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p38 Inhibitors: Piperidine- and 4-Aminopiperidine-Substituted Naphthyridinones, Quinolinones, and Dihydroquinazolinones

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Abstract—We have synthesized a series of C7-piperidine- and 4-aminopiperidine-substituted naphthyridinones, quinolinones, and dihydroquinazolinones that are highly potent inhibitors of both p38 MAP kinase activity and TNF-α release. The 4-aminopentamethylpiperidine naphthyridinone **5**, which was designed to block metabolism at major 'hot spots', combined excellent inhibitory potency with good oral bioavailability in the rat.

The p38 MAP kinase regulates the release from leukocytes of IL-1 and TNF-α, two cytokines that are associated with the progression of rheumatoid arthritis (RA). Inhibitors of p38 activity are known to suppress the release of these cytokines, and thus could be valuable in the treatment of RA.[1] We have previously described a series of piperidine-substituted dihydroquinazolinones (e.g., **1**) that are potent and selective inhibitors of p38 activity and TNF-α release; unfortunately, these compounds showed poor pharmacokinetic properties.[2] We have therefore developed a related series of piperidine-substituted quinolinones (e.g., **3**) and naphthyridinones (e.g., **4** and **5**) with improved pharmacokinetic properties. Of these compounds, the 4-amino-pentamethylpiperidine naphthyridinone **5** proved to be a potent inhibitor of p38 activity and TNF-α release with good oral bioavailability (F% = 44) in the rat.

Isopropyl piperidine-substituted dihydro quinazolinone **1** is an excellent inhibitor of p38 activity and TNF-α release;[3] however, this compound showed low oral bioavailability and high clearance in both rat and rhesus monkey (Table 1). Identification of the metabolites of this compound pointed to metabolism at the C4 benzylic position alpha to the urea moiety (Fig. 1). Thus, we decided to synthesize the analogous dihydroquinolinone **2**, in which the urea was replaced by an amide; and the quinolinone **3** and 1,6-naphthyridinone **4**, each with an sp^2 center at C4.

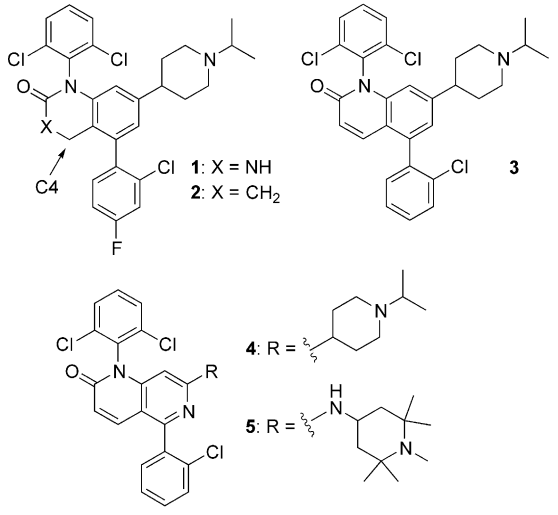

Figure 1. Inhibitors of p38 activity.

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Table 1. Isopropyl piperidines

Compd	p38 IC_{50} (nM)	TNF-α IC_{50} (nM)	F (%)	Cl_p (mL/min/kg)
1	0.6	5.6	16	84
2	0.8	24	10	70
3	0.2	5.5	17	39
4	1.3	4.9	32	51

As shown in Table 1, dihydroquinolinone **2** was a less potent inhibitor of TNF-α release than the lead **1**, and showed no clear advantage in pharmacokinetic properties. However, both quinolinone **3** and 1,6-naphthyridinone **4**, while maintaining similar potency to **1**, showed significantly lower clearance in the rat, and in the case of **4**, a 2-fold increase in rat oral bioavailability. This improvement in pharmacokinetic parameters encouraged us to further investigate the 1,6-naphthyridinone scaffold for p38 inhibitors.

