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Survey reactions of gabapentin with trifluoroacetimidoyl chlorides or trialkyl phosphites

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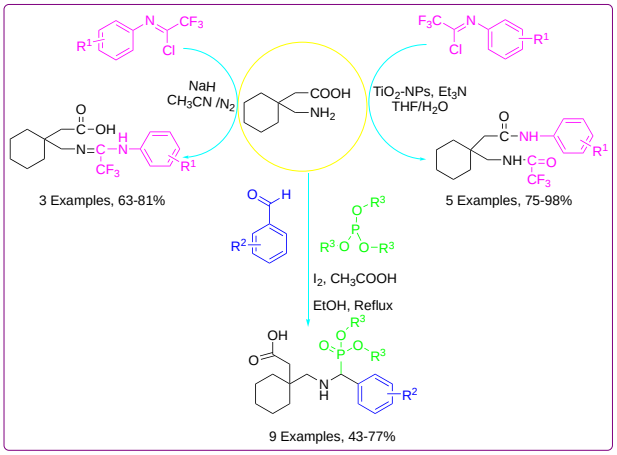
Abstract

Synthesis of a new class of 2-[1-({[2,2,2-trifluoro-1-(arylamino)ethylidene]amino}methyl)cyclohexyl]acetic acids and 2,2,2-trifluoro-*N*-({1-[2-oxo-2-(arylamino)ethyl]cyclohexyl}methyl)acetamides are described by one-pot reaction of gabapentin and trifluoroacetimidoyl chlorides in the presence and absence of titanium dioxide nanoparticles (TiO_2-NPs) as a catalyst and sodium hydride as a base under an N_2 atmosphere. Subsequently, a series of potentially biologically active of 2-[1({[(dialkoxyphosphoryl)(phenyl)methyl]amino}methyl)cyclohexyl] acetic acid derivatives were synthesized via reaction of gabapentin, benzaldehyde imino derivatives and trialkyl phosphites in the presence of I_2/CH_3COOH as catalyst. The structures of products are supported by FT-IR, ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR spectral and X-Ray crystallography data.



Keywords: Gabapentin, Trifluoroacetimidoyl chlorides, Amidine derivatives, Mumm's reaction, Kabachnik-Fields reaction, α-amino phosphonates.

Introduction

Gabapentin (GBP), a structural analogue of gamma-amino butyric acid (GABA), has been extensively studied for its consequential inhibitory actions in the central neural system.[1] Gabapentin displays analgesic effects in remedy of a variety of chronic-pain conditions, for example as an antiepileptic drug used as an add-on therapy.[2-4] GBP has also been shown to have useful effects on postoperative-pain degree, enabling the reduction of analgesic consumption after a variety of surgical procedures.[5] With introduction of GBP and other new anti-epileptic drugs, benign and efficient seizure control could benefit a growing number of epileptic adults. In addition, many theoretical studies have been reported on the GBP molecule, which are related to its structural and medicinal properties.[1]

Fluorine atoms are found in many bioactive compounds.[6] It has been demonstrated that fluorine gives unique effects to the organic molecules that contain it and improves their physicochemical and biological properties. Among fluorinated substituents, the trifluoromethyl group (CF_3) has received attention in the medicinal, agricultural, and material sciences[7] due to its influence on the physical, chemical, and physiological, stability and lipophilicity properties of the molecules incorporating this group.[8] Furthermore, recent research effort on trifluoroacetimidoyl chlorides has led to synthesis of trifluoromethylated heterocycles. Earlier, as an extension of our results, we described the synthesis of trifluoromethylated tetrazoles and pyrroles using trifluoroacetimidoyl chlorides.[9-10]

On the other hand, heterogeneously-catalyzed processes have become important to reduce the number of harmful processes. thereby decreasing waste production, avoiding the calamitous solvents usage, as well as crude catalyst separation and recycling. Amongst the popular heterogeneous catalysts are the TiO_2-NPs, the advantages of which include non-toxicity, chemical stability and low cost, and as a result have been widely used in solar cells, photovoltaic cells and photo applications. Recently, various studies involving the catalytic role of TiO_2-NPs in organic syntheses, such as in deoxygenation, hydrogenation, the water–gas shift reaction, and CO oxidation, have been reported.[11]

α-Amino phosphonates are an important class of compounds due to their numerous applications in biochemistry and integral part of natural bioactive molecules. These types of compounds were first synthesized by Kabachnik-Medved and Fields independently, using a three-component reaction system consisting of a hydrophosphoryl compound, a carbonyl compound (aldehyde or ketone) and an amine.[12] Not surprising, this group of compounds has been widely studied and found application in agriculture, industry, and medicinal chemistry.[13] In our opinion, the most important biological application of α-aminophosphonates involves their extensive range of activities against cancer, tuberculosis, HIV, and bacterial agents.[14]

In addition, α-amino phosphonates have been used as synthons for the preparation of some chemical compounds and the synthesis of amino phosphonates has thus become more prominent. As a result, in last few years several methods have been introduced for the synthesis of α-amino phosphonates using homogenous catalytic systems from aldehydes, amines and triethyl or trimethyl phosphite. For example, $LiClO_4$, $InCl_3$, $AlCl_3$, lanthanide triflates/magnesium sulfate, $SbCl_3/Al_2O_3$, $TaCl_5$-SiO_2, CF_3CO_2H, scandium (tris-dodecyl sulfate), $BF_3{\cdot}Et_2O$, $M(OTf)_n$, and $M(ClO_4)$ have been studied as possible catalysts systems.[15] Albeit that many of these methods suffer from certain disadvantages, such as: long reaction times, low product yields, the need for stoichiometric amounts of catalysts, the use of expensive and moisture susceptible catalysts, and finally using highly toxic catalyst precursors.

In continuing our prior work involving the application of trifluoroacetimidoyl chlorides for the synthesis of fluorinated organic compounds and drug modifications,[8,16] we considered the reaction of gabapentin (GBA) with imidoyl chloride derivatives, which resulted in the formation of 2-[1-({[2,2,2-trifluoro-1-

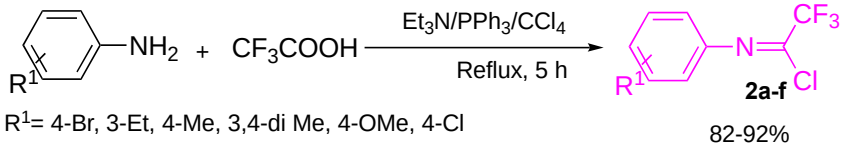
(arylamino)ethylidene]amino}methyl)cyclohexyl]acetic acid derivatives and 2,2,2-trifluoro-*N*-({1-(2-oxo-2-(arylamino)ethyl)cyclohexyl)methyl}acetamides.

In the following paper, we report a viable method for synthesis of ({[(dialkoxyphosphoryl)(aryl)methyl)amino]methyl}cyclohexyl)acetic acid derivatives with great yields via a three-component condensation reaction of aldehydes, GBA and triethyl or trimethyl phosphite in the presence of I_2/CH_3CO_2H, which is both cheap and easily prepared, as catalyst. Our intention was that the functionalizing of GBA would result in products with improved biological activities.

