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## Graphical Abstract

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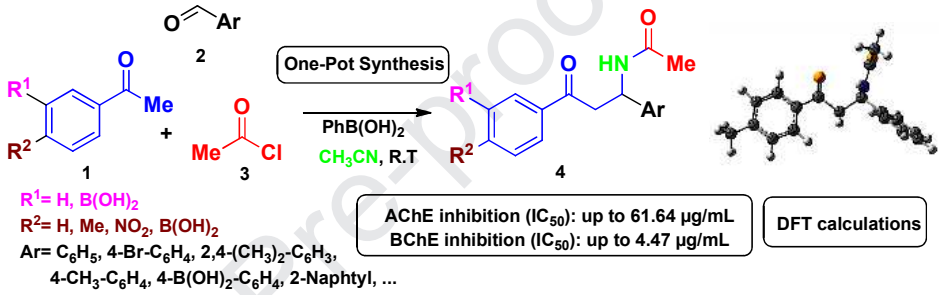

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# Green one-pot multicomponent synthesis, biological evaluation and theoretical investigations of some novel *β*-acetamido ketone derivatives as potent cholinesterase inhibitors.

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ABSTRACT

A series of novel *β*-acetamido ketones have been prepared via a four-component condensation between aromatic aldehydes, enolizable ketones, acyl chloride and acetonitrile in the presence of 10 mol% of phenylboronic acid as a catalyst. The expected products have been obtained in good to excellent yields. In addition, the *in vitro* cholinesterase inhibitory activity of title compounds has been studied and the results indicated that some compounds exhibited remarkable BChE activity. In order to gain insights into the molecular structure and chemical reactivity of the synthesized β-acetamido ketones, density functional theory (DFT) calculations were also carried out.



## 1. Introduction:

*β*-Acetamido ketones possess very interesting biological properties such as antimicrobial,[1] antidiabetic,[2] anti-cancer,[3] HIV protease inhibitors,[4] and antifungal.[5] They have been also used as glycosidase inhibitors.[6] In addition, *β*-acetamido ketones are usually employed as suitable intermediates for the synthesis of 1,3-aminoacids,[7] 1,3-amino alcohols[8] and they also constitute a structural unit of natural antibiotic peptides.[9]

The best-known classical method for the preparation of *β*-acetamido ketones is the Dakin-West reaction[10] between amino acid and ester anhydride in the presence of a base. Some other synthetic methods providing the *β*-acetamido ketones are the photo-isomerization of phthalimides,[11] Michael addition to α,β-unsaturated ketones[12] and acylation of *β*-amino ketones[13] which were reported in recent literature.

In 1994, Bhatia et *al.*[14] described an important method to access this important class of compounds via a four-component reaction between aromatic aldehydes, enolisable ketone, acyl chloride and acetonitrile in the presence of cobalt(II) chloride as catalyst.[15] Since then, this reaction has been extensively studied applying various homogenous or heterogenous catalysts such as $PCl_3$,[16] ZnO,[17] $I_2$,[18] $BiCl_3$,[19] $FeCl_3$,[20] $CoCl_2$,[21] $CeCl_3 \cdot 7H_2O$,[22] $SnCl_4/SiO_2$,[23] $Cu(OTf)_2/Sc(OTf)_3$,[24] $ZrOCl_2 \cdot 8H_2O$,[25] $NaHSO_4 \cdot H_2O$,[26] $Co(HSO_4)_3$ and $Zn(HSO_4)_3$,[27] silica supported perchloric acid,[28] heteropoly acid,[29] Silver(1) triflate,[30] Trifluoroacetic acid,[31] and L-proline.[32] Some of these methods suffer from some disadvantages such as long reaction times, dangerous catalysts or too high temperatures.

In the continuation of our research program directed toward the development of new synthetic methods for the preparation of a variety of heterocyclic compounds via mild and environmentally benign conditions,[33] we propose herein the synthesis of some new acetamido ketones by the method proposed by Bhatia et *al.*[14] using phenylboronic acid as a common, available, low toxic, inexpensive, environmentally friendly and easy-to-handle catalyst (Scheme 1).

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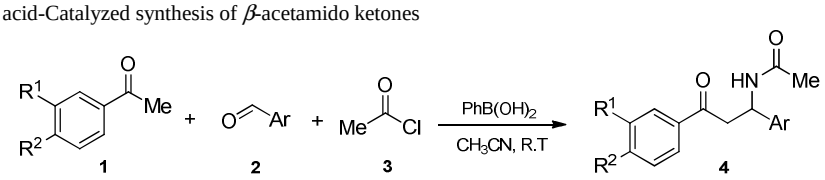
**Scheme 1.** Phenylboronic acid-Catalyzed synthesis of $\beta$-acetamido ketones



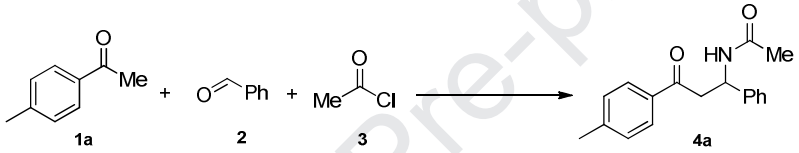

## 2. Results and discussions:

### 2.1. Chemistry

In order to carry out the reaction and optimize the conditions, a model reaction including equimolar ratios of 4-methylacetophenone **1a**, benzaldehyde **2a**, acyl chloride **3** in 3 mL of acetonitrile and 10 mol% of catalyst at room temperature was chosen. This reaction was subjected to different conditions and the results were summarized in Table 1.

We first tried the catalytic activity of triphenylphosphine, pyridinium *p*-toluenesulfonate (PPTS) and phenylboronic acid to see whether the reaction promote or not. The results showed that phenylboronic acid led to the formation of **4a** with a yield of 75% after 3 hours (Table 1, entry 3), while $PPh_3$ (entry 1) and PPTS (Entry 2) gave 50% and 70% after 6 hour reactions, respectively. It is also worth to mention that when multi-component condensation was carried out without any catalyst at room temperature it provided trace amounts of expected product **4a** (Entry 4). Consequently, we have chosen phenylboronic acid as a suitable homogenous catalyst for this reaction affording $\beta$-Acetamido ketones.

