INHIBITION OF TYROSINE PROTEIN KINASE BY SYNTHETIC ERBSTATIN ANALOGS

Sir:

The effective synthesis of the specific tyrosine protein kinase (TPK) inhibitor, erbstatin (1), and its dihydroxy analogs (11 and 12) was reported in the preceding paper1). Herein, mono-, di- and tri-hydroxy analogs of 1 have been synthesized by a similar procedure and their TPK inhibiting activities were evaluated.

Mono-hydroxy analogs such as 2-hydroxy- (2), 3-hydroxy- (3), 4-hydroxy- (4), 5-bromo-2-hydroxy- (5) and 2-hydroxy-5-methoxy-compound (6) were prepared in high yields from corresponding aldehydes and SCHÖLLKOPF's reagent2), diethyl(isocyanomethyl)phosphonate (15), as described in the preceding paper1). On the other hand, similar treatment of 2,4-di- or 2,3,4-tri-hydroxybenzaldehyde with the phosphonate (15) gave no desired products although a large number of variables including bases [NaN(Si(CH3)3)2, BuLi and NaH] were assessed. The protection, however, of the hydroxyl groups in the aldehydes with trimethylsilyl chloride ((CH3)3SiCl - Et3N in THF) gave suitable materials 13 and 14 for subsequent reaction with the reagent (15) to give the intermediary isocyanides (16) [13: 1H NMR (CDCl3) δ 0.30 (18H, s), 6.35 ~ 6.60 (2H, m), 7.80 (1H, d, J = 8.5 Hz), 10.36 (1H, s), 14: 1H NMR (CDCl3) δ 0.20, 0.25 and 0.28 (27H, each s), 6.62 (1H, d, J = 8.5 Hz), 7.42 (1H, d, J = 8.5 Hz), 10.27 (1H, s)] (Fig. 2). By acid hydrolysis (0.1 n HCl - EtOAc)3), the isocyanides (16) were directly converted into the desired formamides (7) and (8) with removal of the trimethylsilyl groups in 57% and 53% overall yields [7: 1H NMR (acetone-d6) δ 6.25 ~ 6.55 (3H, m), 7.15 (1H, d, J = 8.5 Hz), 7.56 (1H, dd, J = 15 and 11 Hz), 8.17 (2H, s), 8.47 (1H, s), 9.1 (1H, br), 8: 1H NMR (acetone-d6) δ 6.43 (1H, d, J = 9 Hz), 6.47 (1H, d, J = 15 Hz), 7.76 (1H, d, J = 9 Hz), 7.4 (2H, br), 7.62 (1H, dd, J = 15 and 10.5 Hz), 8.1 (1H, br), 8.22 (1H, s), 9.2 (1H, br)].

Other related compounds (9) and (10) were prepared as follows. The peracetylation (Ac2O - Et3N - 4-dimethylaminopyridine in THF) of

Fig. 1. Erbstatin and its analogs.

Fig. 2.

1 R1 = 2-OH  R2 = 5-OH  R4 = H  R4 = NHCHO (erbstatin)
2 R1 = 2-OH  R2 = H  R4 = H  R4 = NHCHO
3 R1 = 3-OH  R2 = H  R4 = H  R4 = NHCHO
4 R1 = 4-OH  R2 = H  R4 = H  R4 = NHCHO
5 R1 = 2-OH  R2 = 5-Br  R4 = H  R4 = NHCHO
6 R1 = 2-OH  R2 = 5-OCH3  R4 = H  R4 = NHCHO
7 R1 = 2-OH  R2 = 4-0H  R4 = H  R4 = NHCHO
8 R1 = 2-OH  R2 = 3-OH  R4 = 4-OH  R4 = NHCHO
9 R1 = 2-OH  R2 = 5-OH  R4 = H  R4 = NHAc
10 R1 = 2-OH  R2 = 5-OH  R4 = H  R4 = COOH
11 R1 = 2-OH  R2 = 3-OH  R4 = H  R4 = NHCHO
12 R1 = 3-OH  R2 = 4-OH  R4 = H  R4 = NHCHO
13 R = H
14 R = O-TMS

15 (EtO)2PCH2NC  16
The TPK inhibitory activities of above derivatives are listed in Table 1. The TPK activities were assayed using the A-431 cell membrane fraction as the enzyme/substrate as described previously. As shown in the table, 2-(2,3,4-tri hydroxyphenyl)vinylformamide (8), 2,5-dihydroxy cinnamic acid (10), 2-(2,3-dihydroxyphenyl)vinylformamide (11) and 2-(3,4-dihydroxyphenyl)vinylformamide (12) showed potent inhibitory activities comparable to erbstatin (1). Other biological activities and the stability of these compounds are being studied.

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