Because of both synthetic accessibility (see below) and promising biological activity, we focused on the synthesis and structure–activity relationships of a family of C7-aminopyridines, represented by the generic structure **6** (Fig. 2). In light of our previous work with other p38 inhibitor scaffolds,[1b,2] we were not surprised to discover that piperidine substituents at C7 are potency-enhancing. A representative group of 4-aminopiperidine-substituted naphthyridinones **6** are paired with the analogous dihydroquinazolinones **7** in Figure 2 and Table 2. These 4-aminopiperidines are all excellent inhibitors of p38 activity, and in all cases, the naphthyridinones are as potent as, or more potent than, the analogous dihydroquinazolinones.

Having shown that the naphthyridinones equalled or surpassed the dihydroquinazolinones as inhibitors of p38 activity and TNF-α release, we turned next to an examination of the pharmacokinetic properties of the 4-

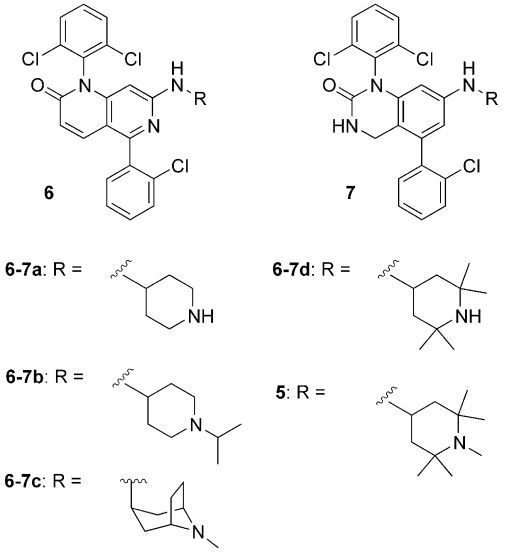

Figure 2. 4-Aminopiperidine-substituted naphthyridinones (**5** and **6**) and dihydroquinazolinones (**7**).

Table 2. Comparison of analogous 4-aminopiperidine-substituted naphthyridinones (**5** and **6**) and dihydroquinazolinones (**7**)

Compd	p38α IC_{50} (nM)	TNF-α IC_{50} (nM)	$nAUC_{iv}$ (μM h)	Cl_p (mL/min/kg)	$t_{1/2}$ (h)	F (%)
6a	0.2	18				
7a	0.5	36				
6b	1.1	51				
7b	1.6	31				
6c	0.4	24	0.82	38	2.6	8.5
7c	0.4	20				
6d	0.8	10	3.38	9.4	2.7	5.9
7d	3.7	200				
5	1.1	13	2.78	11	3.4	44

Table 3. Pharmacokinetics of pentamethylpiperidine naphthyridinone **5** in three animal species

Species	$nAUC_{iv}$ (μM h)	Cl_p (mL/min/kg)	Vd_{ss} (L/kg)	$t_{1/2}$ (h)	$nAUC_{po}$ (μM h)	F (%)
Rat	2.78	11	3.2	3.4	1.2	44
Rhesus	0.64	46	19.5	5.0	0.08	13
Dog	0.68	45	19.8	3.7	0.04	5

aminopiperidine- substituted naphthyridinones. Stabilizing the C4 benzylic position with an sp^2 center markedly lowered clearance and improved oral bioavailability in the naphthyridinones as compared to the analogous dihydroquinazolinones (Table 1). Metabolite identification for dihydroquinazolinone **1** pointed to further metabolism at the C7 piperidine ring. We reasoned that blocking metabolism at both C4 and the two positions alpha to the piperidine nitrogen would further improve the pharmacokinetics of these compounds. Analysis of the pharmacokinetic properties of three naphthyridinones shown in Table 2, **6c**, **6d**, and **5**, corroborates this hypothesis.

Our initial attempt at an α,α′-stabilized piperidine, tropine amine **6c** (conformational constraints on the tropine ring system prevent imine formation), showed clearance similar to that of the isopropyl piperidines, and had poor oral bioavailability, most likely because of metabolism at the tropine *N*-methyl. In contrast, α,α,α′,α′-tetramethylpiperidine **6d** had low clearance, a reasonable half-life, and good intravenous bioavailability, but this compound had disappointingly poor oral bioavailability. Fortunately, methylation of the free piperidine to provide **5** resulted in a compound with low clearance, a respectable half-life, and good oral bioavailability in the rat.