Results and Discussion

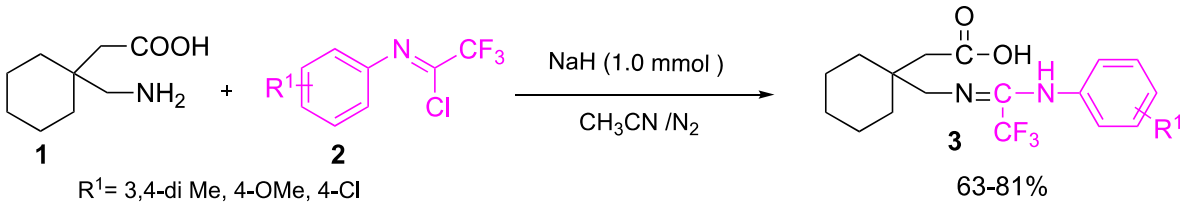
As mentioned in introduction section, Gabapentin (GBP) is an important drug which has various biological activities. Therefore, derivatization of this compound using trifluoroacetimidoyl chlorides could be a valuable approach to modify and improve its biological properties. Considering this subject and in order to increase the biologically activities of GBP, we have thus developed a simple synthetic method for the efficient preparation of new 2-[1-({[2,2,2-trifluoro-1-(arylamino)ethylidene]amino}methyl)cyclohexyl]acetic acid derivatives (**3a-c**), 2,2,2-trifluoro-*N*-({1-(2-oxo-2-(arylamino)ethyl) cyclohexyl}methyl)acetamide derivatives (**4a-e**) and 2-[1 ({[(dialkoxyphosphoryl)(aryl)methyl)amino]methyl}cyclohexyl] acetic acid derivatives (**7a-i**).

Trifluoromethylimidoyl chloride **2**, a set of compounds with three active functional groups, was prepared according to the procedure which had previously been reported, involving the reaction of trifluoroacetic acid, primary arylamines and triphenylphosphine in CCl_4 in the presence of triethylamine. Work-up and distillation of the reaction mixture produced the target imidoyl chlorides **2a-f** in good to excellent yields (Scheme 1).[13]



Scheme 1. Preparation of 2,2,2-trifluoroacetimidoyl chlorides **2a-f**.

In the next step, GBP **1** was reacted with trifluoromethylimidoyl chlorides **2d-f** using the base NaH in CH_3CN as solvent. All reactions were performed at room temperature under N_2 atmosphere to produce the corresponding amidines **3a-c** in good yields (Scheme 2, Table 1).



Scheme 2. Synthesis of 2-[1-({[2,2,2-trifluoro-1-(arylamino)ethylidene]amino}methyl)cyclohexyl]acetic acid derivatives (**3a-c**).

Table 1. Synthesis of 2-[1-({[2,2,2-trifluoro-1-(arylamino)ethylidene]amino}methyl)cyclohexyl]acetic acid derivatives (**3a-c**)[a]

Entry	R^1	Yield (%)
3a	4-Cl	63
3b	4-OMe	81
3c	3,4-di Me	79

a :Reaction Times 12 h

The structure of all the products was confirmed by ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, and IR spectroscopic and also elemental analysis. For example, the IR spectrum of 2-[1-({[1-((4-chlorophenyl)amino)-2,2,2-trifluoroethylidene]amino}methyl)cyclohexyl]acetic acid **3a** displayed characteristic C=N, C=O, CH aliphatic, NH and OH vibrations at 1556, 1679, 2859, 2930 and 3050-3373 cm^{-1} respectively. The ^{1}H-NMR spectrum of **3a** presented multiplets at 1.2-1.4 ppm for the cyclohexyl ring, two singlet signals at 2.2 and 2.5 ppm for protons CH_2CO and CH_2N and multiplets at 7.4-7.7 ppm for the aryl ring protons. A singlet signal observed at 10.9 ppm was postulated to be due to the proton of the OH functional group. The ^{13}C-NMR spectrum showed signals attributable to the cyclohexyl ring carbon atoms at 21.5, 22.9, 26.0, and 34.0 ppm. Other carbons of the compound **3a** appeared at 34.8 (CH_2-CO), 36.6 (CH_2-N), 110.0, 123.2, 129.3 (C-Ar), 168.5 (C-CF_3) and 179.8(COOH) ppm. The mentioned spectral data therefore support the structure of compound **3a**. In addition, X-ray crystallographic analysis confirmed the structure of compound **3c** as illustrated by the ORTEP picture in Figure 1.

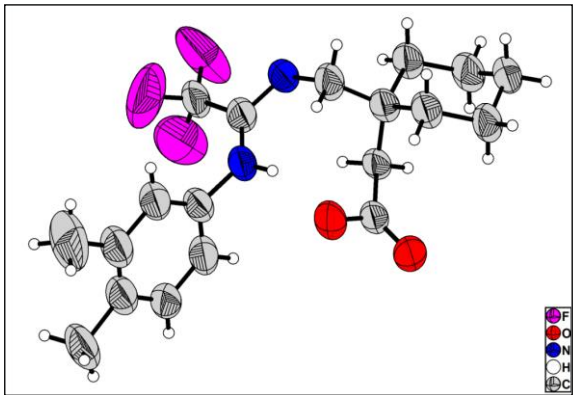
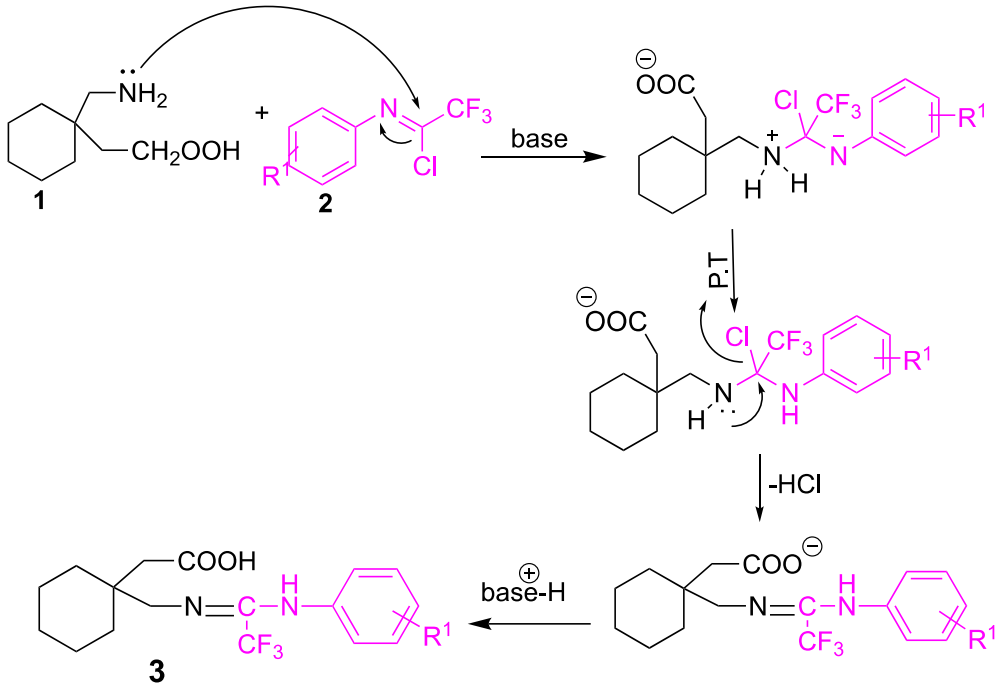


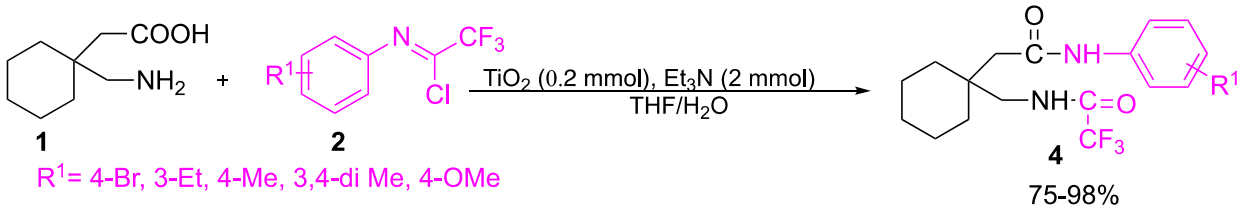
Figure 1. Crystal structure of **3c** (CCDC: 1990418).

