Synthesis and Biopharmaceutical Studies of JLTN as Potential Dasatinib Prodrug

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Dasatinib was identified as a potent orally administered Src/Abl kinase inhibitor with excellent anti-proliferative activity against Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase. The low bioavailability of Dasatinib may be due to both incomplete oral absorption and first-pass metabolism. A prodrug, JLTN, was synthesized to minimize the first-pass effect of Dasatinib and improve the oral bioavailability following oral administration *via* targeting intestinal peptide transporter and enhancing chemical stability. Biological evaluation data indicated that there was a 150%-fold increase in oral bioavailability of this prodrug compared to the parent drug Dasatinib in monkeys.

Key words Dasatinib; prodrug; JLTN

Dasatinib, [*N*-(2-chloro-6-methylphenyl)-2-({6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carboxamide, monohydrate; formula is $C_{22}H_{26}ClN_7O_2S \cdot H_2O$; see Fig. 1] is a novel, small molecule, orally-bioavailable multi-targeted kinase inhibitor, developed by Bristol-Myers Squibb (U.S.A.) for the treatment of adults with chronic phase or advanced phase (accelerated, myeloid blast or lymphoid blast phase) chronic myeloid leukemia (CML) and resistance to or intolerance of prior therapy (including Imatinib). It inhibits breakpoint cluster region/Abelson, v-src sarcoma viral oncogene homolog, proto-oncogene c-kit, ephrin a receptor, platelet-derived growth factor receptors, and other tyrosine kinases. Dasatinib is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ALL) and lymphoid blast CML and resistance or intolerance of prior therapy.[1–8)]

However, Dasatinib suffers from low oral bioavailability (*ca.* 14%), has large individual treatment variability, and more adverse events than Imatinib. It is now used as a second line medication for the treatment of CML and Ph^+ALL patients. The incomplete oral bioavailability of Dasatinib may be low due to poor absorption from the gastrointestinal tract and/or extensive first-pass metabolism. In addition, the literature suggests that the incomplete oral bioavailability of Dasatinib is due to a combination of incomplete absorption and high first pass metabolism.[8)] Peptide transporters (PepT) show sufficiently high-capacity low-affinity specificity and appear to be attractive targets for increasing intestinal absorption of some small molecules. Han and Amidon described this prodrug strategy (by using enzymatically hydrolyzable bonds in preparation of PepT-targeted prodrugs) as "peptide transport associated prodrug therapy." Good examples of prodrugs are valacyclovir (Valtrex®, GlaxoSmithKline, U.K.; L-valylester prodrug of acyclovir) and valganciclovir (Valcyte®, Roche, Swiss Confederation; L-valylester prodrug of ganciclovir). Therefore, it is necessary to increase the absorption rate of Dasatinib as well to decrease the rate of its metabolism.[9–12)]

In this current study, a series of amino acid derivatives (see Fig. 2, 144 compounds) as potential prodrugs of Dasatinib were designed with the aim of improving aqueous solubility and therapeutic efficacy, in terms of use of computer-aided drug design methodologies (small molecule flexible docking, virtual screening, three dimensions (3D) database search, lead optimization, 3D-quantitative structure–activity relationship (3D-QSAR), pharmacophore generation and peptide transporter). According to the principles of PepT prodrug technique, after getting into the digestive system, the compounds should rapidly be converted into Dasatinib by various enzymes in the digestive tract. The compounds interact with intestinal protein transporters so that the compounds can be easily absorbed in an intestinal tract in comparison with the Dasatinib to generate higher Dasatinib bioavailability.[9)] Overall, a series of 42 compounds was synthesized and evaluated. Compared with the existing antitumor compounds, the compound (JLTN) showed better *in vitro* anticancer activities against several cancer cell lines than that of Dasatinib. Also, pharmacodynamics studies have showed that the compound has notable curative effect and lower side effect.[11,12)] In an effort to improve the oral bioavailability of Dasatinib, detailed synthesis route for its prodrug (JLTN) will be presented. The oral bioavailability of the prodrug (JLTN) was evaluated after oral administration in monkeys and compared to the parent drug Dasatinib.

