Exquisite Selectivity For Human Toll-like Receptor 8 in Substituted Furo[2,3-c]quinolines

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Abstract

Toll-like receptor (TLR)-8 agonists activate adaptive immune responses by inducing robust production of T helper 1-polarizing cytokines, suggesting that TLR8-active compounds may be promising candidate adjuvants. We synthesized and evaluated hitherto unexplored furo[2,3-c]quinolines and its regioisomeric furo[3,2-c]quinolines, derived via a tandem, one-pot Sonogashira coupling and intramolecular 5 endo-dig cyclization strategy, in a panel of primary screens. We observed a pure TLR8 agonistic activity profile in select furo[2,3-c]quinolines, with maximal potency conferred by a C2-butyl group (EC50: 1.6 µM); shorter, longer, or substituted homologues, as well as compounds bearing C1 substitutions were inactive, which was rationalized by docking studies using the recently-described crystal structure of human TLR8. The best-in-class compound displayed prominent proinflammatory cytokine induction (including interleukin-12 and interleukin-18), but was bereft of interferon-α-inducing properties, confirming its high selectivity for human TLR8.

Keywords

TLR8; TLR8 agonists; Vaccine adjuvants; Innate immunity; Furoquinolines; Sonogashira coupling

Introduction

Vaccines have played an indispensable role in the dramatic improvement in public health witnessed in modern times, particularly in the prevention of mortality and morbidity attributable to infectious diseases.1 While the successes of active immunization beginning with Jenner’s smallpox vaccine in 1796 are numerous and extraordinary, our failure to develop effective vaccines against diseases such as the human immunodeficiency virus (HIV), tuberculosis, and malaria have served to highlight deficiencies and shortcomings of the state-of-the-art in contemporary vaccine technology, catalyzing a renaissance in rational vaccine design and development.2,3

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Supporting Information Available: Characterization data (1H, 13C, mass spectra), LC-MS analyses of final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.
A component that is being increasingly recognized as pivotal in the design of effective vaccines is the incorporation of appropriate immune potentiators (also termed adjuvants) along with the antigen. Adjuvants initiate early innate immune responses which subsequently lead to the induction of robust and long-lasting adaptive immune responses.\(^4\) Aluminum salts (primarily phosphate and hydroxide), discovered by Glenny and coworkers,\(^5\) have been the only adjuvants in clinical use until the recent approval of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) by the FDA.\(^6\) Aluminum salts are weak adjuvants for antibody induction, promoting a T helper 2 (Th2)-skewed, rather than a Th1 response;\(^7,8\) they are virtually ineffective at inducing cytotoxic T lymphocyte or mucosal immunoglobulin A (IgA) antibody responses, and additionally, also appear to promote the induction of IgE isotype switching, which has been associated with allergic reactions in some subjects.\(^7,8\)

Innate immune afferent signals activated by vaccine adjuvants include those originating from Toll-like receptors (TLRs), as well as retinoic acid-inducible gene 1 (RIG-I)-like receptors\(^9\) and nucleotide oligomerization domain (NOD)-like receptors (NLRs).\(^10,11\) There are 10 functional TLRs encoded in the human genome, which are trans-membrane proteins with an extracellular domain having leucine-rich repeats (LRR) and a cytosolic domain called the Toll/IL-1 receptor (TIR) domain.\(^12\) The ligands for these receptors are highly conserved molecules such as lipopolysaccharides (LPS) (recognized by TLR4), lipopeptides (TLR2 in combination with TLR1 or TLR6), flagellin (TLR5), single stranded RNA (TLR7 and TLR8), double stranded RNA (TLR3), CpG motif-containing DNA (recognized by TLR9), and profilin present on uropathogenic bacteria (TLR11).\(^12\) TLR1, −2, −4, −5, and −6 recognize extracellular stimuli, while TLR3, −7, −8 and −9 function within the endolysosomal compartment.\(^12\) The activation of TLRs by their cognate ligands leads to production of inflammatory cytokines, and up-regulation of major histocompatibility complex (MHC) molecules and co-stimulatory signals in antigen-presenting cells (APCs) as well as activating natural killer (NK) cells (innate immune response), which leads to the priming and amplification of T-, and B-cell effector functions (adaptive immune responses).\(^13–16\)

We have recently embarked on a systematic exploration\(^17,18\) of a variety of TLR agonists with a view to identifying safe and potent vaccine adjuvants. The chemotypes that we have explored thus far include agonists of TLR2,\(^19–21\) TLR7,\(^22–26\) TLR8,\(^27,28\) NOD1,\(^29\) as well as C-C chemokine receptor type 1.\(^30\)

Our efforts are currently focused on evaluating small molecule agonists of TLR8 as potential vaccine adjuvants. TLR8 is expressed in myeloid DCs, monocytes, and monocyte-derived dendritic cells, and engagement of TLR8 agonists induces a dominant proinflammatory cytokine profile including tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), interleukin-12 (IL-12), and IL-18.\(^31\) The prominent nuclear factor-\(\bullet\)B (NF-\(\bullet\)B)- and c-Jun N-terminal kinase-mediated stimulatory effects of TLR8-agonists on APCs\(^32,33\) leads to robust Th1-type responses.\(^34\) Unlike TLR2, −4, or −7 agonists, TLR8 agonists appear unique in markedly upregulating the production of Th1-polarizing cytokines TNF-\(\alpha\) and IL-12 from neonatal APCs,\(^34\) suggesting that TLR8 agonists may be useful as adjuvants for enhancing immune responses in newborns.

Furthermore, human T-regulatory cells (Tregs), classified immunophenotypically as naturally occurring (CD4\(^+\)CD25\(^+\)Foxp3\(^+\)) or induced (CD4\(^+\)CD25\(^{hi}\)), down-regulate and suppress a broad array of immune responses, including the non-specific suppression of both CD4\(^+\) and CD8\(^+\) T-cells via cell-cell contact and via production of immunosuppressive cytokines such as IL-10 and transforming growth factor–\(\beta\) (TGF-\(\beta\)).\(^35–41\) Tregs express abundant TLR8 mRNA, and TLR8 agonists have been shown to reverse Treg function via a
TLR8-MyD88 (myeloid differentiation factor 88)-IRAK4 (IL-1-receptor-associated kinase 4) signaling pathway. Engagement and activation of TLR8 are, therefore, strongly associated with enhanced adaptive immune responses.

A prerequisite for the careful evaluation of TLR8 activators as potential adjuvants for neonatal vaccines is the availability of pure TLR8 agonists with negligible TLR7 activity and, other than the 2,3-diamino-furo[2,3-c]pyridine class of compounds recently described by us, all other known agonists of TLR8 such as the imidazoquinolines (for instance, CL075, thiazoloquinolines (CL075, CL075, CL075, and a 2-aminobenzazepine derivative (VTX-2337, whose complete structure has not been reported. The structures of these mixed agonists are shown in Fig. 1. The 2,3-diamino-furo[2,3-c]pyridines are atypical and noncanonical in that although they activate TLR8-dependent NF-κB signaling, they are devoid of proinflammatory cytokine inducing activities.

Driven by our desire to identify pure TLR8 agonists also capable of inducing IL-12 and IL-18, and drawing from our earlier work in delineating structure-activity relationships (SAR) in the furo[2,3-c]pyridines, we began exploring a variety of fused heterocyclic core structures. Our continuing investigations have led to the discovery of pure TLR8-agonistic activity associated with strong interferon-γ (IFN-γ), IL-12 and IL-18 inducing activities in a series of furo[2,3-c]quinolines. The 4-amino-furo[2,3-c]quinoline chemotype is unprecedented in the literature, and the activity profile of this class of compounds, examined by a range of secondary screens in human ex vivo blood models, including transcriptomal profiling, confirm pure TLR8 agonism with no detectable signatures of TLR7 activity, allowing for the first time a clear path toward the evaluation of such compounds as potential adjuvants for vaccines.

Results and Discussion

Our recent work on the 2,3-diamino-furo[2,3-c]pyridines, which displayed TLR8-dependent NF-κB signaling but dissociated from downstream cytokine induction led us to consider benzologues of the furo[2,3-c]pyridines. The 4-amino-furo[2,3-c]quinoline chemotype is hitherto not described in the literature, and presented a good starting point since its scaffold closely resembles known TLR7/8-active ligands. We envisioned that the furo[2,3-c]quinoline and its regioisomeric core structures could be derived via one-pot Sonogashira coupling of alkynes to either 4-iodoquinolin-3-ol (Scheme 1), or 3-iodoquinolin-4-ol (Scheme 2), followed by a tandem, tethered nucleophile-assisted, intramolecular 5 endo-dig cyclization. Electrophilic iodination of commercially-available 3- and 4-hydroxyquinoline proceeded uneventfully using reported methods (Schemes 1 and 2, respectively). One-pot Sonogashira coupling with a variety of alkynes, followed by 5-endo-dig cyclization yielded compounds the 2-substituted furo[2,3-c]quinolines 6a–y (Scheme 1) and the regioisomeric furo[3,2-c]quinolines 11a–c (Scheme 2) in good yields. The target compounds 8a–y and 13a–c bearing 4-amino groups were obtained using conventional procedures described previously. Compounds 8a–y and 13a–c were screened in a panel of reporter gene assays for human TLR2/3/4/5/7/8/9 and NOD1/2 modulatory activities. We were fortunate that a distinct activity profile was observed in the very first set of compounds that were synthesized. Compounds 8b–f showed pure TLR8 agonistic activity with maximal potency exhibited by 8d with a C2-butyl group (EC50: 1.6 µM, Fig. 2); shorter (8b, 8c) and longer (8e, 8f) homologues displayed lower agonistic potencies with the shortest analogue 8a being inactive (Fig. 2). The dose-response profiles show characteristic biphasic responses (dose-dependent activation, followed by apparent suppression of NF-κB translocation, Fig. 2) as we had previously observed in several chemotypes. We verified that the apparent
suppression was not due to cytotoxicity using LDH release and mitochondrial redox-based assays as described earlier by us.\textsuperscript{53,54}

The SAR pattern with maximal activity conferred by a C2-butyl group is virtually identical to that found in TLR7-active imidazoquinolines,\textsuperscript{23} and the TLR8/7-agonistic thiazoloquinolines,\textsuperscript{27} but unlike the thiazoloquinolines,\textsuperscript{27} 8d was devoid of TLR7-stimulatory activities in primary screens (Fig. 2). The exquisite selectivity for TLR8 was confirmed in secondary screens using ex vivo whole human blood and PBMC models.\textsuperscript{17} We had earlier shown that proinflammatory cytokine induction (TNF-\(\alpha\), IL-1\(\beta\), IL-6 and IL-8) is a consequence of TLR7 activation.\textsuperscript{19} Importantly, Th1-biasing IL-12 and IL-18 induction is also TLR8-dependent, while IFN-\(\alpha\)-production is TLR7-mediated.\textsuperscript{24,52} We therefore examined cytokine and interferon induction profiles of 8d, employing the thiazoloquinoline 2 as a reference compound. Unlike the 2,3-diamino-furo[2,3-c]pyridines,\textsuperscript{28} 8d was observed to induce TNF-\(\alpha\), IL-1\(\beta\), IL-6 and IL-8 in a dose-dependent manner, albeit with a lower potency than 2 (Fig. 3). Compound 8d induced IL-12 and IL-18, but was bereft of IFN-\(\alpha\)-inducing properties (Fig. 4). The selectivity of 8d for TLR8 was also reflected in the absence of natural killer lymphocyte activation\textsuperscript{17,18} in human whole blood models as assessed by cluster of differentiation 69 (CD69) expression (Fig. 5), which we had previously shown to be TLR7-dependent.\textsuperscript{17,18} Consistent with the above findings, transcriptomal profiling experiments showed strong induction of proinflammatory cytokine transcripts (including IL-12 and IL-18) by both 2 and 8d, but IFN-\(\alpha\)-transcription was induced only by 2, owing to its dual TLR8/7 agonistic activity (Table 1). These data collectively confirm the selectivity of 8d for human TLR8.

Given that 8d represents an optimized compound in a uniquely TLR8-specific chemotype, we also profiled cytokine- and chemokine-inducing properties using a 41-analyte, multiplexed assay, comparing 8d to a variety of TLR agonists. We found that of the 41 analytes analyzed, whereas both 8d and 2 induced granulocyte colony-stimulating factor (G-CSF), growth-related oncogene (GRO), and macrophage inflammatory proteins 1-\(\alpha\) and -\(\beta\) (MIP-1\(\alpha\), MIP-1\(\beta\)), a highly potent, pure TLR7-agonistic imidazoquinoline (1-benzyl-2-butyl-1H-imidazo[4,5-c]quinolin-4-amine) that we had identified in our earlier SAR studies\textsuperscript{23} did not (Fig. 6), indicating that this set of analytes could be useful in distinguishing TLR8-specific responses.

Distinct hints that the SAR in the 2-substituted furo[2,3-c]quinolines was much more stringent compared to the thiazoloquinolines\textsuperscript{27} was evident right from the outset. C2 substituents with branched alkyl groups (8g±i) abrogated activity, and analogues with cycloaliphatic (8j±8m) or aromatic (8n, 8o) substituents were inactive, pointing to intolerance of steric bulk at the putative binding site(s). Since the crystal structure of TLR8 was not available at the time, we forged on, surmising that the introduction of polar H-bond donors (or acceptors) on the C2 alkyl group may help us better understand binding site interactions. We therefore examined a number of analogues bearing hydroxyl groups at various positions along the C2-alkyl chain (8p±8v), compounds with C2 substituents terminating with a primary amine (8x, 8y), as well as an analogue with an ether (H-bond acceptor) incorporated in the alkyl group (8w), but none of these compounds were active in any of our primary screens.

Mindful of our earlier observation that regioisomerism in the imidazoquinolines resulted in a switch from agonistic to antagonistic activities,\textsuperscript{22,55} we also synthesized key regioisomeric furo[3,2-c]quinolines, 13a±c (Scheme 2); these compounds were quiescent, displaying neither stimulatory nor inhibitory activity in primary screens. Given the fastidious structural requirements at the C2 position, we next synthesized a furo[2,3-c]isoquinoline with a C2-
butyl substituent (18, Scheme 3) in an order to explore chemical space beyond the fused-quinoline chemotypes, but were disappointed in that 18, too, was inactive.