Mechanistically, the formation of 2-[1-({[2,2,2-trifluoro-1-(arylamino)ethylidene]amino}methyl)cyclohexyl]acetic acids (**3a-c**) could be rationalized by attack of GBP **1**'s amino group on the carbon atom of the electrophilic C=N to ultimately replace the chlorine atom (Scheme 3).



Scheme 3. A possible mechanism for the synthesis of 2-[1-({[2,2,2-trifluoro-1-(arylamino)ethylidene]amino}methyl)cyclohexyl]acetic acid derivatives.

In the next step, GBP **1** was reacted with some of the synthesized trifluoromethylimidoyl chlorides **2** in the presence of TiO_2-NPs catalyst and Et_3N as base in H_2O/THF solvent. Surprisingly, under these conditions, the obtained products were different to that obtained as previously described above. When comparing the spectra of the new compounds with those described in our previous publication,[6] this second approach resulted in the synthesis of 2,2,2-trifluoro-*N*-({1-(2-oxo-2-(arylamino)ethyl)cyclohexyl}methyl)acetamide derivatives **4**. In the presence of the TiO_2-NPs the reaction therefore proceeds via a Mumm-type rearrangement pathway.[6] All of second set of reactions were performed at room temperature and produced the corresponding amides (**4a-e**) in good yields (Scheme 4, Table 2).



Scheme 4. Synthesis of 2,2,2-trifluoro-*N*-({1-(2-oxo-2-(arylamino)ethyl)cyclohexyl}methyl)acetamide derivatives (**4a-e**).

Table 2. Synthesis of 2,2,2-trifluoro-*N*-({1-(2-oxo-2-(arylamino)ethyl) cyclohexyl}methyl)acetamide derivatives (**4a-e**)[a]

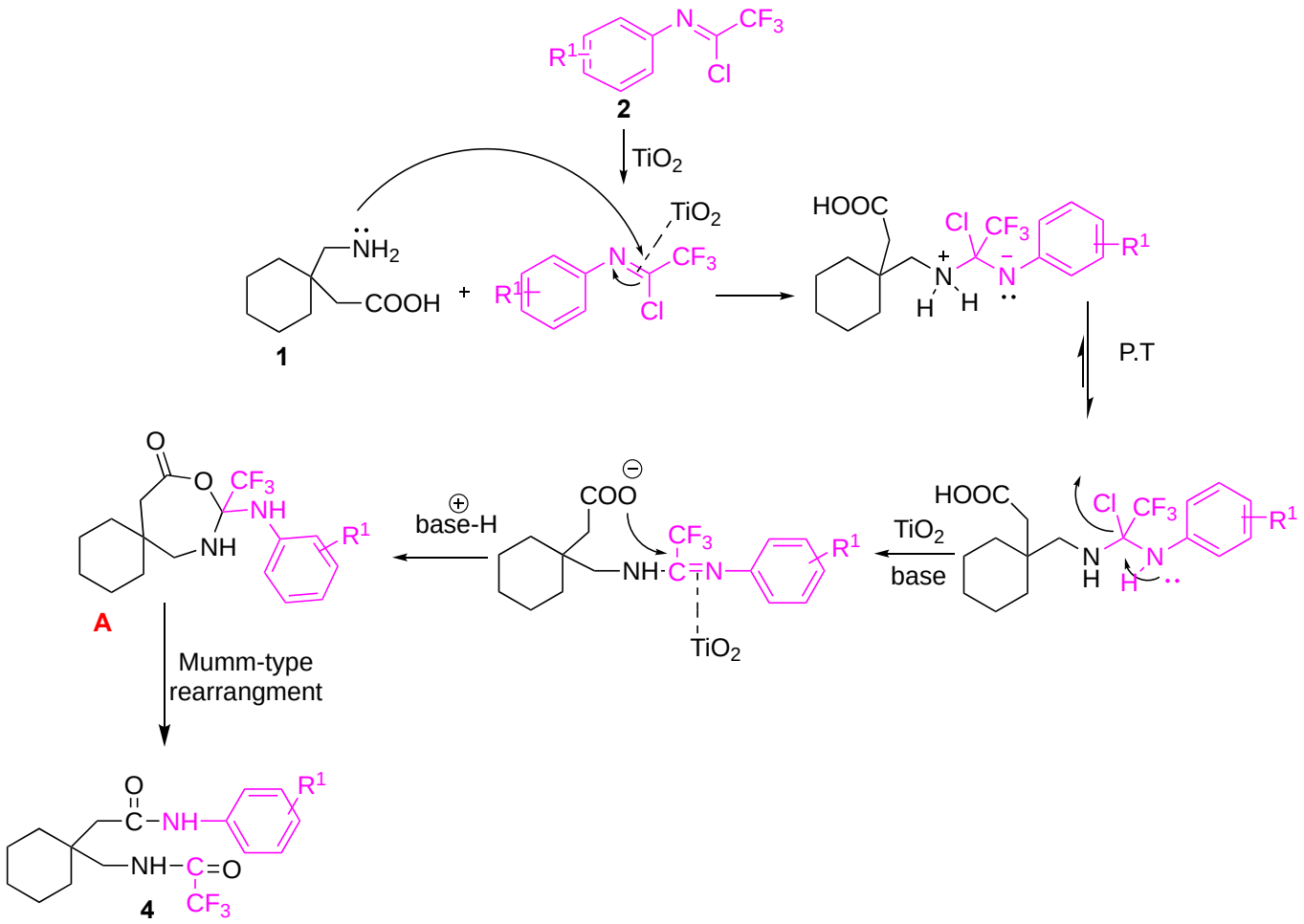
Entry	R^1	Mp(˚C)	Yield (%)
4a	4-Me	108-110	89
4b	4-Br	79-81	75
4c	4-OMe	99-101	98
4d	3-Et	90-92	90
4e	3,4-di Me	112-114	95

a: Reaction Times 8 h

The structures of **4a-e** were confirmed by ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, IR spectroscopy and elemental analysis. For example, the IR spectrum of compound **4a** showed absorption bands at 712, 759 and 778 cm^{-1} for CF_3, 1652 and 1712 cm^{-1} for the C=O groups, 2860 and 2924 cm^{-1} for CH aliphatic and 3078 and 3251 cm^{-1} for the NH groups. In the ^{1}H-NMR spectrum of compound **4a**, multiplets at 1.1-1.4 ppm corresponded to the cyclohexyl ring protons. A singlet at 2.22, and two broad multiplet signals at 2.3 and 3.1-3.4 ppm related to the CH_3 and two CH_2 groups respectively, and multiplets at 6.7-7.0 ppm related to the aryl ring protons. The ^{13}C-NMR spectrum of **4a** displayed signals at δ = 20.8, 21.5, 25.9, and 33.4, 37.4 ppm for CH_3 and cyclohexyl ring carbons. Other carbons in the compound **4a** appeared at 41.3 (CH_2-CO), 47.6 (CH_2-N), 120.7, 129.4, 131.3 (C-Ar), 145.7 (CO-CF_3) and 174.0 (CONH) ppm. In addition, the, ^{19}F-NMR spectrum of **4a** displayed a signal at δ= -73.9 ppm for CF_3. The mentioned spectral data therefore support the structure of compound **4a**.