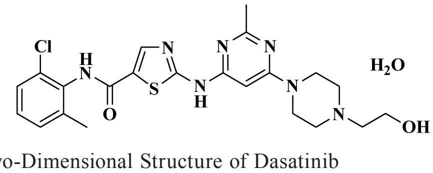

Fig. 1. Two-Dimensional Structure of Dasatinib

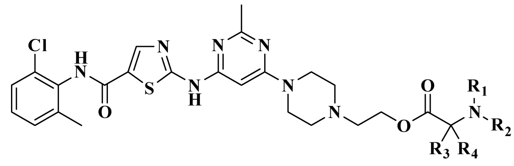

Fig. 2. A Series of Dasatinib Amino Acid Derivatives

The authors declare no conflict of interest.

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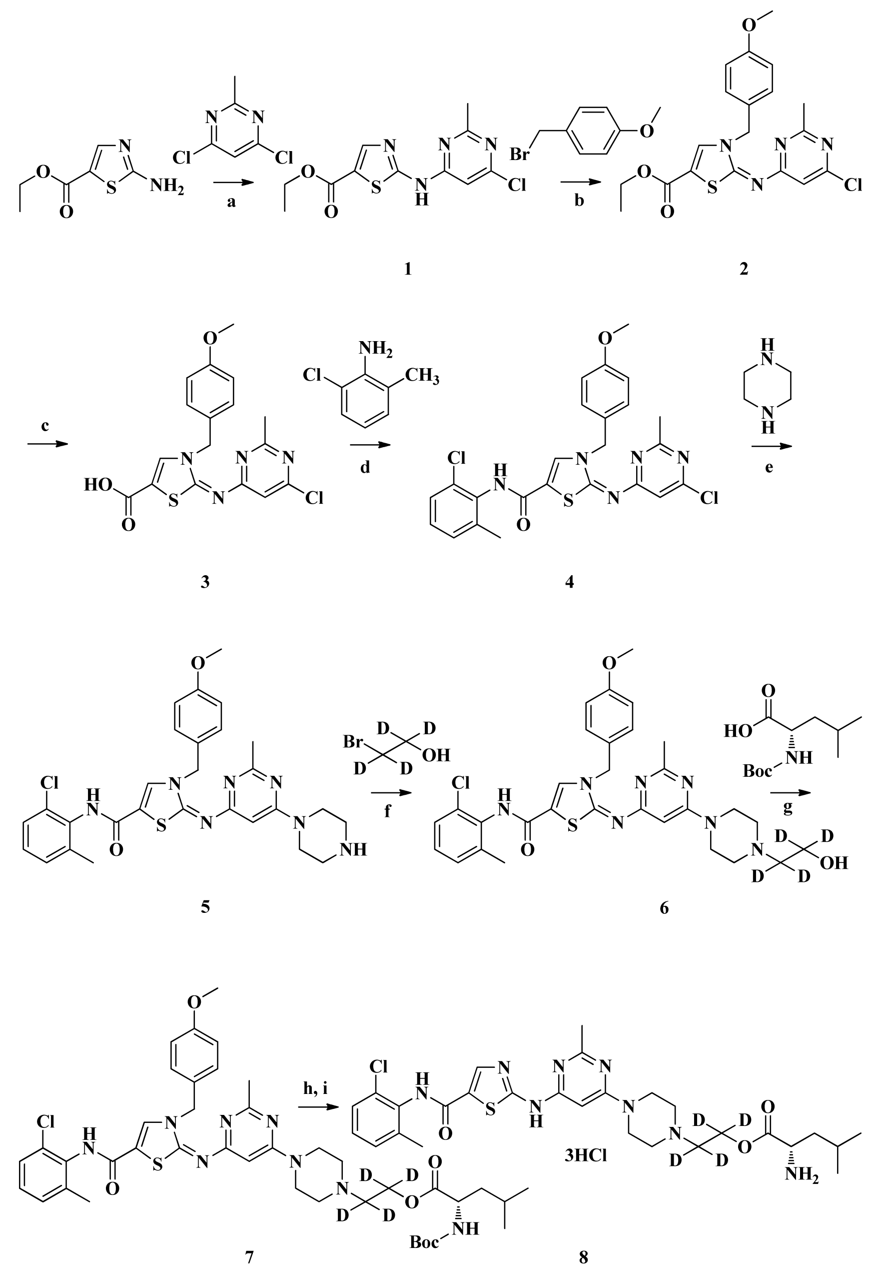

