Bioorganic & Medicinal Chemistry Letters 18 (2008) 4602–4605

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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# Synthesis and biological evaluation of C-12′ substituted vinflunine derivatives

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ARTICLE INFO

*Article history:*
Received 5 May 2008
Revised 4 July 2008
Accepted 9 July 2008
Available online 12 July 2008

*Keywords:*
Vinflunine derivatives
Synthesized
In vitro
A549 cell lines

ABSTRACT

A series of novel C-12′ substituted vinflunine derivatives have been synthesized. Several compounds in this series possess comparable in vitro cytotoxic potency against A549 cell lines.



Compounds interfering with microtubule function form an important class of anticancer agents, they are widely used in combination chemotherapy regimens for treating solid tumors as well as leukemias.[1] One of the best-known classes of these agents is the *Vinca* alkaloids, which inhibit cell proliferation by their effects on the mitotic spindle microtubules.[2] Four drugs are currently available: Vinblastine,[3] Vincristine,[4] Vindesine,[5] and Vinorelbine[6] (Fig. 1). Vinflunine, a novel semi-synthetic fluoride containing *Vinca* alkaloid, is now in clinical development, with marked antitumor activities, reduced neurotoxicity and less P-glycoprotein-mediated drug resistance.[7]

Despite enormous efforts in the fields of both chemistry and biology since Vinblastine was isolated in 1958, it is still necessary to discover new *Vinca* alkaloid derivatives with higher cytotoxic potency, less side effect, and a broader spectrum of anticancer efficacies. Numerous studies indicate that the minor difference in the structure among these *Vinca* alkaloids could often result in significant difference in their potency and clinical toxicity.[5b,8] While previous structure-activity relationship (SAR) studies were focused on the indoline moiety in the *Vinca* alkaloids,[5b,8,9] very little was reported on modification of the indole moiety.[10]

Recently, Vinblastine-binding study indicated that the vindoline moieties, particularly the C-12′ site on the upper aromatic moiety, were involved in the interaction with tubulin heterodimers.[11] Therefore, modification on the upper aromatic moiety of *Vinca* alkaloids might be a probe to aid in elucidating or demonstrating the binding information in detail. Herein, we report our progress in the synthesis and biological evaluation of the novel vinflunine derivatives at C-12′ position on the indole ring.

Our synthesis of the C-12′ substituted derivatives of vinflunine is outlined in Schemes 1 and 2. Vinflunine **1** was formylated at the C-12prime position on the indole ring by treating vinflunine with HMTA in the presence of TFA. Subsequent reductive amination of the C-12′-formyl led to compounds **3–8**. Treatment of intermediate **2** with various Grignard's reagents, followed by Dess–Martin oxidation[12] of the resulting alcohols to the corresponding ketones, generated compounds **9–11**. Cyano vinflunine **12** was obtained by condensing the aldehyde intermediate **2** with hydroxylamine hydrochloride in the presence of triethylamine, followed by dehydration in situ using phthalic acid anhydride under reflux.[13]

As shown in Scheme 2, vinflunine was allowed to react with NIS in the mixture of TFA and dichloromethane at −15 °C for 1 h, providing smoothly the important C-12′ iodinated intermediate **13** in 94% yield. Iodide **13** was coupled with various aryl boronic acids, catalyzed by $Pd(OAc)_2$/dppf system, in the presence of $Cs_2CO_3$ to give compounds **14–23**.[14] Negishi coupling reaction of **13** catalyzed by $Pd(OAc)_2/PPh_3$ system with organozinc species, prepared from the corresponding Grignard's reagents and anhydrous zinc chloride, gave rise to compounds **24–27**. Compound **28** was obtained by coupling **13** with ETMS under Sonogashira conditions,[13c] followed by removing the silyl protective group with TBAF. The alkyloxycarbonyl derivatives **29–32** were furnished using $Pd(OAc)_2$/dppf/$Et_3N$ in carbon monoxide atmosphere in the presence of the corresponding alcohols.[15]

Iodide **13** reacted with sodium azide using CuI as catalyst and L-proline as ligand in the presence of NaOH[16] to furnish the corresponding azide **33**, which was hydrogenated to give amine **34**. Direct alkylation of amine **34** led to compounds **35–37**. Hydroxyl group of the intermediate **13** was protected with silyl group, and

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doi:10.1016/j.bmcl.2008.07.025

