opySynthesis and Antibacterial Activity of α-Aminophosphonates Bearing Neocryptolepine Moiety

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Abstract: A novel amino-substituted neocryptolepine analogues **7** have been synthesized starting from methyl-1H-indole-3-carboxylate and *N*-methylaniline. The three pot reaction of **7** with aldehydes and triphenylphosphite in presence of zinc (II) triflate as a Lewis acid catalyst led to the formation of novel α-aminophosphonate derivatives **10** bearing neocryptolepine moiety in good yields. The synthesized compounds have been characterized on the basis of elemental analysis and spectral studies. The synthesized products have been screened *in vitro* for thei antibacterial.

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Key words: neocryptolepine, α-aminophosphonates, Lewis acid, antibacterial agents

Introduction:

Natural products still play an important role in drug discovery. About 30% of new chemical entities approved as drugs by the U.S. Food and Drug Administrator (FDA) from 1981 to 2002 were natural product derived molecules.[1-4] In search for novel antibactrial agents, we focused on minor alkaloids of *Cryptolepis sanguinolenta* such as neocryptolepine (5-methyl-5H-indolo[2,3-*b*]quinoline) **I**. Neocryptolepine and its derivatives exhibited a wide range of biological properties including antimalarial and anticancer activities.[5] As phosphorus analogs of α-amino acids **II** and their esters, α-aminophosphonates **III** (*cf.* fig. 1), are widely studied as biologically active substances.

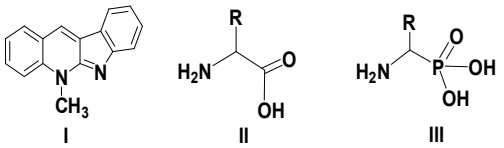


Figure 1: Structures of neocryptolepine I, α-amino acid II and α-aminophosphonates III

They exhibit antibacterial,[6-8] anticancer,[9-13] insecticidal,[14-16] hypoglycemic,[17-18] herbicidal[19-21] properties and are investigated as starting materials for the synthesis of phosphonopeptides.[22] α-Functionalized organic phosphonates are valuable medical compounds and synthetic intermediates. However, the synthesis and biological activities of neocryptolepine modified phosphonates have never been reported. In a further exploration of the biological potential of the neocryptolepine core aiming to increase activity, we will explore the introduction of amino group at the 11th position of the skeleton for structure-activity relationship (SAR) studies. In this paper, we describe the synthesis and in vitro antibacterial activity of synthesized neocryptolepine modified α-aminophosphonates. Moreover, the preliminary structure-activity relationships of these compounds will also investigated.

Materials and Methods

General Methods: All ^{1}HNMR experiments (solvent DMSO and $CDCl_3$) were carried out with a 400 M*Hz* Bruker Avance DRX-400 spectrometer at Okayama University, Japan. Chemical shifts are reported in part per million (ppm) relative to the respective solvent or tetramethylsilane (TMS). Melting points were recorded on Stuart scientific melting point apparatus and are uncorrected. The mass spectroscopy and the microanalysis were performed in microanalysis laboratory at Cairo University. All reactions were followed by thin layer chromatography (TLC) on kiesel gel F254 precoated plates (Merck). Anhydrous THF, MeOH and CH_2Cl_2 were obtained from Sigma-Aldrich. Starting materials were either commercially available or prepared as reported in literature.

Synthesis of methyl-2-(methyl(phenyl)amino)-1H-indole-3-carboxylate (3): To a solution of methyl-1H-indole-3-carboxylate **1** (1 gm, 5.70 mmol) in dichloromethane (25 mL) at 0˚C under argon, *1,4*-dimethylpiperazine (0.37g, 3.36 mmol) and *N*-chlorosuccinimide (0.87 g, 6.52 mmol) were added. The reaction mixture was allowed to stand at 0˚C for 2h and a solution of trichloroacetic acid (0.25 g, 1.53 mmol) and an *N*-methyl aniline **2** (0.61 gm, 5.71 mmol) in dry dichloromethane (25 mL) was added and the reaction mixture was allowed to attain room temperature. The reaction mixture was washed with

