Synthesis of a new serie of quinoline-carboxamides based on methylated aminoesters: NMR characterization and antimicrobial activity

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Abstract: Ten new quinoline-carboxamides have been synthesized using the coupling reaction between 2-oxo-1,2-dihydroquinoline-4-carboxylic acid as a substrate and five different amino ester at room temperature with basic media (triethylamine). The products were obtained with a good yield ranging from 60 to 80 % and were structurally characterized by 1H and 13C NMR spectroscopy and mass spectrometry. The antibacterial activities of the synthesized compounds have been evaluated against 9 strains of bacteria and compared to references (erythromycin, ofloxacin, ticarcillin, oxacillin, ampicillin, norfloxacin, cefazidim, cefotaxim). The results showed that the majority of carboxamides-quinoline ester groups present a larger inhibition diameters than those of the antibiotics references. The highest antibacterial activity in vitro against the Enterococcus faecalis has been revealed for compound 1a (methyl 2-oxo-1,2-dihydroquinoline-4-yl-L-alaninate).

Keywords: Quinoline, peptidic coupling, amino acids, antibacterial activity, 1H and 13C NMR, mass spectrometry.

1. Introduction

Antibiotics based on heterocycles pharmacophore present a great interest and play a central role in the medicinal sector during this century, especially due to their potential effects against bacterial infections, however bacterial cells have developed some resistance and are able to defend themselves against the antibiotic. The increasing of this resistance phenomenon towards antibiotics has been described as a global public health menace 4.

Quinolones is among the most synthesized antibiotics that have been widely used by scientists to synthesize new antibacterial agent. In 1962, the first quinolone directly derived from 7-chloroquinoline was discovered to be nalidixic acid (Figure 1: I), which is indicated for the treatment of urinary tract infection 2.

Other derivatives, such as fluoroquinolones (norfloxacin, levofloxacin, ofloxacin, lomefoxacin, etc), were synthesized by grafting both fluoro group at the position 6 and piperazine at the position 7 of the quinolones substrate. Regarding the norfloxacin (Figure 1: II), it constitutes the second generation of fluoroquinolone presenting an increase in activity against Gram+ 5. While in the case of 3rd generation...
fluoroquinolone, such as, levofloxacin (Figure 1: III), a large spectrum activities was manifested against Gram+ and Gram− bacteria 4. Concerning the structure-activity of moxifloxacin fluoroquinolone drug of 4th generation (Figure 1: IV), it was obtained by incorporating methoxyl group at position 8 and bicyclo-1,5-diamine at the position 7. The structural modification induced a change with improving the activity and conferring some efficiency treatment against pneumonic infections 5.

Some quinoline derivatives have been also synthesized and know by their antibacterial activities 6, potent intestinal antiseptic 7, agent anticancer 8, analgesic 9, antiallergic 10, used for the treatment of Alzheimer’s disease (AD) 11, antinephritic 12, antiplasmodial activity 13, antimalarial 14, antihypertensive 15, anti-HIV 16 and present an antitumoral activities 17.

The development of new synthetic heterocycles quinoline presents a major strategy and challenge for their synthesis and the discovery of new promising drug candidate able to present a potent pharmacological and therapeutic activities.

Amino acids are considered as major constituents of many drugs, such as β-lactams antibiotics 18 and glutamate antagonists 19. Tyrosine, phenylalanine, and tryptophan are well known for their essential role in the living organism and present a potent and wide range of therapeutic activities 20 and also present antioxidant activity 21. In order to study the biological and pharmacological activities of amino acids, some researchers have been carried out the modifications on amino acid groups by coupling than to other heterocyclic compounds, such as coumarine 22-23. Shivaraj et al. 2013 24 have shown that a serie of quinoline-6-carboxamides based on primary amines present an antibacterial activity in vitro against Escherichia coli and Staphylococcus aureus, converting them with glycosidic ring to surfactants 25 to ligand metal complexes 26 and/or to hydrogels 27.

Similarly, Zhang et al. 2003 28 synthesized and demonstrated that Cu(II) complexes with the ligand N-(8-quinolyl) pyridin-2-carboxamide showed cytotoxicity against murine leukaemia P-388 and human leukaemia cell lines HL-60. Recently, Filali Baba et al. 2019 29 have reported that the serie of 2-azo-1,2-dihydroquinoline-4-carboxylate derivatives presents an interesting antioxidant activity. In our case study, we have tried to graft new quinoline heterocyclic compounds to a serie of amino esters groups in order to provide some interesting biological activities.

