8, 33.5, 28.9; ESI-TOF m/z 350.1860 ($\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2 + \text{H}^+$ requires 350.1863).



Cyclopropyl(5-(pyridin-2-yl)oxazol-2-yl)methanone (14d). The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 4-bromobutyryl chloride following general procedure B. PTLC (50% hexanes–EtOAc) afforded **14d** (20 mg, 8%) as a colorless oil: ^1H NMR (CDCl_3 , 500 MHz) δ 8.67 (ddd, $J = 5.0, 1.8, 0.5$ Hz, 1H), 7.91 (s, 1H), 7.87 (app d, $J = 8.0$ Hz, 1H), 7.81 (dt, $J = 7.8, 1.5$ Hz, 1H), 7.31 (ddd, $J = 7.5, 5.0, 1.0$ Hz, 1H), 3.16–3.11 (m, 1H), 1.38–1.35 (m, 2H), 1.21–1.17 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.1, 157.9, 153.2, 150.1, 146.4, 137.1, 127.0, 124.1, 120.4, 18.3, 13.1; ESI–TOF m/z 215.0814 ($\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_2 + \text{H}^+$ requires 215.0815).

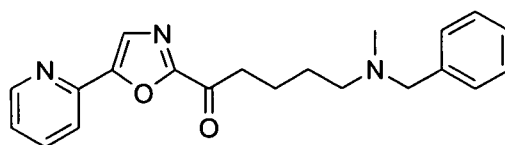
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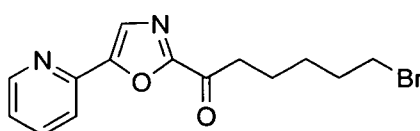
4-(Methyl(phenethyl)amino)-1-(5-(pyridin-2-yl)oxazol-2-yl)butan-1-one (12h).

Cyclopropyl ketone **14d** (24 mg, 0.112 mmol) was dissolved in anhydrous CH_2Cl_2 (0.4 mL) under Ar and *N*-methylphenethylamine (76 mg, 0.56 mmol, 5.0 equiv) was added. The mixture was cooled to 0 °C and TiCl_4 (1.0 M solution in CH_2Cl_2 , 62 μL , 0.55 equiv) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature and stirred for 4 h. The reaction mixture was diluted with CH_2Cl_2 and washed with aqueous 0.05 N NaOH and water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. Two successive PTLC purifications (1st, 3% Et_3N –EtOAc; 2nd, 50% hexanes–EtOAc) afforded **12h** (11 mg, 28%) as light yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (ddd, $J = 4.8, 1.6, 1.2$ Hz, 1H), 7.88 (s, 1H), 7.86 (dt $J = 7.6, 0.8$ Hz, 1H), 7.80 (dt, $J = 7.4, 1.6$ Hz, 1H), 7.31 (ddd, $J = 7.4, 4.8, 1.6$ Hz, 1H), 7.25–7.21 (m, 2H), 7.17–7.13 (m, 3H), 3.08 (t, $J = 6.8$ Hz, 2H), 2.68–2.61 (m, 2H), 2.58–2.47 (m, 4H), 2.21 (s, 3H), 2.06–1.99 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 187.3, 157.9, 152.9, 150.1, 146.4, 140.3, 137.1, 128.7, 128.3, 126.7, 125.9, 124.0, 120.3, 59.1, 56.5, 41.2, 33.2, 29.7; ESI–TOF m/z 350.1863 ($\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2 + \text{H}^+$ requires 350.1863).

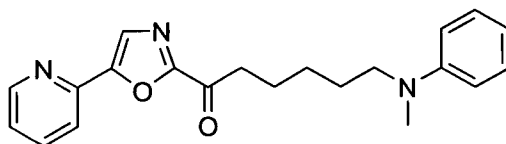
25



5-(Benzyl(methyl)amino)-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (12j). 5-Bromo-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one was prepared from 5-(2-pyridyl)-oxazole (**6**) and 5-bromopentanoyl chloride using general procedure B. Column chromatography (SiO₂, 10–70% EtOAc–hexanes afforded 5-bromo-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (339 mg, 31%) as a colorless oil. 5-Bromo-1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (32 mg, 0.104 mmol) and *N*-methyl benzylamine (11 mg, 0.104 mmol) were dissolved in 2-butanone (0.34 mL) under Ar and K₂CO₃ (43 mg, 0.311 mmol) was added. The mixture was stirred overnight at room temperature and then diluted with H₂O and extracted with EtOAc. The organic phase was dried over anhydrous Na₂SO₄ and concentrated. PTLC (3% Et₃N–EtOAc) afforded a slightly impure product which was repurified on a second plate (50% hexanes–EtOAc) to yield **12j** (16 mg, 44%): ¹H NMR (CDCl₃, 400 MHz) δ 8.67 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H), 7.88 (s, 1H), 7.86 (t, *J* = 1.2 Hz, 1H), 7.81 (dt, *J* = 7.4, 2.0 Hz, 1H), 7.26–7.20 (m, 1H), 7.34–7.27 (m, 5H) 3.48 (s, 2H), 3.13 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 2.19 (s, 3H), 2.86–2.79 (m, 2H), 1.67–1.59 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.3, 157.3, 153.2, 150.1, 146.3, 139.0, 137.1, 129.0, 128.2, 126.9, 126.8, 124.1, 120.4, 62.2, 56.8, 42.1, 38.9, 26.7, 21.7; ESI–TOF *m/z* 350.1869 (C₂₁H₂₃N₃O₂ + H⁺ requires 350.1863).

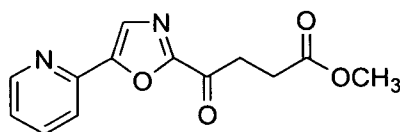


6-Bromo-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (S60). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 6-bromohexanoyl chloride using general procedure B. Column chromatography (SiO₂, 10–60% EtOAc–hexanes) afforded **S60** (824 mg, 70%) as a tan solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.67 (app d, *J* = 4.8 Hz, 1H), 7.88 (s, 1H), 7.86 (app s, 1H), 7.82 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.33 (ddd, *J* = 7.0, 4.8 Hz, 1.2 Hz, 1H), 7.43 (t, *J* = 6.8 Hz, 2H), 3.15 (t, 7.6 Hz, 2H), 1.97–1.90 (m, 2H), 1.86–1.79 (m, 2H), 1.61–1.53 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 188.0, 157.2, 153.3, 150.1, 146.2, 137.1, 126.8, 124.1, 120.3, 38.7, 33.4, 32.4, 27.6, 23.0; ESI–TOF *m/z* 323.0386 (C₁₄H₁₅BrN₂O₂ + H⁺ requires 323.0390).



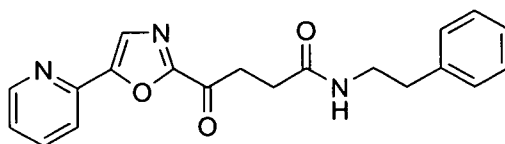
6-(Methyl(phenyl)amino)-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (12o).

Bromo-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (**S60**, 54 mg, 0.167 mmol) was added to a dry $\frac{1}{2}$ dram vial under Ar and *N*-methylaniline (53.7 mg, 0.501 mmol) was added. The neat reactants were stirred overnight before diluting the reaction with CH_2Cl_2 and loading directly onto a PTLC plate. Elution with 1% MeOH- CH_2Cl_2 afforded **12o** (30 mg, 52%) as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (ddd, $J = 4.8, 1.4, 0.8$ Hz, 1H), 8.79 (s, 1H), 8.76 (t, $J = 1.2$ Hz, 1H) 7.81 (dt, $J = 7.6, 1.6$ Hz, 1H), 7.32 (ddd, $J = 7.4, 4.8, 1.6$ Hz, 1H), 7.24–7.19 (m, 2H), 7.70–7.65 (m, 3H), 3.32 (t, $J = 7.2$ Hz, 2H), 3.13 (t, $J = 7.6$ Hz, 2H), 2.92 (s, 3H), 1.86–1.79 (m, 2H), 1.68–1.60 (m, 2H), 1.48–1.40 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 188.3, 157.3, 153.3, 150.1, 149.2, 146.2, 137.1, 129.1, 126.8, 124.1, 120.4, 115.9, 112.1, 52.5, 39.0, 38.3, 26.7, 26.4, 23.9; ESI-TOF m/z 350.1868 ($\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2 + \text{H}^+$ requires 350.1863).



Methyl 4-oxo-4-(5-(pyridin-2-yl)oxazol-2-yl)butanoate (14a). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and methyl succinate using general procedure B. Column chromatography (SiO_2 , 10–60% EtOAc-hexanes) afforded **14a**

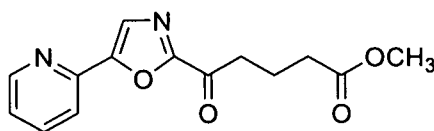
(433 mg, 16%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (app d, $J = 4.0$ Hz, 1H), 7.90 (s, 1H), 7.86 (t, $J = 7.6$ Hz, 1H), 7.82 (t, $J = 7.6$ Hz, 1H), 7.33 (t, $J = 5.6$ Hz, 1H), 3.71 (s, 3H), 3.46 (t, $J = 6.4$ Hz, 2H), 2.82 (t, $J = 6.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 186.3, 172.6, 157.0, 153.4, 150.1, 146.2, 137.1, 127.0, 124.2, 120.4, 52.0, 33.9, 27.7; ESI-TOF m/z 261.0865 ($\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_4 + \text{H}^+$ requires 261.0870).



4-Oxo-N-phenethyl-4-(5-(pyridin-2-yl)oxazol-2-yl)butanamide (13a). The title compound was prepared from methyl 4-oxo-4-(5-(pyridin-2-yl)oxazol-2-yl)butanoate

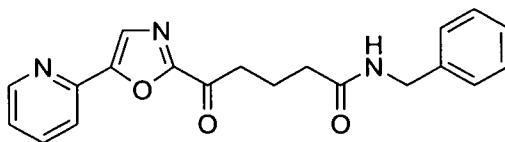
(**14a**) and phenethylamine using general procedure N. PTLC (66% EtOAc–hexanes) afforded **13a** (53 mg, 40%) as clear oil: ^1H NMR (CDCl_3 , 400 MHz) δ 8.64 (ddd, $J = 4.8, 1.8, 0.8$ Hz, 1H), 7.77 (dt, $J = 7.8, 2.0$ Hz, 1H), 7.69 (s, 1H), 7.56 (dt, $J = 7.6, 1.2$ Hz, 1H), 7.28 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 7.22–7.17 (m, 2H), 7.13–7.07 (m, 3H), 4.73 (br s, 1H), 3.49 (ddd, $J = 13.8, 10.4, 5.6$ Hz, 1H), 3.33 (ddd, $J = 14.0, 10.4, 6.0$ Hz, 1H), 2.87–2.62 (m, 4H), 2.53–2.53 (m, 1H), 2.41–2.35 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 174.4, 163.0, 152.6, 150.0, 146.4, 138.6, 137.0, 128.7, 128.4, 126.3, 124.8, 123.6, 119.5, 87.9, 41.6, 34.5, 33.3, 29.0; ESI–TOF m/z 350.1499 ($\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_3 + \text{H}^+$ requires 350.1499).

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Methyl 5-oxo-5-(5-(pyridin-2-yl)oxazol-2-yl)pentanoate (14b). The title compound was prepared from 5-(2-pyridyl)oxazole (**6**) and 4-methoxycarbonylpentanoic acid using general procedure B. Column chromatography (SiO_2 , 10–70% EtOAc–hexanes) afforded **14b** (430 mg, 16%) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (ddd, $J = 4.8, 1.6, 0.8$ Hz, 1H), 7.88 (s, 1H), 7.86 (t, $J = 1.2$ Hz, 1H), 7.82 (dt, $J = 7.4, 2.0$ Hz, 1H), 7.32, (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 3.69, (s, 3H), 3.21 (t, $J = 7.2$ Hz, 2H), 2.47, (t, $J = 7.2$ Hz, 2H), 2.20 (quint, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 187.4, 173.3, 157.1, 153.3, 150.1, 146.2, 137.1, 126.9, 124.1, 120.4, 51.6, 38.0, 32.9, 18.9; ESI–TOF m/z 275.1023 ($\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4 + \text{H}^+$ requires 275.1026).

