Journal Pre-proof

An expeditious entry to rare tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidin-7(8*H*)-ones: A single-step gateway synthesis of glochidine congeners

Jeong Moo Seo, Ahmed H.E. Hassan, Yong Sup Lee

PII: S0040-4020(19)31153-6

DOI: https://doi.org/10.1016/j.tet.2019.130760

Reference: TET 130760

To appear in: *Tetrahedron*

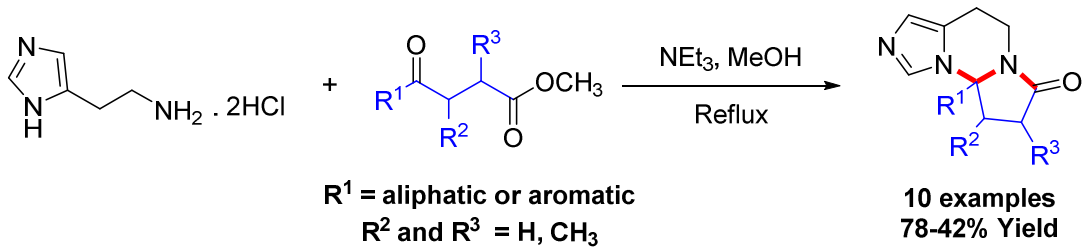
Received Date: 29 August 2019

Revised Date: 13 October 2019

Accepted Date: 1 November 2019

Please cite this article as: Seo JM, Hassan AHE, Lee YS, An expeditious entry to rare tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidin-7(8*H*)-ones: A single-step gateway synthesis of glochidine congeners, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.130760.

Graphical Abstract:



R^1 = aliphatic or aromatic
R^2 and R^3 = H, CH_3

10 examples
78-42% Yield

An expeditious entry to rare tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidin-7(8*H*)-ones: A single-step gateway synthesis of glochidine congeners

Jeong Moo Seo[a,1], Ahmed H.E. Hassan[b,c,1] and Yong Sup Lee[a,b] ∗

[a] Department of Life and Nanopharmaceutical Sciences, Kyung Hee University, Seoul 02447, Korea.

[b] Department of Pharmacy, College of Pharmacy, Kyung Hee University, Seoul 02447, Korea.

[c] Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt.

Abstract

A single-step gateway synthesis of glochidine and its congeners that possess the rare uncommon tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidine core was developed employing histamine and readily available γ-ketoesters. Key features of the developed reaction involve tandem three C-N bonds formation and concomitant annulation of two rings in one pot to access this unique and complex tricyclic structure. Exploration of the unknown bioactivity of these compounds revealed that they elicit antiproliferative activity comparable to the anticancer drug imatinib against 6 cancer cell lines.

Keywords

Imidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidines; tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidin-7(8*H*)-ones; Tandem reaction; Cyclization reactions; Natural products analogs; Anticancers

∗ Corresponding author: e-mail: kyslee@khu.ac.kr

1 Both of Ahmed H.E. Hassan and Jeong Moo Seo contributed equally to this work.

1. Introduction

Imidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidines, dipyrrolo[1,2-*a*:1',2'-*c*]pyrimidines and pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidines (Fig. 1) are unique fused azaheterotricyclic ring systems possessing ring-junction nitrogen atoms. They are rarely encountered in natural products and scarcely found in synthetic reports. As of September 2019, SciFinder sub-structure search presents glochidine as the only known example of natural products having imidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidine ring system and reveals also that there is no known synthetic congener other than the unsubstituted tricyclic skeleton [1]. Meanwhile, several natural tetraponerines T1–8 (dipyrrolo[1,2-*a*:1',2'-*c*]pyrimidines or pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidines; Fig. 1) are known and they were found to possess interesting cytotoxic, neurotoxic, and insecticidal bioactivities [2]. In literature, several reports are found for the synthesis of natural as well as non-natural tetraponerines which afforded multiple synthetic approaches to access tetraponerines [2b,2d,3]. Accordingly, it was possible to explore biological activities of natural tetraponerines and their synthetic congeners. On the opposite, the biological activity of glochidine, which is the sole known member of substituted imidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidines is completely unknown.