In this work, we report the synthesis of ten new quinoline-4-carboxamides compounds. Their structural characterizations by both Nuclear Magnetic Resonance 1H and 13C and mass-spectrometry, as well as, the evaluation of their antibacterial activities against 9 types of bacteria.

2. Results and Discussion

2.1. Synthesis of quinoline-carboxamides

Our study concerned the synthesis of two types of serie of quinoline-carboxamides derivatives, 2-oxo-1,2-dihydroquinoline-4-carboxamides and 6-bromo-2-oxo-1,2-dihydroquinoline-4-carboxamides by reacting a quinolinc acid as a substrate with five types of various amino methyl esters groups (L-alanine-OMe, L-phenylalanine-OMe, L-serine-OMe and L-tryptophane-OMe) during 12 hours at room temperature with the presence of hexafluorophosphate benzotriazole tetramethyl uronium (HBTU) as a coupling agent in basic medium using triethylamine (TEA) and dimethylformamide (DMF) as a suitable solvent for this type of reaction. The five amino acids (alanine, serine, phenylglycine, phenylalanine and tryptophan) were converted towards their methylated esters groups, The synthesized compounds purified on liquid chromatography column using silica gel as a stationary phase and were obtained with good yields ranging from 60 to 80%. Their chemical structures were elucidated by both techniques 1H and 13C NMR and mass-spectrometry.

In order to synthesize the quinoline-carboxamides, the first step requires the preparation of two types of quinoline substrates: 2-oxo-1,2-dihydroquinoline-4-carboxylic acid 1 and 6-bromo-2-oxo-1,2-dihydroquinoline-4-carboxylic acid 2, which are obtained by reacting the malonic acid on both isatin and its bromo-derivatives with the presence of sodium acetate. The reaction was performed under reflux of acetic acid during 24 hours 30 (Scheme 1).

Before the preparation step of quinoline-carboxamides, the five amino acids were converted to their methylated amino esters by the action of thionyl chloride (SOCl2) on amino acid in methanol under reflux 31. In the second step, ten new quinoline-carboxamides products (1a→1e and 2a→2e) were obtained (Scheme 1) by coupling reaction between each substrate (1 and 2) with the five different types of methylated amino esters hydrochloric acid salt (L-alanine-OMe, L-phenylalanine-OMe, L-phenylglycine-OMe, L-serine-OMe and L-tryptophane-OMe). The differentes synthesized products are illustrated in both Scheme 1 and Table 1.
Scheme 1. Reagent: (a) sodium acetate, acetic acid, 24h reflux \(30\); (b) \(\text{SOCl}_2\), Methanol, 2h reflux \(31\); (c) HBTU, TEA, 12h \(32\).

| Quinoline carboxylic Acid substrate | amino esters | Product | Yield % |
|-----------------------------------|-------------|---------|---------|
| 1                                 | L-ala       | ![Image](image1.png) | 75      |
| 1                                 | L-ser       | ![Image](image2.png) | 70      |
| 1                                 | L-phgly     | ![Image](image3.png) | 65      |

Table 1. Synthesized quinoline-carboxamides.
2.2. Antibacterial activity

The antibacterial activity of the all synthesized compounds was tested on nine type of bacteria strains: Gram⁺, such as, Listeria monocytogenes, Staphylococcus aureus, Enterococcus feacalis and Gram⁻ such as: Salmonella sp, Enterobacter sp, Klebsiella pneumonia, Acinetobacter baumannii, Escherichia coli, Haemophlilus influenza, using a Muller-Hinton medium. The preliminary study concerned the antibacterial screening of all synthesized compounds using the disc diffusion method. The second step has been oriented towards the minimum inhibitory concentration values (MIC) of the compounds that showed important diffusion diameters.

