

Design and Synthesis of Some Novel 2,3,4,5-Tetrahydro-1*H*-pyrido[4,3-*b*]indoles as Potential c-Met Inhibitors

by Lianbao Ye, Yuanxin Tian, Zhonghuang Li, Jiajie Zhang*, and Shuguang Wu*

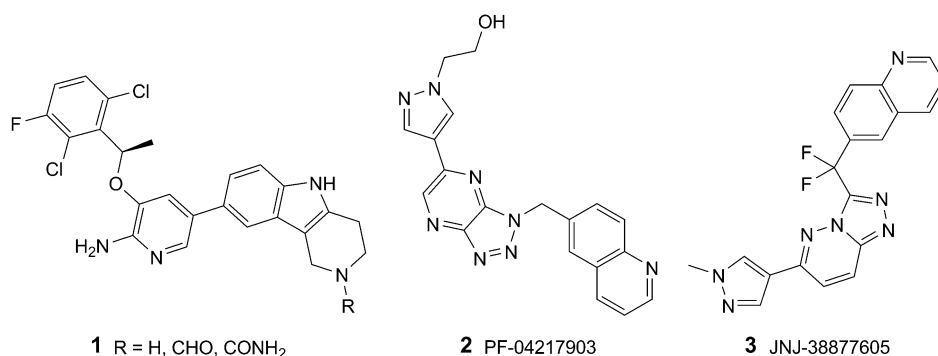
School of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, P. R. China
(phone: +86-20-62789415; fax: +86-20-61648548; e-mail: shuguang@smu.edu.cn;
zhangjj@smu.edu.cn)

Since deregulation of the tyrosine-kinase receptor c-Met is implicated in several human cancers and is an attractive target for small-molecule-drug discovery, we report herein the synthesis of 2,3,4,5-tetrahydro-8-[1-(quinolin-6-ylmethyl)-1*H*-1,2,3-triazolo[4,5-*b*]pyrazin-6-yl]-1*H*-pyrido[4,3-*b*]indoles **4a–4c** and 2,3,4,5-tetrahydro-8-[3-(quinolin-6-ylmethyl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl]-1*H*-pyrido[4,3-*b*]indoles **5a–5c**. These indole derivatives demonstrated inhibition of c-Met kinase activity. Concurrently, five key intermediates were synthesized. These compounds could be prepared in good yields.

Introduction. – c-Met is a tyrosine-kinase receptor for the hepatocyte growth factor (HGF). Both c-Met and HGF are expressed in a number of different tissues [1]. Binding of HGF to the extracellular domain of c-Met can cause multimerization of the receptor and phosphorylation of tyrosine residues. c-Met/HGF signaling is essential for normal cell proliferation, migration, angiogenesis, and tissue regeneration [2]. In addition, aberrant c-Met/HGF signaling plays a major role in tumorigenesis invasion and metastasis in many human tumors [3]. The mutation and over-expression of c-Met proto-oncogene and/or HGF have been detected in different types of malignant solid tumors and correlated with advanced stages and poor prognosis [4]. Therefore, c-Met has become an attractive therapeutic target for cancer therapy. One way to block c-Met signaling is by inhibiting binding of aurintricarboxylic acid (ATA) to the tyrosine-kinase domain of c-Met with small molecular inhibitors [5].

In our previous study, we discovered the structures of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **1** as a potent c-Met inhibitor (*Fig.*) [6]. In an ongoing effort to design novel and selective inhibitors of the c-Met enzyme, we were intrigued by filed applications from *Pfizer* [7] and *Janssen* [8] in which they claimed that a series of 1-(quinolin-6-ylmethyl)-1*H*-1,2,3-triazolo[4,5-*b*]pyrazine derivatives and 3-(quinolin-6-ylmethyl)-1,2,4-triazolo[4,3-*b*]pyridazine derivatives of low molecular mass were potent and selective c-Met inhibitors. The reports [7] and [8] disclosed that representative examples, PF-04217903 (**2**) and JNJ-38877605 (**3**) (*Fig.*), respectively, are in phase-I clinical trials.