The pharmacokinetics of compound **5** were next studied in the rhesus monkey and the dog. As shown in Table 3, the promising pharmacokinetic properties seen in the rat did not translate to the monkey or dog: Clearance was much higher and bioavailability much lower in the latter two species.

Metabolite identification for naphthyridinone **5** elucidated the key pathways for metabolic degradation of this compound. Primarily, the piperidine *N*-methyl was demethylated in all species (leading to compound **6d**). Oxidation followed by phase II conjugation at the

2-chlorophenyl ring constituted a second significant metabolic pathway. Interestingly, a third major pathway involved rearrangement of the tetramethylpiperidine substituent to a ring-contracted pyrrolidine analogue. Because tetramethylpiperidine *N*-oxide (TEMPO) is known to be a stabilized radical, it is likely that the pyrrolidine metabolite arises via oxidation of the piperidine nitrogen followed by rearrangement of a radical intermediate.

Synthesis

Preparation of the dihydroquinolinone core of **2** (Fig. 3) followed the outline of the dihydroquinazolinone synthesis described previously.[2] Benzylic bromination of 2,6-dibromo-4-methoxytoluene **8** followed by alkylation with *t*-butyl acetate and acidolysis of the resulting *t*-butyl propionate provided the corresponding propionic acid. Amidation of this acid (via the acid bromide) with 2,6-dichloroaniline provided amide **9**, which cyclized to dihydroquinolinone **10** under standard Ullmann coupling conditions.[2] Suzuki coupling with 2-chloro-4-fluorophenylboronic acid provided the required dihydroquinolinone core **12**, poised for elaboration at the C7 position. Oxidation of **10** via benzylic bromination followed by spontaneous elimination provided quinolinone **11**, which was elaborated via Suzuki coupling with 2-chlorophenylboronic acid to provide the analogous quinolinone core **13**.

Installment of the C7 isopropyl piperidine followed the same route for both the dihydroquinolinone core **12** and the quinolinone core **13** (Fig. 4). Conversion of the C7-methoxy to the corresponding hydroxy compound was achieved with BBr_3, and the hydroxy moiety was activated as the triflate. Elaboration to isopropyl piperidines **2** and **3** proceeded by Stille coupling with *N*-BOC tetrahydropyridine **14**, reduction of the tetrahydropyridine double bond,[4] BOC deprotection, and reductive alkylation with acetone.

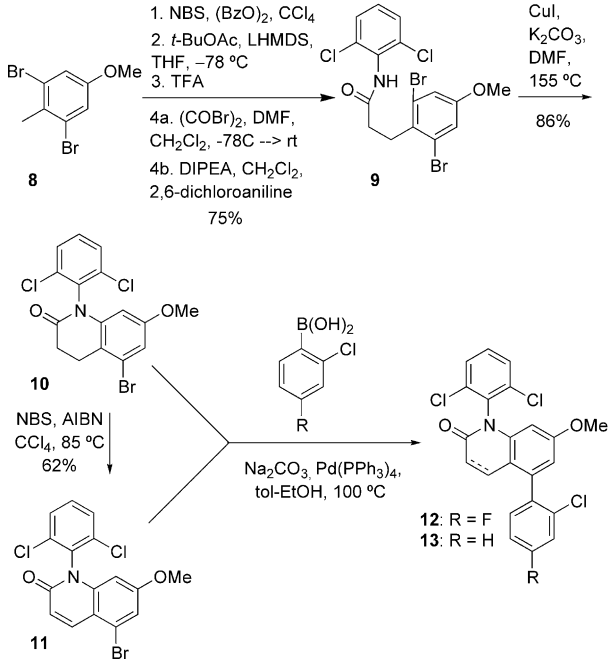

Figure 3. Synthesis of the dihydroquinolinone and quinolinone cores.