Reverting, therefore, to the C2-butyl furo[2,3-c]quinoline, we interrogated the effect of introducing substituents at the C1 position. We were, in particular, desirous of evaluating a C1-benzyl substituent, for this strategy had previously yielded highly potent, TLR7-selective agonists in the imidazoquinoline series.23 Electrophilic bromination of 7d furnished precursor 19 in good yield (Scheme 4) which was carried forward to obtain both the 1-bromo- and 1-benzyl-substituted analogues 21 and 24, respectively (Scheme 4). Both analogues were found to be inactive.

As mentioned earlier, the 2,3-diamino-furo[2,3-c]pyridine class of compounds recently described by us28 activate TLR8 but do not result in downstream cytokine production, suggesting an apparent dissociation between receptor occupancy, and signal transduction events leading to cytokine production, and it was of interest to compare SAR that we had gleaned from the furo[2,3-c]quinolines with select analogues of the 4-amino, C2-alkyl furo[2,3-c]pyridine series. Two such compounds (28a, 28b) were therefore synthesized (Scheme 5). Both these analogues retained TLR8-selective agonistic activities, but were substantially weaker (EC₅₀: 24.4 µM and 46.2 µM, respectively) than 8d (EC₅₀: 1.6 µM).

Although at first glance our attempts at exploring SAR in the furo[2,3-c]quinolines had yielded a large number of inactive compounds, we are delighted in no small measure that we have finally arrived at pure TLR8 agonists that induce the expected complement of TLR8-mediated, Th1-biasing cytokine mediators, but are devoid of TLR7-dependent IFN-α-inducing properties. Just as we were concluding our studies on the furo[2,3-c]quinolines, crystal structures of hTLR8 complexed with mixed TLR7/TLR8-agonistic imidazoquinolines and thiazoloquinolines were reported,56 allowing us to rationalize our experimentally-determined SAR on the pure TLR8-agonistic furo[2,3-c]quinolines. The crystal structure of human TLR8 in complex with 2 (PDB ID: 3W3K)56 was used for docking studies. We employed induced-fit methods,57,58 in which the receptor sites were allowed conformational and torsional flexibility to simulate realistic ligand-receptor interactions to account for conformational changes in the binding site residues. 2 as well as 8d occupy the same binding pocket formed by both the TLR8 protomers (Fig. 7A – B), with the binding geometry of these compounds and interacting residues being virtually identical (Fig. 7C – D). Strong ionic H-bonds (salt bridges) are observed between the C4-amine of both 2 and 8d with Asp543 of protomer B, with additional stabilization derived from a H-bond between Thr574 (protomer B) and either the N₁ atom of the thiazole ring of 2, or the oxygen atom of the furanyl ring of 8d. π-π Interactions of the quinoline moiety of 2 and 8d (Phe405/Tyr353), as well as hydrophobic interactions of the C2-alkyl group (Phe346/Ile403/Gly376) occur exclusively with residues in protomer A (Fig. 7C – D). All of these interactions appear indispensable. The butyl group of 8d allows for excellent nonpolar and van der Waals contacts in the rather shallow hydrophobic cavity, and homologues with increasing C2-chain length (8e±8f) dock poorly with kinked and sterically unfavorable conformations of the alkyl group. Analogues with cycloaliphatic (8j±8m) and aromatic substituents (8n, 8o) do not fit in the hydrophobic pocket at all, leading to unrealistic docked conformations (not shown). The cavity is lined entirely with side-chains of hydrophobic residues, explaining why even length-optimized analogues bearing polar groups at the C2 position such as 8r, 8u and 8v do not display TLR8 agonism. The feeble activity of the furopyridine compounds 28a and 28b imply significant contributions in binding free energies by π-π interactions of the quinoline moiety with Tyr353 and Phe405. The imposition of additional steric bulk at C1 (compound 24) is not tolerated in the cleft bounded by Phe261 and Ser352 (Fig. 7D). Not only is pivotal ionic H-bond between the C4-amine of regioisomeric furo[3,2-c]quinoline 13b and Asp543 weakened (3.8 Å), the
additional H-bond between the oxygen atom of the furan ring and Thr574 is lost, forcing 13b to bind to TLR8 in an inverted fashion, with the C2-alkyl group facing the entrance to the binding site (Fig. 7E). Highly unfavorable H-bonds are also seen in the isoquinoline analogue 18, especially with the loss of H-bonding of the furanyl oxygen (Fig. 7F).

In conclusion, an exploration of furo[2,3-c]quinolines have yielded pure TLR8 agonists, which are expected to possess strong Th1-biasing adjuvant properties as evidenced by prominent IL-12 and IL-18 induction profiles, and are without IFN-α-inducing properties, confirming its exquisite selectivity for human TLR8. The recently published atomic structure of human TLR8 has permitted a careful evaluation of SAR in this hitherto uncharacterized chemotype, and provides clear directions toward rational, structure-based ligand design. Immunization studies employing neonatal animal models are being planned with a view to comparing adjuvanticity of agonists with pure TLR7 and TLR8 agonistic properties vis-à-vis compounds with dual TLR7/8-stimulatory activities.

**Experimental Section**

**Chemistry**

All of the solvents and reagents used were obtained commercially and used as such unless noted otherwise. Moisture- or air-sensitive reactions were conducted under nitrogen atmosphere in oven-dried (120 °C) glass apparatus. The solvents were removed under reduced pressure using standard rotary evaporators. Flash column chromatography was carried out using RediSep Rf ‘Gold’ high performance silica columns on CombiFlash Rf instrument unless otherwise mentioned, while thin-layer chromatography was carried out on silica gel (200 µm) CCM pre-coated aluminum sheets. Purity for all final compounds was confirmed to be greater than 97% by LC-MS using a Zorbax Eclipse Plus 4.6 mm × 150 mm, 5 µm analytical reverse phase C18 column with H₂O-isopropanol or H₂O-CH₃CN gradients and an Agilent ESI-QTOF mass spectrometer (mass accuracy of 3 ppm) operating in the positive ion (or negative ion, as appropriate) acquisition mode.

**Synthesis of 4-iodoquinolin-3-ol (5)**

In an oven dried round bottom flask equipped with a stirring bar was placed 3-hydroxy quinoline (1.0 g, 6.89 mmol) in 2N NaOH (20 mL). To this mixture a solution of iodine (8.27 mmol) in 20% of aqueous potassium iodide (20 mL) was added drop-wise and stirred for 3 h at room temperature. The mixture was then acidified with acetic acid, and the precipitate was filtered and washed with water. After drying under vacuum, 1.50 g of 5 was obtained, which was used without purification. ¹H NMR (500 MHz, DMSO) δ 11.19 (s, 1H), 8.50 (s, 1H), 7.98 – 7.85 (m, 2H), 7.65 – 7.60 (m, 1H), 7.60 – 7.55 (m, 1H). ¹³C NMR (126 MHz, DMSO) δ 152.2, 142.6, 141.3, 130.9, 129.9, 129.2, 128.5, 126.6, 94.5. MS (ESI) calculated for C₉H₆INO, m/z 270.95, found 271.96 (M+H)⁺.

**General procedure for Sonogashira reaction**

To a stirred solution of 4-iodoquinolin-3-ol in acetonitrile:triethylamine (2:1) were added the appropriate alkyne (0.553 mmol), Pd(PPh₃)₄ (0.018 mmol) and CuI (0.018 mmol). The resulting reaction mixture was stirred at 70°C under nitrogen atmosphere for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with ethylacetate (3 × 10 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure, crude material was purified by flash chromatography using CH₂Cl₂:MeOH as an eluent.
2-propylfuro[2,3-c]quinoline (6c)
Yellow solid (60 mg, 78%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.08 (s, 1H), 8.20 (d, $J = 8.2$ Hz, 1H), 8.07 (dd, $J = 8.1, 1.2$ Hz, 1H), 7.67 (ddd, $J = 8.4, 6.9, 1.5$ Hz, 1H), 7.60 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 6.91 (d, $J = 0.8$ Hz, 1H), 2.91 – 2.86 (m, 2H), 1.91 – 1.82 (m, 2H), 1.06 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 163.0, 148.8, 144.3, 136.3, 131.4, 130.1, 127.3, 126.5, 123.7, 123.2, 101.1, 30.8, 21.2, 13.9. MS (ESI) calculated for C$_{14}$H$_{13}$NO, m/z 211.10, found 212.11 (M+H)$^+$. 

2-butylfuro[2,3-c]quinoline (6d)
Yellow solid (70 mg, 83%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.08 (d, $J = 0.5$ Hz, 1H), 8.19 (dd, $J = 8.4, 0.5$ Hz, 1H), 8.09 – 8.08 (m, 1H), 7.66 (ddd, $J = 8.4, 6.9, 1.5$ Hz, 1H), 7.60 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 6.90 (d, $J = 0.8$ Hz, 1H), 2.92 (t, 2H), 1.82 (ddd, $J = 15.2, 8.5, 6.7$ Hz, 2H), 1.51 – 1.42 (m, 2H), 0.99 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 163.2, 148.8, 144.3, 136.4, 131.4, 130.1, 127.3, 126.5, 123.7, 123.2, 101.0, 29.9, 28.5, 22.4, 13.9. MS (ESI) calculated for C$_{15}$H$_{15}$NO, m/z : 225.11, found 226.13 (M+H)$^+$. 

2-pentylfuro[2,3-c]quinoline (6e)
White solid (70 mg, 79%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.08 (d, $J = 0.7$ Hz, 1H), 8.20 (dd, $J = 8.4, 0.6$ Hz, 1H), 8.07 (ddd, $J = 8.1, 1.5, 0.6$ Hz, 1H), 7.66 (ddd, $J = 8.4, 6.9, 1.5$ Hz, 1H), 7.60 (ddd, $J = 8.1, 6.9, 1.3$ Hz, 1H), 6.91 – 6.90 (m, 1H), 2.91 (t, $J = 7.2$ Hz, 2H), 1.88 – 1.80 (m, 2H), 1.46 – 1.35 (m, 4H), 0.93 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 163.3, 148.8, 144.3, 136.4, 131.4, 130.1, 127.3, 126.5, 123.7, 123.2, 101.0, 31.5, 28.8, 27.5, 22.5, 14.1. MS (ESI) calculated for C$_{15}$H$_{15}$NO, m/z : 239.13, found 240.14 (M+H)$^+$. 

2-hexylfuro[2,3-c]quinoline (6f)
White solid (70 mg, 75%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.08 (s, 1H), 8.20 (t, $J = 8.3$ Hz, 1H), 8.07 (dd, $J = 8.1, 1.1$ Hz, 1H), 7.66 (ddd, $J = 8.4, 7.0, 1.5$ Hz, 1H), 7.60 (ddd, 1H), 6.90 (d, $J = 0.6$ Hz, 1H), 2.91 (t, $J = 7.6$ Hz, 2H), 1.87 – 1.79 (m, 2H), 1.50 – 1.40 (m, 2H), 1.39 – 1.28 (m, 4H), 0.90 (t, $J = 8.2$, 5.9 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 163.2, 148.8, 144.3, 136.3, 131.4, 130.1, 127.3, 126.5, 123.7, 123.2, 101.0, 31.7, 29.0, 28.9, 27.8, 22.7, 14.2. MS (ESI) calculated for C$_{16}$H$_{17}$NO, m/z : 253.15, found 254.16 (M+H)$^+$. 

2-isobutylfuro[2,3-c]quinoline (6g)
Liquid (120 mg, 72%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.12 (s, 1H), 8.25 (d, $J = 8.2$ Hz, 1H), 8.08 (d, $J = 7.9$ Hz, 1H), 7.69 – 7.64 (m, 1H), 7.63 – 7.58 (m, 1H), 6.91 (s, 1H), 2.79 (dd, $J = 7.1, 0.5$ Hz, 2H), 2.20 (dp, $J = 13.6, 6.8$ Hz, 1H), 1.03 (d, $J = 6.7$ Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 162.4, 144.3, 136.4, 131.5, 130.2, 127.4, 126.6, 123.7, 102.0, 38.0, 28.1, 22.6. MS (ESI) calculated for C$_{17}$H$_{19}$NO, m/z : 253.12, found 254.13 (M+H)$^+$. 

2-(tert-butyl)furo[2,3-c]quinoline (6h)
White solid (69 mg, 83%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.11 (s, 1H), 8.20 (d, $J = 8.3$ Hz, 1H), 8.08 (d, $J = 7.9$ Hz, 1H), 7.69 – 7.64 (m, 1H), 7.59 (t, $J = 7.4$ Hz, 1H), 6.89 (s, 1H), 1.47 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.7, 148.8, 144.3, 136.4, 131.2, 130.1, 127.3, 126.5, 123.6, 123.4, 98.2, 33.6, 29.1. MS (ESI) calculated for C$_{15}$H$_{15}$NO, m/z : 225.12, found 226.14 (M+H)$^+$. 

2-isopentylfuro[2,3-c]quinoline (6i)
Solid (65 mg, 74%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.10 (s, 1H), 8.21 (d, $J = 8.3$ Hz, 1H), 8.07 (d, $J = 7.9$ Hz, 1H), 7.70 – 7.63 (m, 1H), 7.59 (t, 1H), 6.90 (s, 1H), 2.91 (t, 2H), 1.79 – 1.64 (m, 3H), 0.99 (d, $J = 6.4$ Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 163.4, 148.8, 144.3, 144.2, 163.4, 148.8, 144.3, 136.4, 131.2, 130.1, 127.3, 126.5, 123.6, 123.4, 98.2, 33.6. MS (ESI) calculated for C$_{15}$H$_{15}$NO, m/z : 225.12, found 226.14 (M+H)$^+$. 

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2-cyclopropylfuro[2,3-c]quinoline (6j)
Solid (60 mg, 78%). ¹H NMR (500 MHz, CDCl₃) δ 9.02 (d, J = 0.7 Hz, 1H), 8.17 (dd, J = 8.4, 0.6 Hz, 1H), 8.04 (ddd, J = 8.1, 1.5, 0.6 Hz, 1H), 7.66 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.58 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 6.89 – 6.85 (m, 1H), 2.21 – 2.14 (m, 1H), 1.12 (dqd, J = 6.0, 2.4, 1.2 Hz, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 164.0, 148.3, 144.4, 136.0, 131.7, 130.1, 127.4, 126.4, 123.7, 123.0, 99.4, 10.1, 8.5. MS (ESI) calculated for C₁₆H₁₇NO, m/z : 239.13, found 240.14 (M+H)⁺.

