Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 193–195

BIOORGANIC &
MEDICINAL
CHEMISTRY
LETTERS

Novel 2,2-Dioxide-4,4-disubstituted-1,3-*H*-2,1,3-benzothiadiazines as Non-Nucleoside Reverse Transcriptase Inhibitors

Jeffrey W. Corbett,* Lisa A. Gearhart, Soo S. Ko, James D. Rodgers,
Beverly C. Cordova, Ronald M. Klabe and Susan K. Erickson-Viitanen

DuPont Pharmaceuticals Company, Experimental Station, PO Box 80500, Wilmington, DE 19880-0500, USA

Received 20 October 1999; accepted 24 November 1999

Abstract—Benzothiadiazine non-nucleoside reverse transcriptase inhibitors (NNRTIs) of HIV have been synthesized via a novel process to afford active inhibitors, with the most potent compound exhibiting an $IC_{90} = 180$ nM in a whole cell assay. The 2,2-dioxide-1*H*-2,1,3-benzothiadiazine ring system was constructed in one step from 2-amino-5-chlorobenzonitrile. © 2000 DuPont Pharmaceuticals Company. Published by Elsevier Science Ltd. All rights reserved.

Human Immunodeficiency Virus type 1 (HIV-1) is the etiologic agent responsible for the onset of the Acquired Immune Deficiency Syndrome (AIDS). HIV-1 is a retrovirus which encodes a reverse transcriptase (RT) that is required for viral replication.[1] A new class of drugs, which act by binding to an allosteric site in the HIV-1 RT enzyme,[2] are the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) efavirenz (Sustiva™), delavirdine (Rescriptor®) and nevirapine (Viramune®). As part of a continuing effort to identify novel NNRTIs which might possess increased potency toward wild-type HIV RT and toward mutant forms of virus, the benzothiadiazine ring system was investigated for activity in inhibiting reverse transcriptase. The benzothiadiazine ring system was chosen since it has been demonstrated that structurally similar compounds containing the quinazolin-2(1*H*)-one ring system are potent NNRTIs.[3,4]

Typically, 2,2-dioxide-1*H*-2,1,3-benzothiadiazines are synthesized by adding nucleophiles to an anthranilonitrile followed by hydrolysis of the resulting imine anion to afford the *o*-amino ketone. Treatment of the resulting amino ketones with sulfamide at elevated temperatures delivers the desired benzothiadiazines.[5] We are unaware of any reports in the literature wherein the benzothiadiazine ring system has been synthesized directly from readily available anthranilonitriles.

In an effort to avoid the additional step of forming and isolating a ketone after addition of a nucleophile to an anthranilonitrile, we decided to attempt to trap the intermediate imine anion with sulfuryl chloride. In the event, 2-amino-5-chlorobenzonitrile[6] was treated with cyclopropyl and isopropyl Grignard reagents followed by sulfuryl chloride to afford the desired 1*H*-2,1,3-benzothiadiazines **1**. The unoptimized yields for this one pot transformation were moderate (Fig. 1). The benzothiadiazines **1** were elaborated to the final products **1–9** upon addition of alkynyl lithium reagents in the presence of boron trifluoride etherate.[7,8] A limited range of R^1 groups was examined since it was known from previous structure–activity relationships with quinazolin-2(1*H*)-ones that large R^1 groups result in a loss in activity.[4] Compound **11** with $R^1 = CF_3$, related to the 5,6-difluoroquinazolin-2(1*H*)-one DPC 963,[3] was prepared by an alternate route using intermediate **10** (Fig. 2).[9,10]

The unoptimized yields for the lithium acetylide addition to **1** and **10** are shown in Table 1. These reactions are noteworthy since benzothiadiazines **2–9** are constructed in only two steps from readily available 2-amino-5-chlorobenzonitrile, and no protecting groups were used. Furthermore, there are no reports in the literature wherein the 1*H*-2,1,3-benzothiadiazine ring system **1** or **10** was further elaborated by the addition of nucleophiles. The biological results are reported in Table 1.[11–13] One of these compounds, **2**, exhibited good activity in a whole cell antiviral assay ($IC_{90} = 182$ nM), while the rest of the compounds possessed only moderate activity. The IC_{90} of **2** is approximately 90-fold less than the activity observed for efavirenz and DPC 961 and DPC 963, two quinazolin-2(1*H*)-ones currently in

---

*Corresponding author. Tel.: +1-302-695-4823; fax: +1-302-695-9673; e-mail: jeffrey.w.corbett@dupontpharma.com