Both compounds 1a and 2 showed an antibacterial activity against bacterium Escherichia coli and bacterium Enterococcus feacium, respectively, with the highest diameter of inhibition zones (d=14 mm). However, Listeria monocytogenes and Klebsiella pneumonia strains showed resistance for all the synthesized compounds, no interesting inhibition zones were observed (Figure 2).
In order to test the sensibility of bacterial strains, an antibiotic susceptibility test was performed on eight different types of antibiotics: erythromycin, ofloxacin, ticarcillin, oxacillin, ampicillin, norfloxacin, ceftazidim, cefotaxim. The results showed that all bacterial strains tested present some resistance to the antibiotics, mainly in the case of the bacteria: Acinetobacter baumannii, Escherichia coli and Listeria monocytogenes, as for the following four antibiotics: erythromycin, oxacillin, ticarcillin and ceftazidim. The manifested character was shown at certain bacterial strains without presenting any sensibility for all the strains tested or without matching with those of strains types. The sensibility was very marked for ofloxacin (fluoroquinolone antibiotic family) affecting the following strains Staphylococcus aureus, Klebsiella pneumonia, Haemophilus influenza, and Enterococcus feacalis, as well as, for norfloxacin against bacteria Klebsiella pneumonia, Enterococcus feacalis, Enterobacter sp and Salmonella sp. While in the case of ceftazidim antibiotic, only two strains present some sensitivity towards Klebsiella pneumonia and Salmonella sp, followed by ampicillin towards Salmonella sp. Finally, the most sensitive bacterial strains affected both Klebsiella pneumonia and Salmonella sp followed by Enterococcus feacalis.

The results obtained are encouraging, showed the importance of those quinoline-carboxamides towards bacterial strains, once compared to different antibiotics; and might explain the role of bacterial strains in the acquisition of resistance against antibiotic agents. The nature of amino acid groups could influence the chemical properties of quinoline-derivatives, and then modify the action modes of bacterial activities (Table 2).
Table 2. Results of antibacterial tests on nine type of commercial antibiotics against *Acinetobacter baumannii*, *Escherichia coli*, *Enterococcus faecalis*, *Enterobacter sp*, *Klebsiella pneumonia*, *Haemophilus influenza*, *Listeria Monocytogenes* and *Salmonella sp*.

|                      | AMP  | CAZ  | CTX  | E   | NOR | OFX | OX  | TIC |
|----------------------|------|------|------|-----|-----|-----|-----|-----|
| *Acinetobacter baumannii* (mm) | R (6) | R (6) | R (6) | R (7) | R (12) | R (8) | R (6) | R (6) |
| *Escherichia coli* (mm)      | R (6) | R (6) | R (6) | R (6) | R (6) | R (6) | R (6) | R (6) |
| *Enterococcus faecalis* (mm) | R (6) | -    | -    | R (6) | S (22) | S (22) | R (6) | R (6) |
| *Enterobacter sp* (mm)       | R (6) | R (6) | R (6) | -    | S(20) | R (20) | R (6) | -   |
| *Klebsiella pneumonia* (mm)  | R (6) | R (15) | S (20) | R (6) | S (25) | S (27) | R (6) | -   |
| *Haemophilus influenza* (mm) | R (6) | -    | -    | R (6) | R (15) | S (28) | R (6) | -   |
| *Listeria monocytogenes* (mm) | R (6) | -    | -    | R (6) | -    | -    | R (6) | -   |
| *Staphylococcus aureus* (mm) | -    | R (14) | R (18) | -    | -    | S (26) | R (6) | -   |
| *Salmonella sp* (mm)         | S (22) | -    | S (20) | R (6) | S (20) | R (16) | R (6) | -   |

AMP: ampicillin, CAZ: ceftazidim, CTX: cefotaxim, E: erythromycin, NOR: norfloxacin, OFX: ofloxacin, OX: oxacillin, TIC: ticarcillin, R: Resistant, S: Sensitive, - : antibiotic does not match this strain. ( ): antibiotics diameter.

The in vitro minimum inhibitory concentration (MIC) values of antibacterial activities of tested compounds were determined and illustrated in Table 3. The two marked compounds 1a and 2 showed the lowest antimicrobial MIC at 0.0775 mg/ml against *Enterococcus faecalis* and 0.155 mg/ml against *Acinetobacter baumannii*, respectively, and considered as a promising molecules (pharmacophore) for antimicrobial activities test.