The naphthyridinone core **19** was synthesized from pyridine **17**[5] (Fig. 5) via elaboration to the methyl propionate, aluminum-mediated amidation to form **18**, and Ullmann cyclization to the corresponding dihydronaphthyridinone. Oxidation of the dihydronaphthyridinone via benzylic bromination followed by DBU-promoted elimination[6] provided 7-bromonaphthyridinone **19**, which was elaborated to the isopropyl piperidine **4** as described above for compounds **2** and **3**.[4] The C7-amino-substituted naphthyridinones of structure class **6** (see Fig. 2) were prepared by heating compound **19** with the appropriate amine (neat or as a DMSO solution, 130 °C) to effect nucleophilic substitution of the C7-bromine of **19**.[7]

Finally, the C7-amino-substituted dihydroquinazolinones of structure class **7** were prepared via a modification of our original dihydroquinazolinone

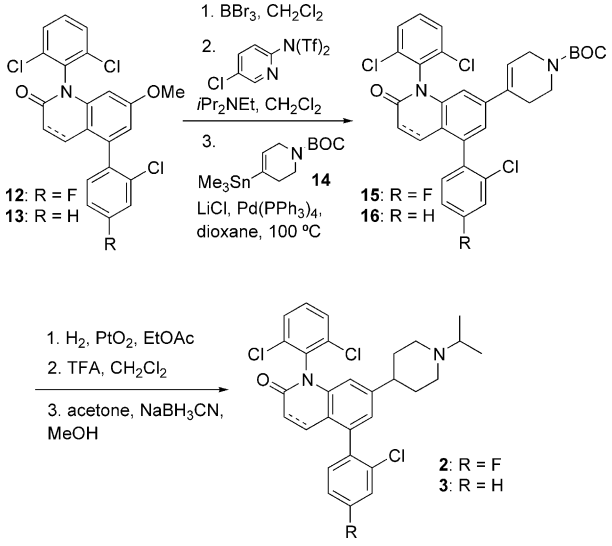

Figure 4. Synthesis of C7 isopropyl piperidines **2** and **3**.

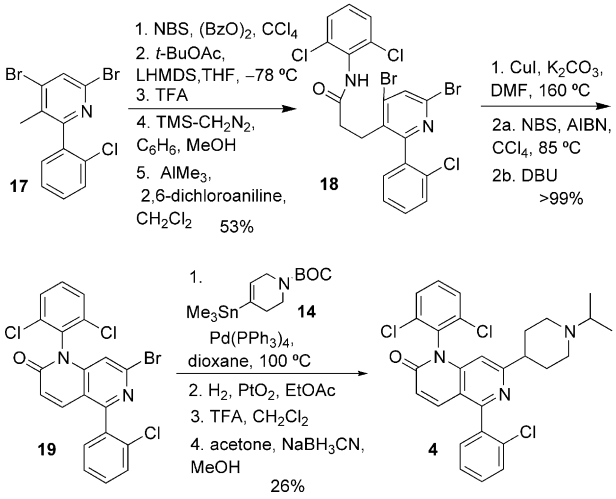

Figure 5. Synthesis of the naphthyridinone core **19** and isopropyl piperidine **4**.

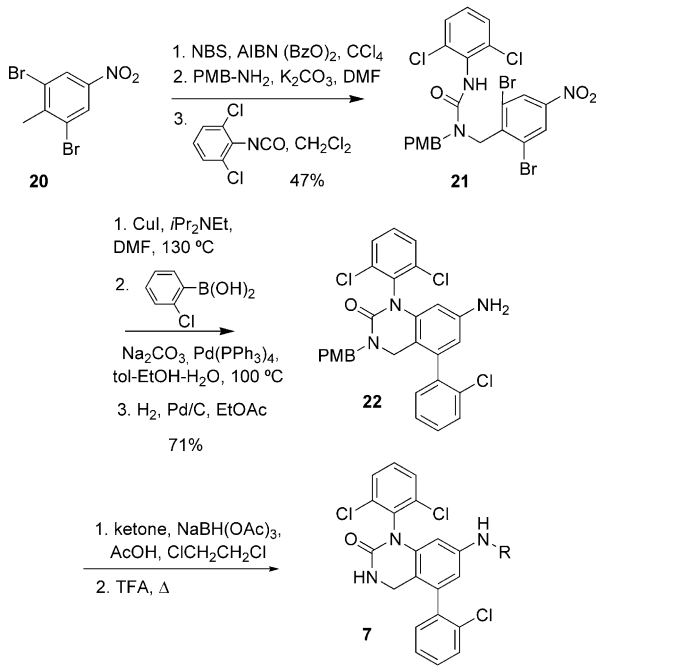

Figure 6. Synthesis of dihydroquinazolinones **7**.

