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TOTAL SYNTHESIS OF PHENYLALANINE ANALOGUES

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ABSTRACT
A total synthesis of two phenyl alanine analogues derived from quinoline and naphthalene has been successfully completed. The synthesis of a set of small molecule intermediates leading to the analogues was carried out in nine steps involving reactions of the Heck and Suzuki cleavage reactions.

KEYWORDS: quinoline, naphthalene, Heck reaction, Suzuki reaction.

1. INTRODUCTION

Phenylalanine is an amino acid essential for the synthesis of proteins and other vital molecules such as neurotransmitters and hormones. Phenylalanine must be supplied by protein in the diet, but can also be consumed as a dietary supplement. Acyl-substituted L-phenylalanine.[1-14] derivatives have been described as highly potent antagonists of VLA-4 binding to VCAM-1. In the search for new antagonists, we identified the target molecules, phenyl alanine analogues derived from quinoline **1** and naphthalene **2** (Fig. 1).

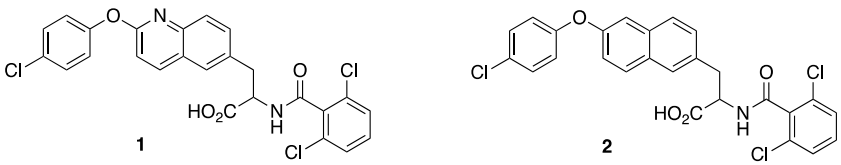
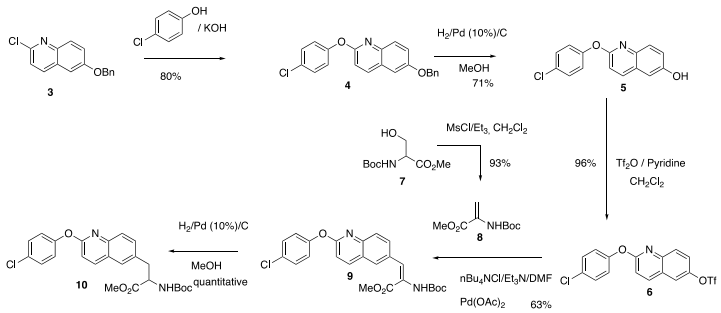


Fig 1: Phenyl alanine analogues derived from quinoline 1 and naphthalene 2

2. METERIALS AND METHODS

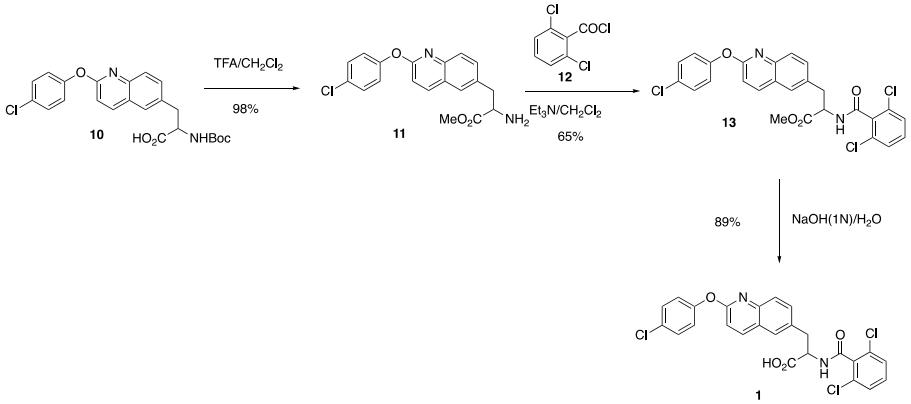
2.1 Method of synthesis of the molecules study

In the search for new agents antagonizing VLA-4 binding to VCAM-1, the synthetic route used for the preparation of the phenyl alanine analog derived from quinoline **1** is described in Scheme 1 and 2. The preparation of this quinoline derivative was carried out in nine steps and in this synthesis, optimized reaction conditions leading to compounds (**3-6, 8-11, 13, 1**) in satisfactory yields were used. As a result, quinoline 3 treated with para-chlorophenol using KOH led to compound **4** (80%). Hydrogenolysis of **4** in methanol provided **5** (71%). Treatment of 5 with anydride triflate gave **8** (96%). Compound **8** (93%) obtained by dehydration of **7**, was engaged in a Heck coupling reaction 15 with 6 to give compound 9 (63%). Hydrogenation[16] of **9** in methanol gave **10** (99%) (Scheme 1).



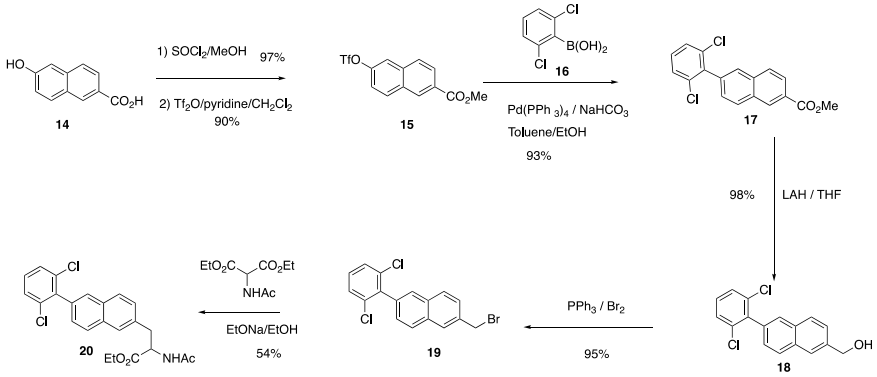
Scheme 1: Synthesis of intermediate 10.