Scheme 5 shows a possible mechanism for the synthesis of 2,2,2-trifluoro-*N*-({1-(2-oxo-2 (arylamino)ethyl)cyclohexyl}methyl)acetamide derivatives **4a-e**. It is presumed that the reaction proceeds by the primary activation of imidoyl chloride **2** by TiO_2-NPs to the formation of TiO_2-imidoyl complex. Then, the activated intermediate is attacked by the GBP **1** nitrogen nucleophile to again replace the chlorine atom. Subsequent attack of the carboxylate anion on the TiO_2-NPs activated imino group next generates the cyclic intermediate **A** which through a Mumm-type rearrangement leads to 2,2,2-trifluoro-*N*-({1-(2-oxo-2-(arylamino)ethyl)cyclohexyl}methyl)acetamide derivatives **4** (Scheme 5).

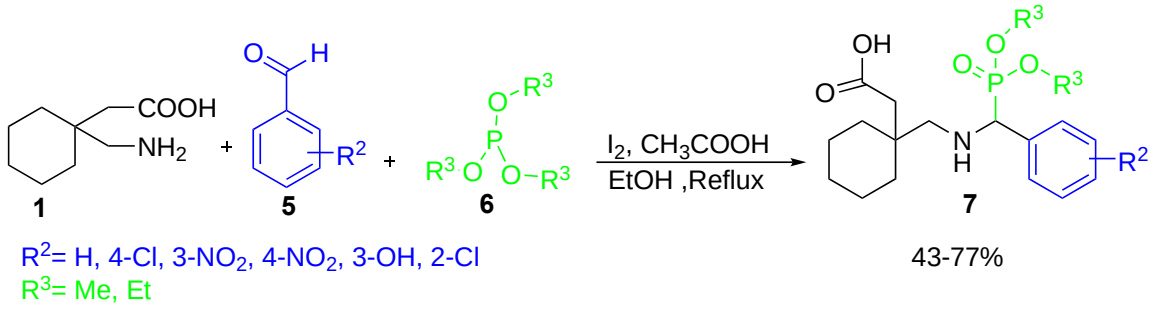
Due to the various biological activities of GBP **1** and also of α-amino phosphonates, we decided to synthesize a new series of α-amino phosphonates based on the GBP **1** scaffold. Therefore, GBP **1** was reacted with benzaldehydes **5** and triethyl phosphite or trimethyl phosphite **6** in the presence of I_2/acetic acid as catalyst in various solvents such as DMF, MeOH, H_2O, THF, CH_3CN and EtOH at ambient temperature and under reflux conditions. When EtOH was used as solvent and u the reaction was performed under reflux conditions for 24 h were found to be the best conditions for the synthesis of 2-[1-({[(dialkoxyphosphoryl)(phenyl)methyl]amino}methyl)cyclohexyl]acetic acid derivatives (**7a-i**) (43-77%, Table 3). As shown in Table 3, steric effects appear to decrease the reaction yields.



Scheme 5. A possible mechanism for the synthesis of 2,2,2-trifluoro-*N*-({1-(2-oxo-2-(arylamino)ethyl)cyclohexyl}methyl)acetamide derivatives 4.

The structures of all of the products were confirmed using spectroscopic techniques. To give an example, the IR spectrum of compound **7a** presented an absorption band at 1681 cm^{-1} assigned to the C=O group, another absorption band at 2994 cm^{-1} assigned to CH aliphatic functionality, and an absorption band at 3680 cm^{-1} assigned to the NH group. Furthermore, the ^{1}H-NMR spectrum of **7a** showed a triplet signal for the protons of methyl groups at δ = 1.1 ppm with a coupling constant of 6.8 Hz. Multiplets at 1.3-2.1 ppm were attributed to the protons of the cyclohexyl ring. A singlet signal at 2.3 ppm was proposed to be due to the NH proton. Signals at δ = 2.9 and δ = 3.6 ppm are corresponding to two protons of CH_2 groups and doublets at δ = 5.6, δ = 7.2 and δ = 7.4 ppm and a singlet signal at δ = 11.2 ppm corresponded to the protons of the aryl ring and the proton of the COOH functional group respectively. In addition, the ^{13}C-NMR spectrum of **7a** displayed a doublet signal at δ = 16.0 ppm with a coupling constant of 5.60 Hz ($^{3}J_{CP}$= 5.6 Hz) for CH_3, δ= 18.5-36.7 ppm due to the cyclohexyl ring, δ = 43.1 ppm for CCOOH, δ = 55.2 ppm with a coupling constant of 159 Hz for CH, δ= 63.1 ppm with a coupling constant of 7.2 Hz for OCH2, δ = 128.2-135.4 ppm for C-Ar and δ = 174.8 ppm for COOH.

All reactions were performed under reflux conditions to give the corresponding dialkoxyphosphoryl (aryl)amines (**7a-i**) in moderate to good yields as summarized in Scheme 6 and Table 3.



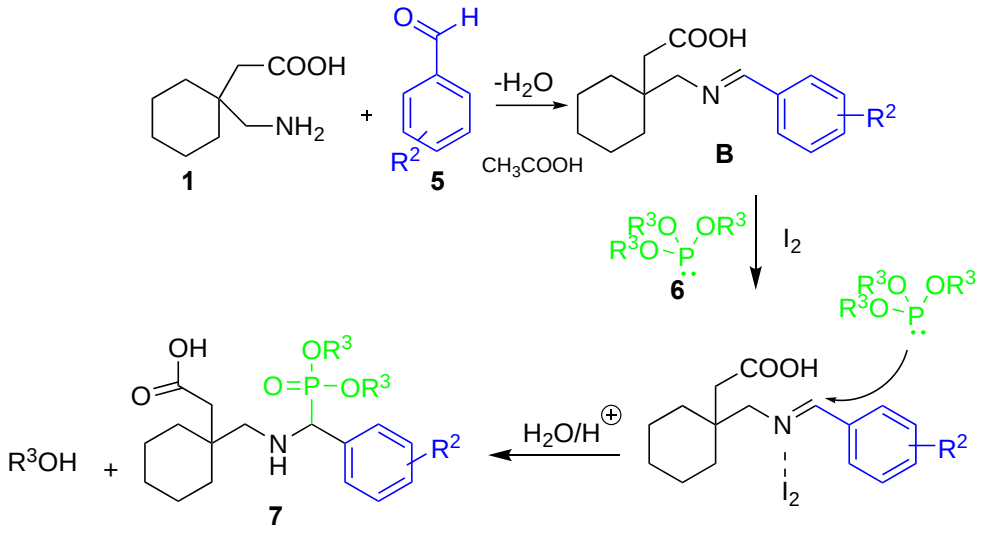
Schème 6. Synthesis of 2-[1({[(dialkoxyphosphoryl)(aryl)methyl]amino}methyl)cyclohexyl]acetic acid derivatives (**7a-i**).

