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# New Synthesis and Biological Screening of some Pyrrolo Quinoline Derivatives

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**Abstract:** The synthesis of a series of substituted pyrrolo[1,2-a]quinoline is described, starting from 2-nitrophenylacetic acid. Their structures have been established on the basis of spectral data. All compounds were evaluated for antibacterial activities against *Escherichia coli* and *Staphyloccus aureus* strains and antifungal activity against *Candida albicans* and *Aspergillus niger* strains by using serial dilution method.
**Keywords** : Synthesis; pyrrolo[1,2-a]quinoline; Derivatives; antibacterial activities; antifungal activity.

## 1. Introduction

The design of new compounds to dead with resistant bacteria and fungi has become one of the most important areas of antibacterial and antifungal research today, since resistance of pathogenic bacteria and fungi toward available antimicrobial drug is rapidly becoming a major problem worldwide. So the discovery of novel and potent antibacterial as well as antifungal agent is more demanding. Despite great effort from the pharmaceutical industry to manage the resistance problem, the discovery and development of new mechanistic classes of antibiotics has found with very little success [1]. The difficulty of this task is demonstrated by the fact that only two antibiotics of new classes, linezolid and daptomycin, have been successfully developed in the past three decades[2].

A large number of heterocyclic compounds are associated with diverse pharmacological properties, such as antiviral, anti-inflammatory, fungicidal and antimicrobial activity[3]. Quinazoline derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity[4]. They are widely used in pharmaceuticals and agrochemicals[5]; for example, fluquinconazole fungicide for the control of agriculture diseases[6]. Several reports have been published on the biological activity of quinazoline derivatives, including their bactiricidal, herbal and anti-tumor activity[7].

Quinoline and isoquinoline alkaloids have been receiving great attention because of their wide range of medicinal and pharmacological applications[8]. On the other hand, pyrrolo[1,2-*a*]quinolines are reported as tumor

inhibitors[9] and pyrrolo[2,1-*a*]isoquinolines have also been found to exhibit a broad spectrum of biological activities[10].

The syntheses of pyrrolo[1,2-a]quinoline and its derivatives were reviewed in 2003 by El-Sayed and El-Sayed [11]. After this date, new methods or the improvement of the earlier methods for preparation of pyrrolo[1,2-a]quinoline were described in the literature [12]. Among these methods the 1,3-dipolar cycloaddition of the quinolinium ylides in presence of suitable dipolarophiles is one of the most convenient [13], given that the heteroaromatic N-ylides proved to be valuable intermediates towards various N-bridgehead heterocycles [14]. The interest in pyrrolo[1,2-a]quinolines is due to their potential biological activity and attractive physicochemical properties [15]. Also the skeleton of pyrrolo[1,2-a]quinoline is present in gephyrotoxin, a natural alkaloid which was the subject of many investigations [16].

In an endeavor to find a new class of antimicrobial agents, we have designed and synthesized some new pyrrolo[1,2-a]quinoline derivatives as potential antimicrobial and antifungal agents. The results of this study are discussed in this paper.

## 2. Material and Methods

### *2.1. Chemistry*

Melting points were determined on a Boëtius hot plate microscope and are uncorrected. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for $^{1}$H-NMR and 75 MHz for $^{13}$C-NMR, the multiplicities were determined through DEPT. Mass spectra were recorded on a Varian MAT 311 spectrometer.

#### *2.1.1. Preparation of 2-aminophenylacetic acid derivatives 2(a-c)*

Substituted ortho-nitrophenylacetic acid 1 (a-b) (5.52 mmol) was added to a solution of Pd/C (20 %) and an excess of ammonium formate in 20 ml of EtOH. The mixture was stirred and refluxed for 2 hours, then filtered and concentrated *in vacuo*. The reaction mixture was poured into H2O and extracted with $Et_2O$. The organic solution was dried over $MgSO_4$ and evaporated. The residue was recrystallized from petroleum ether.