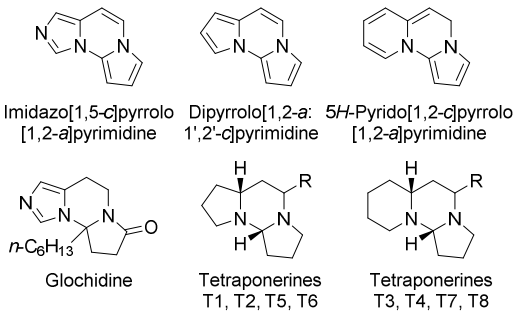


Figure 1. Ring systems and structures of glochidine and tetraponerines

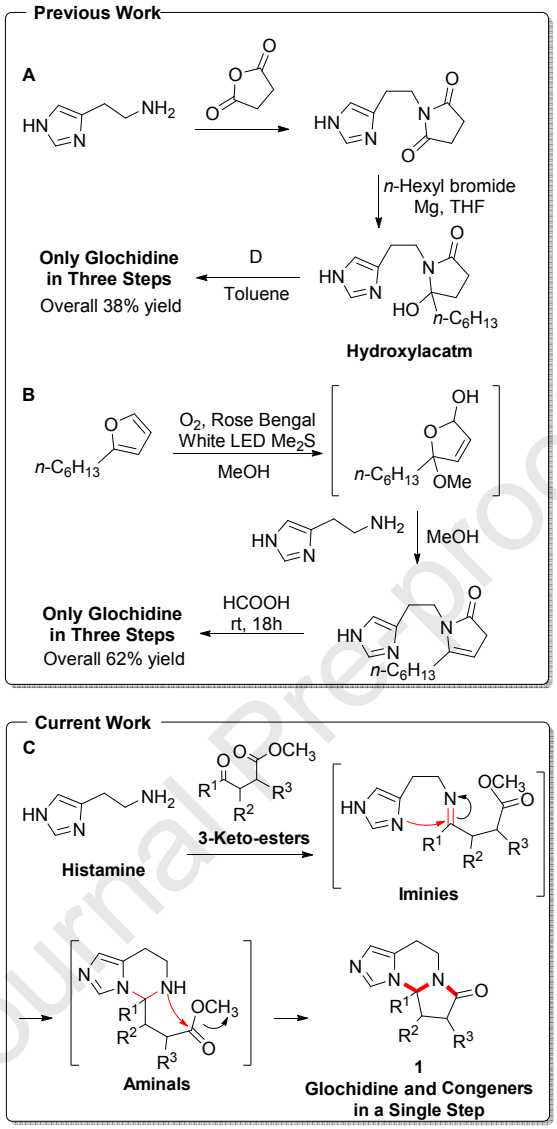
Up-to-date, two synthetic approaches to access glochidine were reported which involves *in situ* generation of *N*-acyliminium cation as a key intermediate [4]. The first approach involves: 1) succinic anhydride-histamine condensation to succinimide followed by 2) Grignard reagent

addition to form the key intermediate hydroxylactam that was employed in 3) *N*-acyliminium cation-mediated cyclization (Scheme 1A) [4a]. Such approach would necessitate the use of custom Grignard reagents if varied angular substituents are desired. The second recently reported method is a photochemical approach includes: 1) LED light-irradiation using a photosensitizer to catalyze photo-oxygenation of furan derivatives followed by 2) condensation with a primary amine to afford 2-pyrrolidinone derivative then 3) treatment with formic acid to generate *N*-acyliminium cation (Scheme 1B) [4b,4c]. Despite its usefulness, such photochemical approach requires special instrumentation [4c]. Despite the presence of these two approaches, we found no attempt was reported up-to-date to synthesize congeners other than glochidine itself or the unsubstituted tricyclic skeleton. In lieu of the complete absence of biological activity information for this unique ring system while the structurally closely related tetraponerines possess interesting bioactivities, addition of an alternative efficient route is needed to access derivatives of unique ring system. Therefore, we conducted this work aiming to develop a novel, more practical, efficient, economic and divergent route to access glochidine and its synthetic congeners in order to fill this vacant chemical space.

2. Results and discussion

Pursuing ideality, economy, and targeting development of diversity enabling reactions are important in planning a successful practical synthetic route [5]. Imines and iminium ions are powerful intermediates for construction of C-N and C-C bonds that enable rapid entry into complex structures employing using simple fragments [6]. Aiming to develop a practical synthetic method to access the almost unknown tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidin-7(8*H*)-ones in a single-step, we envisioned that reacting histamine with the readily

available diverse γ-ketoesters would afford transient imine intermediates that would undergo tandem formation of three C-N bonds with concomitant bicyclization (Scheme 1C). Quite different form the reported *N*-acyliminium cation-mediated cyclizations, we anticipated aminals might be formed *in situ* upon addition of the imidazole's nucleophilic nitrogen atom to the transient imines obtained through condensation of the carbonyl group of γ-ketoesters with the amino group of histamine. Intramolecular aminolysis of the formed aminals would afford the desired tricyclic tetrahydroimidazo[1,5-c]pyrimidines derivatives 1 as a product of one pot tandem reaction (Scheme 1C). The designed route would open a convenient gateway for synthesis of tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidin-7(8*H*)-ones employing the commercially available or readily accessible γ-ketoesters and would circumvent the limitations of the litature reported routes. In addition, the readily available diverse γ-ketoesters array would offers possibilities for divergent synthesis of compounds' library bearing substituents at all available position of the pyrrolidine ring including the angular position.

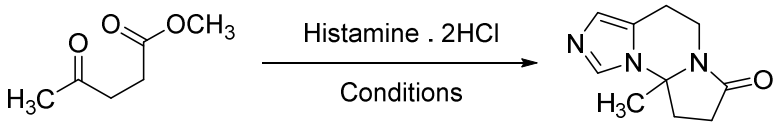


Scheme 1. Literature reported Syntheses of glochidine (A and B) and the designed new route (C).

We started to explore our envisioned synthetic method by investigating the one pot reaction of histamine with methyl levulinate (**2a**). As Table 1 shows, refluxing histamine dihydrochloride with methyl levulinate in methanol did not afford a product (Table 1, entry 1). Replacement of histamine dihydrochloride salt with the freebase afforded exclusively the desired glochidine analog (**1a**) in 41% yield (Table 1, entry 2). This outcome confirmed the crucial role of nucleophilicity of histamine for the reaction's success. Towards more economic route, the use of

histamine dihydrochloride as a starting material is desirable since it is more stable and commercially *ca.* 6 times cheaper. Therefore, sodium carbonate was added to histamine dihydrochloride and methyl levulinate (**2a**) mixture in methanol to generate *in situ* histamine freebase. Successfully, the desired glochidine analog (**1a**) was obtained but in 35% yield after refluxing for 24 h (Table 1, entry 3). Biosynthetic reactions occur in aqueous phase and, in addition, aqueous reactions are more economic, environmentally benign and, furthermore, water might affect the reactivity [7]. Therefore, the carbon–nitrogen bond-forming reaction to be developed was tested in an aqueous solution but, unfortunately, water was not a suitable reaction's solvent (Table 1, entry 4). The use of aprotic polar solvents such as acetonitrile and *N*,*N*-dimethylformamide in the presence of triethylamine (3 equivalents) afforded glochidine analog (**1a**), but in poor yields after heating at 70°C for 48 hours (Table 1, entries 5 and 6). Switching back to methanol while maintaining the use of trimethylamine (3 equivalents) afforded exclusively glochidine analog (**1a**) in satisfactory yields after refluxing for 24 hours (Table 1, entry 7). Increasing the stoichiometric ratio of trimethylamine to 5 equivalents improved the isolated yield to 77% (Table 1, entry 8). Incorporation of molecular sieves or increasing refluxing time did not improve the yield while increasing the stoichiometric ratio of trimethylamine to 10 equivalents lowered the yield (Table 1, entries 9, 10 and 11).