Intrigued by the low molecular mass and unknown binding mode of PF-04217903 and JNJ-38877605 to c-Met and by our previous study, we introduced 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole groups to the 6-position of 1-(quinolin-6-ylmethyl)-1*H*-1,2,3-triazolo[4,5-*b*]pyrazine (= 6-(1*H*-1,2,3-triazolo[4,5-*b*]pyrazin-1-ylmethyl)qui-

Figure. Reported *c-Met* inhibitors

noline) and 3-(quinolin-6-ylmethyl)-1,2,4-triazolo[4,3-*b*]pyridazine (= 6-(1*H*-1,2,4-triazolo[4,3-*b*]pyrazin-3-ylmethyl)quinoline) in order to reach synergy. With the assistance of molecular docking (Table¹), we designed and synthesized the six structurally relevant novel compounds **4a–4c** and **5a–5c**.

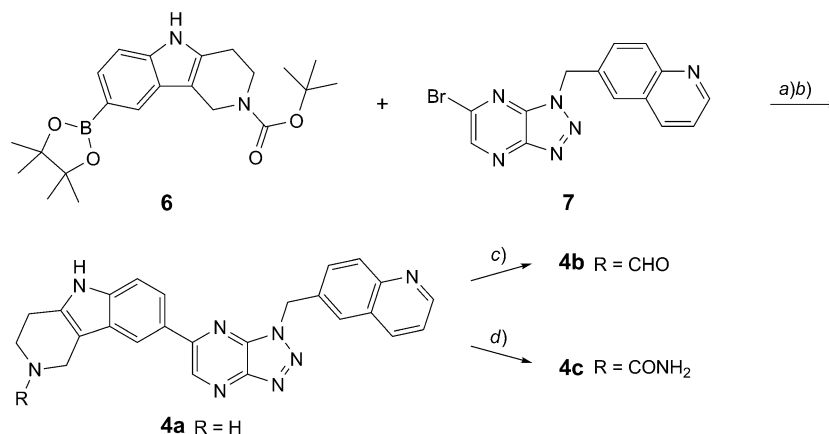
Table. Results of Molecular Docking

	Score		Score
3dkf ligand	5.86	5a	6.35
4a	8.73	5b	8.69
4b	8.18	5c	8.31
4c	7.14		

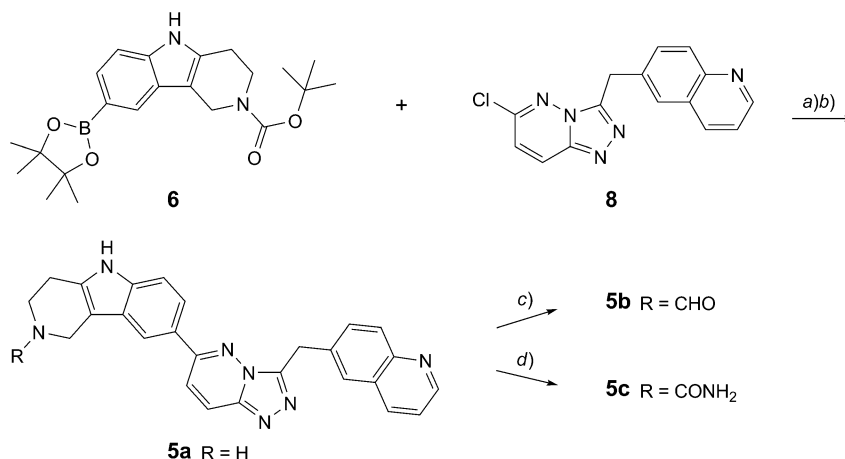
Results and Discussion. – The synthetic pathways for **4a–4c** and **5a–5c** are outlined in Schemes 1 and 2, respectively. The reaction of *tert*-butyl 2,3,4,5-tetrahydro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrido[4,3-*b*]indole-2-carboxylate (**6**) with 6-bromo-1-(quinolin-6-ylmethyl)-1*H*-1,2,3-triazolo[4,5-*b*]pyrazine (= 6-[(6-bromo-1*H*-1,2,3-triazolo[4,5-*b*]pyrazin-1-yl)methyl]quinoline; **7**) [7] or 6-chloro-3-(quinolin-6-ylmethyl)-1,2,4-triazolo[4,3-*b*]pyridazine (= 6-[(6-chloro-1,2,4-triazolo[4,3-*b*]pyrazin-3-yl)methyl]quinoline; **8**) [8], respectively, gave 2,3,4,5-tetrahydro-8-[1-(quinolin-6-ylmethyl)-1*H*-[1,2,3]triazolo[4,5-*b*]pyrazin-6-yl]-1*H*-pyrido[4,3-*b*]indole (**4a**) and 2,3,4,5-tetrahydro-8-[3-(quinolin-6-ylmethyl)-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl]-1*H*-pyrido[4,3-*b*]indole (**5a**) in 80 and 78% yields, respectively, *via Suzuki* coupling reaction (Schemes 1 and 2). Then, **4a** and **5a** were transformed to **4b** and **4c** and to **5b** and **5c**, respectively, by formylation and carbamoylation in 78, 82, 75, and 68% yield.