0960-894X/00/$ - see front matter
PII: S0960-894X(99)00672-1

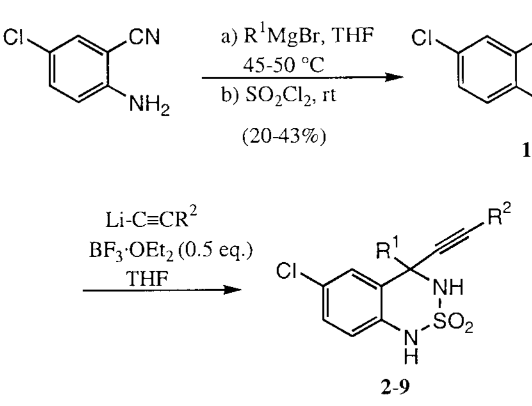

Figure 1. Synthesis of compounds **2**–**9**.

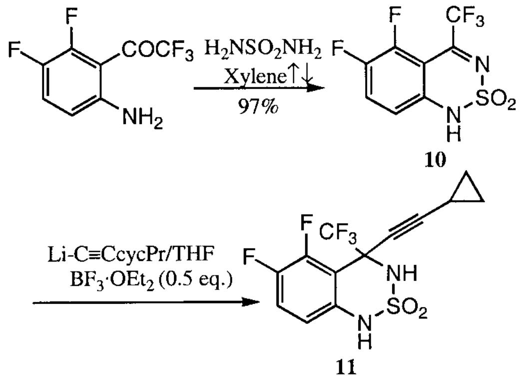

Figure 2. Preparation of compound **11**.

Table 1. Structure and biological activity of compounds **2**–**9** and **11**

Compound	R^1	R^2	mp (°C)	Yield (%)	RNA IC_{90} (nM)[12]	Enzyme IC_{50} (nM)[11]
DPC 961[3]					2.0 ± 0.7^{15}	31 ± 8^{15}
DPC 963[3]					1.3 ± 0.6^{15}	18 ± 5^{15}
Efavirenz					1.7 ± 0.5^{15}	47 ± 25^{15}
Delavirdine					50 ± 10^{15}	422 ± 92^{15}
Nevirapine					37 ± 9^{15}	4848 ± 1739^{15}
2	cycPr	*i*-Pr	153	55	182	4627
3	cycPr	cycPr	174	56	279	35,870
11	CF_3	cycPr	122–125	35	284	24,667
4	cycPr	Et	172 (dec.)	43	611	Inactive
5	*i*-Pr	*i*-Pr	160–161	47	643	24,137
6	*i*-Pr	cycPr	131 (dec.)	45	677	Inactive
7	*i*-Pr	Et	138.5–142	42	961	Inactive
8	cycPr	Ph	44 (dec.)	54	Inactive	Inactive
9	cycPr	2-Pyridyl	93 (dec.)	20	Inactive	Inactive

clinical trials,[3] while it is only 3.6-fold less potent than delavirdine. However, **2** is racemic and the single enantiomer would be expected to be 1.8-fold less potent than delavirdine and only 2.5-fold less potent than nevirapine.[14]

Compounds **5**–**7** containing the *i*-propyl group at the quaternary center (R^1 = *i*-Pr) were found to exhibit modest activity. Incorporating a cyclopropyl group for R^1 resulted in a substantial increase in potency, as evidenced by compounds **2**–**4**. It was also found that an *i*-propyl group at R^2 was marginally more potent than a cyclopropyl group, and significantly better than an ethyl group. This trend held irrespective of the nature of R^1 (for example, see compounds **2**–**4** and **5**–**7**). Therefore, the presence of a cyclopropyl group at R^1 was favored over an isopropyl group, while the incorporation of 3-methyl-1-butyne (R^2 = *i*-Pr) was preferred over cyclopropyl (**3**) and ethyl (**4**). The trifluoromethyl analogue, **11**, exhibited disappointing activity when compared to the corresponding quinazolin-2(1*H*)-one DPC 963. The incorporation of aryl groups onto the alkyne, as in compounds **8** and **9**, was the most disfavored substitution, which is in contrast to a series of quinazolin-2(1*H*)-ones previously identified.[4] None of the benzothiadiazines were tested for their ability to inhibit mutant virus forms since their whole cell activities toward wild type virus were lower than either efavirenz, DPC 961 or DPC 963.