Nitrogen de-protection of compound **10** with TFA gave **11** (98%). Acylation of **11** with acyl chloride **12** provided compound **13** (65%). Finally, saponification [17] of ester **13** led to the phenyl alanine analogue derived from quinoline **1** (89%) (Scheme 2).



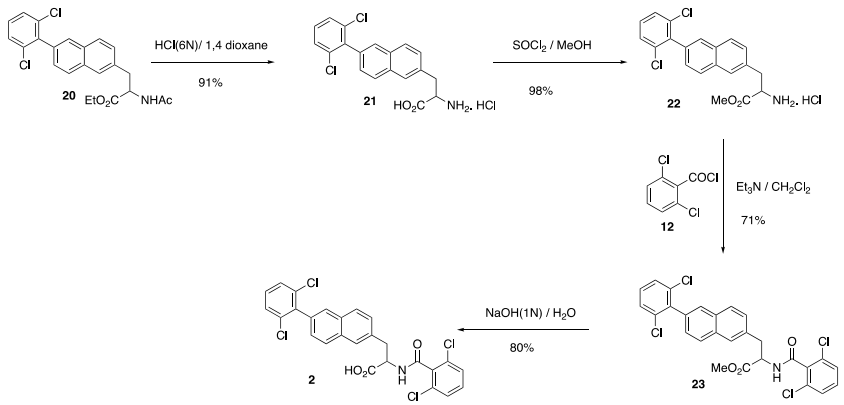
Scheme 2: Synthesis of the phenylalanine analog derived from quinoline 1.

The synthetic route used to prepare the phenyl alanine analog derived from Naphthalene **2** is described in scheme 3 and 4. The preparation of this Naphthalene derivative was carried out in nine steps. In this synthesis, optimized reaction conditions leading to compounds (**15, 17- 23, 2**) were used in satisfactory yields. Compound 15 was obtained in two steps via esterification (97%) followed by hydroxyl transformation to triflate derivative **15** (90%). Suzuki[18] coupling of **16** with **15** gave compound **17** (93%). Reduction of ester **17** with lithium hydride gave molecule **18** (98%). Transformation of benzyl alcohol **18** to benzyl bromide **19** (95%) was achieved with the triphenylphosphine/bromine reagent. Substitution of **19** with amino diester gave compound **20** (90%) (Scheme 3).



Scheme 3: Intermediate 19 synthesis.

Deprotection of the amido-ester **20** with hydrochloric acid (6N) gave compound **21** (91%). Esterification of **21** with $SOCl_2$ in methanol gave **22** (98%). Coupling of amino-ester 22 with acyl chloride 12 gave compound **23** (71%). Final product **2** (80%) was obtained by saponification of molecule **23** (Scheme 4).



Scheme 4: Synthesis of the phenylalanine analog derived from quinoline 2.

2.2 Experimental Details of the Synthesis of compounds

Experimental section

The ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ at ambient temperature on a Bruker AMX 300 spectrometer. Some products secured by DEPT 135, HMQC and HMBC experiments. Chemical shifts are given in δ (ppm) and coupling constants J (Hz) relative to TMS as internal standard; multiplicities were recorded as s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triple), q (quartet) or m (multiplet). Reactions involving anhydrous conditions were conducted in dry glassware under a nitrogen atmosphere. The infrared spectra have been recorded on a spectrometer Perkin-Elmer 842 (reference: polystyrene). The melting point have been measured on a Tottoli S Bucchi device. The microanalysis has been done on a Perkin-Elmer 2400-CMN apparatus. GC/MS conditions: Analyses were performed using a 5890-gas chromatogram connected to a G 1019 A mass spectrometer (both from Hewlett Packard) operating in the electro spray ionization mode (ESI).

2.2.1 Synthesis of phenylalanine derived from quinoline 1

Preparation of 6-benzyloxy-2-(4'-Chlorophenoxy)-quinoline 4

In a bicol equipped with a cooler are added successively a potassium hydroxide solution (0.519 g, 9.275 mmol) and (7.809 g, 60.742 mmol) of p-Chlorophenol. After one hour of stirring at 120°C is added (1 g, 3.71 mmol) **3**. The solution is heated under argon at 140°C for 6 hours with vigorous stirring. 5 mL of a sodium hydroxide solution (50% by mass) is added and the aqueous phase is extracted with ethyl acetate (3x10 mL). The organic phases are pooled, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue thus obtained is purified by chromatography on flash silica gel (eluent: ethyl acetate / petroleum ether (1/9) to give a semi-crystallized oil which by addition of methanol (5mL) a white solid corresponding to the derivative **4** precipitates with a yield of 80% (1.068 g).

Preparation of 6-hydroxy-2-(4'-Chlorophenoxy)-quinoline 5

To a methanol solution (10mL) are added successively **4** (0.470 g, 1.298 mmol) and 10% (0.130 mmol) palladium on charcoal (10%). The reaction is maintained under hydrogen pressure and stirred at room temperature overnight. After filtration on celite. After also concentration under reduced pressure, the residue obtained is purified by chromatography on flash silica gel (eluent: ethyl acetate / petroleum ether (3/7) to give an oil corresponding to the **5** derivatives with a yield of 71% (0.250 g).

Remark: during this hydrogenation, the formation of 2,6 -dihydroquinoline was observed, hence the reaction was followed every half hour by TLC

Preparation of 6-Trifluromethanesulfonyloxy-2-(4'-Chlorophenoxy)-quinoline 6

To a dichloromethane solution (8 mL) are added successively (0.250 g, 0.92mmol) of **5** and (0.223 mL, 2.76 mmol) of pyridine under Argon. After 15 minutes at 0°C is added (0.238 mL, 38 mmol) trifluoromethanesulfonyl anhydride. The temperature is gently raised to room temperature, the reaction left for 5 hours and then neutralized with $NaHCO_3$ solution.

