

Review Article

Design, Synthesis of New Amino Acid Derivatives and Evaluate DNA Binding Activity, Anticancer and Antimicrobial Activity

Ahmed A. Elhenawy^{1,2}¹Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt²Chemistry Department, Faculty of Science and Art, Al-Baha University, Al-Baha, Saudi Arabia

Email address:

elhenawy_sci@hotmail.com

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Abstract: The present review covers the recent synthetic amino acid derivatives with chemical transformations to peptide derivatives. The amino acids were used as starting keys for synthesis peptides and pseudopeptides derived from pyridine, coumarine, imadizole, pyrazole phthalyl, quinoline and sulfonamide rings. these biomolecules have diverse biological and pharmacological actions, as antimicrobial, anti-cancer targeting human carbonic anhydrase (CA) and DNA binding activities.

Keywords: Amino Acid, DNA Binding, Anticancer, Antimicrobial

1. Introduction

Amino acid derivatives are an important group of peptidomimetics with a variety of applications in medicinal chemistry. These derivatives possess several biological activities such as anti-microbial anti-tumour effect and DNA binding activity. Moreover, most natural peptides are widely prevalence and composed of α -amino acids, and limited bio-stability, and low bio-availability. To overcome this problems, the biologically active pseudo-peptides have been developed, which have highly specificity and non-toxicity pharmaceuticals. The present work show synthesis small molecules containing amino acids with antimicrobial, anticancer activities and DNA binding activity.

2. Antimicrobial Activity

2.1. Six Membered Ring Derivatives

2.1.1. Synthesis of Purinylamino Acid Derivatives

During recent years, the purinyl amino acid derivatives were identified as attractive new classes of drug candidates against *Mycobacterium tuberculosis* [1-3]. The formation of the amide linkage between the amino acids and

2-(1,3-dimethyl-2-oxo-1,2,3,6-tetrahydro-7H-purin-7-yl)acetic acid (**1**) were accomplished by procedures developed for peptide synthesis (Figure 1). The water-soluble N-ethyl-N'-dimethylaminopropylcarbodiimide (EDC) was chosen as carboxylic acid activator in combination with N-hydroxybenzotriazole (HOBT). The side products of the reaction were water soluble and easy to remove [4]. The deprotection of the methyl ester group of compounds (**2a-d** and **4**), were achieved with an equivalent of LiOH in methanol/water medium [5], to give the target compounds **3a-d** and **5** (Figure 1).

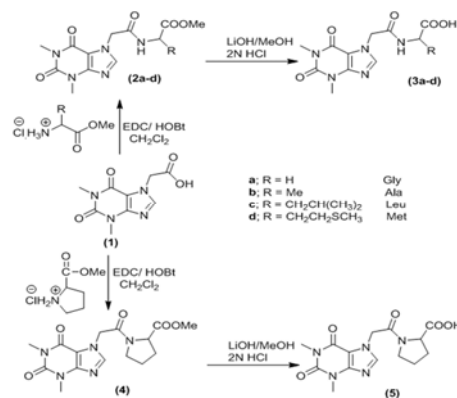


Figure 1. Synthesis of purinyl amino acid derivatives 2-6.

The substances were screened for their anti-bacterial activity against *M. tuberculosis*, and shown excellent activity, between 10 and 25 times higher than the classical anti-TB drug.

2.1.2. Synthesis of Pyridinonylamino Acid Derivatives

Bacterial resistance to available antibiotics is a serious health problem. So, design and synthesis of novel multidrug-resistant bacterial strains proliferate is necessary. Many conjugates of amino acid or peptide residues with bioactive heterocyclic are exert their action with low toxicity, through binding to the membrane receptors [6-8].

Conjugated amino acid with antibiotics (**11-13**) were synthesized [9], by coupling ciprofloxacin(**8**), pipemidic acid (**9**) and nor-floxacin(**10**), with Cbz-N-(aminoacyl)benzotriazoles (**7**) in THF/TEA medium (Figure 2).

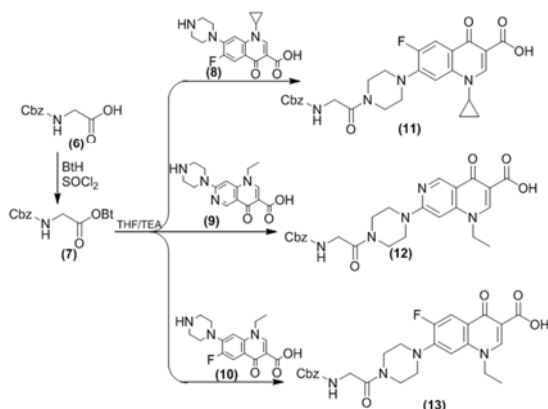


Figure 2. Synthesis of fused pyridinyl amino acid derivatives 7-13.

2.1.3. Synthesis of Coumarinyl Amino Acid Derivatives

i. Synthesis of 7-Hydroxycoumarinyl Amino Acid Derivatives

The 2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)-aceto-hydrazide (**14**) was reacted with sodium nitrite in the presence of hydrochloric acid to give acid azide derivative (**15**, Figure 3) [10]. The azide (**15**) was reacted with amino acid ester such as (glycine, leucine and phenylalanine) ethyl ester hydrochloride to give ethyl (4-methyl-2-oxo-2H-benzopyran-7-yloxy-methylcarbonylamino) alkylacetate (**16a-c**, Figure 3), the Compounds (**16a-c**) showed promising antimicrobial activity [11, 12].

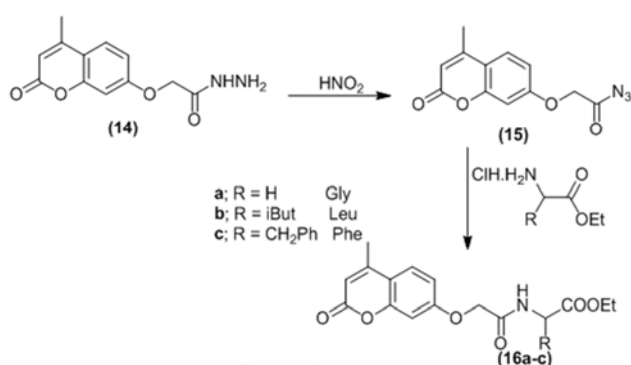


Figure 3. Synthesis of 7-hydroxycoumarinyl amino acid derivatives 14-16.

ii. Synthesis of 7-Aminocoumarinyl Amino Acid Derivatives

Recently, coumarinyl amino acid have been shown important fluorimetry applications, which successfully use as a fluorogenic marker of microbial wall [13].

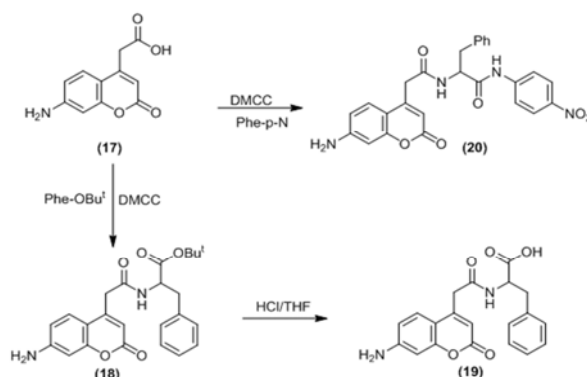


Figure 4. Synthesis of 7-Aminocoumarinyl Amino Acid Derivatives 17-20.

The 7-amino-4-coumarinyl acetyl phenylalaninyl-*tert*-butyl ester (**18**) was prepared, by condensation 7-amino-4-coumarinyl acetic acid (**17**) with phenylalanine-*tert*-butyl ester (Phe-OBu^t) using dimethylaminopropylcarbodiimide (DMPC) as coupling agent in presence of (HOBT) with 65% yield [13], the compound (**18**) was acidolysis to affording 7-amino-4-coumarinylacetylphenylalanine (**19**, Figure 4).

The 7-amino-4-coumarinylacetylphenylalaninyl-*p*-nitroanilide (**20**) was prepared by coupling (**17**) with phenylalaninyl-*p*-nitroanilide using the same coupling method for preparation of compound (**18**). Both coupling took place without any previous protection of NH₂ group due to low nucleophilicity [14, 15].

The esterification of acid (**17**) increase the nucleophilicity of amino group and precluding acylation in solution (Figure 5). Thus, for preparing the ethyl (glycylphenylalaninylamido)-4-coumarinyl acetate (**23**) by heating 7-amino-4-coumarinyl ethyl acetate (**21**) with Boc-Phe for 3 hours to give ethyl 2-(7-(2-((Boc)amino)-3-phenylpropanamido)-2-oxo-2H-chromen-4-yl) acetate (**22**). After removal Boc group from (**22**), the free intermediate reacted with glytric anhydride to give compound (**23**) in good yield [13].

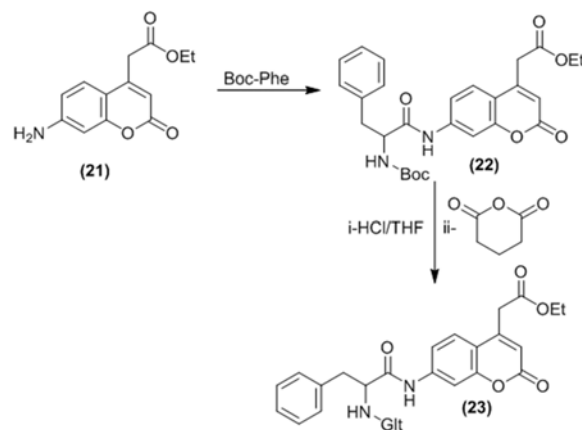


Figure 5. Synthesis of blocked 7-Aminocoumarinyl amino acid derivatives 21-23.