**Table 1.** Optimization of the reaction conditions and yields[a]




| Entry | Solvent | Catalyst | mol (%) | Time (h) | T (°C) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | $CH_3CN$ | $PPh_3$ | 10 | 6 | 25 | 50 |
| 2 | $CH_3CN$ | PPTS | 10 | 6 | 25 | 70 |
| 3 | $CH_3CN$ | $PhB(OH)_2$ | 10 | 3 | 25 | 75 |
| 4 | $CH_3CN$ | - | - | 72 | 25 | Trace |
| 5 | $CH_3CN$ | $PhB(OH)_2$ | 5 | 3 | 25 | 33 |
| 6 | $CH_3CN$ | $PhB(OH)_2$ | 15 | 3 | 25 | 29 |
| 7 | $CH_3CN$ | $PhB(OH)_2$ | 20 | 3 | 25 | 18 |
| 8 | $CH_3CN$ | $PhB(OH)_2$ | 30 | 3 | 25 | 16 |
| 9 | $CH_3CN$ | $PhB(OH)_2$ | 10 | 3 | 50 | 37 |

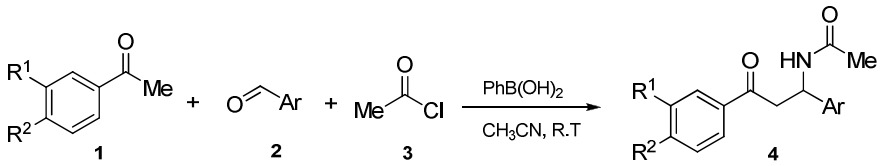
[a] The reactions were carried out by the condensation of 4-methyacetophenone (1 equiv), benzaldehyde (1 equiv), acyl chloride (1.5 equiv) and 3 ml of acetonitrile. [b] Isolated yields.

In order to find out the optimal amount of the catalyst, we carried out the model reaction using 5, 15, 20 and 30 mol% of phenylboronic acid and the expected product **4a** is obtained in 33, 29, 18 and 16% yields respectively (Table 1, Entries 5-8). However, the reaction with 10 mol% of $PhB(OH)_2$ at 50°C furnished only the desired product in 37% yield (Table 1, Entry 9). Therefore, the optimal conditions for the synthesis of $\beta$-acetamido ketone **4a** via a four-component reaction between 4-methylacetophenone, benzaldehyde, and acetyl chloride in acetonitrile required 10 mol% of phenylboronic acid as a homogenous catalyst at room temperature (Table 1, entry 3).

Thereafter, we applied the optimal conditions to the reactions of a variety of aromatic aldehydes and some substituted acetophenone derivatives in the presence of phenyl boronic acid. The obtained results were also summarized in Table 2. Thus, three series of new β-acetamido ketones have been prepared using 4-methylacetophenone (Table 2, entries 1-8), and 4-nitroacetophenone (Entries9-14), 4-acetylphenylboronic acid (Entry 15) and 3-acetylphenylboronic acid (Entries 16-18).

Table 2 shows that whatever the nature of substituent on the acetophenone or the aldehyde, the expected products were obtained in good to excellent yields (65-98%) with only two exceptions (**4b** and **4i)** which are obtained in 60 and 46% yields. In fact, the use of 4-methylacetophenone resulted product yields over 60 to 95% due to electron donation effect of methyl group. However, when the methyl group was replaced with an electron-withdrawing nitro substituent, the reactions also led to good yields ranging from 46 to 98% (Table 2, Entries 7-12). $\beta$-Acetamido ketones **4p**-**4r** with a boronic acid group at 3-position were obtained in good yields (78-73-81%) (Table 2, entries 16-18). While most of the reactions affording the title compounds (**4a-n**) completed within 1.5-3.5 hour, the reactions with borylated acetophenone derivatives required much longer reaction times to complete (Table 2, entries 15-18).

**Table 2.** Synthesis of *β*-acetamido ketones **4a–o** catalyzed by $PhB(OH)_2$ at room temperature[a]




| Entry | $R^1$ | $R^2$ | Ar | Product | Time (h) | Yield (%)[b] | M.p (°C) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Measured | Reported |
| 1 | H | Me | $C_6H_5$ | **4a** | 3 | 75 | 114-116 | 121-123[34a] |
| 2 | H | Me | 4-Br-$C_6H_4$ | **4b** | 3.5 | 60 | 144-146 | 145-146[30] |
| 3 | H | Me | 2,4-$(CH_3)_2$-$C_6H_3$ | **4c** | 2 | 78 | 104-106 | - |
| 4 | H | Me | 4-$CH_3$-$C_6H_4$ | **4d** | 3 | 87 | 108-110 | 117-119[34b] |
| 5 | H | Me | 3-$CH_3$-$C_6H_4$ | **4e** | 3 | 95 | 117-119 | 113.6-115.3[31] |
| 6 | H | Me | 4-$B(OH)_2$-$C_6H_4$ | **4f** | 2 | 78 | 162-164 | - |
| 7 | H | Me | 3-$B(OH)_2$-$C_6H_4$ | **4g** | 2 | 92 | 156-158 | - |
| 8 | H | Me | 2-Naphtyl | **4h** | 1.5 | 75 | 116-118 | 110-112[34b] |
| 9 | H | $NO_2$ | $C_6H_5$ | **4i** | 3 | 46 | 102-104 | 96-98[34a] |
| 10 | H | $NO_2$ | 4-$CH_3$-$C_6H_4$ | **4j** | 2 | 95 | 76-78 | 83-85[34c] |
| 11 | H | $NO_2$ | 4-Br-$C_6H_4$ | **4k** | 2.5 | 80 | 142-144 | 141-143[28] |
| 12 | H | $NO_2$ | 4-$B(OH)_2$-$C_6H_4$ | **4l** | 2 | 98 | 162-164 | - |
| 13 | H | $NO_2$ | 3-$B(OH)_2$-$C_6H_4$ | **4m** | 2 | 97 | 157-159 | - |
| 14 | H | $NO_2$ | 2-Naphtyl | **4n** | 1.5 | 98 | 136-138 | - |
| 15 | H | $B(OH)_2$ | 4-Br-$C_6H_4$ | **4o** | 24 | 65 | 178-180 | - |
| 16 | $B(OH)_2$ | H | 4-Br-$C_6H_4$ | **4p** | 24 | 78 | 156-158 | - |
| 17 | $B(OH)_2$ | H | 4-Cl-$C_6H_4$ | **4q** | 24 | 73 | 164-166 | - |
| 18 | $B(OH)_2$ | H | 4-$NO_2$-$C_6H_4$ | **4r** | 24 | 81 | 165-167 | - |