Table 1. Optimizing conditions using methyl levulinate (**2a**).



2a **1a**

Entry[a]	Solvent[b]	Additive (equiv.)	Time (h)	Yield (%)[c]
1	MeOH	—	24	—[d]
2[e]	MeOH	—	24	41

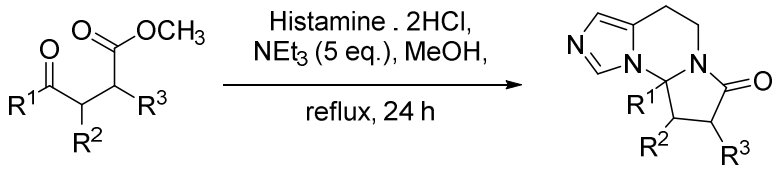
3	MeOH	Na_2CO_3 (10)	24	35
4	H_2O	Na_2CO_3 (10)	24	5
5	CH_3CN	NEt_3 (3)	48	9
6	DMF	NEt_3 (3)	48	15
7	MeOH	NEt_3 (3)	24	66
8	MeOH	NEt_3 (5)	24	77
9[f]	MeOH	NEt_3 (5)	24	75
10	MeOH	NEt_3 (5)	48	78
11	MeOH	NEt_3 (10)	48	65

[a] 1.1 Equivalents of methyl levulinate. [b] Reflux for MeOH and heating at 70°C for other solvents. [c] Isolated yields. [d] No reaction. [e] Histamine freebase. [e] In the presence of 10 wt.% 4 Å molecular sieve.

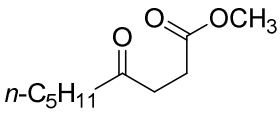
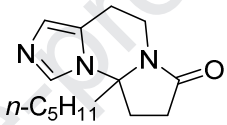
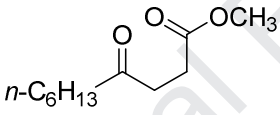
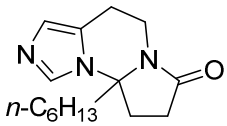
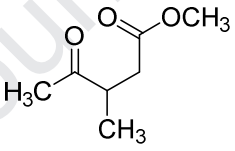
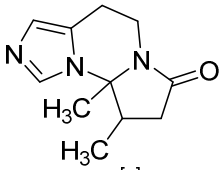
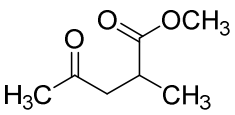
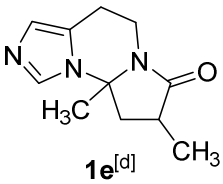
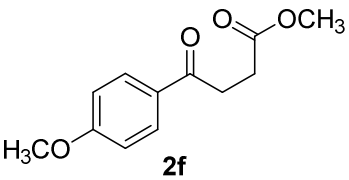
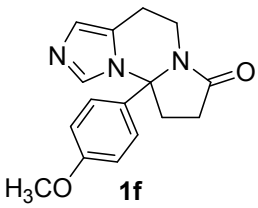
With optimum reaction conditions in hand, we proceeded to explore the scope of the developed method using diverse γ-ketoesters substrates. As shown in Table 2, the reaction of histamine dihydrochloride salt was first explored with γ-ketoesters **2b**–**e** whose R^1 groups were primary aliphatic chains. The reaction of these substrates afforded under the established optimum condition glochidine analogs **1b**–**e** possessing angularly 9a-substituted tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidine ring system in good yields (Table 2, entries 1–4). Glochidine (**1c**) itself could be obtained in 59% isolated yield which is higher than the previously reported three-steps approach A (Scheme 1A) and comparable to approach B that employed photo-oxygenation as initial step to prepare the key substrate (Scheme 1B). Interestingly, β-substituted-γ-ketoester **2d** and aslo α-substituted-γ-ketoester **2e** afforded cyclized products **1d** and **1e** in higher yields than α,β-unsubstituted-γ-ketoester substrates **2b** and **2c**. ^{1}H NMR spectra of the product **1d** showed a weak preferance to form the 1,2-*cis* over the 1,2-*trans* diastereomer (*ca* 1 : 1.23 1,2-*trans* to 1,2-*cis* ratio). The product **1e** showed more predominace for the 1,3-*trans* over the 1,3-*cis* diastereomer (*ca* 1 : 1.74 1,3-*cis* to 1,3-*trans* ratio). These low *cis/trans* ratios for products **1d**

and **1e** might indicate a limited influence of R^2 and R^3 substituents on the products' diastereoselectivity.

Table 2. Scope of the one-pot cyclization reaction.