The antimicrobial activities were manifested in the case of all compounds against *Enterococcus faecalis*, *Salmonella sp*, *Staphylococcus aureus* and *Acinetobacter baumannii*, respectively, are stronger than those against other bacterial strains. The following compounds 1c, 1d, 2b and 2d presented less microbial activities against tested bacterial strains, while the products 1a, 1b, 2b, 4b and 6b showed moderate effect.

Table 3. *In vitro* antibacterial activities result (MIC values in mg/ml) of 12 compounds: 1, 2, 1a, 1b, 1c, 1d, 1e, 2a, 2b, 2c, 2d, 2e against *Listeria monocytogenes*, *Salmonella sp*, *Staphylococcus aureus*, *Enterobacter sp*, *Enterococcus faecalis*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Escherichia coli* and *Haemophilus influenzae* bacteria.

| compounds | Listeria monocytogenes | Staphylococcus aureus | Enterococcus faecalis | Salmonella sp | Enterobacter sp | Klebsiella pneumonia | Acinetobacter baumannii | Escherichia coli | Haemophilus influenza |
|-----------|------------------------|-----------------------|-----------------------|---------------|-----------------|----------------------|------------------------|----------------|---------------------|
|           | Gram +                 | Gram -                |                       |               |                 |                      |                        |                |                     |
| 1         | -                      | 2.5                   | 5                     | 5             | 5               | -                    | 5                      | 2.5            | 2.5                 |
| 2         | 2                      | 10                    | 1.25                  | -             | -               | -                    | 0.155                  | -              | 5                   |
| 1a        | 2                      | 0.0775                | 10                    | 2.5           | -               | -                    | -                      | -              | -                   |
| 1b        | -                      | -                     | -                     | 5             | -               | -                    | 10                     | -              | -                   |
| 1c        | -                      | -                     | 10                    | -             | -               | -                    | -                      | -              | -                   |
|    | 1d | 1e | 2a | 2b | 2c | 2d | 2e | DMSO |
|----|----|----|----|----|----|----|----|------|
|    |-  | -  | -  | -  | 10 | -  | -  | -    |
|    |-  | -  | -  | -  | 10 | 10 | -  | -    |
|    |-  | -  | 1.25| -  | -  | -  | -  | -    |
|    |-  | -  | -  | -  | -  | -  | -  | -    |
|    |-  | -  | -  | -  | -  | -  | -  | -    |
|    |-  | -  | -  | -  | -  | -  | 2.5 | -    |
|    |-  | -  | 0.625| -  | -  | -  | -  | -    |
|    |-  | -  | -  | -  | -  | -  | -  | -    |

- : Presence of growth (no MIC). DMSO: dimethyl sulfoxide as solvent.

### 3. Conclusion

In this work a series of five new compounds of 2-oxo-1,2-dihydroquinoline-6-carboxamides (1a, 1b, 1c, 1d and 1e), as well as another series of 5-bromo-2-oxo-1,2-dihydroquinoline-4-carboxamides containing five new corresponding components (2a, 2b, 2c, 2d, 2e) have been prepared. All synthesized products were purified by silica gel liquid column chromatography and their structures were characterized by both 1H and 13C NMR spectroscopy and mass spectrometry. Their antibacterial activities were evaluated against bacterial strains: *Gram* species, such as, *Listeria monocytogenes*, *Staphylococcus aureus* and *Enterococcus faecalis*; and *Gram* species, such as, *Salmonella sp*, *Enterobacter sp*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Escherichia coli* and *Haemophilus influenza*.

The component 1a presented the highest antibacterial activity against *Acinetobacter baumannii* strain with the MIC= 77.5 µg/ml, while the most synthesized compounds showed moderate antibacterial activity towards nine different bacteria strains.

### 4. Experimental

#### 4.1. General Methods

Reagents: Isatin 97%, malonic Acid 99%, sodium acetate >99%, thionyl chloride SOCl₂ 97%, triethylamine 99.5%, HBTU 98% and amino acids 99% (L-alanine, L-phenylalanine, L-phenylglycine, L-Serine and L-tryptophane), were purchased from Sigma-Aldrich. Analytical solvents: acetic acid 99.5%, dimethylformamide anhydrous 99.8%, ethyl acetate (HPLC-grade) and hexane (HPLC-grade) were purchased from Sigma-Aldrich.