The aqueous phase is extracted with dichloromethane (3x5 mL). The pooled organic phases are dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue thus obtained is purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (1/9)) to give a white solid corresponding to the **6** derivatives in 87% yield (0.793g).

Preparation of 2-methyl-N(tert-butoxycarbonyl)-acrylate 8

To a dichloromethane solution (15 mL) are added successively (7.187g, 32.781 mmol) N (tert-butoxycarbonyl)-D-serine methyl ester and (3.044 mL, 39.337 mmol) mesyl chloride.

At 50°C, triethylamine (13.64 mL, 98.343 mmol) is added under Argon. After 45 min, the reaction is kept at room temperature for 4 hours. The solution is poured into an ice bath (10 mL) and the aqueous phase extracted with dichloromethane (3x10 mL). The pooled organic phases are dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue thus obtained is purified by chromatography on flash silica gel (eluent Ethyl acetate / cyclohexane (2/8)) to give an oil corresponding to the **8** derivatives with a yield of 93% (6.113 g).

Be careful, the product 8 polymerizes very quickly, keep it in the refrigerator.

NB: When concentrating the solvents, the water bath must not exceed 25°C because the product polymerizes rapidly above that temperature.

Preparation 6-[methyl-2'-N(tert-Butoxycarbonyl)-acrylate]-2-(4'-Chlorophenoxy)-quinoline 9

To a DMF solution (8 mL) are added successively (0.671 g, 1.66 mmol) **6** and (0.022 g, 0.0996 mmol) palladium acetate. The solution is degassed under argon for 30 minutes and then (0.835g, 1.992mmol) **8**, (0.554g, 1.992mmol) tetrabutylammonium chloride and (0.276 mL, 1.992mmol) trimethylamine (previously distilled) are added. The solution is heated to 90-110°C for 3 hours and then poured into ice water (20 mL). The aqueous phase is extracted with ethyl acetate (3x15 mL). The pooled organic phases are dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue thus obtained is purified by chromatography on flash silica gel (eluent: ethyl acetate / petroleum ether (3/7)) to give a semi-crystallized oil corresponding to the **9** derivatives with a yield of 63% (0.474g).

Remark: On TLC we observe two spots corresponding to the two isomers E or Z.

Preparation 3-[2'-(4''-chlorophenoxy)-quinolin-6'-yl] N-(ter-Butoxycarbonyl-methyl ester) alanine 10

To a methanol solution (15 mL) are added successively **9** (0.474 g, 1.02 mmol) and 10% (0.104 mmol) palladium on charcoal (10%). The reaction is kept under hydrogen pressure and stirred at room temperature overnight. After filtration on celite, after concentration under reduced pressure, the residue obtained is pump dried to give an oil corresponding to the **10** derivatives with a quantitative yield (0.476 g).

Preparation of 3-(2'-(4''-chlorophenoxy-quinolin-6'-yl)) methyl ester alanine 11

A solution (0.425 g, 0.930 mmol) of **10** diluted in 5 mL of dichloromethane and a drop of anisole under Argon is stirred at 0°C in the presence of trifluoroacetic acid (1 mL, 12.85 mmol).

The temperature is gently raised to room temperature, the reaction left at this temperature for 2 hours. After concentration under reduced pressure, the residue obtained is diluted in ethyl acetate (6 mL) then neutralized with a $NaHCO_3$ solution (5%), the aqueous phase is extracted with ethyl acetate (4x5 mL). The pooled organic phases are dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue thus obtained is purified by flash silica gel chromatography (dichloromethane/methanol (90/10) eluent + 5% trimethylamine) to give an oil corresponding to the **11** derivative in 98% yield (0.326 g).

Preparation of N-[(2,6-dichlorophenyl) carbonyl] -3-[2'-(4''-chlorophenoxy)-quinolin-6'-yl] methyl ester-alanine 13

To a dichloromethanes solution (5 mL) are added successively (0.325 g, 0.911mmol) of **11** and (0.758 mL, 5.466 mmol) of trimethylamine. After 15 min, under argon pressure, 2,6-dichlorophenylcarbonylchloride (0196 mL, 1.366 mmol) is added dropwise. The reaction is maintained for 6 hours at room temperature. After addition of a saturated $NaHCO_3$ solution (5 mL), the aqueous phase is extracted with dichloromethanes (3x5 mL). The pooled organic phases are dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue thus obtained is purified by flash silica gel chromatography (eluent: Ethyl acetate/ petroleum ether (1/9) then (6/4) to give a semi-crystallized oil corresponding to the **13** derivatives with a yield of 65% (0.316 g).

Preparation of N-[(2,6-dichlorophenyl) carbonyl] -3-[2'-(4''-chlorophenoxy)-quinolin-6'-yl] alanine 1

To an acetonitrile solution (6.2 mL) are added successively (0.272g, 0.513 mmol) of **13** and (0.516 mL, 0.513 mmol) of sodium hydroxide (1N titrate) and 0.307 mL of water. The reaction is maintained for 3 hours at room temperature. After addition of a $KHSO_4$ solution (10%, 12.6 mL), the acetonitrile is concentrated under reduced pressure. The aqueous solution is taken up and extracted with ethyl acetate (2x5 mL). The pooled organic phases are washed with a saturated NaCl solution (5 mL) then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (a white foam) thus obtained is deposited on a frit and then washed with pentane (15 mL) to give a white powder corresponding to the **1** derivative in 89% yield (0.236 g).