2-cyclopentylfuro[2,3-c]quinoline (6k)
White solid (72 mg, 82%). ¹H NMR (500 MHz, CDCl₃) δ 9.08 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.59 (t, J = 7.4 Hz, 1H), 3.41 – 3.31 (m, 1H), 2.23 – 2.13 (m, 2H), 1.95 – 1.81 (m, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 166.8, 144.3, 136.4, 131.3, 130.1, 127.3, 126.5, 123.7, 123.2, 99.6, 39.4, 32.1, 25.6. MS (ESI) calculated for C₁₆H₁₅NO, m/z : 237.11, found 238.13 (M⁺H)⁺.

2-(cyclopentylmethyl)furo[2,3-c]quinoline (6l)
Solid (71 mg, 75%). ¹H NMR (500 MHz, CDCl₃) δ 9.10 (s, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.67 (t, J = 7.0 Hz, 1H), 7.60 (t, 1H), 6.91 (s, 1H), 2.91 (d, J = 7.4 Hz, 2H), 2.38 (dt, J = 15.4, 7.8 Hz, 1H), 1.87 (m, 2H), 1.74 – 1.65 (m, 2H), 1.64 – 1.57 (m, 2H), 1.32 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 163.0, 144.3, 136.4, 131.5, 130.2, 127.4, 126.5, 123.7, 101.5, 38.9, 34.9, 32.7, 25.2. MS (ESI) calculated for C₁₇H₁₇NO, m/z : 251.13, found 252.14 (M⁺H)⁺.

2-(cyclohexylmethyl)furo[2,3-c]quinoline (6m)
Solid (170 mg, 87%). ¹H NMR (500 MHz, CDCl₃) δ 9.10 (s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.72 – 7.63 (m, 1H), 7.59 (t, J = 7.4 Hz, 1H), 6.89 (s, 1H), 2.78 (d, J = 6.9 Hz, 2H), 1.89 – 1.64 (m, 6H), 1.33 – 1.12 (m, 3H), 1.05 (qd, J = 12.4, 3.1 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 162.1, 148.8, 144.2, 136.4, 131.5, 130.1, 127.3, 126.5, 123.7, 123.2, 102.0, 37.3, 36.7, 33.3, 26.4, 26.2. MS (ESI) calculated for C₁₈H₁₉NO, m/z : 265.15, found 266.16 (M⁺H)⁺.

2-phenylfuro[2,3-c]quinoline (6n)
White solid (65 mg, 72%). ¹H NMR (500 MHz, CDCl₃) δ 9.20 (d, 1H), 8.23 (dd, J = 8.3, 0.7 Hz, 1H), 8.17 (ddd, J = 8.0, 1.5, 0.5 Hz, 1H), 8.01 – 7.97 (m, 2H), 7.71 (ddd, J = 8.4, 6.9, 1.6 Hz, 1H), 7.65 (dd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.55 – 7.50 (m, 3H), 7.47 – 7.43 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 158.8, 148.9, 144.5, 136.7, 131.6, 130.3, 129.8, 129.8, 129.2, 127.7, 126.9, 125.6, 123.7, 123.2, 99.9. MS (ESI) calculated for C₁₇H₁₁NO, m/z : 245.10, found 246.10 (M⁺H)⁺.

furo[2,3-c]quinolin-2-ylmethanol (6p)
Solid (56 mg, 77%). ¹H NMR (500 MHz, MeOD) δ 9.07 (s, 1H), 8.26 (dd, J = 8.0, 1.2 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.71 – 7.66 (m, 1H), 7.39 (s, 1H), 4.84 (s, 2H). ¹³C NMR (126 MHz, MeOD) δ 163.5, 150.2, 144.8, 137.2, 133.0, 129.7, 129.1, 128.3, 125.0, 124.6, 103.3, 58.1. MS (ESI) calculated for C₁₂H₉NO₂, m/z : 199.10, found 200.07 (M⁺H)⁺.
2-(furo[2,3-c]quinolin-2-yl)ethanol (6q)
Solid (58 mg, 74%). \[^1\]H NMR (500 MHz, MeOD) δ 9.02 (s, 1H), 8.23 (dd, 1H), 8.10 (dd, J = 8.3, 0.5 Hz, 1H), 7.71 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 7.67 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.26 (d, J = 0.7 Hz, 1H), 4.01 (t, J = 6.4 Hz, 2H), 3.17 (td, J = 6.4, 0.6 Hz, 2H). \[^{13}\]C NMR (126 MHz, MeOD) δ 162.9, 149.9, 144.7, 136.7, 133.6, 129.6, 128.9, 128.0, 125.1, 124.4, 103.5, 60.6, 33.1. MS (ESI) calculated for C\textsubscript{13}H\textsubscript{11}NO\textsubscript{2}, m/z : 213.08, found 214.09 (M+H\textsuperscript{+}).

4-(furo[2,3-c]quinolin-2-yl)butan-1-ol (6s)
Solid (68 mg, 77%). \[^1\]H NMR (500 MHz, MeOD) δ 8.99 (s, 1H), 8.22 – 8.18 (m, 1H), 8.09 (dd, J = 8.4, 0.6 Hz, 1H), 7.70 (ddd, J = 8.4, 6.9, 1.6 Hz, 1H), 7.65 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.17 (d, J = 0.8 Hz, 1H), 3.63 (t, J = 6.4 Hz, 2H), 2.98 (t, 2H), 1.96 – 1.88 (m, 2H), 1.71 – 1.63 (m, 2H). \[^{13}\]C NMR (126 MHz, MeOD) δ 165.5, 149.8, 144.7, 136.6, 133.6, 129.5, 128.9, 128.0, 125.1, 124.3, 102.4, 62.4, 33.0, 29.2, 25.2. MS (ESI) calculated for C\textsubscript{15}H\textsubscript{15}NO\textsubscript{2}, m/z : 241.11, found 242.12 (M+H\textsuperscript{+}).

2-(furo[2,3-c]quinolin-2-yl)propan-2-ol (6t)
White solid (60 mg, 72%). \[^1\]H NMR (500 MHz, MeOD) δ 8.91 – 8.10 (m, 1H), 7.73 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.36 (d, J = 0.8 Hz, 1H), 1.72 (s, 6H). \[^{13}\]C NMR (126 MHz, MeOD) δ 169.7, 149.9, 144.8, 137.1, 133.0, 129.7, 129.0, 128.2, 125.0, 124.6, 100.6, 70.1, 29.1. MS (ESI) calculated for C\textsubscript{14}H\textsubscript{13}NO\textsubscript{2}, m/z : 227.10, found 228.11 (M+H\textsuperscript{+}).

1-(furo[2,3-c]quinolin-2-yl)propan-2-ol (6v)
White solid (70 mg, 84%). \[^1\]H NMR (500 MHz, MeOD) δ 9.04 (d, J = 0.5 Hz, 1H), 8.27 – 8.23 (m, 1H), 8.11 (dd, J = 8.4, 0.6 Hz, 1H), 7.73 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 7.68 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.28 (d, J = 0.7 Hz, 1H), 4.32 – 4.25 (m, 1H), 3.09 (d, J = 0.2 Hz, 2H), 1.31 (d, J = 6.2 Hz, 3H). \[^{13}\]C NMR (126 MHz, MeOD) δ 163.0, 149.9, 144.6, 136.7, 133.7, 129.5, 129.0, 128.1, 125.1, 124.4, 104.0, 67.1, 39.2, 23.4. MS (ESI) calculated for C\textsubscript{14}H\textsubscript{13}NO\textsubscript{2}, m/z : 227.10, found 228.11 (M+H\textsuperscript{+}).

2-(ethoxyethyl)furo[2,3-c]quinoline (6w)
Solid (70 mg, 61%). \[^1\]H NMR (500 MHz, CDCl\textsubscript{3}) δ 9.10 (s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.08 (dd, J = 8.1, 1.1 Hz, 1H), 7.68 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.02 (d, 1H), 3.87 (t, J = 6.6 Hz, 2H), 3.57 (q, J = 7.0 Hz, 2H), 3.20 (td, J = 6.6, 0.8 Hz, 2H), 1.23 (t, J = 7.0 Hz, 3H). \[^{13}\]C NMR (126 MHz, CDCl\textsubscript{3}) δ 160.1, 148.8, 144.3, 136.3, 131.4, 130.1, 127.3, 126.6, 123.7, 123.2, 102.3, 68.0, 66.7, 29.8, 15.3. MS (ESI) calculated for C\textsubscript{15}H\textsubscript{15}NO\textsubscript{2}, m/z : 241.11, found 242.11 (M+H\textsuperscript{+}).

2-(furo[2,3-c]quinolin-2-yl)methylisoindoline-1,3-dione (6x)
White solid (33 mg, 61%). \[^1\]H NMR (500 MHz, DMSO) δ 9.20 (d, J = 0.5 Hz, 1H), 8.32 (d, 1H), 8.11 (dd, J = 8.3, 0.7 Hz, 1H), 7.96 (dd, J = 5.5, 3.0 Hz, 2H), 7.89 (dd, J = 5.5, 3.1 Hz, 2H), 7.75 – 7.64 (m, 3H), 5.11 (d, J = 0.4 Hz, 2H). \[^{13}\]C NMR (126 MHz, DMSO) δ 155.6, 148.3, 143.7, 136.6, 134.8, 131.6, 130.1, 129.6, 127.7, 126.9, 124.1, 123.5, 122.6, 103.8, 34.9. MS (ESI) calculated for C\textsubscript{20}H\textsubscript{12}N\textsubscript{2}O\textsubscript{3}, m/z : 328.08, found 329.10 (M+H\textsuperscript{+}).

2-(2-(furo[2,3-c]quinolin-2-yl)ethyl)isoindoline-1,3-dione (6y)
White solid (65 mg, 77%). \[^1\]H NMR (500 MHz, DMSO) δ 9.13 (s, 1H), 8.23 (dd, J = 8.0, 1.4 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.90 – 7.79 (m, 4H), 7.73 – 7.68 (m, 1H), 7.68 – 7.63 (m, 1H), 7.44 (s, 1H), 4.03 (t, J = 6.9 Hz, 2H), 3.30 (t, J = 6.9 Hz, 2H). \[^{13}\]C NMR (126 MHz, DMSO) δ 167.7, 158.9, 148.5, 143.7, 136.2, 134.5, 131.6, 130.4, 129.5, 127.5, 126.7, 124.0,
General procedure for N-Oxidation

To a stirred solution of substrate (0.53 mmol) in CHCl₃ was added m-CPBA (1.06 mmol). The resulting reaction mixture was stirred at r.t. for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by flash chromatography.

2-methylfuro[2,3-c]quinoline 5-oxide (7b)
White solid (80 mg, 74%). ¹H NMR (500 MHz, CDCl₃) δ 8.86 (s, 1H), 8.84 (dd, 1H), 8.08 – 8.03 (m, 1H), 7.76 – 7.68 (m, 2H), 6.87 (t, 1H), 2.59 (d, J = 1.0 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 159.7, 147.2, 138.8, 129.0, 128.6, 124.5, 124.3, 122.7, 121.0, 102.2, 14.5. MS (ESI) calculated for C₁₂H₉NO₂, m/z : 199.10, found 200.06 (M+H)⁺.

2-propylfuro[2,3-c]quinoline 5-oxide (7c)
White solid (78 mg, 72%). ¹H NMR (500 MHz, CDCl₃) δ 8.88 – 8.82 (m, 2H), 8.08 – 8.04 (m, 1H), 7.75 – 7.68 (m, 2H), 6.86 (dd, J = 1.7, 0.8 Hz, 1H), 2.88 – 2.83 (m, 2H), 1.88 – 1.79 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 163.7, 147.1, 138.8, 128.9, 128.5, 124.4, 124.2, 124.1, 122.8, 121.1, 101.4, 30.7, 21.1, 13.9. MS (ESI) calculated for C₁₄H₁₃NO₂, m/z : 227.10, found 228.10 (M+H)⁺.

2-butylfuro[2,3-c]quinoline 5-oxide (7d)
White solid (75 mg, 70%). ¹H NMR (500 MHz, CDCl₃) δ 8.86 (d, J = 0.5 Hz, 1H), 8.85 – 8.83 (m, 1H), 8.08 – 8.04 (m, 1H), 7.75 – 7.68 (m, 2H), 6.86 (d, J = 0.9 Hz, 1H), 2.90 – 2.86 (m, 2H), 1.82 – 1.76 (m, 2H), 1.46 – 1.39 (m, 2H), 1.46 (dq, J = 14.7, 7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 164.0, 147.1, 138.7, 128.9, 128.5, 124.5, 124.2, 122.8, 121.0, 101.3, 29.8, 28.5, 22.4, 13.9. MS (ESI) calculated for C₁₅H₁₅NO₂, m/z : 241.11, found 242.12 (M+H)⁺.

2-pentylfuro[2,3-c]quinoline 5-oxide (7e)
White solid (77 mg, 72%). ¹H NMR (500 MHz, CDCl₃) δ 8.87 – 8.86 (m, 1H), 8.86 – 8.83 (m, 1H), 8.09 – 8.05 (m, 1H), 7.76 – 7.68 (m, 2H), 6.86 (d, J = 0.9 Hz, 1H), 2.90 – 2.86 (m, 2H), 1.80 – 1.76 (m, 2H), 1.40 (dq, J = 4.6, 1.7 Hz, 2H), 0.93 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 164.0, 147.1, 138.7, 128.9, 128.5, 124.5, 124.2, 122.8, 121.1, 101.3, 31.5, 28.8, 27.4, 22.5, 14.1. MS (ESI) calculated for C₁₆H₁₇NO₂, m/z : 255.12, found 256.14 (M+H)⁺.

2-hexylfuro[2,3-c]quinoline 5-oxide (7f)
White solid (105 mg 82%). ¹H NMR (500 MHz, CDCl₃) δ 8.86 (d, J = 0.5 Hz, 1H), 8.85 – 8.82 (m, 1H), 8.08 – 8.05 (m, 1H), 7.76 – 7.68 (m, 2H), 6.86 (d, J = 0.8 Hz, 1H), 2.87 (t, J = 7.4 Hz, 2H), 1.84 – 1.78 (m, 2H), 1.40 (qd, J = 4.6, 1.7 Hz, 2H), 0.93 (t, J = 7.1 Hz, 3H), 1.36 – 1.30 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 164.0, 147.1, 138.7, 128.9, 128.5, 124.5, 124.2, 122.8, 121.1, 101.3, 31.5, 28.8, 27.4, 22.5, 14.1. MS (ESI) calculated for C₁₇H₁₉NO₂, m/z : 269.14, found 270.15 (M+H)⁺.