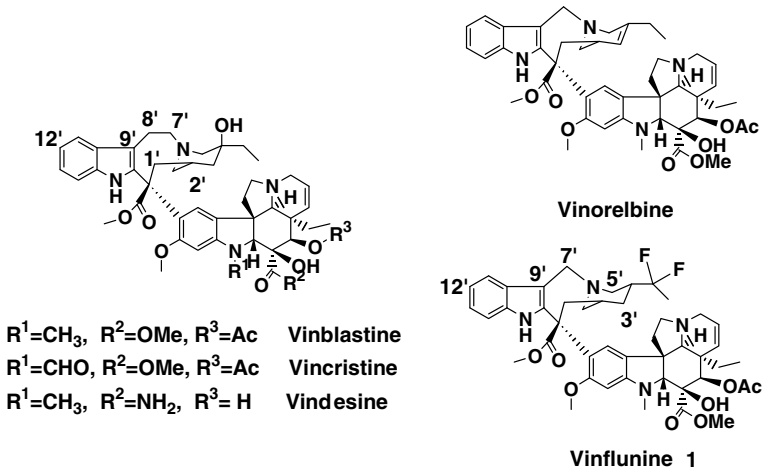
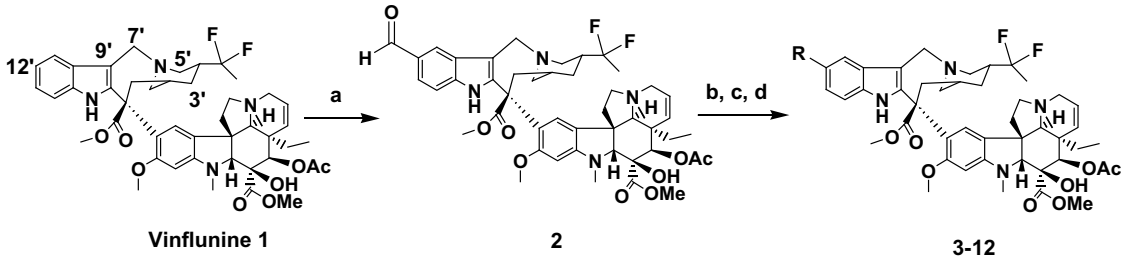



**Figure 1.** Structures of the clinically effective compounds.




**Scheme 1.** Reagents and conditions: (a) hexamethylenetetramine, TFA, 75 °C, 1 h; (b) i—amines, $CH_2Cl_2$, rt, 20 h; ii—$NaBH_3CN$, rt, 3 hr; (c) i—RMgCl, THF, rt, 1 h; ii—Dess–Martin reagent, $CH_2Cl_2$, rt, 20 h; (d) i—$HONH_2$·HCl/$Et_3N$, $CH_3CN$, reflux, 1.5 h; ii—phthalic acid anhydride, reflux, overnight.

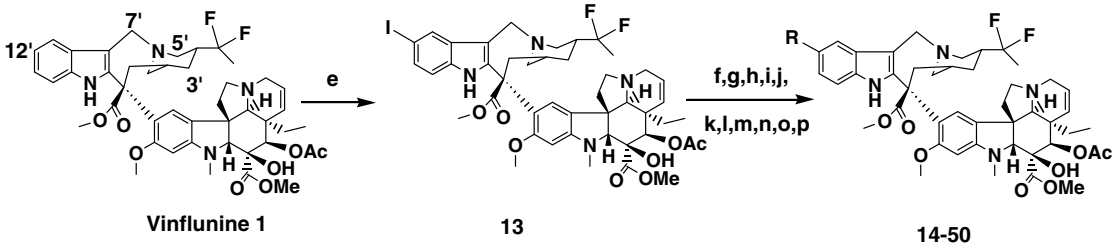
then coupled with aromatic or aliphatic amines, followed by deprotection reaction to give the desired compounds **38–39**. Compound **34** could be further acylated to compounds **40–44**. Amine **34** was reacted with 4-nitrophenyl chloroformate in the presence of triethylamine, and then treated with different organic amines to give compounds **45–48**. Compounds **49** and **50** were prepared conveniently from compound **34** by being treated with alkyl isothiocyanate. All the synthesized compounds are well characterized by spectroscopic methods such as ESI-MS, $^1H$ NMR, $^{13}C$ NMR, HMQC, HMBC, and COSY, and the spectrums of the novel compounds were assigned by comparing to that of vinflunine.[17]

The vinflunine derivatives (**3–50**) were tested in vitro for their anti-proliferative activity as compared with vinflunine. The cytotoxicity assay was carried out by a sulforhodamine B (SRB) method using A549 human lung carcinoma cell lines.[18] Evaluation directly at the cell level is aimed at screening the drug-like candidates from the synthesized compounds.