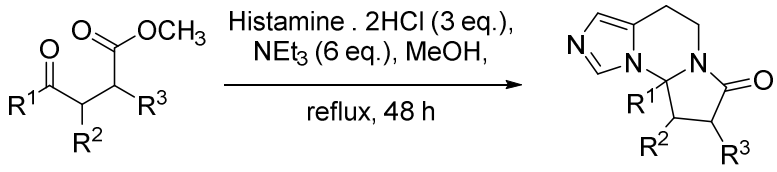
2b-f **1b-f**

Entry[a]	Substrate	Product	Yield (%)[b]
1	 **2b**	 **1b**	52
2	 **2c**	 **1c, glochidine**	59
3	 **2d**	 **1d**[c]	77
4	 **2e**	 **1e**[d]	72
5	 **2f**	 **1f**	18[e]

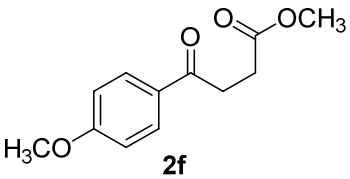
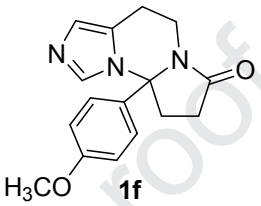
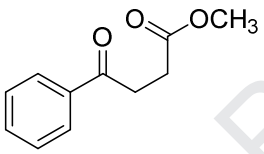
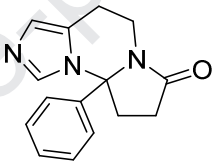
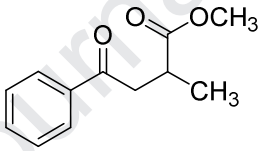
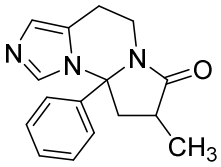
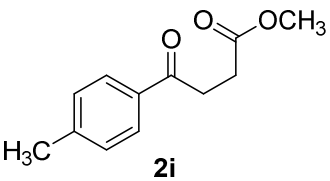
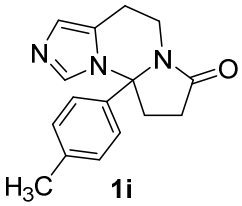
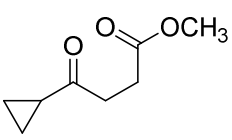
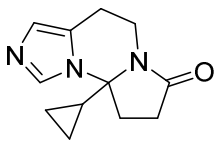
[a] 1.1 Equivalents of histamine dihydrochloride. [b] Isolated yields. [c] Ratio of 1,2-*trans*:1,2-*cis* diastereomers = 1 : 1.23 (^{1}H NMR analyses). [d] Ratio of 1,3-*cis*:1,3-*trans* diastereomers = 1 : 1.74 (^{1}H NMR analyses). [e] Reflux for 4 days.

Next, hindered substrates were used such as γ-ketoester **2f** whose R^1 was the aromatic 4-methoxyphenyl moiety. The reaction of substrate **2f** afforded the cyclized product **1f** in low 18% yield after an extended refluxing time for 4 days (Table 2, entry 5). This might indicate that the steric effect of R^1 was detrimental to the formation of the imine intermediates or to the cyclization step in γ-ketoester substrates in which R^1 set to an aromatic moiety. After several variations of reaction conditions, compound **1f** could be obtained in an improved 54% yield (brsm) by increasing the stoichiometric ratios of histamine hydrochloride to 3 equivalents and the triethylamine to 6 equivalents (Table 3, entry 1). Under the modified reaction conditions, diverse hindered γ-ketoesters substrates **2g**–**j** whose R^1 groups were aromatic or aliphatic cycles were successfully converted to the corresponding glochidine analogs **1g**–**j** in acceptable 65–42% yields (brsm). As shown in Table 3, the α,β-unsubstituted-γ-ketoester substrates **2g**, **2f** and **2i** in which the phenyl ring was unsubstituted or bearing the activating 4-methoxy or 4-methyl substituents, respectively, afforded products **1g**, **1f** and **1i** in almost similar yield (65–54%) which might suggest low impact of 4-substituents on the reaction. Again, the hindered α-substituted-γ-ketoester substrate **2h** afforded the product **1h** that possessed an almost equal ratio of 1,3-*trans and* 1,3-*cis* diastereomers (*ca* 1 : 1.09 1,3-*cis*:1,3-*trans*) which confirms the limited influence of R^2 substituents on the products' diastereoselectivity. Finally, the reaction of the hindered substrate **2j** possessing the aliphatic cyclopropyl ring as a replacement to the aromatic ring afforded also the product **2j** in similar yield. Thus, the scope of this reaction might be extendable to hindered substrates to allow access of the tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidine ring system possessing a cyclic substituent at 9a angular-position.

Table 3. One-pot reaction with hindered substrates.



2f-j **1f-j**

Entry	Substrate	Product	Yield (%)[a]
1	 **2f**	 **1f**	32 (54)
2	 **2g**	 **1g**	40 (56)
3	 **2h**	 **1h**[b]	35 (42)
4	 **2i**	 **1i**	40 (65)
5	 **2j**	 **1j**	46 (55)

[a] Isolated yields. Yields between parentheses are based on recovered γ- ketoesters. [b] Ratio of 1,3-*cis*:1,3-*trans* diastereomers = 1 : 1.09 (^{1}H NMR analyses).

With derivatives in our hands, we started to explore the unknown biological activities of compounds belonging to this ring system. As the structurally related tetraponerines were reported as antiproliferatives [2c], we investigated the cytotoxic activity of glochidine (**1c**) and its analogs **1d–j** on the growth of cancer cells relative to the marketed anticancer drug imatinib at 10 µM dose using SRB assay [8]. Glochidine was more effective than imatinib as a growth inhibitor against HL-60 cancer cells (blood cancers; Table 4). In addition, compounds **1d–j** were more effective growth inhibitors of some cancer cell lines relative to imatinib. Notably, glochidine analogs **1e** and **1j** were more effective against some blood cancers while glochidine analogs **1d**, **1h** and **1i** were more effective against some renal cancers. Furthermore, glochidine and most of tested analogs elicited significant growth inhibition against NCI-H522 cell line (lung cancer).