Column liquid chromatography was performed on 60 Merck silica gel (230-400 mesh ASTM). Thin layer chromatography (TLC) was performed on Merck aluminum plates coated with 60 F254 Merck silica gel (thickness 0.2 mm), and the synthesized components were revealed by an ultra-violet lamp set at 254 nm. Melting points were determined by an Electrothermal IA 9000 Series digital fusimeter using capillary tubes.

NMR spectra were performed on Bruker DRX-300 AVANCE spectrometer at the “Cité Innovation” Sidi Mohamed Ben Abellah University of Fez. 1H NMR spectra were recorded at 300 MHz, and 13C NMR spectra were recorded at 75 MHz. Samples were dissolved in DMSO-d₆ or in CDCl₃. The chemical shift of different peaks was expressed in ppm, and the coupling constants in Hz. For describing the multiplicity of signals, the following abbreviations have been used: s: singlet, d: doublet, dd: doublet doublet, m: multiplet, t: triplet, q: quadruplet.

The high resolution mass spectra (HRMS) were registered in the EI (70 eV) or FAB mode and were reported as m/z (% of relative intensity) at the mass spectrometry service of the University of Valencia, Spain.

#### Synthesis of 2-oxo-1,2-dihydroquinoline-4-carboxylic acid 1

A mixture of isatin (0.013 mol), malonic acid (0.016 mol) and sodium acetate (1.9 mmol) dissolved in acetic acid solvent medium and heated under reflux during 24 hours. After cooling at room temperature, a quantity of water was added until precipitation formed, which will be filtered afterward.

#### Synthesis of 6-bromo-2-oxo-1,2-dihydroquinoline-4-carboxylic acid 2

A mixture of 5-bromo isatin (0.013 mol), malonic acid (0.016 mol) and sodium acetate (1.9 mmol) dissolved in acetic acid. Medium stirred and heated under reflux for 24 hours. The water was added to the mixture until formation of precipitate and then filtered.

#### General procedure for the protection of carboxylic acids groups derived from amino acids

An amount of SOCl₂ (2 mol) was added drop by drop to the methanol (MeOH) at 0 °C. After 15 min, the mixture was added to the amino acid (1 mol), stirred during 2 hours at room temperature and then heated under reflux for 2 hours. The excess of unreacted mixture of MeOH and SOCl₂ was removed using rotary evaporator. The remaining residue has been solubilized in MeOH and then an amount of diethyl ether was added until precipitation, followed by filtration.
General procedure for the preparation of 2-oxo-1,2-dihydroquinoline-4-carboxamides 1a-1e
A mixture of 2-oxo-1,2-dihydroquinoline-4-carboxylic acid (1 mol), amino acid (1.5 mol), hexafluorophosphate benzotriazole tetramethyl ureonium HBTU (1.1 mol) solubilized in 20 ml of DMF, and then 3.3 mol of triethylamine (TEA) was added in small amounts at 0 °C. After 20 min, the reaction is abandoned at room temperature during 12 hours.

General Procedure for the preparation of 6-bromo-2-oxo-1,2-dihydroquinoline-4-carboxamides, 2a-2e
A mixture of 6-bromo-2-oxo-1,2-dihydroquinoline-4-carboxylic acid (1 mol), amino acid (1.5 mol) and HBTU (1.1 mol) in 20 ml of dimethylformamide (DMF), and then 3.3 mol of triethylamine (TEA) was added in small amount at 0 °C. After 20 min, the reaction was abandoned at room temperature during 12 hours.

4.2. Disc diffusion method
The disc diffusion method 33 started by seeding the bacterial strains on the surface of Mueller Hinton agar. After 15 min the sterile waterman N°1 disc (diameter of 6mm) is placed on the surface each agar and impregnated 10 μl of compounds 1-2e (10 mg/ml of DMSO). Then petri dishes were incubated at 37 °C during 24 hours. After incubation, the absence of bacterial growth expressing antimicrobial activity by the presence of a translucent halo around the disc including a diameter measured with a caliper in mm.