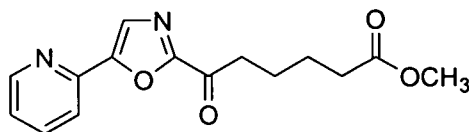
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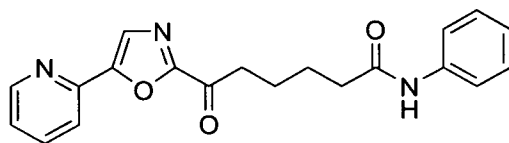
N-Benzyl-5-oxo-5-(5-(pyridin-2-yl)oxazol-2-yl)pentanamide (13b). The title compound was prepared from methyl 5-oxo-5-(5-(pyridin-2-yl)oxazol-2-yl)pentanoate (**14b**) and benzylamine using general procedure N. PTLC (67% EtOAc–hexanes) afforded **13b** (12 mg, 56%) as white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.67 (app d, $J = 4.4$ Hz, 1H), 7.86 (s, 1H), 7.84 (s, 1H), 7.81 (dt, $J = 7.2, 1.6$ Hz, 1H), 7.35–7.25 (m, 6H), 5.97 (br s, 1H), 4.45 (d, $J = 5.6$ Hz, 2H), 3.21 (t, $J = 7.2$ Hz, 2H), 2.36 (t, $J = 7.2$ Hz, 2H), 2.16 (quint, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 187.7, 171.8, 157.1, 153.3, 150.1, 146.2, 138.2, 137.1, 128.7, 127.8, 127.5,

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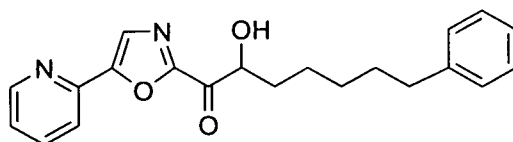
126.9, 124.2, 120.4, 43.7, 38.1, 35.3, 19.9; ESI-TOF m/z 350.1495 ($C_{20}H_{19}N_3O_3 + H^+$ requires 350.1499).



- 5 **Methyl 6-oxo-6-(5-(pyridin-2-yl)oxazol-2-yl)hexanoate (14c).** The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 5-methoxycarbonylhexanoic acid using general procedure B. Column chromatography (SiO_2 , 10–50% EtOAc–hexanes) afforded **14c** (246 mg, 14%) as a white solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.67 (app d, $J = 4.4$ Hz, 1H), 7.88 (s, 1H), 7.87 (d, $J = 8$ Hz, 1H), 7.82 (dt, $J = 7.6, 1.6$ Hz, 1H),
 10 7.33 (ddd, $J = 7.6, 5.0, 1.2$ Hz), 3.68 (2, 3H), 3.15 (t, $J = 6.8$ Hz, 2H), 2.39 (t, $J = 7.2$ Hz, 2H), 1.87–1.72 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.8, 173.7, 157.2, 153.3, 150.1, 146.2, 137.1, 126.8, 124.1, 120.4, 51.5, 38.6, 33.7, 24.3, 23.3; ESI-TOF m/z 289.1178 ($C_{15}H_{16}N_2O_4 + H^+$ requires 289.1183).

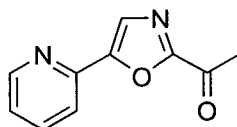


- 15 **6-Oxo-N-phenyl-6-(5-(pyridin-2-yl)oxazol-2-yl)hexanamide (13c).** The title compound was prepared from methyl 6-oxo-6-(5-(pyridin-2-yl)oxazol-2-yl)hexanoate (**14c**) and aniline using general procedure N. PTLC (66% EtOAc–hexanes) afforded **13c** (132 mg, 61%) as white solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.67 (app d, $J = 4.8$
 20 Hz, 1H), 7.88 (s, 1H), 7.86 (s, 1H), 7.82 (dt, $J = 7.6, 8.8$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.50 (br s, 1H), 7.35–7.28 (m, 3H), 7.10 (t, $J = 7.2$ Hz, 3H), 7.20 (t, $J = 6.4$ Hz, 2H), 2.45 (t, $J = 6.8$ Hz, 2H), 1.93–1.83 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.1, 170.7, 157.2, 153.4, 150.1, 146.2, 137.9, 137.1, 129.0, 126.9, 124.2, 120.4, 119.8, 38.7, 37.3, 24.9, 23.2; ESI-TOF m/z 350.1497 ($C_{20}H_{19}N_3O_3 + H^+$ requires
 25 350.1499).



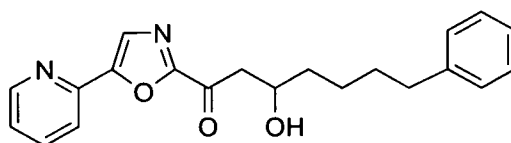
- 2-Hydroxy-7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)heptan-1-one (13d).** KHMDS (0.5 M in toluene, 0.285 mL, 0.142 mmol) was added to a dry flask containing
 30 anhydrous THF (1.7 mL) and the solution was cooled to -78 °C. A solution of OL-

135 (**2b**, 34 mg, 0.102 mmol) in anhydrous THF (0.8 mL) was added dropwise and the solution stirred for 15 min before dropwise addition of a solution of freshly prepared Davis reagent (40 mg, 0.153 mmol) in THF (0.8 mL). The reaction mixture was stirred at -78°C for 15 min before being quenched by the addition of H_2O (0.1 mL). The reaction mixture was allowed to warm to 0°C and Et_3N (0.1 mL) was added. Stirring at 0°C was continued for 5 min before pouring the reaction mixture onto aqueous 5% HCl (10 mL). Stirring was again continued for 15 min at room temperature before extracting with EtOAc . The organic phase was dried over anhydrous Na_2SO_4 and concentrated. Two successive PTLC purifications (1st, 50% hexanes– EtOAc ; 2nd, 1% MeOH – CH_2Cl_2) afforded **13d** (14 mg, 39%): ^1H NMR (CDCl_3 , 600 MHz) δ 8.69 (app d, $J = 4.8$ Hz, 1H), 7.93 (s, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 7.83 (app t, $J = 7.2$ Hz, 1H), 7.35 (dd, $J = 6.9, 4.8$ Hz, 1H), 7.27–7.24 (m, 2H), 7.17–7.15 (m, 3H), 5.04 (app d, $J = 4.8$ Hz, 1H), 3.46 (br s, 1H), 2.60 (t, $J = 7.8$ Hz, 2H), 2.12–2.06 (m, 1H), 1.81–1.35 (m, 7H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 189.4, 155.3, 153.6, 150.2, 145.9, 142.6, 137.2, 128.3, 128.2, 127.1, 125.6, 124.4, 120.6, 74.9, 35.8, 35.0, 31.2, 28.9, 24.9; ESI–TOF m/z 351.1703 ($\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3 + \text{H}^+$ requires 351.1703).

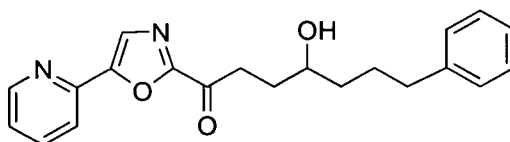


20 **1-(5-(Pyridin-2-yl)oxazol-2-yl)ethanone (S61)**. (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856) 5-(Pyridin-2-yl)oxazole (**X**, 1.5 g, 10.26 mmol) was dissolved in anhydrous THF (60 mL, 0.17 M) and cooled to -78°C under Ar. *n*-BuLi (2.18 M in hexanes, 5.65 mL, 12.32 mmol) was then added dropwise over 10 min. After addition, the dry ice/acetone bath was replaced with an ice bath and ZnCl_2 (1.0 M in Et_2O , 12.83 mL, 12.83 mmol) was added dropwise. After complete addition, stirring was continued for a further 45 min at 0°C before addition of CuI (2.932 g, 15.40 mmol). Stirring was continued for 15 min before adding acetyl chloride (2.12 g, 27 mmol, 2.63 eq; freshly purified by refluxing over PCl_5 followed by distillation and subsequent redistillation from distilled quinoline) dropwise. The reaction was stirred at 0°C for 10 min before removing the ice bath and stirring for 1 h at room temperature. The reaction was quenched by the addition of saturated aqueous NaHCO_3 , diluted with H_2O and extracted with EtOAc . The organic phase

was dried over anhydrous Na_2SO_4 and concentrated. Column chromatography (0–50% EtOAc–hexanes) followed by recrystallization (EtOAc–hexanes) afforded **S61** (960 mg, 50%) as a white solid: ^1H NMR (CDCl_3 , 600 MHz) δ 8.67 (app d, $J = 4.2$ Hz, 1H), 7.90 (s, 1H), 7.88 (app d, $J = 7.8$ Hz, 1H), 7.82 (dt, $J = 7.5$, 1.2 Hz, 1H), 7.33 (app dd, $J = 6.9$, 5.4 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (CDCl_3 , 600 MHz) δ 185.6, 157.5, 153.4, 150.1, 146.2, 137.1, 127.0, 124.2, 120.4, 26.6; ESI–TOF m/z 189.0661 ($\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2 + \text{H}^+$ requires 189.0659).



3-Hydroxy-7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)heptan-1-one (13e). 1-(5-(Pyridin-2-yl)oxazol-2-yl)ethanone (**S61**, 35 mg, 0.186 mmol) was dissolved in anhydrous THF (1.5 mL) and cooled to -78°C under Ar. KHMDS (0.4 M in toluene, 0.512 mL, 0.204 mmol) was added dropwise and stirring was continued at -78°C for 30 min before adding a solution of 5-phenylpentanal (42 mg, 0.26 mmol) in THF (0.5 mL) dropwise. After 15 min, the reaction was quenched by cannulating the cold reaction mixture directly from the flask onto a plug of oven-dried silica gel. The silica plug was rinsed with EtOAc and the organic filtrate concentrated. PTLC (66% EtOAc–hexanes) afforded **13e** (23 mg, 35%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.67 (app d, $J = 4.5$ Hz, 1H), 7.90 (s, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.82 (dt, $J = 7.8$, 2 Hz, 1H), 7.33 (ddd, $J = 7.3$, 4.8, 1.5 Hz, 1H), 7.29–7.26 (m, 2H), 7.19–7.15 (m, 3H), 4.27–4.22 (m, 1H), 3.29 (dd, $J = 17$, 3 Hz, 1H), 3.22 (dd, $J = 17$, 9 Hz, 1H), 2.95–2.80 (br s), 2.64 (t, $J = 7.5$ Hz, 2H), 1.72–1.40 (m, 6H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 188.0, 157.3, 153.6, 150.2, 146.1, 142.5, 137.1, 128.4, 128.3, 127.0, 125.7, 124.3, 120.5, 67.8, 46.3, 36.7, 35.9, 31.3, 25.2; ESI–TOF m/z 351.1706 ($\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3 + \text{H}^+$ requires 351.1703).



4-Hydroxy-7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)heptan-1-one (13f). 4-(Benzyloxy)butan-1-ol was oxidized to 4-(benzyloxy)butanal (7.35 g, 79%) following general procedure P. 4-(Benzyloxy)butanal was converted to (1-(benzyloxy)-7-phenylheptan-4-yl)triisopropylsilane with (3-phenylpropyl)magnesium bromide

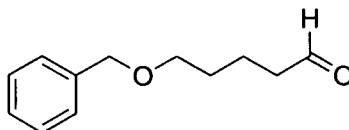
following general procedure Q. Column chromatography (5% EtOAc–hexanes) afforded (1-(benzyloxy)-7-phenylheptan-4-yloxy)triisopropylsilane (5.82 g, 81%) as a pale yellow oil. 7-Phenyl-4-(triisopropylsilyloxy)heptan-1-ol was prepared from (1-(benzyloxy)-7-phenylheptan-4-yloxy)triisopropylsilane following general procedure

5 R. Column chromatography (5–10% EtOAc–hexanes) afforded 7-phenyl-4-(triisopropylsilyloxy)heptan-1-ol (3.31 g, 73%) as a clear oil. 7-Phenyl-4-(triisopropylsilyloxy)heptanoic acid was prepared from 7-phenyl-4-(triisopropylsilyloxy)heptan-1-ol following general procedure S. Column chromatography (5% EtOAc–hexanes) afforded 7-phenyl-4-

10 (triisopropylsilyloxy)heptanoic acid (1.52, 47%) as a white solid. 7-Phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-4-(triisopropylsilyloxy)heptan-1-one was prepared from 5-(2-pyridyl)oxazole (6) and 7-phenyl-4-(triisopropylsilyloxy)heptanoic acid using general procedure B. Column chromatography (SiO₂, 10–50% EtOAc–hexanes) afforded 7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-4-(triisopropylsilyloxy)heptan-1-

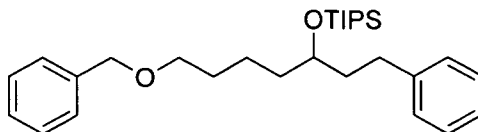
15 one (689 mg, 54%) as a clear oil. The title compound was prepared from 7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-4-(triisopropylsilyloxy)heptan-1-one using general procedure O. PTLC (50% EtOAc–hexanes) afforded **13f** (16 mg, 40%) as a white solid: ¹H NMR (CDCl₃, 600 MHz) δ 8.66 (app d, *J* = 4.2 Hz, 0.5H), 8.62 (app d, *J* = 4.2 Hz, 0.5H), 7.89 (s, 0.5H), 7.86 (app d, *J* = 7.8 Hz, 0.5H), 7.80 (app t, *J* = 7.8 Hz, 0.5H), 7.73 (app q, *J* = 8.4 Hz, 0.5H), 7.65–7.61 (m, 0.75H), 7.57, (d, *J* = 8.4 Hz, 0.25H), 7.32–7.21 (m, 3H), 7.19–7.14 (m, 3H), 4.45–4.43 (m, 0.5H), 4.35–4.30 (m, 0.5H), 3.72–3.69 (m, 0.5H), 3.29–3.21 (m, 1H), 2.68–2.59 (m, 2.75H), 2.40–2.30 (m, 0.75H), 2.23–2.19 (m, 0.25H), 2.04–1.96 (m, 1.25H), 1.89–1.53 (m, 3.5H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.6, 163.8, 163.7, 157.3, 153.3, 151.4, 150.1, 149.9, 147.0,

20 146.2, 142.2, 142.1, 137.1, 136.8, 136.7, 128.4, 128.3, 128.2, 126.9, 125.8, 125.7, 125.6, 125.0, 124.9, 124.1, 123.0, 120.4, 119.4, 119.3, 100.9, 100.5, 82.4, 80.4, 70.9, 37.6, 37.1, 36.9, 36.5, 35.8, 35.7, 35.5, 34.9, 31.6, 30.4, 30.3, 27.8, 27.5, 27.4; ESI–TOF *m/z* 351.1701 (C₂₁H₂₂N₂O₃ + H⁺ requires 351.1703).