***a. 2-aminophenylacetic acid 2a***

Yield=72%; mp =124 °C. $^{1}$H NMR ($CDCl_3$ , 300 MHz): 6.46 (dd, 1H, H3); 6.94 (t, 1H, H4); 6.62 (t, 1H, H5); 6.93 (dd, 1H, H6); 3.62 (s, 2H, $CH_2$); 4,3 (br s, 2H, $NH_2$); 5.0 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 121.9 (C1); 148.4 (C2); 115.8 (C3); 128.4 (C4); 119.3 (C5); 130.9 (C6); 32.6 ($CH_2$); 178,5 (CO). IR (KBr) : 3200 (OH), 1685 (C=O), 3300 ($NH_2$), 3400 ($NH_2$). HRMS, m/z: 151(M), calcd. for $C_8H_9NO_2$ : 151.060, found: 251.093.

***b. (2-Amino-5-methyl-phenyl)-acetic acid 2b***

Yield=72%; mp =146°C. $^{1}$H NMR ($CDCl_3$ , 300 MHz): 6.33 (d, 1H, H3); 6.74 (d, 1H, H4); 6.74 (s, 1H, H6); 2.47 (s, 3H, $CH_3$); 3.60 (s, 2H, $CH_2$); 4,27 (br s, 2H, $NH_2$); 5.2 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 122.4 (C1); 146.0 (C2); 116.3 (C3); 129.2 (C4); 129.3 (C5); 132.5 (C6); 23.1 ($CH_3$); 33.5 ($CH_2$); 178,1 (CO). IR (KBr) : 3200 (OH), 1685 (C=O), 3300 ($NH_2$), 3400 ($NH_2$). HRMS, m/z: 165(M), calcd. for $C_9H_{11}NO_2$ : 165.070, found: 165.079.

***c. (2-Amino-5-chloro-phenyl)-acetic acid 2c***

Yield=72%; mp =153 °C. $^{1}$H NMR ($CDCl_3$ , 300 MHz): 6.19 (d, 1H, H3); 6.79 (d, 1H, H4); 6.83 (s, 1H, H6); 3.45 (s, 2H, $CH_2$); 4,27 (br s, 2H, $NH_2$); 5.1 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 123.5 (C1); 146.7 (C2); 117.3 (C3); 128.2 (C4); 124.5 (C5); 131.2 (C6); 31.5 ($CH_2$); 177,9 (CO). IR (KBr) : 3200 (OH), 1685 (C=O), 3300 ($NH_2$), 3400 ($NH_2$). HRMS, m/z: 185(M), calcd. for $C_8H_8ClNO_2$ : 185.020, found: 185.024.

### *2.1.2. Preparation of 2-(1-pyrrolyl)phenylacetic acid derivatives 3(a-c)*

2-aminophenylacetic acid derivatives 2(a-c) (1.98 mmol) was stared and refluxed for 3 hours with 4-chloropyridinium chlorohydrate (7.9 mmole), and 2,5-dimethoxytetrahydrofurane (15 mmol) in 20 ml of dioxane. Having removed the solvent *in vacuo*, The reaction mixture was poured into H2O and extracted with $Et_2O$. The organic solution was dried over $MgSO_4$ and evaporated. The residue was recrystallized from petroleum ether.

#### *a. 2-(1-pyrrolyl)phenylacetic acid 3a*

Yield=65%; mp= 40°C. $^1$H NMR ($CDCl_3$ , 300 MHz): 6.76 (dd, 1H, H3); 7.24 (t, 1H, H4); 6.92 (t, 1H, H5); 7.23 (dd, 1H, H6); 3.42 (s, 2H, $CH_2$); 6,85 (d, 2H, H2'H5'); 6.26 (t, 2H, H3'H4'); 4.9 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 126.6 (C1); 142.4 (C2); 120.4 (C3); 127.5 (C4); 125.5 (C5); 130.6 (C6); 34.1 ($CH_2$); 179,0 (CO); 119.5 (C2'); 110.6 (C3'); 110.6 (C4'); 119,5 (C5'). IR (KBr) : 3500 (OH), 1720 (C=O). HRMS, m/z: 201(M), calcd. for $C_{12}H_{11}NO_2$: 201.070, found: 201.079.