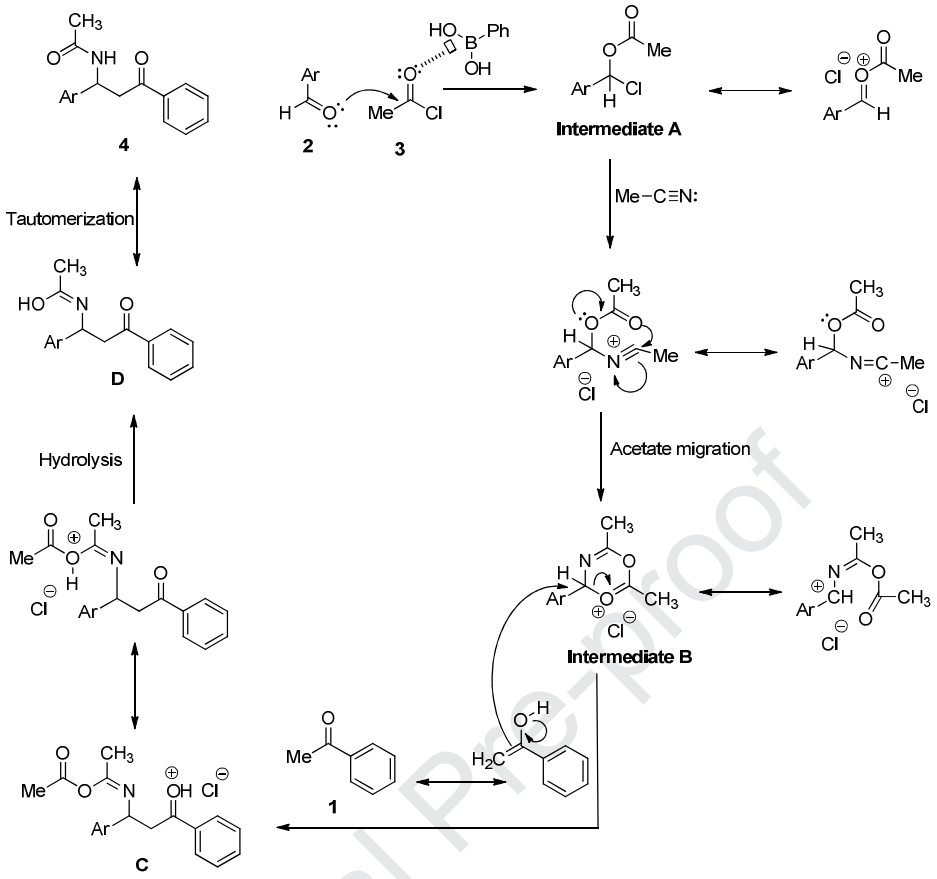
[a]All reactions were carried out by the condensation of acetophenones **1** (1 equiv.), aldehydes **2** (1 equiv.), acyl chloride **3** (1.5 equiv.) and 10 mol% of $PhB(OH)_2$ in acetonitrile (3 ml) at room temperature. [b]Isolated yields.

A plausible mechanism can be proposed for the formation of *β*-acetamido ketones **4** (Scheme 2). This involves first the formation of intermediate **A** with the support of boronic acid catalyst that complexes with acyl chloride **3** and this makes easier the attack on the aldehyde **2**. Condensation of **A** with acetonitrile leads to the formation of another key intermediate **B** which reacts with the enol form of acetophenone **1** to furnish **C**. The removal of hydrogen chloride and acetate molecules by hydrolysis provides N-(3-oxo-1,3-diphenylpropyl)acedimic acid **D** whose tautomerization results in the title compound **4**.

### 2.2. Biology

Examination of Table **4** shows that compounds tested have moderate AChE activity with $IC_{50}$ values varying between 61.64 ± 1.66 μg/mL for **4l** and 122.36 ± 1.50 μg/mL for **4m**. On the other hand, all studied compounds exhibited remarkable BChE activity with $IC_{50}$ values ranging from 4.47 ± 0.08 μg/mL to 101.63 ± 0.15 μg/mL.

**Scheme 2.** Plausible mechanism for the formation of *β*-acetamido ketones catalyzed by phenylboronic acid.




Surprisingly, some derivatives such as **4p** and **4q** with remarkable $IC_{50}$ values of 4.47 ± 0.08, and 6.96 ± 0.04 μg/mL have the stronger inhibitory capacities than the standard reference drug, Glantamine, whose $IC_{50}$ under the conditions of study is 10.85 ± 0.22 μg/mL. The other derivatives gave also interesting and lower values than that of standard drug, galanthamine.

**Table 4.**The inhibitory concentration ($IC_{50}$), calculated Binding energy and selectivity of selected *β*-acetamido ketones **4** investigated against AChE and BChE**.**

| Compound | AChE | | BChE | |
|---|---|---|---|---|
| | $IC_{50}$ (μg/mL)[a] | Selectivity[b] | $IC_{50}$ (μg/mL)[a] | Selectivity[c] |
| **4f** | > 200 | 0.226 | 45.28 ± 0.87 | 4.417 |
| **4g** | > 200 | 0.198 | 39.5 ± 0.58 | 5.063 |
| **4l** | 61.64 ± 1.66 | 1.649 | 101.63 ± 0.15 | 0.607 |
| **4m** | 122.36 ± 1.50 | 0.483 | 59.08 ± 1.20 | 2.071 |
| **4o** | >200 | 0.063 | 12.61 ± 0.32 | 15.86 |
| **4p** | >200 | 0.022 | 4.47 ± 0.08 | 44.743 |
| **4q** | >200 | 0.035 | 6.96 ± 0.04 | 28.736 |
| Galantamine[d] | 6.27±1.15 | 1.73 | 10.85 ± 0.22 | 0.578 |

[a]$IC_{50}$ values expressed are means ± SD of three parallel measurements ($p < 0.05$). [b] Selectivity for AChE defined as $IC_{50}$(BChE)/$IC_{50}$(AChE). [c] Selectivity for BChE defined as $IC_{50}$(AChE)/$IC_{50}$(BChE).

## 2.3. Theoretical investigations

In order to gain insights into the molecular structure of the synthesized β-acetamido ketones, density functional theory (DFT) calculations at B3LYP/6-311++G(d,p) level of theory was carried out for compound **(*S*)-4a** as a representative molecule. Firstly, a full geometry optimization has been performed and all the possible conformers of compound **(*S*)-4a** have been studied. Fig. 1 shows the obtained most stable conformers. As can be seen from Fig. 1, compound **(*S*)-4a**, in both conformations, adopts a non-planar structure. Conformer 2 presents an intramolecular hydrogen

bond (IHB) between the NH and the acetophenone carbonyl group (2.17 Å), while non IHB was found for conformer 1. By comparison, conformer 1 is slightly stable than conformer 2 by about 0.41 kcal/mol. This small energy suggests that both conformers could exist in solution. The selected geometry parameters of conformers 1 and 2 of compound **(*S*)-4a** are listed in Table 5.

