Convenient synthesis of new 3-(4-chloro-phenyl)-3-hydroxy-2,2-dimethyl-propionic acid methyl ester derivatives of expected Anticancer Activity

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Abstract

A series of 25 compounds were synthesized based on structure modification of the model methyl 3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoateas potent HDACIs. Saponification and hydrazinolysis of the model ester afforded the corresponding acid and hydrazide, respectively.The model ester was transformed into corresponding trichloroacetimidate or acetate by the reaction with trichloroacetonitrile and acetic anhydride, respectively. *N*-alkyl-3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropan-amides and methyl 2-[(3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoyl)amino] alkanoates were obtained by the reaction ofcorresponding acid or hydrazide with amines andamino acid esters*via*DCC and azidecoupling methods. Methyl 3-aryl-3-(4-chlorophenyl)-2,2-dimethylpropanoates were obtainedin good yields and short reaction timefrom the corresponding trichloroacetimidate or acetate by the reaction with *C*-active nucleophiles in the presence of TMSOTf(0.1eq %)*via* C-C bond formation.

Keywords

carboxamides, Amino acids, DCC coupling, azide coupling, C-nucleophiles trichloroacetimidateand acetate coupling methods.

Introduction

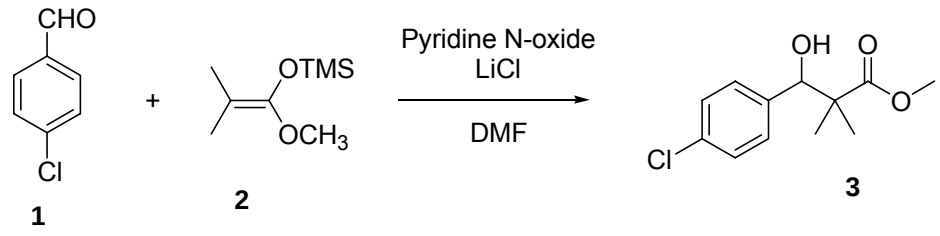
Malignancy is one of the significant factors behind loss of life in the developed countries.[1-3] Chemotherapy with cytotoxic medications is one of the primary approaches to dealing with established malignancy.[4,5] The primary drawbacks of malignancy chemotherapy is the severe poisonous results such as emesis and myelosuppression, as well as the insufficient selectivity of the drugs against cyst tumor cellular material in comparison with normal cellular material.[1, 6] Hence, search for newer anticancer drugs is never-ending job. Key interactions at protein–protein interfaces constitute important targets for small molecule inhibition because of their specific arrangements and biological importance[7].

Recently, we reported the synthesis of 3-(4-(2-chloroacetamido)phenyl)-3-hydroxy-2,2-dimethylpropanoate and 3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoate as potent HDACIs.[8] We also showed the antiproliferative activity for these compounds against Hela cells(IC_{50}; 11-0.69μM)was perfect in comparison with the standard drug Doxorubicin (IC_{50}; 2.29 μM).[8]Our compounds are peptide in nature that mimic peptide inhibitors and non-peptide inhibitors together with being more suitable for pharmaceutical manipulations and development and this work consider as integration of our research group effort in discovering and modification of new anticancer agents.[8,9]

Results and Discussions

2.1. Chemistry

Herein, we report the synthesis of a series of compounds based on structure modification of the model methyl 3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoate (**3**)as promising HDACIs.The model compound **3**was prepared by the reaction of 4-chlorobenzaldehyde **1** and trimethylsilyl ketene acetal **2** in the presence of pyridine-*N*-oxide and LiCl in DMF at room temperature under nitrogen atmosphere to afford **3** in 69% yield, Scheme 1.