The starting material **6** was prepared from 8-bromo-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**11**) by treatment with di(*tert*-butyl) dicarbonate (Boc)₂O and an electrophilic substitution reaction in 62.4% yield *via 12*, while **11** was synthesized by a modification of a reported route [9] *via* condensation of commercially available (4-

¹) Molecular docking was performed with Sybyl7.3. A crystal structure of the *c-Met* complex with SGX523 was obtained from the protein data bank (pdb entry: 3dkf).

Scheme 1. Synthesis of **4a–4c**

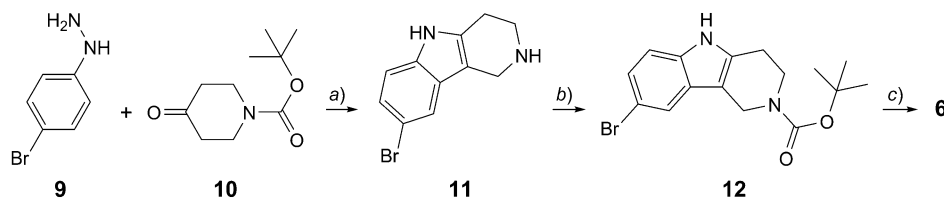
a) [Pd(PPh₃)₄], DMF/H₂O, K₂CO₃, 80°, 18 h. b) 4M HCl, 1,4-dioxane, CH₂Cl₂, r.t., 1 h. c) *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC · HCl), HCOOH, *N,N*-diisopropylethylamine, CH₂Cl₂, r.t., 2 h. d) Me₃Si–NCO, CH₂Cl₂, r.t., 16 h.

Scheme 2. Synthesis of **5a–5c**

a) [Pd(PPh₃)₄], DMF/H₂O, K₂CO₃, 80°, 18 h. b) 4M HCl, 1,4-dioxane, CH₂Cl₂, r.t., 1 h. c) EDC · HCl, HCOOH, *N,N*-diisopropylethylamine, CH₂Cl₂, r.t., 2 h. d) Me₃Si–NCO, CH₂Cl₂, r.t., 16 h.

bromophenyl)hydrazine (**9**) and *tert*-butyl 4-oxopiperidine-1-carboxylate (**10**) in 78 % yield (Scheme 3). Compounds **6**, **7**, **11**, and **12** have been reported previously [6][7][9].

Molecular docking was performed with Sybyl7.3. A crystal structure of the c-Met complex with SGX523 was obtained from the protein data bank (pdb entry: 3dkf). At the beginning of docking, all the H₂O and ligands were removed, and the random H-atoms were added. Then, the receptor structure was minimized in 10000 cycles with the Powell method in sybyl7.3. After the construction of the compounds, H-atoms and the

Scheme 3. Synthesis of **6**

a) HCl, EtOH, reflux, 3 h. b) *N,N*-Diisopropylethylamine, (Boc)₂O, CH₂Cl₂, r.t., 1 h. c) Bis(pinacolato)diboron (= 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane), AcOK, [PdCl₂(dppf)]/CH₂Cl₂ (dppf = 1,1'-bis(diphenylphosphino)ferrocene), DMSO, N₂, 80°, 16 h.

Gasteiger–Hückel charges were added. Then, their geometries were optimized by the conjugate gradient method in the TRIPOS force field. The energy convergence criterion was 0.001 kcal/mol. Except for some special notes, default values were chosen to finish this work. To validate the docking reliability, the ligand SGX523 was removed from the active site and docked back into the binding pocket. The root-mean-square deviation (r.m.s.d.) between the predicted conformation and the actual conformation from the crystal structure of the ligand was 0.6 Å, which is smaller than the resolution of X-ray crystallography. It indicated that the parameter set for the Surflex-dock simulation was reasonable to reproduce the X-ray structure. So, the results of molecular docking in the *Table* were reasonable.