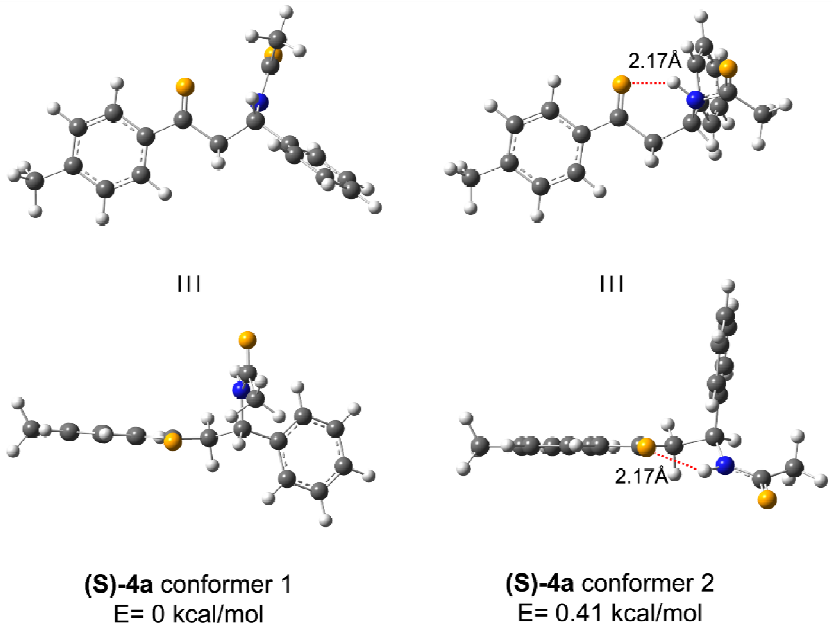



**Fig. 1.** The most stable conformers of compound **(*S*)-4a** obtained at B3LYP/6-311G++(d,p) level of theory.

The obtained molecular geometries for both conformers of compound **(*S*)-4a** were used to calculate some structural characteristics such as frontier molecular orbitals, atomic polar tensor charges, and molecular electrostatic potential mapping. Frontier molecular orbitals (FMO) are important parameters that provide useful information for the reactivity of molecules as well as electronic transitions within molecules.[43] Highest occupied molecular orbital (HOMO) is the easiest orbital to donate electrons, whereas lowest unoccupied molecular orbital (LUMO) is the easiest orbital to accept electrons. The energy levels and distributions of the FMO of conformers of compound **(*S*)-4a** have been computed at B3LYP/6-311G++(d,p) level of theory in the gas-phase. 3D plots of HOMO/LUMO are shown in Fig. 2. The results showed that the HOMOs of both the conformers are mainly localized over the amide and phenyl moieties, while the LUMOs are localized on the acetophenone unit. These clearly elucidate the transfer of electron density from the amide and phenyl moieties to the acetophenone unit. The gap energies of conformers 1 and 2 are, respectively, 4.77 eV and 4.62 eV, suggesting high kinetic stability and low chemical reactivity.[44-45]

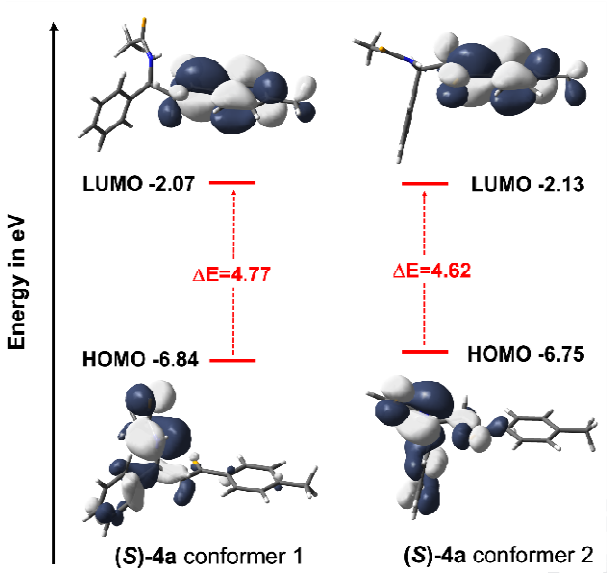



**Fig. 2.** Frontier molecular orbitals of conformers 1 and 2 of compound **(*S*)-4a** obtained in the gas-phase at B3LYP/6-311G++(d,p) level of theory.

Electric charge distribution in molecules is related to several physicochemical properties such as electrostatic potential, chemical reactivity, stability, solubility, acid-base properties, vibrational spectroscopy and dipole moment.[46-47] The electric charge distribution of the conformers of compound **(*S*)-4a** have been computed at B3LYP/6-311G++(d,p) level of theory in the gas-phase using atomic polar tensor (APT) method. The obtained results are shown in Fig. 3 and Table S1 in supporting information. It was found that the highest positive charges for both the conformers are on the carbonyl carbon atoms C7 and C18, whereas the highest negative charges are on the carbonyl oxygen atoms O9 and O19 as well as the N17 atom. To visualise the charge distributions, molecular electrostatic potential has been computed at the same level of theory, and obtained 3D diagrams of compound **(*S*)-4a** are shown in Fig. 3. Considering the results, the most electron-rich sites for both the conformers are located around the two carbonyl oxygen atoms and the nitrogen atom. On the other hands, the most electron-deficient sites are distributed on around the carbonyl carbon atoms and hydrogen atom of the NH bonds. These results suggest that these sites are the preferred sites for electrophilic and nucleophilic attacks, respectively.

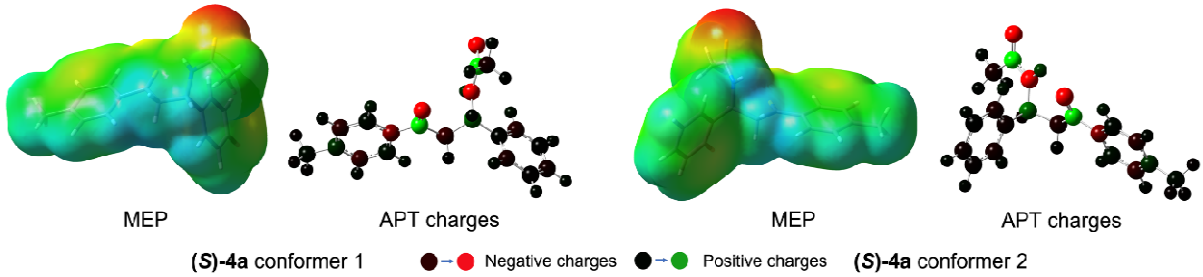



**Fig. 3.** Molecular electrostatic potential (MEP) and atomic polar tensor charges (APT) of conformers 1 and 2 of compound **(*S*)-4a** obtained in the gas-phase at B3LYP/6-311G++(d,p) level of theory.