10% aqueous $NaHCO_3$ and 1.0 M aqueous HCl and finally with water and brine. The resulting solution was dried, filtered and evaporated. The residue was chromatographed using (hexane/EtOAc 3:1) as eluent to yield title compounds.Yield: 1.2 g (75%), m.p 146-147ºC. ^{1}H NMR ($CDCl_3$, 400M*Hz*, δ ppm) 3.65 (s, 3H, O-CH_3), 3.35 (s, 3H, CH_3), 6.7- 6.8 (m, 2H, Ph), 6.82 (t, 1H, Ph, *J*= 7 *Hz*) 7.15-7.30 (m, 4H, Ph), 7.33 (m, 1H, Ph), 7.95 (m, 1H, Ph), 11.97 (s, 1H, NH). for $C_{17}H_{16}N_2O_2$ *calc.*: C, 72.84; H, 5.75; N, 9.99. *Found:* C, 73.02; H, 5.63; N, 9.83.

Synthesis of 5-methyl-5H-indolo[2,3-*b*]quinolin-11(6H)-one 4.

The ester **3** (1.2 gm, 4.28 mmol) in diphenyl ether (6 mL) was heated at reflux (250ºC) for 4h. When the reaction completed, wash the ppt. by petroleum ether then make filteration and drying. Yield: 1.00 g (94%), m.p >360ºC. ^{1}H NMR ($CDCl_3$, 400M*Hz*, δ ppm) 3.98 (s, 3H, CH3); 7.20- 7.30 (m, 2H, Ph); 7.42 (d, 1H, Ph, *J*= 7.9 *Hz*); 7.45 (d, 1H, *J* = 7 *Hz*); 7.73 (m, 2H, Ph); 8.19 (d, 1H, *J* = 7 *Hz*); 8.39 (d, 1H, *J*= 7 *Hz*); 12.07 (s, 1H, NH).

Synthesis of 11-chloro-5-methyl-5H-indolo[2,3-*b*]quinoline 5. A solution of **4** (0.045 gm, 0.2 mmol) in dry toluene (1 mL) and $POCl_3$ (1 mL) was refluxed for 4h. The reaction mixture was cooled, poured into ice, basified with a cold saturated solution of $NaHCO_3$ while keeping the internal temperature below 30 °C, and then extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extract was washed with water and brine, dried (anhydrous Na_2SO_4), and then concentrated. Purification by flash chromatography, eluting with EtOAc-hexane (1:1) to afford compound **5**. Yield: 0.10 g (75%); M.p >360ºC, ^{1}H NMR ($CDCl_3$, 400M*Hz*, δ ppm) 4.34 (s, 3H), 7.30 (m, 1H), 7.51 (m, 1H), 7.73 (m, 3H), 8.36 (d, 1H, *J* = 8.4 Hz), 8.44 (m, 1H), 8.87 (d, 1H, *J* = 8.4 Hz); HPLC: 214 nm : t_r 16.79 min 100 %; LC/MS: t_r 11.9 min 94 %; MS (ESI): *m/z* = 267 $[M+H]^+$.

General procedure for the synthesis of N^1-(5-methyl-5H-indolo[2,3-*b*]quinolin-11-yl)ethane-1,2-diamine 7a: Chloroindoloquinoline **5** (0.05 gm, 0.18 mmol) dissolved in dry DMF and an excess of the appropriate amine **6a-c** were heated at reflux at 135-155 ºC in presence of 10 eqs. of triethyl amine for 4h. TLC monitoring was used to ensure the completion of reaction. The resulting crude poured into ice water and the solid formed was collected by filtration , dried and purified by flash chromatography using CH_2Cl_2/2N ammonia in MeOH (90:10) as the eluent.

Yield= 49 mg (98%), m.p 95-98ºC. ^{1}H NMR (DMSO) (400 M*Hz*, δ ppm) 4,17 (s, 3H, *N*-CH_3); 3.83 (t, 2H, CH_2, *J*= 4 *Hz*); 2.86 (t, 2H, CH_2, *J*= 4 *Hz*); 7.06 (d, 1H, H_{arom}, *J*= 8 *Hz*); 7.29 (t, 1H, H_{arom}, *J*= 8 *Hz*); 7.40 (d, 1H, H_{arom}, *J*= 8 *Hz*); 7.50 (t, 1H, H_{arom}, *J*= 8 *Hz*); 7.79-7.84 (m, 2H, H_{arom}); 7.99 (d, 1H, H_{arom}, *J*= 4 *Hz*); 8.48 (d, 1H, H_{arom}, *J*= 12 *Hz*).