Table 3. Synthesis of 2-[1({[(dialkoxyphosphoryl)(aryl)methyl]amino}methyl)cyclohexyl]acetic acid derivatives (**7a-i**)[a]

Entry	R^2	R^3	Yield (%)
7a	4-Cl	Et	77
7b	4-Cl, 3-NO_2	Et	56
7c	2-Cl	Et	43
7d	4-NO_2	Et	66
7e	3-OH	Et	46
7f	4-H	Et	74
7g	4-Cl	Me	72
7h	3-NO_2	Me	63
7i	4-NO_2	Me	52

a :Reaction Time 24 h

In terms of the proposed mechanism, the initial reaction of **1** with **5** gives an initial imine B, which reacts with trialkyl phosphite 6 in the presence of iodine as a catalyst. Finally, the elimination of MeOH or EtOH produces the structure **7** (Scheme 7).



Scheme 7. A possible mechanism for the synthesis of 2-[1({[(dialkoxyphosphoryl)(aryl)methyl]amino}methyl)cyclohexyl]acetic acid derivatives.

Conclusions

In the final analysis, a generic approach for the synthesis of 2-[1-({[2,2,2-trifluoro-1-(arylamino)ethylidene]amino}methyl)cyclohexyl]acetic acid and 2,2,2-trifluoro-*N*-({1-(2-oxo-2-(arylamino)ethyl)cyclohexyl}methyl)acetamide derivatives which contain trifluoromethyl group and GBP **1** core in either absence or presence of TiO_2-NPs as catalyst has been reported respectively. In addition, a facile and inexpensive route to obtain 2-[1({[(dialkoxyphosphoryl)(phenyl)methyl]amino}methyl)cyclohexyl] acetic acid derivatives as bioactive molecules which can be used in agriculture, industrial and medicinal chemistry, in the presence of I_2/CH_3COOH as catalyst, has been reported. In these approaches, the synthetic procedures utilize can be considered to have many advantages such as cleaner reaction profiles, good to excellent yields, shorter reaction times and purer products.

Experimental Section

General. All chemicals and solvents were procured from commercial sources and applied without any purification unless otherwise was reported. Melting points were specified on a Melt-Tem II melting point apparatus and are uncorrected. IR spectra were acquired on a Matson-1000 FTIR spectrometer. Peaks are related in wave numbers (cm^{-1}). All NMR spectra have been recorded on a Bruker model DRX-400 AVANCE (^1H: 400, ^{13}C: 100 MHz) and on a Varian model (^1H: 500, ^{13}C: 125, ^{19}F: 470.3 MHz) spectrometer. Chemical shifts of ^1H and ^{13}C-NMR have been related in parts per million (ppm) from tetramethylsilane as an internal standard in DMSO-d_6 and $CDCl_3$ as solvents. Elemental analyses (CHN) were performed with a EUROVECTOR EuroEA3000 CHNSO analyzer.

General procedure for the synthesis of compounds 3. In a typical and tentative procedure, a one- necked 50 mL round bottomed flask was charged with 5 mL of dry MeCN, 1.0 mmol of gabapentin (GBP) **1** and 1.0 mmol

NaH. The solution was stirred at room temperature for 20 min, after which a solution of 2,2,2-trifluoro acetimidoyl chloride derivative **2** (1.0 mmol in 2 mL of dry MeCN) was added dropwise over a period of 10 min. The mixture was subsequently stirred at room temperature for 12 h under an N_2 atmosphere. After the completion of reaction, the mixture was filtered and then the solvent was removed by a rotary evaporator to give crude product, which was purified by washing with diethyl ether and *n*-hexane (twice).

2-[1-({[1-({4-Chlorophenyl)amino}-2,2,2-trifluoroethylidene]amino}methyl)cyclohexyl] acetic acid (3a). Yellow Oil, IR(KBr)ν_{max}= 1556 (C=N), 1679 (CO), 2859, 2930 (CH-Aliphatic), 3050-3373 (NH and OH) cm^{-1}; ^{1}H-NMR(DMSO-d_6, 500 MHz): δ = 1.2-1.4 (10H, m, CH-cyclohexyl), 2.2 (2H, s, CH_2-CO), 3.5 (2H, s, CH_2N), 7.4-7.7 (4H, m, Ar), 10.9 (1H, s, OH); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ = 21.5, 22.9, 26.0, 34.0 (C-cyclohexyl), 34.8 (CH_2-CO), 36.6 (CH_2-N), 110.0, 123.2, 129.3 (C-Ar), 168.5 (C-CF_3) ,179.8(COOH) ppm. Anal. Calcd for ($C_{17}H_{20}ClF_3N_2O_2$); C, 54.19; H, 5.35; N, 7.43%. Found: C, 54.43; H, 5.26; N, 7.57%.

2-[1-({[2,2,2-Trifluoro-1-({4-methoxyphenyl}amino)ethylidene]amino}methyl)cyclohexyl] acetic acid (3b). Light yellow Oil, IR(KBr)ν_{max}= 1708 (CO), 2856, 2930 (CH-Aliphatic), 3050-3424 (NH and OH) cm^{-1}; ^{1}H-NMR(DMSO-d_6, 500 MHz) δ = 1.2-1.4 (10H, m, CH-cyclohexyl), 2.1 (2H, s, CH), 3.2 (2H, s, CH), 3.7 (3H, s, OCH_3), 6.6-7.0(4H, m, Ar), 11.0(1H, s, O-H); ^{13}C-NMR(DMSO-d_6, 125MHz): δ = 21.8, 22.5, 26.3, 35.1 (C-cyclohexyl), 35.7 ($2CH_2$-N, CH_2-CO), 55.6 (OCH_3), 114.1, 121.9, 142.5, 142.5 (C-Ar), 154.7 (C-CF_3), 176.7 (CO) ppm. Anal. Calcd for ($C_{18}H_{23}F_3N_2O_3$); C, 58.06; H, 6.23; N, 7.52%. Found: C, 58.20; H, 6.17; N, 7.64%.

2-[1-({[1-({3,4-Dimethylphenyl}amino)-2,2,2-trifluoroethylidene]amino}methyl)cyclohexyl] acetic acid (3c). Light green solid, IR(KBr)ν_{max}= 710, 724, 818 (CF_3), 1671 (CO), 2860, 2928 (CH-Aliphatic), 3050-3393 (NH and OH) cm^{-1}; ^{1}H-NMR(DMSO-d_6, 500 MHz): δ = 1.1-1.4 (10H, m, CH-cyclohexyl), 2.0-2.2(8H, s, $2CH_3$ and CH_2-CO), 3.5 (2H, s, CH_2N), 6.4 (1H, s, H-Ar), 6.5 (1H, s, H-Ar), 6.9-7.0 (1H, d, *J* = 7.5Hz, H-Ar); ^{13}C-NMR (DMSO-d_6, 125MHz): 19.8 (CH_3), 21.7 (CH_3), 26.2, 31.4, 34.6, 36.40 (C-cyclohexyl), 46.9 (CH_2-CO), 48.6 (CH_2-N), 118.2, 122.2, 129.8, 136.3 (C-Ar), 146.4 (CO-CF_3), 178.2 (COOH); ^{19}F-NMR($CFCl_3$ 470.3 MHz): δ = -73.8 (CF_3) ppm. Anal. Calcd for ($C_{19}H_{25}F_3N_2O_2$); C, 61.61; H, 6.80; N, 7.56 %. Found: C, 61.49; H, 6.68; N, 7.40%.