Electronegativity (χ), chemical hardness (η), chemical softness (S) and electrophilic index (ω) are also important parameters that characterize the stability and reactivity of organic compounds. [48-49] Electronegativity is a physical quantity which characterizes the capacity of a molecule to attract electrons. The chemical hardness (η) and chemical softness (S) are measure of resistance to charge transfer. Compounds with high chemical hardness and low chemical softness have a high reactivity. The electrophilic index can be interpreted as a measure of energy lowering associated with a maximum amount of electron flow between a donor and an acceptor.[50] All these molecular descriptors were calculated for both conformers of compound **(*S*)-4a** at B3LYP/6-311++G(d,p) level of theory in the gas-phase, and the obtained results are shown in Table 5. From the obtained results it is clearly

observed that both the conformers of compound **(*S*)-4a** have a high chemical hardness (2.31 and 2.39 eV) and low chemical softness (0.21 and 0.22 eV), suggesting low chemical reactivity and high kinetic stability. The conformers have also relatively high electronegativity (4.44 and 4.45) and electrophilic index (4.16 and 4.27, indicating that **(*S*)-4a** prefers to act as electron acceptor rather than electron donor.[38]

**Table 5.** Molecular descriptors of conformers 1 and 2 of compound **(*S*)-4a** obtained in the gas-phase at B3LYP/6-311G++(d,p) level of theory.

| Molecular descriptors (eV) | **(*S*)-4a** conformer 1 | **(*S*)-4a** conformer 2 |
|---|---|---|
| χ | 4.45 | 4.44 |
| η | 2.39 | 2.31 |
| S | 0.21 | 0.22 |
| ω | 4.16 | 4.27 |

## 3. Conclusion

In this work, we report a simple procedure for the preparation of β-acetamidoketones by a four-component reaction between aromatic aldehydes, enolizable ketones, acyl chloride and acetonitrile promoted by phenylboronic acid as a homogenous catalyst, available, non-toxic, inexpensive, environmentally friendly and easy to handle. Selected β-acetamidoketones were evaluated for the effect on AChE and BChE. The results indicated that all compounds revealed moderate inhibitory activity against AChE, and some possessed high selectivity for BuChE over AChE. Among them, compounds **4p** and **4q** revealed the strongest BChE inhibitory activity with remarkable $IC_{50}$ values of 4.47 ± 0.08, and 6.96 ± 0.04 μg/mL respectively and highest selectivity. Theoretical investigations using DFT/B3LYP method have been carried out in order to get insight on the molecular structure and chemical reactivity of compound **(S)-4a** as representative molecule.

## 4. Experimental part

### 4.1. Chemistry

*General*

All the chemicals were purchased from the Sigma-Aldrich and used without further purification. All solvents used for spectroscopic and synthesis studies were reagent grades and further purified by literature methods. Thin layer chromatography (TLC) was performed using mixture of EtOAc and hexane (1:2) as eluents and silica gel 60 $F_{254}$ (Merck) plates. Melting points were determined on an Electrothermal capillary fine control apparatus. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance 400/100 MHz or Bruker Avance 250/62.9 MHz, in $CDCl_3$ or DMSO–$d_6$. Chemical shifts ($\delta$) are given in part per million downfield from TMS as an internal standard for $^1$H and $^{13}$C NMR. Coupling constants ($J$) values were indicated in Hz. The chemicals were used as obtained commercially. High Resolution Mass Spectra (HRMS) were recorded with a High Resolution Time–of–Flight Mass Spectrometer coupled with Liquid Chromatography System (Agilent 1200/6210) or MicroTof–Q 98.

*General procedure for the preparation of β-acetamidoketones:*

In a 100-mL roud-bottomed flask, 1 mmol of aldehyde, 1 mmol of acetophenone derivative, 2 mmol of acetyl chloride in 3 ml of acetonitrile as solvent and reagent were introduced in the presence of 10 mol% of phenylboronic acid as catalyst. The reaction mixture was left under magnetic stirring at room temperature. When the reaction was completed (followed by TLC), ice water was added to the mixture and it was left under stirring for 20 minutes. The obtained solid was then filtered and dried. If no solid was formed, the mixture was extracted with ethyl acetate (2 x 10 mL), the organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated to give the desired product. All products were purified by recrystallization from ethyl acetate / hexane (1/4).

All synthesized β-acetamido ketone derivatives were fully characterized by $^1$H NMR, $^{13}$C NMR and HRMS analyses.

**N-(3-Oxo-1-phenyl-3-*p*-tolylpropyl) acetamide (4a):** Yield = 75 %. M.p. = 114-116 °C. $^1$H NMR (250 MHz, $CDCl_3$, ppm) $\delta$: 7.82 (d, 2H, $J$ = 8.1 Hz), 7.36-7.23 (m, 7H), 6.95 (d, 1H, $J$ = 7.6 Hz, NH), 5.57 (q, 1H, $J$ = 5.6 Hz), 3.73 (dd, 1H, $J$ = 16.8 and $J$= 5.4 Hz), 3.41 (dd, 1H, $J$ = 16.8 and $J$= 5.8 Hz), 2.41 (s ; 3H; $CH_3$), 2.02 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$, ppm) $\delta$: 198.2, 169.7, 144.5, 141.3, 134.1, 129.4, 129.4, 128.6, 128.6, 128.3, 128.3, 127.4, 126.5, 126.5, 50.0, 43.1, 23.4, 21.7.

**N-(3-Oxo-1-(4-bromophenyl)-3-*p*-tolylpropyl) acetamide (4b):** Yield = 60 %. M.p. = 144-146 °C. $^1$H NMR (250 MHz, $CDCl_3$, ppm) $\delta$: 7.80 (d, 2H, $J$ = 8.2 Hz), 7.74 (d, 2H, $J$ = 8.2 Hz), 7.44-7.21 (m, 4H), 6.93 (d, 1H, $J$ = 8.0 Hz, NH), 5.52 (q, 1H, $J$ = 5.5 Hz), 3.71 (dd, 1H, $J$ = 17.1 and $J$ = 5.1 Hz), 3.39 (dd, 1H, $J$ = 17.1 and $J$ = 5.8 Hz), 2.42 (s, 3H, $CH_3$), 2.04 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$, ppm) $\delta$: 198.2,

169.6, 144.8, 140.3, 134.0, 131.7, 131.7, 129.5, 129.5, 128.3, 128.3, 121.2, 49.4, 42.7, 23.5, 21.8.

