Bioorganic & Medicinal Chemistry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and evaluation of the 2,4-diaminoquinazoline series as anti-tubercular agents

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ARTICLE INFO

Article history:
Received 4 August 2014
Revised 4 October 2014
Accepted 9 October 2014
Available online xxxx

Keywords:
Tuberculosis
Mycobacterium tuberculosis
Antibacterial activity
2,4-Diaminoquinazoline
Dioxygenase

ABSTRACT

The 2,4-diaminoquinazoline class of compounds has previously been identified as an effective inhibitor of *Mycobacterium tuberculosis* growth. We conducted an extensive evaluation of the series for its potential as a lead candidate for tuberculosis drug discovery. Three segments of the representative molecule *N*-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine were examined systematically to explore structure–activity relationships influencing potency. We determined that the benzylic amine at the 4-position, the piperidine at 2-position and the N-1 (but not N-3) are key activity determinants. The 3-deaza analog retained similar activity to the parent molecule. Biological activity was not dependent on iron or carbon source availability. We demonstrated through pharmacokinetic studies in rats that good in vivo compound exposure is achievable. A representative compound demonstrated bactericidal activity against both replicating and non-replicating *M. tuberculosis*. We isolated and sequenced *M. tuberculosis* mutants resistant to this compound and observed mutations in Rv3161c, a gene predicted to encode a dioxygenase, suggesting that the compound may act as a pro-drug.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is an infectious disease for which there is still a great need for discovery and development of novel drugs to improve therapy.[1] In 2010 alone, the World Health Organization reported 8.8 million new cases and 1.4 million deaths from the disease.[2] In addition, billions of people harbor latent infections with no clinical symptoms, but with the potential to advance to active form. Current TB treatment requires a combination of four drugs, isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (ETH) for 2 months followed by an additional 4 months of INH and RIF. These drugs have been in use for many decades, contributing to a rise in the emergence of multidrug resistant (MDR) and extensively drug-resistant (XDR) strains of *M. tuberculosis*. New drugs are needed urgently to shorten the duration of therapy and to treat drug-resistant strains.

Diaminoquinazolines (DAQ) have been reported with activity against a diverse range of biological diseases including lupus, rheumatoid arthritis, malaria and hypertension.[3] The DAQ series is active against *M. tuberculosis*[4] and effective at preventing the growth of *M. tuberculosis*[5] with minimum inhibitory concentrations (MICs) reported in the range of 1.3–6.1 μg/mL. The DAQ series is less effective against other bacterial species, with weak activity against *Escherichia coli* and *Pseudomonas aeruginosa*, suggesting some element of selectivity.[6]

We were interested in the potential of the DAQ series as a starting point for drug discovery. We conducted an exploratory study to evaluate the potential of the series for progression as a drug lead molecule.

2. Results and discussion

To investigate the biological activity, and the pharmaceutical and pharmacokinetic (PK) properties of the DAQ class of compounds, we conducted a systematic structural modification of a

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http://dx.doi.org/10.1016/j.bmc.2014.10.007
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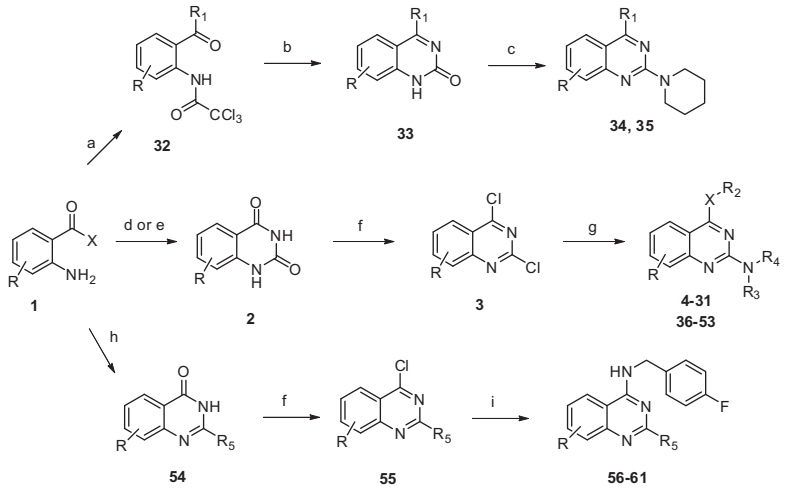
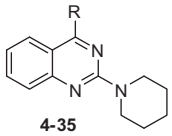


Scheme 1. Synthesis of 2,4-substituted quinazolines. Reagents and conditions: (a) X = R_1: Cl_3CCOCl, DMAP, CH_2Cl_2; (b) NH_4OAc, DMSO; (c) (i) $POCl_3$, (ii) Piperidine, *i*-PrOH, reflux; (d) X = OH: KOCN, NaOH; (e) X = NH_2: phosgene; (f) $POCl_3$, *NN*-dimethylaniline, reflux; (g) (i) nucleophile (R_2XH: X = O,S,NH), THF, room temperature, (ii) R_3R_4NH, *i*-PrOH, reflux; (h) X = OH: R_5CONH_2, HCO_2H (i) 4-fluorobenzylamine, THF, room temperature.