Preliminary results showed that **4a–4c** and **5a–5c** obviously inhibit the c-Met enzyme, in which **4a** had the best inhibitory effect with an *IC*₅₀ of 0.0145 μM, and the inhibitory effects were consistent with the results of molecular docking in the *Table*. Thus, we could make sure that the designed compounds should be well worth studying based on the molecular-docking theory and preliminary biological tests. Further research on activities is currently under investigation and will be reported in due course.

This study was supported by grants from the *International Science and Technology Cooperation Base of Guangdong Provincial Department of Science and Technology* (No. 2009B050900006) and the *Science and Technology Bureau of Guangzhou* (No. 2009A1-E011-8 and No. 2010 V1-E00531-3).

Experimental Part

General. All chemicals were obtained from *Aladdin* or *J&K Science*. Solvents were purified and dried by standard procedures, and stored over 3-Å molecular sieves. TLC: *SILG/UV 254* silica-gel plates. Flash chromatography (FC): silica gel (SiO₂; 40 μm, 230–400 mesh). ¹H- and ¹³C-NMR Spectra: *Bruker* digital NMR spectrometer; δ in ppm rel. to Me₄Si as internal standard, *J* in Hz. EI-MS: *Waters ZQ4000*; in *m/z*. Elemental analyses (CHNS): *Perkin–Elmer-240-B* micro-analyzer.

8-Bromo-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (11). A mixture of (4-bromophenyl)hydrazine hydrochloride (**9**·HCl; 224 mg, 1 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (**10**; 199 mg, 1 mmol) were dissolved under stirring in EtOH saturated with HCl (10 ml). Then, the mixture was heated under reflux for 3 h under stirring (TLC control). The solvent was evaporated and the residue treated with NaHCO₃ soln. (10 ml) and extracted with CH₂Cl₂ (3 × 20 ml). The combined org. layer was dried (Na₂SO₄, 3 g) and concentrated to afford the crude product, which was purified by FC (MeOH/CH₂Cl₂): **11** [6] [9] (78%). ¹H-NMR (CD₃OD): 2.82 (*t*, *J* = 5.6, 2 H); 3.15 (*t*, *J* = 5.6, 2 H); 3.95 (*s*, 2 H);

7.11 (*dd*, $J = 1.6, 8.8, 1$ H); 7.18 (*d*, $J = 8.4, 1$ H); 7.46 (*d*, $J = 1.6, 1$ H). EI-MS: 251.01 ($[M(^{79}\text{Br}) + \text{H}]^+$), 252.99 ($[M(^{81}\text{Br}) + \text{H}]^+$).

tert-Butyl 8-Bromo-2,3,4,5-tetrahydro-1H-pyrido[4,3-*b*]indole-2-carboxylate. A soln. of **11** (251 mg, 1 mmol), (Boc)₂O (262 mg, 1.2 mmol), and *N,N*-diisopropylethylamine (258 mg, 2 mmol) in CH₂Cl₂ was stirred for 1 h at r.t. (TLC control). The solvent was evaporated, and the crude product purified by FC (MeOH/CH₂Cl₂): **12** [6][9] (78%). ¹H-NMR (CDCl₃): 1.50 (*s*, 9 H); 2.83 (*t*, $J = 5.2, 2$ H); 3.81 (*t*, $J = 5.2, 2$ H); 4.58 (*s*, 2 H); 7.17 (*d*, $J = 8.4, 1$ H); 7.24 (*d*, $J = 8.4, 1$ H); 7.57 (*s*, 1 H); 7.92 (*br. s*, 1 H). EI-MS: 350.99 ($[M(^{79}\text{Br}) + \text{H}]^+$), 352.97 ($[M(^{81}\text{Br}) + \text{H}]^+$).