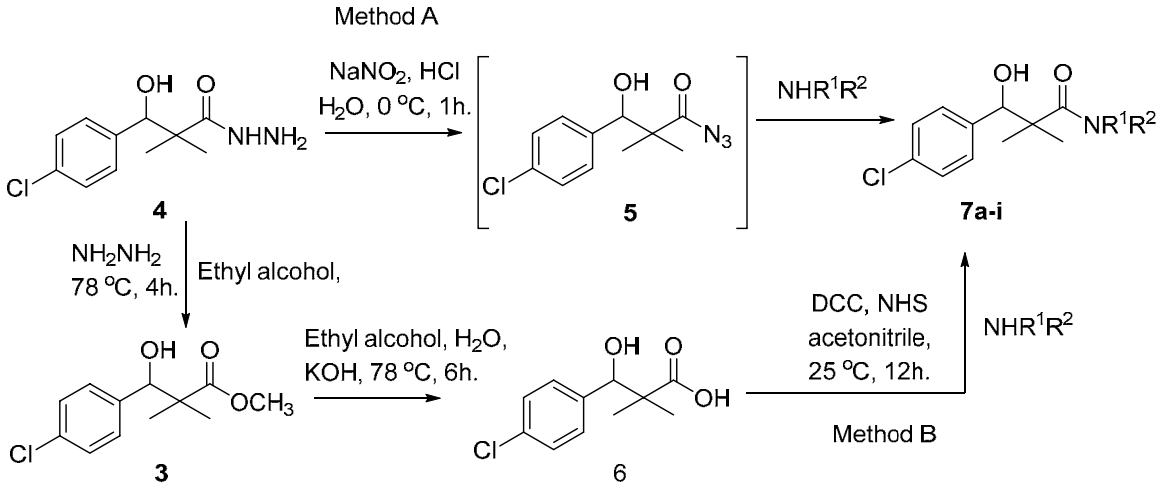
Scheme 1 Synthesis of methyl 3-hydroxy-2,2-dimethyl-3-(4-chlorophenyl)propanoate (**3**).

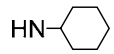
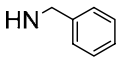
DCC and azide coupling methods are well-recognized in peptide synthesis centered on carboxylic acid-carbonyl group activation to be attacked by nucleophiles as amines or even weaker nucleophiles as amino acids to form a peptide bond.[10-14]Structure modification of ester **3** could be achieved by attachment of alkane amine or amino acids to the carbonyl group of **3***via*DCC or azide coupling and the formation of peptide bond. Thus, the reaction of methyl 3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoate (**3**) with hydrazine hydrate in ethanol under reflux condition for 4h afforded the corresponding hydrazide **4**. The model ester **3**was hydrolyzed using KOH solution in 50% alcohol water mixture at 78^{o}C for 6h. to afford the corresponding carboxylic acid **6**,Scheme 2.

Hydrazide **4**was reacted with $NaNO_2$ and HCl in water at 0 ^{o}C for 1h. to afford the corresponding azide**5** and were extracted with ethyl acetate. The *insitu* generated azide **5** solution was successively added to primary amines; propyl amine, butyl amine, allyl amine, tetradecyl amine, cyclohexyl amine and benzyl amine or secondary amines; piperidine, morpholine and *N*-methylpiperazine at 0 ^{o}C for 12h. to afford the corresponding *N*-alkyl-3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanamides **7a-i**following the azide coupling method,Scheme 2.

The reaction of carboxylic acid derivatives **6**with primary aminesand secondary amines in the presence of *N*,*N*'-dicyclohexylcarbodiimide and *N*-hydroxylsuccinimide (NHS) in acetonitrile at room temperature for 12h. afforded our product **7a-i**as an equivocal method of preparation following HOSu-DCC coupling method, Scheme 2. Comparing both coupling methods leading to **7a-i** we found out that azide coupling was more efficient respect to % of yield and simple reaction workup.

The structure assignment of the prepared *N*-alkyl-3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanamides **7a-i** is based on ^{1}H and ^{13}C NMR spectral and physicochemical analysis. The ^{1}H NMR spectrum of 3-(4-chlorophenyl)-3-hydroxy-2,2-dimethyl-*N*-propylpropanamide **7a** shows signals at δ 5.72, 4.68,4.07 and4.05-4.02ppm corresponding to NH, OCH, OH and CH_2groups respectively. The ^{13}C NMR spectrum of **7a**shows signals at 178.9, 80.9, 60.8 ppm (C=O), (OCH) and (C) groups respectively.