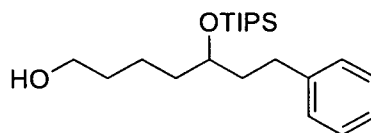


30 **5-(Benzyloxy)pentanal (S62)**. The title compound was prepared from 5-(benzyloxy)-1-pentanol following general procedure P. Column chromatography (15% EtOAc–

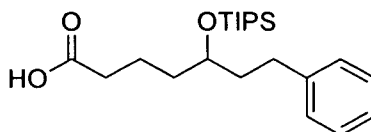
hexanes) afforded **S62** (11.0 g, 68%) as a pale yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 9.77 (m, 1H), 7.36–7.29 (m, 5H), 4.51 (s, 2H), 3.50 (t, J = 6.2 Hz, 2H), 2.49–2.45 (m, 2H), 1.79–1.63 (m, 4H).



(7-(Benzyloxy)-1-phenylheptan-3-yloxy)triisopropylsilane (S63). The title compound was prepared from 5-(benzyloxy)pentanal (**S62**) following general procedure Q. Column chromatography (5% EtOAc–hexanes) afforded **S63** (2.7 g, 85%) as a pale yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.37–7.28 (m, 7H), 7.21–7.19 (m, 2H), 4.53 (s, 2H), 3.95–3.88 (m, 1H), 3.51 (t, J = 6.4 Hz, 2H), 2.68 (t, J = 8.2 Hz, 2H), 1.91–1.75 (m, 2H), 1.70–1.58 (m, 4H), 1.50–1.43 (m, 2H), 1.09 (s, 18H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 142.8, 138.6, 128.3 (4C), 127.6 (4C), 127.4, 125.6, 72.9, 71.8, 70.4, 38.4, 36.3, 31.2, 30.0, 21.6, 18.2, 12.7.

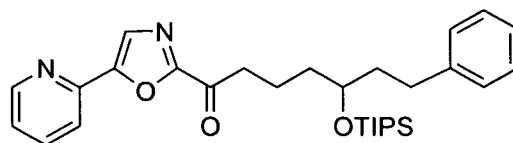


7-Phenyl-5-(triisopropylsilyloxy)heptan-1-ol (S64). A solution of the (7-(benzyloxy)-1-phenylheptan-3-yloxy)triisopropylsilane (**S63**, 2.6 g, 5.7 mmol) in 30 mL of EtOAc was treated with 10% Pd/C (400 mg). The reaction mixture was purged with H_2 and stirred overnight at 25 °C. The suspension was concentrated and purified by column chromatography (15% EtOAc–hexanes) to afford **S64** (1.0 g, 50%) as a pale yellow oil: ^1H NMR (CDCl_3 , 500 MHz) δ 7.38–7.34 (m, 2H), 7.28–7.24 (m, 3H), 4.01–3.97 (m, 1H), 3.74 (t, J = 6.6 Hz, 2H), 1.97–1.84 (m, 2H), 1.70–1.64 (m, 4H), 1.53–1.48 (m, 2H), 1.16 (s, 18H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 142.7, 128.3 (4C), 125.6, 71.8, 62.9, 38.2, 36.3, 33.0, 31.2, 21.0, 18.2, 12.7.

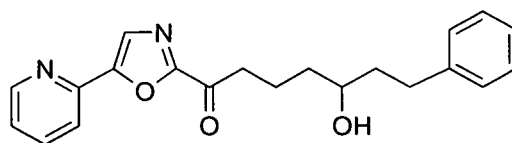


7-Phenyl-5-(triisopropylsilyloxy)heptanoic acid (S65). The title compound was prepared from 7-phenyl-5-(triisopropylsilyloxy)heptan-1-ol (**S64**) following general procedure S. Column chromatography (10–20% EtOAc–hexanes) afforded **S65** (445 mg, 49%) as a yellow oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.30–7.28 (m, 2H), 7.20–

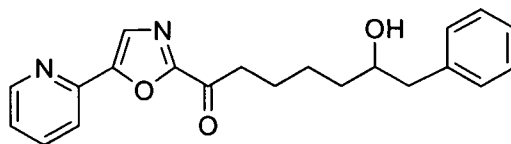
7.18 (m, 3H), 3.95–3.90 (m, 1H), 2.66 (t, $J = 8.2$ Hz, 2H), 2.39 (t, $J = 7.4$ Hz, 2H), 1.87–1.79 (m, 2H), 1.75–1.68 (m, 2H), 1.65–1.59 (m, 2H), 1.07 (s, 18H).



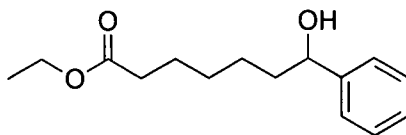
- 5 **7-Phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-5-(triisopropylsilyloxy)heptan-1-one (S66).** The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-phenyl-5-(triisopropylsilyloxy)heptanoic acid (S65) using general procedure B. Column chromatography (SiO₂, 10–40% EtOAc–hexanes) afforded **S66** (55 mg, 21%) as a clear oil: ¹H NMR (CDCl₃, 400 MHz) δ 8.67 (app d, $J = 4.8$ Hz, 1H), 7.88 (s, 1.5H), 7.86 (s, 0.5H), 7.81 (dt, $J = 7.6, 1.6$ Hz, 1H), 7.33–7.25 (m, 3H), 7.20–7.15 (m, 3H), 3.95 (quint, $J = 5.2$ Hz, 1H), 3.14 (t, $J = 7.2$ Hz, 2H), 2.67 (t, $J = 8.8$ Hz, 2H), 1.91–1.79 (m, 4H), 1.74–1.63 (m, 2H), 1.06 (s, 21H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.2, 157.3, 153.3, 150.1, 146.3, 142.5, 137.1, 128.4, 128.3, 126.9, 125.6, 124.1, 120.4, 71.6, 39.3, 38.3, 35.8, 31.2, 19.3, 18.2, 12.7; ESI–TOF m/z 507.3033
- 10 (C₃₀H₄₂N₂O₃Si + H⁺ requires 507.3037).
- 15



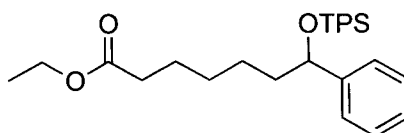
- 5-Hydroxy-7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)heptan-1-one (13g).** The title compound was prepared from 7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-5-(triisopropylsilyloxy)heptan-1-one (**S66**) using general procedure O. PTLC (33% EtOAc–hexanes) afforded **13g** (15 mg, 57%): ¹H NMR (CDCl₃, 400 MHz) δ 8.67 (app d, $J = 4.8$ Hz, 0.5H), 8.64 (app d, $J = 4.4$ Hz, 0.5H), 7.88 (s, 0.7H), 7.86 (s, 0.3H), 7.81 (dt, $J = 7.6, 1.6$ Hz, 0.5H), 7.76 (dt, $J = 7.6, 1.6$ Hz, 0.5H), 7.70 (s, 0.3H), 7.68–7.65 (m, 0.7H), 7.35–7.10 (m, 6H), 4.31 (br ex s, 1H), 4.15–4.05 (m, 0.5H), 3.92 (br s, 1H), 3.72–3.66 (m, 0.5H), 3.22–3.09 (m, 1H), 2.88–2.61 (m, 2H), 2.25–1.37 (m, 7H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.3, 164.7, 157.2, 153.3, 151.1, 150.1, 149.9, 147.1, 146.2, 142.1, 142.0, 137.1, 136.9, 128.4, 128.3, 128.2, 126.9, 125.8, 125.7, 124.9, 124.2, 123.1, 120.4, 119.5, 93.2, 70.7, 70.5, 39.1, 38.8, 37.4, 36.7, 32.1, 32.0, 31.6, 30.4, 20.0, 18.5; ESI–TOF m/z 351.1705 (C₂₁H₂₂N₂O₃ + H⁺ requires 351.1703).
- 20
- 25
- 30



6-Hydroxy-7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)heptan-1-one (13h). 6-(Benzyloxy)hexan-1-ol was oxidized to 6-(benzyloxy)hexanal following general procedure P. 6-(Benzyloxy)hexanal was converted to (7-(benzyloxy)-1-phenylheptan-2-yloxy)triisopropylsilane with benzylmagnesium chloride following general procedure Q. Column chromatography (5% EtOAc–hexanes) afforded (7-(benzyloxy)-1-phenylheptan-2-yloxy)triisopropylsilane (2.7 g, 85%) as a pale yellow oil. 7-Phenyl-6-(triisopropylsilyloxy)heptan-1-ol was prepared from (7-(benzyloxy)-1-phenylheptan-2-yloxy)triisopropylsilane following general procedure R. Column chromatography (5–40% EtOAc–hexanes) afforded 7-phenyl-6-(triisopropylsilyloxy)heptan-1-ol (810 mg, 80%) as a clear oil. 7-Phenyl-6-(triisopropylsilyloxy)heptanoic acid was prepared from 7-Phenyl-6-(triisopropylsilyloxy)heptan-1-ol following general procedure S. Column chromatography (5% EtOAc–hexanes) afforded 7-phenyl-6-(triisopropylsilyloxy)heptanoic acid (400 mg, 55%) as a white solid. 7-Phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-6-(triisopropylsilyloxy)heptan-1-one was prepared from 5-(2-pyridyl)oxazole (**6**) and 7-phenyl-6-(triisopropylsilyloxy)heptanoic acid using general procedure B. Column chromatography (SiO₂, 10–40% EtOAc–hexanes) afforded 7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-6-(triisopropylsilyloxy)heptan-1-one (84 mg, 26%) as a clear oil. The title compound was prepared from 7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-6-(triisopropylsilyloxy)heptan-1-one using general procedure O. PTLC (50% EtOAc–hexanes) afforded **13h** (7 mg, 20%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 8.67 (app d, *J* = 4.5 Hz, 1H), 7.88 (s, 1H), 7.87 (d, *J* = 9.5 Hz, 1H), 7.82 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.33–7.29 (m, 3H), 7.25–7.20 (m, 3H), 3.88–3.83 (m, 1H), 3.14 (t, *J* = 7.5 Hz, 2H), 2.84 (dd, *J* = 13.5, 4.0 Hz, 1H), 2.66 (dd, *J* = 13.8, 8.0 Hz, 1H), 1.88–1.78 (m, 2H), 1.78–1.67 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.3, 157.3, 150.1, 146.3, 138.4, 137.1, 129.4, 128.6, 126.9, 126.5, 124.1, 120.4, 72.4, 44.1, 39.0, 36.4, 25.3, 23.9; ESI–TOF *m/z* 373.1522 (C₂₁H₂₂N₂O₃ + Na⁺ requires 373.1523).

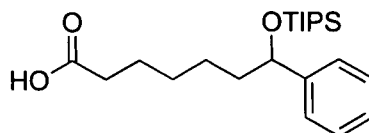


Ethyl 7-hydroxy-7-phenylheptanoate (S67). Ethyl 6-bromohexanoate (5.0 g, 22.4 mmol) was dissolved in anhydrous acetone (35 mL) under Ar and NaI (6.7 g, 44.8 mmol) was added. The reaction mixture was warmed at reflux for 1 h after which the acetone was removed *in vacuo*. The residue was taken up in EtOAc, washed with H₂O, dried over Na₂SO₄ and concentrated to afford a quantitative yield of ethyl 6-iodohexanoate. Ethyl 6-iodohexanoate (1.621 g, 6.0 mmol) was dissolved in a solution of anhydrous DMF (10 mL) containing benzaldehyde (318 mg, 3.0 mmol) and this mixture was then added at 30 °C to a dark blue/green suspension containing CrCl₂ (1.475 g, 12 mmol) and cobalt phthalocyanine (343 mg, 0.6 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature for 1 h and then filtered through a pad of Celite. The Celite was rinsed with Et₂O and the filtrate poured onto saturated aqueous NaCl and extracted with Et₂O. The combined Et₂O extracts were washed with saturated aqueous NaCl, dried over anhydrous MgSO₄ and concentrated. Column chromatography (0–50% EtOAc–hexanes) afforded **S67** (504 mg, 67%): ¹H NMR (CDCl₃, 400 MHz) δ 7.28–7.24 (m, 4H), 7.23–7.17 (m, 1H), 4.55 (t, *J* = 6 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 2.20 (t, *J* = 7.6 Hz, 2H), 1.77–1.51 (m, 4H), 1.41–1.22 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 173.5, 144.8, 127.8, 126.8, 125.5, 73.7, 59.8, 38.6, 33.8, 28.6, 25.0, 24.4, 13.8.