tert-Butyl 2,3,4,5-Tetrahydro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrido[4,3-*b*]indole-2-carboxylate (6). [PdCl₂(dppf)CH₂Cl₂] (20.4 mg, 0.025 mmol) was added portion-wise to a soln. of **12** (175 mg, 0.5 mmol), bis(pinacolato)diboron (140 mg, 0.55 mmol), and AcOK (147 mg, 1.5 mmol) in DMSO (5 ml), and N₂ was bubbled through the mixture for 2 min. Then, the mixture was stirred for 16 h at 80° (LC/MS control). After cooling to r.t., H₂O (2 ml) was added, and the mixture was extracted with CH₂Cl₂ (3 × 5 ml). The org. layer was dried (Na₂SO₄, 1 g) and concentrated: **6** [6][9] (80%). ¹H-NMR (CDCl₃): 1.50 (*s*, 9 H); 2.82 (*t*, $J = 5.2, 2$ H); 3.82 (*t*, $J = 5.2, 2$ H); 4.60 (*s*, 2 H); 7.17 (*d*, $J = 8.4, 1$ H); 7.23 (*dd*, $J = 2.0, 8.0, 1$ H); 7.62 (*s*, 1 H); 7.96 (*br. s*, 1 H). EI-MS: 399.14 ($[M + \text{H}]^+$).

6-[(6-Bromo-1H-1,2,3-triazolo[4,5-*b*]pyrazin-1-yl)methyl]quinoline (7) [7]. Yield 60%. ¹H-NMR ((D₆)DMSO): 6.28 (*s*, 2 H); 7.61 (*dd*, $J = 8.34, 4.55, 1$ H); 7.83 (*dd*, $J = 8.72, 1.89, 1$ H); 7.94 (*s*, 1 H); 8.02 (*d*, $J = 8.84, 1$ H); 8.74 (*d*, $J = 8.08, 1$ H); 8.95 (*dd*, $J = 4.42, 1.64, 1$ H); 9.34 (*s*, 1 H). EI-MS: 341.01 ($[M(^{79}\text{Br}) + \text{H}]^+$), 342.97 ($[M(^{81}\text{Br}) + \text{H}]^+$).

6-[(6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl)methyl]quinoline (8) [8]. Yield 70%. ¹H-NMR (CDCl₃): 4.74 (*s*, 2 H); 7.10 (*d*, $J = 10.0, 1$ H); 7.39 (*dd*, $J = 4.0, 8.0, 1$ H); 7.80 (*dd*, $J = 2.0, 8.4, 1$ H); 7.85 (*s*, 1 H); 8.05–8.08 (*m*, 2 H); 8.11 (*dd*, $J = 0.8, 8.4, 1$ H); 8.88 (*dd*, $J = 1.6, 4.0, 1$ H). EI-MS: 296.02 ($[M(^{35}\text{Cl}) + \text{H}]^+$), 297.99 ($[M(^{37}\text{Cl}) + \text{H}]^+$).

2,3,4,5-Tetrahydro-8-[1-(quinolin-6-ylmethyl)-1H-1,2,3-triazolo[4,5-*b*]pyrazin-6-yl]-1H-pyrido[4,3-*b*]indole (4a). [Pd(PPh₃)₄] (11.6 mg, 0.01 mmol) was added portion-wise to a soln. of **7** (68.2 mg, 0.2 mmol) [7], **6** (95.6 mg, 0.24 mmol), and K₂CO₃ (82.9 mg, 0.6 mmol) in DMF/H₂O 4 : 1 (2.0 ml), and N₂ was bubbled through the mixture for 2 min. The mixture was stirred for 18 h at 80° (LC/MS control) and then cooled to r. t. H₂O (5 ml) was added, and the mixture was extracted with CH₂Cl₂ (3 × 10 ml). The org. layer was dried (Na₂SO₄, 1 g), and concentrated. The obtained solid was dissolved in CH₂Cl₂ (5 ml), and a 4M 1,4-dioxane soln. of HCl was added. The mixture was stirred for 1 h at r.t. and filtered: **4a** (80 mg, 80%). ¹H-NMR (CD₃OD): 2.91 (*t*, $J = 5.6, 2$ H); 3.27 (*t*, $J = 5.2, 2$ H); 4.15 (*s*, 2 H); 6.24 (*s*, 2 H); 7.45 (*d*, $J = 8.8, 1$ H); 7.56 (*dd*, $J = 4.4, 8.4, 1$ H); 7.94 (*dd*, $J = 2.0, 8.8, 1$ H); 8.01 (*dd*, $J = 2.0, 8.8, 1$ H); 8.05 (*d*, $J = 8.8, 1$ H); 8.10 (*s*, 1 H); 8.29 (*d*, $J = 2.0, 1$ H); 8.39 (*d*, $J = 8.4, 1$ H); 8.85 (*dd*, $J = 2.0, 4.4, 1$ H); 9.37 (*s*, 1 H). ¹³C-NMR ((D₆)DMSO): 31.5; 43.4; 45.7; 53.1; 110.2; 112.3; 116.8; 120.3; 122.2; 127.1; 128.5; 129.3; 131.1; 131.9; 133.7; 135.7; 136.9; 137.1; 137.7; 138.1; 145.9; 147.5; 148.6; 149.7; 155.4. EI-MS: 433.10 ($[M + \text{H}]^+$). Anal. calc. for C₂₅H₂₀N₈ (432.48): C 69.43, H 4.66, N 25.91; found: C 69.42, H 4.68, N 25.90.

