Journal of Medicinal Chemistry

BRIEF ARTICLE

pubs.acs.org/jmc

Scaffold-Hopping Strategy: Synthesis and Biological Evaluation of 5,6-Fused Bicyclic Heteroaromatics To Identify Orally Bioavailable Anticancer Agents

Yen-Shih Tung,[†,‡,●] Mohane Selvaraj Coumar,[§,●] Yu-Shan Wu,[∥] Hui-Yi Shiao,[†] Jang-Yang Chang,[⊥] Jing-Ping Liou,[#] Paritosh Shukla,[†] Chun-Wei Chang,[†] Chi-Yen Chang,[⊥] Ching-Chuan Kuo,[⊥] Teng-Kuang Yeh,[†] Chin-Yu Lin,[†] Jian-Sung Wu,[†] Su-Ying Wu,[†] Chun-Chen Liao,[‡,∞] and Hsing-Pang Hsieh*[,†]

[†]Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes, 35 Keyan Road, Zhunan, Miaoli County 350, Taiwan, ROC

[‡]Department of Chemistry, National Tsing Hua University, 101, Section 2, Guangfu Road, Hsinchu 300, Taiwan, ROC

[§]Centre for Bioinformatics, School of Life Sciences, Pondicherry University, Kalapet, Puducherry 605014, India

[∥]Department of Chemistry, Tunghai University, 181 Taichung Harbor Road Section 3, Taichung 407, Taiwan, ROC

[⊥]National Institute of Cancer Research, National Health Research Institutes, Tainan 704, Taiwan, ROC.

[#]College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan, ROC

[∞]Department of Chemistry, Chung Yuan Christian University, Chungli 320, Taiwan, ROC

Supporting Information

ABSTRACT: Utilizing scaffold-hopping drug-design strategy, we sought to identify a backup drug candidate for BPR0L075 (**1**), an indole-based anticancer agent. For this purpose, 5,6-fused bicyclic heteroaromatic scaffolds were designed and synthesized through shuffling of the nitrogen from the N-1 position or by insertion of one or two nitrogen atoms into the indole core of **1**. Among these, 7-azaindole core **12** showed potent in vitro anticancer activity and improved oral bioavailability (F = 35%) compared with **1** (F < 10%).

INTRODUCTION

Scaffold-hopping, a medicinal chemistry method for molecular backbone replacements, is an important drug-design strategy that could be used to develop novel molecules with potent activity, altered physicochemical attributes, and ADMET properties, as well as molecules with new intellectual property (IP) positions.[1] For example, manipulation of the scaffold of sildenafil forms the basis for the successful identification of vardenafil for the treatment of erectile dysfunction (Figure 1); similarly atorvastatin → rosuvastatin for the treatment of dyslipidemia. Such drug-design strategies depend on the ability to synthesize new scaffolds in short, easy steps and are essentially chemistry-driven approaches. Here we present our synthetic strategies for the replacement of the indole ring of **1** (a potent anticancer agent, targeting tubulin, which has already undergone extensive preclinical testing)[2] with alternative 5,6-fused bicyclic heteroaromatics to identify backup drug candidates with altered drug properties and new IP rights.

For the scaffold-hopping design, we scrutinized a variety of scaffolds (1) by shuffling the nitrogen from the N-1 position to other positions of the indole moiety, leading to indolizine, and (2) by inserting one or two nitrogen atoms into the indole ring, leading to indazole, 7-azaindole, imidazo[1,2-*a*]pyridine, 7*H*-pyrrolo[2,3-*d*]pyrimidine, pyrazolo[1,5-*b*]pyridazine (Figure 2). The presence of the 6-methoxy group in **1** is essential for maintaining potent anticancer activity, as it is well-known that removing or just moving the methoxy group to another position on the indole ring leads to dramatic loss of potency.[2] Hence, in all the new scaffolds contemplated, we introduced this methoxy group, a highly challenging synthetic task, and the 3,4,5-trimethoxybenzoyl group. The indole derivative **1** was synthesized in a one-step Friedel−Crafts acylation of commercially available 6-methoxyindole with 3,4,5-trimethoxybenzoyl chloride;[2] however, for **2**−**10**, the 5,6-fused heteroaromatic cores needed to be constructed from six-membered rings (pyridine or benzene) with appropriate substitution followed by introduction of the 3,4,5-trimethoxybenzoyl group. For some, the 3,4,5-trimethoxybenzoyl group was introduced into commercially available 5,6-fused heteroaromatic cores. Our scaffold-hopping medicinal chemistry design strategy has resulted in the successful identification of 7-azaindole **12**, which has better aqueous solubility and oral bioavailability than **1**. Although scaffold-hopping medicinal chemistry design concepts have previously been utilized for developing therapeutic agents, our application of this strategy to our lead **1** has resulted not only in the identification of a backup candidate but also in the securing of new IP rights and hence is interesting not only academically but also from a commercial point of view. Additionally, the presence of a methoxy group at the appropriate position on the new scaffolds makes the scaffold-hopping design strategy synthetically challenging. Along with in vitro and in vivo evaluation of