2-isobutylfuro[2,3-c]quinoline 5-oxide (7g)
Solid (100 mg, 78%). ¹H NMR (500 MHz, CDCl₃) δ 8.87 (s, 1H), 8.85 (dt, J = 7.2, 3.9 Hz, 1H), 8.09 – 8.06 (m, 1H), 7.76 – 7.69 (m, 2H), 6.88 (d, J = 0.7 Hz, 1H), 2.76 (dd, J = 7.1, 0.5 Hz, 3H).
Hz, 2H), 2.22 – 2.12 (m, 1H), 1.03 (d, J = 6.7 Hz, 6H). 13C NMR (126 MHz, CDCl3) δ 163.0, 147.2, 138.8, 128.9, 128.5, 124.5, 124.3, 124.1, 122.8, 121.1, 102.3, 37.9, 28.0, 22.6. MS (ESI) calculated for C15H15NO2, m/z : 241.11, found 242.13 (M+H)+.

2-(tert-butyl)furo[2,3-c]quinoline 5-oxide (7h)
White solid (72 mg, 68%). 1H NMR (500 MHz, CDCl3) δ 8.88 (d, J = 0.6 Hz, 1H), 8.85 (dd, J = 7.8, 2.1 Hz, 1H), 8.09 – 8.06 (m, 1H), 7.75 – 7.69 (m, 2H), 6.85 (d, J = 0.9 Hz, 1H), 1.45 (s, 9H). 13C NMR (126 MHz, CDCl3) δ 171.5, 147.1, 138.7, 128.9, 128.5, 124.6, 124.2, 124.1, 123.0, 121.1, 102.8, 37.6, 28.9. MS (ESI) calculated for C15H15NO2, m/z : 241.11, found 242.12 (M+H)+.

2-isopentylfuro[2,3-c]quinoline 5-oxide (7i)
Solid (60 mg, 77%). 1H NMR (500 MHz, MeOD) δ 9.13 (d, J = 0.5 Hz, 1H), 8.72 (dd, J = 8.1, 1.6 Hz, 1H), 8.36 – 8.30 (m, 1H), 7.96 – 7.78 (m, 2H), 7.24 (s, 1H), 3.01 – 2.96 (m, 2H), 1.78 – 1.72 (m, 2H), 1.72 – 1.65 (m, 1H), 1.01 (d, J = 6.5 Hz, 6H). 13C NMR (126 MHz, MeOD) δ 167.7, 147.9, 138.8, 130.6, 130.5, 128.7, 126.7, 126.0, 124.0, 120.8, 102.8, 37.6, 28.9, 27.5, 22.7. MS (ESI) calculated for C16H17NO2, m/z : 255.12, found 256.13 (M+H)+.

2-cyclopropylfuro[2,3-c]quinoline 5-oxide (7j)
Solid (40 mg, 74%). 1H NMR (500 MHz, MeOD) δ 9.11 – 8.99 (m, 1H), 8.73 (t, J = 13.1 Hz, 1H), 8.36 – 8.30 (m, 1H), 7.89 – 7.81 (m, 2H), 7.24 (s, 1H), 2.35 – 2.24 (m, 1H), 1.27 – 1.16 (m, 2H), 1.15 – 1.09 (m, 2H). 13C NMR (126 MHz, MeOD) δ 168.84, 130.7, 130.3, 129.8, 129.3, 126.0, 125.1, 123.6, 120.7, 100.9, 10.6, 9.2. MS (ESI) calculated for C14H11NO2, m/z : 225.10, found 226.09 (M+H)+.

2-cyclopentylfuro[2,3-c]quinoline 5-oxide (7k)
White solid (77 mg, 72%). 1H NMR (500 MHz, MeOD) δ 9.12 (d, J = 0.4 Hz, 1H), 8.71 (dd, J = 7.5, 1.8 Hz, 1H), 8.36 – 8.30 (m, 1H), 7.96 – 7.78 (m, 2H), 7.24 (s, 1H), 2.96 (d, J = 7.4 Hz, 2H), 2.44 – 2.37 (m, 1H), 1.96 – 1.85 (m, 4H), 1.81 – 1.72 (m, 2H). 13C NMR (126 MHz, MeOD) δ 171.0, 147.9, 138.8, 130.6, 130.5, 128.7, 126.7, 126.0, 124.0, 120.8, 101.5, 40.0, 32.8, 26.4. MS (ESI) calculated for C17H15NO2, m/z : 253.11, found 254.12 (M+H)+.

2-(cyclopentylmethyl)furo[2,3-c]quinoline 5-oxide (7l)
White solid (75 mg, 70%). 1H NMR (500 MHz, MeOD) δ 9.13 (s, 1H), 8.74 – 8.70 (m, 1H), 8.36 (dd, J = 7.5, 1.8 Hz, 1H), 7.91 – 7.82 (m, 2H), 7.29 (d, J = 0.5 Hz, 1H), 2.96 (d, J = 7.4 Hz, 2H), 2.44 – 2.37 (m, 1H), 1.93 – 1.85 (m, 2H), 1.75 – 1.67 (m, 2H), 1.65 – 1.58 (m, 2H), 1.40 – 1.32 (m, 2H). 13C NMR (126 MHz, MeOD) δ 167.2, 147.9, 138.8, 130.6, 130.5, 128.7, 126.7, 126.0, 124.0, 103.3, 40.0, 35.5, 33.5, 25.7, 26.2. MS (ESI) calculated for C18H19NO2, m/z : 267.12, found 268.14 (M+H)+.

2-(cyclohexylmethyl)furo[2,3-c]quinoline 5-oxide (7m)
Solid (160 mg, 84%). 1H NMR (500 MHz, CDCl3) δ 8.87 (s, 1H), 8.84 (dd, J = 0.9 Hz, 1H), 8.09 – 8.05 (m, 1H), 7.76 – 7.69 (m, 2H), 6.86 (d, J = 0.7 Hz, 1H), 2.76 (d, J = 6.8 Hz, 2H), 1.90 – 1.52 (m, 6H), 1.33 – 1.14 (m, 3H), 1.08 – 0.97 (m, 2H). 13C NMR (126 MHz, CDCl3) δ 162.9, 147.2, 138.7, 128.9, 128.5, 124.5, 124.3, 123.7, 122.8, 121.0, 102.3, 37.3, 36.6, 33.3, 29.9, 26.4, 26.2. MS (ESI) calculated for C18H19NO2, m/z : 281.14, found 282.16 (M+H)+.

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2-phenylfuro[2,3-c]quinoline 5-oxide (7n)
White solid (73 mg, 68%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.96 (d, $J = 0.7$ Hz, 1H), 8.89 – 8.85 (m, 1H), 8.17 (ddd, $J = 3.2, 2.2, 0.5$ Hz, 1H), 7.94 – 7.90 (m, 2H), 7.80 – 7.74 (m, 2H), 7.53 – 7.49 (m, 2H), 7.47 (d, $J = 0.9$ Hz, 1H), 7.46 – 7.42 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 159.6, 147.5, 139.1, 129.9, 129.3, 129.2, 128.8, 125.3, 124.5, 124.4, 124.3, 122.9, 121.2, 100.2. MS (ESI) calculated for C$_{17}$H$_{11}$NO$_2$, m/z : 261.08, found 262.09 (M+H)$^+$. 

2-benzylfuro[2,3-c]quinoline 5-oxide (7o)
White solid (96 mg 90%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.85 (d, $J = 0.6$ Hz, 1H), 8.83 (dd, 1H), 8.04 – 8.01 (m, 1H), 7.75 – 7.67 (m, 2H), 7.38 (ddd, $J = 7.2, 4.4, 1.6$ Hz, 2H), 7.35 – 7.30 (m, 3H), 6.82 (d, $J = 0.9$ Hz, 1H), 4.21 (s, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 162.0, 147.5, 138.9, 136.1, 129.1, 129.1, 129.0, 128.6, 127.4, 124.5, 124.2, 123.8, 122.8, 121.1, 102.7, 35.3. MS (ESI) calculated for C$_{18}$H$_{13}$NO$_2$, m/z : 275.10, found 276.11 (M+H)$^+$. 

2-(hydroxymethyl)furo[2,3-c]quinoline 5-oxide (7p)
Yellow solid (77 mg, 79%). $^1$H NMR (500 MHz, MeOD) $\delta$ 9.15 (s, 1H), 8.72 (d, $J = 0.6$ Hz, 1H), 8.38 – 8.31 (m, 1H), 7.91 – 7.82 (m, 2H), 7.43 (d, $J = 0.6$ Hz, 1H). $^{13}$C NMR (126 MHz, MeOD) $\delta$ 165.1, 148.4, 139.0, 130.7, 130.7, 127.8, 127.0, 125.9, 124.2, 120.9, 103.9, 57.9. MS (ESI) calculated for C$_{12}$H$_{9}$NO$_3$, m/z : 215.10, found 216.07 (M+H)$^+$. 

2-(2-hydroxyethyl)furo[2,3-c]quinoline 5-oxide (7q)
White solid (75 mg, 78%). $^1$H NMR (500 MHz, MeOD) $\delta$ 9.09 (d, $J = 0.5$ Hz, 1H), 8.68 (dd, 1H), 8.31 – 8.27 (m, 1H), 7.88 – 7.78 (m, 2H), 7.29 (d, $J = 0.8$ Hz, 1H), 3.99 (t, $J = 6.3$ Hz, 2H), 3.15 (td, $J = 6.3, 0.7$ Hz, 2H). $^{13}$C NMR (126 MHz, MeOD) $\delta$ 164.6, 147.9, 138.8, 130.6, 130.5, 128.5, 126.7, 125.9, 123.9, 120.8, 104.1, 60.5, 33.1. MS (ESI) calculated for C$_{13}$H$_{11}$NO$_3$, m/z : 229.10, found 230.09 (M+H)$^+$. 

2-(3-hydroxypropyl)furo[2,3-c]quinoline 5-oxide (7r)
White solid (75 mg, 88%). $^1$H NMR (500 MHz, MeOD) $\delta$ 9.13 (s, 1H), 8.75 – 8.69 (m, 1H), 8.38 – 8.33 (m, 1H), 7.90 – 7.82 (m, 2H), 7.30 (d, $J = 0.9$ Hz, 1H), 3.69 (t, $J = 6.2$ Hz, 2H), 3.06 (t, 2H), 2.10 – 2.00 (m, 2H). $^{13}$C NMR (126 MHz, MeOD) $\delta$ 167.0, 148.0, 138.8, 130.6, 130.5, 128.7, 126.7, 126.0, 124.0, 120.8, 103.0, 61.8, 31.5, 26.0. MS (ESI) calculated for C$_{14}$H$_{13}$NO$_3$, m/z : 243.10, found 244.10 (M+H)$^+$. 

2-(4-hydroxybutyl)furo[2,3-c]quinoline 5-oxide (7s)
Solid (60 mg, 76%). $^1$H NMR (500 MHz, MeOD) $\delta$ 8.99 (s, 1H), 8.22 – 8.18 (m, 1H), 8.09 (d, $J = 8.4$ Hz, 1H), 7.70 (ddd, $J = 8.4, 6.9, 1.6$ Hz, 1H), 7.65 (ddd, $J = 8.1, 7.0, 1.3$ Hz, 1H), 7.17 (d, $J = 0.8$ Hz, 1H), 3.63 (t, $J = 6.4$ Hz, 2H), 2.98 (t, 2H), 1.96 – 1.88 (m, 2H), 1.71 – 1.63 (m, 2H). $^{13}$C NMR (126 MHz, MeOD) $\delta$ 165.5, 149.8, 144.7, 136.6, 133.6, 129.5, 128.9, 128.0, 125.1, 124.3, 102.4, 62.4, 33.0, 29.2, 25.2. MS (ESI) calculated for C$_{15}$H$_{15}$NO$_3$, m/z : 257.10, found 258.11 (M+H)$^+$. 

2-(2-hydroxypropan-2-yl)furo[2,3-c]quinoline 5-oxide (7t)
White solid (63 mg 74%). $^1$H NMR (500 MHz, MeOD) $\delta$ 9.17 (s, 1H), 8.73 (d, 1H), 8.38 (dd, $J = 8.4, 6.9$ Hz, 1H), 7.42 (d, 1H), 1.70 (s, 6H). $^{13}$C NMR (126 MHz, MeOD) $\delta$ 171.2, 148.0, 139.0, 130.8, 130.7, 127.9, 127.0, 126.0, 124.3, 120.9, 101.3, 70.0, 29.0. MS (ESI) calculated for C$_{14}$H$_{13}$NO$_3$, m/z : 243.10, found 244.10 (M+H)$^+$. 

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2-(1-hydroxy-3-methylbutyl)furo[2,3-c]quinoline 5-oxide (7u)
Solid (60 mg, 70%). $^1$H NMR (500 MHz, MeOD) δ 9.18 (s, 1H), 8.74 (dd, 1H), 8.40 (dd, 1H), 7.92 – 7.85 (m, 2H), 7.46 (s, 1H), 4.98 (dd, $J = 8.5, 5.1$ Hz, 1H), 1.91 – 1.85 (m, 2H), 1.84 – 1.78 (m, 1H), 1.02 (dd, $J = 6.3, 3.0$ Hz, 6H). $^{13}$C NMR (126 MHz, MeOD) δ 168.3, 148.1, 139.0, 130.7, 130.7, 127.9, 127.0, 126.0, 124.3, 120.9, 102.8, 66.9, 45.7, 25.7, 23.6, 22.3. MS (ESI) calculated for C$_{16}$H$_{17}$NO$_3$, m/z : 271.12, found 272.12 (M+H)$^+$.  

2-(2-hydroxypropyl)furo[2,3-c]quinoline 5-oxide (7v)
Solid (65 mg, 81%). $^1$H NMR (500 MHz, MeOD) δ 9.04 (d, $J = 0.6$ Hz, 1H), 8.63 – 8.60 (m, 1H), 8.27 – 8.24 (m, 1H), 7.80 – 7.72 (m, 2H), 7.23 (d, $J = 0.7$ Hz, 1H), 4.20 – 4.11 (m, 1H), 2.97 (ddd, $J = 3.9, 2.6, 0.5$ Hz, 2H), 1.21 (d, $J = 6.2$ Hz, 3H). $^{13}$C NMR (126 MHz, MeOD) δ 164.5, 148.0, 138.8, 130.6, 130.5, 128.59, 126.8, 126.0, 124.0, 104.6, 67.0, 39.2, 23.4. MS (ESI) calculated for C$_{14}$H$_{13}$NO$_3$, m/z : 243.10, found 244.10 (M+H)$^+$.  