General procedure for the synthesis of compounds 4. Et_3N (2 mmol) and TiO_2 (0.2 mmol) were added to a stirred solution of gabapentin **1** (1.0 mmol) in water (5 mL). To this a solution of acetimidoyl chloride derivative **2** (1.0 mmol) in THF (5 mL) was added during a period of 10 min. drop-wise. The mixture was then stirred at room temperature for 8 h under a N_2 atmosphere. After completion of the reaction (monitored by TLC, EtOAc/*n*-hexane (1:4)), ethyl acetate (10 mL) was added. The organic layer was separated, and the aqueous layer extracted with ethyl acetate (2 x 10 mL). The aqueous layer contained TiO_2 and was separated using filtration. The organic phase was dried over $MgSO_4$ and the solvent removed on a rotary evaporator to give crude product, which was purified by washing with diethyl ether and *n*-hexane (twice).

2,2,2-Trifluoro-*N*-[(1-(2-oxo-2-(p-tolylamino)ethyl)cyclohexyl)methyl]acetamide (4a). White powder, Mp= 108-110°C. IR(KBr)ν_{max}= 712, 759, 778 (CF_3), 1652 (CO), 1712 (CO), 2860, 2924 (CH-Aliphatic), 3251, 3078 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ = 1.1-1.4 (10H, m, CH-cyclohexyl), 2.2 (3H, s, CH_3), 2.3 (2H, bs, CH_2), 3.1-3.4 (2H, m, CH_2), 6.7-7.0 (4H, m, H-Ar); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ =20.8 (CH_3), 21.5, 25.9, 33.4, 37.4 (C-cyclohexyl), 41.3 (CH_2CO), 47.6 (CH_2N), 120.7, 129.4, 131.3 (C-Ar), 145.7 (CO), 174.0 (NH-CO); ^{19}F-NMR($CFCl_3$ 470.3 MHz): δ = -73.9 (CF_3) ppm. Anal. Calcd for ($C_{18}H_{23}F_3N_2O_2$); C, 60.66; H, 6.51; N, 7.86%. Found: C, 60.38; H, 6.39; N, 7.74%.

***N*-[(1-(2-[(4-Bromophenyl)amino]-2-oxoethyl)cyclohexyl)methyl]-2,2,2-trifluoroacetamide (4b).** Creamy powder, Mp= 79-81°C. IR(KBr)ν_{max}= 1672 (CO), 1710 (CO), 2930 (CH-aliphatic), 3193 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ = 1.22-1.4 (10H, m, CH-cyclohexyl), 2.2 (2H, s, CH_2CO), 3.5 (2H, s, CH_2N), 6.6 (1H, s, NH), 7.6-7.7 (4H, m, H-Ar), 9.8 (1H, s, NH); ^{13}C-NMR(DMSO-d_6, 125 MHz): δ =21.5, 22.9, 26.0, 36.6 (C-cyclohexyl), 44.9 (CH_2-

CO), 48.6 (CH_2N), 123.1, 123.4, 131.6, 132.3 (C-Ar), 176.2 (CO-CF_3), 180.1 (CO-N) ppm. Anal. Calcd for ($C_{17}H_{20}BrF_3N_2O_2$): C, 48.47; H, 4.79; N, 6.65%. Found: C, 48.55; H, 5.03; N, 6.49%.

2,2,2-Trifluoro-*N*-[(1-(2-[(4-methoxyphenyl)amino]-2-oxoethyl)cyclohexyl)methyl]acetamide (4c). Creamy powder, Mp= 99-101°C. IR(KBr)ν_{max}=1639, 1699 (CO), 2929, 2929 (CH-aliphatic), 3260, 3099 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ = 1.22-1.7 (10H, m, CH-cyclohexyl), 2.3 (2H, s, CH_2-CO), 3.4-3.5 (2H, m, CH_2-N), 3.68(3H, s, OMe), 6.6-6.8 (4H, m, Ar), 12.9 (1H, s, NH); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ = 19.6, 21.6, 23.0, 33.3 (C-cyclohexyl), 41.3 (CH_2-CO), 47.3 (CH_2-NH), 55.5 (OMe), 114.2, 114.5, 121.5, 123.1 (C-Ar), 155.1 (CO-CF_3), 173.9 (CO) ^{19}F-NMR($CFCl_3$ 470.3 MHz): δ= -77.9 (CF_3) ppm. Anal. Calcd for ($C_{18}H_{23}F_3N_2O_3$): C, 58.06; H, 6.23; N, 7.52; %. Found: C, 57.84; H, 6.39; N, 7.78%.

***N*-[(1-(2-[(3-Ethylphenyl)amino]-2-oxoethyl)cyclohexyl)methyl]-2,2,2-trifluoroacetamide (4d).** Bright orange powder, Mp= 90-92°C. IR (KBr)ν_{max}= 1643, 1721 (CO), ,2859, 2929 (CH-aliphatic), 3311(NH) cm^{-1}; ^{1}H-NMR(DMSO-d_6, 500 MHz): δ = 1.3-1.4 (10H, m, CH-cyclohexyl), 2.2 (2H, s, CH_2-CO), 2.6 (2H, q, $^3J_{HH}$=7.5 Hz, CH_2-CH_3), 3.3-3.4 (5H, m, CH_3 and CH_2-N), 7.4-7.5 (4H, m, H-Ar); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ = 9.0, 19.9, 21.2, 22.9, 25.8, 33.3 (C-cyclohexyl and C_2H_5), 36.6 (CH_2-CO), 45.8 (CH_2-N), 110.0, 122.4, 144.6, 162.8 (C-Ar), 166.6 (CO-CF_3), 170.8 (CO-N) ppm. Anal. Calcd for ($C_{19}H_{25}F_3N_2O_2$): C, 61.61; H, 6.80; N, 7.56%. Found: C, 61.73; H, 6.48; N, 7.80%.

***N*-[(1-(2-[(3,4-Dimethylphenyl)amino]-2-oxoethyl)cyclohexyl)methyl]-2,2,2-trifluoroacetamide (4e).** White powder, Mp= 112-114°C. IR(KBr)ν_{max}= 780-826 (CF_3), 1696, 1680 (CO), 2853, 2925 (CH-aliphatic), 3302 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ = 1.5-1.5 (10H, m, CH-cyclohexyl), 3.1 (6H, s, $2CH_3$), 3.3-3.4 (4H, m, CH_2-N and CH_2-CO), 6.5-7.0 (3H, m, H-Ar), 8.7 (1H, s, NH), 9.0 (1H, s, NH); ^{13}C-NMR(DMSO-d_6, 125 MHz): δ = 19.7, 19.8, 22.8, 25.7, 29.7, 34.4 (C-cyclohexyl and $2CH_3$), 39.4 (CH_2-CO), 53.8 (CH_2N), 118.2, 122.0, 130.1, 133.2, 134.6, 137.5 (C-Ar), 154.7 (C-CF_3), 178.7 (CO-N)ppm. Anal. Calcd for ($C_{19}H_{25}F_3N_2O_2$): C, 61.61; H, 6.80; N, 7.56%. Found: C, 61.53; H, 6.54; N, 7.68%.