Table 1
Effect of C-2 and C-4 substitutions on biological potency of DAQ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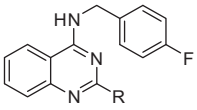
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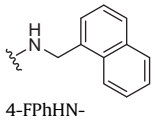
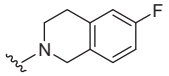
Compd	R-group	MIC	I	Compd	R-group	MIC	*I*
4	$PhCH_2HN$-	9.2	96	**34**	H-	469	<30
5	2-$FPhCH_2HN$-	nd	97	**35**	4-$FPhCH_2CH_2$-	nd	<30
6	3-$FPhCH_2HN$-	nd	98	**7**	Piperidin-1-yl	7.4	97
7	4-$FPhCH_2HN$-	7.4	97	**36**	4-(CH_3)piperidin-1-yl	nd	97
8	3-$MePhCH_2HN$-	nd	99	**37**	4-(OH)piperidin-1-yl	nd	<30
9	3-$IPhCH_2HN$-	nd	98	**38**	4-(NH_2)piperidin-1-yl	nd	<30
10	4-$MePhCH_2HN$-	nd	98	**39**	4-(NHMe)piperidin-1-yl	nd	33
11	4-$MeOPhCH_2HN$-	nd	97	**40**	4-(NMe2)piperidin-1-yl	nd	<30
12	4-OCF_3PhCH_2HN-	nd	95	**41**	4-(CO_2H)piperidin-1-yl	nd	<30
13	4-$ClPhCH_2HN$-	nd	99	**42**	3,5-(Me)piperidin-1-yl	nd	<30
14	4-CF_3PhCH_2HN-	6.6	99	**43**	4-(CH_2OH)piperidin-1-yl	nd	<30
15	4-NH_2PhCH_2HN-	nd	<30	**44**	4-$(NHCH_2CO_2H)$piperidin-1-yl	nd	<30
16	2,4-$FPhCH_2HN$-	nd	97	**45**	2-(CH_2CO_2H)piperidin-1-yl	nd	<30
17	3,4-$FPhCH_2HN$-	nd	96	**46**	H_2N-	93	<30
18	2,4-$ClPhCH_2HN$-	nd	98	**47**	MeHN-	35	44
19	3,4-$ClPhCH_2HN$-	nd	98	**48**	Me_2N-	34	40
20	2,5-$ClPhCH_2HN$-	nd	97	**49**	Pyrrolidin-1-yl	31	97
21	3-Cl, 4-$MeOPhCH_2HN$-	nd	98	**50**	Isoindolin-2-yl	nd	78
22	4-$FPhCH_2O$-	296	<30	**51**	Piperazinyl	148	<30
23	4-$FPhCH_2S$-	282	<30	**52**	4-(4-Anilinyl)piperazin-1-yl	nd	94
24	MeHN-	206	<30	**53**	$(HOCH_2CH_2)_2HN$-	nd	<30
25	*i*PrHN-	25	37	**56**	(Piperidin-1-yl)CH_2HN-	29	<30
26	cyclohexylCH_2HN-	nd	99	**57**	H-	99	<30
27	4-$CF_3PhCH_2CH_2HN$-	5.7	97	**58**	Me-	94	<30
28		nd	97	**59**	F_3C-	nd	<30
29	4-FPhHN-	39	<30	**60**	Ph-	76	<30
30	Piperidin-1-yl	nd	<30	**61**	Cyclohexyl-	15	47
31		nd	94	Rifampicin[a]		0.013/0.004	100

Compounds were tested for inhibition of *M. tuberculosis* in liquid and on solid medium. The percent inhibition (*I*) of growth at 20 μM in liquid medium is reported. Compounds were considered inactive if %*I* <30 at 20 μM. Minimum inhibitory concentrations (MIC) were determined using the serial proportion method on solid agar.

[a] MIC reported for solid/liquid medium. nd = not determined.

Please cite this article in press as: Odingo, J.; et al. *Bioorg. Med. Chem.* (2014), http://dx.doi.org/10.1016/j.bmc.2014.10.007