2-(2-ethoxyethyl)furo[2,3-c]quinoline 5-oxide (7w)
Solid (30 mg, 70%). $^1$H NMR (500 MHz, MeOD) δ 9.15 (d, $J = 0.7$ Hz, 1H), 8.74 – 8.71 (m, 1H), 8.39 – 8.35 (m, 1H), 7.91 – 7.84 (m, 2H), 7.34 (d, $J = 0.9$ Hz, 1H), 3.89 (t, $J = 6.3$ Hz, 2H), 3.58 (q, $J = 7.0$ Hz, 2H), 3.24 – 3.21 (m, 2H), 1.19 (t, $J = 7.0$ Hz, 3H). $^{13}$C NMR (126 MHz, MeOD) δ 164.7, 147.9, 138.9, 130.6, 130.6, 128.6, 126.8, 126.0, 124.0, 103.9, 68.6, 67.4, 30.4, 15.4. MS (ESI) calculated for C$_{15}$H$_{15}$NO$_3$, m/z : 257.10, found 258.11 (M+H)$^+$.  

2-((1,3-dioxoisoindolin-2-yl)methyl)furo[2,3-c]quinoline 5-oxide (7x)
Solid (33 mg, 61%). $^1$H NMR (500 MHz, DMSO) δ 9.22 (s, 1H), 8.63 – 8.59 (m, 1H), 8.41 – 8.36 (m, 1H), 7.97 – 7.93 (m, 2H), 7.91 – 7.87 (m, 2H), 7.83 – 7.76 (m, 2H), 7.67 (d, $J = 0.7$ Hz, 1H), 5.06 (s, 2H). $^{13}$C NMR (126 MHz, DMSO) δ 167.2, 155.4, 147.4, 138.5, 134.8, 131.6, 129.3, 128.6, 124.9, 123.5, 121.6, 120.0, 104.4, 34.7. MS (ESI) calculated for C$_{20}$H$_{12}$N$_2$O$_4$, m/z : 344.08, found 345.09 (M+H)$^+$.  

2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)furo[2,3-c]quinoline 5-oxide (7y)
Solid (65 mg, 77%). $^1$H NMR (500 MHz, MeOD) δ 8.92 (d, $J = 0.7$ Hz, 1H), 8.70 (dd, $J = 8.2, 1.5$ Hz, 1H), 8.21 – 8.17 (m, 1H), 8.13 – 8.08 (m, 2H), 7.83 – 7.76 (m, 2H), 7.77 – 7.73 (m, 2H), 7.19 (d, $J = 0.8$ Hz, 1H), 4.15 (t, $J = 6.7$ Hz, 2H), 3.35 (t, $J = 7.1, 6.5$ Hz, 2H). $^{13}$C NMR (126 MHz, MeOD) δ 168.9, 161.8, 147.5, 138.4, 135.0, 134.9, 132.4, 132.3, 130.0, 127.3, 125.8, 125.3, 124.0, 123.9, 123.4, 120.5, 104.0, 36.6, 28.3. MS (ESI) calculated for C$_{21}$H$_{14}$N$_2$O$_4$, m/z : 358.10, found 359.11 (M+H)$^+$.  

General procedure for installation of the 4-amino group
To a stirred solution of N-oxide (0.414 mmol) in CH$_2$Cl$_2$ was added benzoxylisocyanate (1.24 mmol). The resulting reaction mixture was stirred at 55°C for 2 h. After completion of reaction (monitored by TLC), the solvent was evaporated. The residue was re-dissolved in MeOH (4 mL), and NaOMe (2.07 mmole) was added and refluxed for 4 h. The solvent was evaporated and the crude material was purified by flash chromatography using CH$_2$Cl$_2$:MeOH as an eluent. For compounds 8x and 8y, after reaction with benzoylisocyanate (1st step), the solvent was evaporated, ethylenediamine (2 mL) was added and stirred at 70°C for 12 h.

furo[2,3-c]quinolin-4-amine (8a)
Solid (16 mg, 68%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.93 (ddd, $J = 8.0, 1.5, 0.5$ Hz, 1H), 7.81 (ddd, $J = 8.4, 1.1, 0.5$ Hz, 1H), 7.79 (d, $J = 2.0$ Hz, 1H), 7.55 (ddd, $J = 8.5, 7.0, 1.5$ Hz,
2-propylfuro[2,3-c]quinolin-4-amine (8b)

Solid (38 mg, 78%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, $J = 8.9$, 5.0, 0.8 Hz, 2H), 7.55 (d, $J = 8.4$, 7.0, 1.5 Hz, 1H), 7.36 (d, $J = 8.1$, 7.1, 1.2 Hz, 1H), 6.81 (d, $J = 1.0$ Hz, 1H), 5.88 (s, 2H), 2.57 (d, $J = 1.0$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 158.3, 144.9, 138.3, 132.0, 131.3, 129.7, 128.0, 125.3, 123.5, 123.1, 102.7, 14.5. HRMS (ESI) calculated for C$_{13}$H$_{10}$N$_2$O, m/z : 198.0793, found 199.0859 (M+H)$^+$.  

2-propylfuro[2,3-c]quinolin-4-amine (8c)

Solid (38 mg, 78%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.52 (dd, $J = 8.4$, 7.0, 1.5 Hz, 1H), 7.34 (dd, $J = 8.0$, 7.0, 1.1 Hz, 1H), 6.81 (t, $J = 0.8$ Hz, 1H), 5.12 (s, 2H), 2.89 – 2.81 (m, 2H), 1.88 – 1.80 (m, 2H), 1.05 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.7, 144.8, 144.1, 138.6, 131.4, 127.6, 126.5, 123.4, 122.8, 120.4, 101.8, 30.7, 21.3, 13.9. HRMS (ESI) calculated for C$_{14}$H$_{14}$N$_2$O, m/z : 226.1106, found 227.1183 (M+H)$^+$.  

2-butylfuro[2,3-c]quinolin-4-amine (8d)

Solid (39 mg, 80%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.87 (ddd, $J = 8.0$, 1.4, 0.4 Hz, 1H), 7.80 – 7.76 (m, 1H), 7.52 (dd, $J = 8.4$, 7.0, 1.5 Hz, 1H), 7.34 (ddd, $J = 8.1$, 7.0, 1.2 Hz, 1H), 6.80 (t, $J = 0.8$ Hz, 1H), 5.11 (s, 2H), 2.90 – 2.83 (m, 2H), 1.79 (ddd, $J = 13.3$, 8.5, 6.7 Hz, 2H), 1.51 – 1.40 (m, 2H), 0.98 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.9, 144.8, 144.1, 138.6, 131.3, 127.6, 126.5, 123.4, 122.8, 120.4, 101.7, 30.0, 28.4, 22.4, 13.9. HRMS (ESI) calculated for C$_{15}$H$_{16}$N$_2$O, m/z : 240.1263, found 241.1349 (M+H)$^+$.  

2-pentylfuro[2,3-c]quinolin-4-amine (8e)

Solid (34 mg, 69%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (dd, $J = 8.0$, 1.1 Hz, 1H), 7.78 (dd, $J = 8.4$, 0.5 Hz, 1H), 7.52 (ddd, $J = 8.4$, 7.0, 1.5 Hz, 1H), 7.34 (ddd, $J = 8.1$, 7.0, 1.2 Hz, 1H), 6.80 (s, 1H), 5.09 (s, 2H), 2.88 – 2.83 (m, 2H), 1.84 – 1.77 (m, 2H), 1.46 – 1.34 (m, 4H), 0.93 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.9, 144.8, 144.2, 138.6, 131.3, 127.6, 126.5, 123.4, 122.8, 120.4, 101.7, 31.5, 28.7, 27.6, 22.5, 14.1. HRMS (ESI) calculated for C$_{16}$H$_{18}$N$_2$O, m/z : 254.1419, found 255.1496 (M+H)$^+$.  

2-hexylfuro[2,3-c]quinolin-4-amine (8f)

Yellow solid (60 mg 67%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.90 – 7.86 (m, 1H), 7.79 (dd, $J = 8.4$, 0.5 Hz, 1H), 7.52 (ddd, $J = 8.5$, 7.0, 1.5 Hz, 1H), 7.34 (ddd, $J = 8.1$, 7.0, 1.2 Hz, 1H), 6.80 (s, 1H), 5.21 (s, 2H), 2.86 (t, 2H), 1.84 – 1.76 (m, 2H), 1.47 – 1.39 (m, 2H), 1.38 – 1.29 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.8, 144.8, 138.4, 131.2, 128.6, 127.5, 126.2, 123.3, 122.7, 120.2, 101.5, 31.5, 28.9, 28.6, 27.8, 22.6, 14.1. HRMS (ESI) calculated for C$_{17}$H$_{20}$N$_2$O, m/z : 268.1576, found 269.1658 (M+H)$^+$.  

2-isobutylfuro[2,3-c]quinolin-4-amine (8g)

Solid (55 mg, 70%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.87 (ddd, $J = 7.9$, 1.4, 0.4 Hz, 1H), 7.80 (ddd, $J = 8.5$, 1.1, 0.5 Hz, 1H), 7.53 (ddd, $J = 8.4$, 7.0, 1.5 Hz, 1H), 7.34 (ddd, $J = 8.1$, 7.0, 1.2 Hz, 1H), 6.81 (s, 1H), 5.36 (s, 2H), 2.73 (ddd, $J = 7.1$, 0.6 Hz, 2H), 2.15 (dp, $J = 13.6$, 6.8 Hz, 1H), 1.02 (d, $J = 6.7$ Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.1, 144.9, 143.8, 138.6, 131.4, 127.6, 126.2, 123.4, 122.8, 120.2, 102.7, 37.9, 28.0, 22.6. HRMS (ESI) calculated for C$_{15}$H$_{16}$N$_2$O, m/z : 240.1263, found 241.1337 (M+H)$^+$.  

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2-(tert-butyl)furo[2,3-c]quinolin-4-amine (8h)

{\textsuperscript{1}H NMR (500 MHz, CDCl}_{3} \ \delta \ 7.89 (dd, J = 8.0, 1.5, 0.5 Hz, 1H), 7.79 (dd, J = 8.4, 0.5 Hz, 1H), 7.53 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.35 (dd, J = 8.1, 7.1, 1.2 Hz, 1H), 6.80 (s, 1H), 5.27 (s, 2H), 1.45 (s, 9H).{\textsuperscript{13}C NMR (126 MHz, CDCl}_{3} \ \delta \ 169.8, 144.8, 143.6, 138.4, 131.3, 127.7, 126.1, 123.4, 123.0, 120.4, 99.0, 33.6, 29.2. HRMS (ESI) calculated for C_{15}H_{16}N_{2}O, m/z : 240.1263, found 241.1342 (M+H){+}.}

2-isopentylfuro[2,3-c]quinolin-4-amine (8i)

Solid (35 mg, 70%). {\textsuperscript{1}H NMR (500 MHz, CDCl}_{3} \ \delta \ 7.87 (dd, J = 8.0, 1.0 Hz, 1H), 7.79 (dd, J = 8.4, 0.5 Hz, 1H), 7.53 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.35 (dd, J = 8.1, 7.1, 1.2 Hz, 1H), 6.81 (d, J = 0.8 Hz, 1H), 5.45 – 5.18 (m, 2H), 2.87 (t, 2H), 1.73 – 1.64 (m, 3H), 0.99 (d, J = 6.4 Hz, 6H).{\textsuperscript{13}C NMR (126 MHz, CDCl}_{3} \ \delta \ 162.5, 144.8, 138.3, 131.6, 128.8, 127.8, 126.0, 123.4, 123.0, 120.2, 101.6, 36.8, 27.8, 26.7, 22.5. HRMS (ESI) calculated for C_{16}H_{18}N_{2}O, m/z : 254.1419, found 255.1496 (M+H){+}.}

2-cyclopropylfuro[2,3-c]quinolin-4-amine (8j)

Solid (28 mg, 74%). {\textsuperscript{1}H NMR (500 MHz, CDCl}_{3} \ \delta \ 7.85 (dd, J = 8.0, 1.1 Hz, 1H), 7.77 (dd, J = 8.4, 0.5 Hz, 1H), 7.52 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.34 (dd, J = 8.1, 7.0, 1.2 Hz, 1H), 6.78 – 6.75 (m, 1H), 5.15 – 5.03 (m, 2H), 2.14 (tt, J = 8.4, 5.1 Hz, 1H), 1.10 (tdd, J = 11.1, 7.0, 4.3 Hz, 2H), 1.05 – 0.99 (m, 2H).{\textsuperscript{13}C NMR (126 MHz, CDCl}_{3} \ \delta \ 162.7, 144.5, 143.9, 137.9, 131.5, 127.5, 126.3, 126.3, 122.7, 120.1, 99.9, 29.7, 9.6, 8.0. HRMS (ESI) calculated for C_{14}H_{12}N_{2}O, m/z : 224.0950, found 225.1016 (M+H){+}.}

2-cyclopentylfuro[2,3-c]quinolin-4-amine (8k)

Solid (40 mg, 68%). {\textsuperscript{1}H NMR (500 MHz, CDCl}_{3} \ \delta \ 7.87 (dd, J = 8.0, 1.1 Hz, 1H), 7.78 (dd, J = 8.4, 0.5 Hz, 1H), 7.52 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.34 (dd, J = 8.1, 7.0, 1.2 Hz, 1H), 6.81 (d, J = 0.9 Hz, 1H), 5.13 (s, 2H), 3.35 – 3.27 (m, 1H), 2.20 – 2.11 (m, 2H), 1.89 – 1.82 (m, 3H), 1.79 – 1.70 (m, 3H).{\textsuperscript{13}C NMR (126 MHz, CDCl}_{3} \ \delta \ 165.5, 144.8, 144.0, 138.5, 131.3, 127.6, 126.4, 123.4, 122.8, 120.4, 100.2, 39.3, 32.1, 29.9, 25.5. HRMS (ESI) calculated for C_{16}H_{16}N_{2}O, m/z : 252.1263, found 253.1338 (M+H){+}.}

2-(cyclopentylmethyl)furo[2,3-c]quinolin-4-amine (8l)