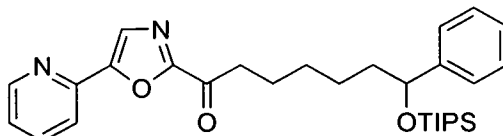


Ethyl 7-phenyl-7-(triisopropylsilyloxy)heptanoate (S68). Ethyl 7-hydroxy-7-phenylheptanoate (**S67**, 258 mg, 1.03 mmol) was dissolved in anhydrous THF (4.0 mL) under Ar and cooled to 0 °C. TIPS-OTf (505 mg, 1.65 mmol) was added and the reaction mixture stirred for 2 min before adding NaH (60 % dispersion in oil, 54 mg, 1.34 mmol) portionwise. After 10 min, the reaction was quenched by the addition of H₂O and then extracted with CH₂Cl₂. The organic phase was dried over anhydrous Na₂SO₄ and concentrated. Column chromatography (0–4% EtOAc–hexanes) afforded **S68** (368 mg, 88%): ¹H NMR (CDCl₃, 400 MHz) δ 7.29–7.26 (m, 4H), 7.23–7.18 (m, 1H), 4.75 (t, *J* = 6.0 Hz, 1H), 4.09 (q, *J* = 6.8 Hz, 2H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.82–1.64 (m, 2H), 1.59–1.52 (m, 2H), 1.30–1.21 (m, 7H), 1.06–0.95 (m, 21H); ¹³C NMR

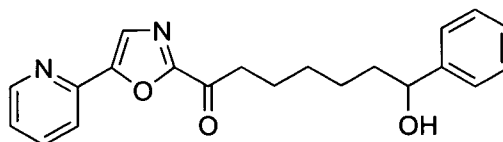
(CDCl₃, 100 MHz) δ 173.7, 145.4, 127.8, 126.8, 126.1, 75.0, 60.0, 40.5, 34.2, 29.2, 24.9, 24.3, 18.0, 17.9, 14.2, 12.3.



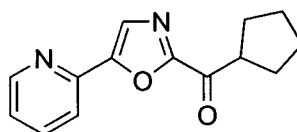
- 5 **7-Phenyl-7-(triisopropylsilyloxy)heptanoic acid (S69).** Ethyl 7-phenyl-7-(triisopropylsilyloxy)heptanoate (S68, 319 mg, 0.78 mmol, 1.0 equiv) was dissolved in THF (2 mL) and a LiOH solution (362 mg LiOH in 10 mL H₂O; use 1.0 mL, 0.863 mmol) was added. EtOH (1.0 mL) was added to bring the solution to homogeneity. After stirring at room temperature for 8 h, the reaction mixture was diluted with H₂O
 10 and acidified to pH 2 with aqueous 1 N HCl. The acidic aqueous solution was extracted with CH₂Cl₂ and the combined organic phase dried over anhydrous Na₂SO₄ and concentrated. Column chromatography (0–15% EtOAc–hexanes) afforded S69 (270 mg, 91%): ¹H NMR (CDCl₃, 600 MHz) δ 7.29–7.27 (m, 4H), 7.22–7.19 (m, 1H), 4.75 (t, *J* = 6.0 Hz, 1H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.80–1.75 (m, 1H), 1.72–1.66 (m, 1H), 1.59–1.54 (m, 2H), 1.29–1.21 (m, 4H), 1.06–1.00 (m, 12H), 0.95 (d, 6.6 Hz, 9H); ¹³C NMR (CDCl₃, 150 MHz) δ 180.3, 145.5, 127.8, 126.8, 126.1, 75.0, 40.6, 34.0, 29.1, 24.6, 24.4, 18.0, 17.9, 12.3.



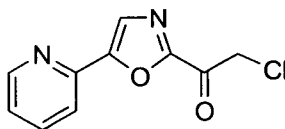
- 20 **7-Phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-7-(triisopropylsilyloxy)heptan-1-one (S70).** The title compound was prepared from 5-(2-pyridyl)oxazole (6) and 7-phenyl-7-(triisopropylsilyloxy)heptanoic acid (S69) using general procedure B. Column chromatography (SiO₂, 5–40% EtOAc–hexanes) afforded S70 (47 mg, 21%) as a clear oil: ¹H NMR (CDCl₃, 600 MHz) δ 8.67 (app d, *J* = 4.8 Hz, 1H), 7.87 (s, 1H), 7.85 (s, 1H), 7.81 (app t, *J* = 7.2 Hz, 1H), 7.32–7.27 (m, 5H), 7.22–7.20 (m, 1H), 4.76 (t, *J* = 6.0 Hz, 1H), 3.05 (t, *J* = 7.8 Hz, 2H), 1.83–1.77 (m, 1H), 1.74–1.68 (m, 3H), 1.37–1.33 (m, 2H), 1.29–1.23 (m, 2H), 1.06–1.00 (m, 12H), 0.95 (d, *J* = 6.6 Hz, 9H); ¹³C NMR (CDCl₃, 150 MHz) δ 188.4, 157.3, 153.2, 150.1, 146.3, 145.5, 137.1, 127.8, 126.8, 126.7, 126.1, 124.1, 120.3, 75.0, 40.7, 39.0, 29.2, 24.5, 23.9, 18.0, 17.9,
 30 12.3; ESI–TOF *m/z* 529.2849 (C₃₀H₄₂N₂O₃Si + Na⁺ requires 529.2857).



7-Hydroxy-7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)heptan-1-one (13i). The title compound was prepared from 7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)-7-(triisopropylsilyloxy)heptan-1-one (**S70**) using general procedure O. Column chromatography (SiO₂, 50% EtOAc–hexanes) afforded **13i** (7 mg, 51%) as a white solid: ¹H NMR (CDCl₃, 600 MHz) δ 8.67 (app d, *J* = 4.2 Hz, 1H), 7.88 (s, 1H), 7.86, (d, *J* = 10.8 Hz, 1H), 7.82 (dt, *J* = 7.5, 1.8 Hz, 1H), 7.35–7.31 (m, 5H), 7.29–7.26 (m, 1H), 4.68 (dd, *J* = 7.2, 6.0 Hz, 1H), 3.10 (t, *J* = 7.8 Hz, 2H), 1.86–1.70 (m, 4H), 1.53–1.32 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 188.4, 157.3, 153.2, 150.1, 146.2, 144.8, 137.2, 128.4, 127.5, 126.9, 125.8, 124.1, 120.4, 74.5, 39.0, 38.8, 29.0, 25.5, 23.9; ESI–TOF *m/z* 373.1525 (C₂₁H₂₂N₂O₃ + Na⁺ requires 373.1523).

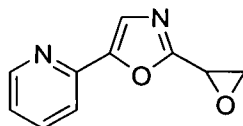


Cyclopentyl(5-(pyridin-2-yl)oxazol-2-yl)methanone (14e). 6-Bromo-1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (**S60**, 89 mg, 0.275 mmol) was dissolved in anhydrous DMF (0.3 mL) and K₂CO₃ (114 mg, 0.826 mmol) and KI (46 mg, 0.275 mmol) were added followed by *N*-methylaniline (29.5 mg, 0.275 mmol). The reaction mixture was stirred overnight at room temperature before being diluted with EtOAc. The EtOAc mixture was washed with H₂O, dried over anhydrous Na₂SO₄ and concentrated. PTLC (66% hexanes–EtOAc) afforded **14e** (34 mg, 59%): ¹H NMR (CDCl₃, 600 MHz) δ 8.67 (app d, *J* = 4.8 Hz, 1H), 7.89 (s, 1H), 7.87 (app d, *J* = 7.8 Hz, 1H), 7.82 (app t, *J* = 7.2, Hz, 1H), 7.32 (app dd, *J* = 7.2, 4.8 Hz, 1H), 3.93 (quint, *J* = 8.4 Hz, 1H), 2.07–2.01 (m, 2H), 1.97–1.91 (m, 2H), 1.80–1.73 (m, 2H), 1.73–1.67 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 190.9, 157.5, 153.1, 150.0, 146.3, 137.0, 126.8, 124.0, 120.3, 47.4, 29.7, 26.2; ESI–TOF *m/z* 243.1133 (C₁₄H₁₄N₂O₂ + H⁺ requires 243.1128).



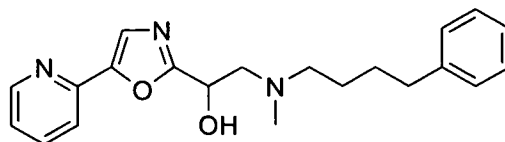
2-Chloro-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (14f). 5-(Pyridin-2-yl)oxazole (6, 269 mg, 1.84 mmol) was dissolved in anhydrous Et₂O (5.0 mL, 0.37 M) and cooled to

–78 °C under Ar. *n*-BuLi (1.5 M in hexanes, 1.35 mL, 1.1 equiv) was then added dropwise and the reaction mixture was stirred for 30 min. Bu₃SnCl (599 mg, 1.84 mmol) in anhydrous Et₂O (1.5 mL) was then added dropwise. After complete addition, the cooling bath was removed and the mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was then filtered through oven dried Celite using anhydrous Et₂O to rinse the filter cake. The filtrate was concentrated *in vacuo* to yield 5-(pyridin-2-yl)-2-(tributylstannyl)oxazole which was immediately redissolved in anhydrous THF (10 mL) under Ar. A solution of chloroacetyl chloride in THF (4 mL) was added dropwise and the reaction mixture was stirred for 2 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl, diluted with H₂O and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄ and concentrated. Column chromatography (EtOAc–hexanes) followed by PTLC (1% MeOH–CH₂Cl₂) afforded **14f** (105 mg, 26%) as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 8.68 (app d, *J* = 4.4 Hz, 1H), 7.92 (s, 1H), 7.89 (app d, *J* = 7.6 Hz, 1H), 7.84 (dt, *J* = 7.2, 1.6 Hz, 1H), 7.36 (ddd, *J* = 7.2, 4.8, 1.6 Hz, 1H), 4.90 (s, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 178.8, 155.2, 154.1, 150.1, 145.7, 137.1, 127.1, 124.4, 120.5, 45.7; ESI–TOF *m/z* 223.0269 (C₁₀H₇N₂O₂Cl + H⁺ requires 223.0269).



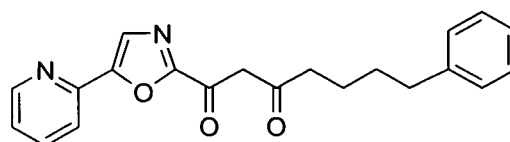
2-(Oxiran-2-yl)-5-(pyridin-2-yl)oxazole (S71). 2-Chloro-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanone (**14f**, 70 mg, 0.315 mmol) was dissolved in EtOH (5.0 mL) and NaBH₄ (24 mg, 0.63 mmol) was added in one portion. After 10 min, the reaction mixture was diluted with H₂O, stirred for 10 min and then extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to yield 2-chloro-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanol (70 mg, 99%). 2-Chloro-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanol (52 mg, 0.231 mmol) was dissolved in EtOH (2.0 mL) and a 50% solution of NaOH in H₂O (37 mL, 0.463 mmol) was added. The reaction mixture was stirred at room temperature for 30 min before diluting with H₂O and extracting with EtOAc. The organic phase was dried over anhydrous Na₂SO₄ and concentrated. PTLC (50% hexanes–EtOAc) afforded **S71** (26 mg, 59%) as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 8.63 (ddd, *J* = 4.6, 1.4, 0.8 Hz, 1H), 7.77 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.68 (s, 1H), 7.63 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.25 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 4.10 (dd, *J* =

4.0, 2.4 Hz, 1H), 3.44 (dd, $J = 5.6, 2.4$ Hz, 1H), 3.25 (dd, $J = 5.8, 4.4$ Hz, 1H); ^{13}C NMR (CDCl_3 , 600 MHz) δ 160.1, 151.7, 150.0, 146.8, 136.9, 125.9, 123.2, 119.3, 48.0, 45.5; ESI-TOF m/z 189.0662 ($\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2 + \text{H}^+$ requires 189.0659).