2,3,4,5-Tetrahydro-8-[1-(quinolin-6-ylmethyl)-1H-1,2,3-triazolo[4,5-*b*]pyrazin-6-yl]-1H-pyrido[4,3-*b*]indole-2-carboxaldehyde (4b). *N,N*-Diisopropylethylamine (38 mg, 0.296 mmol) was added portion-wise to a soln. of HCOOH (6.8 mg, 0.148 mmol) and EDC·HCl (28.4 mg, 0.148 mmol) in CH₂Cl₂ (4/1, 20 ml). The mixture was stirred for 0.5 h at r.t., then **4a** was added and the mixture stirred for 2 h at r.t. The solvent was evaporated and the crude product purified by FC (MeOH/CH₂Cl₂): **4b** (26.5 mg, 78%). ¹H-NMR (CD₃OD): 2.98 (*t*, $J = 5.6, 2$ H); 3.89 (*t*, $J = 5.6, 2$ H); 4.80 (*s*, 2 H); 6.25 (*s*, 2 H); 7.47 (*d*, $J = 8.4, 1$ H); 7.56 (*dd*, $J = 4.8, 8.8, 1$ H); 7.95 (*dd*, $J = 2.0, 8.8, 1$ H); 8.03 (*d*, $J = 8.4, 1$ H); 8.08 (*d*, $J = 8.8, 1$ H); 8.14 (*s*, 1 H); 8.27 (*s*, 1 H); 8.37 (*s*, 1 H); 8.42 (*d*, $J = 8.8, 1$ H); 8.85 (*d*, $J = 4.4, 1$ H); 9.40 (*s*, 1 H). ¹³C-NMR ((D₆)DMSO): 29.1; 42.3; 47.7; 52.5; 111.4; 113.1; 117.1; 119.7; 123.1; 126.9; 129.1; 129.6; 130.1; 131.5; 132.7; 135.1; 135.9; 136.1; 136.7; 138.1; 146.1; 147.3; 148.2; 149.1; 153.4; 162.5. EI-MS: 461.00 ($[M + \text{H}]^+$). Anal. calc. for C₂₆H₂₀N₈O (460.49): C 67.81, H 4.38, N 24.33; found: C 67.83, H 4.36, N 24.33.

2,3,4,5-Tetrahydro-8-[1-(quinolin-6-ylmethyl)-1H-1,2,3-triazolo[4,5-*b*]pyrazin-6-yl]-1H-pyrido[4,3-*b*]indole-2-carboxamide (4c). *N,N*-Diisopropylethylamine (64.2 mg, 0.5 mmol) and Me₃Si–NCO (28.8 mg, 0.25 mmol) were added portion-wise to a soln. of **4a** (25 mg, 0.05 mmol) in CH₂Cl₂ (2 ml). The mixture was stirred for 16 h at r.t. The solvent was evaporated and the crude product purified by FC (MeOH/CH₂Cl₂): **4c** (19.5 mg, 82%). ¹H-NMR (CD₃OD): 2.88 (*t*, $J = 4.8, 2$ H); 3.85 (*t*, $J = 5.2, 2$ H); 4.70

(s, 2 H); 6.23 (s, 2 H); 7.45 (d, $J = 8.4$, 1 H); 7.55 (dd, $J = 4.4$, 8.4, 1 H); 7.94 (dd, $J = 2.0$, 8.8, 1 H); 8.01 (d, $J = 8.4$, 1 H); 8.06 (d, $J = 8.8$, 1 H); 8.09 (s, 1 H); 8.32 (s, 1 H); 8.39 (d, $J = 8.0$, 1 H); 8.84 (d, $J = 4.0$, 1 H); 9.36 (s, 1 H). $^{13}\text{C-NMR}$ ((D_6) DMSO): 28.3; 44.9; 51.3; 52.5; 110.8; 112.9; 116.8; 119.7; 122.1; 126.8; 129.1; 129.8; 130.4; 131.3; 132.5; 135.3; 135.7; 136.3; 136.7; 137.9; 146.3; 146.9; 147.8; 149.2; 152.9; 163.3. EI-MS: 476.08 ($[M + \text{H}]^+$). Anal. calc. for $\text{C}_{26}\text{H}_{21}\text{N}_9\text{O}$ (475.5): C 65.67, H 4.45, N 26.51; found: C 65.65, H 4.47, N 26.49.