Solid (44 mg, 75%). {\textsuperscript{1}H NMR (500 MHz, CDCl}_{3} \ \delta \ 7.88 (ddd, J = 7.9, 1.4, 0.4 Hz, 1H), 7.78 (dd, J = 8.4, 0.6 Hz, 1H), 7.52 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.34 (dd, J = 8.1, 7.0, 1.2 Hz, 1H), 6.81 (s, 1H), 5.09 (s, 2H), 2.88 – 2.83 (m, 2H), 2.40 – 2.29 (m, 1H), 1.90 – 1.82 (m, 2H), 1.69 (qqd, J = 7.1, 6.7, 4.7 Hz, 2H), 1.64 – 1.54 (m, 2H), 1.36 – 1.26 (m, 2H).{\textsuperscript{13}C NMR (126 MHz, CDCl}_{3} \ \delta \ 161.6, 144.8, 144.1, 138.6, 131.3, 127.6, 126.4, 123.4, 122.8, 120.4, 102.1, 38.9, 34.8, 32.7, 25.2. HRMS (ESI) calculated for C_{17}H_{18}N_{2}O, m/z : 266.1419, found 267.1495 (M+H){+}.}

2-(cyclohexylmethyl)furo[2,3-c]quinolin-4-amine (8m)

White solid (75 mg, 71%). {\textsuperscript{1}H NMR (500 MHz, CDCl}_{3} \ \delta \ 7.89 – 7.86 (m, 1H), 7.78 (dd, J = 8.4, 0.5 Hz, 1H), 7.52 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.34 (dd, J = 8.1, 7.1, 1.1 Hz, 1H), 6.79 (s, 1H), 5.19 (s, 2H), 2.74 (d, J = 6.6 Hz, 2H), 1.81 – 1.65 (m, 6H), 1.32 – 1.14 (m, 4H), 1.04 (qd, J = 12.9, 2.8 Hz, 1H).{\textsuperscript{13}C NMR (126 MHz, CDCl}_{3} \ \delta \ 160.8, 144.9, 144.1, 138.6, 131.3, 127.6, 126.4, 123.4, 122.8, 120.4, 102.7, 37.4, 36.6, 33.3, 26.4, 26.3. HRMS (ESI) calculated for C_{18}H_{20}N_{2}O, m/z : 280.1576, found 281.1656 (M+H){+}.
2-phenylfuro[2,3-c]quinolin-4-amine (8n)
Solid (30 mg, 75%). ¹H NMR (500 MHz, CDCl₃) δ 7.97 (dd, J = 8.0, 1.4, 0.4 Hz, 1H), 7.94 – 7.90 (m, 2H), 7.83 – 7.79 (m, 1H), 7.56 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.45 – 7.41 (m, 2H), 7.39 (dd, J = 8.1, 7.0, 1.2 Hz, 1H), 5.23 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 157.8, 145.0, 144.4, 139.0, 131.7, 129.9, 129.5, 129.1, 127.9, 126.7, 125.3, 123.4, 123.1, 120.3, 100.8. HRMS (ESI) calculated for C₁₇H₁₂N₂O, m/z : 260.0950, found 261.1023 (M+H)⁺.

2-benzylfuro[2,3-c]quinolin-4-amine (8o)
Solid (45 mg, 65%). ¹H NMR (500 MHz, CDCl₃) δ 7.86 – 7.82 (m, 1H), 7.77 (dd, J = 8.4, 0.6 Hz, 1H), 7.52 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.35 – 7.28 (m, 4H), 6.79 (t, J = 0.9 Hz, 1H), 5.10 (s, 2H), 4.21 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 159.8, 144.9, 144.2, 139.0, 136.7, 131.2, 129.1, 129.0, 127.7, 127.2, 126.5, 123.4, 122.9, 120.4, 103.2, 35.2. HRMS (ESI) calculated for C₁₇H₁₂N₂O, m/z : 274.1106, found 275.1182 (M+H)⁺.

(4-aminofuro[2,3-c]quinolin-2-yl)methanol (8p)
White solid (12 mg, 67%). ¹H NMR (500 MHz, DMSO) δ 8.00 (dd, J = 7.9, 1.2 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.45 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.31 (s, 1H), 7.25 (dd, J = 8.0, 7.0, 1.1 Hz, 1H), 6.78 (s, 2H), 4.67 (s, 2H). ¹³C NMR (126 MHz, DMSO) δ 159.9, 146.1, 144.4, 138.6, 129.6, 127.1, 125.5, 123.5, 121.5, 119.4, 103.0, 56.4. HRMS (ESI) calculated for C₁₉H₁₀N₂O₂, m/z : 214.0742, found 215.0805 (M+H)⁺.

2-(4-aminofuro[2,3-c]quinolin-2-yl)ethanol (8q)
White solid (20 mg, 65%). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 8.3 Hz, 1H), 7.65 (dd, J = 8.0, 1.1 Hz, 1H), 7.50 (dd, J = 8.4, 5.9, 1.5 Hz, 1H), 7.30 – 7.26 (m, 1H), 6.79 (s, 1H), 5.28 (s, 2H), 4.10 (t, J = 6.0 Hz, 2H), 3.11 (t, J = 5.8 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 158.9, 144.6, 143.0, 138.3, 131.3, 127.8, 125.7, 123.4, 123.0, 119.8, 103.6, 60.5, 32.5. HRMS (ESI) calculated for C₁₃H₁₂N₂O₂, m/z : 228.0899, found 229.0962 (M+H)⁺.

3-(4-aminofuro[2,3-c]quinolin-2-yl)propan-1-ol (8r)
Solid (70 mg, 75%). ¹H NMR (500 MHz, CDCl₃) δ 7.86 (dd, J = 8.0, 1.3 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.52 (dd, J = 8.4, 7.1, 1.5 Hz, 1H), 7.37 – 7.32 (m, 1H), 6.84 (s, 1H), 5.24 (s, 2H), 3.78 (t, J = 6.2 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 2.12 – 2.03 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 161.1, 144.8, 143.8, 138.6, 131.4, 127.8, 126.2, 123.4, 123.0, 120.2, 102.1, 61.8, 30.8, 25.1. HRMS (ESI) calculated for C₁₄H₁₄N₂O₂, m/z : 242.1055, found 243.1120 (M+H)⁺.

4-(4-aminofuro[2,3-c]quinolin-2-yl)butan-1-ol (8s)
Solid (28 mg, 70%). ¹H NMR (500 MHz, MeOD) δ 7.95 – 7.91 (m, 1H), 7.65 (dd, J = 8.4, 0.5 Hz, 1H), 7.49 (dd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.31 (dd, J = 8.1, 7.1, 1.1 Hz, 1H), 7.01 (s, 1H), 3.63 (t, J = 6.5 Hz, 2H), 2.94 (t, J = 7.5 Hz, 2H), 1.95 – 1.87 (m, 2H), 1.70 – 1.63 (m, 2H). ¹³C NMR (126 MHz, MeOD) δ 163.9, 147.2, 144.2, 139.5, 133.0, 128.8, 125.5, 124.6, 123.7, 120.8, 102.8, 62.5, 33.0, 29.1, 25.3. HRMS (ESI) calculated for C₁₅H₁₆N₂O₂, m/z : 256.1212, found 257.1282 (M+H)⁺.

2-(4-aminofuro[2,3-c]quinolin-2-yl)propan-2-ol (8t)
Solid (46 mg, 76%). ¹H NMR (500 MHz, CDCl₃) δ 7.77 – 7.71 (m, 2H), 7.52 – 7.47 (m, 1H), 7.29 (dd, J = 8.1, 7.1, 1.0 Hz, 1H), 6.86 (s, 1H), 1.72 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 165.5, 145.1, 143.3, 138.4, 130.8, 127.9, 125.8, 123.3, 123.1, 120.0, 100.3, 77.2.
1-(4-aminofuro[2,3-c]quinolin-2-yl)-3-methylbutan-1-ol (8u)

Solid (35 mg, 77%). $^1$H NMR (500 MHz, MeOD) δ 8.00 (d, 1H), 7.67 (d, $J = 8.2$ Hz, 1H), 7.53 (ddd, $J = 8.4$, 7.1, 1.4 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.24 (d, $J = 2.6$ Hz, 1H), 4.96 (t, $J = 6.7$ Hz, 1H), 1.92 – 1.80 (m, 3H), 1.02 (dd, $J = 6.2$, 4.0 Hz, 6H). $^{13}$C NMR (126 MHz, MeOD) δ 165.7, 147.3, 143.5, 132.8, 130.6, 129.2, 125.0, 124.7, 124.1, 120.6, 102.9, 45.8, 25.7, 23.6, 22.3. HRMS MS (ESI) calculated for C$_{16}$H$_{18}$N$_2$O$_2$, m/z : 270.1368, found 271.1468 (M+H)$^+$.

1-(4-aminofuro[2,3-c]quinolin-2-yl)propan-2-ol (8v)

Solid (30 mg, 73%). $^1$H NMR (500 MHz, MeOD) δ 7.96 (dd, $J = 8.2$, 1.3 Hz, 1H), 7.65 (dd, $J = 8.4$, 0.4 Hz, 1H), 7.50 (ddd, $J = 8.5$, 7.1, 0.4 Hz, 1H), 7.33 (ddd, $J = 8.1$, 7.1, 1.1 Hz, 1H), 7.10 (s, 1H), 4.29 – 4.22 (m, 1H), 3.05 – 3.01 (m, 2H), 1.30 (d, $J = 6.2$ Hz, 3H). $^{13}$C NMR (126 MHz, MeOD) δ 161.3, 147.2, 144.0, 133.0, 130.4, 128.9, 125.3, 124.6, 123.8, 120.7, 104.4, 67.2, 39.0, 23.4. HRMS (ESI) calculated for C$_{14}$H$_{14}$N$_2$O$_2$, m/z : 242.1055, found 243.1121 (M+H)$^+$.

2-(2-ethoxyethyl)furo[2,3-c]quinolin-4-amine (8w)

Solid (15 mg, 71%). $^1$H NMR (500 MHz, MeOD) δ 8.01 (ddd, $J = 8.0$, 2.3, 1.2 Hz, 1H), 7.68 (d, $J = 8.2$ Hz, 1H), 7.57 (t, $J = 7.3$ Hz, 1H), 7.45 – 7.38 (m, 1H), 7.16 (s, 1H), 3.89 (t, $J = 6.4$ Hz, 2H), 3.58 (q, $J = 7.0$ Hz, 2H), 3.20 (dt, $J = 6.5$, 3.1 Hz, 2H), 1.20 (t, $J = 7.0$, 3H). $^{13}$C NMR (126 MHz, MeOD) δ 163.1, 146.5, 134.2, 133.1, 130.6, 129.7, 129.2, 125.0, 124.7, 123.3, 104.2, 68.9, 67.4, 30.3, 15.4. HRMS (ESI) calculated for C$_{15}$H$_{16}$N$_2$O$_2$, m/z : 256.1212, found 257.1280 (M+H)$^+$.

2-(aminomethyl)furo[2,3-c]quinolin-4-amine (8x)

Solid (24 mg, 65%). $^1$H NMR (500 MHz, MeOD) δ 7.93 (dd, $J = 8.0$, 1.1 Hz, 1H), 7.65 (dd, $J = 8.4$, 0.4 Hz, 1H), 7.49 (ddd, $J = 8.4$, 7.0, 1.5 Hz, 1H), 7.31 (ddd, $J = 8.1$, 7.1, 1.1 Hz, 1H), 7.15 (s, 1H), 4.03 (s, 2H). $^{13}$C NMR (126 MHz, MeOD) δ 162.7, 147.6, 145.0, 140.0, 132.4, 128.7, 126.0, 124.5, 123.6, 121.0, 102.9, 39.8. HRMS (ESI) calculated for C$_{12}$H$_{11}$N$_3$O, m/z : 213.0902, found 214.0967 (M+H)$^+$.

2-(2-aminoethyl)furo[2,3-c]quinolin-4-amine (8y)

Solid (25 mg, 66%). $^1$H NMR (500 MHz, MeOD) δ 7.94 (dd, $J = 8.0$, 1.1 Hz, 1H), 7.64 (dd, $J = 8.4$, 0.5 Hz, 1H), 7.48 (ddd, $J = 8.5$, 7.0, 1.5 Hz, 1H), 7.30 (ddd, $J = 8.1$, 7.1, 1.1 Hz, 1H), 7.07 (s, 1H), 3.14 – 3.02 (m, 4H). $^{13}$C NMR (126 MHz, MeOD) δ 161.1, 147.4, 145.0, 140.0, 132.6, 128.6, 126.0, 124.5, 123.5, 120.9, 103.7, 40.9, 32.7. HRMS (ESI) calculated for C$_{13}$H$_{13}$N$_3$O, m/z : 227.1059, found 228.1121 (M+H)$^+$.

Compound 10 was synthesized similarly as compound 5

3-idoquinolin-4-ol (10)—Solid (1.6g). $^1$H NMR (500 MHz, DMSO) δ 11.19 (s, 1H), 8.50 (s, 1H), 7.98 – 7.85 (m, 2H), 7.65 – 7.60 (m, 1H), 7.60 – 7.55 (m, 1H). $^{13}$C NMR (126 MHz, DMSO) δ 152.2, 142.6, 141.3, 130.9, 129.9, 129.2, 128.5, 126.6, 94.5. MS (ESI) calculated for C$_9$H$_6$INO, m/z : 270.95, found 271.96 (M+H)$^+$.

Compounds 11a–11c were synthesized similarly as compound 6c

2-propylfuro[3,2-c]quinoline (11a)—Solid (55 mg, 71%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.10 (s, 1H), 8.28 – 8.23 (m, 1H), 8.19 (dd, $J = 8.0$, 0.8 Hz, 1H), 7.67 (dd, $J = 8.5$, 6.9, 1.6

69.2, 29.0. HRMS (ESI) calculated for C$_{14}$H$_{14}$N$_2$O$_2$, m/z : 242.1055, found 243.1123 (M+H)$^+$. 

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Hz, 1H), 7.61 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 6.60 (t, J = 0.9 Hz, 1H), 2.91 – 2.86 (m, 2H), 1.90 – 1.81 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 160.1, 155.1, 145.4, 145.2, 129.8, 127.8, 126.8, 121.6, 119.9, 117.3, 101.4, 30.5, 21.3, 13.9. MS (ESI) calculated for C14H13N0, m/z : 211.10, found 212.11 (M+H)^+.