Received: August 7, 2010
Published: March 24, 2011

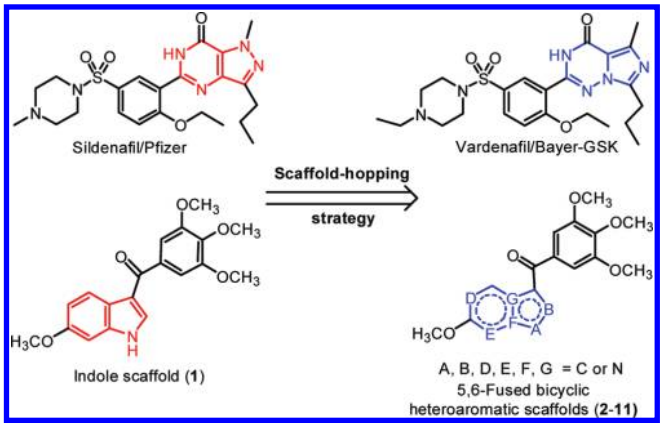


Figure 1. Scaffold-hopping drug design strategy.

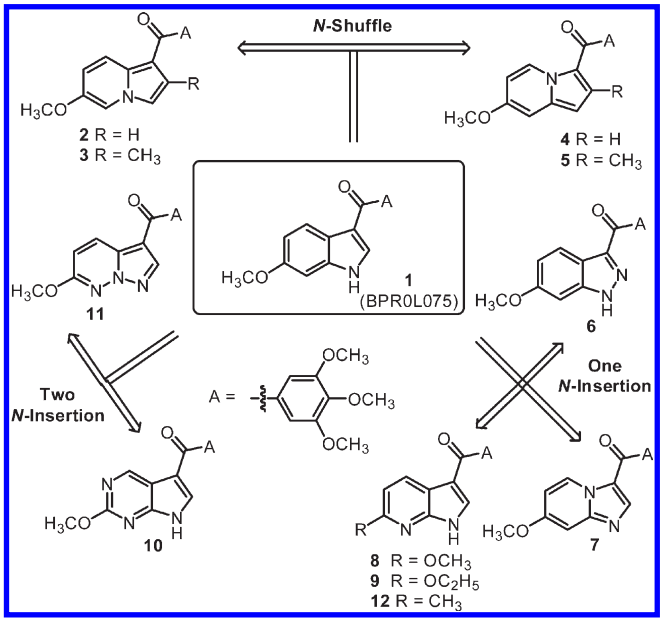


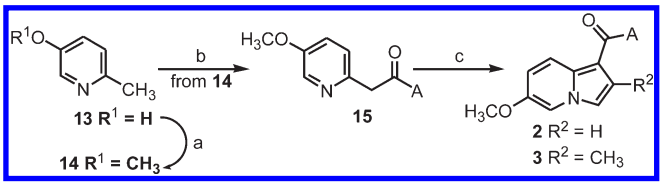
Figure 2. 5,6-Fused bicyclic heteroaromatic analogues of **1** synthesized in this study.

the compounds, which resulted in the identification of **12** with improved properties, the synthetic difficulties encountered and the strategies used to overcome these are the subject of this paper.