2.2.2 Synthesis of phenyl alanine derived from naphthalene 2

Preparation of 6-Trifluoromethanesulfonyloxy-2-methylester-naphthalene 15

To a methanol solution (5 mL) at 0°C is added slowly (exothermic reaction), (0.1 mL, 1.276 mmol) of thionyl chloride. After 15 min under Argon pressure is added dropwise (0.200 g, 1.064 mmol) of 6-hydroxy-2-naphthaloic acid. The reaction is maintained for 12 hours at room temperature. The reaction is concentrated under reduced pressure and the residue thus obtained is purified by chromatography on flash silica gel (eluent gradient: ethyl acetate/cyclohexane (9/1) then (7/3) to give a brown solid corresponding to Ester derivative with a yield of 97% (0.209 g). And to a dichloromethane solution (83 mL) are added successively (2.481 g, 12.282 mmol of ester derivative (1.986 mL, 24.564 mmol) of pyridine under Argon.

After 15 min at -20°C is added (3.09 mL, 18.42 mmol) trifluoromethanesulfonyl anhydride. The temperature is gently raised to room temperature and stirred for 6 hours then the reaction is neutralized by a saturated solution of $NaHCO_3$. The aqueous phase is extracted with dichloromethane (3x15 mL). The pooled organic phases are dried on $MgS0_4$, filtered and concentrated under reduced pressure. The residue thus obtained is purified by flash silica gel chromatography (eluent: ethyl acetate / cyclohexane (8/2) to give a solid corresponding to the **15** derivatives in 90% yield (3.684 g).

Preparation of 6-(2,6-dichlorophenyl)-2-metyhl ester-naphthalene 17

To a toluene solution (9 mL) are added successively (0.150 g, 0.448 mmol) of **15** and (0.0255 g, 0.0224 mmol) of freshly prepared Tetrakis (Tetraphenylpalladium). The homogeneous solution is stirred for 30 min under Argon at room temperature then boronic acid **16** (0.128 g, 0.612 mmol) diluted in 5.4 mL ethanol and 3.6 mL of a saturated solution of $NaHCO_3$ are added successively. After cooling, the reaction medium is extracted with toluene (3x5 mL) The pooled organic phases are dried on $MgS0_4$, filtered and concentrated under reduced pressure. The residue thus obtained is purified by chromatography on flash silica gel (eluent: ethyl acetate / cyclohexane (4/6) to give a semi-crystallized oil corresponding to the **17** derivatives with a yield of 93% (0.139 g).

Preparation of 6-(2,6-dichlorophenyl)-2-hydroxymetyhlene-naphthalene 18

To a THF solution (10 mL) are added successively (0.170 g, 4.497 mmol) of aluminum lithium tetrahydride and (0.596 g, 1.799 mmol) of **17**. The solution is stirred under Argon at room temperature for 2 hours. The reaction medium is treated by pelletization, using water and then filtered on celite. The residue is concentrated under reduced pressure to give an oil corresponding to the **18** derivatives in 98% yield (0.537 g).

Preparation of 6-(2,6-dichlorophenyl)-2-bromomethylene-naphthalene 19

To a dichloromethane solution (1 mL) containing (0 .9576 mmol) triphenylphosphine is added dropwise at 0°C (0 .049 mL, 0.9576 mmol) bromine previously diluted in 1 mL dichloromethane. After 30 min, (0.242 g, 0.798 mmol) of **18** is added and the solution is stirred under Argon at room temperature for 6 hours. The reaction is treated by addition of water (2 mL) and the aqueous phrase is extracted with dichloromethane (3x5 mL). The pooled organic phrases are dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue is purified by flash silica gel chromatography (eluent: ethyl acetate/cyclohexane (4/6)) to give a semi-crystallized oil corresponding to the **19** derivative in 95% yield (0.278 g).

Preparation of N-(Acetamido)-3-(6-(2,6-dichlorophenyl) naphthalen-2-yl) alanine ethyl ester 20

To an ethanol solution (5 mL) containing (0.092 g, 4.010 mmol) sodium is added (0.870 g, 4.007 mmol) N-acetamidomalonate after total dissolution of sodium. The solution is stirred for 1 h then through a cannula a solution of {(0.978 g, 2.671 mmol) **19** and 5 mL ethanol} is added under Argon. The reaction medium is refluxed with ethanol for 5 hours. After addition of 5 mL of water, the solution is concentrated under reduced pressure then diluted with ethyl acetate (5 mL). The aqueous phase is extracted with ethyl acetate (3x15 mL). The pooled organic phases are dried over MgSO4, filtered and concentrated under reduced pressure. The residue thus obtained is purified by chromatography on silica gel (eluent gradient: ethyl acetate/cyclohexane (2/8) then (4/6)) to give a semi-crystallized oil corresponding to the **20** derivatives with a yield of 54% (0.625 g)

Preparation of 6-[(2,6-dichlorophenyl) naphthalen-2-yl] alanine chloride 21

To a solution of 1,4-dioxane (2.2 mL) are added successively 8.33 mL of hydrochloric acid (6N) and (0.625 g, 1.452 mmol) of **20**. The solution is stirred and heated under reflux of 1 ,4-dioxane for 4 hours. After cooling the reaction medium, ethyl ether (5 mL) is added. The aqueous phase is extracted with ethyl ether (3x5 mL) and concentrated under reduced pressure. The residue thus obtained is evaporated to dryness to give a white solid corresponding to the **21** derivatives with a yield of 91% (0.527 g).