Data for selected compounds are presented in Tables 1–3. As shown in Table 1, the basic substituents at the C-12′ position, which may improve the solubility, have an evident effect on the activity. Trying to introduce various amino groups at the benzyl position (see compounds **3, 4, and 7**) gives rise to a marginal cytotoxic activity, and attaching a bulky group or a hydrophilic group on the terminal of the substituents results in complete loss of cytotoxicity (see compounds **5, 6, and 8**). Compound **34** exhibits a rather weak activity against A549 cell with $IC_{50}$ of 37.8μM, but introduction of alkyl or phenyl group on the amino group leads to an improved activity (see compounds **35**, **37**, and **38**), and the alkyl group seems to be superior to the phenyl group. Furthermore, the increased alkyl substituents to the amino group resulted in good activity with $IC_{50}$ of 0.22–0.64 μM (see compounds **36** and **39**), suggesting that the vinflunine derivatives substituted at C-12′ position are required to maintain good cell-permeability and suitable size for a promising activity. Those above results also indicate that the indole moiety of vinflunine remains the limited space to modify without loss of the desired activity.

Encouraged by the knowledge, the compounds bearing different protics but permeable substituents at C-12′ position were assessed by the same assay, and the biological result was summarized in Table 2. The ketones (compounds **9, 10, and 11**) and the esters (compounds **29, 30, and 31**) show weak activities compared with vinflunine, and a notable exception was compound **32** with a good $IC_{50}$ of 0.28 μM. However, the amides (compounds **42, 43, and 44**) exhibit potent activities with $IC_{50}$ of 0.20–0.42 μM except compounds **40** and **41** with $IC_{50}$ of 41.0 and 1.81μM, respectively, while the corresponding urinyl or thiourinyl compounds lead to poor activities (compounds **45, 46, 47, 48, 49, and 50**). It appeared that hydrophilic substituents at C-12′ position might improve the cytotoxicity to a limited extension.

As shown in Table 3, the series of compounds bearing hydrophobic substituents with different sizes at C-12′ position gives an interesting result. In general, the compounds bearing a aryl or heteroaryl group (see compounds **14, 15, 16, 17, 18, 19, 20, 21, 22, and 23**) have a less potent activity than vinflunine, and the substituents on the aryl ring have a slight modified effect on the activity (see compounds **15 and 21**). However, the compounds containing the small hydrophobic group such as alkyl, cyano, or azide) possess good to excellent activities (see compounds **12, 24, 25, 26, 28, and 33**) with $IC_{50}$ of 0.92–0.037 μM, and increasing the substituent size leads to decreasing activity. The most potent compound exhibits a $IC_{50}$ up to 0.037 μM, which is twofold as potent as vinflunine (see compounds **24** and **28**).




**Scheme 2.** Reagents and conditions: (e) NIS, $CH_2Cl_2$/dioxane, −15 °C, 1 h; (f) $ArB(OH)_2$, $Pd(OAc)_2$/dppf, $Cs_2CO_3$, dioxane, 60 °C,24 h; (g) Grignard's reagents/$ZnCl_2$, $Pd(OAc)_2$/$PPh_3$, THF, rt, 1–3 h; (h) i—ethynyltrimethylsilane, CuI, $Pd(PPh_3)_2Cl_2$, DIPEA, toluene, 60 °C, 18 h; ii—$Bu_4NF.3H_2O$, THF, rt, 1 h; (i) alcohols, CO, $Et_3N$, $Pd(OAc)_2$/$PPh_3$; rt, overnight; (j) $NaN_3$, CuI/L-Proline(cat.), NaOH, DMSO; (k) $H_2$, 10% Pd/C, 1 atm, rt, overnight; (l) aldehydes, $NaBH_3CN$; (m) i—TESOTf, DIPEA, $CH_2Cl_2$, rt, 2 h; ii—amines, $Pd_2(dba)_3$/$Cy_2P(2',4',6'$-tri-i-propyl-1,1′biphenyl) (cat.), toluene, 80 °C, 2 h; iii—$Bu_4NF.3H_2O$, THF; (*n*) acyl chlorides, $Et_3N$, DMPA(cat.), THF, rt, 1–4 h; (o) i—4-nitrophenyl chloroformate, $Et_3N$, DMAP (cat.), THF, rt, 1 h; ii—amines, THF, 1 h; (p) RNCS, EtOH, 70 °C, 2 h.