CHEMISTRY

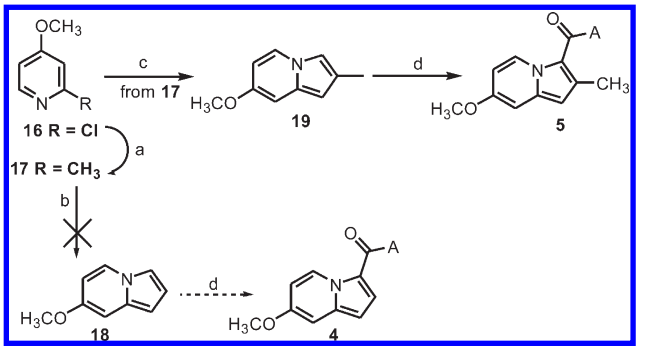
For the preparation of the nitrogen-shuffled scaffold indolizines **2**−**5**, a modified version of the procedure in Ohtani et al.[3] was used. Preparation of **2** and **3** was straightforward, starting from the pyridine **14**,[4] which was obtained by methylation of the commercially available pyridine **13** in 90% yield. The key intermediate **15** was obtained from **14** through LDA-mediated carbanion generation and the addition of benzonitrile. Base-catalyzed cyclization of **15** with 2-chloroacetaldehyde or with 2-bromoacetone gave **2** and **3**, respectively (Scheme 1). For the preparation of **4** and **5**, N-alkylation of **17** with chloroacetaldehyde or with 1-bromoacetone followed by base-induced cyclization to get intermediates **18** and **19**, respectively, was attempted. However, because of the chemical instability of **18**, only the

Scheme 1. Synthesis of Indolizines 2 and 3[a]



[a] Reagents and conditions: (a) ^{t}BuOK, CH_3I, THF, room temp, 8 h, 90%; (b) LDA, 3,4,5-trimethoxybenzonitrile, THF, −78 °C → room temp, 2 h, 75%; (c) $NaHCO_3$, acetone, reflux, 8 h, 2-chloroacetaldehyde for **2** (85%) and 1-bromoacetone for **3** (95%). A = 3,4,5-trimethoxybenzene group.

Scheme 2. Synthesis of Indolizine 5[a]



[a] Reagents and conditions: (a) CH_3ZnCl, $Pd(PPh_3)_4$, THF, reflux, 40 h, 50%; (b) (i) chloroacetaldehyde, CH_3CN, 95 °C, 2 h, (ii) DBU, benzene, 1 h; (c) (i) 1-bromoacetone, CH_3CN, 95 °C, 2 h, (ii) DBU, benzene, 1 h, 31%; (d) 3,4,5-trimethoxybenzoyl chloride, Et_3N, 90 °C, 5 h, 74%. A = 3,4,5-trimethoxybenzene group.

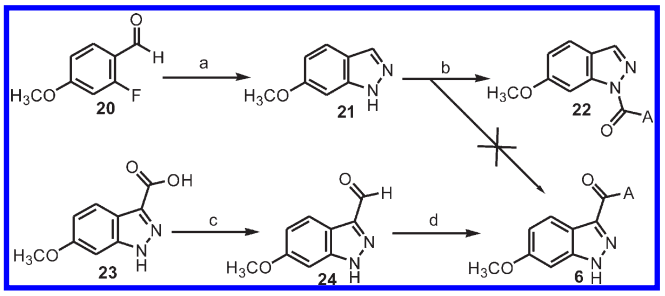
methyl analogue **19** could be obtained, which was acylated with trimethoxybenzoyl chloride to give **5** (Scheme 2).

For the preparation of scaffolds with N-insertion into the indole ring (indazole **6**, imidazo[1,2-*a*]pyridine **7**, 7-azaindoles **8**, **9**, and **12**, 7*H*-pyrrolo[2,3-*d*]pyrimidine **10**, and pyrazolo[1,5-*b*]pyridazine **11**), various strategies were used. To construct the indazole derivative **6**, Friedel−Crafts acylation of 6-methoxyindazole **21**[5] with trimethoxybenzoyl chloride, in a manner similar to the construction of **1**,[2] was envisaged. However, Friedel−Crafts acylation of **21** gave exclusively the undesired N-acylated product **22**. Hence, an alternative method to obtaining **6** was used, consisting of Grignard addition of trimethoxybenzylmagnesium bromide to the aldehyde **24** followed by MnO_2 oxidation. The indazole intermediate **24** was prepared from commercially available acid **23** by first converting it to alcohol by LAH reduction followed by MnO_2 oxidation to get the aldehyde (Scheme 3). Recently, Matteucci et al. reported the synthesis of **6** through an alternative synthetic route.[6]