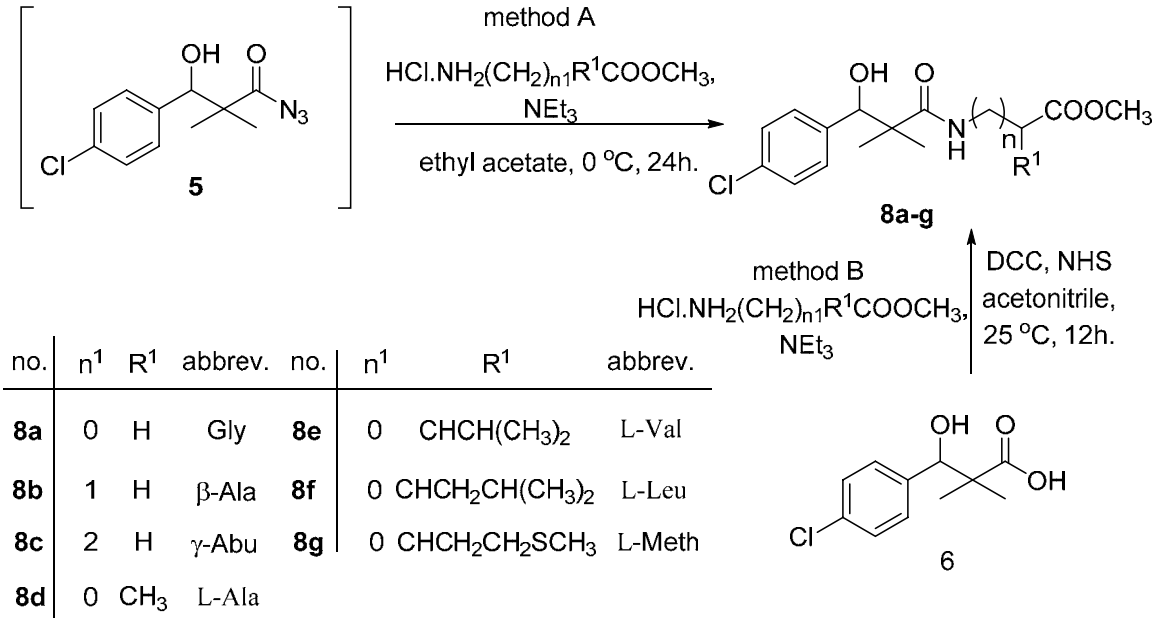


no.	NR^1R^2	abbrev.	no.	NR^1R^2	abbrev.	no.	NR^1R^2	abbrev.
7a	$NHCH_2CH_2CH_3$	propyl amine	7d	$NH(CH_2)_{13}CH_3$	tetradecyl amine	7g		piperidine
7b	$NH(CH_2)_3CH_3$	butyl amine	7e		cyclohexyl amine	7h		morpholine
7c	$NHCH_2CH=CH_2$	allyl amine	7f		benzyl amine	7i		N-Me-piperazine

Scheme 2 Synthesis of *N*-alkyl-3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanamides **7a-i**.

Similarly,methyl 2-[(3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoyl)-amino] alkanoates**8a-g** were prepared by the reaction of the *insitu* generated azide **5** solution in ethyl acetate with amino acid ester hydrochlorides; glycine, β-alanine, γ-amino butyric acid, L-alanine, L-valine, L leucine and L-metheonine in the presence of triethyl amine to give **8a-g** in excellent yields, Scheme 3. An equivocal synthesis of **8a-g** was achieved by the reaction of acid **6** with amino acid ester hydrochlorides in the presence of *N*,*N*'-dicyclohexylcarbodiimide and *N*-hydroxylsuccinimide (NHS) in acetonitrile at room temperature for 12h. afforded our product**8a-g**, Scheme 3.