Preparation of 6-[(2,6-dichlorophenyl) alanine methyl ester chloride acid 22

To a methanol solution (10 mL) at 0°C is added slowly (hexothermic reaction) (0.776 mL, 10.63 mmol) thionyl chloride. After 15min under argon pressure is added dropwise (0.527 g, 1.328 mmol) of **21**. The reaction is maintained for 12 hours at room temperature. The solution is diluted with 5 mL of toluene and concentrated under reduced pressure to give a white solid corresponding to the **22** derivatives in 98% yield (0.534 g).

Preparation of N-[(2,6-dichlorophenyl) carbonyl]-3-[6-(2,6-dichlorophenyl) naphthalen -2-yl] alanine methyl ester 23

To a solution of dichloromethanes (5 mL) are added successively (0.141 g, 0.3431 mmol) of **22** and (0.285 mL, 2.058 mmol) of trimethylamine. After 15 min, under argon pressure, 2,6-dichlorophenylcarbonylchloride (0.086 mL, 0.412 mmol) is added dropwise.

The reaction is maintained for 6 hours at room temperature. After addition of a saturated $NaHCO_3$ solution (5 mL), the aqueous phase is extracted with dichloromethanes (3x10 mL).

The pooled organic phases are dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue thus obtained is purified by flash silica gel chromatography (eluent gradient: Ethyl acetate/cyclohexane (3/7) then (6/4) to give a semi-crystallized oil corresponding to the **23** derivatives with a yield of 71% (0.133 g).

Preparation of N-[(2,6-dichlorophenyl) carbonyl]-3-[6-(2,6-dichlorophenyl) naphthalen-2-yl] alanine 2

To an acetonitrile solution (2.5mL) are added successively (0.113 g, 0.206 mmol) of **23** and (0.208 mL, 0.206 mmol) of sodium hydroxide (1N titrated) and 0.124 mL of water.

The reaction is maintained for 3 hours at room temperature. After addition of a $KHSO_4$ solution (10%, 5.1 mL), the acetonitrile is concentrated under reduced pressure. The aqueous solution is taken up and extracted with ethyl acetate (2x 5 mL). The pooled organic phases are washed with a saturated solution of NaCl (5 mL) then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue thus obtained is triturated in a solution of ethyl acetate/pentane (2/8) to give a white powder corresponding to the 2 derivatives with a yield of 80% (0.089 g).

3. RESULTS

Characteristics of Synthetic Molecules

6-benzyloxy-2-(4'-Chlorophenoxy)-quinoline 4

IR (KBr) cm^{-1}: 1621,01(C=C aromatic); 1210,05(=C-O-C=) SM (spray ion): 362.0 $(M+1)^+$

^1H NMR (250MHz, $CDCl_3$) δppm: 5.21 (s, 2H, CH_2); 8.02-7.05 (m, 14 H aromatic). **^{13}C** NMR (62. 5MHz, $CDCl_3$) δppm: 70.7 CH_2; 107.7=CH; 113.3 =CH; 122.7=CH; 123.1 (2_XCH); 127.3 Cq; 128.0 (2x=CH); 128.6=CH; 129.1 (2_XCH); 129.7=CH; 129.9 (2x=CH); 137.4 Cq; 138.3=CH; 139.7 Cq; 142.6 Cq; 153.4 Cq; 160.7 Cq.

RF: 0.25 [ethyl acetate/petroleum ether (1/9)]

bp=86°C

6-hydroxy-2-(4'-Chlorophenoxy)-quinoline 5

IR (NaCl) cm^{-1}: 3418.09 (OH); SM (spray ion): 272.0 $(M+1)^+$

^1H NMR (250MHz, $dmsod_6$) δppm: 8.22-7.15 (m, 9 H aromatic); 12.70 (s broad, 1H, OH).

^{13}C NMR (62.5MHz, $CDCl_3$) δppm: 110.7=CH; 114.5=CH; 123.4=CH; 124.9 (2x=CH); 128, 44 Cq; 130.0 =CH; 131.1 (2x=CH); 140.5=CH; 141.6 Cq; 155.5Cq; 160.9 Cq.

RF: 0.3 [ethyl acetate / petroleum ether (3/7)]

6-Trifluromethanesulfonyloxy-2-(4'-Chlorophenoxy)-quinoline 6

IR (KBr) cm^{-1}: 1613.61(C=C aromatic); 1251.03 (=C-O-); SM (spray ion): 404.0 $(M+1)^+$

^1H NMR (250 MH_Z, $CDCl_3$) δppm: 8.54-7.23 (m, 9 H aromatics). ^{13}C NMR (62.5 MHz, $CDCl_3$) δppm: 117.0 =CH; 121.0 =CH; 122.1 (2xCH); 122.9 =CH; 124.9 =CH; 126.9 Cq; 127.9 Cq; 127.0 Cq; 130.5 (2x =CH); 141.8 =CH; 146.1 Cq; 146.6 Cq; 154.3 Cq; 163.4 Cq; 163.6 Cq.

bp= 114°C

2-methyl-N(tert-butoxycarbonyl)-acrylate 8

IR (NaCl) cm^{-1}: 3423.62(NH); 1715.25 (CO ester); SM (spray ion): 202.0 $(M+1)^+$

^1H NMR (250 MH_Z, $CDCl_3$) δppm: 1.91 (s, 9H, $C(CH_3)_3$); 3.92 (s, 3H, CH_3); 5.71(s, 1H, CH); 6.10 (s, 1H, CH); 6.95(wide s, 1H, NH). ^{13}C NMR (62.5 MH_Z, $CDCl_3$) δppm: 28.5 $C(CH_3)_3$; 53.1 CH_3; 80.8 Cq; 105.3 $=CH_2$; 131.6 Cq; 152.8 Cq; 164.7 Cq.