**N-(3-Oxo-1-(2,4-dimethylphenyl)-3-*p*-tolylpropyl) acetamide (4c):** Yield = 78 %. M.p. = 104-106 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 8.24 (d, 1H ; $J$= 12.00 Hz), 8.05 (s, 1H), 7.84 (d, 2H, $J$= 8.0 Hz), 7.32 (d, 2H, $J$= 12.0 Hz), 7.23 (d, 1H, $J$= 8.0 Hz), 6.92 (s, 1H, NH), 5.51 (q, 1H, $J$= 20.0 Hz), 3.44 (dd, 1H, $J$ = 24.0 and $J$ = 12.0 Hz), 3.30 (dd, 1H, $J$ = 24.0 and $J$ = 8.0 Hz), 2.40 (s, 3H, $CH_3$), 2.29 (s, 3H, $CH_3$), 2.21 (s, 3H, $CH_3$), 1.75 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 197.2, 168.5, 144.0, 138.6, 136.0, 135.2, 134.5, 131.0, 129.6, 129.6, 128.5, 128.5, 126.9, 126.2, 45.5, 44.2, 23.0, 21.6, 20.9, 19.2.

**N-(3-Oxo-1-*p*-tolyl-3-*p*-tolylpropyl) acetamide (4d):** Yield = 78 %. M.p. = 108-110 °C. $^1$H NMR (250 MHz, $CDCl_3$, ppm) $\delta$: 7.84 (d, 2H, $J$ = 8.4 Hz), 7.27-7.23 (m, 4H), 7.13 (d, 2H, $J$= 6.1 Hz), 6.77 (d, 1H, $J$= 6.3 Hz, NH), 5.60-5.50 (m, 1H), 3.73 (dd, 1H, $J$ = 16.6 and $J$ = 3.0 Hz), 3.41 (dd, 1H, $J$ = 16.6 and $J$ = 3.9 Hz), 2.42 (s, 3H, $CH_3$), 2.32 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$, ppm) $\delta$: 198.3, 169.5, 144.4, 138.1, 137.1, 134.2, 129.4, 129.4, 129.3, 129.3, 128.3, 128.3, 126.4, 126.4, 49.8, 43.1, 23.5, 21.7, 21.1.

**N-(3-Oxo-1-*m*-methylphenyl-3-*p*-tolylpropyl) acetamide (4e):** Yield = 95 %. M.p. = 117-119 °C. $^1$H NMR (250 MHz, $CDCl_3$, ppm) $\delta$: 7.83 (d, 2H, $J$ = 8.2 Hz), 7.26 (d, 2H, $J$ = 8.1 Hz), 7.21-7.04 (m, 4H), 6.78 (d, 1H, $J$ = 7.6 Hz, NH), 5.53 (q, 1H, $J$= 6.4 Hz), 3.71 (dd, 1H, $J$ = 16.7 and $J$ = 5.4 Hz), 3.41 (dd, 1H, $J$ = 16.7 and $J$ = 5.35 Hz), 2.42 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$, ppm) $\delta$: 198.3, 169.5, 144.5, 141.0, 138.3, 134.2, 129.4, 129.4, 128.6, 128.3, 128.3, 128.2, 127.4, 123.4, 50.0, 43.2, 23.5, 21.7, 21.6.

**4-(1-Acetamido-3-oxo-3-*p*-tolylpropyl) phenylboronic acid (4f):** Yield = 98 %. M.p. = 162-164 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 8.33 (d ; 1H ; $J$= 12.00 Hz, NH), 8.01 (s, 2H, $B(OH)_2$), 7.85 (d, 2H, $J$= 12.0 Hz), 7.73 (d, 2H, $J$= 12.0 Hz), 7.31 (2d, 4H, $J$= 12.0 Hz), 5.36 (td, 1H, $J$= 12.0 Hz), 3.50 (dd, 1H, $J$= 24.0 and $J$= 12.0 Hz), 3.34 (dd, 1H, $J$= 24.0 and $J$= 8.0 Hz), 2.36 (s, 3H, $CH_3$), 1.79 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 197.0, 168.7, 145.2, 144.0, 134.5, 134.5, 134.5, 134.5, 129.7, 129.7, 128.5, 128.5, 126.1, 126.1, 49.4, 44.8, 23.1, 21.6. HRMS (ESI$^-$) m/z 324.14145 [M-H]$^-$, calcd for $C_{18}H_{19}BNO_4$: 324.14071.

**3-(1-Acetamido-3-oxo-3-*p*-tolylpropyl) phenylboronic acid (4g):** Yield = 80 %. M.p. = 156-158 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 8.32 (d, 1H, $J$= 12.00 Hz), 8.05 (s, 2H, $B(OH)_2$), 7.86 (d, 2H ; $J$= 12.00 Hz), 7.78 (s, 1H), 7.65 (d, 1H, $J$= 12.0 Hz), 7.38 (d, 1H, $J$= 12.0 Hz), 7.32 (d, 2H, $J$= 12.0 Hz), 7.26 (d, 1H, $J$= 12.0 Hz, NH), 5.38 (q, 1H, $J$= 12.0 Hz), 3.52 (dd, 1H, $J$= 24.0 and $J$= 12.0 Hz), 3.33 (dd, 1H, $J$= 24.0 et $J$= 12.0 Hz), 2.36 (s, 3H, $CH_3$), 1.79 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 196.7, 168.3, 143.6, 141.8, 134.1, 132.6, 129.2, 129.2, 129.2, 128.4, 128.1, 128.1, 128.1, 127.3, 49.2, 44.5, 22.7, 21.2. HRMS (ESI$^-$) m/z 324.14059 [M-H]$^-$, calcd for $C_{18}H_{19}BNO_4$: 324.14071.

**N-(3-oxo-1-(naphth-2-yl)-3-*p*-tolylpropyl) acetamide (4h):** Yield = 46 %. M.p. = 166-168 °C. $^1$H NMR (250 MHz, $CDCl_3$, ppm) $\delta$ : 7.85-7.23 (m, 11H), 6.99 (d, 1H, $J$ = 7.9 Hz, NH), 5.74 (q, 1H, $J$ = 5.5 Hz), 3.81 (dd, 1H, $J$= 16.8 and $J$ = 5.2 Hz), 3.35 (dd, 1H ; $J$= 16.8 and $J$= 5.9 Hz), 2.41 (s, 3H, $CH_3$), 2.06 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$, ppm) $\delta$: 198.3, 169.7, 144.6, 138.5, 134.2, 133.3, 132.7, 129.5, 129.5, 128.5, 128.3, 128.3, 128.0, 127.7, 126.3, 126.0, 125.2, 124.8, 50.1, 43.1, 23.6, 21.8.

**N-(3-oxo-1-phenyl-3-*p*-nitrophenylpropyl) acetamide (4i):** Yield = 75 %. M.p. = 102-104 °C. $^1$H NMR (250 MHz, $CDCl_3$, ppm) $\delta$ : 8.29 (d, 2H, $J$= 8.4 Hz), 8.07 (d, 2H, $J$= 8.4 Hz), 7.40-7.20 (m, 5H), 6.56 (s, 1H, NH), 5.55 (q, 1H, $J$= 5.9 Hz), 3.84 (dd, 1H, $J$= 16.7 and $J$= 5.3 Hz), 3.49 (dd, 1H, $J$= 16.68 and $J$= 5.3 Hz), 2.03 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$, ppm) $\delta$: 196.8, 169.8, 150.5, 141.0, 140.3, 129.3, 129.3, 128.9, 128.0, 126.6, 126.6, 124.0, 124.0, 104.9, 50.3, 44.2, 23.4.