4.3. Minimum inhibitory concentration (MIC)
The minimum inhibitory concentrations of the synthesized compounds were determined and based on the literature data by the method of Bouhid et al. 34 with some modification. The product was serially diluted in DMSO and the Brain Heart Infusion (BHI) nutrient agar has been sterilized. 140 μl of the sterilized medium was added to all microtiter wells using the microdilution method, containing 20 μl DMSO and a series of test product dilutions ranging from 10mg/ml to 0.0025 mg/ml. Then, 20 μl of bacterial inoculum was added to each well. The 12th well was considered as growth control. The microtplate was incubated at 37 °C during 24 hours and 10μl of triphenyltetrazolium (TTC) chloride was added to each well as a growth indicator. After 2h in incubation at 37°C the MIC is the lowest concentration that does not cause any change in TCC staining and corresponds to the absence of bacterial growth.

4.5. Characterization
Compound 1: 2-oxo-1,2-dihydroquinoline-4-carboxylic acid
Gray solid, mp=280 °C.
NMR 1H δ (ppm) 300 MHz, DMSO-d6 : 13.9 (s, broad, 1 H, OH), 12.17 (s, 1 H, NHquinoline), 8.15 (dd, 1 H, 3JH,H=8.1Hz, 4JH,H=1.2Hz, H2), 7.63 (tt, 1 H, 3JH,H=8.3Hz, 4JH,H=1.2Hz, H8), 7.23 (dd, 1 H, 3JH,H=8.28Hz, 4JH,H=1.2Hz, H6), 6.86 (s, 1 H, CH=CH=CH).
NMR 13C δ (ppm) 300 MHz, DMSO-d6: 167.2 (C=O acid), 163 (C=O amide quinoline), 141.7-139.8 (C4a-C6a), 131.3 (C5s), 126.5 (C7t), 123.8 (=C=O), 120 (C6s), 122.6 (C4s), 116.2 (C7s).
Mass Spectrometry: [MH]+ m/z=190.05.

Compound 2: 6-bromo-2-oxo-1,2-dihydroquinoline-4-carboxylic acid
Gray solid, mp=285°C.
NMR 1H δ (ppm) 300 MHz, DMSO-d6: 14.05 (s, broad, 1 H, OH), 12.22 (s, 1 H, NHquinoline), 8.42 (dd, 1 H, 3JH,H=1.8Hz, H2), 7.7 (dd, 1 H, 3JH,H=9Hz, 4JH,H=6.8Hz, H3), 7.30 (dd, 1 H, 3JH,H=9Hz, H6), 6.98 (s, 1 H, CH=CH=CH).
RMN 13C δ (ppm) 300 MHz, DMSO-d6: 166.7 (C=Oacid), 161.2 (C=Oamide), 139.6-139.0 (C4a-C6a), 133.8 (C5s), 128.7 (C7t), 125.9 (Croyl), 117.9 (C4s), 114.5 (C7s).
Mass Spectrometry: [MH]+ m/z=268, m/z=270 (M+2).

Compound 1a: methyl (2-oxo-1,2-dihydroquinoline-4-yl)-L-alaninate
White solid, mp=247°C.
NMR 1H δ (ppm) 300 MHz, DMSO-d6 : 11.94 (s, 1 H, NHquinoline), 9.17 (s, 1 H, 3JH,H=6.9Hz, NH), 7.75-7.21 (m, 4H, CH=CH=CH), 6.50 (s, 1 H, C=CH=CH), 4.69 (qd, 1 H, 3JH,H=7.2Hz, 4JH,H=6.9Hz, *CH=CH), 3.67 (d, 3H, CH3-O), 1.48 (d, 3H, CH3).
NMR 13C δ (ppm) 300 MHz, DMSO-d6: 173.19 (C=Oamide), 163 (C=Oamide quinoline), 161.70 (C=Oester), 146.29-139.65 (C4a-C6a), 131.37 (C5s), 126.39 (C7t), 122.67 (=C=CR), 122.42 (C4s), 120 (C6s), 116.1 (C5s), 52.62 (*CH=CH), 48.5 (CH3-O), 16.6 (CH3).
Mass Spectrometry: [MH]+ m/z=275.10, m/z=276.10 (M+1).