2.2. Five Membered Ring

2.2.1. Synthesis of Imidazolyl Amino Acid Derivatives

N-Acylbenzotriazoles are efficient reagents for N-, O-, S- and C-acylation when prepared from N-protected α -amino acids have been utilized for the synthesis of di-, tripeptides [14, 16]. The Cbz-N-(aminoacyl)benzotriazoles were reacted with metronidazole (2-(2-methyl-1H-imidazol-1-yl)ethan-1-ol; **24**) in the presence of a catalytic amount of dimethyl-aminopyridine (DMAP) under microwave irradiations at 60°C and 50 W for 1 hour to afford a novel amino acid-metronidazole (**25a-c**, Figure 6) in a good yields 72–85% [8]. The compounds (**25a-c**) were used as antibiotic with percent inhibiting growth nearly (45–67%).

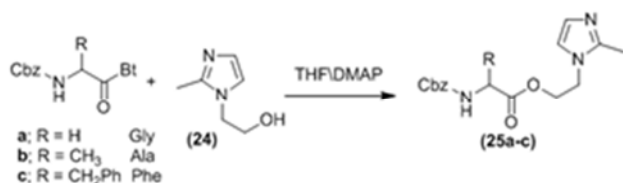


Figure 6. Synthesis of imidazolyl amino acid derivatives (**25**).

2.2.2. Synthesis of Thiazolyl Amino Acid Derivatives

i. Synthesis of 5-Phenylthiazolyl Amino Acid Derivatives

Thiazol is a versatile bioactive heterocycle with biocidal S-CN moiety having their wide presence in many synthetic drugs as antimicrobial agent [17].

2-Amino-4-phenylthiazole (**28**) were prepared, by fused acetophenone (**26**) with thiourea (**27**) in presence of iodine at 80°C for 2 hours [17–21]. The Boc amino acids phenylthiazol (**29a,b**) were prepared by coupling different Boc - amino acids with compound (**28**) using IBCF/ HOBt and NMM as coupling agents. The Boc groups of compounds (**29a,b**) were removed with 4N HCl in dioxane to affording (**30a,b**), which used for antimicrobial screening with percent inhibiting growth >80%, (Figure 7).

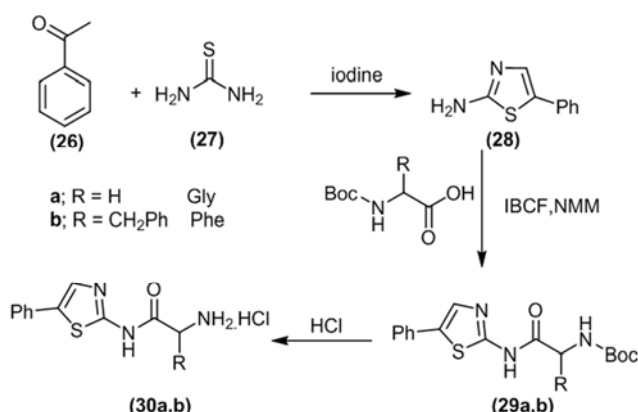


Figure 7. Synthesis of 5-Phenylthiazolyl Amino Acid Derivatives (**28-30**).

ii. Synthesis of Thiazoloneamino Acid Derivatives

To obtain compounds (**33**) and (**35a,b**, Figure 8), a symmetrical anhydride (Boc)₂O (di-tert-butylpyrocarbonate) was used to protect the amine function of thiosemicarbazide.

The intermediate compound (**32**) was obtained with a yield of 55%. The cyclization step was accomplished through the reaction of the Boc-thiosemicarbazide and chloroacetic acid (**32**) to obtain (**33**) with a yield of 78%. The Boc-protecting group of 4-thiazolidone was removed using the classical cleavage conditions TFA/CH₂Cl₂ (1:1) to give unprotected 4-thiazolidone (**34**) with 98% yield.

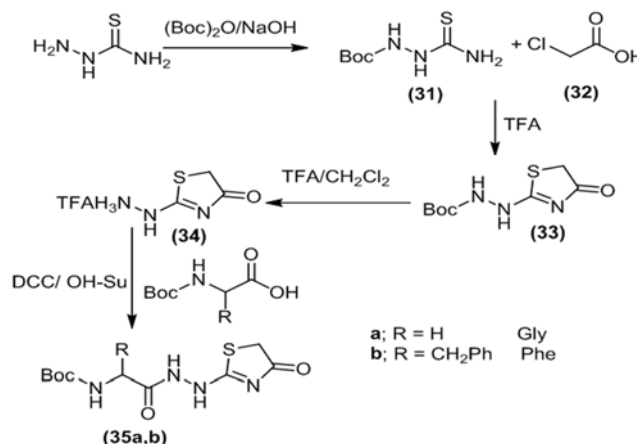


Figure 8. Synthesis of thiazoloneamino acid derivatives (**32-35**).

The last stage involves condensation of the α -amino acids (tert-butyloxycarbonylphenylalanine, or a tert-butyloxycarbonylglycine) with the hydrazinyl moiety of the 4-thiazol-4(5H)-one (**34**) using dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide (OH-Su) as carbonyl activating agents [22–24]. The product (**35**) of this method resulted in average yields of 68–80%.

2.2.3. Synthesis of Methylthiosemicarb-Azide Amino Acid Derivatives

In order to obtain the aminoacyl-2-methyl-3-thiosemicabazides (**37a-c**), by condensation reaction between 2-methyl-3-thiosemicabazide (**36**) with Boc amino acids in the presence of efficient carbonyl activation reagent BOP (benzotriazolyl-oxy-tris-(dimethyl-amino)phosphoniumhexafluorophosphate) [24, 25]. Compounds (**37a-c**) were obtained with a yield of 32–46% (Figure 9).

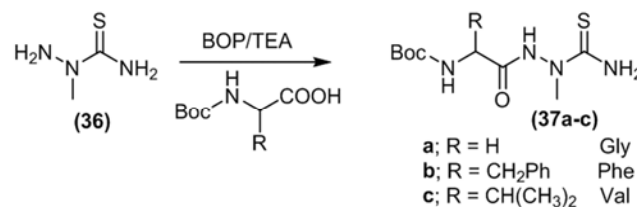


Figure 9. Synthesis of methylthiosemicarb-azide amino acid derivatives (**37**).

2.2.4. Synthesis of Quinolinyamino Acid Derivatives

7-hydroxy-4-methyl-quinoliny[1,5-c]-mercapto-triazole (**38**) reacted with formaldehyde solution and amino acid in ethanol yielded 7-hydroxy-4-methyl-8-(N-methylaminoacid)-quinoliny[1,5-c]-2-mercaptotriazoles (**39a-c**), which were interacted with o-phenylenediamine in pyridine to yielding 7-hydroxy-4-methyl-8-(aminobenzimidazolyl)-quinoliny[1,5-

-c]-2-mercaptotriazole derivatives (**40a-c**, Figure 10). Anti-microbial screening showed, benzimidazolylquinolinyl-mercaptotriazole containing alaninyl moiety (**40b**) is the best antifungal agent than the other compounds [26].

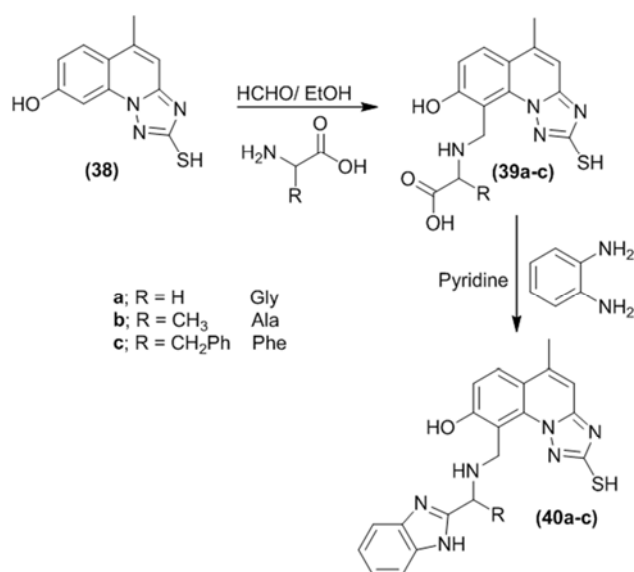


Figure 10. Synthesis of Quinolinylamino amino acid derivatives (39-40).

2.2.5. Synthesis of Pyrazolyl Amino Acid Derivatives

The N-terminal protected amino acids namely L-valine, L-threonine, L-phenylalanine were using (Boc) as protecting groups [27]. The coupling of Boc-amino acids took place using (DCC) method [28], and (HOBT) as a catalyst to afford 1-Phenyl-2,3-dimethyl-4-[3-(5-aminoacid-4-cyano)-1H-pyrazolyl-amino]-pyrazolin-5-one derivatives (**41a-c**), which reacted with compound **(42)** to give compounds **(43a-c)**. The deprotection of **(43a-c)** took place to furnish Phenyl-2,3-dimethyl-4-[-3-5-amino acid-4-carbomethoxy]-1H-pyrazolyl-amino]-pyrazolin-5-one derivatives (**44a-c**), Figure 11, [29].

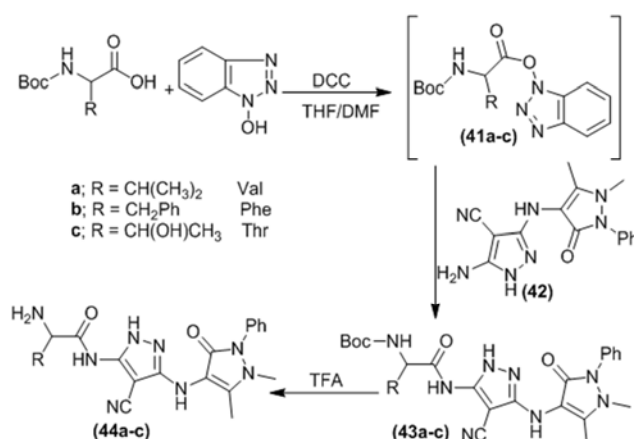


Figure 11. Synthesis of Pyrazolyl amino acid derivatives.

2.3. Aromatic Amino Acid Derivatives

2.3.1. Synthesis of Phthalyl Amino Acid Derivatives

The alanine was reduced to amino alcohol (**45**) using the

NaBH_4 system [30], and phthaloylated with phthalic anhydride to give N-phthalimido-protected amino alcohol (**46**) in high yield. The later alcohol was mesylated with methanesulfonyl chloride (MSCl) and Et_3N in CH_2Cl_2 .

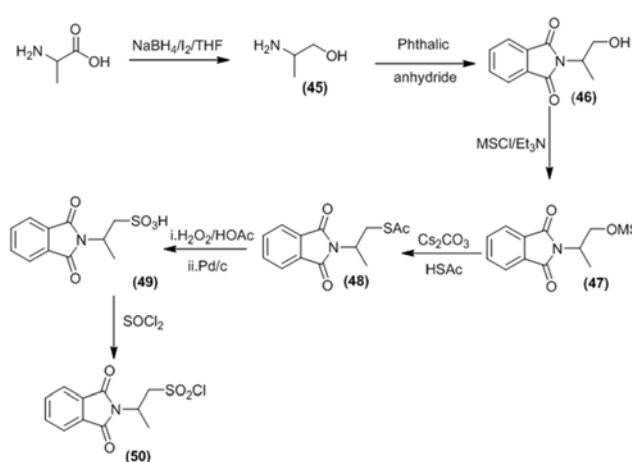


Figure 12. Synthesis of amino acid derivatives (46-60).

Then, mesylate (**47**) was added to the mixture of thioacetic acid and Caesium carbonate in DMF yielded phthalimido thioacetate derivative (**48**), which oxidized to the corresponding sulfonic acid (**49**) using aqueous hydrogen peroxide and acetic acid, after 24 hours, the excess peroxide was destroyed by adding 10% Pd/C. The resulting crude sulfonic acid (**49**) was finally refluxed in excess thionyl chloride to give sulfonylchloride (**50**), (Scheme 12), in high yield [31].

2.3.2. Synthesis of Thiophenyl Amino Acid Derivatives

The alanine as reduced to amino alcohol (**45**) using the NaBH_4 system [30], and phthaloylated with phthalic anhydride to give N-phthalimido-protected amino alcohol (**46**) in high yield.

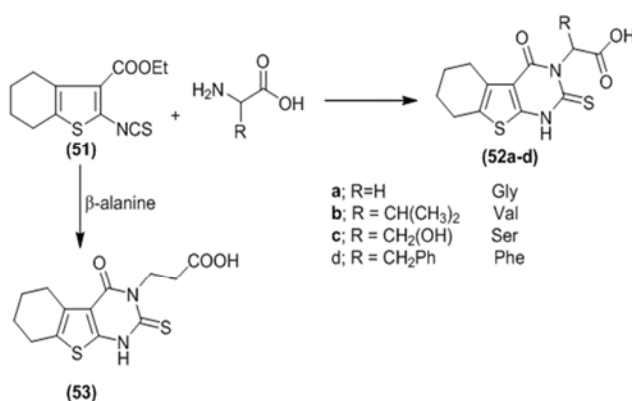


Figure 13. Synthesis of thiophenylamino acid derivatives (52-53).

The later alcohol was mesylated with methanesulfonyl chloride (MSCl) and Et_3N in CH_2Cl_2 . Then, mesylate (**47**) was added to the mixture of thioacetic acid and Caesium carbonate in DMF yielded phthalimidothioacetate derivative (**48**), which oxidized to the corresponding sulfonic acid (**49**) using aqueous hydrogen peroxide and acetic acid, after 24

hours, the excess peroxide was destroyed by adding 10% Pd/C. The resulting crude sulfonic acid (**49**) was finally refluxed in excess thionyl chloride to give sulfonylchloride(**50**), (Figure 12), in high yield [31].

2.4. Synthesis of Sulfonamide Amino Acid Derivatives

2.4.1. Synthesis of Sulfaglutmylamino Acid Derivatives

The sulfonyl chloride (**50**) was coupled with C-protected glutamic acid to give (**54**), its reaction displays a high level of chemoselectivity between methyl esters and the phthalimido protecting group (Figure 14). Hydrazinolysis of the protected phthalimido compound (**54**) produced the amine intermediate (**55**), which converted by alkaline hydrolysis into (**56**), [31].

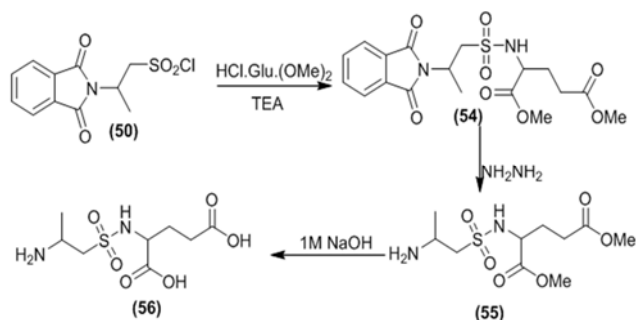


Figure 14. Synthesis of Sulfaglutmylamino amino acid derivatives (54-56).

2.4.2. Synthesis of Benzenesulphonyl Morpholine Amino Acid Derivatives

The N-(4-aminobenzenesulphonyl)morpholine (**57**), was coupled with phthalyl-(Pht-) or tosyl-(Tos-)amino acids in anhydrous THF containing POCl₃ at -15°C, to obtain N-[4-(Pht-or-Tos-aminoacyl)-aminobenzenesulphonyl]-morpholine (**58a,b** and **59a,b**) (Figure 15). The phosphorus oxychloride method led to high yields and the products were isolated in a high degree of analytical purity prior to crystallization [34]. The N-(4-Amino-5-mercapto-4H-[1,2,4]-triazol-3-yl)-p-toluene sulfonamide derivatives (**60a,b**) were formed by fusion of thiocarbohydrazide and tosylamino acids at 170-179°C [35].

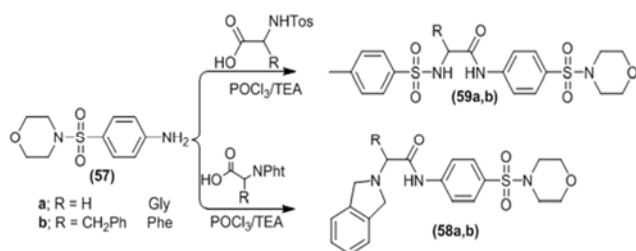


Figure 15. Synthesis of Benzenesulphonyl amino acid derivatives (58-59).

The coupling compound (**57**) with chloroacetyl chloride gave N-[4-(chloroacetyl)aminobenzenesulphonyl]-morpholine (**61**), which was reacted with (**60a,b**), in acetone or DMF, to afford N-[4-(alkoxy-acetyl)aminobenzenesulphonyl]-morpholines (**62a,b**, Figure 16) [34].

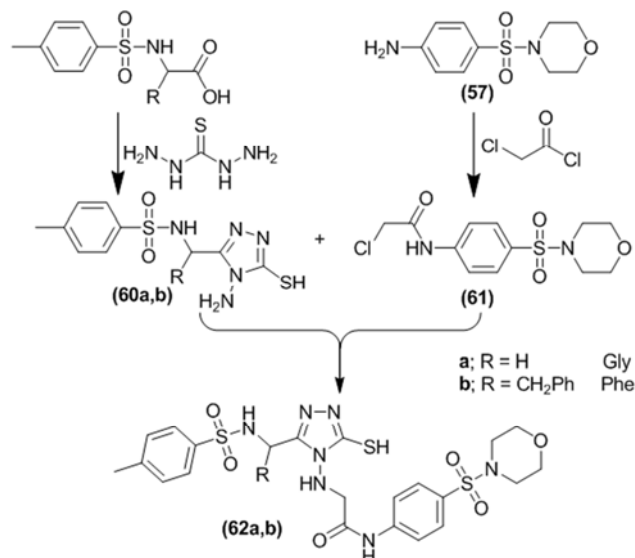


Figure 16. Synthesis of aminobenzenesulphonyl-morpholineamino acid derivatives (57-62).

2.4.3. Synthesis of Sulfadiazinyl Amino Acid Derivatives

Coupling of sulfadiazine (**63**) with Cbz-protected amino acids in THF in the presence of N-methylmorpholine (NMM) and isobutyl chloroformate (IBCF) at room temperature to formation of amino acid sulfadiazine derivatives (**64a-c**, Figure 17), [9].

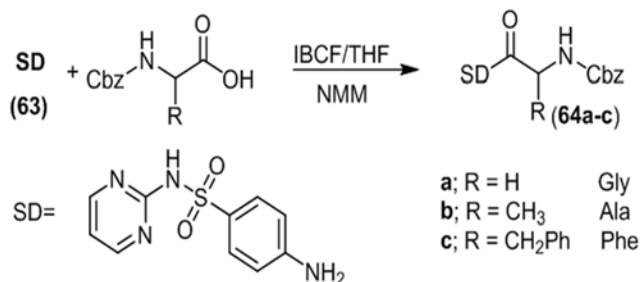


Figure 17. Synthesis of Sulfadiazinyl Cbz-protected amino acid derivatives (64).

The synthetic route for designed the pseudopeptide derivatives (**67a-c -69**), were summarized in (Figure 18). The reaction of acid chloride with amino acids as nucleophiles might seem hard to conduct, due to amphoteric nature of amino acids in solution, a dipolar ion (⁺NH₃CH(R)COO⁻) is formed by a proton transformation from the carboxyl group to the nitrogen atom of amino group. The amphoteric natures of amino acids decrease the electron density on nitrogen atom. Thus, the zwitterions for amino acids possess lower nucleophilicity than amines and are difficult to react with acid chloride, (Figure 18). In order to facilitate the reaction, adding an organic base such as Et₃N to improve the reaction rate. The formations of sulfadiazinyl-acetylamino acids (**67a-c-69**) were achieved by the reaction of acid chloride (**66**) with α- or β-amino acids and imino acid in tetrahydrofuran (THF/ TEA) media [35].

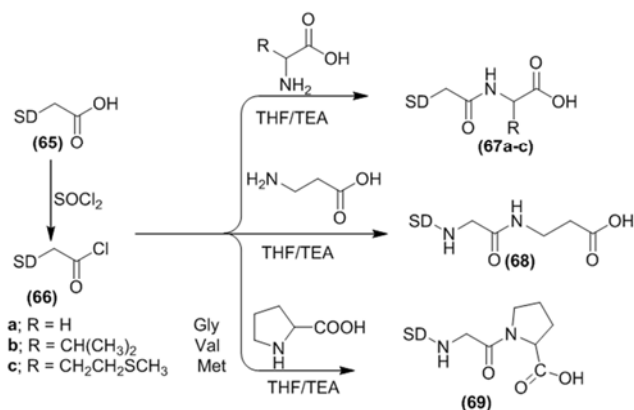


Figure 18. Synthesis of Sulfadiazinyl amino acid derivatives (67-69).

The reaction of acid chloride with amino acids as nucleophiles might seem hard to conduct, due to amphoteric nature of amino acids in solution, a dipolar ion ($^+\text{NH}_3\text{CH(R)COO}^-$) is formed by a proton transformation from the carboxyl group to the nitrogen atom of amino group. The amphoteric natures of amino acids decrease the electron density on nitrogen atom. Thus, the zwitterions for amino acids possess lower nucleophilicity than amines and are difficult to react with acid chloride, (Figure 18). In order to facilitate the reaction, adding an organic base such as Et₃N to improve the reaction rate. The formations of sulfadiazinylacetamino acids (67a-c-69) were achieved by the reaction of acid chloride (66) with α- or β-amino acids and imino acid in tetrahydrofuran (THF/ TEA) media [35].

2.4.4. Synthesis of Benzylbenzamides Sulfonamide Amino Acid Derivatives

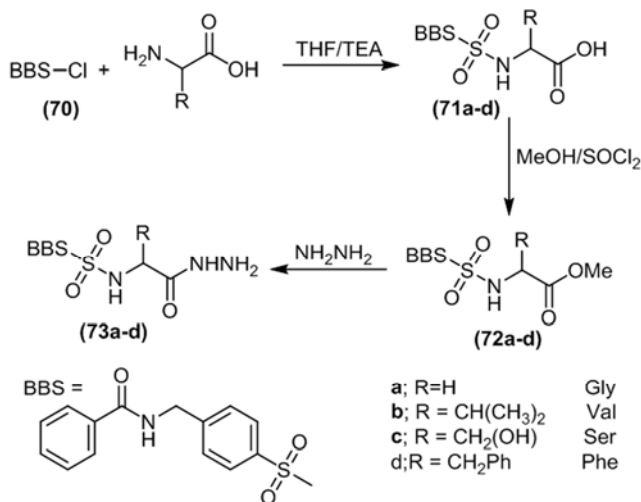


Figure 19. Synthesis of benzylbenzamides sulfonamide amino acid derivatives (71-73).

The reaction of some benzylbenzamide with chlorosulfonic acid was studied. The orientation of sulfonation is governed by the electron releasing effect of the methylene group. The other aromatic center is deactivated towards electrophilic substitution by the adjacent electron withdrawing carbonyl group [37].

2.5. Synthesis Thiadiazolylamino Acid Derivatives

The 1,3,4-thiadiazole compounds was performed in several steps (Figure 20).

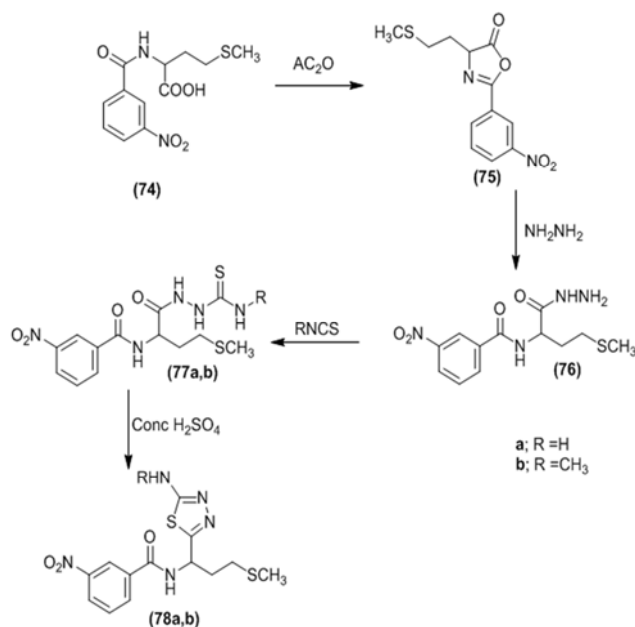


Figure 20. Synthesis of Thiadiazolylamino amino acid derivatives (75-78).

In the first step, 2-(3-nitrophenyl)-4-(2-methyl-thioethyl)-2,5-oxazolinone (75) was obtained by cyclization of N-(3-nitrobenzoyl)-D,L-methionine (74) in the presence of acetic anhydride, which reacted with 98% hydrazine hydrate solution in a dioxane medium, gave the hydrazide of N-(3-nitrobenzoyl)-D,L-methionine (76), which reacted with different isothiocyanates, the new 1,4-disubstituted thiosemicarbazides (77a,b) were obtained. In the last step new 1,3,4-thiadiazole (78a,b) were obtained by intramolecular cyclization of the thiosemicarbazides (77a,b) in acid media [38].

3. Anticancer Activity

3.1. Synthesis Amino Acids Derivatives Antiapoptotic Inhibitor

The protected amino acid with rhodanine (82a-d) were synthesized from heating amino acids with carbon disulfide (CS₂) in presence of NaOH in 80–92 % yield [50], (Figure 21). The 2-bromo-5-formylpyridine (79) coupled with commercially available boronic acid (80). Catalytic Pd(OAc)₂ was utilized for the coupling reaction [51], the biaryl (81) were obtained in 77% yield, (Figure 21). Knoevenagel condensation of the 2-aryl-3-formylpyridine (81) with the corresponding rhodanines (82a-d) in acetic acid to furnish the desired pyridylrhodanine amino acids (83a-d), in 65–98 % yield [52].

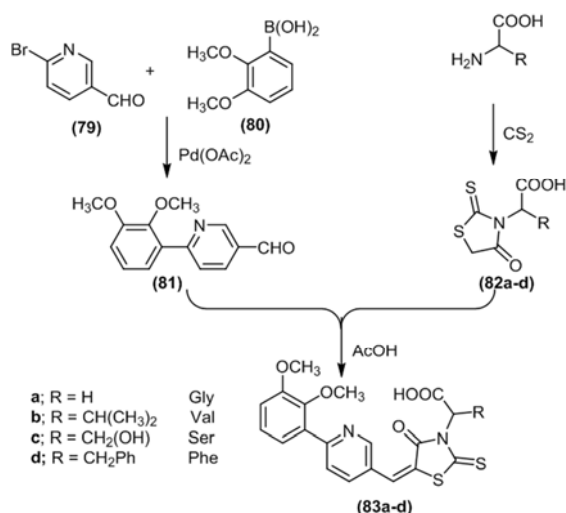


Figure 21. Synthesis of rhodaninylamino acid derivatives (81-83).

The protected amino acid with rhodanine (82a-d) were synthesized from heating amino acids with carbon disulfide (CS_2) in presence of NaOH in 80–92 % yield [50], (Figure 21). The 2-bromo-5-formylpyridine (79) coupled with commercially available boronic acid (80). Catalytic $\text{Pd}(\text{OAc})_2$ was utilized for the coupling reaction [51], the biaryl (81) were obtained in 77% yield, (Figure 21). Knoevenagel condensation of the 2-aryl-3-formylpyridine (81) with the corresponding rhodanines (82a-d) in acetic acid to furnish the desired pyridylrhodanine amino acids (83a-d), in 65–98% yield [52].

3.2. Synthesis Amino Acids Derivatives as Amino- Peptidase N Inhibitors

Amino-peptidase N (APN) is a zinc-dependent metallo-proteinase, that cleaves neutral or basic amino acids from the N-terminus of oligopeptides. Scientist found that, outside the hematopoietic system, APN was widely expressed on various kinds of cells. APN has been a target for anti-tumor agents due to its important role in tumor cells invasion and tumor angiogenesis [53-55]. Therefore, the development of APN inhibitors may be of clinical significance for the discovery of anti-cancer agents.

3.3. Synthesis Chloramphenicol Amino Acids Derivatives

Chloramphenicolamine (84) was protected by $(\text{Boc})_2\text{O}$, then the selectively oxidized was applied at the terminal hydroxyl group to give the N-Boc-protected acid (85, Figure 22), [56]. The acid can be coupled with different amino acids (α -amino acids and ω -amino acids) using the classical EDCI/HOBT method, to obtain (86a,b and 89a,b), respectively, (Figure 22), [57]. Finally (Figure 22), the esters were hydrolyzed to carboxylic acid by NaOH in methanol to yield (87a,b and 90a,b). Compounds (88a,b) containing hydroxamic groups were obtained from reacting (86a,b) with NH_2OK [57]. Dipeptide derivatives (92a,b) were prepared by coupling N-Boc-protected acid (85) with dipeptide methyl esters using the EDCI as coupling agent in presence of HOBT,

to obtain dipeptide methyl ester derivatives (91a,b), (Figure 23), the later compounds were hydrolyzed using NaOH to give the desired compounds [57].

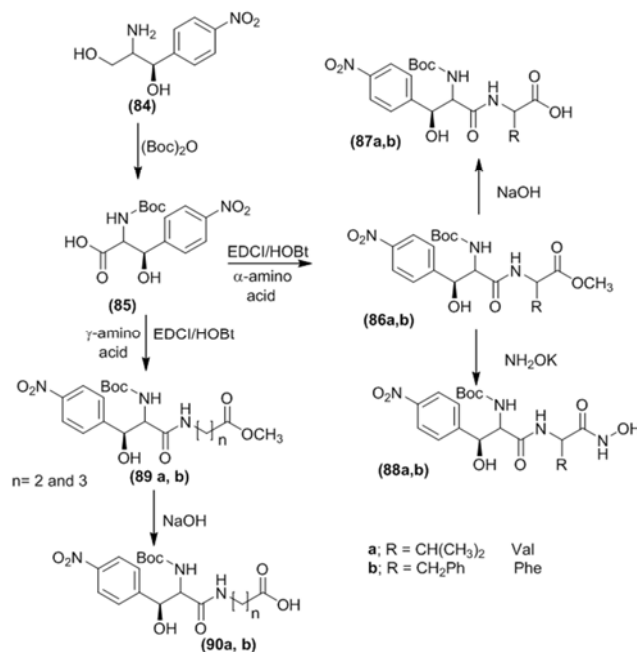


Figure 22. Synthesis of chloramphenicolamino acid derivatives (85-90).

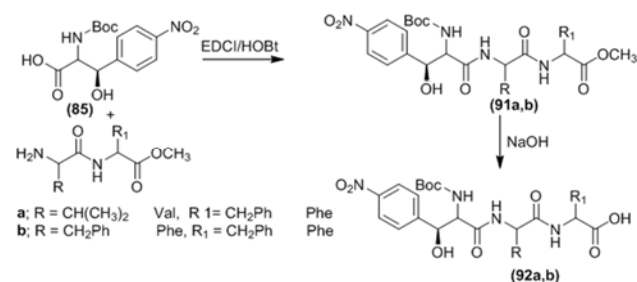


Figure 23. Synthesis of dipeptide methyl ester derivatives (91-92).

Dipeptide derivatives (92a,b) were prepared by coupling N-Boc-protected acid (85) with dipeptide methyl esters using the EDCI as coupling agent in presence of HOBT, the later compounds were hydrolyzed using NaOH to give the desired compounds [57].

3.4. Synthesis Guandine Amino Acid Derivatives

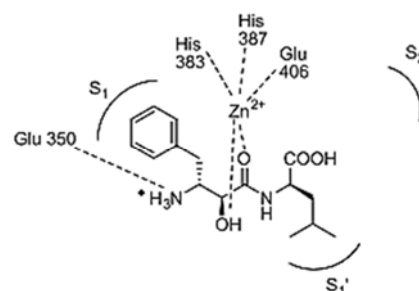


Figure 24. The binding mode of inhibitor derivatives into the active sites APN.

With the help of the computer-aided molecular design, and X-ray crystallographic studies on the co-crystal of the enzyme and various inhibitors, the 3D-structures of APN have been investigated (Figure 24). The result showed that, the preferred amino acid is, in decreasing order, arginine, lysine, tyrosine and phenylalanine, which bind with their backbone atoms close to the active-site zinc ion and their side chain occupying the S1 pocket of APN.

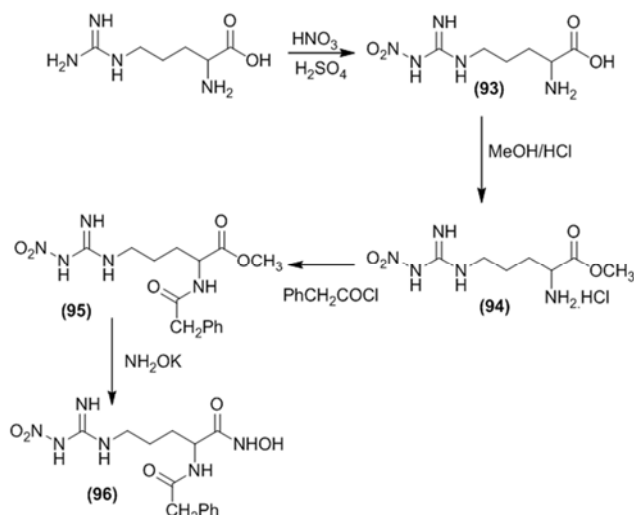


Figure 25. Synthesis of nitroguanidiny acid derivatives (93-96).

According to the former reasons, we choose L-arginine as the starting material in order to get more efficient and potential APN inhibitors [58, 59]. The guanidyl group of arginine was protected by nitro group to get 2-amino-5-(3-nitroguanidino)pentanoic acid (**93**, Figure 25), [60]. The acid was esterified with methanol under HCl atmosphere to get Methyl 2-amino-5-(3-nitroguanidino)pentanoate hydrochloride (**94**), the methyl 5-(3-nitroguanidino)-2-(2-phenylacetamido)pentanoate (**95**) was obtained from acylated with phenylacetyl chloride [61]. Then was treated with NH_2OK in anhydrous methanol to get N-Hydroxy-5-(3-nitroguanidino)-2-(2-phenylacetamido)pentanamide (**96**), [61], (Figure 25).

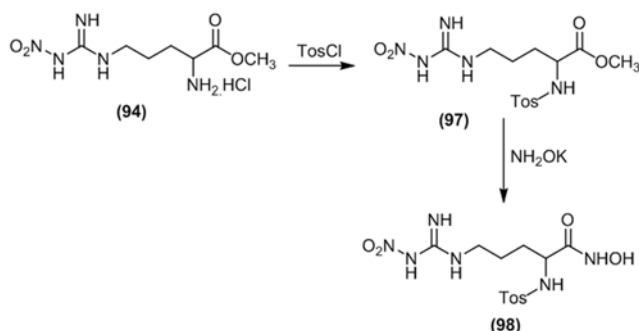


Figure 26. Synthesis of methyl ester amino acid of nitroguanidiny acid derivatives (97-98).

The acylation of compound (**94**) with tosyl chloride, led to compounds (**97**). The Final step (Figure 26), the ester groups of (**97**) was treated with NH_2OK in anhydrous methanol to get the target compounds (**98**), [61, 62].

3.5. Synthesis Peptide Derivatives

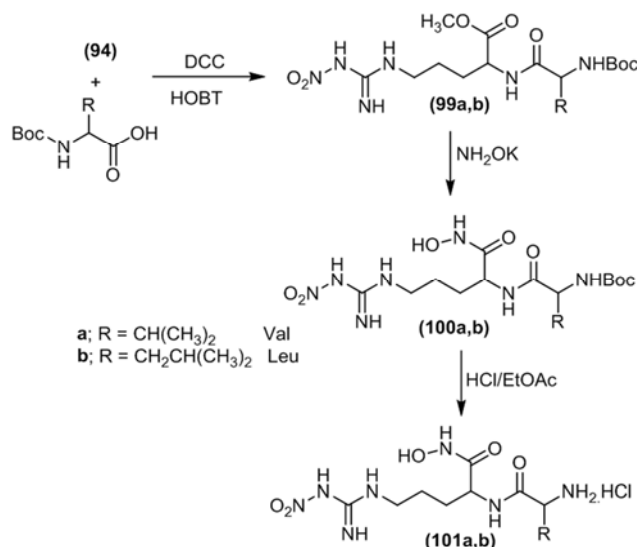


Figure 27. Synthesis di-peptide nitroguanidine derivatives (101).

3.5.1. Synthesis Di-Peptide Derivatives

The compound (**94**) was coupled with protected amino acids using DCC as coupling agent in presence of HOBT, led to methyl N₂-((tert-butoxycarbonyl) amino acid)-N-nitroargininate (**99a,b**), which reacted with NH_2OK to convert into hydroxamic derivatives (**100a,b**), the later compounds were hydrolyzed with HCl led to the desired bipeptide (**101**), [63], (Figure 27).