For the construction of imidazo[1,2-*a*]pyridine **7**, the key intermediate **28** was synthesized by base-catalyzed condensation of chloroacetaldehyde with **27**. The 2-aminopyridine **27** was prepared by the introduction of methoxy group at C-4 position followed by Curtius rearrangement starting from picolinic acid **25** as reported.[7] Attempts to carry out Friedel−Crafts acylation of **28** with 3,4,5-trimethoxybenzoyl chloride (dichloromethane at room temperature, 1,2-dichloroethane at reflux, or toluene under microwave irradiation up to 130 °C) were unsuccessful, with the recovery of starting material. Hence an alternative route through formylation using Vilsmeier−Haack reagent was applied

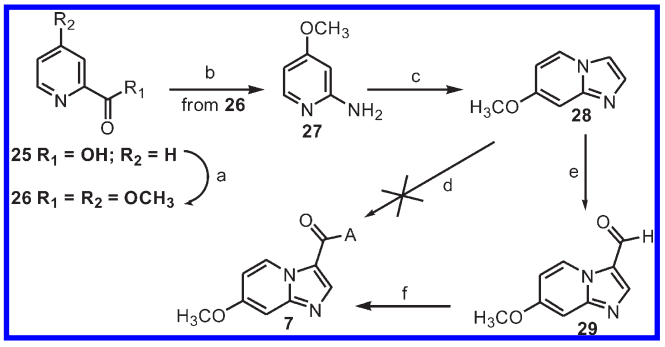
dx.doi.org/10.1021/jm101027s |*J. Med. Chem.* 2011, 54, 3076–3080

Scheme 3. Synthesis of Indazole 6[a]



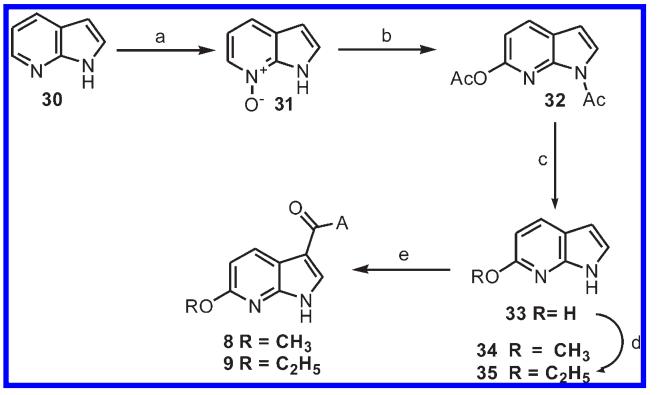
[a] Reagents and conditions: (a) hydrazine hydrate, room temp, (4 h) → 150 °C, 48 h, 72%; (b) EtMgBr, $ZnCl_2$, CH_2Cl_2, 3,4,5-trimethoxybenzoyl chloride, $AlCl_3$, room temp, 8 h, 30%; (c) (i) LAH, THF, room temp, 0.5 h, (ii) MnO_2, CH_2Cl_2, room temp, 24 h, 51%; (d) (i) 3,4,5-trimethoxyphenylmagnesium bromide, THF, 0 °C, 20 min, (ii) MnO_2, CH_2Cl_2, room temp, 24 h, 53%. A = 3,4,5-trimethoxybenzene group.

Scheme 4. Synthesis of Imidazo[1,2-*a*]pyridine 7[a]



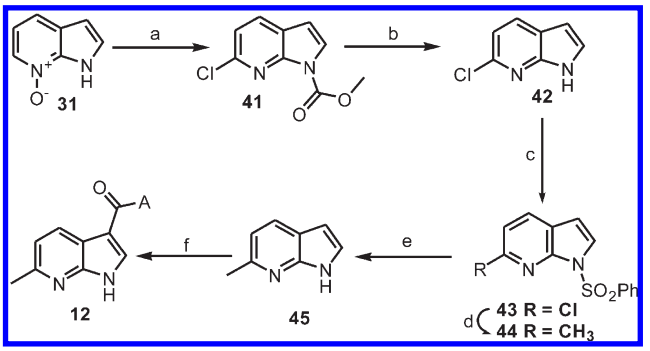
[a] Reagents and conditions: (a) (i) $SOCl_2$, 5 mol % NaBr, 24 h, (ii) CH_3OH, 24 h, 38%; (b) hydrazine, CH_3OH, reflux, 94%; (c) chloroacetaldehyde, $NaHCO_{3(aq)}$, EtOH, reflux, 3 h, 57%; (d) 3,4,5-trimethoxybenzoyl chloride, $AlCl_3$, reflux, 12 h; (e) $POCl_3$, DMF, 90 °C, 12 h, 69%; (f) (i) 3,4,5-trimethoxyphenylmagnesium bromide, THF, room temp, 20 min, (ii) MnO_2, CH_2Cl_2, room temp, 24 h, 51%. A = 3,4,5-trimethoxybenzene group.