synthesis.[2] As shown in Figure 6, benzylic bromination of 2,6-dibromo-4-nitrotoluene **20** followed by reaction with 4-methoxybenzylamine provided a PMB-protected amine, which was treated with 2,6-dichloroisocyanate to give urea **21**. Ullmann cyclization was followed by Suzuki coupling with 2-chlorophenyl boronic acid, and the resulting 7-nitrodihydroquinazolinone **22** was then reduced to the corresponding 7-amino analogue. This amine was reductively alkylated with the appropriate ketones and then deprotected to provide compounds **7a**–**c**.[7]

We have synthesized a series of C7-piperidine- and 4-aminopiperidine-substituted naphthyridinones, quinolinones, and dihydroquinazolinones that are highly potent inhibitors of both p38 MAP kinase activity and TNF-α release. The quinolinone and naphthyridinone inhibitors showed markedly improved pharmacokinetic properties over the lead compound **1** because of the stabilization of a metabolic 'hot spot' at the C4 benzylic position in the dihydroquinazolinone core.

Naphthyridinone **5**, in which both the C4 benzylic position and the positions alpha to the piperidine nitrogen were blocked, had a particularly promising pharmacokinetic profile in the rat. Disappointingly, this promise was not fulfilled in other animal species. However, analysis of the metabolites of **5**, which pointed to demethylation at the piperidine *N*-methyl, radical-mediated rearrangement of the piperidine ring, and oxidation followed by conjugation of the 2-chlorophenyl ring, allowed us to design compounds which would not suffer from the metabolic fate of naphthyridinone **5**. We will describe the synthesis and biological properties of these compounds in a subsequent publication.[8]

Acknowledgements

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References and Notes

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2. Stelmach; J. E.; Liu; L.; Patel; S. B.; Pivnichny; J. V.; Scapin; G.; Singh; S.; Hop; C. E. C. A.; Wang; Z.; Strauss; J. R.; Cameron; P. M.; Nichols; E. A.; O'Keefe; S. J.; O'Neill; E. A.; Schmatz; D. M.; Schwartz; C. D.; Thompson; C. M.; Zaller; D. M.; Doherty; J. B. *Bioorg. Med. Chem. Lett*. In press.
3. For assay details, see ref 1b.
4. For both quinolinone **3** and naphthyridinone **4**, the C7 tetrahydropyridine double bond was reduced selectively (<4 h for **4**, and <2 h for **3**) in the presence of the C3–C4 double bond by monitoring of the reaction progression.
5. Pyridine **17** was prepared from 2-chloro-3-methyl-5-nitropyridine (Hawkins, G. F.; Roe, A. *J. Org. Chem.* **1949**, *14*, 328) via the following four steps: (1) 2-Cl-phenylboronic acid, Cs_2CO_3, $Pd(PPh_3)_4$. (2) RaNi. (3) Br_2, HCl. (4) *t*-BuONO. Synthetic details will be provided: S. R. Natarajan et al., manuscript in preparation.
6. The benzyl bromide was stable to flash chromatography, however, the oxidation-elimination was performed in one pot.
7. Isopropyl piperidines **6b** and **7b** were prepared from **6a** and **7a**, respectively, by reductive alkylation with acetone.
8. Bao; J.; Hunt; J. A.; Miao; S.; Rupprecht; K. M.; Stelmach; J. E.; Liu; L.; Ruzek; R. D.; Sinclair; P. J.; Pivnichny; J. V.; Hop; C. E. C. A.; Kumar; S.; Zaller; D. M.; Shoop; W. L.; O'Neill; E. A.; O'Keefe; S. J.; Thompson; C. M.; Doherty, J. B. In preparation.