2-butylfuro[3,2-c]quinoline (11b)—Solid (258 mg, 69%). 1H NMR (500 MHz, CDCl3) δ 9.13 (s, 1H), 8.25 (dd, J = 7.9, 1.6 Hz, 2H), 7.68 – 7.59 (m, 2H), 6.59 (t, J = 0.8 Hz, 1H), 2.94 – 2.87 (m, 2H), 1.81 (dd, J = 15.2, 8.4, 6.7 Hz, 2H), 1.53 – 1.42 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 160.5, 155.1, 145.4, 145.3, 129.9, 127.9, 126.8, 121.7, 119.9, 117.3, 101.3, 30.0, 28.3, 22.4, 13.9. MS (ESI) calculated for C15H15N0, m/z : 225.11, found 226.13 (M+H)^+.

2-phenylfuro[3,2-c]quinoline (11c)—Solid (68 mg, 75%). 1H NMR (500 MHz, CDCl3) δ 9.18 (s, 1H), 8.38 (dd, J = 8.1, 1.2 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.98 – 7.93 (m, 2H), 7.74 – 7.64 (m, 2H), 7.51 (t, J = 7.7 Hz, 2H), 7.44 – 7.39 (m, 1H), 7.21 (s, 1H). 13C NMR (126 MHz, CDCl3) δ 156.6, 155.3, 145.9, 145.5, 130.0, 129.9, 129.1, 129.1, 128.3, 127.1, 125.1, 122.05, 120.1, 117.3, 100.6. MS (ESI) calculated for C17H11N0, m/z : 245.10, found 246.09 (M+H)^+.

Compounds 12a–12c were synthesized similarly as compound 7b

2-propylfuro[3,2-c]quinolin-5-oxide (12a)—Solid (88 mg, 82%). 1H NMR (500 MHz, CDCl3) δ 8.87 – 8.82 (m, 1H), 8.79 (s, 1H), 8.26 – 8.20 (m, 1H), 7.76 – 7.70 (m, 2H), 6.51 (t, J = 0.9 Hz, 1H), 2.89 – 2.83 (m, 2H), 1.89 – 1.80 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 162.4, 147.4, 138.7, 130.7, 129.1, 128.8, 121.3, 121.0, 120.6, 117.9, 101.1, 29.9, 28.3, 22.4, 13.9. MS (ESI) calculated for C14H13NO2, m/z : 227.10, found 228.10 (M+H)^+.

2-butylfuro[3,2-c]quinolin-5-oxide (12b)—Yellow solid (100 mg, 79%). 1H NMR (500 MHz, CDCl3) δ 8.88 – 8.82 (m, 1H), 8.79 (s, 1H), 8.26 – 8.20 (m, 1H), 7.76 – 7.70 (m, 2H), 6.51 (t, J = 0.9 Hz, 1H), 2.91 – 2.85 (m, 2H), 1.83 – 1.76 (m, 2H), 1.51 – 1.43 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 162.4, 147.4, 138.7, 130.7, 129.1, 128.8, 121.3, 121.0, 120.6, 117.9, 101.1, 29.9, 28.3, 22.4, 13.9. MS (ESI) calculated for C15H15NO2, m/z : 241.11, found 242.12 (M+H)^+.

2-phenylfuro[3,2-c]quinolin-5-oxide (12c)—Solid (90 mg, 85%). 1H NMR (500 MHz, CDCl3) δ 8.90 – 8.86 (m, 2H), 8.37 – 8.33 (m, 1H), 7.94 – 7.90 (m, 2H), 7.78 (dd, J = 6.5, 3.3 Hz, 2H), 7.54 – 7.49 (m, 2H), 7.46 – 7.41 (m, 1H), 7.11 (s, 1H). 13C NMR (126 MHz, CDCl3) δ 158.4, 147.6, 139.3, 130.7, 129.7, 129.4, 129.2, 129.2, 125.2, 121.4, 121.4, 120.8, 118.1, 100.0. MS (ESI) calculated for C17H11N02, m/z : 261.10, found 262.09 (M+H)^+.

Compounds 13a–13c were synthesized similarly as compound 8a

2-propylfuro[3,2-c]quinolin-4-amine (13a)—Solid (35 mg, 71%). 1H NMR (500 MHz, CDCl3) δ 8.05 (dd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.52 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.34 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 6.40 (t, J = 0.9 Hz, 1H), 5.10 (s, 2H), 2.86 – 2.81 (m, 2H), 1.87 – 1.78 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 159.1, 156.1, 151.9, 145.0, 128.2, 126.1, 122.9, 119.8, 114.7, 111.0, 99.7, 30.5, 21.4, 13.9. HRMS (ESI) calculated for C14H14N2O, m/z : 226.1106, found 227.1177 (M+H)^+.

2-butylfuro[3,2-c]quinolin-4-amine (13b)—White solid (55 mg 69%). 1H NMR (500 MHz, CDCl3) δ 8.05 (ddd, J = 8.0, 1.5, 0.5 Hz, 1H), 7.79 – 7.73 (m, 1H), 7.52 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.34 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 6.39 (t, J = 0.9 Hz, 1H), 5.14 (s, 2H), 2.86 – 2.81 (m, 2H), 1.87 – 1.78 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 162.4, 147.4, 138.7, 130.7, 129.7, 129.4, 129.2, 129.2, 125.2, 121.4, 121.4, 120.8, 118.1, 100.0. MS (ESI) calculated for C17H11N02, m/z : 261.10, found 262.09 (M+H)^+.
2.89 – 2.83 (m, 2H), 1.77 (ddd, J = 13.3, 8.5, 6.6 Hz, 2H), 1.50 – 1.41 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 159.3, 156.0, 151.9, 144.9, 128.3, 126.0, 123.0, 119.8, 114.7, 111.0, 99.6, 30.1, 28.2, 22.4, 13.9. HRMS (ESI) calculated for C\(_{15}\)H\(_{16}\)N\(_2\)O, \(m/z\) : 240.1263, found 241.1340 (M+H\(^+\)).

**2-phenylfuro[3,2-c]quinolin-4-amine (13c)**—Solid (33 mg, 67%). \(^1\)H NMR (500 MHz, MeOD) \(\delta\) 8.93 (ddd, J = 8.0, 1.4, 0.4 Hz, 1H), 8.73 (dd, J = 8.4, 1.2 Hz, 2H), 8.47 – 8.44 (m, 1H), 8.35 – 8.31 (m, 1H), 8.31 – 8.27 (m, 2H), 8.21 – 8.12 (m, 3H). \(^{13}\)C NMR (126 MHz, MeOD) \(\delta\) 156.9, 156.5, 154.3, 145.9, 130.9, 129.7, 129.5, 129.4, 125.5, 125.6, 123.5, 120.6, 114.9, 112.9, 100.7, 49.0. HRMS (ESI) calculated for C\(_{17}\)H\(_{12}\)N\(_2\)O, \(m/z\) : 260.0950, found 261.1027 (M+H\(^+\)).

**Compound 15 was synthesized similarly as compound 5**

**4-iodoisoquinolin-3-ol (15)**—Solid (1.4 g). \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 8.84 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.76 (dd, J = 8.5, 0.6 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.37 (ddd, J = 7.9, 6.8, 0.9 Hz, 1H). \(^{13}\)C NMR (126 MHz, DMSO) \(\delta\) 159.8, 149.4, 140.9, 132.8, 128.8, 128.5, 123.8, 123.5. MS (ESI) calculated for C\(_{9}\)H\(_{6}\)INO, \(m/z\) : 270.95, found 271.96 (M+H\(^+\)).

**Compound 16 was synthesized similarly as compound 6c**

**2-butylfuro[2,3-c]isoquinoline (16)**—Solid (68 mg, 81%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.87 (s, 1H), 8.06 (dd, J = 8.5, 0.8 Hz, 2H), 7.74 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H), 7.57 – 7.52 (m, 1H), 6.85 (t, J = 0.9 Hz, 1H), 2.93 – 2.87 (m, 2H), 1.82 (dd, J = 13.3, 8.5, 6.7 Hz, 2H), 1.46 (dq, J = 14.8, 7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 158.6, 158.3, 146.3, 131.3, 130.2, 128.8, 126.4, 125.2, 123.0, 114.4, 100.5, 29.9, 28.6, 22.4, 14.0. MS (ESI) calculated for C\(_{15}\)H\(_{15}\)NO, \(m/z\) : 225.12, found 226.12 (M+H\(^+\)).

**Compound 17 was synthesized similarly as compound 7b**

**2-butylfuro[2,3-c]isoquinoline 4-oxide (17)**—Solid (20 mg, 74%). \(^1\)H NMR (500 MHz, MeOD) \(\delta\) 8.94 (s, 1H), 8.24 (dd, J = 8.3, 1.1, 0.7 Hz, 1H), 7.69 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.62 (t, J = 0.9 Hz, 1H), 7.30 (t, J = 0.9 Hz, 1H), 7.25 – 7.18 (m, 2H), 1.90 – 1.83 (m, 2H), 1.54 – 1.46 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H). \(^{13}\)C NMR (126 MHz, MeOD) \(\delta\) 162.3, 134.6, 134.6, 131.8, 131.1, 130.5, 128.9, 128.1, 124.2, 121.7, 103.5, 30.8, 28.9, 23.3, 14.1. MS (ESI) calculated for C\(_{15}\)H\(_{15}\)NO\(_2\), \(m/z\) : 241.11, found 242.11 (M+H\(^+\)).

**Compound 18 was synthesized similarly as compound 8a**

**2-butylfuro[2,3-c]isoquinolin-5-amine (18)**—Solid (15 mg, 62%). \(^1\)H NMR (500 MHz, MeOD) \(\delta\) 8.17 – 8.13 (m, 1H), 7.96 (ddd, J = 8.3, 1.1, 0.7 Hz, 1H), 7.69 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H), 7.43 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 6.74 (t, J = 0.9 Hz, 1H), 2.82 – 2.75 (m, 2H), 1.79 – 1.71 (m, 2H), 1.51 – 1.41 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). \(^{13}\)C NMR (126 MHz, MeOD) \(\delta\) 158.0, 156.0, 154.4, 131.7, 125.9, 124.9, 124.1, 117.0, 106.1, 101.2, 31.3, 29.0, 23.3, 14.2. HRMS (ESI) calculated for C\(_{15}\)H\(_{16}\)N\(_2\)O, \(m/z\) : 240.1263, found 241.1350 (M+H\(^+\)).

**1-bromo-2-butylfuro[2,3-c]quinoline (19)**—To a stirred solution of 2-butylfuro[2,3-c]quinoline 7d (100 mg, 0.44 mmol) in CH\(_2\)Cl\(_2\) was added bromine (80 µL, 1.55 mmol) and stirred at room temperature for 6 h. After completion of reaction (monitored by TLC), the solvent was evaporated, the crude material was purified by flash chromatography using CH\(_2\)Cl\(_2\) : MeOH to furnish \(19\) as yellow solid (50 mg, 75%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.08 (s, 1H), 8.90 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 7.71 (dd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.68 – 7.63 (m, 1H), 2.98 – 2.92 (m, 2H), 1.84 – 1.76 (m, 2H), 1.44 (dq, J = 14.8, 7.4 Hz, 2H).
7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 159.4, 147.4, 144.5, 136.2, 130.1, 127.9, 127.7, 126.8, 122.9, 122.3, 94.0, 29.6, 26.6, 22.4, 13.9. MS (ESI) calculated for C$_{15}$H$_{14}$BrNO, m/z : 303.03, found 304.04 (M+H)$^+$. 

**Compound 21 was synthesized similarly as compound 8a**

1-bromo-2-butylfuro[2,3-c]quinolin-4-amine (21)—Solid (21 mg, 72%). $^1$H NMR (500 MHz, MeOD) δ 8.67 (ddd, J = 8.2, 1.4, 0.5 Hz, 1H), 7.68 (ddd, J = 8.4, 1.1, 0.5 Hz, 1H), 7.53 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.35 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 2.97 (t, J = 7.5 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.50 – 1.41 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, MeOD) δ 159.7, 147.2, 145.3, 138.9, 129.1, 128.5, 126.3, 123.4, 123.1, 120.4, 95.0, 30.7, 27.2, 23.3, 14.1. HRMS (ESI) calculated for C$_{15}$H$_{15}$BrN$_2$O, m/z : 318.0368, found 319.0429 (M+H)$^+$. 

1-benzyl-2-butylfuro[2,3-c]quinoline (22)—To a stirred solution of 19 (50 mg, 0.164 mmol) in 1,4-dioxane were added 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (54 mg, 0.246 mmol), Pd(dppf)Cl$_2$ (8 mg, 0.009 mmol), Cs$_2$CO$_3$ (160 mg, 0.492 mmol) and 0.1 ml of water. The resulting reaction mixture was stirred at 70°C under nitrogen atmosphere for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with ethylacetate (3 × 10 mL). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure, crude material was purified by flash chromatography using CH$_2$Cl$_2$:MeOH as an eluent to obtain 22 (24 mg, 92%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.11 (d, J = 5.7 Hz, 1H), 8.19 – 8.14 (m, 1H), 7.94 (dd, J = 8.3, 0.8 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.44 – 7.37 (m, 1H), 7.28 – 7.24 (m, 3H), 7.19 (dd, J = 10.3, 4.3 Hz, 2H), 4.38 (s, 2H), 2.91 – 2.86 (m, 2H), 1.80 – 1.72 (m, 2H), 1.44 – 1.35 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 159.8, 148.3, 144.7, 138.9, 136.5, 136.3, 130.3, 130.1, 128.9, 128.0, 127.4, 126.9, 126.6, 126.5, 123.6, 113.9, 101.0, 30.6, 30.5, 26.4, 22.6, 13.9. MS (ESI) calculated for C$_{22}$H$_{21}$NO, m/z : 315.20, found 316.18 (M+H)$^+$. 

**Compound 24 was synthesized similarly as compound 8a**

1-benzyl-2-butylfuro[2,3-c]quinolin-4-amine (24)—Solid (31 mg, 75%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.79 – 7.73 (m, 2H), 7.44 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.30 – 7.23 (m, 3H), 7.23 – 7.18 (m, 2H), 7.15 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 5.09 (s, 2H), 4.33 (s, 2H), 2.87 – 2.81 (m, 2H), 1.73 (ddd, J = 13.0, 8.5, 6.7 Hz, 2H), 1.39 (dq, J = 14.7, 7.4 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 158.4, 144.9, 144.4, 139.1, 138.9, 136.5, 136.3, 130.3, 130.1, 128.9, 128.0, 127.4, 126.9, 126.6, 126.5, 123.6, 113.9, 101.0, 30.6, 30.5, 26.3, 22.6, 13.9. MS (ESI) calculated for C$_{22}$H$_{22}$N$_2$O, m/z : 330.1732, found 331.1808 (M+H)$^+$. 