Scheme 5. Synthesis of 7-Azaindole 8 and 9[a]



[a] Reagents and conditions: (a) *m*-CPBA, EtOAc, room temp, 2 h, 94%; (b) Ac_2O, reflux, 8 h, 70%; (c) K_2CO_3, H_2O/MeOH, reflux, 8 h, 60%; (d) K_2CO_3, RI, acetone, 50 °C, 8 h, 30% for **34**, 80% for **35**; (e) EtMgBr, $ZnCl_2$, CH_2Cl_2, 3,4,5-trimethoxybenzoyl chloride, $AlCl_3$, room temp, 8 h, 76% for **8**, 70% for **9**. A = 3,4,5-trimethoxybenzene group.

Scheme 6. Synthesis of 7-Azaindole 12[a]



[a] Reagents and conditions: (a) HMDS, $ClCO_2CH_3$, THF, 1 h, 62%; (b) 1 N $NaOH_{(aq)}$, THF, room temp, 16 h, 95%; (c) NaOH, TBAS, $ClSO_2Ph$, CH_2Cl_2, room temp, 8 h, 91%; (d) CH_3ZnCl, $Pd(PPh_3)_4$, THF, reflux, 40 h, 89%; (e) 50% $NaOH_{(aq)}$, EtOH, reflux, 8 h, 78%; (f) EtMgBr, $ZnCl_2$, CH_2Cl_2, 3,4,5-trimethoxybenzoyl chloride, $AlCl_3$, room temp, 8 h, 71%. A = 3,4,5-trimethoxybenzene group.

to get **29**, which was finally subjected to Grignard addition followed by MnO_2 oxidation to produce the desired **7** (Scheme 4).

For the construction of the 7-azaindole analogues **8** and **9**, commercially available 7-azaindole **30** was oxidized to 7-azaindole *N*-oxide **31**[8] by *m*-CPBA, which was followed by regioselective acylation at the 6-position in a manner similar to that reported by Wang et al.[9] to give **32**. Deprotection of acetyl protection under basic conditions gave **33**, which was alkylated to give the 6-methoxy (**34**) or 6-ethyoxy-7-azaindole (**35**). Final Friedel−Crafts acylation of **34**/**35** with 3,4,5-trimethoxybenzoyl chloride then completed the formation of the desired products **8** and **9** (Scheme 5). 7*H*-Pyrrolo[2,3-*d*]pyrimidine **10** was obtained through Friedel−Crafts acylation of **37**. The intermediate **37**[10] was obtained by dechlorination of **36** using H_2/Pd/C in methanol followed by MnO_2 oxidation (Scheme 1s, Supporrting Information).

Preparation of pyrazolo[1,5-*b*]pyridazine **11** was accomplished by utilizing [2 + 3] cycloaddition between acetylene **39** and 3-methoxypyridazine **40** through modification of the method reported by Zhou et al.[11] The terminal alkyne **39** was obtained from aldehyde **38** by sodium monoacetylide addition followed by Jones oxidation (Scheme 2s, Supporting Information).

For the synthesis of 7-azaindole **12**, 6-chloro-7-azaindole (**42**) was synthesized as reported by Ohshiro et al.[8] from 7-azaindole **30**. Protection of indole NH as sulfonamide (**43**) followed by palladium mediated Negishi cross-coupling with CH_3ZnCl was carried out to introduce the sixth position methyl group in 7-azaindole **44**. Deprotection followed by final Friedel−Crafts acylation with 3,4,5-trimethoxybenzoyl chloride then completed the formation of the desired product **12** (Scheme 6).

BIOLOGICAL RESULTS AND DISCUSSION

Newly synthesized compounds were evaluated for growth inhibitory activity against two types of human cancer cell lines (cervical carcinoma KB cells and gastric carcinoma MKN-45 cells). The results were compared to **1** (Table 1). In general, replacing the indole scaffold with other 5,6-fused heteroaromatic rings through N-shuffle or N-insertion led to decreased cytotoxicity. Particularly indolizine **5**, imidazo[1,2-*a*]pyridine **7**, and pyrazolo[1,5-*b*]pyridazine **11** had lost >100-fold activity when compared to indole **1**. All other compounds showed activity with two-digit nanomolar ranges. It is interesting that the 7-azaindole

9 was only 2- to 3-fold less active than **1** in both cell lines tested. Most of the 5,6-fused heteroaromatic analogues the retaining NH group (**6**, **8**, and **9**) showed anticancer activity below 100 nM, indicating that the NH group may play some role in the biological activity.