Reagents and conditions: (a) 4,6-Dichloro-2-methylpyrimidine (1.5 eq.), Cs_2CO_3 (2.0 eq.), DMF, 25°C, 24 h, 83%; (b) K_2CO_3 (1.5 eq.), 1-(bromomethyl)-4-methoxybenzene (1.2 eq.), DMF, 25°C, 18 h, 46%; (c) NaOH–H_2O (2.0 eq., 20%), THF–CH_3OH–H_2O (3 : 3 : 1), 25°C, 20 h, 70%; (d) thionyl dichloride (6.0 eq.), THF, 50°C, 5 h, then (2-chloro-6-methylphenyl)amine (3.0 eq.), 50°C, 18 h, 80%; (e) piperazine (10.0 eq.), 1,4-dioxane, reflux, 24 h, 95%; (f) 2-bromoethanol-d_4 (0.7 eq.), *N*,*N*-diethylethanamine (1.4 eq.), DMF, 60°C, 24 h, 57%; (g) *N*-(*tert*-butoxycarbonyl)-L-leucine (1.2 eq.), EDC·HCl (1.5 eq.), HOBT (1.5 eq.), CH_2Cl_2, 25°C, 20 h, 65%; (h) trifluoroacetic acid (0.2 eq.), CH_2Cl_2, 30°C, 48 h; (i) hydrogen chloride–propan-2-ol (5.0 eq.), ethyl acetate, 25°C, 0.5 h, 78% (two steps).

Chart 1. Synthesis of JLTN-d_4 (**8**)

Results and Discussion

Chemistry In the present study, the synthetic routes to the Dasatinib amino acid derivative are outlined in Chart 1.[13,14]

JLTN-d_4 (**8**) was prepared from (2*E*)-*N*-(2-chloro-6-methylphenyl)-2-({6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl}imino)-3-(4-methoxybenzyl)-2,3-dihydro-1,3-thiazole-5-carboxamide-d_4 (**6**) and *N*-(*tert*-butoxycarbonyl)-L-leucine through three steps, including condensation, deprotection and salification. Compound **6** was obtained from the ethyl 2-amino-1,3-thiazole-5-carboxylate by nucleophilic substitution, protection, hydrolysis, amidation and alkylation with ethyl 2-bromoethanol-d_4.

Reference standards for high-performance liquid chromatography (HPLC) and mass spectrometry, namely, Dasatinib-d_4, *N*-(2-chloro-6-methylphenyl)-2-({6-[4-(2-hydroxyethyl)-piperazin-1-yl]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carboxamide-d_4; JLTN-d_4, 2-(4-{6-[(5-{[(2-chloro-6-methylphenyl)amino]carbonyl}-1,3-thiazol-2-yl)amino]-2-methylpyrimidin-4-yl}piperazin-1-yl)ethyl L-leucinate trihydrochloride-d_4 (**8**) were synthesized at BL Pharmaceuticals.

Conclusions and Discussion In order to improve the aqueous solubility and therapeutic efficacy of Dasatinib, the prodrug JLTN was synthesized and evaluated bioavailability by oral administration to monkeys. Biological evaluation data indicated that there was a 150%-fold increase in oral bioavailability of this prodrug compared to the parent drug Dasatinib.

In conclusion, JLTN could improve the oral bioavailability of Dasatinib in monkeys through PepT-mediated absorption and enhanced chemical stability. The prodrug strategy targeted to intestinal PepT could offer a promising strategy to improve oral bioavailability of poorly absorbed Dasatinib. Preliminary *in vivo* studies indicated that this prodrug has significantly improved oral bioavailability (rat) than of the reference drug,[8] but additional pharmacokinetic studies of JLTN for preclinical studies need to get confirmed by further investigations.

Experimental

General All reagents were purchased from commercial manufacturers unless otherwise indicated. All chemicals used were reagent grade or better.

Proton NMR spectra were recorded on a Bruker DRX-600 spectrometer using $CDCl_3$ or dimethyl sulfoxide-d_6 (DMSO-d_6) as solvent at ambient temperature and tetramethylsilane (TMS) as an internal standard. All reactions were monitored by Merck Millipore classical Silica gel 60 F_{254} TLC plates. All compounds were of >90% purity by analytical HPLC analyses.

All procedures used for the animal studies were approved by the BL Pharmaceuticals Animal Care and Use Committee.