**N-(3-oxo-1-*p*-tolyl-3-*p*-nitrophenylpropyl) acetamide (4j):** Yield = 92 %. M.p. = 76-78 °C. $^1$H NMR (250 MHz, $CDCl_3$, ppm) $\delta$: 8.31 (d, 2H, $J$= 8.6 Hz), 8.09 (d, 2H, $J$= 8.6 Hz), 7.29-7.10 (m, 4H), 6.39 (d, 1H, $J$= 7.0 Hz, NH), 5.50 (q, 1H, $J$= 6.6 Hz), 3.84 (dd, 1H, $J$= 16.5 and $J$= 5.1 Hz), 3.48 (dd, 1H, $J$= 16.5 and $J$= 6.92 Hz), 2.33 (s, 3H, $CH_3$), 2.03 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$, ppm) $\delta$: 196.9, 169.8, 150.5, 141.0, 137.9, 137.2, 129.7, 129.7, 129.3, 129.3, 126.6, 126.6, 124.0, 124.0, 50.2, 44.3, 23.5, 21.1.

**N-(3-Oxo-1-*p*-bromophenyl-3-*p*-nitrophenylpropyl) acetamide (4k):** Yield = 87 %. M.p. = 142-144 °C. $^1$H NMR (250 MHz, $CDCl_3$, ppm) $\delta$: 8.32 (d, 2H, $J$= 8.6 Hz), 8.08 (d, 2H, $J$= 8.6 Hz), 7.47 (d, 2, $J$= 8.4 Hz), 7.23 (d, 2H, $J$= 8.4 Hz), 6.55 (d, 1H, $J$= 7.5 Hz, NH), 5.52 (q, 1H, $J$= 6.1 Hz), 3.83 (dd, 1H, $J$= 17.1 and $J$= 5.1 Hz), 3.48 (dd, 1H, $J$= 17.1 and $J$= 5.1 Hz), 2.04 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$, ppm) $\delta$: 196.6, 169.7, 150.6, 140.7, 139.4, 132.0, 132.0, 129.2, 129.2, 128.4, 128.4, 124.1, 124.1, 121.8, 104.7, 49.5, 43.8, 23.5.

**4-(1-acetamido-3-(4-nitrophenyl)-3-oxopropyl) phenylboronic acid (4l):** Yield = 98 %. M.p. = 162-164 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 8.37 (s, 1H, NH), 8.33 (d, 2H, $J$= 8.0 Hz), 8.18 (d, 2H, $J$ = 8.0 Hz), 8.02 (s, 2H, $B(OH)_2$), 7.74 (d, 2H, $J$ = 12.0 Hz), 7.33 (d, 2H, $J$= 8.0 Hz), 5.37 (td, 1H, $J$= 12.0 Hz), 3.61 (dd, 1H, $J$= 24.0 and $J$= 12.0 Hz), 3.50 (dd, 1H, $J$ = 24.0 and $J$= 12.0 Hz), 1.80 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 196.5, 168.5, 149.9, 144.5, 141.1, 134.2, 134.2, 134.2, 129.5, 129.5, 125.7, 125.7, 123.8, 123.8, 48.9, 45.1, 22.6. HRMS (ESI$^-$) m/z 355.10904 [M-H]$^-$, calcd for $C_{17}H_{16}BN_2O_6$: 355.11014.

**3-(1-acetamido-3-(4-nitrophenyl)-3-oxopropyl) phenylboronic acid (4m):** Yield = 97 %. M.p. = 157-159 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 8.33 (d, 2H, *J*= 12.0 Hz), 8.32 (s, 1H, NH), 8.18 (d, 2H, *J*= 12.0 Hz), 8.05 (s, 2H, $B(OH)_2$), 7.78 (s, 1H), 7.66 (d, 1H, *J*= 12.0 Hz), 7.40 (d, 1H, *J*= 12.0 Hz), 7.29 (t, 1H, *J*= 12.0 Hz), 5.36 (td, 1H, *J*= 12.0 Hz), 3.63 (dd, 1H, *J*= 24.0 and *J*= 12.00 Hz), 3.48 (dd, 1H, *J* = 20.0 and *J* = 12.0 Hz), 1.79 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 196.5, 168.3, 149.9, 141.4, 141.1, 132.7, 132.5, 129.4, 129.4, 129.4, 128.4, 127.3, 123.8, 123.8, 49.0, 45.2, 22.6. HRMS (ESI$^-$) m/z 355.10863 $[M-H]^-$, calcd for $C_{17}H_{16}BN_2O_6$: 355.11014.

**N-(3-oxo-1-(naphthalen-2-yl)-3-(4-nitrophenyl)propyl) acetamide (4n):** Yield = 95 %. M.p. = 136-138 °C. $^1$H NMR (250 MHz, $CDCl_3$, ppm) $\delta$: 8.25 (d, 2H, *J*= 7.6 Hz), 8.07 (d, 2H, *J*= 8.6 Hz), 8.02 (s, 1H), 7.75-7.41 (m, 6H), 7.38 (d, 1H, *J*= 4.7 Hz, NH), 5.62 (q, 1H, *J*= 6.9 Hz), 3.77 (dd, 1H, *J*= 16.7 and *J*= 7.0 Hz), 3.49 (dd, 1H, *J*= 16.7 and *J*= 6.5 Hz), 1.91 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$, ppm) $\delta$: 195.6, 169.5, 149.6, 140.6, 138.4, 132.6, 128.8, 128.8, 128.8, 127.8, 127.3, 127.0, 125.7, 125.4, 124.9, 124.7, 123.3, 49.3, 44.4, 22.5.

**4-(3-Acetamido-3-(4-bromophenyl)propanoyl) phenylboronic acid (4o):** Yield = 65 %. M.p. = 178-180 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 8.36 (d ; 1H ; *J*= 12.00 Hz, NH), 8.30 (s, 2H, $B(OH)_2$), 7.90 (s, 4H ), 7.51 (d, 2H, *J* = 12.0 Hz), 7.31 (d, 2H, *J* = 12.0 Hz), 5.32 (td, 1H, *J*= 12.0 Hz), 3.56 (dd, 1H, *J*= 24.0 and *J*= 12.00 Hz). 3.39 (dd, 1H, *J*= 24.0 and *J*= 12.0 Hz), 1.79 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 197.1, 168.4, 142.5, 137.5, 134.3, 134.3, 131.1, 131.1, 131.1, 128.9, 128.9, 128.9, 126.8, 119.8, 48.4, 44.3, 22.6. HRMS (ESI$^-$) m/z 388.04833 $[M-H]^-$, calcd for $C_{17}H_{16}BBrNO_4$: 388.03558.