The structure assignment of the prepared methyl 2-[(3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoyl)amino] alkanoates**8a-g** is based on ^1H and ^{13}C NMR spectral and physicochemical analysis. The ^1H NMR spectrum of methyl 2-[(3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoyl)amino] acetate **8a** shows signals at δ 6.67, 5.22, 4.63, 3.92 and 3.68 ppmcorresponding to NH, OH, CH, NCH_2 and OCH_3 groups respectively. The ^{13}CNMR spectrum of **8a**shows signals at177.6, 170.1, 79.7, 51.5, 45.2, 41.4 (C=O), (C=O), (OCH), (OCH_3), (C) and (NCH_2) groups,respectively.

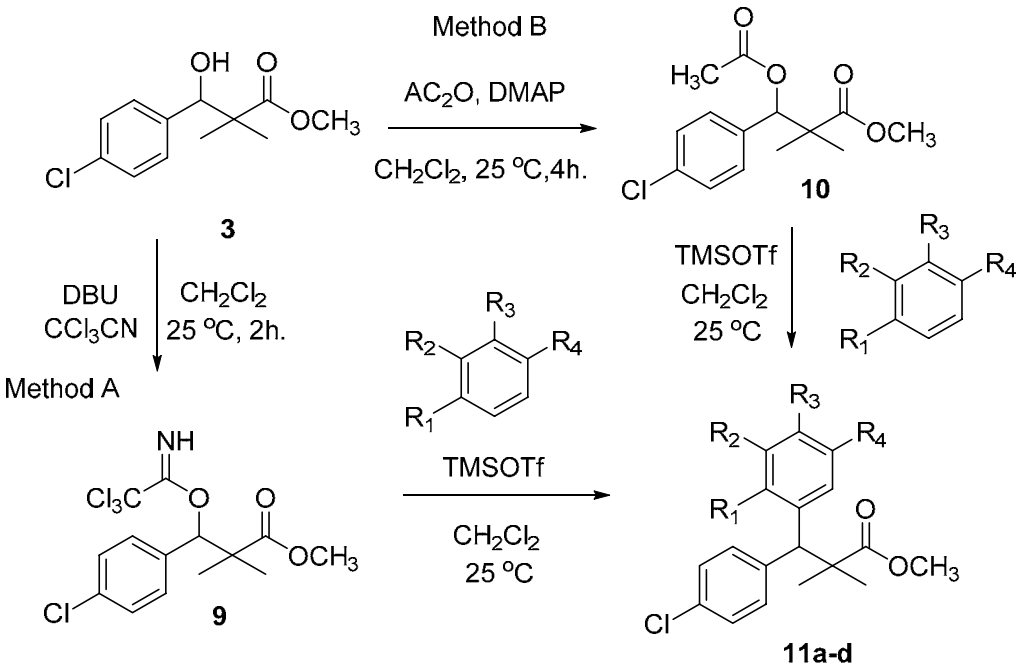


no.	n^1	R^1	abbrev.	no.	n^1	R^1	abbrev.
8a	0	H	Gly	**8e**	0	$CHCH(CH_3)_2$	L-Val
8b	1	H	β-Ala	**8f**	0	$CHCH_2CH(CH_3)_2$	L-Leu
8c	2	H	γ-Abu	**8g**	0	$CHCH_2CH_2SCH_3$	L-Meth
8d	0	CH_3	L-Ala				

Scheme 3 Synthesis of methyl 2-[(3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoyl)amino] alkanoates **8a-g**.