Syntheses. Synthesis of Compound 1, Ethyl 2-[(6-Chloro-2-methylpyrimidin-4-yl)amino]-1,3-thiazole-5-carboxylate To an ice-cooled solution of ethyl 2-amino-1,3-thiazole-5-carboxylate (35.0 g, 1.0 eq.), Cs_2CO_3 in *N*,*N*-dimethylformamide (DMF) (2.0 eq., 250 mL) was added dropwise a solution of 4,6-dichloro-2-methylpyrimidine in DMF (1.5 eq., 70 mL). The solution was warmed to room temperature, stirred for 24 h. The reaction was monitored using TLC with petroleum ether–ethyl acetate (2 : 1) as eluent. The mixture was poured onto crushed ice (1000 g), vigorously stirred for 10 min and collected by filtration. The residue was washed with water, ethyl acetate, and dried *in vacuo* to obtain compound **1** (50.7 g, 83.5%) as a yellow solid. HPLC Purity: 96.2%. Electrospray ionization mass spectrometry (ESI-MS) *m/z* ($M+H^+$) Calcd 299.0, Obsd 299.3. ^{1}H-NMR (600 MHz, DMSO-d_6) δ ppm 1.29 (3H, t, J=6.0 Hz), 2.59 (3H, s), 4.28 (2H, q, J=6.0 Hz), 6.94 (1H, s), 8.13 (1H, s), 12.36 (1H, s). ^{13}C NMR (150 MHz, DMSO-d_6) δ ppm 14.23, 25.25, 60.74, 103.61, 121.59, 145.46, 157.39, 158.60, 161.49, 162.36, 167.40.

Synthesis of Compound 2, Ethyl (2*E*)-2-[(6-Chloro-2-methylpyrimidin-4-yl)imino]-3-(4-methoxybenzyl)-2,3-dihydro-1,3-thiazole-5-carboxylate To an ice-cooled solution of compound **1** (48.3 g, 1.0 eq.), K_2CO_3 in DMF (1.5 eq., 480 mL) was added dropwise 1-(bromomethyl)-4-methoxybenzene (1.5 eq.). The solution was warmed to room temperature, stirred for 18 h. The mixture was poured onto crushed ice (500 g), vigorously stirred for 10 min and collected by filtration. The residue was washed with water, petroleum ether–ethyl acetate (1 : 2), and dried *in vacuo* to obtain compound **2** (31.5 g, 46.5%) as a white solid. HPLC Purity: 93.3%. ESI-MS *m/z* ($M+H^+$) Calcd 419.1, Obsd 419.3. ^{1}H-NMR (600 MHz, DMSO-d_6) δ ppm 1.27 (3H, t, J=7.2 Hz), 2.56 (3H, s), 3.70 (3H, s), 4.27 (2H, q, J=7.2 Hz), 5.31 (2H, s), 6.89–6.90 (2H, m), 7.02 (1H, s), 7.42–7.43 (2H, m), 8.51 (1H, s). ^{13}C-NMR (150 MHz, DMSO-d_6) δ ppm 14.18, 25.10, 50.38, 55.05, 61.12, 111.40, 113.30, 114.00, 127.90, 130.02, 135.75, 158.79, 159.01, 160.73, 161.48, 163.53, 166.31.

Synthesis of Compound 3, (2*E*)-2-[(6-Chloro-2-methylpyrimidin-4-yl)imino]-3-(4-methoxybenzyl)-2,3-dihydro-1,3-thiazole-5-carboxylic Acid To a solution of compound **2** (25.0 g) in CH_3OH–tetrahydrofuran (THF)–H_2O (3 : 3 : 1, 350 mL) was added dropwise a 5 N aq. NaOH solution (25 mL) at 5°C. The solution was warmed to room temperature, stirred for 18 h. The mixture was concentrated *in vacuo*, and the residue was washed with water, and dried *in vacuo* to obtain compound **3** (16.3 g, 69.8%) as a white solid. HPLC Purity: 91.2%. ESI-MS *m/z* ($M+H^+$) Calcd 391.1, Obsd 391.4. ^{1}H-NMR (600 MHz, DMSO-d_6) δ ppm 2.49 (3H, s), 3.66 (3H, s), 5.22 (2H, s), 6.80–6.82 (3H, m), 7.31–7.32 (2H, m), 7.82 (1H, s). ^{13}C-NMR (150 MHz, DMSO-d_6) δ ppm 25.18, 49.76, 55.00, 110.54, 114.96, 128.43, 129.77, 158.12, 158.86, 162.70, 164.06, 166.17.

