Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1185–1187

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Structure–Activity Relationships of a Novel Series of HIV-1 Protease Inhibitors Encompassing ABT-378 (Lopinavir)

Hing L. Sham,* David A. Betebenner, Xiaoqi Chen, Ayda Saldivar, Sudthida Vasavanonda, Dale J. Kempf, Jacob J. Plattner and Daniel W. Norbeck

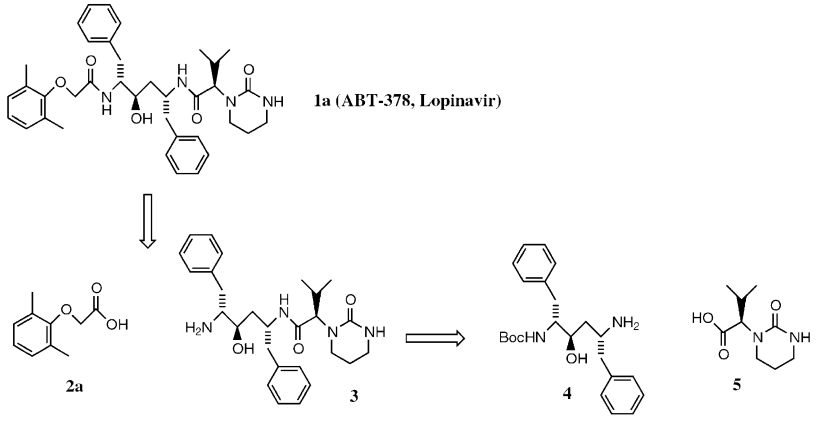
Pharmaceutical Discovery, D47B, Building AP-10, Abbott Laboratories, Abbott Park, IL 60064-6101, USA

Received 11 January 2002; accepted 6 February 2002

Abstract—The HIV protease inhibitor ABT-378 (Lopinavir) has a 2,6-dimethylphenoxyacetyl group in the P-2′ position. Analogues in which this group is replaced with various substituted phenyl or heteroaryl groups were synthesized and the structure–activity relationships explored.

The HIV protease inhibitor ABT-378[1] (Lopinavir) is the anti-viral component of Kaletra™ (approved by FDA in September, 2000), the latest approved HIV protease inhibitor for the treatment of human immunodeficiency virus (HIV) infection. ABT-378 (**1a**) possesses high potency against wild-type and mutant HIV protease ($K_i = 1.3$–28 pM).[1,2] The synthesis of ABT-378[3] and its major metabolites[4] have been reported. At the P-2′ position of ABT-378 is the 2,6-dimethylphenoxyacetyl group, which is fairly lipophilic. In order to explore the structure–activity relationship at this position, various analogues of ABT-378 were synthesized. These analogues possess different substitutions in the aryl or heteroaryl ring or the oxygen atom of the phenoxy linkage is varied to sulfur and carbon. Following synthesis, these compounds were tested to determine their inhibitory potencies against HIV-1 protease and their antiviral activities.

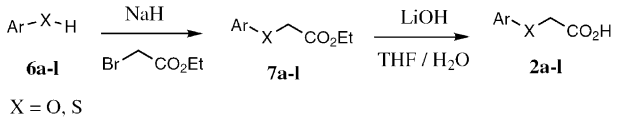
The retrosynthetic analysis for the synthesis of ABT-378 is shown in Scheme 1. Coupling of the key intermediate 2,6-dimethylphenoxyacetic acid (**2a**) with amine **3** using



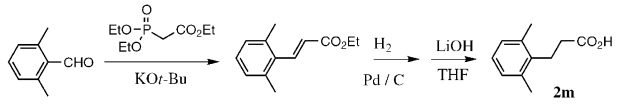
Scheme 1. Retrosynthetic scheme for ABT-378 and key intermediates.

*Corresponding author. Fax: +1-847-935-5165; e-mail: hing.l.sham@abbott.com

0960-894X/02/$ - see front matter
PII: S0960-894X(02)00134-8



Scheme 2. Synthesis of acids **2a–l**.

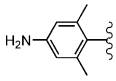


Scheme 3. Synthesis of acid **2m**.

EDAC/HOBt provided ABT-378 (**1a**). Thus, the synthesis of various analogues of ABT-378 (**1b–m**) necessitated the synthesis of acids **2a–m**. The synthesis of acids **2a–l** is shown in Scheme 2. The phenols and thiophenol **6a–i** are commercially available and the phenols **6j–l** were synthesized according to literature procedures.[5–7] Treatment of **6a–l** with sodium hydride followed by addition of ethyl 2-bromoacetate provided the corresponding ethyl esters **7a–l** (68–85%). Hydrolysis of the esters with lithium hydroxide in aqueous THF gave acids **2a–l**. The synthesis of acid **2m** is shown in Scheme 3. Horner–Wadsworth–Emmons[8] reaction of 2,6-dimethylbenzaldehyde with triethylphosphonoacetate in the presence of potassium *t*-butoxide provided the α,β-unsaturated ester (89%). Hydrogenation followed by hydrolysis provided acid **2m** (90%). Coupling of the acids **2a–m** with the previously reported amine **3**,[3] using EDAC/HOBt provided the HIV protease inhibitors **1a–m**.