Compounds **5a–5c** were prepared in analogy to **4a–4c**.

2,3,4,5-Tetrahydro-8-[3-(quinolin-6-ylmethyl)-1,2,4-triazolo[4,3-b]pyridazin-6-yl]-1H-pyrido[4,3-b]indole (5a). Yield 78%. $^1\text{H-NMR}$ (CD_3OD): 3.22 (t, $J = 5.6$, 2 H); 3.65 (t, $J = 5.6$, 2 H); 4.58 (s, 2 H); 5.13 (s, 2 H); 7.56 (d, $J = 8.0$, 1 H); 8.03 (d, $J = 8.0$, 1 H); 8.13 (t, $J = 8.0$, 1 H); 8.32 (d, $J = 7.6$, 1 H); 8.36–8.41 (m, 2 H); 8.52–8.57 (m, 3 H); 8.22–8.23 (m, 2 H). $^{13}\text{C-NMR}$ ((D_6) DMSO): 30.2; 31.3; 42.8; 45.5; 109.5; 112.1; 116.7; 120.0; 121.7; 125.6; 127.1; 127.8; 128.1; 129.3; 129.7; 131.2; 135.7; 136.1; 136.4; 136.9; 143.5; 145.3; 147.2; 149.1; 160.3; 162.1. EI-MS: 432.08 ($[M + \text{H}]^+$). Anal. calc. for $\text{C}_{26}\text{H}_{21}\text{N}_7$ (431.49): C 72.37, H 4.91, N 22.72; found: C 72.39, H 4.89, N 22.72.

2,3,4,5-Tetrahydro-8-[3-(quinolin-6-ylmethyl)-1,2,4-triazolo[4,3-b]pyridazin-6-yl]-1H-pyrido[4,3-b]indole-2-carboxaldehyde (5b). Yield 75%. $^1\text{H-NMR}$ (CD_3OD): 2.94 (t, $J = 5.6$, 2 H); 3.86 (t, $J = 5.6$, 2 H); 4.73 (s, 2 H); 4.83 (s, 2 H); 7.38 (d, $J = 8.4$, 1 H); 7.53 (dd, $J = 4.4$, 8.8, 1 H); 7.78 (d, $J = 8.4$, 1 H); 7.84–7.91 (m, 2 H); 7.99 (s, 1 H); 8.03–8.04 (m, 2 H); 8.10 (d, $J = 10.0$, 1 H); 8.27 (s, 1 H); 8.36 (d, $J = 8.8$, 1 H); 8.78 (d, $J = 2.8$, 1 H). $^{13}\text{C-NMR}$ ((D_6) DMSO): 27.9; 29.8; 41.7; 46.9; 110.1; 111.9; 117.1; 120.5; 122.1; 125.9; 126.9; 128.1; 128.4; 129.8; 130.3; 133.1; 136.3; 136.5; 136.7; 137.1; 144.0; 145.5; 147.2; 149.1; 161.1; 162.7; 164.5. EI-MS: 460.05 ($[M + \text{H}]^+$). Anal. calc. for $\text{C}_{27}\text{H}_{21}\text{N}_7\text{O}$ (459.51): C 70.57, H 4.61, N 21.34; found: C 70.57, H 4.63, N 21.33.