Synthesis of Compound 4, (2*E*)-*N*-(2-Chloro-6-methylphenyl)-2-[(6-chloro-2-methylpyrimidin-4-yl)-imino]-3-(4-methoxybenzyl)-2,3-dihydro-1,3-thiazole-5-carboxamide To a solution of compound **3** (15.0 g, 1.0 eq.) in dry THF (230 mL) was added dropwise thionyl chloride (6.0 eq.). The reaction mixture was heated to 45°C for about 5 h. Then, the excess of thionyl chloride was removed by repeated evaporation with dry THF *in vacuo*. The crude acyl chloride was dissolved in dry THF (240 mL) and added dropwise a solution of the 2-chloro-6-methylaniline (3.0 eq.) in dry THF (10 mL). Then, the reaction mixture was stirred at 45°C for about 18 h. The reaction was monitored using TLC with petroleum ether–ethyl acetate (5 : 1) as eluent. The solution was concentrated. The residue was suspended in 1 N aq. hydrogen chloride solution (150 mL), washed with water. The residue was suspended in benzene–1,4-dioxane (6 : 1, 225 mL) and filtered. The residue was triturated with benzene. The solid was filtered and dried *in vacuo* to obtain compound **4** (15.8 g, 80.0%) as a tan solid. HPLC Purity: 97.9%. ESI-MS *m/z* ($M+H^+$) Calcd 514.1, Obsd 514.4. ^{1}H-NMR (600 MHz, DMSO-d_6) δ ppm 2.20 (3H, s), 2.57 (3H, s), 3.73 (3H, s), 5.37 (2H, s), 6.94–7.42 (7H, m), 8.38 (1H, s), 10.03 (1H, s). ^{13}C-NMR (150 MHz, DMSO-d_6) δ ppm 18.25, 25.11, 50.32, 55.08, 111.14, 114.20, 118.34, 127.05, 127.90, 128.35, 129.10, 129.98, 131.11, 132.14, 132.94, 138.59, 158.61, 158.70, 159.11, 161.69, 163.74, 166.30.

Synthesis of Compound 5, (2*E*)-*N*-(2-Chloro-6-methylphenyl)-3-(4-methoxybenzyl)-2-[(2-methyl-6-piperazin-1-ylpyrimidin-4-yl)imino]-2,3-dihydro-1,3-thiazole-5-carboxamide To a solution of compound **4** (11.0 g, 1.0 eq.), piperazine (10.0 eq.) in 1,4-dioxane (110 mL) was refluxed for 24 h. The mixture was concentrated under vacuum, and the solid was triturated successively with water and vigorously stirred for 10 min. The precipitate was collected by filtration and purified by column chromatography (CH_2Cl_2–CH_3OH= 10 : 1) to give compound **5** (11.5 g, 95.3%) as a light yellow solid. HPLC Purity: 93.3%. ESI-MS *m/z* ($M+H^+$) Calcd 564.2, Obsd 564.4. ^{1}H-NMR (600 MHz, $CDCl_3$) δ ppm 2.30 (3H, s), 2.55 (3H, s), 2.98 (4H, m), 3.65 (4H, m), 3.80 (3H, s), 5.22 (2H, s), 6.11 (1H, s), 6.85–7.34 (7H, m), 7.57 (1H, s).

Synthesis of Compound 6, (2*E*)-*N*-(2-Chloro-6-methylphenyl)-2-({6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl}imino)-3-(4-methoxybenzyl)-2,3-dihydro-1,3-thiazole-5-carboxamide-d_4 To an ice-cooled solution of ethyl 2-bromoethanol-d_4 (1.0 eq.), compound **5** (9.47 g, 1.5 eq.) in DMF (60 mL) was added dropwise Et_3N (2.0 eq.). The reaction mixture was heated to 60°C for 20 h. The mixture was concentrated under vacuum, and the solid was triturated successively with water and vigorously stirred for 20 min. The precipitate was collected by filtration and purified by column chromatography (CH_2Cl_2–CH_3OH=10 : 1) to give compound **6** (5.85 g, 56.9%) as a light yellow solid. HPLC Purity: 95.6%. ESI-MS *m/z* ($M+H^+$) Calcd 612.2, Obsd 612.3. ^{1}H-NMR (600 MHz, $CDCl_3$) δ ppm 2.30 (3H, s), 2.55 (3H, s), 2.65 (4H, m), 3.69–3.73 (4H, m), 3.80 (3H, s), 5.22 (2H, s), 6.12 (1H, s), 6.85–7.33 (7H, m), 7.57 (1H, s). ^{13}C-NMR (150 MHz, DMSO-d_6) δ ppm 18.28, 25.62, 43.67, 49.61, 52.90, 55.08, 58.52, 60.27, 91.74, 114.61, 116.40, 127.00, 128.18, 128.46, 129.04, 129.65, 130.79, 132.20, 133.20, 138.63, 158.96, 159.17, 159.26, 162.81, 163.32, 164.11.