11-hydrazinyl-5-methyl-5H-indolo[2,3-*b*]quinoline 7b:

The procedure as given for **7a** was followed. Orange ppt. will be formed. Yield= 40 mg (90%), m.p 210ºC. IR (KBR): 3335.60 cm^{-1} (υ $_{NH}$). ^{1}H NMR (DMSO, 400 M*Hz*, δ ppm) 4.32 (s, 3H, *N*-CH_3); 9.98 (s, 1H, NH); 7.18 (t, 1H, H_{arom}, *J*= 8 *Hz*); 7.45-7.53 (m, 2H, H_{arom}); 7.57 (d, 1H, H_{arom}, *J*= 8 *Hz*); 8.14-8.17 (m, 2H, H_{arom}); 8.55 (d, 1H, H_{arom}, *J*= 4 *Hz*); 8.80 (d, 1H, H_{arom}, *J*= 8 *Hz*).

N^1-(5-methyl-5H-indolo[2,3-*b*]quinolin-11-yl)propane -1,3-diamine 7c:

The procedure as given for **7a** was followed. yellow ppt. will be formed. Yield= 49 mg (98%), m.p 70ºC. ^{1}H NMR (DMSO, 400 M*Hz*, δ ppm) 4.15 (s, 3H, *N*-CH_3); 3.94 (t, 2H, CH_2, *J*= 4 *Hz*); 2.65 (t, 2H, CH_2, *J*= 4 *Hz*); 1.72-1.82 (m, 2H, CH_2); 9.98 (s, 1H, NH); 7.06 (d, 1H, H_{arom}, *J*= 4 *Hz*); 7.27 (d, 1H, H_{arom}, *J*= 8 *Hz*); 7.40 (d, 1H, H_{arom}, *J*= 8 *Hz*); 7.48-7.51 (m, 1H, H_{arom}); 7.77-7.84 (m, 2H, H_{arom}); 7.92 (t, 1H, H_{arom}, *J*= 8 Hz); 8.50-8.53 (m, 1H, H_{arom}). **General procedure for the Synthesis of diphenyl(1H-indol-3-yl)(2-(5-methyl-5H-indolo[2,3-*b*]quinolin-11-ylamino) ethyl amino)methylphosphonate 10a.**

(0.05gm, 0.172 mmol) of **7a** was dissolved in (5 mL) of dichloromethane then add (0.03 gm, 0.2 mmol) of 3-formyl indole (**8a**), (0.035 gm, 0.112 mmol) of triphenylphosphite **9** and (0.06 gm, 0.165 mmol) of zinc triflate in equivalent ratios then make stirring at room temperature for 2h. Pale white ppt. will be formed in the reaction mixture. Make filteration and drying to obtain the product.

Yield= 40 mg (90%), m.p 230ºC. IR (KBR): 3437.39 cm^{-1} (υ $_{NH}$). ^{1}H NMR (DMSO) (400 M*Hz*, δ ppm) 4.15 (s, 3H, *N*-CH_3); 3.82 (t, 2H, CH_2 , *J*= 4 *Hz*); 2.85 (t, 2H, CH_2, *J*= 8 *Hz*); 7.06 (d, 1H, H_{arom}, *J*= 8 *Hz*); 7.27 (d, 1H, H_{arom}, *J*= 8 *Hz*); 7.40-7.46 (m, 8H, H_{arom}); δ 7.49 (t, 1H, H_{rom}, *J*= 8 *Hz*); 7.77-7.84 (m, 11H, H_{arom}) 7.97 (d, 1H, H_{arom}, *J*= 8 *Hz*); δ 8.49 (d, 1H, H_{arom}, *J*= 8 *Hz*). MS:*m/z*= 652 $(M+H)^+$. For $C_{39}N_5O_3H_{34}P$, M.Wt= **651** *found* :C, 70.44; H, 4.88; N, 9.36. *Calc*: C, 71.87; H, 5.25; N, 10.74 (0.2 CH_2Cl_2).

diphenyl(2-hydroxyphenyl)-(2-(5-methyl-5H-indol[2,3-b]quinolin-11-yl amino) ethylamino)methyl- phosphonate 10b.