Table 4. Percentage inhibition of cancer cells growth by 10 µM dose of imatinib, glochidine (**1c**) and glochidine congeners (**1d**–**j**).

Cancer Disease	Cell Line	Imatinib [a]	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**	**1j**
Blood Cancers	HL60	NI[b]	15	NI	38	12	2	4	4	44
	K562	NT[c]	NI	NI	13	NI	NI	NI	NI	NI
	MOLT4	18	NI	NI	12	NI	NI	NI	NI	35
Lung Cancer	H522	NT[c]	10	8	15	13	14	1	12	1
Renal Cancers	RXF393	6	8	6	NI	1	2	12	13	3
	UO31	8	NI	10	7	2	3	6	3	NI

[a] Imatinib; an FDA approved drug as a standard. [b] NI: No inhibition of cancer cells growth. [c] NT: Not tested.

3. Conclusion

In summary, a single-step one-pot synthesis was developed to access glochidine and its congeners which possess the very uncommon tetrahydroimidazo[1,5-*c*]pyrrolo[1,2-*a*]pyrimidine ring system starting from the readily available γ-ketoesters and histamine. The key feature of the developed method is a tandem formation of three C-N bonds in a single-step. The developed method allow simple and convenient preparation of this class of compounds that circumvent limitations of other methods. The reaction scope was extened to hindered substrates to afford the desired products in acceptable yields. This methods opens a gateway to access unprecedented diverse library of glochidine analogs. Finally, the unkown biological activity of this class of compounds were explored for the first time and they were found to possess antiproliferative activity comprarable to imatinib against six cancer cell lines.

4. Experimental Section

General instrumentation and chemicals

NMR spectra were recorded on Bruker AC 400 spectrometer operating at 400 MHz for ^{1}H-NMR and 100 MHz or 125 MHz for ^{13}C-NMR. Chemical shifts (δ) are reported in ppm, downfield from internal TMS standard. High resolution mass spectra (HRMS) were recorded on Jeol accuTOF (JMS-T100TD) equipped with a DART (direct analysis in real time) ion source from ionsense, Tokyo, Japan in the positive modes. Flash column chromatography was performed using Merck Kiesegel 60 Art 9385 (230-400 mesh).

Reaction of methyl levulinate (2a) with histamine dihydrochloride using Na_2CO_3

A solution of histamine dihydrochloride (276 mg, 1.5 mmol), methyl levulinate (**2a**, 215 mg, 1.7 mmol) and sodium carbonate (1.59 g, 15.0 mmol) in MeOH (10 mL) was heated at reflux for 24

h. The mixture was evaporated in vacuo and the residue was treated with water followed by extraction with CH_2Cl_2. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography (CH_2Cl_2/CH_3OH/NH_4OH = 20:1:0.01) to afford **1a** (100 mg, 35%).

9a-methyl-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one (***1a***): White solid; mp 140.1 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, s, H-1), 6.78 (1H, s, H-3), 4.34 (1H, ddd, J = 13.7, 4.9, 3.4 Hz, H-5a), 3.14 (1H, dt, J = 13.7, 8.3 Hz, H-5b), 2.88-2.85 (2H, m, H-4), 2.67-2.43 (4H, m, H-8, H-9), 1.72 (3H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 127.4, 120.1(2C), 71.0, 29.6, 28.5, 24.9, 23.8, 15.6; HR-MS calcd for $C_{10}H_{14}N_3O$ $[M+H]^+$ 192.1131, found 192.1145.

General Procedure for reaction of γ-ketoesters (2a–e) with histamine dihydrochloride in MeOH using trimethylamine

A solution of histamine dihydrochloride (184 mg, 1.0 mmol), γ-ketoesters (**2a–e**, 1.2 mmol) and triethylamine (0.69 ml, 5.0 mmol) in MeOH (10 mL) was heated at reflux for 24 h. The mixture was evaporated in vacuo and the residue was treated with water followed by extraction with CH_2Cl_2. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography to afford the desired products **1a–e**.

9a-Pentyl-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one ***(1b)****:* orange semisolid; Yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, s, H-1), 6.79 (1H, s, H-3), 4.34 (1H, ddd, J = 13.2, 6.4, 2.4 Hz, H-5a), 3.10 (1H, ddd, J = 13.2, 10.7, 6.4 Hz, H-5b), 2.95-2.82 (2H, m, H-4), 2.66-2.40 (4H, m, H-8, H-9), 1.98-1.94 (2H, m, H-1'), 1.39-1.22 (6H, m, H-2', H-3', H-4'), 0.88 (3H, t, J = 6.5 Hz, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 132.5, 125.2, 125.0, 78.7, 41.7, 33.7, 31.6, 31.6, 30.1, 23.6, 22.6, 20.3, 14.1; HR-MS calcd for $C_{14}H_{22}N_3O$ $[M+H]^+$ 248.1757, found 248.1770.

*9a-Hexyl-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one (****1c****, Glochidine)*: White solid; mp 44.3 ºC; Yield 59%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (1H, s, H-1), 6.79 (1H, s, H-3), 4.36-4.32 (1H, m, H-5a), 3.13-3.07 (1H, m, H-5b), 2.94-2.83 (2H, m, H-4), 2.65-2.40 (4H, m, H-8, H-9), 1.98-1.94 (2H, m, H-1'), 1.36-1.21 (8H, m, H-2', H-3', H-4', H-5'), 0.87 (3H, t, J = 6.9 Hz, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 132.5, 125.3, 125.0, 78.7, 41.8, 33.7, 31.8, 31.7, 30.1, 29.1, 23.9, 22.7, 20.4, 14.2; HR-MS calcd for $C_{15}H_{24}N_3O$ $[M+H]^+$ 262.1914, found 262.1867.