Synthesis of Compound 7, 2-[4-(6-{[(2*E*)-5-{[(2-Chloro-6-methylphenyl)amino]carbonyl}-3-(4-methoxybenzyl)-1,3-thiazol-2(3*H*)-ylidene]amino}-2-methylpyrimidin-4-yl)-piperazin-1-yl]ethyl *N*-(*tert*-Butoxycarbonyl)-L-leucinate-d_4 To an ice-cooled solution of compound **6** (2.5 g, 1.0 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl, 1.5 eq.), 1*H*-1,2,3-benzotriazol-1-ol (HOBT, 1.5 eq.) in CH_2Cl_2 (30 mL) was added dropwise a solution of *N*-(*tert*-butoxycarbonyl)-L-leucine (Boc-Leu-OH) in CH_2Cl_2 (1.2 eq., 10 mL) and the solution was warmed to room temperature. The mixture was stirred for 20 h. The organic phase was washed with 6–7% aq. $NH_3 \cdot H_2O$ solution, dried, evaporated and purified by column chromatography (petroleum ether–ethyl acetate=1 : 2) to give compound **7** (2.18 g, 64.7%) as a light yellow solid. HPLC Purity: 97.9%. ESI-MS *m/z* ($M+H^+$) Calcd 825.4, Obsd 825.3. ^{1}H-NMR (600 MHz, $CDCl_3$) δ ppm 0.95 (6H, m), 1.44 (9H, s), 1.55–1.67 (2H, m), 1.73 (1H, m), 2.30 (3H, s), 2.55 (3H, s), 2.56–2.64 (4H, m), 3.56–3.71 (4H, m), 3.80 (3H, s), 4.26–4.38 (1H, m), 4.89 (1H, m), 5.21 (2H, s), 6.11 (1H, s), 6.86–7.32 (7H, m), 7.58 (1H, s). ^{13}C NMR (150 MHz, DMSO-d_6) δ ppm 18.27, 21.36, 22.69, 24.24, 25.60, 27.94, 28.16, 43.66, 49.60, 51.96, 52.50, 55.08, 55.99, 61.69, 78.10, 91.73, 114.15, 116.38, 127.00, 128.19, 128.45, 129.05, 129.65, 130.80, 132.19, 133.19, 138.62, 155.50, 158.96, 159.14, 159.26, 162.82, 163.25, 164.11, 172.99.

Synthesis of Compound 8, JLTN-d_4, 2-(4-{6-[(5-{[(2-Chloro-6-methylphenyl)amino]carbonyl}-1,3-thiazol-2-yl)-amino]-2-methylpyrimidin-4-yl}piperazin-1-yl)ethyl L-Leucinate Trihydrochloride-d_4 To an ice-cooled solution of compound **7** (2.18 g, 1.0 eq.) in CH_2Cl_2 (30 mL) was added dropwise CF_3CO_2H (30 mL) and the solution was warmed to room temperature. The solution was stirred for 48 h, evaporated and the residual crude oil was added ethyl acetate (40 mL). The solution was treated with hydrogen chloride–ethyl acetate (5.0 eq.) and vigorously stirred for 30 min. The solid was filtered and dried *in vacuo*. The residue was suspended in DMF (35 mL) and filtered. Then the filtrate was added dropwise THF (70 mL). The solid was filtered, washed with ethyl acetate and dried *in vacuo* to obtain compound **8** (1.46 g, 77.9%) as a white solid. HPLC Purity: 99.6%, isotopic abundance: 98.58 atom %D. ESI-MS *m/z* ($M+H^+$) Calcd 605.3, Obsd 605.2. ^{1}H-NMR (600 MHz, DMSO-d_6) δ ppm 0.91 (6H, s), 1.63–1.74 (2H, m), 1.75–1.82 (1H, m), 2.24 (3H, s), 2.47 (3H, s), 3.10–3.25 (2H, m), 3.50–3.61 (2H, m), 3.62–3.78 (2H, m), 4.02–4.05 (1H, m), 4.26–4.46 (4H, m), 6.24 (2H, s), 7.20–7.40 (3H, m), 8.30 (1H, s), 8.80 (3H, s), 10.00 (1H, s), 11.49 (1H, s), 11.74 (1H, br s). ^{13}C-NMR (150 MHz, DMSO-d_6) δ ppm 18.53, 22.20, 22.32, 23.99, 24.34, 41.51, 50.55, 50.91, 50.98, 53.98, 59.38, 84.40, 127.25, 128.58, 129.30, 132.63, 133.37, 133.51, 139.02, 156.84, 159.75, 160.42, 162.52, 164.12, 168.72.