The HIV protease inhibitory potencies (% inhibition @ 0.5 nM) and the antiviral activities (against the cytopathic effects of HIV_{IIIB} in MT-4 cells) of the inhibitors **1a–m** are reported in Table 1. Removal of one or two of the methyl groups (**1b** and **1c**) in the 2,6-dimethylphenoxyacetyl group of ABT-378 resulted in loss of potency, as did addition of a 4-methyl group (**1d**). Replacement of the 2,6-dimethyl substituents with 2,6-dichloro (**1f**), 2,6-dimethoxy (**1e**), and 3,5-dimethyl (**1h**) all resulted in significant loss of antiviral activity (EC_{50}'s, Table 1). We initially hypothesize that this maybe due to the increase in lipophilicity and the inability of these compounds to cross the cell membrane effectively. However, although the clogP of **1f** (6.3) is greater than that of **1a** (6.1), the clogP value of **1e** (4.5) and **1h** (6.1) are actually lower or similar. This indicates that lipophilicity is not the only factor that can affect the anti-viral potency of these analogues. Increasing the polarity of the analogues, such as in **1g** (4-amino), **1k** (4-fluoro), and **1l** (3-pyridyl) significantly restores the antiviral activity. The compound **1j** (clogP = 4.3) with increased polarity, actually is significantly less potent in its anti-viral activity when compared to **1a**, further demonstrating that lipophilicity/polarity is not the only factor determining the antiviral potency. Replacement of the ether oxygen in **1a** with sulfur or carbon, as in compounds **1i** and **1m** resulted in 25- to 40-fold loss of anti-viral activity. Compared to the analogues[9] shown in Table 1, ABT-378 (**1a**) has the best HIV protease inhibitory activity and antiviral potency. In addition, its good pharmacokinetic profiles in several animal species led to its selection as the clinical candidate to enter human trials.

Table 1. Inhibition of HIV protease and anti-viral activities in MT-4 cells

Compd	Ar	X	% inhibiton @ 0.5 nM	Antiviral EC_{50}[a] (μM)
1a (ABT-378)		O	93	0.10
1b	Phenyl	O	67	1.3
1c		O	84	0.43
1d		O	85	0.39
1e		O	38	14
1f		O	87	2.8
1g		O	86	0.16
1h		O	37	38
1i		S	55	4.1
1j		O	79	4.2
1k		O	90	0.49
1l		O	75	0.77
1m		C	70	2.6

[a]In the presence of 50% human serum.

Acknowledgement

We thank Dr. Stephen L. Gwaltney, II for his assistance in the preparation of this manuscript.

References and Notes

1. Sham, H. L.; Kempf, D. J.; Molla, A.; Marsh, K. C.; Kumar, G. N.; Chen, C. M.; Kati, W.; Stewart, K.; Lal, R.; Hsu, A.; Betebenner, D. A.; Korneyeva, M.; Vasavanonda, S.; McDonald, E.; Saldivar, A.; Wideburg, N.; Chen, X.; Niu, P.; Park, O.; Jayanti, V.; Grabowski, B.; Granneman, G. R.; Sun, E.; Japour, A. J.; Leonard, J. M.; Plattner, J. J.; Norbeck, D. W. *Antimicrob. Agents Chemother.* **1998**, *42*, 3218.
2. Molla, A.; Vasavanonda, S.; Kumar, G. N.; Sham, H. L.; Johnson, M.; Grabowski, B.; Denissen, J. F.; Kohlbrenner, W.; Plattner, J. J.; Leonard, J. M.; Norbeck, D. W.; Kempf, D. J. *Virology* **1998**, *250*, 255.
3. Stoner, E. J.; Cooper, A. J.; Dickman, D. A.; Kolaczkowski, L.; Lallaman, J. E.; Liu, J. H.; Oliver-Shaffer, P. A.; Patel, K. M.; Paterson, J. B.; Plata, D. J.; Riley, D. A.; Sham, H. L.; Stengel, P. J.; Tien, J. H. J. *J. Org. Process Res. Dev.* **2000**, *4*, 264.
4. Sham, H. L.; Betebenner, D. A.; Herrin, T.; Kumar, G.; Saldivar, A.; Vasavanonda, S.; Molla, A.; Kempf, D. J.; Plattner, J. J.; Norbeck, D. W. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1351.
5. Dorrow, A.; Hell, H. *Chem. Ber.* **1960**, *93*, 1998.
6. Dewar, M. J. S.; Takeuchi, Y. *J. Am. Chem. Soc.* **1967**, *89*, 390.
7. Wang, Y.; Liu, M. C.; Lin, T. S.; Sartorelli, A. *J. Med. Chem.* **1992**, *20*, 3667.
8. Wadsworth, W. S.; Emmons, W. D. *Org. Syn.* **1965**, *45*, 44.
9. All compounds reported have mass, NMR, and analytical data consistent with the structures assigned.