9,9a-Dimethyl-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one ***(1d)****:* Yellowish white solid; mp 111.3 ºC; Yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (0.55H, s, H-1), 7.45 (0.45H, s, H-1), 6.82 (0.45H, s, H-3), 6.80 (0.55H, s, H-3), 4.41-4.35 (1H, m, H-5a), 3.08-2.97 (1H, m, H-5b), 2.94-2.80 (2H, m, H-4), 2.79-2.56 (2H, m, H-8), 2.29-2.18 (1H, m, H-9), 1.74 (1.35H, s, -CH_3), 1.60 (1.65H, s, -CH_3), 1.41 (1.65H, d, J = 6.9 Hz, -CH_3), 0.76 (1.35H, d, J = 6.9 Hz, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 171.0, 133.5, 132.0, 126.2, 125.2,

124.9, 124.7, 78.3, 77.9, 41.4, 39.7, 39.1, 38.4, 33.6, 33.5, 27.5, 22.8, 21.6, 21.3, 16.5, 14.8; HR-MS calcd for $C_{11}H_{16}N_3O$ $[M+H]^+$ 206.1288, found 206.1365.

*8,9a-Dimethyl-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one (**1e**):* White solid; mp 113.5 ºC; Yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (0.37H, s, H-1), 7.48 (0.63H, s, H-1), 6.78 (0.63H, s, H-3), 6.76 (0.37H, s, H-3), 4.36-4.28 (1H, m, H-5a), 3.25-3.08 (1H, m, H-5b), 2.96-2.77 (3H, m, H-4, H-9a), 2.65 (1H, m, H-8), 2.05 (1H, m, H-9), 1.76 (1.11H, s, -CH_3), 1.72 (1.89H, s, -CH_3), 1.31 (1.11H, d, J = 7.3 Hz, -CH_3), 1.23 (1.89H, d, J = 7.3 Hz, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 174.5, 132.6, 132.3, 125.5, 125.3, 124.9, 75.0, 73.9, 44.1, 41.9, 36.1, 35.7, 34.0, 33.4, 30.5, 27.9, 21.0, 20.1, 16.8, 15.9; HR-MS calcd for $C_{11}H_{16}N_3O$ $[M+H]^+$ 206.1288, found 206.1381.

General Procedure for reaction of hindered γ-ketoesters (2f–j) with histamine dihydrochloride in MeOH using trimethylamine:

A solution of histamine dihydrochloride (806 mg, 4.4 mmol), γ-ketoesters (**2f–j**, 1.5 mmol), and triethylamine (1.25 ml, 9.0 mmol) in MeOH (10 mL) was heated at reflux for 48 h. The mixture was evaporated in vacuo and the residue was treated with water followed by extraction with CH_2Cl_2. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography (CH_2Cl_2/CH_3OH/NH_4OH = 20/1/0.01) to afford the desired products **1f–j**.

9a-(4-Methoxyphenyl)-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one ***(1f)****:* White solid; mp 115.1 ºC; Yield 54% (brsm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, s, H-1), 6.91 (1H, s, H-3), 6.85 (2H, d, J = 8.8 Hz, Ar-2', Ar-6'), 6.76 (2H, d, J = 8.8 Hz, Ar-3', Ar-5'), 4.09 (1H, ddd, J = 13.2, 7.3, 2.4 Hz, H-5a), 3.79 (3H, s, -OCH_3), 3.04-2.96 (1H, m, H-5b), 2.93-2.77 (4H, m, H-4, H-8), 2.73-2.59 (2H, m, H-9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 160.0, 133.7, 126.3(2C), 126.1, 125.7, 114.9, 114.3(2C), 80.3, 55.4, 35.0, 33.8, 29.8, 19.4; HR-MS calcd for $C_{16}H_{18}N_3O_2$ $[M+H]^+$ 284.1394, found 284.1459.

9a-Phenyl-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one ***(1g)****:* White solid; mp 179.6 ºC; Yield 56% (brsm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (1H, s, H-1), 7.37-7.34 (3H, m, Ar-2', Ar-4', Ar-6'), 6.92 (1H, s, H-3), 6.88-6.85 (2H, m, H-3', H-5'), 4.10 (1H, ddd, 13.2, 7.3, 2.5 Hz, H-5a), 3.05-2.94 (1H, m, H-5b), 2.92-2.79 (4H, m, H-4, H-8), 2.72-2.64 (2H, m, H-9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 137.0, 128.9, 124.38(2C), 124.35, 121.5, 121.0(2C), 120.1, 75.7, 30.2, 29.2, 25.0, 14.6; HR-MS calcd for $C_{15}H_{16}N_3O$ $[M+H]^+$ 254.1288, found 254.1278.

8-Methyl-9a-phenyl-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one ***(1h)****:* White solid; mp 138.0 ºC; Yield 42% (brsm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (0.48H, s, H-1), 7.69 (0.52H, s, H-1), 7.36-7.33 (3H, m, H-2', H-4', H-6'), 6.91 (1H, s, H-3), 6.90-6.85 (2H, m, H-3', H-5'), 4.09 (1H, m, H-5a), 3.18 (0.48H, dd, J = 13.7, 8.8 Hz, H-5b), 3.12 (0.52H, dd, J = 13.7, 8.8 Hz, H-5b), 3.06-2.94 (2H, m, H-4), 2.88-2.59 (2H, m, H-8, H-9a), 2.51 (0.52H, dd, J = 13.7, 7.3 Hz, H-9b), 2.51 (0.48H, dd, J = 13.7, 9.8 Hz, H-9b), 1.41 (1.44H, d, J = 7.3 Hz, -CH_3), 1.28 (1.52H, d, J = 7.3 Hz, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 175.8, 141.9, 141.7,

134.1, 133.6, 129.4(2C), 129.3(3C), 129.3, 126.5, 126.4, 126.3, 125.54, 125.49(2C), 124.9(2C), 79.8, 78.4, 44.3, 43.5, 36.3, 35.9, 34.5, 34.4, 19.7, 19.3, 16.9, 16.3; HR-MS calcd for $C_{16}H_{18}N_3O$ $[M+H]^+$ 268.1444, found 268.1467.

9a-p-Tolyl-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one ***(1i)****:* White solid; mp 145.0 ºC; Yield 65% (brsm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, s, H-1), 7.14 (2H, d, J = 8.3 Hz, Ar-2', Ar-6'), 6.91 (1H, s, H-3), 6.74 (2H, d, J = 8.3 Hz, Ar-3', Ar-5'), 4.09 (1H, ddd, J = 13.2, 7.4, 1.5 Hz, H-5a), 3.00 (1H, m, H-5b), 2.92-2.77 (2H, m, H-4), 2.72-2.59 (4H, m, H-8, H-9), 2.34 (3H, s, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 139.1, 138.8, 133.6, 129.7(2C), 126.3, 125.7, 124.8(2C), 80.4, 35.0, 33.9, 29.8, 21.0, 19.3; HR-MS calcd for $C_{16}H_{18}N_3O$ $[M+H]^+$ 268.1444, found 268.1493.

9a-Cyclopropyl-4,5,9,9a-tetrahydroimidazo[1,5-c]pyrrolo[1,2-a]pyrimidin-7(8H)-one ***(1j)****:* White solid; mp 138.3 ºC; Yield 55% (brsm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, s, H-1), 6.78 (1H, s, H-3), 4.32 (1H, ddd, J = 13.7, 6.8, 2.0 Hz, H-5a), 3.43 (1H, m, H-5b), 2.98-2.84 (2H, m, H-4), 2.64-2.35 (4H, m, H-8, H-9), 1.37 (1H, m, H-1'), 0.69-0.57`(2H, m, H-2a', H-3a'), 0.36 (1H, m, H-2a'), 0.10 (1H, m, H-2b'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 132.7, 125.7, 125.4, 78.7, 33.7, 31.2, 29.9, 20.9, 20.1, 2.7, 1.2; HR-MS calcd for $C_{12}H_{16}N_3O$ $[M+H]^+$ 218.1288, found 218.1317.

Acknowledgments

We acknowledge NCI for in vitro evaluation of the anticancer activity of tested compounds.

References

[1] a) Johns, S.; Lamberton, J. *Chem. Commun.*, **1966**, 312, https://doi.org/10.1039/c1966000312b; b) Johns, S., Lamberton, J. *Aust. J. Chem.*, **1967**, *20*, 555, https://doi.org/10.1071/CH9670555.

[2] a) Braekman, J.C.; Daloze, D.; Pasteeis, J.; Van Hecke, P.; Declercq, J.P.; Sinnwell, V.; Francke, W. *Z. Naturforsch., C, J. Biosci.* **1987**, *42*, 627, https://doi.org/10.1515/znc-1987-0520; b) Merlin, P.; Braekman, J.C.; Daloze, D.; Pasteels, J.M. *J. Chem. Ecol.* **1988**, *14*, 517, https://doi.org/10.1007/BF01013903; c) Bosque, I.; Gonzalez-Gomez, J.C.; Loza, M.I.; Brea, J. *J. Org. Chem.* **2014**, *79*, 3982, https://doi.org/10.1021/jo500446f; d) Kem, W.R.; Wildeboer, K.; LeFrancois, S.; Marszalec, W.; Braekman, J.C. *Cell. Mol. Neurobiol.* **2004**, *24*, 535, https://doi.org/10.1023/B:CEMN.0000023628.65936.a7; e) Rouchaud, A.; Braekman, J.C. *Eur. J. Org. Chem.* **2009**, 2666, https://doi.org/10.1002/ejoc.200900064; f) Blum, M.S. *J. Toxicol. Pharmacol.* **1992**, *11*, 115, https://doi.org/10.3109/15569549209033107.

[3] a) Plehiers, M.; Heilporn, S.; Ekelmans, D.; Leclercq, S.; Sangermano, M.; Braekman, J.C.; Daloze, D. *Can. J. Chem.* **2000**, *78*, 1030, https://doi.org/10.1139/v00-096; b) Devijver, C.; Macours, P.; Braekman, J.C.; Daloze, D.; Pasteels, J.M. *Tetrahedron* **1995**, *51*, 10913, https://doi.org/10.1016/0040-4020(95)00667-W; c) Strassnig, I.; Körber, K.; Hünger, U.; Kunz, H. *Synthesis* **2015**, *47*, 2299, https://doi.org/10.1055/s-0034-1380215; d) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584, https://doi.org/10.1021/ja001688i; e) Kim, J.T.; Butt, J.; Gevorgyan, V. *J. Org. Chem.* **2004**, *69*, 5638, https://doi.org/10.1021/jo049259g; f) Bosque, I.; González-Gómez, J.C.; Guijarro, A.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 10340, https://doi.org/10.1021/jo302045y; g) Orejarena Pacheco, J.C.; Lipp, A.; Nauth, A.M.; Acke, F.;