The procedure as given for **10a** was followed. Yield= 40 mg (90%) , m.p 242-245ºC. ^{1}H NMR (DMSO) (400 M*Hz*, δ ppm) 4.17 (s, 3H, *N*-CH_3); 4.00 (t, 2H, CH_2, *J*= 6 *Hz*); 3.01 (t, 2H, CH_2, *J*= 8 *Hz*); 7.12 (t, 1H, H_{arom}, *J*= 8 *Hz*); 7.33 (t, 1H, H_{arom}, *J*= 8 *Hz*); 7.46 (t, 1H, H_{arom}, *J*= 8 *Hz*); 7.52 (d, 1H, H_{arom}, *J*= 8 *Hz*); 7.82-7.49 (m, 17H, H_{arom}) δ 8.48 (d, 1H, H_{arom}, *J*=

8 *Hz*). **diphenyl(1H-indol-3-yl)(2-(5-methyl-5H-indolo[2,3-*b*]quinolin-11-yl amino) hydrazinyl methylphosphonate 10c.**

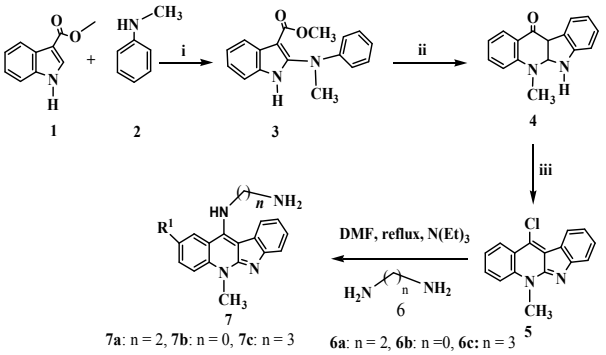
The procedure as given for **10a** was followed. Yellow ppt. will be formed. Yield= 40 mg (90%), m.p 290ºC. ^{1}H NMR (DMSO) (400 M*Hz*, δ ppm) 4.08 (s, 3H, *N*-CH_3); 5.54 (s, 1H, CH); 7.19 (t, 1H, H_{arom}, *J*= 8 *Hz*); 7.34 (t, 1H, H_{arom}, *J*= 8 *Hz*); 7.48-7.52 (m, 18H, H_{arom}); 7.86 (d, 1H, H_{arom}, *J*= 8 *Hz*); 7.92 (d, 1H, H_{arom}, *J*= 8 *Hz*) 8.60 (d, 1H, H_{arom}, *J*= 8 *Hz*); 8.90 (d, 1H, H_{arom}, *J*= 8 *Hz*). MS:*m/z*= 624 $(M+H)^+$. For $C_{37}N_5O_3H_{30}P$, M.Wt= **623** *Found*: C, 70.21; H, 3.88; N, 10.35. *Calc*: C, 71.25; H, 4.84; N, 11.22 (0.1 CH_2Cl_2)

diphenyl(1H-indol-3-yl)(3-(5-methyl-5H-indolo[2,3-b]quinolin-11-ylamino) propylamino)methyl phosphonate 10d.

The procedure as given for **10a** was followed. Yield= 40 mg (90%), m.p, over 300ºC. IR (KBR): 3439.54 cm^{-1} (υ_{NH}). ^{1}H NMR (DMSO) (400 M*Hz*, δ ppm) 4.18 (s, 3H, *N*-CH_3); 3.90 (t, 2H, CH_2, *J*= 4 *Hz*); 2.73 (t, 2H, CH_2, *J* = 8 *Hz*); 1.90-1.93 (m, 2H, CH_2); 7.14-7.16 (m, 11H, H_{arom}); 7.34-7.54 (m, 10H, H_{arom}); 7.75 (t, 1H, H_{arom}); 7.91 (t, 1H, H_{arom}, *J*= 12 *Hz*); 8.52 (d, 1H, H_{arom}, *J*= 8 *Hz*).