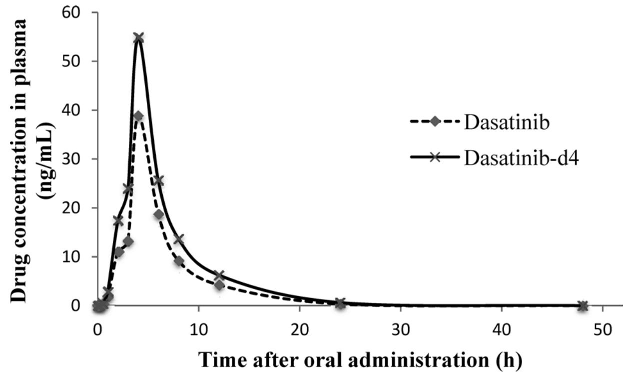

Fig. 3. Mean Plasma Concentration–Time Profiles of Dasatinib and Dasatinib-d_4 after an Oral Dose of Equimolar Mixture of Dasatinib (5 mg/kg) and JLTN-d_4 in Male Rhesus Monkeys (N=3)

Table 1. Mean Pharmacokinetic Parameters of Dasatinib and Dasatinib-d_4 in the Monkey

PK parameter	Dasatinib	Dasatinib-d_4
C_{max} (ng·mL^{-1})	38.9	54.9
T_{max} (h)	4	4
MRT_{last} (h)	6.8	6.7
AUC_{all} (ng·h·mL^{-1}) (RSD%)	173.5 (48.1%)	255.4 (47.8%)

Pharmacokinetics and Oral Bioavailability in Monkeys The pharmacokinetics of equimolar mixture of Dasatinib (5 mg/kg) and JLTN-d_4 were investigated in male Rhesus monkeys (approximately 4–5 kg, N=3) following an oral dose (capsule) by gavage in study design. The monkeys were fasted overnight and fed 4 h post dose. Blood samples were collected at 0, 5, 10, 30 min, 1, 2, 3, 4, 6, 8, 12, 24 and 48 h after oral dosing. Approximately 1 mL of blood was collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and plasma was obtained by centrifugation. Plasma samples were stored at −80°C until analysis. Samples were analyzed for Dasatinib and Dasatinib-d_4 by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS-MS).[15–18)]

The pharmacokinetic parameters were computed by non-compartmental analysis using Phoenix WinNonlin (Version 6.3, Pharsight Corporation, CA, U.S.A.).

Mean pharmacokinetic parameters of Dasatinib and Dasatinib-d_4 in the monkey are summarized in Table 1 and the plasma concentration time profiles are presented in Fig. 3. The T_{max} of Dasatinib and Dasatinib-d_4 were both 4 h. The C_{max} obtained directly from the concentration–time data were 38.9 ng·mL^{-1}, 54.9 ng·h·mL^{-1}; the MRT_{last} were 6.8 h, 6.7 h; the AUC_{all} were 173.5 ng·h·mL^{-1} (RSD% 48.1%), 255.4 ng·h·mL^{-1} (RSD% 47.8%); respectively. The geometric mean ratio (Dasatinib-d_4/Dasatinib) was 1.5 for AUC_{all} and 1.4 for C_{max}.

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