Potent **3**, **8**, **9** identified in this study and the less potent **11** were, along with **1**, subjected to in vitro metabolic stability testing using human microsome to access the effect of different scaffolds on the metabolism. After 30 min of incubation with the microsomes, the lead **1** was only 54% stable; however, the most potent compound identified in this study, 7-azaindole **9**, had an excellent metabolic stability of >95%. The pyrazolo[1,5-*b*]pyridazine core **11** showed the best metabolic stability, with >99% remaining unchanged after 30 min of incubation with microsomes, suggesting that the presence of N-7 nitrogen next to the 6-methoxy group significantly improved the metabolic stability of these compounds compared to **1**. We have previously shown that the O-demethylation of the 6-methoxy group of the indole **1** by microsome leads to the formation of major 6-hydroxy metabolite of **1**, which is inactive in vivo.[12] Moreover, replacing the 6-methoxy group of **1** with the ethoxy group increased the in vitro metabolic stability by decreasing the rate of O-dealkylation, which ultimately resulted in an improved in vivo pharmacokinetic (PK) profile and in vivo anticancer activity in rats for the 6-ethyoxy analogue of **1**.[12] On the basis of this line of reasoning, the 7-azaindole core, which possesses an optimal anticancer activity and better in vitro metabolic stability among the new cores synthesized, was selected for further investigation.

Table 1. Cytotoxicity and Metabolic Stability of New Analogues

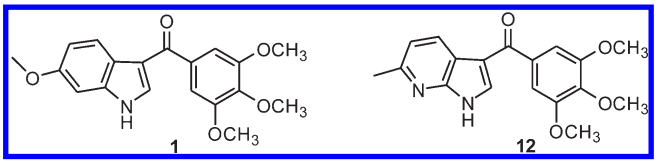
	cyctotoxicity (IC_{50}, nM)[a]		
compd	KB	MKN-45	metabolic stability[b]
2	284	80	
3	31	26	35.4
5	>1000	354	
6	70	95	
7	770	730	
8	20	16	88.3
9	12	14	96.4
10	284	80	
11	>1000	>1000	99.6
1	6	5	54.1

[a] Values are expressed as the mean of at least three independent determinations and are within ±15%. [b] Metabolic stability calculated as % compound remaining after 30 min of incubation with human liver microsome.

A previous structure−activity relationship (SAR) investigation of indole core **1** showed that the 6-methoxy group could be replaced by an electron-donating methyl group without loss of activity.[13] Accordingly, we replaced the 6-methoxy group of 7-azaindole **8** with the 6-methyl group; and **12** showed double-digit nanomolar antiproliferative activity (Table 2). Furthermore, 7-azaindole cores **8**, **9**, and **12** were also evaluated for their solubility profiles in aqueous solution and in phosphate buffer solution (PBS) of pH 7.4. Neither **8** nor **9** showed improved solubility (<2 μg/mL) when compared to the indole **1** (<1 μg/mL). However, **12** with the 6-methyl substitution showed an improved solubility in aqueous solution and PBS. Most interestingly the hydrochloride salt of **12** showed around 100-fold improvement in solubility compared to **1** (Table 2).

To show that the antiproliferative activity of the newly synthesized compounds was due to tubulin inhibition, we carried out tubulin polymerization assay in vitro. Three potent compounds **3**, **9**, and **12** inhibited tubulin polymerization potently in vitro (Table 1s, Supporting Information), showing that the antiproliferative mechanism for the newly synthesized compounds is similar to that of the lead **1**. Furthermore, we also carried out docking studies of **3**, **9**, and **12** in the colchicine binding site of tubulin (PDB code 1SA0). All three compounds docked to the colchicine binding site in a fashion similar to that of **1** (Figures 1s, 2s, and 3s, Supporting Information), suggesting antiproliferative mechanism similar to that of the lead **1**.