**Compounds 27a–b were synthesized similarly as compound 7b**

2-propylfuro[2,3-c]pyridine 6-oxide (27a)—Oil (85 mg, 78%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.48 (s, 1H), 8.08 (dd, J = 6.7, 1.5 Hz, 1H), 7.44 (dd, J = 6.7 Hz, 1H), 6.41 (d, J = 0.8 Hz, 1H), 2.75 (t, J = 7.5 Hz, 2H), 1.81 – 1.72 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.3, 152.0, 135.0, 128.5, 124.7, 115.8, 102.0, 30.5, 20.8, 13.8. MS (ESI) calculated for C$_{10}$H$_{11}$NO$_2$, m/z : 177.08, found 178.08 (M+H)$^+$. 

2-butylfuro[2,3-c]pyridine 6-oxide (27b)—Oil (80 mg, 73%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.52 – 8.47 (m, 1H), 8.10 (dd, J = 6.7, 1.5 Hz, 1H), 7.31 (d, J = 6.7 Hz, 1H), 6.42 (d, J = 0.9 Hz, 1H), 2.79 (t, 2H), 1.78 – 1.67 (m, 2H), 1.48 – 1.37 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.5, 152.0, 135.1, 128.4, 124.8, 115.8, 101.9.
Compounds 28a–b was synthesized similarly as compound 8a

2-propylfuro[2,3-c]pyridin-7-amine (28a)—Oil (33 mg, 67%). 

\[
\begin{align*}
\delta & 7.80 (d, J = 5.5 \text{ Hz}, 1H), 6.85 (d, J = 5.5 \text{ Hz}, 1H), 6.34 (t, J = 0.8 \text{ Hz}, 1H), 4.67 (s, 2H), 2.79 - 2.71 (m, 2H), 1.82 - 1.74 (m, 2H), 1.01 (t, J = 7.4 \text{ Hz}, 3H). \\
\delta & 161.8, 144.1, 140.5, 139.2, 135.3, 107.5, 102.4, 30.6, 21.1, 13.9.
\end{align*}
\]

HRMS (ESI) calculated for C_{10}H_{12}N_{2}O, m/z : 176.0950, found 177.1067 (M+H)^+.

2-butylfuro[2,3-c]pyridin-7-amine (28b)—Oil (35 mg, 71%). 

\[
\begin{align*}
\delta & 7.80 (d, J = 5.5 \text{ Hz}, 1H), 6.85 (d, J = 5.5 \text{ Hz}, 1H), 6.33 (t, J = 0.8 \text{ Hz}, 1H), 4.68 (s, 2H), 2.80 - 2.74 (m, 2H), 1.77 - 1.69 (m, 2H), 1.47 - 1.38 (m, 2H), 0.96 (t, J = 7.4 \text{ Hz}, 3H). \\
\delta & 162.0, 144.0, 140.4, 139.2, 135.3, 107.5, 102.3, 29.8, 28.3, 22.4, 13.9.
\end{align*}
\]

HRMS (ESI) calculated for C_{11}H_{14}N_{2}O, m/z: 190.1106, found 191.1231 (M+H)^+.

Human TLR2/–3/–4/–5/–7/–8/–9 Reporter Gene assays (NF-κB induction)

The induction of NF-κB was quantified using human TLR2/–3/–4/–5/–7/–8/–9-specific HEK-Blue™ reporter gene assays as previously described by us. HEK293 cells stably co-transfected with the appropriate hTLR, MD2, and secreted alkaline phosphatase (sAP), were maintained in HEK-Blue™ Selection medium containing zeocin and normocin. Stable expression of secreted alkaline phosphatase (sAP) under control of NF-κB/AP-1 promoters is inducible by appropriate TLR agonists, and extracellular sAP in the supernatant is proportional to NF-κB induction. HEK-Blue™ cells were incubated at a density of ~10^5 cells/ml in a volume of 80 µl/well, in 384-well, flat-bottomed, cell culture-treated microtiter plates until confluency was achieved, and subsequently stimulated with graded concentrations of stimuli. sAP was assayed spectrophotometrically using an alkaline phosphatase-specific chromogen (present in HEK-detection medium as supplied by the vendor) at 620 nm.

Immuonassays for cytokines

Fresh human peripheral blood mononuclear cells (hPBMC) were isolated from human blood obtained by venipuncture with informed consent and as per institutional guidelines on Ficoll-Hypaque gradients as described elsewhere. Aliquots of PBMCs (10^5 cells in 100 µL/well) were stimulated for 12 h with graded concentrations of test compounds. Supernatants were isolated by centrifugation, and were assayed in triplicates using analyte-specific multiplexed cytokine/chemokine bead assays as reported by us previously. PBMC supernatants were also analyzed for 41 chemokines and cytokines (EGF, Eotaxin, FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO, IFN-β, IFN-α, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17, IL-1ra, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IP-10, MCP-1, MCP-3, MDC (CCL22), MIP-1α, MIP-1β, PDGF-AA, PDGF-AB/BB, RANTES, TGF-β, TNF-α, TNF-β, VEGF, sCD40L) using a magnetic bead-based multiplexed assay kit (Milliplex MAP Human Cytokine/Chemokine kit). Data were acquired and processed on a MAGPIX instrument (EMD Millipore, Billerica, MA) with an intra-assay coefficients of variation ranging from 4–8% for the 41 analytes.

Flow-cytometric immunostimulation experiments

CD69 upregulation was determined by flow cytometry using protocols published by us previously. Briefly, heparin-anticoagulated whole blood samples were obtained by venipuncture from healthy human volunteers with informed consent and as per guidelines.
approved by the University of Kansas Human Subjects Experimentation Committee. Aliquots of whole human blood samples were stimulated with graded concentrations of either 8d or 2 (used as a reference compound) in a 6-well polystyrene plate and incubated at 37°C in a rotary (100 rpm) incubator for 16.5 h. Negative (endotoxin free water) controls were included in each experiment. Following incubation, 200 µL aliquots of anticoagulated whole blood were stained with 20 µL of fluorochrome-conjugated antibodies at 37°C in the dark for 30 min. For triple color flow cytometry experiments, CD3-PE, CD56-APC, CD69-PE-Cy7 were used to analyze CD69 activation of each of the main peripheral blood lymphocyte populations: natural killer lymphocytes (NK cells: CD3−CD56+), cytokine-induced killer phenotype (CIK cells: CD3+CD56+), nominal B lymphocytes (CD3−CD56−), and nominal T lymphocytes (CD3+CD56−). Following staining, erythrocytes were lysed and leukocytes fixed in one step by mixing 200 µL of the samples in 4 mL pre-warmed Whole Blood Lyse/Fix Buffer (Becton-Dickinson Biosciences, San Jose, CA). After washing the cells twice at 200 g for 8 minutes in saline, the cells were transferred to a 96-well plate. Flow cytometry was performed using a BD FACSArray instrument in the tri-color mode (tri-color flow experiment) and two-color mode (two-color flow experiment) for acquisition on 100,000 gated events. Post-acquisition analyses were performed using FlowJo v 7.0 software (Treestar, Ashland, OR). Compensation for spillover was computed for each experiment on singly-stained samples.

Transcriptomal profiling in human PBMCs

Detailed procedures for transcriptomal profiling have been described by us previously. Briefly, fresh human PBMC samples were stimulated with 10 µg/mL of 8d and 2 for two hours, and total RNA was extracted from treated and negative control blood samples with QIAamp RNA Blood Mini Kit (Qiagen). Subsequently, 160 ng of each of the RNA samples was used. The Human Genome GeneChip U133 plus 2.0 oligonucleotide array (Affymetrix, Santa Clara, CA) was employed. Established standard protocols at the KU Genomics Facility were performed on cRNA target preparation, array hybridization, washing, staining and image scanning. The microarray data was first subjected to quality assessment using the Affymetrix GeneChip Operating Software (GCOS). QC criteria included low background, low noise, detection of positive controls, and a 5′/3′ ratio of < 3.0. To facilitate direct comparison of gene expression data between different samples, the GeneChip data were first subjected to preprocessing. This step involved scaling (in GCOS) data from all chips to a target intensity value of 500, and further normalizations steps in GeneSpring GX (Agilent Technologies, Santa Clara, CA). Prior to identifying target genes, genes that were detected as non-expressed in all samples, i.e., those with absence calls, were filtered out. To identify genes whose expression was changed by our compounds, a fold change threshold of 2.0 between the compound treatment and the negative control was used.

Molecular modeling and induced fit docking

We used quantum mechanics/molecular mechanics (QM/MM) methods for induced fit docking by calculating quantum mechanical charges for the ligand, while the macromolecule was handled using conventional molecular mechanics force fields. Correct bond orders were assigned, hydrogen atoms were added to the residues, and formal partial charges were assigned to atoms using OPLS-all atom force field. The docking grid was generated using co-crystallized ligand as grid center. Ligands were modeled in Schrödinger molecular modeling software (Schrödinger, New York, NY) and were minimized to a gradient of 0.001 KCal/MolÅ². The QM charges for ligands were obtained from Jaguar (Schrödinger), using the 3–21G basis set with the BLYP density functional theory. Initial docking was performed with Glide using 0.5 van der Waals (vdW) radius scaling factor for both ligand and protein. This soft docking procedure was applied to generate diverse docking solutions and top 20 poses for each ligand were retained. Finally, each ligand was
re-docked into its corresponding structures and the resulting complexes were ranked according to GlideScore.65,66

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<td>APCs</td>
<td>antigen-presenting cells</td>
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<td>CD69</td>
<td>cluster of differentiation 69</td>
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<td>DCs</td>
<td>dendritic cells</td>
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<tr>
<td>EC50</td>
<td>Half-maximal effective concentration</td>
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<td>TLR</td>
<td>Toll like receptor</td>
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**References**


Figure 1.
Representative TLR8/7 dual-agonistic heterocyclic small molecules.
Figure 2.
Dose-response profiles of human TLR8 (Panel A) and human TLR7 (Panel B) agonism by select C2-alkyl furo[2,3-c]quinolines. Error bars represent standard deviations obtained on quadruplicates. Dual TLR7/8-agonistic compounds 1 and 2 were used as comparators. C. Potency of TLR8 agonism (EC50 values) of a homologous series of C2-alkyl analogues. Compound 8a was inactive.
Figure 3.
Proinflammatory cytokine induction profiles of 8d in human blood. 2 was used as reference/comparator compound. Means of duplicate values of a representative experiment is shown.
Figure 4.
Dose-response profiles of IL-12p40 and IL-18 induction and the absence of IFN-α by 8d. 2 was used as reference/comparator compound. Means of duplicate values of a representative experiment is shown.
Figure 5.
Absence of CD69 upregulation in human natural killer cells by 8d. Inset: gating on lymphocytes showing CD3^+CD56^- (T cells, Quadrant A), CD3^-CD56^- (nominal B cells, Quadrant B), CD3^-CD56^+ (cytokine-induced killer cells, Quadrant C), and CD3^-CD56^+ (natural killer cells, Quadrant D).
Figure 6.
Disparate responses in select analytes (out of 41 analytes) in human PBMCs. G-CSF, GRO, MIP-1α and MIP-1β are induced by 8d (and 2, data not shown), but not by a pure TLR7 agonistic imidazoquinoline. Dose responses represent percent maximal response (G-CSF: 622 pg/mL, GRO: 515 pg/mL, MIP-1α 10780 pg/mL, and MIP-1β 10374 pg/mL). Means of duplicate values of a representative experiment is shown. Analytes were below detection limits for negative controls (medium alone), and are not shown for clarity.
Figure 7. Induced fit docking of ligands in human TLR8 (PDB ID: 3W3K). A. Both 2 and 8d occupy the same binding pocket. B. The binding modes of the TLR7/8-dual active imidazoquinoline CL097 and 8d are superimposable. C–F. Binding site interactions of 2, 8d, 13b, and 18, respectively.
Scheme 1.
Syntheses of C2-alkylfuro[2,3-c]quinoline analogues. Reagents: (i) I$_2$, KI, NaOH; (ii) Pd(PPh$_3$)$_4$, Cul alkyne, Et$_3$N:CH$_3$CN (1:3); (iii) m-CPBA, CHCl$_3$; (iv) (a) benzoyl isocyanate, CH$_2$Cl$_2$, (b) NaOCH$_3$, MeOH.

For 8x: R = CH$_2$NH$_2$, 8y: R = C$_2$H$_4$NH$_2$
Scheme 2.
Syntheses of C2-alkylfuro[3,2-c]quinoline analogues. Reagents: (i) I₂, KI, NaOH; (ii) Pd(PPh₃)₄ CuI alkyne, Et₃N:CH₃CN (1:3); (iii) m-CPBA, CHCl₃; (iv) (a) benzoyl isocyanate, CH₂Cl₂, (b) NaOCH₃, MeOH.
Scheme 3.
Syntheses of C2-alkylfuro[2,3-c]isoquinoline analogues. Reagents: (i) I$_2$, KI, NaOH; (ii) Pd(PPh$_3$)$_4$, CuI alkyne, Et$_3$N:CH$_3$CN (1:3); (iii) m-CPBA, CHCl$_3$; (iv) (a) benzoyl isocyanate, CH$_2$Cl$_2$, (b) NaOCH$_3$, MeOH.
Scheme 4.
Syntheses of C1- substituted furo[2,3-c]quinoline analogues. Reagents: (i) Br₂, CH₂Cl₂; (ii) m-CPBA CHCl₃; (iii) (a) benzoyl isocyanate, CH₂Cl₂, (b) NaOCH₃, MeOH; (iv) Pd(dppf)Cl₂, 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, Cs₂CO₃ 1,4-Dioxane
Scheme 5.
Syntheses of C2-alkylfuro[2,3-c]pyridine analogues. Reagents: (i) Pd(PPh₃)₄, CuI alkyn, Et₃N:CH₃CN (1:3); (ii) m-CPBA, CHCl₃; (iii) (a) benzoyl isocyanate, CH₂Cl₂, (b) NaOCH₃, MeOH.

25

26a-b

27a-b

28a-b

a: R = C₃H₇
b: R = C₄H₉
Table 1

Transcriptomal profiling of 8d in human PBMCs

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