In summary, the synthesis of 2,2-dioxide-4,4-disubstituted-1,3-*H*-2,1,3-benzothiadiazines has been accomplished in two steps from a readily available anthranilonitrile without the use of protecting groups. These compounds exhibited moderate NNRTI activity. An examination of the scope and limitations of the one-step methodology for the construction of 2,2-dioxide 1*H*-2,1,3-benzothiadiazines and the subsequent addition of nucleophiles to afford 4,4-disubstituted benzothiadiazines will be reported in due course.

References and Notes

1. Levy, J. A. *Microbiol. Rev.* **1993**, *57*, 183.
2. Esnouf, R.; Ran, J.; Ross, C.; Jones, Y.; Stammers, D.; Stuart, D. *Nat. Struct. Biol.* **1995**, *2*, 303.
3. Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Jeffrey, S.; Bacheler, L. T.; Klabe, R. M.; Diamond, S.; Lai, C.-M.; Rabel, S. R.; Saye, J. A.; Adams, S. P.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *Antimicrob. Agents Chemother.* **1999**, *12*, 2893.
4. Tucker, T. J.; Lyle, T. A.; Wiscount, C. M.; Britcher, S. F.; Young, S. D.; Sanders, W. M.; Lumma, W. C.; Goldman, M. E.; O'Brien, J. A.; Ball, R. G.; Homnick, C. F.; Schleif, W. A.; Emini, E. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 2437 and references contained therein.
5. Wright, J. B. *J. Org. Chem.* **1965**, *30*, 3960.
6. The 2-amino-5-chlorobenzonitrile used in the preparation of the compounds described herein was obtained from Aldrich Chemical Company. However, there are currently no commercial

sources for this chemical. A literature preparation of 2-amino-5-chlorobenzonitrile can be found in: Nickson, T. E.; Roche-Dolson, C. A. A. *Synthesis* **1985**, 669.

7. Experimental procedure for compound **1**: A solution of 5-chloro-2-aminobenzonitrile (1.0 equiv) in anhydrous THF (1 M) was added dropwise to a 50 °C solution of the Grignard reagent (3.6 equiv) in anhydrous THF (1.6 M). The mixture was stirred at 45–50 °C until the reaction was complete, as determined by TLC, at which time the mixture was cooled to rt. Sulfuryl chloride (3.5 equiv) was carefully added dropwise to the imine anion. The resulting mixture was stirred at rt for 1.5 h, quenched by the addition of 1 M citric acid and extracted with CH_2Cl_2. The organic phase was washed with 10% Na_2CO_3 followed by saturated aqueous NaCl, dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography. Experimental procedure for compound **2**: A 0 °C solution of the requisite alkyne (4.5 equiv) in anhydrous THF (0.5 M) was treated with *n*-BuLi (4.0 equiv) and aged at 0 °C for 0.5 h. The acetylide was cannulated into a −78 °C solution of **1** (1.0 equiv) in anhydrous THF (0.2 M) followed by $BF_3{\cdot}OEt_2$ (0.5 equiv). The cooling bath was removed and the mixture was aged for 2 h at rt. The reaction was quenched by addition of 1 M citric acid, and extracted with EtOAc. The organic phase was washed with 10% Na_2CO_3 followed by saturated aqueous NaCl, dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography.

8. All final products had satisfactory CHN analyses.

9. For the preparation of the ketone, see: Patel, M.; Ko, S. S.; McHugh, R. J.; Markwalder, J. A.; Srivastava, A. S.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S. K.; Trainor, G. L.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2805.

10. Compounds related to **1**, where $R^1 = CF_3$, can be prepared by condensing sulfamide with an *o*-aminotrifluoromethyl ketone (as exhibited in Fig. 2). See ref 5 for an example of the condensation of sulfamide with an *o*-aminomethyl ketone to yield a 2,1,3-benzothiadiazine 2,2-dioxide.

11. All compounds were assayed for enzyme inhibitory activity according to the protocol described in ref 3.

12. All compounds were assayed for whole cell based antiviral activity according to the protocol described in: Bacheler, L. T.; Paul, M.; Jadhav, P. K.; Otto, M.; Stone, B.; Miller, J. *Antiviral Chem. Chemother.* **1994**, *5*, 111.

13. The biological results are reported as the results from a single assay.

14. The biological activity of the pure enantiomer of the structurally related 2(1*H*)-quinazolinone ring system is typically one-half that of the racemate. For examples of this phenomena, see ref 3.

15. Data shown represents the mean ± standard deviation for 2–6 independent determinations.