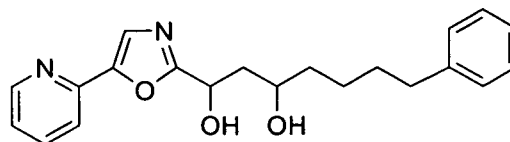
- 5 **2-(Methyl(4-phenylbutyl)amino)-1-(5-(pyridin-2-yl)oxazol-2-yl)ethanol (14i).** 2-(Oxiran-2-yl)-5-(pyridin-2-yl)oxazole (**S71**, 23 mg, 0.123 mmol) was dissolved in anhydrous THF (0.5 mL) under Ar and *N*-methyl-4-phenylbutylamine (Ding, C. Z.; Lu, X.; et al. *J. Med. Chem.* **1993**, *36*, 1711–1715) (40 mg, 0.245 mmol) was added. The reaction mixture was warmed at 60 °C and stirred overnight. After cooling to
- 10 room temperature, the reaction mixture was loaded directly onto a PTLC plate and eluted with 2% MeOH, 1% NH_4OH in CH_2Cl_2 to yield **14i** (39 mg, 91%) as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz) δ 8.63 (app d, $J = 4.4$ Hz, 1H), 7.75 (dt, $J = 7.8, 2.0$ Hz, 1H), 7.69 (app d, $J = 7.6$ Hz, 1H), 7.65 (s, 1H), 7.30–7.26 (m, 2H), 7.23 (ddd, $J = 7.2, 4.8, 1.2$ Hz, 1H), 7.20–7.16 (m, 3H), 4.90 (dd, $J = 9.6, 4.0$ Hz, 1H), 2.99
- 15 (dd, $J = 12.4, 10.0$ Hz, 1H), 2.79 (dd, $J = 12.4, 4.0$ Hz, 1H), 2.63 (t, $J = 7.2$ Hz, 2H), 2.61–2.56 (m, 1H), 2.52–2.45 (m, 1H), 2.33 (s, 3H), 1.69–1.52 (m, 4H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 163.9, 151.2, 149.9, 147.2, 142.2, 136.8, 128.4, 128.3, 125.8, 125.3, 122.9, 119.4, 63.7, 60.9, 57.7, 41.8, 35.7, 29.0, 26.7; ESI-TOF m/z 352.2023 ($\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_2 + \text{H}^+$ requires 352.2019).

20



- 7-Phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)heptane-1,3-dione (14g).** 3-Hydroxy-7-phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)heptan-1-one (**13e**, 12 mg, 0.0342 mmol) was dissolved in anhydrous CH_2Cl_2 (0.25 mL) under Ar and Dess–Martin periodinane
- 25 (17.4 mg, 0.0411 mmol) was added. The reaction mixture was stirred at room temperature for 20 min before being filtered through Celite. The Celite pad was rinsed with CH_2Cl_2 and the filtrate concentrated. PTLC (50% hexanes–EtOAc) afforded **14g** as a white solid (8.2 mg, 69%): ^1H NMR (CDCl_3 , 600 MHz) δ 8.68 (app d, $J = 4.2$ Hz, 1H), 7.89 (s, 1H), 7.86–7.80 (m, 2H), 7.32–7.26 (m, 3H), 7.19–7.18 (m, 3H), 6.54
- 30 (s, 1H), 2.66 (t, $J = 7.2$ Hz, 2H), 2.48 (t, $J = 7.2$ Hz, 2H), 1.75–1.66 (m, 4H); ^{13}C

NMR (CDCl₃, 150 MHz) δ 195.3, 171.7, 157.0, 153.1, 150.1, 146.3, 141.9, 137.1, 128.4, 128.3, 127.4, 125.8, 123.9, 120.2, 98.3, 38.3, 35.6, 30.9, 25.3; ESI-TOF m/z 349.1549 (C₂₁H₂₀N₂O₃ + H⁺ requires 349.1547).



5

7-Phenyl-1-(5-(pyridin-2-yl)oxazol-2-yl)heptane-1,3-diol (14h). α -Hydroxyketone **13d** (11 mg, 0.314 mmol) was dissolved in MeOH (0.2 mL) and NaBH₄ (1.5 mg, 0.408 mmol) was added. The mixture was stirred for 10 min before being quenched with H₂O (1.0 mL) and stirred for an additional 10 min. An additional amount of H₂O (5 mL) was added and the mixture extracted with EtOAc. The organic phase was washed with H₂O, dried over anhydrous Na₂SO₄ and concentrated to yield **14h** (9 mg, 99%) as a mixture of 4 diastereomers. ¹H NMR shows that the *syn* (S,S:R,R) and *anti* (R,S:S,R) pairs of enantiomers are present in a 0.63:0.37 ratio: ¹H NMR (CDCl₃, 600 MHz) δ 8.62 (app d, J = 4.8 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.62–7.65 (m, 2H), 7.24–7.27 (m, 3H), 7.14–7.17 (m, 3H), 4.79 (d, J = 4.2, 0.63H), 4.71 (d, J = 3.0 Hz, 0.37H), 2.59 (app q, J = 8.4 Hz, 2H), 1.55–1.71 (m, 4H), 1.31–1.51 (m, 4H); ¹³C NMR (CDCl₃, 150 MHz) δ 149.5, 149.4, 146.5, 146.5, 142.7, 142.6, 139.6, 137.4, 137.3, 128.4, 128.2, 125.6, 125.3, 125.3, 123.2, 123.2, 119.6, 119.6, 73.9, 72.7, 70.3, 69.9, 35.8, 35.8, 32.7, 32.6, 31.4, 31.3., 29.1, 29.1, 25.5, 25.5; ESI-TOF m/z 353.1860 (C₂₁H₂₄N₂O₃ + H⁺ requires 353.1868).

Compounds **5j**, **5k**, **5aa**, **5jj**, **5mm**, **4ss**, **4jj**, **12a**, **12f**, **12n**, **14a**, and **14d** had a purity greater than 99%. Compounds **5f**, **5l**, **5o**, **5ff**, **5ii**, **4y**, **4z**, **4aa**, **4cc**, **4gg**, **12g**, **12i**, and **13b** had a purity of 99%. Compounds **5g**, **5h**, **5i**, **5v**, **5w**, **5y**, **5gg**, **4f**, **4qq**, **4p**, **4q**, **4r**, **4x**, **12k**, **12l**, **12m**, **12p**, **12q**, **12r**, **13a**, **13f**, **14c**, **14f**, and **14g** had a purity of 98%. Compounds **5e**, **5n**, **5r**, **5u**, **5bb**, **5ee**, **5hh**, **5ll**, **4e**, **4pp**, **12c**, **12d**, **12e**, **12h**, **14b**, **14h**, and **14i** had a purity of 97%. Compounds **5b**, **5c**, **5d**, **5p**, **5t**, **5x**, **5z**, **5kk**, **5nn**, **4s**, **4rr**, **4w**, **4bb**, **4hh**, **4ii**, **12b**, **12j**, **12o**, **13c**, and **13e** had a purity of 96%. Compounds **5a**, **5m**, **5q**, **5s**, **5cc**, **5dd**, **5oo**, **4o**, **13d**, **13g**, **13h**, **13i**, and **14e** had a purity of 95%. Purity of each compound was determined on an Agilent 1100 LC/MS instrument on a ZORBAX® SB-C18, 3.5 mm, 4.6x50, a flow rate of 0.75 mL/min, detection at 220

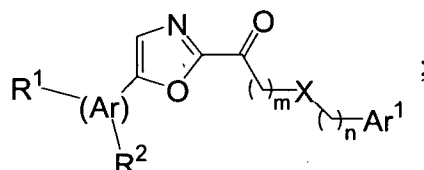
and 254 nm, with a 10–98% acetonitrile/water/0.1% formic acid gradient and a 50–98% acetonitrile/water/0.1% formic acid gradient.

FAAH Inhibition. ^{14}C -labeled oleamide was prepared from ^{14}C -labeled oleic acid as described (Cravatt, B. F.; et al. *Science* **1995**, 268, 1506–1509). The truncated rat FAAH (rFAAH) was expressed in *E. coli* and purified as described (Patricelli, M. P.; Lashuel, H. A.; et al. *Biochemistry* **1998**, 37, 15177–15187). The purified recombinant rFAAH was used in the inhibition assays unless otherwise indicated. The full-length human FAAH (hFAAH) was expressed in COS-7 cells as described (Giang, D. K.; Cravatt, B. F. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, 94, 2238–2242), and the lysate of hFAAH-transfected COS-7 cells was used in the inhibition assays where explicitly indicated.

The inhibition assays were performed as described (Cravatt, B. F.; et al. *Science* **1995**, 268, 1506–1509). In brief, the enzyme reaction was initiated by mixing 1 nM of rFAAH (800, 500, or 200 pM rFAAH for inhibitors with $K_i \leq 1\text{--}2\text{ nM}$) with 10 μM of ^{14}C -labeled oleamide in 500 μL of reaction buffer (125 mM TrisCl, 1 mM EDTA, 0.2% glycerol, 0.02% Triton X-100, 0.4 mM Hepes, pH 9.0) at room temperature in the presence of three different concentrations of inhibitor. The enzyme reaction was terminated by transferring 20 μL of the reaction mixture to 500 μL of 0.1 N HCl at three different time points. The ^{14}C -labeled oleamide (substrate) and oleic acid (product) were extracted with EtOAc and analyzed by TLC as detailed (Cravatt, B. F.; et al. *Science* **1995**, 268, 1506–1509). The K_i of the inhibitor was calculated using a Dixon plot as described (standard deviations are provided in the Supporting Information tables) (Boger, D. L.; Sato, H.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, 97, 5044–5049). Lineweaver-Burk analysis was performed as described confirming competitive, reversible inhibition (Boger, D. L.; Miyauchi, H.; et al. *J. Med. Chem.* **2005**, 48, 1849–1856).

WHAT IS CLAIMED IS:

1. A compound having the following structure:



wherein Ar is a 5- or 6-membered aryl or heteroaryl ring having a carbon as its point of attachment to the oxazole;

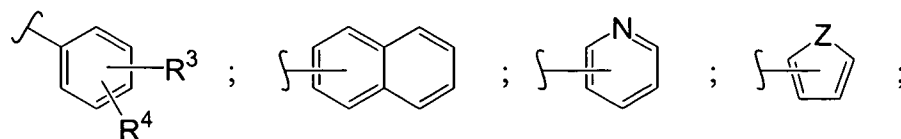
R¹ is independently selected from the group consisting of $-(C_1-C_6 \text{ alkyl})$, $-(C_3-C_6 \text{ alkyl})$, $-CF_3$, $-CN$, $-C(O)C_1-C_4 \text{ alkyl}$ optionally substituted with one, two, or three fluoro substituents, $-CO_2(C_1-C_4 \text{ alkyl})$, $-CO_2H$, $-C(O)N(R^a)R^b$, $-OH$, $-O(C_1-C_6 \text{ alkyl})$, halo, $-NO_2$, $-NR^aR^b$, $-N(R^a)C(O)R^b$, $-N(R^a)SO_2R^b$, $-SO_2N(R^a)R^b$, $-SR^a$, $-S(O)R^a$, and $-SO_2R^a$;

where R^a and R^b are each independently selected from the group consisting of $-H$, $-(C_1-C_6 \text{ alkyl})$, and $-(C_3-C_6 \text{ cycloalkyl})$; and

R² is independently selected from the group consisting of $-(C_1-C_6 \text{ alkyl})$, $-(C_3-C_6 \text{ alkyl})$, $-CF_3$, $-CN$, $-C(O)C_1-C_4 \text{ alkyl}$ optionally substituted with one, two, or three fluoro substituents, $-CO_2(C_1-C_4 \text{ alkyl})$, $-CO_2H$, $-C(O)N(R^c)R^d$, $-OH$, $-O(C_1-C_6 \text{ alkyl})$, $-halo$, $-NO_2$, $-NR^cR^d$, $-N(R^c)C(O)R^d$, $-N(R^c)SO_2R^d$, $-SO_2N(R^c)R^d$, $-SR^c$, $-S(O)R^c$, $-SO_2R^c$;

where R^c and R^d are each independently selected from the group consisting of $-H$, $-(C_1-C_6 \text{ alkyl})$, and $-(C_3-C_6 \text{ cycloalkyl})$; and

Ar¹ is selected from the group of radicals consisting of:



X is selected from the group of diradicals consisting of $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{NR}^5-$,

5 $-\text{C}\equiv\text{C}-$, $-\text{CH}(\text{OH})-$, and $-\text{C}(\text{O})\text{NH}-$; and

R^3 and R^4 are independently selected from the group consisting of $-\text{H}$, $-\text{NHBOC}$, $-\text{F}$, $-\text{Cl}$,

10 $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{O}(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-\text{S}(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-\text{S}(\text{O})(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-\text{S}(\text{O})_2(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-\text{CF}_3$, $-\text{COOH}$, $-\text{CO}_2(\text{C}_1-\text{C}_6 \text{ alkyl})$, and $-(\text{C}_1-\text{C}_6 \text{ alkyl})$; and

R^5 is selected from the group consisting $-\text{H}$, and $-(\text{C}_1-\text{C}_6 \text{ alkyl})$; and

15 Z is selected from the group of diradicals consisting of $-\text{O}-$, $-\text{S}-$, and $-\text{NR}^5-$; and

m is an integer between 0 and 6; and

n is an integer between 0 and 6;

20

with the following provisos:

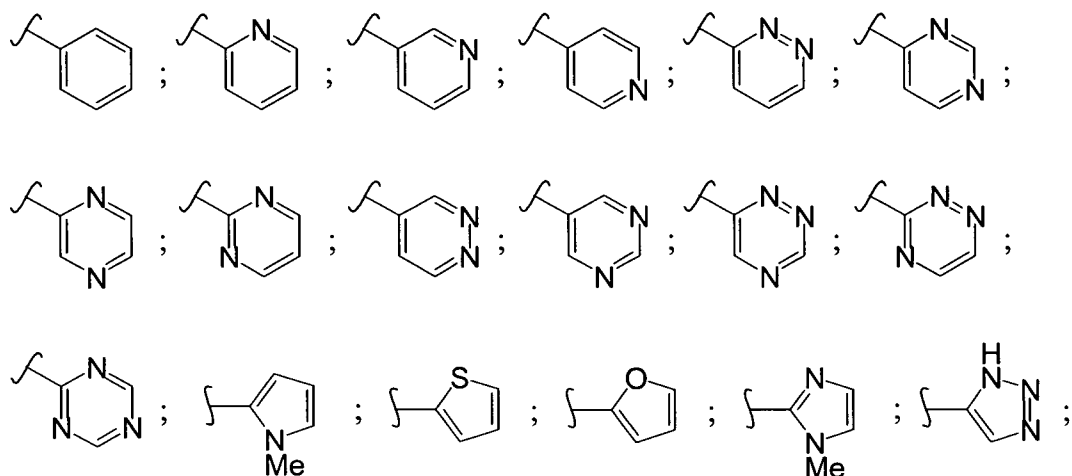
if m is 0, then n cannot be 0; and

25 if X is $-\text{CH}_2-$, then Ar^1 cannot be phenyl;

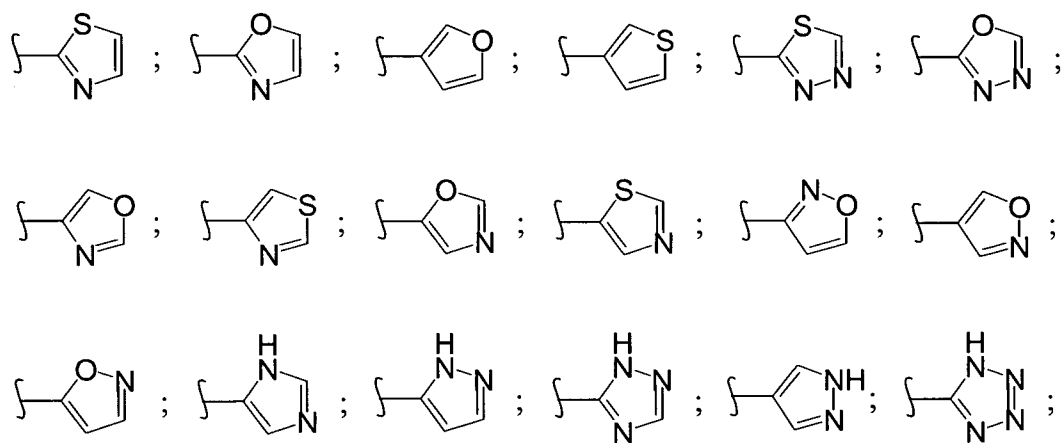
and a pharmaceutically acceptable salt, prodrug or biologically active metabolite of a compound of Formula I.

2. A compound according to claim 1, wherein Ar is selected from the group
30 consisting of phenyl, pyridyl, pyridazinyl, pyrimidinyl, pyrimidinedione, pyrazinyl, thiophenyl, furanyl, imidazolyl, oxazolyl, triazolyl and tetrazolyl.

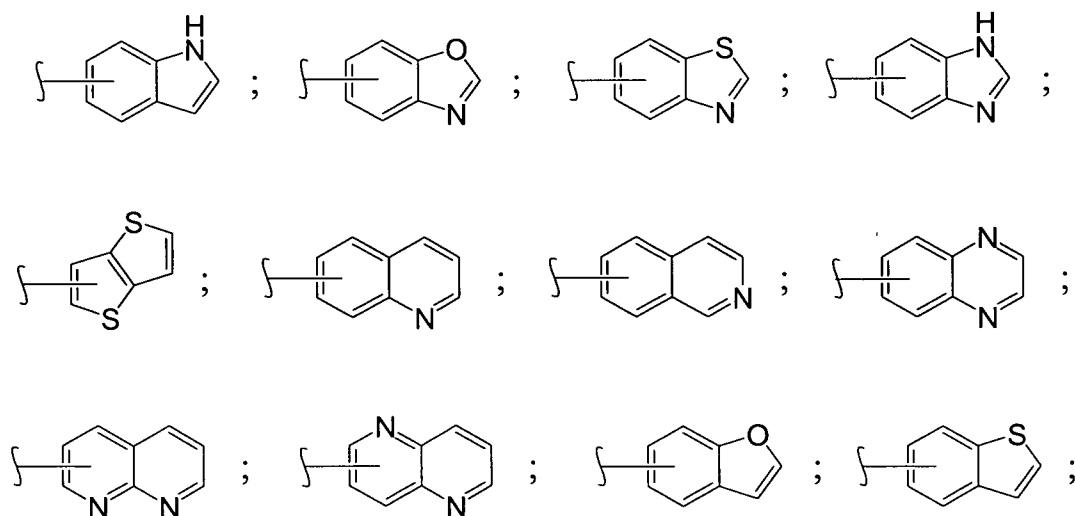
3. A compound according to claim 1, wherein Ar is selected from the group consisting of radical represented as follows:

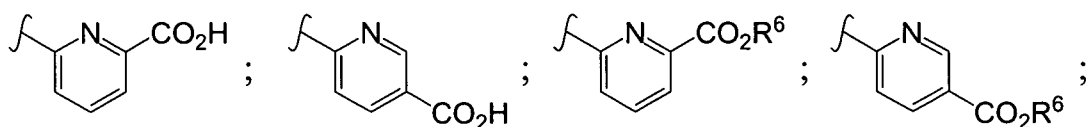
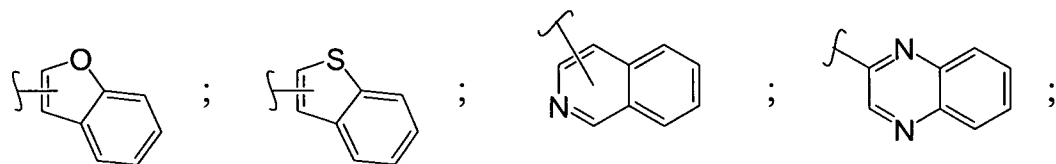
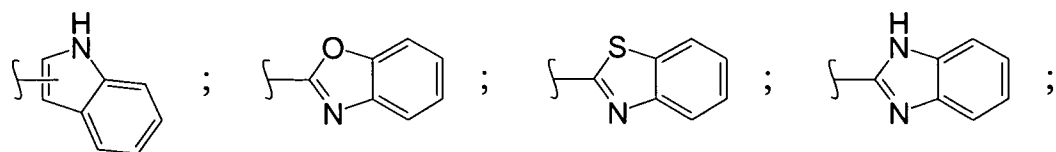


5

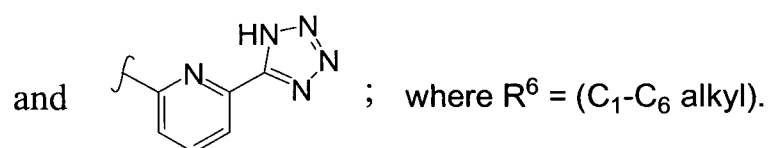
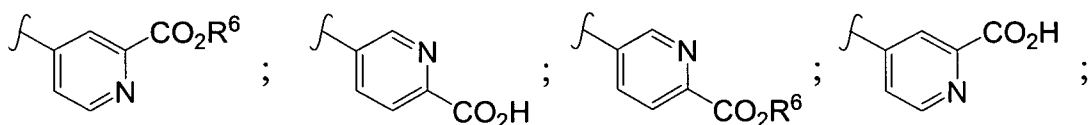


10





5



- 10 4. A compound according to claim 1, wherein R¹ is selected from the group consisting of
 -CH₃, -CF₃, -CN, -C(O)CF₃, -CO₂CH₃, -CO₂H, -C(O)NH₂, -OH, -OCH₃, -F, -NO₂, -NH₂, and
 -SO₂NH₂.

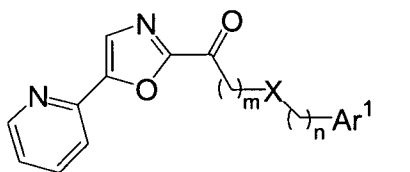
15

5. A compound according to claim 1, wherein R² is -H.

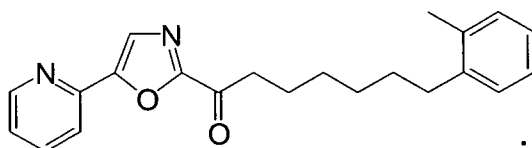
6. A compound according to claim 2, wherein R¹ is selected from the group consisting of
 20 -CH₃, -CF₃, -CN, -C(O)CF₃, -CO₂CH₃, -CO₂H, -C(O)NH₂, -OH, -OCH₃, -F, -NO₂, -NH₂, and
 -SO₂NH₂.

7. A compound according to claim 2, wherein R² is -H.

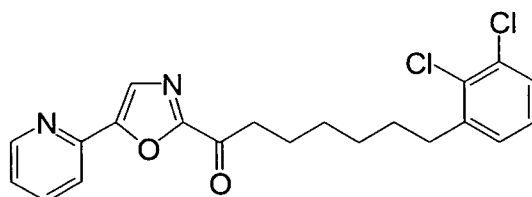
8. A compound according to claim 3, wherein R^1 is selected from the group consisting of
- CH₃, –CF₃, –CN, –C(O)CF₃, –CO₂CH₃, –CO₂H, –C(O)NH₂, –OH, –OCH₃, –F, –NO₂, –NH₂, and –SO₂NH₂.
9. A compound according to claim 3, wherein R^2 is –H.
10. A compound according to claim 8, wherein R^2 is –H.
11. A compound according to claim 1, having the following structure:



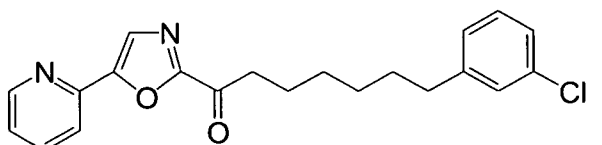
12. A compound according to claim 11, having the following structure:



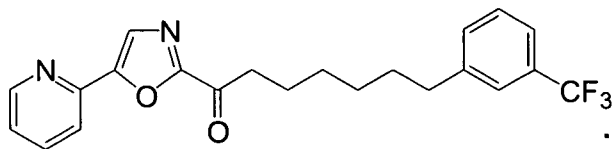
13. A compound according to claim 11, having the following structure:



14. A compound according to claim 11, having the following structure:

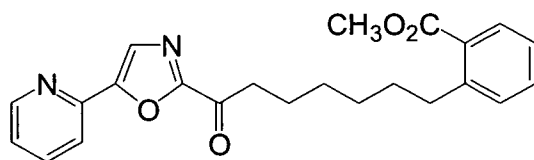


15. A compound according to claim 11, having the following structure:

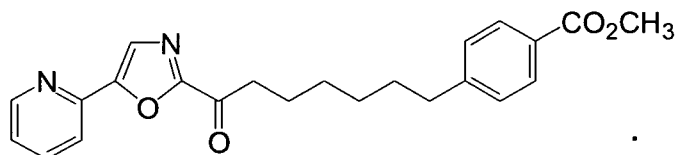


5

16. A compound according to claim 11, having the following structure:

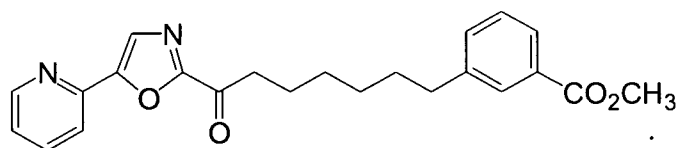


10 17. A compound according to claim 11, having the following structure:

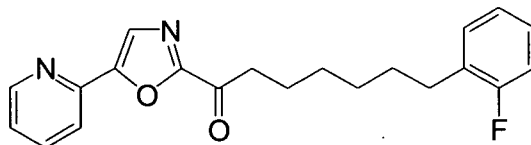


18. A compound according to claim 11, having the following structure:

15



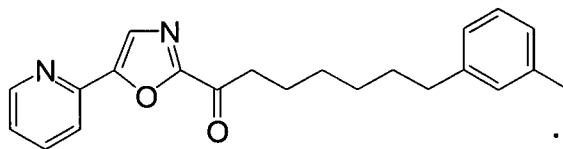
19. A compound according to claim 11, having the following structure:



20

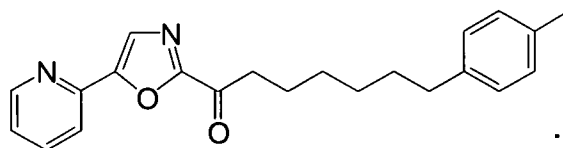
20. A compound according to claim 11, having the following structure:

5



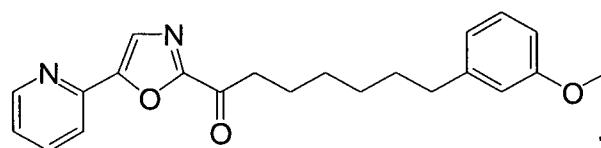
21. A compound according to claim 11, having the following structure:

10

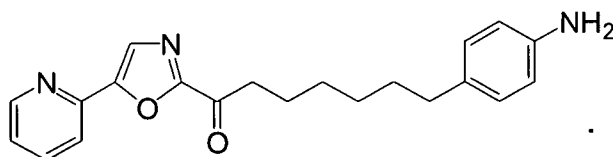


22. A compound according to claim 11, having the following structure:

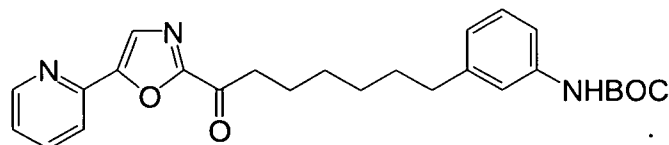
15



23. A compound according to claim 11, having the following structure:

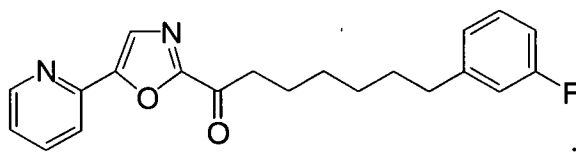


24. A compound according to claim 11, having the following structure:

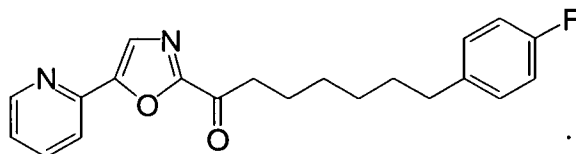


20

25. A compound according to claim 11, having the following structure:

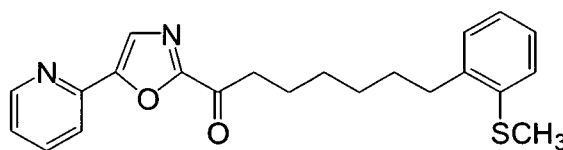


26. A compound according to claim 11, having the following structure:

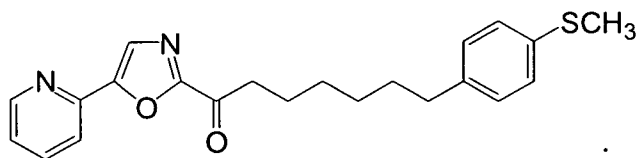


5

27. A compound according to claim 11, having the following structure:

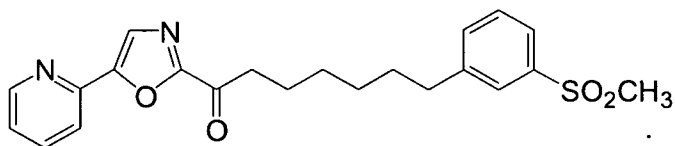


10 28. A compound according to claim 11, having the following structure:

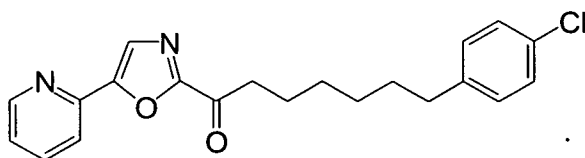


29. A compound according to claim 11, having the following structure:

15

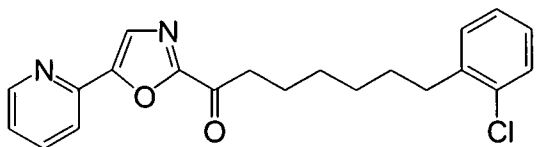


30. A compound according to claim 11, having the following structure:



20

31. A compound according to claim 11, having the following structure:



5

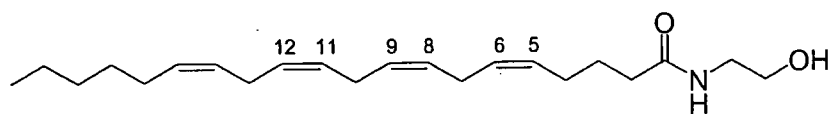
32. A process for inhibiting the catalytic activity of fatty acid amide hydrolase comprising the step of contacting the fatty acid amide hydrolase with a solution having an inhibitory concentration of a compound of claim 1.

10 33. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

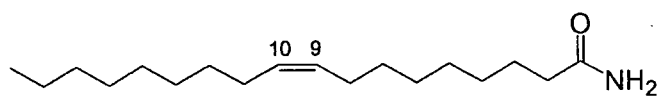
34. A pharmaceutical combination comprising a compound of claim 1 in combination with another FAAH modulator or another biologically active agent.

15

35. A pharmaceutical combination of claim 34 wherein the active ingredient is an opiod, an NSAID, gabapentin, pregabalin, tramadol, acetomminophen or aspirin.

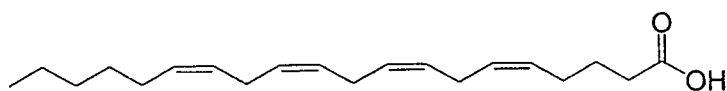


Anandamide (1a)

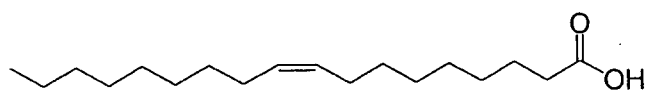


Oleamide (1b)

Fatty Acid Amide Hydrolase
(FAAH)

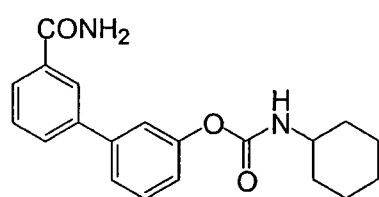


Arachidonic Acid (1c)

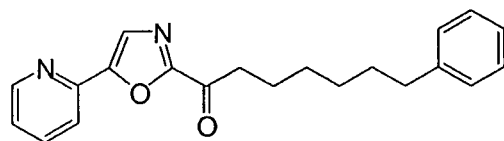


Oleic Acid (1d)

Figure 1



URB-597 (2a)
 $\text{IC}_{50} = 0.0046 \mu\text{M}$



OL-135 (2b)
 $K_i = 0.0047 \mu\text{M}$

Figure 2

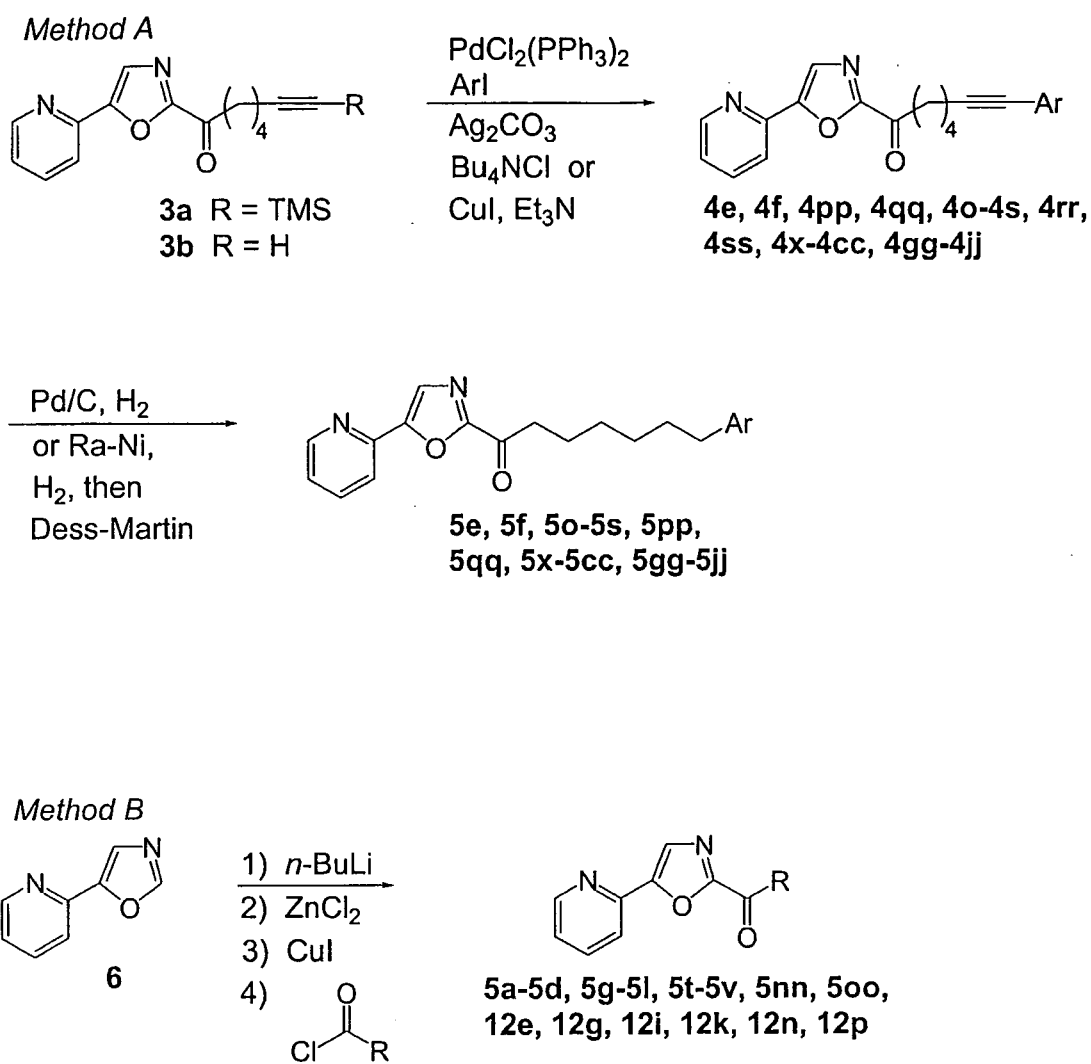


Figure 3

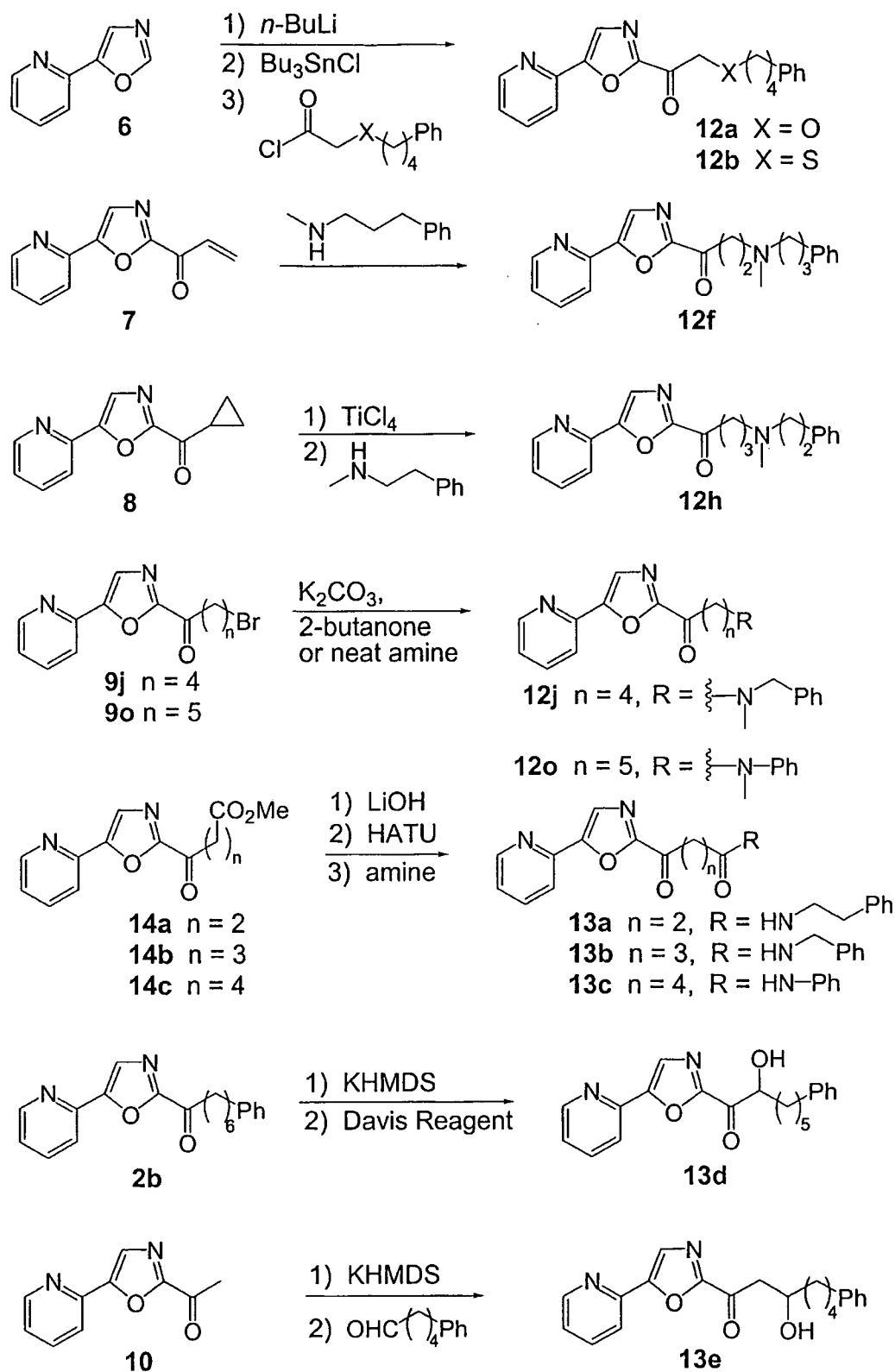
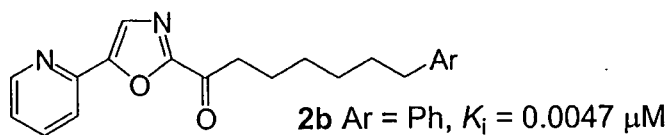
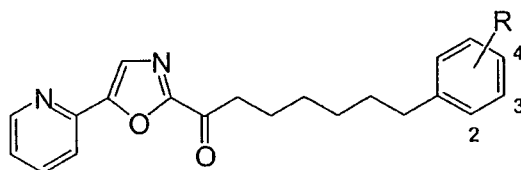