Compound 1b: methyl (2-oxo-1,2-dihydroquinoline-4-yl)-L-serinate
White solid, mp=211°C.
NMR 1H δ (ppm) 300 MHz, DMSO-d6 : 11.94 (s, 1 H, NHquinoline), 9.17 (s, 1 H, 3JH,H=6.9Hz, NH), 7.75-7.21 (m, 4H, CH=CH=CH), 6.50 (s, 1 H, C=CH=CH), 4.69 (qd, 1 H, 3JH,H=7.2Hz, 4JH,H=6.9Hz, *CH=CH), 3.8 (d, 2H, 3JH,H=9Hz, CH2-OH), 3.4 (s, 3H, CH3-O).
NMR 13C δ (ppm) 300 MHz, DMSO-d6: 171.01 (C=Oamide), 166.65 (C=Oamide quinoline), 161.70 (C=Oester), 146.29-139.65 (C4a-C6a), 131.32 (C5s), 126.39 (C7t), 122.42 (=C=CR), 122.42 (C4s), 120.42 (C6s), 116.70 (C5s), 61.3 (CH2-O), 55.77 (*CH=CH), 53.06 (CH3-O).
Mass Spectrometry: [MH]+ m/z=291.10, m/z=289.10 (M+1).

Compound 1c: methyl (2-oxo-1,2-dihydroquinoline-4-yl)-L-phenylglycinate
White solid, mp=211°C.
NMR 1H δ (ppm) 300 MHz, DMSO-d6 : 11.94 (s, 1 H, NHquinoline), 9.66 (s, 1 H, 3JH,H=5.6Hz, NH), 7.9-7
Compound 1d: methyl (2-oxo-1,2-dihydroquinoline-4-yl)-L-phenylalaninate

white solid, mp=211°C.

NMR: \( \delta \) (ppm) 300 MHz, DMSO-d6: 11.94 (s, 1 H, NH\( _{\text{quinoline}} \)), 9.17 (s, 1 H, \( ^3J_{\text{H-H}}=8 \text{Hz}, \text{NH} \)), 7.5-7 (m, 9H, Ar), 6.25 (s, 1H, CH\( _{\text{amide}} \)), 4.69 (dd, 1H, \( ^3J_{\text{H-H}}=8 \text{Hz}, \text{J}1\text{H}=10.8 \text{Hz}, \text{J}2\text{H}=4.8 \text{Hz}, \text{J}3\text{H}=13.8 \text{Hz}, \text{CH}_2\text{Ar}), 3.0 (dd, 1H, \( ^3J_{\text{H-H}}=10.8 \text{Hz}, \text{J}1\text{H}=13.8 \text{Hz}, \text{CH}_2\text{Ar})), 2.24 (s, 3H). Mass Spectrometry: [MH\(^+\)] m/z =357.13, m/z=352.13 (M+1).

Compound 1e: methyl (2-oxo-1,2-dihydroquinoline-4-yl)-L-tryptophan

Grey solide, mp=211°C.

NMR: \( \delta \) (ppm) 300 MHz, DMSO-d6: 11.94 (s, 1 H, NH\( _{\text{quinoline}} \)), 9.17 (s, 1 H, \( ^3J_{\text{H-H}}=8 \text{Hz}, \text{NH} \)), 7.5-7 (m, 9H, Ar), 6.25 (s, 1H, CH\( _{\text{amide}} \)), 4.69 (dd, 1H, \( ^3J_{\text{H-H}}=8 \text{Hz}, \text{J}1\text{H}=10.8 \text{Hz}, \text{J}2\text{H}=4.8 \text{Hz}, \text{J}3\text{H}=13.8 \text{Hz}, \text{CH}_2\text{Ar}), 3.0 (dd, 1H, \( ^3J_{\text{H-H}}=10.8 \text{Hz}, \text{J}1\text{H}=13.8 \text{Hz}, \text{CH}_2\text{Ar})), 2.24 (s, 3H). Mass Spectrometry: [MH\(^+\)] m/z =357.13, m/z=352.13 (M+1).

Compound 2a: methyl (6-bromo-2-oxo-1,2-dihydroquinoline-4-yl)-L-alanine

White solid, mp=290°C.