Table 2. Comparative in Vitro and in Vivo Profile of Indole 1 and 7-Azaindole Analogue 12[a]



	in vitro profile[b]					in vivo pharmacokinetics profile[b]								
	antiproliferative activity IC_{50} (nM)			solubility (μg/mL)		iv (5 mg/kg)				po (20 mg/kg)				
compd	KB	MKN-45	metabolic stability[c]	water	PBS	$t_{1/2}$	CL	V_{ss}	AUC	$t_{1/2}$	C_{max}	T_{max}	AUC	*F*
1	6	5	54.1	0.90	0.61	0.9	31.5	1.6	2712	2.8	179	4.0	1311	9.7
12	23	22	86.7	14.3	8.3	0.4	31.7	0.7	2653	1.3	3753	0.5	4640	35
12·HCl				91.3	79.6									

[a] AUC, area under curve (ng·h/mL). CL, clearance (mL/h·kg). *F*, oral bioavailability (%). V_{ss}, volume at steady state (L/kg). $t_{1/2}$, plasma half-life (h). C_{max} (ng/mL). T_{max} (h). [b] Values are expressed as the mean of at least three independent experiments. [c] Metabolic stability calculated as % compound remaining after 30 min of incubation with human liver microsome.

dx.doi.org/10.1021/jm101027s |*J. Med. Chem.* 2011, 54, 3076–3080

On the basis of these results, **12** was selected for in vivo PK evaluation in rats. Compound **12**/**1** (dissolved in PEG 400/dehydrated ethanol/Solutol = 20:30:50) was administered to rats intravenously (iv) at 5 mg/kg body weight and orally at 20 mg/kg body weight. Blood samples were taken, and the plasma was analyzed for concentration of **12**/**1** using an LC−MS/MS system. The 7-azaindole **12** displayed drug exposure similar to that of indole **1** after intravenous (iv) administration (Table 2). Most interestingly **12** showed improved oral bioavailability (F = 35%) when compared to **1** (F = 9.5%). Overall, these results suggest that the 7-azaindole **12** has potential for development as an orally bioavailable anticancer agent that could serve as a backup drug candidate for **1**.

CONCLUSIONS

5,6-Fused bicyclic heteroaromatic scaffolds that bear essential structural features for anticancer activity based on the lead **1** were designed. The 5,6-fused heteroaromatic cores **2**−**12** were synthesized in a total of two to seven steps from six-membered rings (pyridine/benzene) or commercially available 5,6-fused heteroaromatic cores. Appropriate placement of both the methoxy and trimethoxybenzoyl groups (prerequisite groups for anticancer activity) in the core structures of **2**−**11** proved synthetically challenging and was not always as straightforward as envisaged; alternative synthetic strategies were developed, when necessary, to overcome difficulties encountered. Among the compounds synthesized, presence of an NH group in the first position of the heteroaromatic core resulted in potent anticancer activity and presence of an N atom in the seventh position improved metabolic stability. The 7-azaindole **9** and pyrazolo[1,5-*b*]pyridazine **10** core containing compounds showed potent anticancer activity and greater in vitro metabolic stability than the indole (**1**) core. Most interestingly, 7-azaindole core **12** with 6-methyl substitution showed potent in vitro anticancer activity with improved metabolic stability, solubility, and oral bioavailability (F) compared with **1**. Therefore, the scaffold-hopping drug-design strategy has provided us with backup drug candidate **12**, an orally bioavailable anticancer agent, with altered drug properties and broader IP rights.[14]

EXPERIMENTAL SECTION

(6-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-(3,4,5-trimethoxyphenyl)methanone (12). Compound **12** was synthesized in 66% yield from **45** and 3,4,5-trimethoxybenzoyl chloride, using $AlCl_3$. See Supporting Information for details.

ASSOCIATED CONTENT

Supporting Information. Docking and tubulin polymerization inhibition of **1**, **3**, **9**, and **12**; schemes for **10** and **11**; synthesis and spectral data for **2**−**12**; and in vitro and in vivo biological evaluation protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Phone, +886-37-246-166, ext 35708. Fax: +886-37-586-456. E-mail: hphsieh@nhri.org.tw.

Author Contributions

●These authors contributed equally to this work.

ACKNOWLEDGMENT

The study was financially supported by the National Health Research Institutes and the National Science Council (Grant NSC-95-2113-M-400-001-MY3), Taiwan, ROC. We thank Mark Swofford for helping with the English editing.

REFERENCES

(1) Ciapetti, P.; Giethlen, B. Molecular Variations Based on Isosteric Replacements. In *The Practice of Medicinal Chemistry*, 3rd ed.; Wermuth, C. G., Ed.; Academic Press: Boston, MA, 2008; pp 290−342.