#### *b. 5-Methyl-2-(1-pyrrolyl)phenyl acetic acid 3b*

Yield=47%; mp= 86°C. $^1$H NMR ($CDCl_3$ , 300 MHz): 6.93 (d, 1H, H3); 7.34 (d, 1H, H4); 7.34 (s, 1H, H6); 2.67 (s, 3H, $CH_3$); 3.80 (s, 2H, $CH_2$); 6,94 (d, 2H, H2'H5'); 6.39 (t, 2H, H3'H4'); 5.7 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 126.8 (C1); 138.2 (C2); 120.7 (C3); 128.3 (C4); 134.6 (C5); 131.6 (C6); 34.1 ($CH_2$); 22.1 ($CH_2$); 178,4 (CO); 119.2 (C2'); 110.4 (C3'); 110.4 (C4'); 119,2 (C5'). IR (KBr) : 3350 (OH), 1720 (C=O). HRMS, m/z: 215(M), calcd. for $C_{12}H_{11}NO_2$: 215.090, found: 215.091.

#### *c. 5-Chloro-2-(1-pyrrolyl)phenyl acetic acid 3c*

Yield=57%; mp= 106°C. $^1$H NMR ($CDCl_3$ , 300 MHz): 6.39 (d, 1H, H3); 7.01 (d, 1H, H4); 7.15 (s, 1H, H6); 3.75 (s, 2H, $CH_2$); 6,75 (d, 2H, H2'H5'); 6.36 (t, 2H, H3'H4'); 4.9 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 128.3 (C1); 139.8 (C2); 122.1 (C3); 128.3 (C4); 131.0 (C5); 131.1 (C6); 32.4 ($CH_2$); 178,2 (CO); 119.2 (C2'); 110.3 (C3'); 110.3 (C4'); 119,2 (C5'). IR (KBr): 3500 (OH), 1720 (C=O). HRMS, m/z: 235(M), calcd. for $C_{12}H_{10}ClNO_2$: 235.038, found: 235.04.

### *2.1.3. Preparation of pyrrolo[1,2-a]quinoline derivatives 4(a-c)*

2-(1-pyrrolyl)phenylacetic acid derivatives **3(a-c)** (0.5 mmole) was stired and refluxed for 4 hours with 2 ml of acetic anhydride. Having removed the solvent *in vacuo*, the reaction mixture was stirred with 4 ml of saturated $NaHCO_3$ solution for 1 hour. After the mixture was diluted with $H_2O$ and the aqueous mixture was extracted twice with ether, the ether fraction were combined, washed with water, and dried over $MgSO_4$, and the solvent was removed in *vacuo*. The residue was recrystallized from petroleum ether.

#### *a. 4-Acetoxy pyrrolo[1,2-a]quinoline 4a*

Yield=47%. $^1$H NMR ($CDCl_3$ , 300 MHz): 8.29 (d, 1H, H1); 6.89 (t, 1H, H2); 6.53 (d, 1H, H3); 7.12 (s, 1H, H5); 7,97 (d, 1H, H6); 7.8 (t, 2H, H7H8); 8.37 (d, 1H, H9); 3.05 (s, 3H, $CH_3$). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 113.2 (C1); 114.3 (C2); 99.6 (C3); 145.4 (C4); 143.3 (C5); 126.2 (C6); 128.1 (C7); 127,4 (C8); 126.7 (C9); 128.9 (C10); 129.0 (C11); 146,1 (C12); 168.4 (CO); 17.1 ($CH_3$). IR (KBr): 1750 (CO); 1650; 1540; 1460. HRMS, m/z: 225(M), calcd. for $C_{14}H_{11}NO_2$: 225.070, found: 225.079.

#### **b. 4-Acetoxy-7-methyl pyrrolo[1,2-a]quinoline 4b**

Yield=56%; mp= 78°C. $^1$H NMR ($CDCl_3$ , 300 MHz): 7.23 (d, 1H, H1); 6.73 (t, 1H, H2); 6.33 (d, 1H, H3); 7.72 (s, 1H, H5); 7,57 (s, 1H, H6); 7.46 (d, 1H, H8); 8.37 (d, 1H, H9); 3.15 (s, 3H, $CH_3$); 3.24 (s, 3H, $CH_3$). $^{13}$C.NMR ($CDCl_3$: 75 MHz); 113.3(C1); 114.2 (C2); 99.5 (C3); 144.4 (C4); 143.7 (C5); 125.2 (C6); 128.4 (C7); 125,8 (C8); 136.3 (C9); 129.9 (C10); 128.1 (C11); 143,7 (C12); 168.1 (CO); 17.3 ($CH_3$); 21.5 ($CH_3$).