Rf= 0.3 [ethyl acetate /cyclohexane (2/8)]

6-[methyl-2'-N(tert-Butoxycarbonyl)-acrylate]-2-(4'-Chlorophenoxy)-quinoline 9

IR (KBr) cm^{-1}: 3372.93(NH); 1737.75 (CO ester); 1698.49 (CO amide); SM (spray ion): 455.0 $(M+1)^+$

^1H NMR (250 MHz, $CDCl_3$) δppm: 1.38 (s, 9 H $C(CH_3)3$); 3.85(s, 3H, CH_3); 4.63(s broad, 1H, NH); 6.59(s, 1H, CH); 7.03-8.05(m, 9 H aromatic). ^{13}C NMR (62. 5 MHz, $CDCl_3$) δppm: 29.8C $(CH_3)_3$; 54.4 CH_3; 82.8C$(CH_3)_3$; 121.8 =CH; 123.3 =CH; 125.3= CH; 127.6 Cp; 128.1= CH; 129.8 =CH; 129.8 =CH; 130.0=CH; 130.9=CH; 131.7Cq; 132.3= CH; 140.4 Cq; 140.6 Cq; 148.1 Cq; 153.7 Cq; 155.4 8 Cq; 163.7 Cq; 164.1 Cq; 167.7 Cq;

Rf: 0.25 [ethyl acetate/petroleum ether (3/7)]

3-[2'-(4''-chlorophenoxy)-quinolin-6'-yl] N-(ter-Butoxycarbonyl-methyl ester) alanine 10

IR (NaCl) cm^{-1}: 3433.36(NH); 1745.84 (CO ester); 1714.93 (CO amide); SM (spray ion): 457.0 $(M+1)^+$

^1H NMR (250 MHz, $CDCl_3$) δppm: 1.41 (s, 9 H $C(CH_3)3$); 3.24(m, 2H, CH_2); 3.71(s, 3H, CH_3); 4.64 (m, 1H, CH); 5.09 (wide s, 1H NH);8.09-7.06 (m, 9 H aromatic). ^{13}C NMR (62. 5 MHz, $CDCl_3$) δppm: 28.7 $C(CH_3)3$; 38.6 CH_2; 52.8 CH_3; 54.9CH; 80.5 $C(CH_3)3$; 113.3= CH; 121.7=CH; 123.2= CH; 125.9 =CH; 127.9 Cp; 128.2=CH; 129.9=CH; 131.8=CH; 132.0= Cq; 140.2 CH; 140.4 CH; 145.6 Cq; 154.1 Cq; 155.5 Cp; 163.7 Cq; 161.9 Cp; 172.6 Cp;

Rf: 0.3 [ethyl acetate/petroleum ether (4/6)]

3-(2'-(4''-chlorophénoxy-quinolin-6'-yl) methyl ester alanine 11

IR (NaCl) cm^{-1}: 3440.93(NH_2); 1738.64 (CO ester); SM (spray ion): 357.81 $(M+1)^+$

^1H NMR (250 MHz, $CDCl_3$) δppm: 2.80-3.45 (m, 4H, CH_2+NH_2); 3.66 (s broad, 4H, CH+CH_3); 8.01-6.88 (m, 9H aromatic). ^{13}C NMR (62. 5 MHz, $CDCl_3$) δppm: 38.5 CH_2; 52.9 CH_3; 5.4 CH; 113.3 =CH; 121.2 =CH; 123.2 = CH; 125.1 = CH; 127.9 =Cq; 127.8 = CH; 128.3 =CH; 128.5 =CH; 129.9 =CH; 130.0=CH; 131.4 = CH; 140.1 =CH ;154.6 Cp; 156.1 Cp; 161.6 Cp; 163.6 Cp; 164.0 Cq; 173.7 Cp.

Rf :0,3 [dichloromethanes /methanol (90/10) + 5% trimethylamine (9/1)]

N-[(2,6-dichlorophenyl) carbonyl] -3-[2'-(4''-chlorophenoxy)-quinolin-6'-yl] methyl ester-alanine 13

IR (NaCl) cm^{-1}: 3418,4 (NH); 1746,43 (CO ester); 1651,59 (CO amide); SM (spray ion) :530,0 $(M+1)^+$

^1H NMR (250 MHz, $CDCl_3$) δppm: 3.42 (m, 2H, CH_2); 3.76 (s, 3H, CH_3); 5.26 (m, 1H, CH), 6.41 (d, J=7.54Hz, 1H, NH); 8.12 - 7.04 (m,12 H aromatic). ^{13}C NMR (62. 5 MHz, $CDCl_3$) δppm: 39.5 CH_2; 54.1 CH_3; 55.0 CH; 114.5 =CH; 122.9 =CH; 124.4 = CH; 126.2 = CH; 127.1=CH; 127.4 Cq; 129.6 (3x=CH); 131.0=CH; 132.4 =CH; 132.8 Cq; 132.9 CH; 133.7 Cq; 133.8 Cq; 136.8 (2xCq); 140.9 =CH;147.1 Cq; 153.7 Cp; 155. 3 Cp; 163.2 Cp; 165.4 Cp; 172.8 Cp.