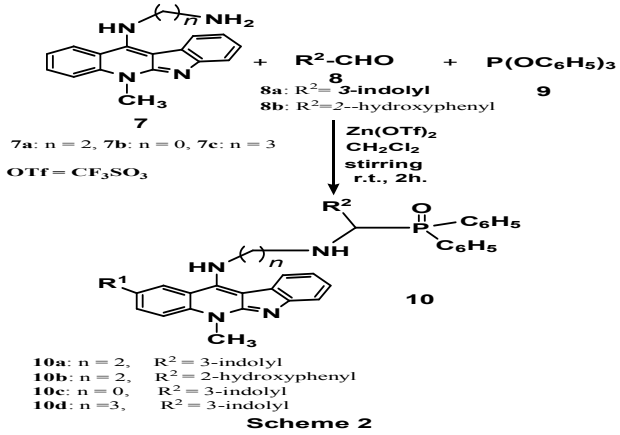
Antibacterial screening:

The synthesized compounds were screened *in vitro* for their antibacterial activities against *Escherichia coli* (Gram -ve bacteria), *Bacillus subtilis* (gram +ve bacteria) and *Staphylococcus aureus* (Gram +ve bacteria), *Klebsiela Spp* (gram –ve bacteria). The antimicrobial activity was determined by the well diffusion method.[23] Wells of (6 mm diameter) were made in Nutrient agar. Plates were seeded with a 24 h. old culture of the bacterial strains. Compounds of indoloquinoline derivatives were added to the wells, a concentration of 20 mg/L. Triplicates of each concentration for each bacteria species, [*E.coli* (gram negative), *Bacillus Subtilis* (gram positive), *Staphylococcus Aureus* (gram positive), *Klebsiela Spp* (gram negative)], were prepared. The inoculated plates were incubated at 37°C for 24h. The diameter of the inhibition zones were measured for each plate and the average reading of the three replicates for each antibacterial species are shown in Table 1. The standard tetracycline disk (20 mg/L) was used as a control. **Results and Discussio** Chemistry**:** Several methods have been used for the synthesis of neocryptolepine.[24] Our strategy for synthesis of neocryptolepine analogues was based on the amination of chlorosubstituted neocryptolepine compound **5** obtained through scheme 1. This method is used for synthesis of neocryptolepines with substitutions on both A (2-substitution) and B rings (*11*-substitution). Thus, aminoneocryptolepines **7a-c** were prepared with various amino- containing groups in position 11 starting from methyl-1H-indole-3-carboxylate **1** and *N*-methylaniline **2**. The intermediate methyl-2-(methyl(phenyl)amino)-1H-indole-3-carboxylate **3** obtained via chlorination with *N*-chlorosuccinimide in the presence of *1,4*-dimethylpiperazine followed by addition of the *N*-methyl aniline as trichloroacetate salt, were cyclised in boiling diphenyl ether to 5-methyl-5H-indolo[2,3-*b*]quinolin-11(6H)-one **4** which were dehydroxychlorinated with $POCl_3$ to afford *11*-chloroneocryptolepine **5**, which was aminated via SN_{Ar} in DMF with the appropriate amines at high temperature, yielding target compounds **7a-c** as shown in Scheme 1.



Scheme 1

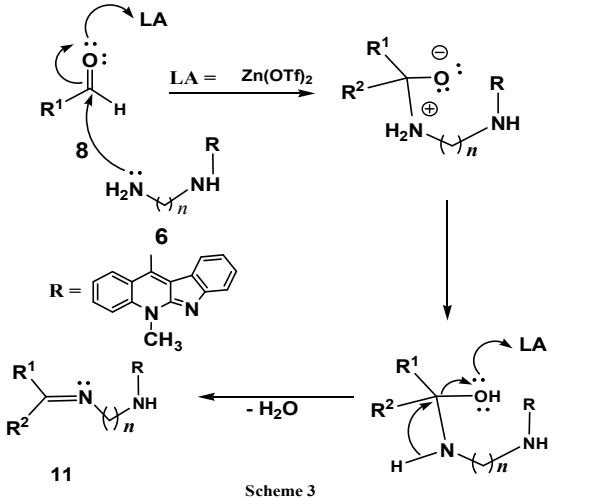
The synthesis of α-aminophosphonates **9** bearing neocryptolepine skeleton were accomplished in good yield using aminoneocryptolepines **6**, *3*-indolealdehyde or salicylaldehyde and triphenyl Phosphate in the presence of a Lewis acid such as zinc (II) triflate according to scheme 2.