General procedure for the synthesis of compounds 7. In a typical procedure, a one-necked, 50 mL round bottomed flask was charged with 5 mL of EtOH, 1.0 mmol of gabapentin **1**, 1.0 mmol benzaldehyde **5**, 1.0 mmol triethyl or trimethyl phosphite 6, I_2 (0.2 mmol) and 3 drops ACOH. The reaction mixture was stirred and heated under reflux conditions for 24 h. After completion of the reaction, the reaction mixture was filtered and the solvent was evaporated on a rotary evaporator to give the crude product, which was purified by column chromatography (EtOAc/*n*-hexane (1:3)) to afford the corresponding product **7**.

2-[1-({[(4-Chlorophenyl)(diethoxyphosphoryl)methyl]amino}methyl)cyclohexyl]acetic acid (7a). Colorless Oil, IR(KBr)ν_{max}= 1492, 1681, 2994, 3680 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.1(6H, t, $^3J_{HH}$= 6.8 Hz, $2CH_3$), 1.3-2.1 (10H, m, cyclohexyl), 2.3(H, s, NH), 2.9 (2H,s, -CH_2COOH), 3.6 (2H, m, -CH_2NH), 4.1-4.2 (4H, m, $2OCH_2$), 5.6 (H, d, $^1J_{HP}$= 20.0 Hz, CH), 7.2 (2H, d, $^3J_{HH}$= 8.0 Hz, 2CH, H-Ar), 7.4 (2H, d, $^3J_{HH}$= 8.0 Hz, 2CH, H-Ar), 11.2 (OH, s, COOH); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 16.0 (d, $^3J_{CP}$= 5.6 Hz, $2CH_3$), 20.0, 22.50, 22.60, 25.4, 30.8,36.1 (cyclohexyl), 43.1 (-CCOOH), 57.0 (-CNH), 63.1 (d, $^2J_{CP}$=7.2 Hz, $2OCH_2$), 55.2 (d, $^1J_{CP}$= 159.0 Hz, CH), 128.2-135.4 (C-Ar), 174.8 (COOH) ppm. Anal. Calcd for ($C_{20}H_{31}ClNO_5P$): C, 55.62; H, 7.24; N, 3.24%. Found: C, 55.54; H, 7.60; N, 3.50%.

2-[1-({[(4-Chloro-3-nitrophenyl)(diethoxyphosphoryl)methyl]amino}methyl)cyclohexyl] acetic acid (7b). Yellow Oil, IR(KBr)ν_{max}= 1512, 1611, 1695, 3078 , 3078, 3368 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.1 (6H, t, $^3J_{HH}$=7.2 Hz, $2CH_3$), 1.2-1.5 (10H, cyclohexyl), 2.2(H, s, NH), 2.9 (2H, s, -CH_2COOH), 3.4-3.7 (2H,m CH_2NH), 5.7 (H, d, $^1J_{HP}$= 24.0 Hz, CH), 4.0-4.2 (4H, m, $2OCH_2$), 7.5 (H, t, $^3J_{HH}$= 8.0 Hz, CH, H-Ar), 7.9 (2H, d, $^3J_{HH}$= 7.6 Hz, 2CH, H-Ar), 8.1 (2H, d, $^3J_{HH}$= 9.6 Hz, 2CH, Ar), 8.3 (H, s, CH, H-Ar), 10.1 (OH, s, COOH); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 16.2 (d, $^3J_{CP}$= 5.8 Hz, $2CH_3$), 20.0, 22.6, 25.5, 22. 29.6, 36.3 36.8 (cyclohexyl), 43.3 (-CCOOH), 56.06 (-CNH), 63.2 (d, $^2J_{CP}$= 6.8 Hz, $2OCH_2$), 50.2 (d, $^1J_{CP}$= 157.0 Hz, CH), 123.4-148.4 (C-Ar), 174.2 (COOH) ppm. Anal. Calcd for ($C_{20}H_{30}ClN_2O_7P$): C, 50.37; H, 6.34; N, 5.87%. Found: C, 50.49; H, 6.44; N, 5.63%.

2-[1-({[(2-Chlorophenyl)(diethoxyphosphoryl)methyl]amino}methyl)cyclohexyl]acetic acid (7c). Yellow Oil, IR(KBr)ν_{max}= 1478, 1588, 1600, 1685, 2929, 3259 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.0 (6H, t, $^3J_{HH}$= 7.1 Hz, $2CH_3$), 1.0- 1.7 (10H, m, cyclohexyl), 2.0 (H, s, NH), 3.2 (2H,s, -CH_2COOH), 3.6-3.8 (2H, m, -CH_2-NH), 4.1-4.3 (4H, m, $2OCH_2$) 6.2 (H, d, $^1J_{HP}$= 20.4 Hz, CH), 7.3-7.4 (H, H-Ar); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 16.2 (d, $^3J_{CP}$= 5.6 Hz, $2CH_3$), 19.3, 22.6, 25.6, 29.2, 36.2, 36.7 (cyclohexyl), 39.9 (-CH_2COOH), 53.8 (-CH_2NH), 63.0 (d, $^2J_{CP}$= 20.0 Hz, $2OCH_2$), 36.4 (d, $^1J_{CP}$= 35.0 Hz, CH), 114.1-135.4 (C-Ar), 184.0 (COOH) ppm. Anal. Calcd for ($C_{20}H_{31}ClNO_5P$): C, 55.62; H, 7.24; N, 3.24%. Found: C, 55.52; H, 7.16; N, 3.12%.

2-[1-({[(Diethoxyphosphoryl)(4-nitrophenyl)methyl]amino}methyl)cyclohexyl]acetic acid (7d). Yellow Oil, IR(KBr)ν_{max}= 1522, 1604, 1694, 2924, 3400 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.0 (6H, t, $^3J_{HH}$= 7.6 Hz, $2CH_3$), 1.2-1.6 (10H, m, cyclohexyl), 2.0 (H, s, NH), 2.6 (2H, s, -CH_2COOH), 3.1-3.4 (2H, m, CH_2NH), 3.5-37 (4H, m, $2OCH_2$), 4.4(H, CH), 7.4 (2H, d, $^3J_{HH}$= 4.0 Hz, 2CH, H-Ar), 7.6 (2H, d, $^3J_{HH}$= 1.6 Hz, 2CH, H-Ar), 10.2 (OH, s, COOH); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 14.1 ($2CH_3$), 22.7, 22.8, 24.7, 29.4, 31.9, 36.8(cyclohexyl), 39.5 (-CH_2COOH), 39.6 (-CH_2NH), 123.6-140.1(C-Ar), 190.3(COOH) ppm. Anal. Calcd for ($C_{20}H_{31}ClNO_5P$): C, 55.62; H, 7.24; N, 3.24%. Found: C, 55.52; H, 7.16; N, 3.12%.