IR (KBr): 1750 (CO); 1490; 1420; 1360. HRMS, m/z: 239(M), calcd. for $C_{15}H_{13}NO_2$: 239.090, found: 239.095.

***c. 4-Acetoxy-7-chloro pyrrolo[1,2-a]quinoline 4c***

Yield=66%; mp= 40°C. mp =108 °C. $^{1}$H NMR ($CDCl_3$ , 300 MHz): 7.19 (d, 1H, H1); 6.69 (t, 1H, H2); 6.23 (d, 1H, H3); 7.82 (s, 1H, H5); 7,78 (s, 1H, H6); 7.57 (d, 1H, H8); 8.11 (d, 1H, H9); 2.24 (s, 3H, $CH_3$). $^{13}$C.NMR ($CDCl_3$ , 75 MHz): 113.2 (C1); 114.4 (C2); 99.4 (C3); 145.3 (C4); 144.3 (C5); 125.7 (C6); 128.9 (C7); 126,1 (C8); 132.8 (C9); 129.9 (C10); 139.1 (C11); 144,1 (C12); 168.2 (CO); 17.0 ($CH_3$). IR (KBr): 1750 (CO); 1490; 1430; 1360; 1250; 1200. HRMS, m/z: 259(M), calcd. for $C_{15}H_{13}NO_2$: 259.038, found: 259.040.

### *2.2. Determination of the in vitro antimicrobial activity*

All the synthesized compounds were tested for their in vitro antimicrobial activity against a panel of standard strains of the Gram-positive bacteria, *Staphylococcus aureus* ATCC 19433 (SA) and Bacillus subtilis ATCC 6633 (BS), the Gram-negative bacteria, *Escherichia coli* ATCC 25922 (EC) and *Pseudomonas aeruginosa* ATCC 27853 (PA), and the yeast-like pathogenic fungus *Candida albicans* ATCC 753 (CA). The primary screening was carried out using the agar-disk diffusion method using Muller-Hinton agar medium [17]. Sterile filter paper disks (8 mm diameter) were moistened with the test compound solution in dimethylsulfoxide of specific concentration (200µg/disk). The disks containing the compounds under test, the antimicrobial antibiotic ampicillin trihydrate (100 µg/disk) and antifungal drug clotrimazole (100 µg/disk), were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms suspension at 106 Colony Forming Unit/mL (CFU/mL) concentration. The plates were incubated at 37 °C, and the diameter of the growth inhibition zones was measured after 24 h in case of bacteria and 48 h in case of *C. albicans*. The minimal inhibitory concentration (MIC) for the most active compounds against the same microorganisms used in the primary screening was carried out using the microdilution susceptibility method in Muller-Hinton broth and Sabouraud liquid medium. The compounds, ampicillin trihydrate, and clotrimazole were dissolved in dimethylsufoxide at concentration 800 µg/mL. The twofold dilutions of the solution were prepared (400, 200, 100, … 6.25 µg/mL). The microorganism suspensions at 106 CFU/mL concentrations were inoculated to the corresponding wells. The plates were incubated at 37 °C for 24 and 48 h for the bacteria and *C. albicans*, respectively. The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms as detected by unaided eye.