Figure 4



compd	Ar	$K_i, \mu\text{M}$	compd	Ar	$K_i, \mu\text{M}$
5a	2-thienyl	0.0043 ± 0.0008	5d	2-naphthyl	0.011 ± 0.001
5b	3-thienyl	0.0051 ± 0.0006	5e	2-pyridyl	0.12 ± 0.005
5c	1-naphthyl	0.0026 ± 0.003	5f	3-pyridyl	0.032 ± 0.032



compd	R	$K_i, \mu\text{M}$	compd	R	$K_i, \mu\text{M}$
5g	2-CH ₃	0.0030 ± 0.0009	5x	2-CF ₃	0.004 ± 0.0001
5h	3-CH ₃	0.0033 ± 0.0001	5y	3-CF ₃	0.001 ± 0.0001
5i	4-CH ₃	0.0028 ± 0.0006	5z	4-CF ₃	0.004 ± 0.0007
5j	2-OCH ₃	0.0058 ± 0.0001	5aa	2-CO ₂ CH ₃	0.001 ± 0.0003
5k	3-OCH ₃	0.0025 ± 0.0005	5bb	3-CO ₂ CH ₃	0.0019 ± 0.0005
5l	4-OCH ₃	0.0062 ± 0.0007	5cc	4-CO ₂ CH ₃	0.0015 ± 0.0001
5m	3-NH ₂	0.030 ± 0.001	5dd	2-CO ₂ H	>0.6
5n	4-NH ₂	0.0030 ± 0.0002	5ee	3-CO ₂ H	>0.6
5o	3-NHBOC	0.0024 ± 0.0006	5ff	4-CO ₂ H	>0.6
5p	4-NHBOC	0.0056 ± 0.0002	5gg	2-Cl	0.0019 ± 0.0001
5q	2-F	0.0017 ± 0.0002	5hh	3-Cl	0.0009 ± 0.00005
5r	3-F	0.0022 ± 0.0003	5ii	4-Cl	0.0027 ± 0.0001
5s	4-F	0.0032 ± 0.0005	5jj	2,3-Cl ₂	0.0009 ± 0.00005
5t	2-SCH ₃	0.0033 ± 0.0001	5kk	2-SO ₂ CH ₃	0.037 ± 0.0015
5u	3-SCH ₃	0.0042 ± 0.0003	5ll	3-SO ₂ CH ₃	0.0013 ± 0.0001
5v	4-SCH ₃	0.0025 ± 0.0001	5mm	4-SO ₂ CH ₃	0.019 ± 0.001
5w	4-NO ₂	0.0065 ± 0.0005			

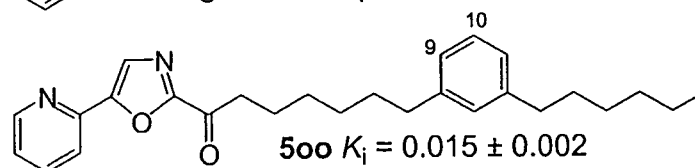
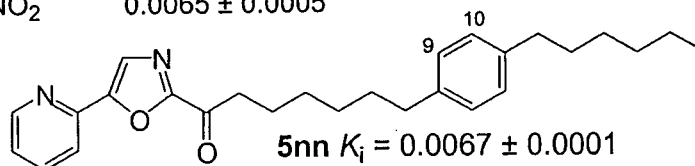
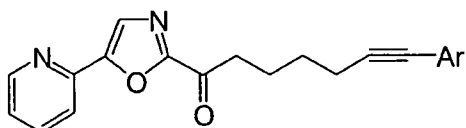
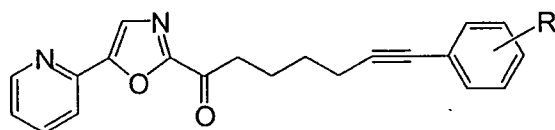


Figure 5

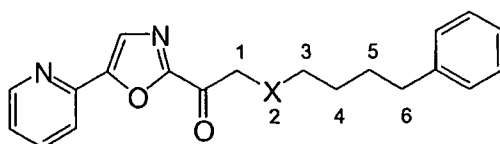


compd	Ar	K_i , μM	compd	Ar	K_i , μM
4e	2-pyridyl	0.28 ± 0.015	4pp	4-pyridyl	0.15 ± 0.008
4f	3-pyridyl	0.3 ± 0.018			



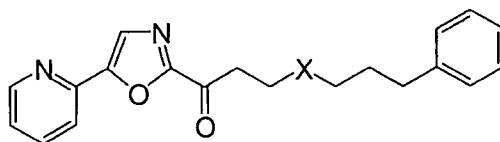
compd	R	K_i , μM	compd	R	K_i , μM
4qq	H	0.025 ± 0.0014	4y	3- CF_3	0.01 ± 0.0006
4o	3-NHBOC	0.012 ± 0.0008	4z	4- CF_3	0.075 ± 0.004
4p	4-NHBOC	0.023 ± 0.0013	4aa	2- CO_2CH_3	0.034 ± 0.002
4q	2-F	0.008 ± 0.0006	4bb	3- CO_2CH_3	0.030 ± 0.0018
4r	3-F	0.0032 ± 0.0002	4cc	4- CO_2CH_3	0.025 ± 0.0014
4s	4-F	0.036 ± 0.002	4gg	2-Cl	0.013 ± 0.0007
4rr	2- NO_2	0.017 ± 0.001	4hh	3-Cl	0.007 ± 0.0004
4ss	3- NO_2	0.0048 ± 0.0003	4ii	4-Cl	0.020 ± 0.0011
4w	4- NO_2	0.031 ± 0.0018	4jj	2,3- Cl_2	0.005 ± 0.0003
4x	2- CF_3	0.016 ± 0.001			

Figure 6

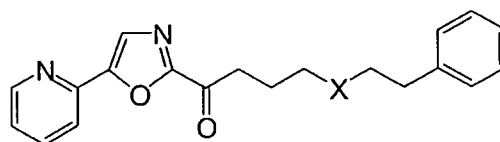


2b X = CH₂, K_i = 0.0047 μM

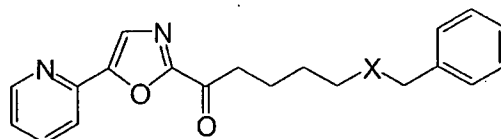
compd	X	K _i , μM	compd	X	K _i , μM
12a	O	0.06 ± 0.005	12c	SO	1 ± 0.08
12b	S	0.004 ± 0.0002	12d	SO ₂	20 ± 1.2



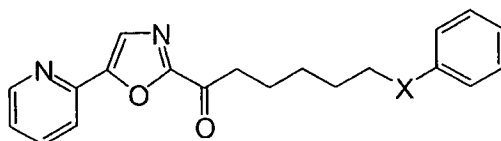
compd	X	K _i , μM	compd	X	K _i , μM
12e	O	0.09 ± 0.005	12f	NCH ₃	0.2 ± 0.015



compd	X	K _i , μM	compd	X	K _i , μM
12g	O	0.063 ± 0.006	12h	NCH ₃	3.5 ± 0.2

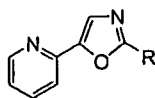


compd	X	K _i , μM	compd	X	K _i , μM
12i	O	0.055 ± 0.005	12l	SO	2.5 ± 0.13
12j	NCH ₃	0.20 ± 0.012	12m	SO ₂	>10
12k	S	0.025 ± 0.0018			



compd	X	K _i , μM	compd	X	K _i , μM
12n	O	0.014 ± 0.0013	12q	SO	1 ± 0.06
12o	NCH ₃	0.04 ± 0.003	12r	SO ₂	6 ± 0.4
12p	S	0.003 ± 0.0002			

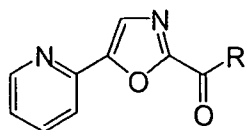
Figure 7



2b R = C(O)(CH₂)₆Ph, K_i = 0.0047 μM

compd	R	K _i , μM
13a		>100
13b		20 ± 1.2
13c		3.1 ± 0.1
13d		0.008 ± 0.0006
13e		0.035 ± 0.002
13f		0.5 ± 0.03
13g		1.5 ± 0.08
13h		0.2 ± 0.015
13i		0.035 ± 0.0025

Figure 8



2b R = (CH₂)₆Ph, K_i = 0.0047 μM

compd	R	K _i , μM
14a		>100
14b		7 ± 0.4
14c		1.8 ± 0.13
14d		>50
14e		2.5 ± 0.15
14f		0.8 ± 0.05
14g		>2

compd	K _i , μM
 14h	2 ± 0.1
 14i	>100

Figure 9

compd	K_i , μM (human)	K_i , μM (rat)
5jj	$0.0012 \pm .001$	0.0009

Figure 10

compd	K_i , μ M	FAAH	KIAA1363	TGH
2b	0.0047	0.002	>100 (>50000)	0.6 (300)
5a	0.0043	0.02	>100 (>5000)	0.7 (35)
5b	0.0051	0.04	>100 (>3300)	0.8 (27)
5c	0.0026	0.01	>100 (>10000)	0.3 (30)
5d	0.011	0.04	>100 (>2500)	0.02 (0.5)
5e	0.12	0.03	>100 (>3300)	1 (33)
5f	0.032	0.02	>100 (>5000)	1 (50)
5g	0.003	0.03	>100 (>3300)	3 (100)
5h	0.0033	0.03	>100 (>3300)	5 (170)
5i	0.0028	0.04	>100 (>2500)	5 (125)
5j	0.0058	0.01	>100 (>10000)	5 (500)
5k	0.0025	0.02	>100 (>5000)	1 (50)
5l	0.0062	0.02	>100 (>5000)	5 (250)
5n	0.003	0.004	>100 (>25000)	3 (750)
5q	0.0017	0.03	>100 (>3300)	0.5 (17)
5r	0.0022	0.01	>100 (>10000)	1 (100)
5s	0.0032	0.02	>100 (>5000)	1 (50)
5t	0.0033	0.03	>100 (>3300)	10 (330)
5u	0.0042	0.01	>100 (>10000)	0.3 (30)
5v	0.0025	0.02	>100 (>5000)	0.8 (40)
5w	0.0065	0.0005	>100 (>200000)	50 (100000)
5x	0.004	0.03	>100 (>3300)	7 (230)
5y	0.001	0.02	>100 (>5000)	0.2 (10)
5z	0.004	0.009	>100 (>10000)	0.2 (20)
5aa	0.001	0.0004	>100 (>250000)	10 (25000)
5bb	0.0019	0.0004	>100 (>250000)	10 (25000)
5cc	0.0015	0.00024	>100 (>400000)	6 (25000)
5gg	0.0019	0.02	>100 (>5000)	0.6 (30)
5hh	0.0009	0.002	>100 (>50000)	0.5 (250)
5ii	0.0027	0.03	>100 (>3300)	2 (67)
5jj	0.0009	0.007	>100 (>14000)	0.5 (70)
5kk	0.037	0.1	>100 (>1000)	3 (30)
5ll	0.0013	0.004	>100 (>25000)	4 (1000)
5mm	0.019	0.05	>100 (>2000)	2 (40)
5nn	0.0067	0.03	>100 (>3300)	30 (1000)
5oo	0.015	0.08	>100 (>1250)	20 (250)
12a	0.06	0.01	0.58 (>58)	0.34 (34)

Figure 11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/06913

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/76; A61K 31/42 (2008.04)

USPC - 514/374

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/374

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/236.8, 340, 375 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubEAST(USPT,PGPB,EPAB,JPAB); GoogleScholar

Search fatty acid amide hydrolase inhibitors, FAAH, pyridine, oxazole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2006/0111359 A1 (BOGER) 25 May 2006 (25.05.2006) para [0007], [0010]	1-11 ----- 12-35
Y	US 2004/0127518 A1 (PIOMELLI et al.) 1 July 2004 (01.07.2004) para [0063], [0071], [0078], [0118], [0124], [0194]	12-28 and 30-35
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Date of the actual completion of the international search

3 October 2008 (03.10.2008)

Date of mailing of the international search report

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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

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