Trichloroacetimidateand acetate C-C coupling proved to be excellent methods for structure modifications of alcohols.[14-18]These methods are related to transform hydroxyl group substrates into the appropriate trichloroacetimidate or acetate excellentleaving groups by the reaction with trichloroacetonitrile or acetic anhydride, respectively. The successive addition of *C*-nucleophiles mainly activated arenes, allyltrimethylsilaneand trimethylsiloxy alkenesto the active trichloroacetimidate or acetate intermediates in the presence of Lewis acid gave the desired products.[14-18]We find it interesting to apply the trichloroacetimidate and acetate coupling methods in the structure modification of methyl 3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoate **(3**)*via* C-C coupling with methoxybenzene derivatives. Thus, the reaction of the ester **3** with trichloroacetonitrilein the presence of DBU in dichloromethane at 25°C for 2h. afforded the trichloroacetimidate **9**.Similarly, the reaction of ester **3**with acetic anhydride in the presence of DMAP (*N*,*N*-dimethyl aminopyridine)in dichloromethane at 25°C for 4hafforded methyl 3-acetoxy-3-(4-chlorophenyl)-2,2-dimethylpropanoate (**10**).The reaction of trichloroacetimidates **9** or acetate **10**with arene C-nucleophiles; anisole, 1,4-dimethoxybenzene, 1,2-dimethoxybenzene and 1,2,3-trimethoxybenzenein the presence of catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf)(0.1 eq %) at room temperature gave

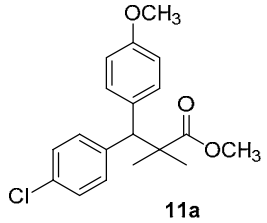
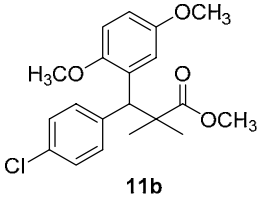
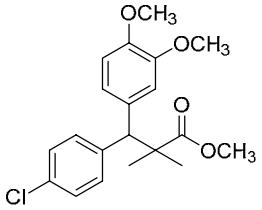
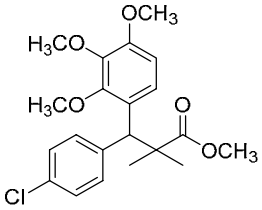
readily themethyl 3-aryl-3-(4-chlorophenyl)-2,2-dimethylpropanoate **11a-d** in excellent yields, Scheme 4.



no.	R^1	R^2	R^3	R^4	abbrev. C-nucleophile
11a	H	H	OCH_3	H	anisole
11b	OCH_3	H	H	OCH_3	1,4-dimethoxy benzene
11c	H	OCH_3	OCH_3	H	1,2-dimethoxy benzene
11d	OCH_3	OCH_3	OCH_3	H	1,2,3-triimethoxy benzene

Scheme 4 Synthesis of methyl 3-aryl-3-(4-chlorophenyl)-2,2-dimethylpropanoate**11a-d**.

Comparing the efficiency of both C-C coupling methods according toreaction time and % of yield, results showed that, although, all compounds were prepared in good yields, there was a slight improvement in the % of yield and in the reaction time (monitored by TLC) using trichloroacetimidate method. Table **1**.

No.	Structure	Yields (isolated)	No.	Structure	Yields (isolated)
11a	 **11a**	84%[a], 77%[b] 2 hrs.	**11b**	 **11b**	81%[a], 76%[b] 2 hrs.
11c	 **11c**	78%[a], 65%[b] 2 hrs.	**11d**	 **11d**	88%[a], 74%[b] 2 hrs.

[a]: yield respect to trichloroacetimidate coupling method.

[b]: yield respect to acetate coupling method.

Table 1. Comparing the efficiency of trichloroacetimidate and acetate coupling methods

The structure assignment of the prepared methyl 3-aryl-3-(4-chlorophenyl)-2,2-dimethylpropanoate**11a-d**is based on ^{1}H and ^{13}C NMR spectral and physicochemical analysis. The ^{1}H NMR spectrum of methyl 3-(4-chlorophenyl)-3-(4-methoxyphenyl)-2,2-dimethylpropanoate **(10a)** shows signals at δ 4.23, 3.68, 3.44 ppm corresponding toCH, OCH_3 and OCH_3 groups, respectively. The ^{13}CNMR spectrumof **10a**shows signals atδ176.2, 56.1, 53.2, 48.5, 47.2ppm corresponding to(C=O), (OCH_3), (OCH_3), (CH) and (C) groups,respectively.

5. **Acknowledgements**

We would like to thank the Science & Technology Development Fund in Egypt STDF Project ID: 22909 for funding this research proposal.

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