## 3. Results and Discussion

### *3.1. Chemistry*

The preparation of the target compounds is outlined in Schema 1. The reduction of 2-nitrophenylacetic acid derivatives **1(a-c)** to the corresponding amine **2(a-c)** using classical reducing reagents such as Iron in acidic media [18], Sodium hydrosulfite[19], Samarium [20], Sodium sulfide[21] and Zinc metal in aqueous ammonium chloride [22] gave the oxyindol with intramolecular cyclisation . This problem was overcome, with a good yield, by Pd/C catalysed hydrogenolysis using ammonium formate as a source of hydrogen [23]. With a Clauson-Kaas reaction [24], 2-aminophenylacetic acid derivatives 2(a-c) was then heated to reflux with stirring in dioxane, in the presence of 4-chloropyridinium chlorohydrate and 2,5-dimethoxytetrahydrofurane to obtain 2-(1-pyrrolyl) phenylacetic acid derivatives **3(a-c)**, whose cyclisation was accomplished by heating at reflux in acetic anhydride [25], finally leading to the target compound pyrrolo[1,2-a]quinoline derivatives **4(a-c)**.

#### *3.1.1. Preparation of 2-aminophenylacetic acid* **derivatives 2(a-c)**

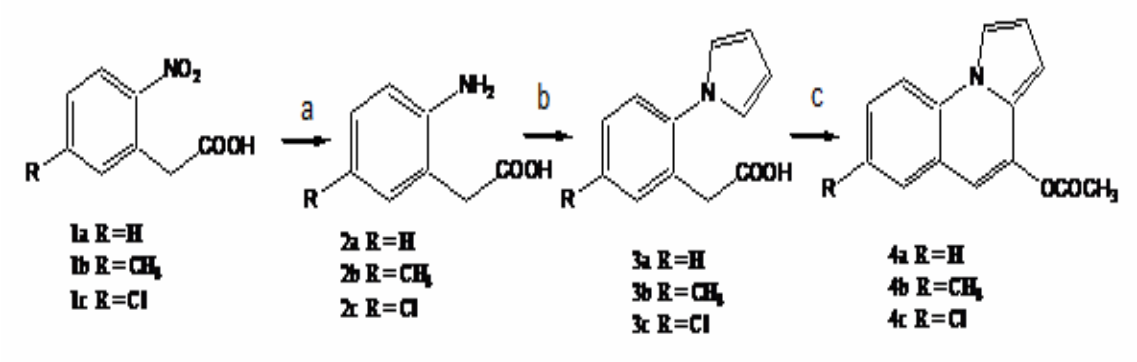
2-aminophenylacetic acid derivatives **2(a-c)** were prepared starting from 2-nitrophenylacetic acid derivatives **1(a-c)** via catalytic hydrogenation using and an excess of ammonium formate in EtOH. The mixture was stirred and refluxed for 2 hours then filtered and concentrated *in vacuo*. After dilution of the reaction mixture with ethyl acetate, washing with brine, and evaporation, the reaction mixture, was crystallized from hexane, affording 2-aminophenylacetic acid derivatives **2(a-c)** in 72% yield. The identification of the amino phenylacetic acid derivatives **2(a-c)** was based on spectroscopic data. In the $^{1}$HNMR spectra of these products, we noted the appearance of the signal as the massif at 3.6 due to protons of amine group $NH_2$.

### *3.1.2. Preparation of 2-(1-pyrrolyl)phenylacetic acid* derivatives 3(a-c)

For the synthesis of the *2-(1-pyrrolyl)phenylacetic acid* derivatives 3(a-c), we have used the Clauson-Kaas reaction[24], the reaction between the 2-aminophenylacetic acid derivatives **2(a-c)** and 2,5-dimethoxy tetrahydrofurane was heated to reflux and stirring in dioxane, in the presence of 4-chloropyridinium chlorohydrate to obtain 2-(1-pyrrolyl)phenylacetic acid derivatives **3(a-c)**. The identification of the 2-(1-pyrrolyl)phenylacetic acid derivatives 3(a-c) was based on spectroscopic data. In the $^1$HNMR spectra of these products, we noted the disappearance of the massif at 3.6 due to protons $NH_2$ and the appearance of two singlets at 9.16 and 9.91 due to protons of the pyrrolyle group.

### *3.1.3. Preparation of pyrrolo[1,2-a]quinoline* derivatives 4(a-c)

2-(1-pyrrolyl)phenylacetic acid derivatives 3(a-c), whose cyclisation was accomplished by heating at reflux in acetic anhydride, finally leading to the target compound pyrrolo[1,2-a]quinoline derivatives 4(a-c). The identification of the *pyrrolo[1,2-a]quinoline* derivatives 4(a-c) was based on spectroscopic data. In the $^1$HNMR spectra of these products, we noted the appearance of the singlet at 2.45 due to protons of methyl of acetoxyl group.




Reagents: a, $CH_5NO_2$/Pd/C; b, 2,5-Dimethoxy-tetrahydro-furan/Chloropyridine; c, $AC_2O$

**Scheme 1**

### *3.2. Antimicrobial activity*

The results of the preliminary antimicrobial testing of compounds **2a-4c** (200 µg/disk) and the broad-spectrum antibacterial antibiotic ampicillin trihydrate (100 µg/disk) are shown in Table 1. The results revealed that the majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the inhibitory activity against the tested Gram-positive bacteria was higher than that of the Gram-negative one. Compounds **2b–3a**, **3b–4b** and **4c** displayed broad-spectrum antimicrobial activity; they possessed excellent activity against the Gram-positive bacteria, moderate activity against *E. coli*, and weak activity against *C. albicans*. The least susceptible organisms were *P. aeruginosa* and *C. albicans*. Only compound **2b**, was moderately active against *C. albicans* and compounds **3c** and **4c** showed moderate activity against *E. coli*. However, compound **4a** exhibited moderate activity against *E. coli* and *P. aeruginosa* in addition to weak activity against *C. albicans.* None of the tested compounds were found to be as strong as clotrimazole. The compound **2a** are completely inactive against the tested strains.

**Table 1**. Antimicrobial activity of compounds (200 µg/8 mm disk), the broad-spectrum antibacterial drug ampicillin trihydrate (100 µg/8 mm disk) and the antifungal drug Clotrimazole (100 µg/8 mm disk) against *S. aureus ATCC 19433 (SA), B. subtilis ATCC 6633 (BS), E. coli ATCC 25922 (EC), P. aeruginosa ATCC 27853 (PA), and C. albicans ATCC 753 (CA).*

| Cpd | MIC (µg/mL) | | | | |
|---|---|---|---|---|---|
| | SA | BS | EC | PA | CA |
| **2b** | 37 | 41 | 77 | 126 | 78 |
| **2c** | 50 | 55 | 125 | 124 | 123 |
| **3a** | 75 | 73 | 131 | 136 | 135 |
| **3b** | 76 | 125 | 126 | 133 | 133 |
| **3c** | 78 | 76 | 70 | 130 | 122 |
| **4a** | 39 | 35 | 72 | 75 | 124 |
| **4b** | 77 | 78 | 125 | 126 | 127 |
| **4c** | 74 | 74 | 71 | 125 | 125 |
| **Ampicillin** | < 10 | < 10 | < 10 | < 10 | NT |
| **Clotrimazole** | NT | NT | NT | NT | 14 |

NT, not tested.

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## References

1. Taun, P.T., Edmund, L.E., Joseph, P.S., Brian, M.W., Michael, A.S., Hollis, S., John, M.D., Martin, A.S., Themis, J., Stephen, J.G., Dai, Q.N., Paul, B., Judy, Y., Anurag, S., Chan, H., Saeed, R., Xiujuan, W., Rajeshwar, S., Structure activity relationshipsof 3-aminoquinazolinediones, a new class of bacterial type-2 topoisomerase (DNA gyrase and topo IV) inhibitors. *Bioorg. Med. Chem., Lett*. 2007, 17, 1312–1320.
2. Weigelt, J., Itani, K., Stevens, D., Lau, W., Dryden, M., Knirsch, C., Linzolid versus vancomycin in treatment of complicated skin and soft tissue infections. *Antimicrob. Agents Chemother*., 2005, 49, 2260–2266.
3. Bhat A.R., Bhat G.V., Shenoy G.G., Synthesis and in vitro antimicrobial activity of new 1,2,4-triazoles, *J. Pharm. Pharmacol*. ,2001, 53, 267-272
4. Apfel, C., Banner, D.W., Bur, D., Dietz, M., Hubschwerlen, C., Locher, H., Marlin, F., Masciadri, R., Pirson, W., Stalder, H., 2-(2-Oxo-1,4-dihydro-2H-quinazoli-3-yl)- and 2-(2,2-dioxo-1,4-dihydro-2H-6 benzo[1,2,6]thiadiazin-3-yl)-N-hydroxy-acetamides as potent and selective peptide deformylase inhibitors. *J. Med. Chem*., 2001, 44, 1847–1852.