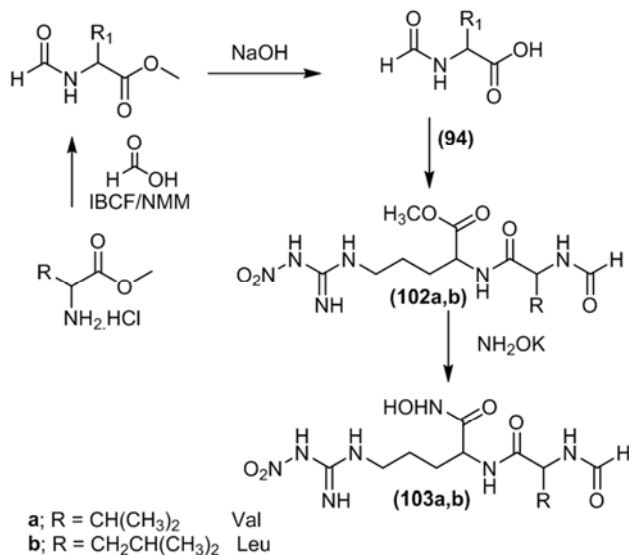


Figure 28. Synthesis of dipeptide derivatives (103).

The formyl di-peptide compounds (**103a,b**), were prepared (Figure 28), by reacting of formic acid with amino acid methyl esters in presence of IBCF/NMM to give formyl amino acid methyl esters, which hydrolyzed with NaOH to corresponding formyl amino acids, then coupled with (**94**) in presence of DCC [63], led to the bi-peptide methyl esters (**102a,b**). Then the ester groups of compound (**102a,b**) were treated with NH_2OK in anhydrous methanol to get compounds (**103a,b**).

3.5.2. Synthesis Tri-peptide Derivatives

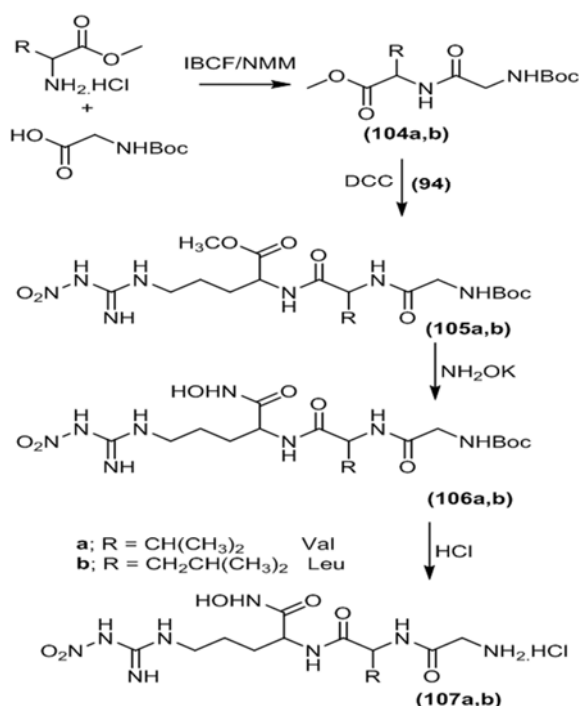


Figure 29. Synthesis of tri-peptide nitroguanidyl derivatives (105-107).

The tri-peptide compounds (**105a,b**), were prepared, (Figure 29), first, by reacting of Boc protected glycine with amino acid methyl esters in presence of IBCF/NMM to give Bocglycyl amino acid methyl ester (**104a,b**), which coupled with (**94**) [63], led to the tri-peptides derivatives (**105a,b**), and the ester groups were treated with NH₂OK in anhydrous methanol to get hydroxamic derivatives compounds (**106a,b**). The Boc group of hydroxamic derivatives can be easily removed by 2 N HCl in ethyl acetate to get the target compounds (**107a,b**), [63].

3.6. Synthesis Acryloyl Amino Acid Derivatives

The novel peptidomimetic compounds with different L-iso-glutamic derivatives were designed and synthesized via the route outlined in (Figure 30). Starting from 3-(3,4-dimethoxyphenyl)acrylic acid (**108**), the key intermediate 3-(3,4-dimethoxyphenyl)acryloylglutamic acid (**111**) was obtained via the sequence [64]:

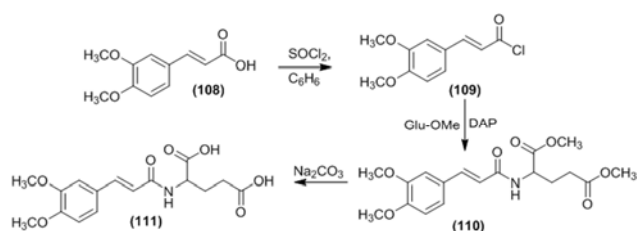


Figure 30. Synthesis of dimethoxyphenylacrylyl amino acid derivatives (109-111).

- i. Chlorination using SOCl₂, led to 3-(3,4-dimethoxy-

phenyl)acryloyl chloride (**109**).

- ii. Nucleophilic substitution, led to dimethyl-(3-(3,4-dimethoxyphenyl)acryloyl)glutamate (**110**).
- iii. Finally, hydrolysis led to (**111**).

The primary amide peptidomimetics (**113a-c**) were prepared [64], by coupling of 3-(3,4-dimethoxyphenyl)acryloylglutamic acid (**111**) with one equivalent of various amino acid methyl esters, in the presence of DCC to afford N²-(3-(3,4-dimethoxyphenyl)acryloyl)-N⁵-(amino acid methyl ester)-glutamine (**113a-c**), instead of (**112a-c**) and when the (**111**) was treated with two equivalent of amino acid methyl esters, to give (**114a-c**), (Figure 31).

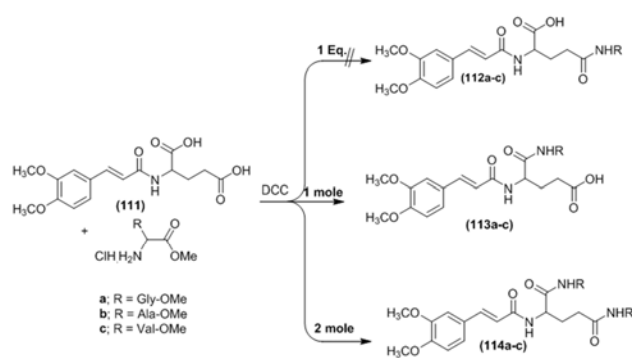


Figure 31. Synthesis of peptidomimetics acid amino acid derivatives (112-114).

3.7. Synthesis Pseudo Peptides

3.7.1. Synthesis Amino Acid Ureido Derivatives

The ureido or carbamate linker were synthesized from the isocyanates of the chosen amino acids [65], then coupled with the corresponding amino acids, amines or alcohols. They were directly transformed into hydroxamic acids as the target products (Figure 32-34).

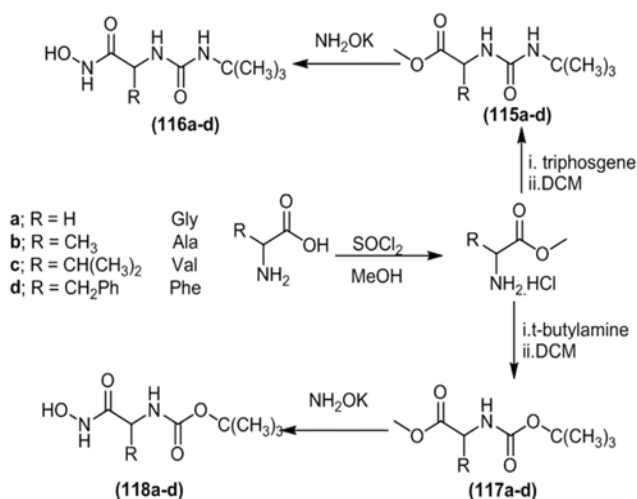


Figure 32. Synthesis of carbamate amino acid derivatives (115-118).

The main synthetic methods of the amino acid ureido or carbamate derivatives (**115a-d** and **117a-d**) are shown in (Figure 32). The amino acid methyl esters were treated with triethylamine, followed by tri-n-butylamine or benzyl alcohol in

presence of DCM to give compounds (**115a-d** and **117a-d**), respectively, which treated by NH_2OK to obtained corresponding hydroxamic acid (**116a-d** and **118a-d**), [66].

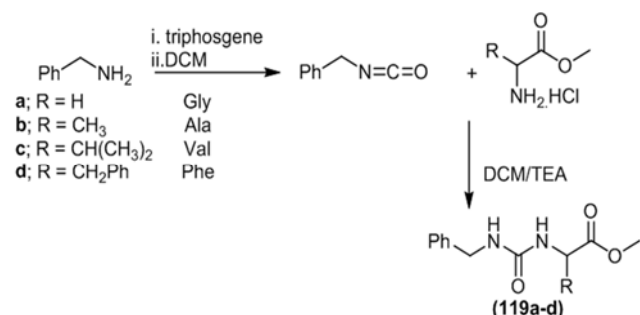


Figure 33. Synthesis ureido amino acid of derivatives (119).

The benzylamine is a starting material, was converted into isocyanate, and then coupled with amino acid methyl esters, to obtain the ureido linker compounds (**119a-d**), (Figure 33) as the target compounds [66].

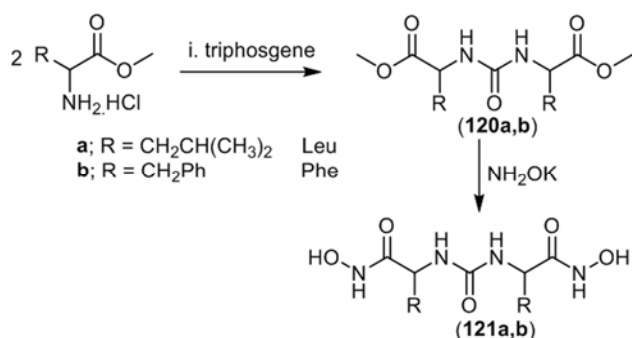


Figure 34. Synthesis of hydroxamic amino acid of derivatives (120-121).

Ureido derivatives of double amino acids (**120a,b**) were synthesized using triphosgen to give compounds (**120a,b**), which convert to hydroxamic compounds (**121a,b**) according to (Figure 34), [66].

3.7.2. Synthesis Phenylpropanol Amino Acid Derivatives

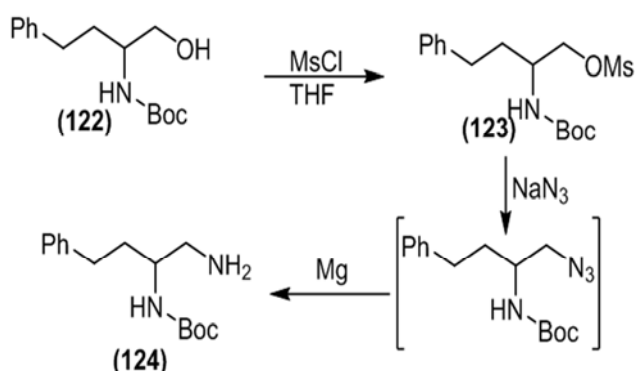


Figure 35. Synthesis of phenylpropanol amino acid derivatives (123-124).

The starting material is compound Boc-3-phenylpropanol (**122**) was prepared from phenylalanine [67], (Figure 35). The hydroxyl group was converted to methyl group by methanesulfonyl chloride to give (**123**), and then reacted with

sodium azide to generate azide intermediate. The compound (**124**) converted to amine (**125**), using magnesium in methanol.

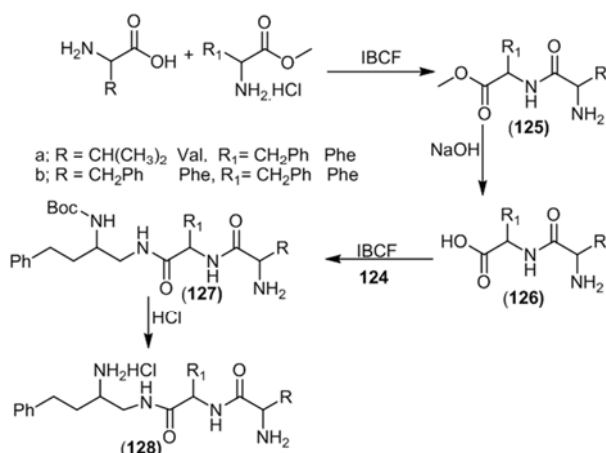


Figure 36. Synthesis of di-peptidomimetics amino acid of derivatives (125-128).

The compound (**125**) was obtained by the condensation of the amino acid methyl ester and amino acid using isobutyl chloroformate (IBCF). Hydrolysis of the compound (**125**) with $\text{NaOH}/\text{H}_2\text{O}$ yielded the di-peptidomimetics (**126**), which activated with (IBCF) and N-methyl morpholine, then coupled with compound (**124**) to yield (**127**). The Boc-protecting group can be easily removed by 3 N HCl in ethyl acetate to give hydrochloride salts (**128**), (Figure 36), [68].

3.7.3. Synthesis Quinoxalinone Derivatives

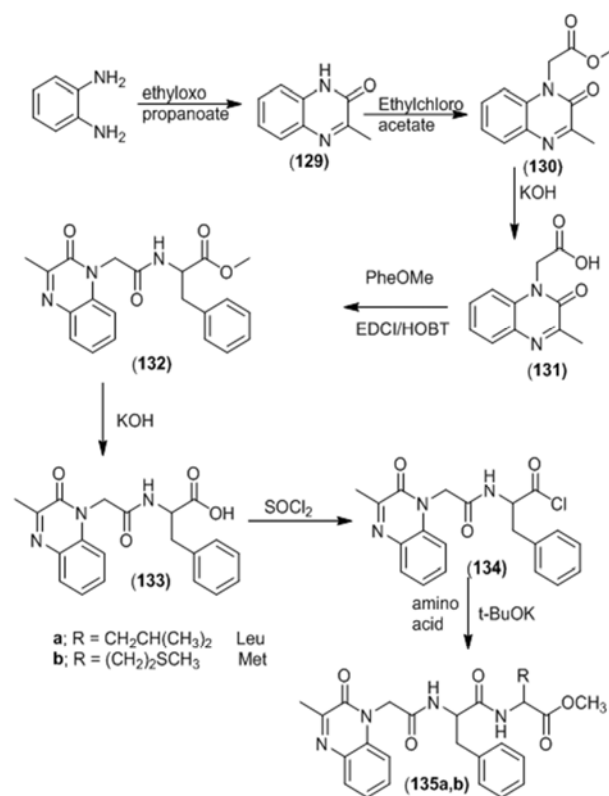


Figure 37. Synthesis of quinoxalinone amino acid of derivatives (130-135).

The quinoxalinone scaffold (**129**) was easily prepared from the commercially available o-phenylenediamine [69, 70].

Subsequent nucleophilic substitution was accomplished using ethyl chloro acetate in the presence of anhydrous ethanol, followed by hydrolyzation of ester group to the carboxylic acid (**131**), which was condensed with L-phenylalanine methyl ester to provide compound (**132**). This compound was further hydrolyzed to offer the carboxylic compound (**133**), and the key intermediate acyl chloride (**134**) was then obtained via the action of SOCl_2 . This was followed by coupling with various amino acids in the existence of t-BuOK in anhydrous CH_2Cl_2 to provide the target compounds (**135a,b**, Figure 37).

3.7.4. Synthesis Pyrrolidinedione Derivatives

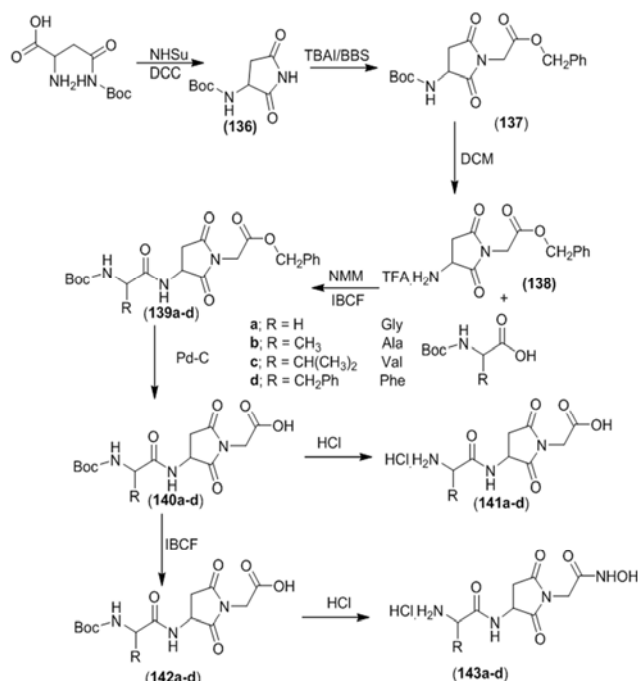


Figure 38. Synthesis of Pyrrolidinedionylamino acid derivatives (136-143).

The tert-butyl 2,5-dioxypyrrolidin-3-ylcarbamate (**136**) was prepared from cyclization reaction of commercially available Boc-L-Asn-OH amino acid in the presence of NHSu and DCC [71, 72], (Figure 38). The NH group in 2,5-dioxypyrrolidine (**136**) was then alkylated by benzyl bromoacetate using tetrabutylammonium iodide (TBAI) as phase transfer catalyst to afford compound (**137**), which was Boc-deprotected with TFA/DCM to obtain critical free amine TFA-salt (**138**) and coupled with various α -substituted amino acids (Boc-AA-OH) in the presence of N-methylmorpholine (NMM), IBCF /THF to give (**139a-d**). Pd/C hydrogenation of (**139a-d**) in ethanol at 40°C led to the corresponding acid derivatives (**140a-d**). In (Figure 38), acid compounds (**140a-d**) were converted to N-hydroxyacetamide derivatives (**142a-d**) in the presence of IBCF, Et₃N/THF. Compounds (**140a-d** and **142a-d**) were Boc-deprotected with 1N HCl to give (**141a-d** and **143a-d**) as hydrochloride salt in high yield [71, 72].

3.7.5. Synthesis Thiadizol Derivatives

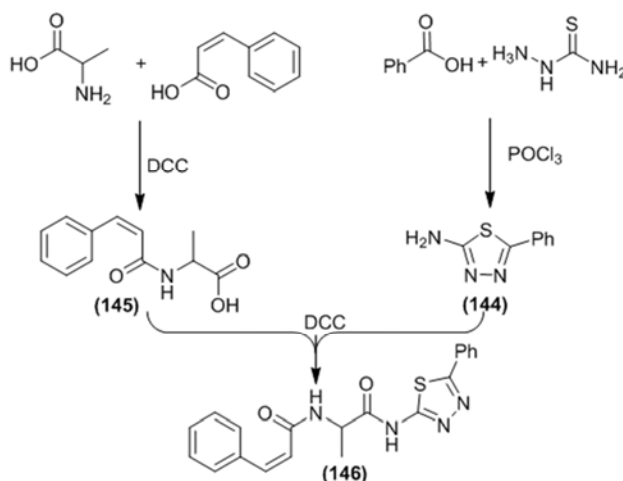


Figure 39. Synthesis Thiadizolyl peptidomimetic Derivatives (**146**).

The novel compounds, containing 1,3,4-thiadiazole derivatives were designed and synthesized via the route outlined in (Figure 39).

The novel peptidomimetic compounds, containing 1,3,4-thiadiazole derivatives were designed and synthesized via the route outlined in (Figure 39). The carboxylic acid was condensed with thiosemicarbazide in presence of Phosphorus oxychloride, yielding 1,3,4-thiadiazol-2-amine (**144**), [25]. The coupling of alanine with phenylacrylic acid to give amide derivatives (**145**) [73]. Finally, the intermediate (**144**) and (**145**) were reacted using DCC to give target compounds (**146**), [74-76].

4. Synthesis Amino Acids Derivatives as -Carbonic Anhydrase Inhibitors

There are a variety of mechanisms for the anticancer activity, and the most famous mechanism is through the inhibition of carbonic anhydrase isozymes [77-81]. In brief, the CA is a family of metalloenzymes involved in the catalysis of an important physiological reaction: the hydration of CO₂ to bicarbonate and hydrogen proton, which bicarbonate necessary to synthesis of nucleotides and other cell components such as membrane lipids. The synthesized compounds may decrease supplying of bicarbonate.

4.1. Synthesis Coumarinylamino Acids Derivatives

From CA X-ray crystallography of enzyme-inhibitor adducts (Figure 40). The 2-hydroxycinnamic acids, bind in an unprecedented way to the enzyme [82-84] at the entrance of the active site cavity, as shown in Figure 2. Only very recently, some coumarin derivatives were shown to bind in a similar way to the CAs [85]. Occlusion of the CA active site entrance, by hydrolyzed coumarins to 2-hydroxy-cinnamic acids, thus constitutes a totally novel mechanism of CA inhibition, which may be exploited to design compounds with various applications.

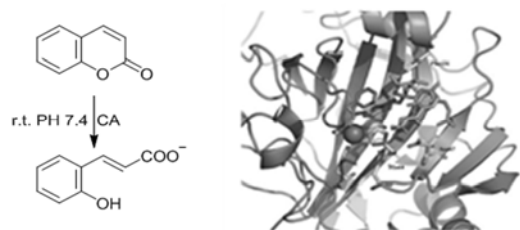


Figure 40. Inhibition CA through formation cinammic acid from hydrolysis of coumarin.

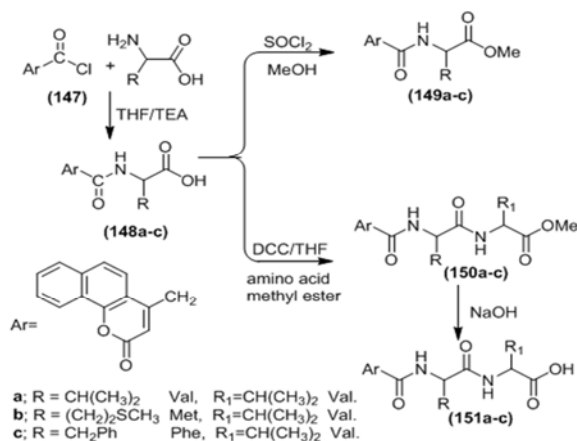


Figure 41. Synthesis coumarinyl peptidomimetic Derivatives (149-151).

The formation of 2-(2-oxo-2H-benzo[h]chromen-4-yl) acetyl amino acids (**148a-c**) were achieved by the reaction of 2-(2-oxo-2H-benzo[h]chromen-4-yl) acetyl chloride (**147**) with different type of amino acids (Figure 40). This compounds (**148a-c**) were reacted with thionyl chloride (molar ratio) in methanol to give the corresponding amino acid methyl esters (**149a-c**), (Figure 41).

Dipeptide methyl esters (**150a-c**) were prepared by the reaction compounds (**148a-c**) with amino acid methyl esters in presence of tetrahydrofuran (THF) and few drops of triethyl amine (TEA) using carbodiimide technique [86]. The compounds (**150a-c**) were treated with sodium hydroxide were converted into corresponding dipeptides (**151a-c**).

4.2. Synthesis Sulfonamide Amino Acid Derivatives

From analysis feature of the CA active site [87], and carbonic anhydrase inhibitors shown in Figure 3 [88].

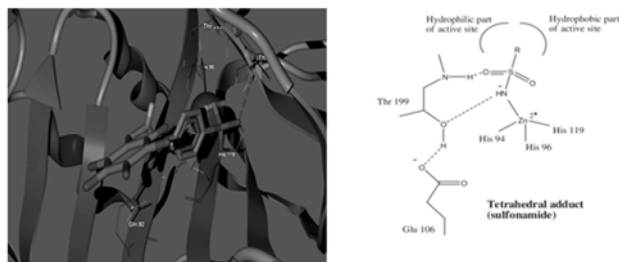


Figure 42. The inhibition CA using sulfonamide derivatives.

This structural element should be present in the compounds to acting as CA inhibitors: (i) presence of a sulfonamide

moiety, which coordinates with the zinc ion of the active site of the CA, and attaching to a scaffold which is usually a benzene ring. (ii) The side chain might possess a hydrophilic link able to interact with the hydrophilic part of the active site, and a hydrophobic moiety which can interact with the hydrophobic part of the CA active site. So that, the synthesized compounds were designed to comply with general features of pharmacophore described earlier [88] (figure 42).

4.2.1. Synthesis Phenylacetyl Sulfonamide Amino Acid Derivatives

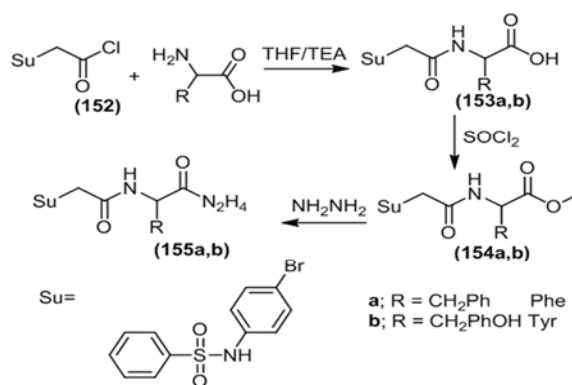


Figure 43. Synthesis Phenylacetyl Sulfonamide Amino Acid derivatives (153-155).

The α -amino acids (L-Phenylalanine and L-Tyrosine) were coupling with acid chloride (**152**), to accomplish free α -amino acid derivatives (**153a,b**), which converted into corresponding methyl ester derivatives (**154a,b**) under SOCl_2 -methanol condition [89]. The hydrazides derivatives (**155a,b**) were carried out by refluxing compounds (**154a,b**) with hydrazine hydrate in absolute ethanol (Figure 43).

4.2.2. Synthesis Sulfadiazine Amino Acid Derivatives

The Sulfadiazinylacetyl amino acid methyl ester derivatives (**156a-c**) were prepared using $\text{SOCl}_2/\text{CH}_3\text{OH}$. The Sulfadiazinylacetyl amino acid triazole and/or thiazole derivatives (**157a-c**, **158a-c**) were prepared by the reaction of compounds (**67a-c**) with 2-aminothiazole and/or 3-amino-1,2,4-triazole in presence of (DCC/THF) media, (Figure 44) [35].

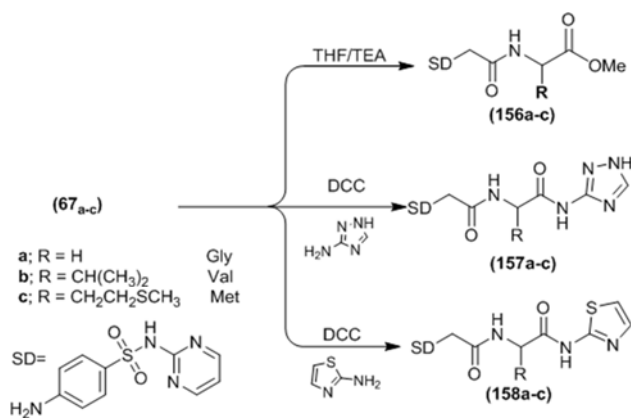


Figure 44. Synthesis sulfadiazine Amino Acid Derivatives (156-158).

4.2.3. Synthesis Complexes Sulfadiazineamino Acid Derivatives

The copper complexes amino acid (161) was prepared according (Figure 45). First, the protected amino acid was coupled with sulfadiazine using DCC method[90], which led to Fom- β -alanylsulfadiazine (159), the deprotection of compound (159) using HCl yielded β -alanylsulfadiazine hydrochloride (160). The final stage, preparation of Cu complex (161) by reaction of CuCl_2 with ligand (160), (Figure 45).

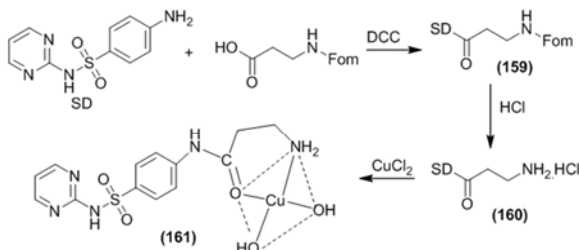


Figure 45. Synthesis metal complex Amino Acid Derivatives (160).

5. Conclusion

The present work discuss the recent synthetic route for synthesis peptides and pseudopeptides derived from aromatic and heterocyclic rings. The reported synthetic compounds act as antimicrobial, anti-cancer and DNA binding agents.

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