(2) Liou, J. P.; Chang, Y. L.; Kuo, F. M.; Chang, C. W.; Tseng, H. Y.; Wang, C. C.; Yang, Y. N.; Chang, J. Y.; Lee, S. J.; Hsieh, H. P. Concise synthesis and structure−activity relationships of combretastatin A-4 analogues, 1-aroylindoles and 3-aroylindoles, as novel classes of potent antitubulin agents. *J. Med. Chem.* **2004**, *47*, 4247–4257.

(3) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. Potent inhibitors of secretory phospholipase A2: synthesis and inhibitory activities of indolizine and indene derivatives. *J. Med. Chem.* **1996**, *39*, 3636–3658.

(4) Hatanaka, M.; Takahashi, K.; Nakamura, S.; Mashino, T. Preparation and antioxidant activity of alpha-pyridoin and its derivatives. *Bioorg. Med. Chem.* **2005**, *13*, 6763–6770.

(5) Lukin, K.; Hsu, M. C.; Fernando, D.; Leanna, M. R. New practical synthesis of indazoles via condensation of *o*-fluorobenzaldehydes and their *O*-methyloximes with hydrazine. *J. Org. Chem.* **2006**, *71*, 8166–8172.

(6) Duan, J. X.; Cai, X.; Meng, F.; Lan, L.; Hart, C.; Matteucci, M. Potent antitubulin tumor cell cytotoxins based on 3-aroyl indazoles. *J. Med. Chem.* **2007**, *50*, 1001–1006.

(7) Sundberg, R. J.; Songchun, J. Improved procedures for preparation of 4-hydroxy- and 2-amino-4-methoxypyridines. *Org. Prep. Proced. Int.* **1997**, *29*, 117–122.

(8) Ohshiro, Y.; Komatsu, M.; Minakata, S. Regioselective functionalization of 1*H*-pyrrolo[2,3-*b*]pyridine via its *N*-oxide. *Synthesis* **1992**, *1992*, 661–663.

(9) Wang, T.; Wallace, O. B.; Zhang, Z.; Meanwell, N. A.; Bender, J. A. Antiviral Azaindole Derivatives. WO0162255A1, 2001.

(10) Seela, F.; Chen, Y.; Bindig, U.; Kazimierczuk, Z. Synthesis of 2′-deoxyisoinosine and related 2′-deoxyribonucleosides. *Helv. Chim. Acta* **1994**, *77*, 194–202.

(11) Tavares, F. X.; Boucheron, J. A.; Dickerson, S. H.; Griffin, R. J.; Preugschat, F.; Thomson, S. A.; Wang, T. Y.; Zhou, H. Q. *N*-Phenyl-4-pyrazolo[1,5-*b*]pyridazin-3-ylpyrimidin-2-amines as potent and selective inhibitors of glycogen synthase kinase 3 with good cellular efficacy. *J. Med. Chem.* **2004**, *47*, 4716–4730.

(12) Wu, Y. S.; Coumar, M. S.; Chang, J. Y.; Sun, H. Y.; Kuo, F. M.; Kuo, C. C.; Chen, Y. J.; Chang, C. Y.; Hsiao, C. L.; Liou, J. P.; Chen, C. P.; Yao, H. T.; Chiang, Y. K.; Tan, U. K.; Chen, C. T.; Chu, C. Y.; Wu, S. Y.; Yeh, T. K.; Lin, C. Y.; Hsieh, H. P. Synthesis and evaluation of 3-aroylindoles as anticancer agents: metabolite approach. *J. Med. Chem.* **2009**, *52*, 4941–4945.

(13) Liou, J. P.; Mahindroo, N.; Chang, C. W.; Guo, F. M.; Lee, S. W.; Tan, U. K.; Yeh, T. K.; Kuo, C. C.; Chang, Y. W.; Lu, P. H.; Tung, Y. S.; Lin, K. T.; Chang, J. Y.; Hsieh, H. P. Structure−activity relationship studies of 3-aroylindoles as potent antimitotic agents. *ChemMedChem* **2006**, *1*, 1106–1118.

(14) Hsieh, H.-P.; Chao, Y.-S.; Liou, J.-P.; Chang, J.-Y.; Tung, Y.-S. Anti-Tumor Compounds. US7456289, 2008.