Dietz, J.P.; Opatz, T. *Chem. Eur. J.* **2016**, *22*, 5409, https://doi.org/10.1002/chem.201504845; h) Davies, S.G.; Fletcher, A.M.; Houlsby, I.T.; Roberts, P.M.; Thomson, J.E. *J. Org. Chem.* **2017**, *82*, 6689, https://doi.org/10.1021/acs.joc.7b00837; i) Kim, J.T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697, https://doi.org/10.1021/ol027129t; j) Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594, https://doi.org/10.1021/jo991034w; k) Charette, A.B.; Mathieu, S.; Martel, J. *Org. Lett.* **2005**, *7*, 5401, https://doi.org/10.1021/ol052069n; l) Yue, C.; Gauthier, I.; Royer, J.; Husson, H.P. *J. Org. Chem.* **1996**, *61*, 4949, https://doi.org/10.1021/jo960398a; m) Bisai, A.; Singh, V.K. *Tetrahedron Lett.* **2007**, *48*, 1907, https://doi.org/10.1016/j.tetlet.2007.01.082; n) Macours, P.; Braekman, J.C.; Daloze, D. *Tetrahedron* **1995**, *51*, 1415, https://doi.org/10.1016/0040-4020(94)01030-4; o) Barluenga, J.; Tomas, M.; Kouznetsov, V.; Rubio, E. *J. Org. Chem.* **1994**, *59*, 3699, https://doi.org/10.1021/jo00092a035; p) Jones, T.H. *Tetrahedron Lett.* **1990**, *31*, 1535, https://doi.org/10.1016/0040-4039(90)80009-B; q) Jones, T.H. *Tetrahedron Lett.* **1990**, *31*, 4543, https://doi.org/10.1016/S0040-4039(00)97670-6; r) Zhu, J.; Quirion, J.C.; Husson, H.P. *Tetrahedron lett.* **1989**, *30*, 5137, https://doi.org/10.1016/S0040-4039(01)93468-9; s) Merlin, P.; Braekman, J.C.; Daloze, D. *Tetrahedron lett.* **1988**, *29*, 1691, https://doi.org/10.1016/S0040-4039(00)82019-5.

[4] a) Lee, Y.S.; Kim, S.H.; Jung, S.H.; Lee, S.J.; Park, H. *Heterocycles* **1994**, *37*, 303, https://doi.org/10.3987/COM-93-S2; b) Ioannou, G.I.; Kalaitzakis, D.; Vassilikogiannakis, G. *Eur. J. Org. Chem.* **2016**, 3304, https://doi.org/10.1002/ejoc.201600524; c) Ioannou, G.I.; Montagnon, T.; Kalaitzakis, D.; Pergantis, S.A.; Vassilikogiannakis, G. *ChemPhotoChem* **2018**, *2*, 860, https://doi.org/10.1002/cptc.201800068.

[5] a) Gaich, T.; Baran, P.S. *J. Org. Chem.* **2010**, *75*, 4657, https://doi.org/10.1021/jo1006812; b) Newhouse, T.; Baran, P.S.; Hoffmann, R.W. *Chem. Soc.*

Rev. **2009**, *38*, 3010, https://doi.org/10.1039/B821200G; c) Galloway, W.R.; Isidro-Llobet, A.; Spring, D.R. *Nat. Commun.* **2010**, *1*, 80, https://doi.org/10.1038/ncomms1081.

[6] a) Wu, P.; Nielsen, T.E.; *Chem. Rev.* **2017**, *117*, 7811, https://doi.org/10.1021/acs.chemrev.6b00806; b) Lee, Y.S.; Alam M.M.; Keri, R.S.; *Chem. Asian J.* **2013**, *8*, 2906, https://doi.org/10.1002/asia.201300814; c) Martin, S.F. *Pure Appl. Chem.* **2009**, *81*, 195, https://doi.org/10.1351/PAC-CON-08-07-03; d) Jo, H.; Hassan, A.H.E.; Jung, S.Y.; Lee, J.K.; Cho, Y.S.; Min, S.J. *Org. Lett.* **2018**, *20*, 1175, https://doi.org/10.1021/acs.orglett.8b00098.

[7] a) Li, C.J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68, https://doi.org/10.1039/B507207G; b) Li, C.J. *Chem. Rev.* **2005**, *105*, 3095, https://doi.org/10.1021/cr030009u; c) Kobayashi, S. *Pure Appl. Chem.* **2013**, *85*, 1089, https://doi.org/10.1351/PAC-CON-12-10-11; d) Dicks, A.P. *Green Chem. Lett. Rev.* **2009**, *2*, 9, https://doi.org/10.1080/17518250902820182.

[8] a) Hassan, A.H.E.; Choi, E.; Yoon, Y.M.; Lee, K.W.; Yoo, S.Y.; Cho, M.C.; Yang, J.S.; Kim, H.I.; Hong, J.Y.; Shin, J.S.; Chung, K.S.; Lee, J.H.; Lee, K.T.; Lee, Y.S. *Eur. J. Med. Chem.* **2019**, *161*, 559, https://doi.org/10.1016/j.ejmech.2018.10.062; b) Elkamhawy, A.; Paik, S.; Hassan, A.H.E.; Lee, Y.S.; Roh, E.J. *Bioorg. Chem.* **2017**, *75*, 393, https://doi.org/10.1016/j.bioorg.2017.10.009. c) Orellana, E.A.; Kasinski, A.L. *Bio Protoc.* **2016**, *6*, https://doi.org/10.21769/BioProtoc.1984.

Highlights:

- Single-step one-pot gateway synthesis of glochidine and its congeners.
- Tandem formation of three C-N bonds and annulation of two rings in a single-step
- Employs the readily available γ-ketoesters and histamine as starting materials.
- For the first time, the unknown biological activity was explored for this rare class of compounds.

Declaration of Interest Statement

The authors declare no competing financial interest