NMR: \( \delta \) (ppm) 300 MHz, DMSO-d6: 12.1 (s, 1 H, NH\( _{\text{quinoline}} \)), 9.17 (s, 1 H, \( ^3J_{\text{H-H}}=6.9 \text{Hz}, \text{NH} \)), 7.7-7.4 (m, 3H, Ar), 6.36 (s, 1H, CH\( _{\text{amide}} \)), 4.5 (qd, 1H, \( ^3J_{\text{H-H}}=7.5 \text{Hz}, \text{J}1\text{H}=6.9 \text{Hz}, \text{NH} \)), 7.3 (s, 3H, CH\( _2\text{Ar} \)), 1.40 (d, 3H, \( ^3J_{\text{H-H}}=6.9 \text{Hz}, \text{CH} \)). Mass Spectrometry: [MH\(^+\)] m/z =334.95, m/z=330.95 (M+1).

Compound 2b: methyl (6-bromo-2-oxo-1,2-dihydroquinoline-4-yl)-L-serinate

White solid, mp=270°C.

NMR: \( \delta \) (ppm) 300 MHz, DMSO-d6: 12.1 (s, 1 H, NH\( _{\text{quinoline}} \)), 9.17 (s, 1H, \( ^3J_{\text{H-H}}=8 \text{Hz}, \text{NH} \)), 7.7-7.4 (m, 3H, Ar), 6.36 (s, 1H, CH\( _{\text{amide}} \)), 5.64 (d, 1H, \( ^3J_{\text{H-H}}=7.6 \text{Hz}, \text{J}1\text{H}=8 \text{Hz}, \text{J}2\text{H}=4.8 \text{Hz} \)), 5.64 (d, 1H, \( ^3J_{\text{H-H}}=7.6 \text{Hz}, \text{J}1\text{H}=10.8 \text{Hz}, \text{J}2\text{H}=4.8 \text{Hz} \)), 3.7 (s, 3H, CH\( _2\text{O} \)). Mass Spectrometry: [MH\(^+\)] m/z =415, m/z=411 (M+2).

Compound 2c: methyl (6-bromo-2-oxo-1,2-dihydroquinoline-4-yl)-L-phenylglycinate

White solid, mp=270°C.

NMR: \( \delta \) (ppm) 300 MHz, DMSO-d6: 12.1 (s, 1H, NH\( _{\text{quinoline}} \)), 9.17 (s, 1H, \( ^3J_{\text{H-H}}=8 \text{Hz}, \text{NH} \)), 7.7-7.4 (m, 3H, Ar), 6.36 (s, 1H, CH\( _{\text{amide}} \)), 5.64 (d, 1H, \( ^3J_{\text{H-H}}=7.6 \text{Hz}, \text{J}1\text{H}=8 \text{Hz}, \text{J}2\text{H}=4.8 \text{Hz} \)), 7.8-7.2 (s, 3H, CH\( _2\text{O} \)). Mass Spectrometry: [MH\(^+\)] m/z =415, m/z=411 (M+2).
Mass Spectrometry: [MH]+ m/z = 429, m/z = 431 (M+2).

**Compound 2e**: methyl (6-bromo-2-oxo-1,2-dihydroquinoline-4-yl)-L-tryptophan.

White solid. mp=219°C.

NMR: 1H δ (ppm) 300 MHz, DMSO-d6: 12.1 (s, 1H, NH quinolone), 10.91 (s, 1H, NHtryptophane), 9.3 (d, 1H, J=7.5 Hz, NH), 7.2-6.99 (m, 8H, Ar and H4), 6.4 (CH3), 5.75 (dd, 1H, J1=9.6 Hz, J2=4.8 Hz, *CH-N), 3.72 (s, 3H, CH3-3), 3.2 (dd, 1H, J1=4.8 Hz, J2=4.8 Hz, CH2-Ar), 3 (dd, 1H, J1H=9.6 Hz, J2H=14.7 Hz, CH2-Ar).

NMR: 13C δ (ppm) 300 MHz, DMSO-d6: 171.95 (C=Oamide), 165.93 (C=Oamide quinolone), 161.30 (C=Oamide), 144.83-138.65 (C=Oamide), 136.61 (C=Oamide), 133.98 (C=C), 128.34 (C=C), 127.49 (C=C), 124.24 (C=C), 122.82 (C=C), 121.51 (C=ethylene), 118.92 (C=C), 118.49 (C=C), 118.26 (C=C), 114.29 (C=ethylene), 112.03 (C=C), 110.03 (C=C), 57.31 (*CH-N), 52.51 (CH2-O), 26 (CH2-Ar).

Mass Spectrometry: [MH]+ m/z = 468, m/z = 470(M+2).

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