2,3,4,5-Tetrahydro-8-[3-(quinolin-6-ylmethyl)-1,2,4-triazolo[4,3-b]pyridazin-6-yl]-1H-pyrido[4,3-b]indole-2-carboxamide (5c). Yield 68%. $^1\text{H-NMR}$ (CD_3OD): 2.88 (t, $J = 4.8$, 2 H); 3.84 (t, $J = 5.6$, 2 H); 4.68 (s, 2 H); 4.87 (s, 2 H); 7.42 (d, $J = 8.8$, 1 H); 7.53 (dd, $J = 4.4$, 8.4, 1 H); 7.81 (d, $J = 8.4$, 1 H); 7.91 (d, $J = 8.4$, 1 H); 7.96 (d, $J = 9.6$, 1 H); 8.01–8.05 (m, 3 H); 8.17 (d, $J = 10.0$, 1 H); 8.34 (d, $J = 7.6$, 1 H); 8.80 (d, $J = 2.8$, 1 H). $^{13}\text{C-NMR}$ ((D_6) DMSO): 27.6; 29.8; 45.1; 50.4; 110.1; 112.5; 116.9; 120.7; 123.3; 124.4; 126.9; 127.8; 128.3; 128.9; 131.7; 132.9; 136.1; 136.5; 136.9; 137.4; 144.2; 145.8; 146.9; 148.8; 161.2; 163.1; 165.1. EI-MS: 475.06 ($[M + \text{H}]^+$). Anal. calc. for $\text{C}_{27}\text{H}_{22}\text{N}_8\text{O}$ (474.52): C 68.34, H 4.67, N 23.61; found: C 68.35, H 4.68, N 23.57.

REFERENCES

- [1] C. Birchmeier, W. Birchmeier, E. Gherardi, G. F. V. Woude, *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 915.
- [2] P. G. Dharmawardana, A. Giubellino, D. P. Bottaro, *Curr. Mol. Med.* **2004**, *4*, 855.
- [3] B. Peruzzi, D. P. Bottaro, *Clin. Cancer Res.* **2006**, *12*, 3657.
- [4] J. P. Eder, G. F. V. Woude, S. A. Boerner, P. M. LoRusso, *Clin. Cancer Res.* **2009**, *7*, 2207.
- [5] S. C. Hopkins, R. D. Vale, I. D. Kundz, *Biochemistry* **2000**, *39*, 2805; J. J. Cui, *Expert Opin. Ther. Pat.* **2007**, *17*, 1035; B. Cao, Y. Su, M. Oskarsson, P. Zhao, E. J. Kort, R. J. Fisher, L.-M. Wang, G. F. V. Woude, *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7443; J. Porter, *Expert Opin. Ther. Pat.* **2010**, *2*, 159; T. A. Yap, D. Olmos, A. T. Brunetto, N. Tunariu, J. Barriuso, R. Riisnaes, L. Pope, J. Clark, A. Futreal, M. Germuska, D. Collins, N. M. deSouza, M. O. Leach, R. E. Savage, C. Waghorne, F. Chai, E. Garmey, B. Schwartz, S. B. Kaye, J. S. de Bono, *J. Clin. Oncol.* **2011**, *29*, 1271.
- [6] S. G. Wu, J. J. Zhang, S. Y. Wu, W. Xu, H. T. Wang, Z. Q. Liu, S. H. Wan, to *Southern Medical University*, China Patent CN 2010/101857594, 13.10.2010, pp. 1–66; *Chem. Abstr.* **2010**, *153*, 580285.
- [7] H. M. Cheng, J. J. Cui, J. E. Hoffman, L. Jia, C. Johnson, R. S. Kania, P. T. Q. Le, M. D. Nambu, M. A. Pairish, H. Shen, M. B. Tran-Dube, to *Pfizer Products Inc.*, World Patent WO 2007/132308, 22.11.2007, pp. 1–110; *Chem. Abstr.* **2007**, *147*, 541902.
- [8] T. B. Lu, R. Alexander, R. W. Connors, M. D. Cummings, R. A. Galemno, H. R. Hufnagel, D. L. Johnson, E. Khalil, K. A. Leonard, T. P. Markotan, A. C. Maroney, J. L. Sechler, J. M. Trawins, R. W.

- Tuman, to *Janssen Pharmaceutica, N.V.*, World Patent WO 2007/075567, 05.07.2007, pp. 1–220; *Chem. Abstr.* **2007**, 147, 143449.
- [9] A. Bridoux, L. Goossens, R. Houssin, J. P. Hénichart, *J. Heterocycl. Chem.* **2006**, 43, 571; P. Guzzo, M. D. Suarman, A. J. Henderson, M. X. Jiang, M. Hadden, J. Grabowski, to *Albany Molecular Research Inc.*, World Patent WO 2009/089482, 16.07.2009, pp. 1–311; *Chem. Abstr.* **2009**, 151, 173472.

Received June 2, 2011