Rf :0,25 [petroleum ether / ethyl acetate (4/6)]

N-[(2,6-dichlorophenyl) carbonyl] -3-[2'-(4''-chlorophenoxy)-quinolin-6'-yl] alanine 1

IR (NaCl) cm^{-1}: 3395.79 - 3067.72 (NH+ OH acid); 1737.04 (CO acid); 1651.49 (CO amide)

SM (spray ion): 516.0 $(M+1)^+$

^1H NMR (250 MHz, $dmso-d_6$) δppm: 3.01-3.33 (m, 2H, CH_2); 4.81 (m, 1H, CH);7.22-8.32 (m, 12H aromatics); 9.16 (d, J= 6.2 Hz, 1H, NH); 12.62 (s broad, 1 H, OH acid). ^{13}C NMR (62. 5 MHz, $dmso-d_6$) δppm: 37.4 CH_2;

54.3 CH_3; 113.7 =CH; 122.4 =CH; 124.4= CH; 125.6 = CH; 126.4= Cq; 127.6=CH; 128.8 (2x= CH); 130.5 =CH; 131.7=CH; 132,6=CH; 132,7=CH; 135,2 Cq; 135,3 Cq; 137,2 Cq; 141,1= CH; 145,6 Cq; 153,2 Cq; 154,5 Cq; 161,8 Cq; 162,1 Cq; 164,5 Cq; 173,3 Cq.
bp :118-120°C

6-hydroxy-2-methyl ester-naphthalene (ester)
IR (KBr) cm^{-1}:3450. 52 (OH); 1693. 26 (CO ester). SM (spray ion): 202. 0 $(M+1)^+$
^1H NMR (250 MHz, dmso-d_6) δppm: 3, 96 (s, 3H, CH_3) 7-7.14 (m, 6H aromatic). ^{13}C NMR (62.5 MHz, dmso-d_6) δppm: 52.8 CH_3; 109.5 =CH; 120.5 =CH; 123.2 Cq; 124.6 =CH; 125.9 =CH; 126.2 Cq; 130.1=CH; 130.8=CH; 136.7 Cq; 157.4 Cq; 166.1 Cq.
Rf: 0, 25 (ethyl acetate / cyclohexane (7/3)
bp= 172°C

6-Trifluoromethanesulfonyloxy-2-methylester-naphthalene 15
IR (KBr) cm^{-1}: 1719, 79 (CO ester); SM (spray ion): 334, 0 $(M+1)^+$
^1H NMR (250 MHz, dmso-d_6) δppm: 3, 95 (s, 3H, CH_3) 8, 72-7, 55(m, 6H aromatic). ^{13}C NMR (62.5 MHz, dmso-d_6) δppm: 53.2 CH_3; 120.2 =CH; 121.5 =CH; 126.8 Cq; 127.2 =CH; 129.1 =CH; 129.6 Cq; 131.3 Cq; 132.1 =CH; 133.5 =CH; 139.6 Cq; 154.2 Cq; 166.7 Cq.
Rf: 0, 25 (ethyl acetate / cyclohexane (8/2)
bp= 66°C

6-(2,6-dichlorophenyl)-2-metyhl ester-naphthalene 17
IR (NaCl) cm^{-1}: 1716, 46 (CO ester); SM (spray ion): 331, 0 $(M+1)^+$
^1H NMR (250 MHz, dmso-d_6) δppm: 3, 92 (s, 3H, CH_3) 8, 73-7, 65(m, 9H aromatic). **^{13}C** NMR (62.5 MHz, dmso-d_6) δppm: 53.1 CH_3; 126.1 =CH; 128.3 Cq; 129.0 =CH; 129.2 =CH; 129.3 (3x=CH); 129.5=CH; 130.4 =CH; 131.2 =CH; 131.3 =CH; 132.4 Cq; 134.7 (2xCq); 135.6 Cq; 137.3 Cq; 139.1 Cq; 167.1 Cq.
Rf: 0, 25 (ethyl acetate / cyclohexane (8/2)
bp= 66°C

6-(2,6-dichlorophenyl)-2-hydroxymetyhlene-naphthalene 18
IR (NaCl) cm^{-1}: 3355, 06 (OH); SM (spray ion): 303, 0 $(M+1)^+$
^1H NMR (250 MHz, $CDCl_3$) δppm: 2, 76 (s, broad 1H, OH); 4, 82 (s, 2H, CH_2); 7, 87-7, 22 (m, 9H aromatic). ^{13}C NMR (62.5 MHz, $CDCl_3$) δppm: 64.4 CH_2; 125.6 =CH; 126.0 Cq; 127.4 =CH; 127.9 =CH; 128.1 (2x=CH); 128.4=CH; 128.6 =CH; 130.5 =CH; 132.1 =CH; 132.4 Cq; 134.4 (2xCq); 135.7 Cq; 137.6 Cq; 138.3 Cq.
Rf: 0.3 (ethyl acetate / cyclohexane (4/6)

6-(2,6-dichlorophenyl)-2-bromomethylene-naphthalene 19
IR (NaCl) cm^{-1}: 1557.07; SM (spray ion): 366,0 $(M+1)^+$
^1H NMR (250 MHz, $CDCl_3$) δppm: 4.70 (s, 2H, CH2); 7.94 -7.22 (m, 9 H aromatic). **^{13}C** NMR (62.5 MHz, $CDCl_3$) δppm: 34.3 CH2; 127.6 =CH; 128.2 Cq; 128.2 =CH; 128.4 +CH; 128.5 (2x=CH); 129.1 =CH; 129.6 =CH; 129.8 =CH; 133.0 =CH; 133.1 Cq; 135.4 (2xCq); 135 Cq; 136.2 Cq; 139.6 Cq.
Rf: 0.3 (ethyl acetate / cyclohexane (4/6)

N-(Acetamido)-3-(6-(2,6-dichlorophenyl) naphthalen-2-yl) alanine ethyl ester 20
IR (NaCl) cm^{-1}: 1737.77 (CO ester); 1660.23 (CO amide); SM (spray ion): 430.0 $(M+1)^+$
^1H NMR (250 MHz, $CDCl_3$) δppm: 1.11 (t, J = 8.1 Hz, 3 H, CH_3); 1.88 (s, 3 H, CH_3); 3.41-3.15 (m, 2 H, CH_2); 4.24 (q, J = 8.1 Hz, 2H, CH_2); 4.42 (m, 1H, CH); 7.92-7.22 (m, 9 H aramatic). ^{13}C NMR (62.5 MHz, $CDCl_3$) δppm: 13.6 CH_3; 21.4 CH3; 37.4 CH_2; 54.5 CH; 67.6 CH_2; 127.5 =CH; 127.8 Cq; 127.9 =CH; 128.0 =CH; 128.1 (2x=CH); 128.5 =CH; 128.7 =CH; 129.3 =CH; 129.4 =CH; 132.7 Cq; 134.8 (2xCq); 135.3 Cq; 135.7 Cq; 139.9 Cq; 171.97 Cq; 172.37 Cq.
Rf: 0.25 (ethyl acetate / cyclohexane (4/6)

6-[(2,6-dichlorophenyl) naphthalen-2-yl] alanine chloride 21
IR (KBr) cm^{-1}: 3500 - 300 (NH_2, Acid); 1758,31 (CO acid); SM (spray ion): 396,0 $(M+1)^+$
^1H NMR (250 MHz, MeOD) δppm: 3.53-3.90 (m, 2H, CH_2); 4.65 (m, 1 H, CH); 7.55-8.20 (m, 9H aromatic). ^{13}C NMR (62. 5 MHz, MeOD) δppm: 37.4 CH_2; 54.9 CH_3; 127.2=CH; 128.4Cq; 128.8= CH; 128.9 = CH; 129.3 (2x=CH); 129.5=CH; 129.6 = CH; 130.1 =CH; 130.8=CH; 133.7 Cq; 134.3 (2xCq); 136.0 Cq; 136.1 Cq;140.5 Cq; 171.16 Cq.
bp: 212-216°C

6-[(2,6-dichlorophenyl) alanine methyl ester chloride acid 22
IR (KBr) cm^{-1}: 3460.54 (NH_2); 1744.41 (CO ester); SM (spray ion): 410,0 $(M+1)^+$
^1H NMR (250 MHz, dmso-d_6) δppm**:** 3.30-3.72 (m, 2 H, CH_2); 3.80 (s, 3 H, CH_3); 4.43(m, 1H, CH), 7.90-7.08 (m, 9H aromatic). ^{13}C NMR (62. 5 MHz, dmso-d_6) δppm: 37.2 CH_2; 53.6 CH_3; 54.8 CH; 125.8=CH; 128.0 Cq; 128.4 = CH; 128.5=CH;129.1 (2x=CH); 129.2 = CH; 129.4 =CH; 129.8=CH; 130.5=CH; 130.7 Cq; 133.0 Cq; 133.9 Cq; 135.5 Cq; 138.3 Cq, 140.0 Cq; 169.91 Cq.
bp:146-148°C

N-[(2,6-dichlorophenyl) carbonyl]-3-[6-(2,6-dichlorophenyl) naphthalen -2-yl] alanine methyl ester 23
IR (NaCl) cm^{-1}: 3276,19 (NH); 1740,80 (CO ester); 1654,91 (CO amide); SM (spray ion): 548.0 $(M+1)^+$
^1H NMR (250 MHz, $CDCl_3$) δppm: 3.46 (m, 2 H, CH_2); 3.81 (s, 3 H, CH_3);5.31 (m, 1 H, CH), 6.37 (d, J=7.54 Hz, 1 H, NH); 7.70 - 7.20 (m,12 H aromatic). ^{13}C NMR (62. 5 MHz, $CDCl_3$) δppm: 37.8 CH_2; 52.0 CH_3; 52.7 CH; 126.09 =CH; 127.0 Cq; 127.9 = CH; 128.1 = CH; 128.2=CH; 128 5 (3x=CH); 128.9=CH; 129.0=CH;

129.5=CH; 131.3=CH; 131.8= CH; 132.3 Cq; 134.5 (2x Cq) ;135.5Cq; 138.815 Cq; 163.4Cq; 170.7 Cp.
Rf: 0.25 [ethyl acetate/cyclohexane (6/4)]

N-[(2,6-dichlorophenyl) carbonyl]-3-[6-(2,6-dichlorophenyl) naphthalen-2-yl] alanine 2

IR (KBr) cm^{-1}: 3395.5-3274.94 (NH, OH acid); 1737.14 (CO acid); 1654.62 (CO amide).
SM (spray ion): 534.0 $(M+1)^+$
^1H NMR (250 MHz, dmso-d_6) δppm: 3.17 (m, 2 H, CH_2); 4.82 (m, 1 H, CH); 7.94-7.34 (m, 12 H, aromatic), 9.16 (d, J =6, 1 Hz, 1 H, NH). ^{13}C NMR (62.5 MHz, dmso-d_6) δppm: 37.3 CH_2; 53.7 CH; 126.1=CH; 128.3 Cq; 129.0 = CH; 129.2=CH ;128.6=CH; 129.3(3x = CH); 129.7 =CH; 130.5=CH; 131.5=CH; 131.9=CH; 132.6= CH; 133.7 Cq ;134.4 (2xCq); 136.0 Cq, 136.4 Cq; 139.1 Cq; 163.7 Cq; 172.5 Cq.
bp:118°C

4. CONCLUSION

In this study we have described the total synthesis of two phenyl alanine analogues in nine studies using a highly flexible chemistry. All synthetic intermediate steps were optimized with good yields. Biological evaluation of these compounds is currently underway in our laboratory and will be described later.

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