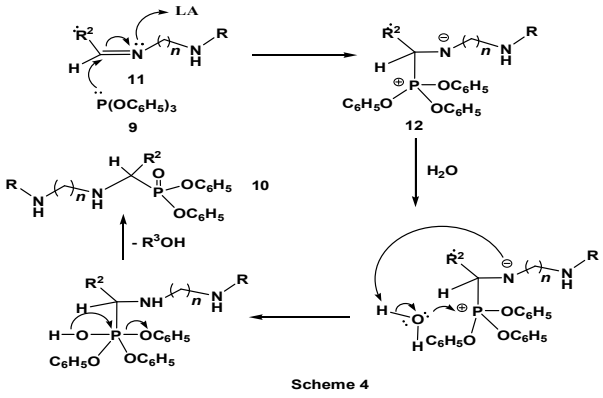
Scheme 2

Optimal conditions for the Lewis acid were found to be 10 mol% in dry dichloromethane. At 5 mol%, the reaction afforded the same yield but required longer reaction times. The reaction is clean and completed within 2 hours. The reaction conditions are very mild and α-aminophosphonates are exclusively formed without the formation of any undesired side- products.

Moreover, the mechanism of this reaction has not been investigated in detail. However, we firstly proposed that the reaction of the aldehydes **8a-b** with the amino-compounds **7a-c** in the presence of zinc triflate as a lewis acid (LA) catalyst afforded the corresponding imine- intermediates **11** according to scheme 3.



Scheme 3



Scheme 4

The imine intermediate **11** is attacked by nucleophilic phosphite **9** leading to the formation of a phosphonium intermediate **12** and most likely this step is catalyzed by the Lewis acid (LA). Reaction of phosphonium intermediates **12** with water afforded the target α-aminophosphonates **10** after elimination of phenol as shown in scheme **4**.

Antibacterial screening:

The diverse biological activities of neocryptolepine and the α-aminophosphonates prompted us to test and study the antibacterial activities of some of the newly synthesized products. Many antimicrobial agents have been introduced into therapy; however the field still needs extensive efforts for the development of new antibacterial agents to overcome the highly resistant strains of microorganisms. The newly synthesized compounds **7a-c** and **10a-d** were tested in vitro for their antibacterial activity against *Escherichia coli* (Gram -ve bacteria), *Bacillus subtilis* (gram +ve bacteria) and *Staphylococcus aureus* (Gram +ve bacteria), *Klebsiela Spp* (gram –ve bacteria). DMSO was used as a control solvent and tetracycline, as a reference drug. After 48 h incubation at 37ºC, the zone of inhibition was measured in cm. The results are depicted in Table 1. The results showed that when amino group is present as a substituent in case of aminoneocryptolepines **7a-c**, they showed a significant activity against all the tested bacterial species. When these amino- compounds are converted into the corresponding α-aminophosphonates **10a-d** system increase in the biological strength for all the bacterial strains is observed. It is worth noting that the presence of α-aminophosphonate moiety at eleventh position of the indoloquinoline system significantly increases the antibacterial activity against bac terial strains.

Table 1: *In Vitro* Screening of neocryptolepine derivatives for antibacterial test after 48 h.:

Tested compounds	*Escherichi Coli*	*Bacillus subtilis*	*Staph Aure*	*Klebsiela Spp*
7a	4.4	2.9 (1.6) *C.Z*	4.6	5 (1.7) *C.Z*
7b	4.5	3.6 (1.7) *C.Z*	5	5.1
7c	5.4	3.3	5.1	6 (2.4) *C.Z*
10a	4.5	2.7	4.7	5.2
10b	3.9	3	4.2	4.6
10c	4.5	3.3	4.5	5.7
10d	4.6	3	5	5.5
Tetracycline *(ref.)*	4	2.6	3.6	4.2

C.Z: clearing zone

Conclusion:

New aminoneocryptolepine derivatives and their aminophosphonates analogues were synthesized and evaluated for their antibacterial activities. All tested compounds showed strong antimicrobial activity against all tested pathogenic bacterial.

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