2-[1-({[(Diethoxyphosphoryl)(3-hydroxyphenyl)methyl]amino}methyl)cyclohexyl]acetic acid (7e). Yellow Oil, IR(KBr)ν_{max}= 1588, 1600, 1685, 3242, 2921 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.1 (6H, t, $^3J_{HH}$= 7.2Hz, $2CH_3$), 1.1-1.4 (10H, m, cyclohexyl), 2.0 (H, s, NH), 3.0 (2H, -CH_2COOH), 3.2 (2H, CH_2NH), 4.1-4.3 (4H, m, $2OCH_2$), 5.7 (H, d, $^1J_{HP}$= 25.2 Hz, CH), 6.6-7.5 (H, H-Ar), 10.0 (OH, s, COOH); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 16.7 (d, $^3J_{CP}$= 6.0 Hz, $2CH_3$), 19.4, 22.8, 25.3, 28.1, 31.7, 36.3 (cyclohexyl), 43.5 (-CH_2COOH), 56.0 (-CH_2NH), 63.5 (d, $^2J_{CP}$= 7.0 Hz, $2OCH_2$), 50.9 (d, $^1J_{CP}$= 159.0 Hz, CH), 116.2-157.6 (C-Ar), 174.4 (COOH) ppm. Anal. Calcd for ($C_{20}H_{31}ClNO_5P$): C, 55.62; H, 7.24; N, 3.24%. Found: C, 55.52; H, 7.16; N, 3.12%.

2-[1-({[(Diethoxyphosphoryl)(phenyl)methyl]amino}methyl)cyclohexyl]acetic acid (7f). Yellow Oil, IR(KBr)ν_{max}= 1493, 1602, 1667, 3088, 3242, 2983 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.1 (6H, t, $^3J_{HH}$= 7.2Hz, $2CH_3$), 1.3-1.9 (10H, m, cyclohexyl), 2.2 (H, s, NH), 3.0 (2H, s, -CH_2COOH), 3.6-3.8 (2H, m, CH_2NH), 5.0 (H, d, $^1J_{HP}$= 10.8 Hz, CH), 4.0-4.1 (4H, m, $2OCH_2$), 7.2 (2H, d, $^3J_{HH}$= 8.8 Hz, 2CH, H-Ar), 7.3 (1H, t, $^3J_{HH}$= 7.6 Hz, CH, H-Ar), 7.5(2H, d, $^3J_{HH}$= 7.2 Hz, 2CH, H-Ar), 10.0 (OH, s, COOH); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 16.4 (d, $^3J_{CP}$= 5.0 Hz, $2CH_3$), 19.3, 22.6, 22.8, 25.6, 29.7, 36.7 (cyclohexyl), 43.6 (-CH_2COOH), 55.9 (-CH_2NH), 62.6 (d, $^2J_{CP}$= 7.0 Hz, $2OCH_2$), 50.8(d, $^1J_{CP}$= 158.0 Hz, CH), 127.1-136.9(C-Ar), 174.1(COOH) ppm. Anal. Calcd for ($C_{20}H_{32}NO_5P$): C, 60.44; H, 8.12; N, 3.52%. Found: C, 66.28; H, 8.26; N, 3.38%.

2-[1-({[(4-Chlorophenyl)(dimethoxyphosphoryl)methyl]amino}methyl)cyclohexyl]acetic acid (7g). Yellow Oil, IR(KBr)ν_{max}=1488, 1667, 1695, 3227, 2914 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.9-1.5 (10H, m, cyclohexyl), 2.1 (H, s, NH), 2.3 (2H, s, -CH_2COOH), 3.4-3.6 (2H, m, -CH_2NH), 3.5 (6H, d, $^2J_{HH}$= 8.8 Hz, $2OCH_3$), 3.8 (H, d, $^1J_{HP}$= 3.2 Hz, CH), 7.1 (2H, d, $^3J_{HH}$= 8.4 Hz, 2CH, Aromatic), 7.3 (2H, d, $^3J_{HH}$= 7.6 Hz, 2CH, H-Ar), 10.0 (OH, s, COOH); ^{13}C-NMR($CDCl_3$, 100 MHz): δ = 19.3, 22.7, 25.6, 29.7, 36.8 (cyclohexyl), 43.8 (-CCOOH), 53.8 (-CNH), 61.4(d, $^2J_{CP}$= 10.0 Hz, $2OCH_3$), 70.1 (d, $^1J_{CP}$= 5.0 Hz, CH), 127.1-134.0 (C-Ar), 178.3 (COOH) ppm. Anal. Calcd for ($C_{18}H_{27}ClNO_5P$): C, 53.54; H, 6.74; N, 3.47%. Found: C, 53.48; H, 6.68; N, 3.53%.

2-[1-({[(Dimethoxyphosphoryl)(3-nitrophenyl)methyl]amino}methyl)cyclohexyl]acetic acid (7h). Yellow Oil, IR(KBr)ν_{max}= 1685,1617, 1584, 1522, 3091, 2975 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.2-1.3 (10H, m, cyclohexyl), 2.0 (H, s, NH), 2.6 (2H, s, CH_2-COOH), 3.1-3-3 (2H, m, -CH_2NH), 3.7 (6H, d, $^2J_{HP}$= 6.8 Hz, $2OCH_3$), 4.4 (H, d, $^1J_{HP}$= 6.8 Hz, CH), 7.6-8.3 (H, H-Ar), 10.1 (OH, s, COOH); ^{13}C-NMR($CDCl_3$, 100 MHz): δ = 22.6, 25.5, 29.3, 29.7,30.95, 36.5 (cyclohexyl), 44.3 (-CCOOH), 52.4 (-CNH), 53.8 ($2OCH_3$), 36.9 (d, $^1J_{CP}$= 10Hz, CH), 121.4-148.4 (C-Ar), 178.3 (COOH) ppm. Anal. Calcd for ($C_{18}H_{27}N_2O_7P$): C, 52.17; H, 6.57; N, 6.76%. Found: C, 52.29; H, 6.45; N, 6.48%.

2-[1-({[(Dimethoxyphosphoryl)(4-nitrophenyl)methyl]amino{methyl)cyclohexyl]acetic acid (7i). Yellow Oil, IR (KBr)ν_{max}= 1527, 1611, 1692, 3251, 2920 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.3-1.5 (10H, m, cyclohexyl), 2.1 (H, s, NH), 2.9 (2H, s, -CH_2COOH), 3.1-3.3 (2H, m, -CH_2NH), 3.2 (6H, d $^2J_{HP}$= 6.8 Hz, 2OCH_3), 4.4 (H, d, $^1J_{HP}$= 3.2 Hz, CH), 7.1-8.7 (H, H-Ar), 9.4 (OH, s, COOH); ^{13}C-NMR($CDCl_3$, 100 MHz): δ = 25.5, 25.5, 29.7,31.9,36.4, 39.5(cyclohexyl), 43.2 (CCOOH), 47.4 (-CNH), 53.2 (2OCH_3), 45.9 (d, $^1J_{CP}$=14.0 Hz CH), 118.8-143.6 (C-Ar), 178.2 (COOH) ppm. Anal. Calcd for ($C_{18}H_{27}N_2O_7P$): C, 52.17; H, 6.57; N, 6.76%. Found: C, 52.13; H, 6.35; N, 6.60%.

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