**Table 1**
In vitro cytotoxicity of vinflunine derivatives against A549

| Compound | R | Yield % | $IC_{50}$ (μM) |
|---|---|---|---|
| Vinflunine | H | | 0.08 |
| 3 | (4-Methoxy-phenylamino)-methyl | 62 | 3.52 |
| 4 | Morpholin-4-ylmethyl | 25 | 3.93 |
| 5 | (2-Morpholin-4-yl-ethylamino)-methyl | 52 | >100 |
| 6 | (3-Morpholin-4-yl-propylamino)-methyl | 53 | >100 |
| 7 | Butylaminomethyl | 17 | 1.74 |
| 8 | (2-Hydroxy-ethylamino)-methyl | 40 | 95.5 |
| 34 | $NH_2$ | 74 | 37.8 |
| 35 | MeNH | 25 | 6.91 |
| 36 | $Me_2N$ | 33 | 0.22 |
| 37 | Allylamino | 56 | 0.51 |
| 38 | PhNH | 11 | 1.86 |
| 39 | Pyrrolidin-1-yl | 8 | 0.64 |

**Table 2**
In vitro cytotoxicity of vinflunine derivatives against A549

| Compound | R | Yield % | $IC_{50}$ (μM) |
|---|---|---|---|
| Vinflunine | H | | 0.08 |
| 9 | Acetyl | 57, 41 | 4.72 |
| 10 | Propionyl | 47, 79 | 17.4 |
| 11 | Cyclopropanecarbonyl | 14, 41 | 4.45 |
| 29 | MeOCO | 52 | 8.73 |
| 30 | EtOCO | 76 | 1.03 |
| 31 | i-PrOCO | 64 | 3.26 |
| 32 | BnOCO | 15 | 0.28 |
| 40 | AcNH | 59 | 41.0 |
| 41 | $CF_3CONH$ | 50 | 1.81 |
| 42 | $Cl_2CHCONH$ | 68 | 0.20 |
| 43 | MsNH | 26 | 0.32 |
| 44 | MeOCONH | 41 | 0.42 |
| 45 | $NH_2CONH$ | 23 | >100 |
| 46 | MeNHCONH | 49 | 35.1 |
| 47 | $Me_2NHCONH$ | 46 | >100 |
| 48 | Morpholine-4-carboxamido | 51 | >100 |
| 49 | EtNHCSNH | 60 | 5.68 |
| 50 | Cyclopropylthioureido | 67 | 27.5 |

In conclusion, we have prepared a series of new C-12′ substituted derivatives of vinflunine, and performed biological assay of those compounds. Among them, several compounds were discovered to exhibit promising cytotoxicity against A549 cell lines in contrast to that of vinflunine. From the SAR analysis, it appeared evident that the modification on the upper aromatic moiety of vinflunine has an important effect on the cytotoxicity, and that the small hydrophobic group was required to possess the cytotoxicity against A549 cell lines. Studies aiming at further exploring the characteristic features of biological activity for some compounds, including the interaction with tubulin, are in progress.

**Table 3**
In vitro cytotoxicity of vinflunine derivatives against A549

| Compound | R | Yield % | $IC_{50}$ (μM) |
|---|---|---|---|
| Vinflunine | H | | 0.08 |
| 12 | Cyano | 47 | **0.29** |
| 14 | Ph | 73 | 2.16 |
| 15 | 4-Me-Ph | 60 | 0.56 |
| 16 | 4-Cl-Ph | 53 | 1.17 |
| 17 | 2-Cl-Ph | 20 | 1.01 |
| 18 | 2,4-di-F-Ph | 57 | 1.02 |
| 19 | 4-NC-Ph | 46 | 2.50 |
| 20 | 4-F-Ph | 80 | 2.56 |
| 21 | 2-$CF_3$-Ph | 39 | 0.29 |
| 22 | Furan-3-yl | 39 | 2.28 |
| 23 | Thiophen-3-yl | 32 | 3.00 |
| 24 | Me | 44 | **0.037** |
| 25 | Et | 31 | 0.92 |
| 26 | Cyclopropyl | 31 | 0.12 |
| 27 | *n*-Bu | 22 | 1.88 |
| 28 | Ethynyl | 68, 25 | **0.05** |
| 33 | $N_3$ | 68 | **0.16** |

## Acknowledgments

The authors gratefully acknowledge the work of Mr. LV Ai Feng for providing vinflunine and Mr. YUAN Kai Hong for his responsibility for the biological evaluation of the compounds, both from Hengrui Medicine Co., Ltd., Lianyungang, China.

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