5. Tobe, M., Isobe, Y., Tomizawa, H., Nagasaki, T., Obara, F., Hayashi, H., Structure–activity relationships of 6-fluoroquinazolines: dual-acting compounds with inhibitory activities toward both TNF alpha production and T cell proliferation. *Bioorg. Med. Chem*., 2003, 11, 609–616.
6. Guang-Fang, X., Bao-An, S., Pinaki, S.B., Song, Y., Pei-Quan, Z., Lin-Hong, J., Wei, X., De-Yu, H., Ping, L., Synthesis and antifungal activity of novel S-substituted 6-fluoro-4-alkyl(aryl)thioquinazoline derivatives. *Bioorg. Med. Chem*., 2007, 15, 3768–3774.
7. Chenard, B.L., Welch, W.M., Blake, J.F., Butler, T.W., Reinhold, A., Ewing, F.E., Menniti, F.S., Pagnozzi, M.J., Quinazolin-4-one a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists: structure–activity relationship of the C-2 side chain tether. J. Med. Chem.; 2001; 44, 1710–1717.
8. Lee M.K., *Bioorg. Med. Chem.* 2001, *9*, 2871.
9. Sui, Z.; Altom, J.; Nguyen, V. N.; Fernandez, J.; Bernstein, J. I.; Hiliard, J. J.; Barrett, J. F.; Podlogar, B. L.; Ohemeng, K. A. *Bioorg. Med. Chem.* 1998, *6*, 735.
10. Montalbano, A.; Diana, P.; Barraja, P.; Lauria, A.; Cirrincione, G.; Dattolo, G.; Almerico, A. M. *Arkivoc.*, 2002, *11*, 264.
11. El-Sayed, I. I.; El-Sayed, H. E.-A. *Adv. Heterocycl. Chem*., 2003, 84, 83.
12. Jones, C. P.; Anderson, K. W.; Buchwald, S. L. J. Org. Chem., 2007, 72, 7968.
13. Dumitrascu, F.; Mitan, C. I.; Drăghici, C.; Căproiu, M. T.; Răileanu D. *Tetrahedron Lett.*, 2001, *42*, 8379.
14. Dumitrascu, F.; Caira, M. R.; Vasilescu, M.; Barbu, L.; Drăghici, C.; Dumitrescu, D.G. *Arkivoc*, 2007**,** (*xvi*).
15. Cappelli, A.; Giuliani, G.; Anzini, M.; Riitano, D.; Giorgi, G.; Vomero, S. *Bioorg. Med. Chem*., 2008, 16, 6850.
16. Santarem, M.; Vanucci-Bacqué, C.; Lhommet, G. *J. Org. Chem.* 2008, *73*, 6466.
17. Patrick, P.M., Ellen, B.J., Michael, A.P., Fred, C.T., Robert, H.Y., Clinical laboratory standards. In: Wood, G.L., Washington, (Eds.), Manual of Clinical Microbiology. Am Soc Microbiol, Washington, DC, 1995, pp. 273–286.
18. Fox, B. A., Threlfall, T. L., *Org. Synth*., 1973, 5, 346
19. Redemann, C. T., Redemann, C. E., *Org. Synth.* 1955, 3, 69
20. Basu, M. K., *Tetrahedron Lett.*, 2000, 30, 41
21. Hartman, W. W., Silloway, H. L., *Synthesis* 1984, 11, 938.
22. Kamm, O., *Org. Synth.* 1941, 1, 445
23. Jiro T., Teruo S., Masami Y., Ichiro M., *Chem. Commun.*, 1986, 922-924
24. Clauson-Kaas, N., Tyle, Z., *Acta Chem. Scand.* 1952, *6*, 667.
25. Avetisyan, S. A., Korachov, S. L., Azaryan, L. V., Karapetyan, A. A., Struchkov, T., *Chemistry of Heterocyclic Compounds* 1995, 31, 28

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