**3-(3-Acetamido-3-(4-bromophenyl)propanoyl) phenylboronic acid (4p):** Yield = 78 %. M.p. = 156-158 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 8.40 (s, 1H), 8.35 (d, 1H, *J* = 8.0 Hz), 8.26 (s, 2H, $B(OH)_2$), 8.03 (d, 1H, *J* = 8.0 Hz, NH), 7.97 (d, 1H, *J* = 8.0 Hz), 7.50 (m 3H), 7.32 (d, 2H, *J* = 8.0 Hz), 5.34 (td, 1H, *J* = 8.0 Hz), 3.57 (dd, 1H, *J* = 20.0 and *J*= 8.0 Hz), 3.41 (dd, 1H, *J* = 20.0 and *J* = 8.0 Hz), 1.80 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 197.0, 168.4, 142.6, 138.9, 135.6, 133.8, 131.7, 131.7, 131.7, 129.4, 128.9, 128.9, 127.8, 119.7, 48.3, 44.2, 22.6. HRMS (ESI$^-$) m/z 388.04727 $[M-H]^-$, calcd for $C_{17}H_{16}BBrNO_4$: 388.03558.

**3-(3-Acetamido-3-(4-chlorophenyl)propanoyl) phenylboronic acid (4q):** Yield = 73 %. M.p. = 164-166 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 8.41 (s, 1H ), 8.37 (d, 1H, *J*= 12.0 Hz), 8.30 (s, 2H, $B(OH)_2$), 8.03 (d, 1H, *J*= 8.00 Hz), 7.97 (d, 1H, *J*= 8.0 Hz, NH), 7.49 (t, 1H, *J*= 12.0 Hz), 7.38 (s, 4H), 5.36 (td, 1H, *J*= 12.0 Hz). 3.58 (dd, 1H, *J*= 24.0 and *J*= 8.0 Hz), 3.40 (dd, 1H, *J*= 24.0 and *J*= 8.0 Hz), 1.80 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 197.4, 168.8, 142.7, 139.3, 136.1, 134.2, 131.7, 129.8, 128.9, 128.9, 128.6, 128.6, 128.6, 128.3, 48.7, 44.8, 23.0. HRMS (ESI$^-$) m/z 344.09990 $[M-H]^-$, calcd for $C_{17}H_{16}BClNO_4$: 344.08609.

**3-(3-Acetamido-3-(4-nitrophenyl)propanoyl)phenylboronic acid (4r):** Yield = 81 %. M.p. = 165-167 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, ppm) $\delta$: 8.48 (d, 1H, *J*= 8.00 Hz), 8.41 (s, 1H), 8.26 (s, 2H, $B(OH)_2$), 8.19 (d, 2H, *J* = 8.0 Hz), 8.03 (d, 1H, *J* = 8.0 Hz, NH), 7.98 (d, 2H, *J* = 8.0 Hz), 7.64 (d, 2H, *J* = 8.0 Hz), 5.46 (td, 1H, *J*= 8.0 Hz), 3.66 (dd, 1H *J*= 24.0 and *J*= 8.0 Hz), 3.47 (dd, 1H, *J*= 20.0 and *J*= 8.0 Hz), 1.83 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm) $\delta$: 196.6, 168.6, 151.2, 146.3, 138.9, 135.5, 133.8, 129.4, 127.9, 127.9, 127.8, 127.8, 123.4, 123.4, 48.5, 44.0, 22.5. HRMS (ESI$^-$) m/z 355.10906 $[M-H]^-$, calcd for $C_{17}H_{16}BN_2O_6$: 355.11014.

### 4.2. *In vitro* cholinesterase inhibition activity

Acetyl cholinesterase (AChE) and butyryl cholinesterase (BChE) inhibitory activity was measured, by the spectrophotometric method developed by Ellman, G.L., et *al.*[35] Briefly, 150 µL of 100 mM sodium phosphate buffer (pH 8.0), 10 µL of sample (**4**) solution dissolved in methanol at different concentrations and 20 µL AChE (5.32 x$10^{-3}$ U) or BChE (6.85 x$10^{-3}$U) solution were mixed and incubated for 15 min at 25 ºC, and 10 µl of 0.5 mM DTNB [5,5´-dithio-bis(2-nitrobenzoic) acid] were added. The reaction was then initiated by the addition of 10 µLof acetylthiocholine iodide (0.71 mM) or butyrylthiocholine chloride (0.2 mM). The hydrolysis of these substrates were monitored spectrophotometrically by the formation of yellow 5-thio-2-nitrobenzoate anion, as the result of the reaction of DTNB with thiocholine, released by the enzymatic hydrolysis of acetylthiocholine iodide or butyrylthiocholine chloride, respectively, at a wavelength of 412 nm, every 5 min for 15 min, utilizing a 96-well microplate reader (Perkin Elmer Multimode Plate Reader EnSpire, USA) in triplicate experiments. Galanthamine was used as reference compound. The results were given as 50% inhibition concentration ($IC_{50}$) and the percentage of inhibition of AChE or BChE was determined by comparison of reaction rates of samples relative to blank sample (methanol in phosphate buffer, pH 8) using the formula:

$$\text{Inhibition of AChE or BChE (\%)} = \frac{E - S}{E} \times 100$$

Where E is the activity of enzyme without test sample, and S is the activity of enzyme with test sample. The obtained results are given in Table 4.

### 4.3. Computational details

All the DFT (density functional theory) calculations have been carried on the optimized geometries using Gaussian 09 software.[36] The B3LYP

functional [37-38] and the 6-311G++(d,p) basis set for C, H, N and O atoms were employed. The reliability of this methodology has been confirmed by previous studies.[39-42] All the ground states were confirmed by vibrational frequency analysis (no imaginary frequency). Molecular descriptors (Electronegativity, chemical softness, chemical hardness and electrophilic index**)** were calculated from HOMO/LUMO energies method as reported in our previous studies.[38-39]

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## Highlights

- A series of novel *β*-acetamido ketones have been prepared via a four-component condensation between aromatic aldehydes, enolizable ketones, acyl chloride and acetonitrile.
- Phenylboronic acid has been used as an efficient catalyst for the present methodology.
- The *in vitro* cholinesterase inhibitory activity of title compounds has been studied.
- Theoretical investigations have been carried out in order to understand molecular structure and chemical reactivity of the synthesized compounds.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: