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ORIGINAL PAPER

# Synthesis, characterization and quantum-chemical calculations of novel series of pyridones, quinazolinones and pyrazoles heterocyclic compounds

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**Abstract** This paper presents a combined synthesis and computational study of novel series of pyridones, quinazolinones and pyrazoles heterocyclic compounds that were characterized by elemental analyses and spectral dada. Michael addition of substituted-2-methoxycarbonylacetanilide **2a**, **b** on the α-substituted cinnamonitriles **3a–d** gave the corresponding pyridone and quinazolinone derivatives **5**, **6a–c, 7a–d,** and **14a–e**, respectively. Reaction of ethyl-2-cyano3-ethoxyacrylate with **2a**, **b** afforded the corresponding pyridone **10a, b**. Also, spiro pyridine derivative **12** was synthesized through the reaction of **2a**, **b** with indandione malononitrile (**11**). Reaction of hydrazine and phenyl hydrazine with acrylamido derivatives **15a–d** afforded the novel pyrazoles **16** and **17**. The molecular modeling of the synthesized compounds has been drawn and their molecular parameters were calculated. Also, valuable information is obtained from the calculation of molecular parameters including electronegativity of the coordination sites, net dipole moment of the compounds, total energy, electronic energy, binding energy, HOMO and LUMO energy.

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**Keywords** Pyridones · Quinazolinones · Pyrazoles · Molecular modeling · Michael addition

## Introduction

The importance of heterocyclic compounds has long been recognized in the field of synthetic organic chemistry and has been extensively studied due to their important properties and applications at present. It is well known that a number of heterocyclic compounds containing nitrogen exhibited a wide variety of biological activity. Also, in recent years, the high therapeutic properties of the heterocyclic compounds have attracted the attention of pharmaceutical chemists to synthesize a large number of novel chemotherapeutic agents and many pharmaceuticals are synthetic compounds and heterocyclic in nature. Among these compounds, pyridines [1], quinazolinone derivatives [2] and pyrazoles [3] have become especially noteworthy in recent years.

Quinazoline and quinazolinone nuclei have drawn a great attention due to their wide range of chemotherapeutic activities including antiviral [3], antibacterial [4], antifungal [5, 6], antimalarial [7], anticancer [8–10], antihypertensive [11], diuretic [12, 13], inhibitors of derived growth factor receptor phosphorylation [14], anticonvulsant [15], anti-inflammatory and analgesic [16, 17]. Additionally, pyridones have a wide range of biological activities like antitumor, cytotoxic activities, anti-inflammatory and analgesic activities [18–22]. Also, pyrazoles act as an important class of compounds for new drug development that attracted much attention due to their broad spectrum of biological activities, such as anti-inflammatory [23], antifungal [24], anticancer [25], antibacterial [26], antiviral [27], antidepressant [28], antidiabetic [29] and antioxidant [30] activities. Computational chemistry

has become of great importance, especially in recent years [31]. It allows us to understand the probable behavior of the compound during reactions and further to know an important information about the compounds under investigations, like total energy, binding energy, electronic energy, dipole moment, bond lengths, HOMO, LUMO [32], and the value of this information increases especially when it agrees with the experimental data. The applicability of the semi-empirical methods PM3 for the calculation of novel synthesized compounds has been evaluated [33, 34].

In view of the above facts and in continuation of our research program [35–43] directed to synthesize new compounds, our current work highlights design, synthesis, characterization and molecular modeling of various pyridones, pyrazoles and quinazolinone derivatives.

## Results and discussion

### Chemistry

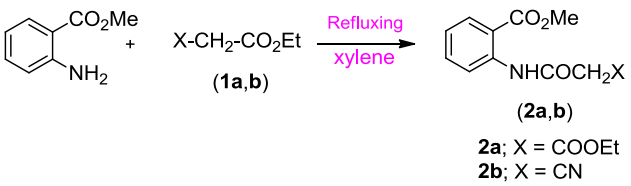
The required starting material **2a**, **b** [44] was synthesized in good yield (80 %) through the reaction of methyl 2-aminobenzoate with diethylmalonate **1a** or ethyl cyanoacetate **1b** in refluxing xylene (Scheme 1).

Reaction of methyl 2-(2-cyanoacetamido)benzoate (**2a**) with α-substituted cinnamonitriles **3a–c** in refluxing ethanol in the presence of catalytic amount of piperidine gave the corresponding pyridones of type **5** and **6a–c**, respectively. The structures of the synthesized products were confirmed on the basis of their elemental analyses and spectral data (see "Experimental" part). The formation of pyridones **5** and **6** was assumed to be proceeded via the Michael addition of active methylene group of compound **2a** on the β-carbon atom of cinnamonitrile derivatives to give the Michael adduct **4**, intramolecular cyclization of **4** followed by elimination of HX or $H_2$ molecule, afforded pyridones **5** and **6**, respectively, (Scheme 2).

Similarly, treatment of methyl 2-(3-ethoxy-3-oxopropanamido)benzoate **2b** with α-substituted cinnamonitriles **3a–c** in refluxing ethanol in the presence of catalytic amount of piperidine afforded the corresponding pyridones derivatives **7a–d** via the intramolecular cyclization of the Michael adduct **4a** through addition–elimination reaction on the carbonyl group followed by elimination of HX or $H_2$ molecule (Scheme 3). The structures of the latter products were established on the basis of their elemental analyses and spectral data. For example, $^{13}$C NMR spectrum (DMSO-$d_6$) of compound **7a** revealed signals at $\delta$ 13.91, 21.26, 52.29, 62.19, 115.67, 161.91, and 167.08 ppm attributed to ethoxy carbonyl, methyl, methoxy, cyano and carbonyl carbon atoms.

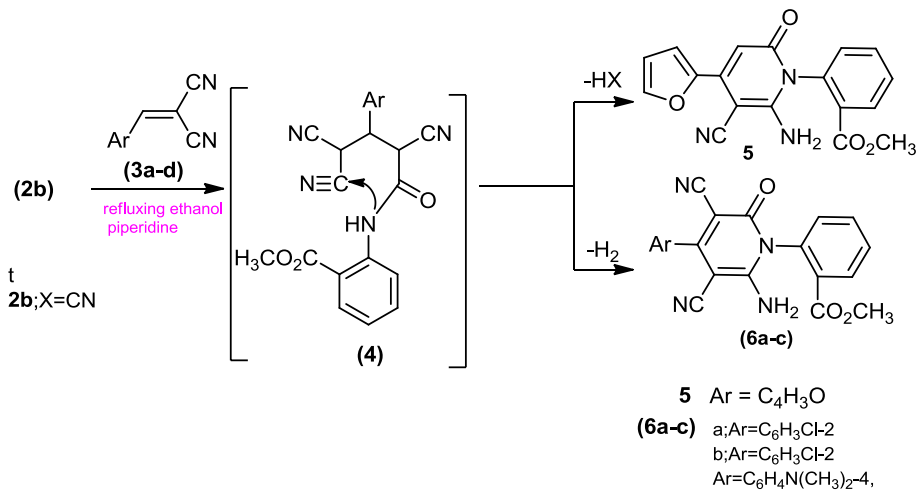
Also, 3, 4-dihydropyridone derivative **8** was obtained via the reaction of acetanilide derivative **2a** with 2-cyano-3-(fuan-2-yl) acylamide **3d** as shown in Scheme 4. $^1$HNMR spectrum (DMSO-$d_6$) of pyridone derivative **8** showed two doublets at 3.70 and 3.86 ppm for pyridine-H3 and H4, respectively, that was compatible with the proposed structure.

Ternary condensation of **2a** or **2b** with acetaldehyde and malononitrile in refluxing ethanol containing piperidine as catalyst afforded 5-cyanopyridone derivative **9** through releasing of HCN molecule. Also, reaction of **2a**, **b** with

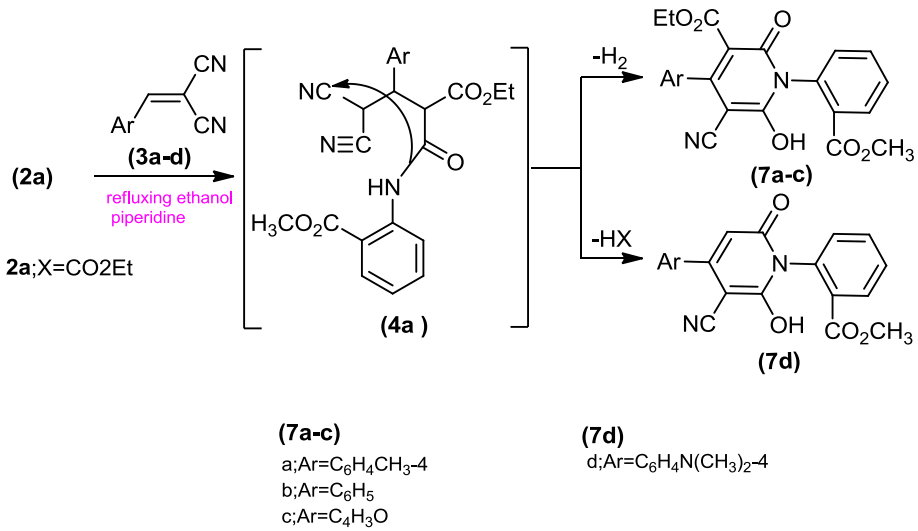



**Scheme 1** Synthesis of acetanilide derivatives **2a**, **b**

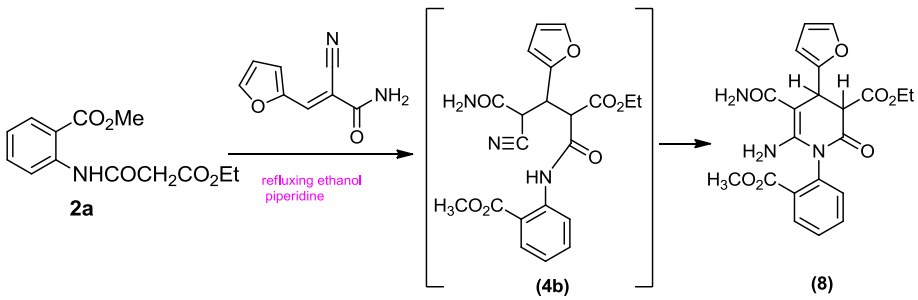
**Scheme 2** Synthesis of 2-pyridones derivatives **5** and **6**



**Scheme 3** Synthesis of 2-pyridinone derivatives **7**




**Scheme 4** Synthesis of amido pyridine derivative **8**



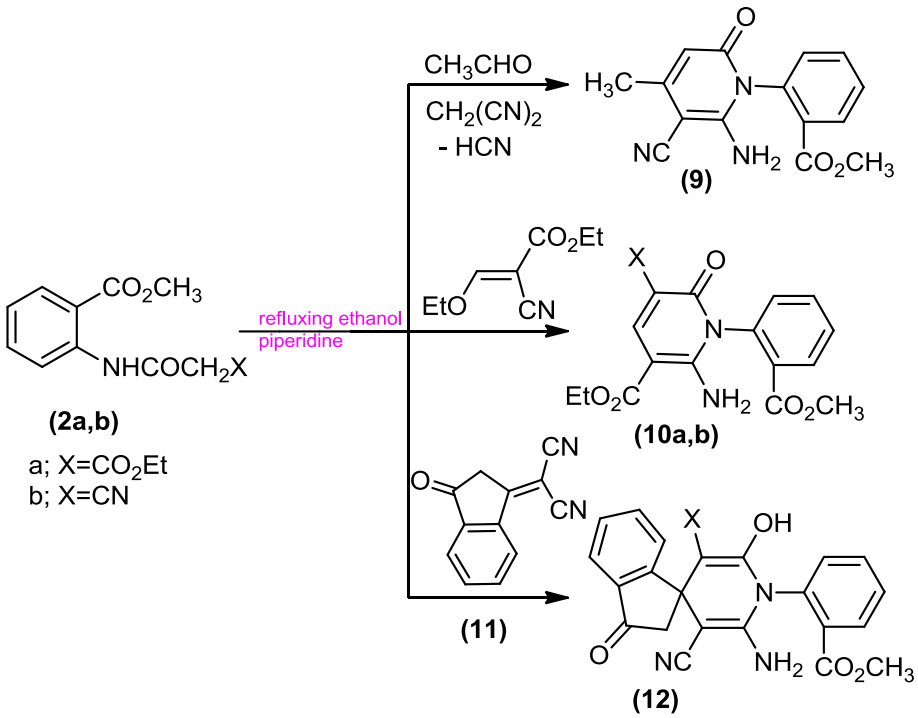

diethoxy acrylonitrile furnished the pyridone types **10a**, **b** (Scheme 5). The structures of the synthesized compounds **9** and **10** were elucidated on the basis of their elemental and spectral data. For example, the IR spectrum of compound **9** showed bands at 3337, 3242 ($NH_2$). 2200 (C≡N) and 1670 $cm^{-1}$ (C=O). The appearance of three singlet signals in $^1H$ NMR spectrum (DMSO-$d_6$) at $\delta$ 2.18, 3.85 and 6.25 ppm attributed to $CH_3$, $CH_3O$ and pyridine-H3 protons, respectively, in addition to aromatic protons with $NH_2$ in the region 7.20–8.30 ppm. Its mass spectrum exhibited a peak at 283 due to molecular ion that confirmed the assigned structure (Scheme 5).

In a similar manner, **2a**, **b** was reacted with 1, 3-indandione malononitrile (**11**) and gave the corresponding spiro pyridine derivatives **12** (Scheme 5) whose structure was established on the basis of its elemental analysis and spectral data. For example, IR spectrum of compound **12** afforded bands at 3355, 3144 ($NH_2$), 2202 (C≡N),1670 (C=O) $cm^{-1}$ and its $^1H$ NMR spectrum (DMSO-$d_6$) showed triplet and quartet signals at $\delta = 1.07$, 4.03 ppm for ethoxy protons, a singlet signal at $\delta$ 2.74 ppm for ($CH_2$), a singlet signal at $\delta$ 3.80 ppm ($OCH_3$), and multiple signals at $\delta$ 7.27–8.24 ppm (Ar–H + $NH_2$) in addition to a singlet signal at $\delta$ 12.19 ppm for hydroxyl group.

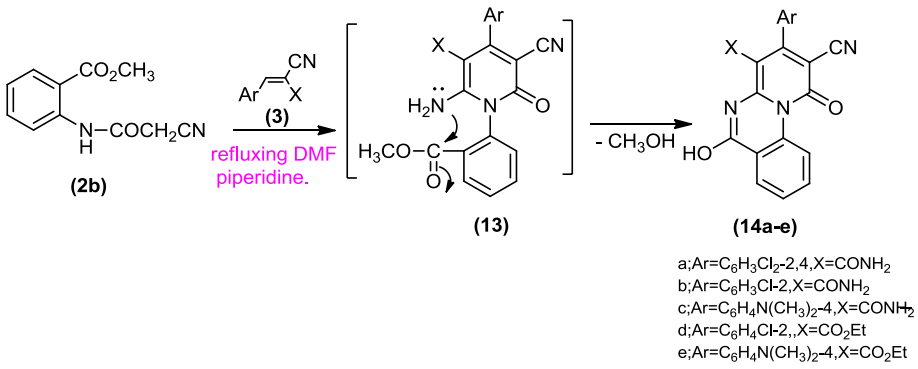
On the other hand, quinazolines **14a–e** were synthesized via reaction of compound **2b** with α-substituted cinnamonitriles **3** in refluxing DMF containing catalytic amounts of piperidine. The structure of the isolated products was confirmed based on their elemental analyses and spectral data. For example, $^1H$ NMR spectrum (DMSO-$d_6$) of compound **14d** revealed a triplet signal at $\delta$ 1.25 ppm for $CH_3$ group and a quartet signal at $\delta$ 4.38 ppm corresponding to $CH_2$ group in addition to the presence of aromatic and OH protons at $\delta$ 7.54–8.12 and 9.53 ppm, respectively. The isolated product **14** was assumed to proceed via the formation of pyridine intermediate **13** followed by elimination of methanol molecule (Scheme 6).

In this part of research the study was extended to synthesis quinazoline derivatives containing pyrazole functionalities. Thus, the reactivity of the substituted-2-methoxycarbonyl acetanilide **2a**, **b** towards some electrophiles was investigated. Condensation of **2a**, **b** with aromatic aldehydes in ethanol in the presence of piperidine under reflux gave the corresponding methyl 2-(substituted-3-arylacrylamido) benzoate **15a–d**, (Scheme 7). The elemental analyses and spectral data were in a complete accordance with expected structures **15a–d**. The reaction of hydrazine hydrate with **15d** and reaction of phenyl hydrazine with

**Scheme 5** Synthesis of 2-pyridones **9**, **10** and pyridine derivative **12**




**Scheme 6** Synthesis of pyrido[1,2-a]quinazoline derivatives **14a–e**



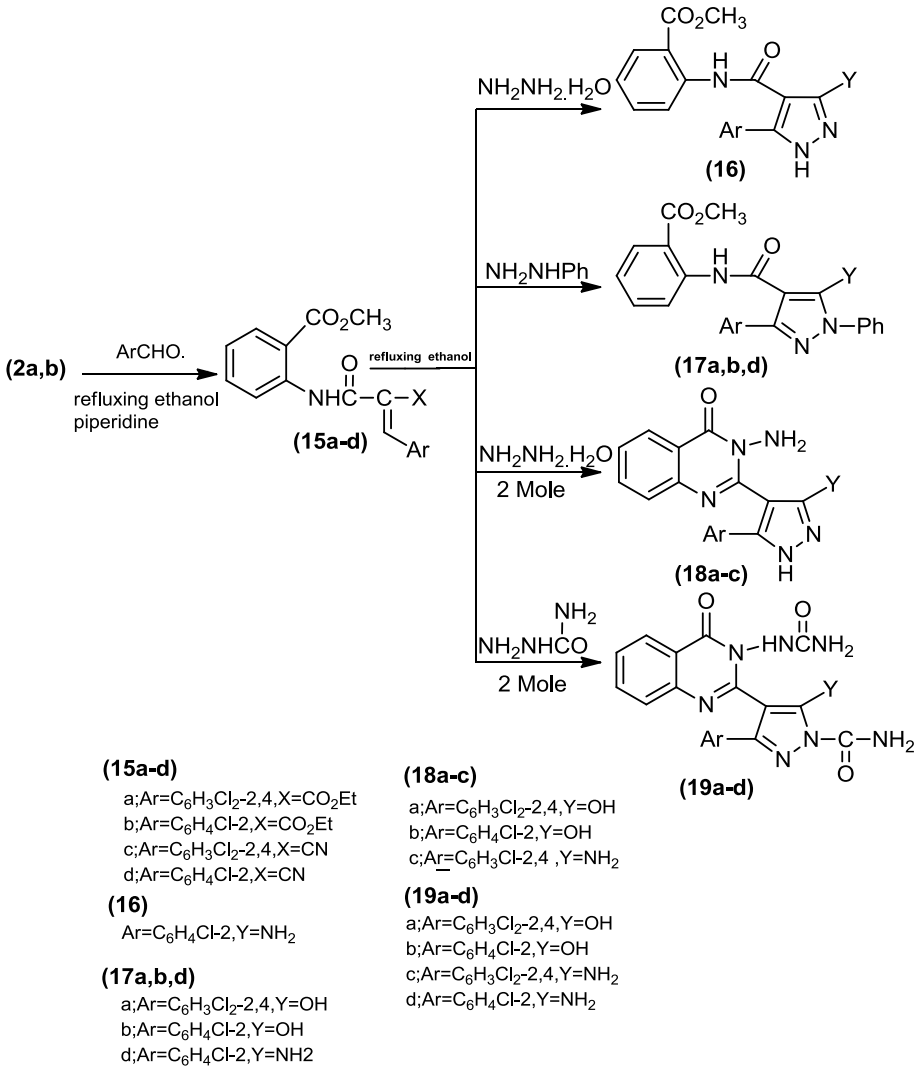

**15a**, **b**, **d** in refluxing ethanol afforded the novel pyrazoles **16** and **17 a**, **b**, **d**, respectively (Scheme 7). The structures of the synthesized products were confirmed on the basis of their elemental analyses and spectral data (see "Experimental" part). On the other hand, 3-amino or hydroxy-5-aryl-1*H*-pyrazol-4-yl) quinazolin-4(3*H*)-one derivatives **18a–c** and **19a–d** were formed through consumption of 2 mol of hydrazine hydrate or semicarbazide in reaction with arylacrylamido derivatives **15** depending on elemental analyses and spectral data (see "Experimental" part) (Scheme 7).

## Molecular modeling and computational study

In the absence of a crystal structure, to obtain the molecular conformation of a compound, energy minimization studies were carried out on the basis of the semi-empirical PM3 level provided by HyperChem 7.5 software. The most stable structures obtained were subsequently optimized to the closest local minimum at the semiempirical level using PM3 parameterizations. The calculated dipole moment ($\mu$), total energy ($E_T$), binding energy ($E_B$), and electronic energy ($E_E$) after geometrical optimization of the structures of complexes are given in Table 1.

The values of the following parameters: the highest occupied molecular orbital energy ($E_{HOMO}$), the lowest unoccupied molecular orbital energy ($E_{LUMO}$), the difference between HOMO and LUMO energy levels ($\Delta E$), Mulliken electronegativity ($\chi$), chemical potential (Pi), global hardness ($\eta$), global softness ($S$), global electrophilicity ($\omega$) [45–49] and additional electronic charge ($\Delta N_{max}$) have been calculated [50] using semi-empirical PM3 method as implemented in HyperChem [51]. In a first step, the molecular geometries of all compounds

**Scheme 7** Synthesis of pyrazoles **16**, **17** in addition to quinazolinones **18** and **19**




were fully optimized in the gas phase to gradients of 0.01 kcal $mol^{-1}$ $Å^{-1}$ and afterwards the molecular descriptors were determined.

Equations (1)–(7) are used in calculations of molecular parameters as given below:

$$\chi = -1/2(E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}}) \quad (1)$$

$$\mathrm{Pi} = -\chi \quad (2)$$

$$\eta = 1/2(E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}}) \quad (3)$$

$$S = 1/2\eta \quad (4)$$

$$\omega = \mathrm{Pi}^2/2\eta \quad (5)$$

$$\sigma = 1/\eta \quad (6)$$

$$\Delta N_{\max} = -\mathrm{Pi}/\eta \quad (7)$$

The concepts of the parameters $\chi$ and Pi are related to each other. The inverse of the global hardness is designated as the absolute softness $\sigma$.

Recently, quantum-chemical calculation methods have become available to provide a powerful approach for crystal structure prediction [52–57].

## Molecular parameters

According to the obtained data given in Table 2, we can deduce each of the following:

(a) Absolute hardness ($\eta$) and softness ($\sigma$) are important properties to measure the molecular stability and reactivity. A hard molecule has a large energy gap and a soft molecule has a small energy gap. Soft molecules are more reactive than hard ones because they could easily offer electrons to an acceptor.

**Table 1** Some energetic properties of synthesized compounds calculated by PM3 method

| Compound | Total energy (kcal mol$^{-1}$) | Binding energy (kcal mol$^{-1}$) | Electronic energy (kcal mol$^{-1}$) | Dipole moment |
|---|---|---|---|---|
| **5** | −109,849.5 | −5568.3 | −908,290.4 | 3.45 |
| **6a** | −111,066.0 | −4789.2 | −894,354.1 | 4.68 |
| **6b** | −104,504.8 | −4893.9 | −863,642.2 | 5.72 |
| **6c** | −108,546.0 | −5630.1 | −944,900.8 | 6.40 |
| **7a** | −102,956.7 | −4657.2 | −794,702.6 | 2.95 |
| **7b** | −99,505.7 | −4374.2 | −733,827.6 | 4.74 |
| **7c** | −117,885.2 | −5217.9 | −973,030.1 | 2.77 |
| **7d** | −87,323.4 | −4165.8 | −650,543.1 | 2.65 |
| **9** | −77,113.1 | −3796.1 | −550,277.4 | 3.76 |
| **10a** | −113,912.3 | −5169.3 | −915,394.6 | 3.36 |
| **10b** | −96,833.1 | −4437.9 | −732,917.2 | 6.47 |
| **12** | −127,334.5 | −5937.0 | −1,120,130.6 | 11.58 |
| **14a** | −107,961.5 | −4551.3 | −861,262.0 | 4.52 |
| **14b** | −101,012.4 | −4569.4 | −812,342.0 | 5.85 |
| **14c** | −105,124.2 | −5376.3 | −891,516.4 | 8.42 |
| **14d** | −110,646.0 | −5130.7 | −924,543.8 | 6.52 |
| **14e** | −121,636.3 | −5848.8 | −1,085,935.9 | 5.65 |
| **15a** | −954,149.2 | −4556.1 | −729,224.8 | 6.90 |
| **15b** | −105,907.5 | −4913.7 | −833,867.7 | 4.24 |
| **15c** | −95,800.3 | −4186.8 | −672,873.6 | 4.98 |
| **15d** | −88,748.5 | −4102.2 | −656,031.7 | 4.05 |
| **16** | −96,863.2 | −4344.2 | −710,672.2 | 7.62 |
| **17a** | −124,477.8 | −5659.2 | −1,069,852.6 | 4.71 |
| **17b** | −117,394.2 | −5542.8 | −1,003,366.0 | 5.81 |
| **17c** | −114,702.0 | −5587.0 | −995,974.4 | 6.30 |
| **18a** | −97,150.0 | −4171.3 | −770,606.0 | 7.31 |
| **18b** | −90,198.6 | −4187.2 | −720,513.5 | 7.93 |
| **18c** | −94,475.7 | −4233.3 | −767,778.7 | 7.91 |
| **19a** | −124,370.0 | −5043.7 | −1,068,524.0 | 6.55 |
| **19b** | −117,389.6 | −5030.6 | −1,025,429.3 | 6.06 |
| **19c** | −121,670.1 | −5080.1 | −1,081,919.1 | 6.16 |
| **19d** | −114,724.6 | −5101.9 | −1,046,102.2 | 6.96 |

(b) The reactivity index measures the stabilization in energy when the system acquires an additional electronic charge ($\Delta N_{max}$) from the environment. The electrophilicity index is positive quantity and the direction of the charge transfer is completely determined by the electronic chemical potential (Pi) of the molecule because an electrophile is a chemical species capable of accepting electrons from the environment and its energy must decrease upon accepting electronic charge. Therefore, the electronic chemical potential must be negative, exactly as supported by the values in Table 2.

(c) The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very popular quantum-chemical parameters. These molecular orbitals are also called the frontier molecular orbitals (FMOs) and determine the way of interaction for the molecule with other species. The FMOs are important in molecular reactivity. HOMO energy is closely related to reactivity to electrophilic attack (i.e., could act as an electron donor), since it is the highest energy orbital containing electrons while LUMO energy is closely related to reactivity to nucleophilic attack (i.e., could act as the electron accepter), since it is the lowest energy orbital that can accept electrons.

(d) The energies of the HOMO and LUMO are negative, which indicate that the title molecules are stable [55].

(e) However, the LUMO energy presents the ability of a molecule receiving an electron, thus the lower value of $E_{LUMO}$ indicates that the high ability of the molecule

**Table 2** The calculated quantum-chemical parameters of the synthesized compounds

| Compound | HOMO | LUMO | $\Delta E$ | $x$ | $\eta$ | $\sigma$ | Pi | $\omega$ | $\Delta N_{max}$ |
|---|---|---|---|---|---|---|---|---|---|
| **5** | −8.72 | −0.82 | 7.9 | 4.77 | 5.39 | 0.1855 | −4.77 | 2.1107 | 0.8850 |
| **6a** | −4.56 | −1.27 | 3.29 | 2.915 | 10.39 | 0.0962 | −2.915 | 0.4089 | 0.2806 |
| **6b** | −8.99 | −1.28 | 7.71 | 5.135 | 11.39 | 0.0878 | −5.135 | 1.1575 | 0.4508 |
| **6c** | −8.98 | −1.24 | 7.74 | 5.11 | 12.39 | 0.0807 | −5.11 | 1.0538 | 0.4124 |
| **7a** | −9.22 | −0.95 | 8.27 | 5.085 | 13.39 | 0.0747 | −5.085 | 0.9655 | 0.3798 |
| **7b** | −9.28 | −1.02 | 8.26 | 5.15 | 14.39 | 0.0695 | −5.15 | 0.9216 | 0.3579 |
| **7c** | −9.24 | −1.09 | 8.15 | 5.165 | 15.39 | 0.0650 | −5.165 | 0.8667 | 0.3356 |
| **7d** | −9 | −0.69 | 8.31 | 4.845 | 16.39 | 0.0610 | −4.845 | 0.7161 | 0.2956 |
| **9** | −8.75 | −0.76 | 7.99 | 4.755 | 17.39 | 0.0575 | −4.755 | 0.6501 | 0.2734 |
| **10a** | −8.83 | −0.79 | 8.04 | 4.81 | 18.39 | 0.0544 | −4.81 | 0.6290 | 0.2616 |
| **10b** | −8.93 | −1.04 | 7.89 | 4.985 | 19.39 | 0.0516 | −4.985 | 0.6408 | 0.2571 |
| **12** | −6.9 | −3.83 | 3.07 | 5.365 | 20.39 | 0.0490 | −5.365 | 0.7058 | 0.2631 |
| **14a** | −8.2 | −2.19 | 6.01 | 5.195 | 21.39 | 0.0468 | −5.195 | 0.6309 | 0.2429 |
| **14b** | −8.12 | −2.04 | 6.08 | 5.08 | 22.39 | 0.0447 | −5.08 | 0.5763 | 0.2269 |
| **14c** | −8.99 | −1.75 | 7.24 | 5.37 | 23.39 | 0.0428 | −5.37 | 0.6164 | 0.2296 |
| **14d** | −8.96 | −1.73 | 7.23 | 5.345 | 24.39 | 0.0410 | −5.345 | 0.5857 | 0.2191 |
| **15a** | −7.81 | −1.31 | 6.5 | 4.56 | 25.39 | 0.0394 | −4.56 | 0.4095 | 0.1796 |
| **15b** | −9.32 | −0.94 | 8.38 | 5.13 | 26.39 | 0.0379 | −5.13 | 0.4986 | 0.1944 |
| **15c** | −9.13 | −1.17 | 7.96 | 5.15 | 27.39 | 0.0365 | −5.15 | 0.4842 | 0.1880 |
| **15d** | −8.32 | −1.68 | 6.64 | 5 | 28.39 | 0.0352 | −5 | 0.4403 | 0.1761 |
| **16** | −8.85 | −2.32 | 6.53 | 5.585 | 29.39 | 0.0340 | −5.585 | 0.5307 | 0.1900 |
| **17a** | −9.03 | −0.88 | 8.15 | 4.955 | 30.39 | 0.0329 | −4.955 | 0.4039 | 0.1630 |
| **17b** | −8.83 | −2.64 | 6.19 | 5.735 | 31.39 | 0.0319 | −5.735 | 0.5239 | 0.1827 |
| **17c** | −8.2 | −2.37 | 5.83 | 5.285 | 32.39 | 0.0309 | −5.285 | 0.4312 | 0.1632 |
| **18a** | −7.59 | −2.46 | 5.13 | 5.025 | 33.39 | 0.0299 | −5.025 | 0.3781 | 0.1505 |
| **18b** | −7.48 | −2.39 | 5.09 | 4.935 | 34.39 | 0.0291 | −4.935 | 0.3541 | 0.1435 |
| **18c** | −7.62 | −2.48 | 5.14 | 5.05 | 35.39 | 0.0283 | −5.05 | 0.3603 | 0.1427 |
| **19a** | −7.88 | −1.03 | 6.85 | 4.455 | 36.39 | 0.0275 | −4.455 | 0.2727 | 0.1224 |
| **19b** | −6.48 | −2.36 | 4.12 | 4.42 | 37.39 | 0.0267 | −4.42 | 0.2613 | 0.1182 |
| **19c** | −7.06 | −2.34 | 4.72 | 4.7 | 38.39 | 0.0260 | −4.7 | 0.2877 | 0.1224 |
| **19d** | −9.01 | −2.36 | 6.65 | 5.685 | 39.39 | 0.0254 | −5.685 | 0.4102 | 0.1443 |

is to accept electrons [56, 57]. The HOMO energy implies that the molecule is a good electron donor so the lower HOMO energy values show that the molecule donating electron ability is weaker.

(f) The HOMO–LUMO energy gap, $\Delta E$, which is an important stability index, is applied to develop theoretical models for explaining the structure and conformation barriers in many molecular systems. A molecule with a small gap is more polarized and is known as soft molecule. Soft molecules are more reactive than hard ones because they easily offer electrons to an acceptor [58, 59].

(g) The HOMO–LUMO energy separation has been used as a simple indicator of kinetic stability and chemical reactivity of the molecule. The values of the energy separation between the HOMO and LUMO for the synthesized compounds lie in the range 3.07–8.38. The large HOMO–LUMO gap automatically means high excitation energies, good stability and a large chemical hardness for the title compounds.

## Bond length and bond angle calculations

Theoretical calculations have paid a considerable attention to the characterization and inferences of geometrical optimization of the prepared compounds; therefore, we could obtain the optimized structure for the prepared compounds by computing the theoretical physical parameters, such as bond lengths and bond angles using the HyperChem 7.5 software. The optimized structures for the **5**, **14a** and **17a** with the atomic numbering scheme as a representative example of pyridines, quinazolinones and pyrazoles heterocyclic compounds, respectively, are shown in the Figs. 1, 2 and 3. The bond angles and bond lengths (Å) obtained from

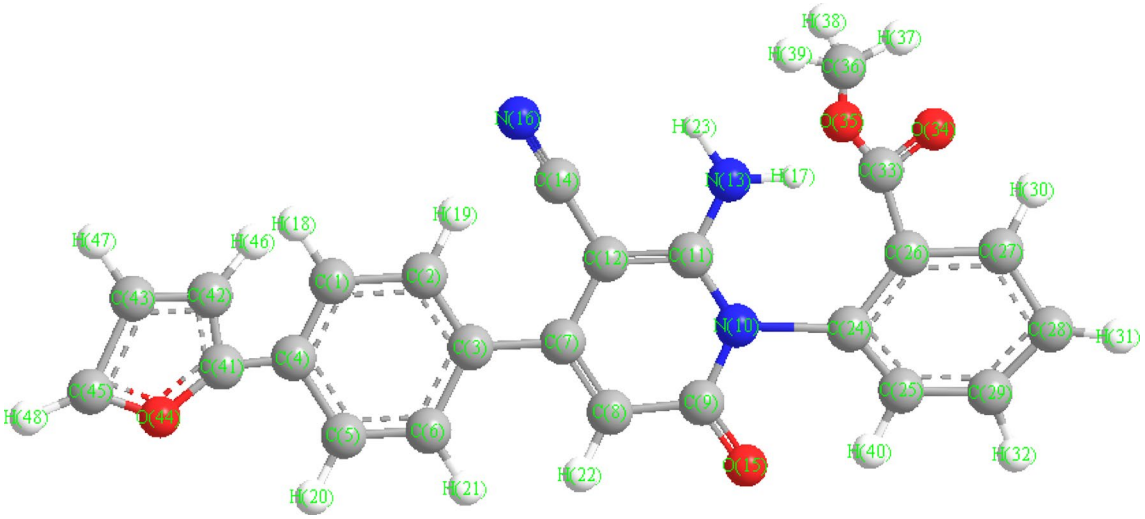



**Fig. 1** The molecular structure of compound **5** along with the atom numbering scheme

the minimization of energy for the structure of **17a** as a representative example of the reported compounds are given in the Table 3. In most of the cases, the actual bond lengths and bond angles are close to the optimal values, and thus the proposed structure of the compound is acceptable.

## Conclusion

We report a facile route for the formation of a novel series of pyridones, quinazolinones and pyrazoles heterocyclic compounds. The compounds have been characterized by elemental analyses and spectral like IR, $^{1}$H NMR, $^{13}$C NMR and MS studies. Geometry optimization and conformational analysis have been performed and molecular parameters were calculated. Further investigations on biological activities with these derivatives are still underway in our laboratory.

## Experimental

### Materials and methods

All melting points (m.p.) are uncorrected. IR spectra were recorded on "Buck scientific infrared spectroscopy M500 spectrophotometer" using KBr pellets. All the NMR spectra were recorded on Gemini 200 MHz spectrometer using TMS as internal standard; chemical shifts are reported as (ppm), s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet. The mass spectra (MS) were recorded on GCMS/QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center, Faculty of Science (Cairo University, Egypt).

### Chemistry

*General procedure for preparation of **5** and **6a–c***

A mixture of compounds either **2a** (2.18 g) or **2b** (2.65 g) (0.01 mmol), α-cyanocinnamonitriles **3** (1.54 g, 0.01 mmol) and piperidine (0.05 mL) in ethanol (30 mL) were refluxed for 3 h; the solid product was receipted out on heating, then collected and recrystallized from suitable solvent to give **5** and **6a–c**.

Methyl-2-(6-amino-5-cyano-4-(furan-2-yl)-2-oxopyridin-1(2*H*)-yl) benzoate **(5):** Brown powder (MeOH); m.p.: yield 60 %; 164–166 °C; IR (KBr, $\bar{\nu}$, cm$^{-1}$): 3330, 3270, ($NH_2$), 2213(C≡N) and 1660 (C=O); $^{1}$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.85 (s, 3H, $OCH_3$),6.51 (s, 1H, pyridine-H), 7.14–8.33 (m, 7H, Ar–H), 9.50 (s, 2H, $NH_2$); Anal. Calcd for $C_{18}H_{13}N_3O_4$ (335): C, 64.47; H, 3.91; N, 12.53. Found: C, 64.89; H, 3.39 N, 12.07 %.

Methyl-2-(6-amino-3,5-dicyano-4-(2,4-dichlorophenyl)-2-oxopyridin-1(2*H*)-yl)benzoate **(6a):** White powder (EtOH); yield 74 %; m.p.: 168–170 °C; IR (KBr, $\bar{\nu}$, cm$^{-1}$): 34213, 3200 ($NH_2$) 2218(C≡N) and 1697 (C=O). $^{1}$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.89 (s, 3H, $OCH_3$), 7.24–8.00 (m, 9H, Ar–H + $NH_2$); Anal. Calcd for $C_{21}H_{12}Cl_2N_4O_3$ (438): C, 57.42; H, 2.75; N, 12.76. Found: C, 57.22; H, 3.01 N, 13.27 %.

Methyl-2-(6-amino-4-(2-chlorophenyl)-3,5-dicyano-2-oxopyridin-1(2*H*)-yl)benzoate **(6b):** Brown powder (EtOH), yield 71 %; m.p.: 174–176 °C; IR (KBr, $\bar{\nu}$, cm$^{-1}$): 3423, 3180 ($NH_2$), 2218(C≡N) and 1693 (C=O); $^{1}$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.91 (s, 3H, $OCH_3$), 7.29–8.15 (m, 8H, Ar–H),9.21 (s, 2H, $NH_2$); MS: 405 (M + 1: 0.78 %); Anal. Calcd for $C_{21}$ $H_{13}ClN_4O_3$ (404): C, 62.31; H, 3.24; N, 13.84. Found: C, 62.22; H, 3.21 N, 13.84 %.

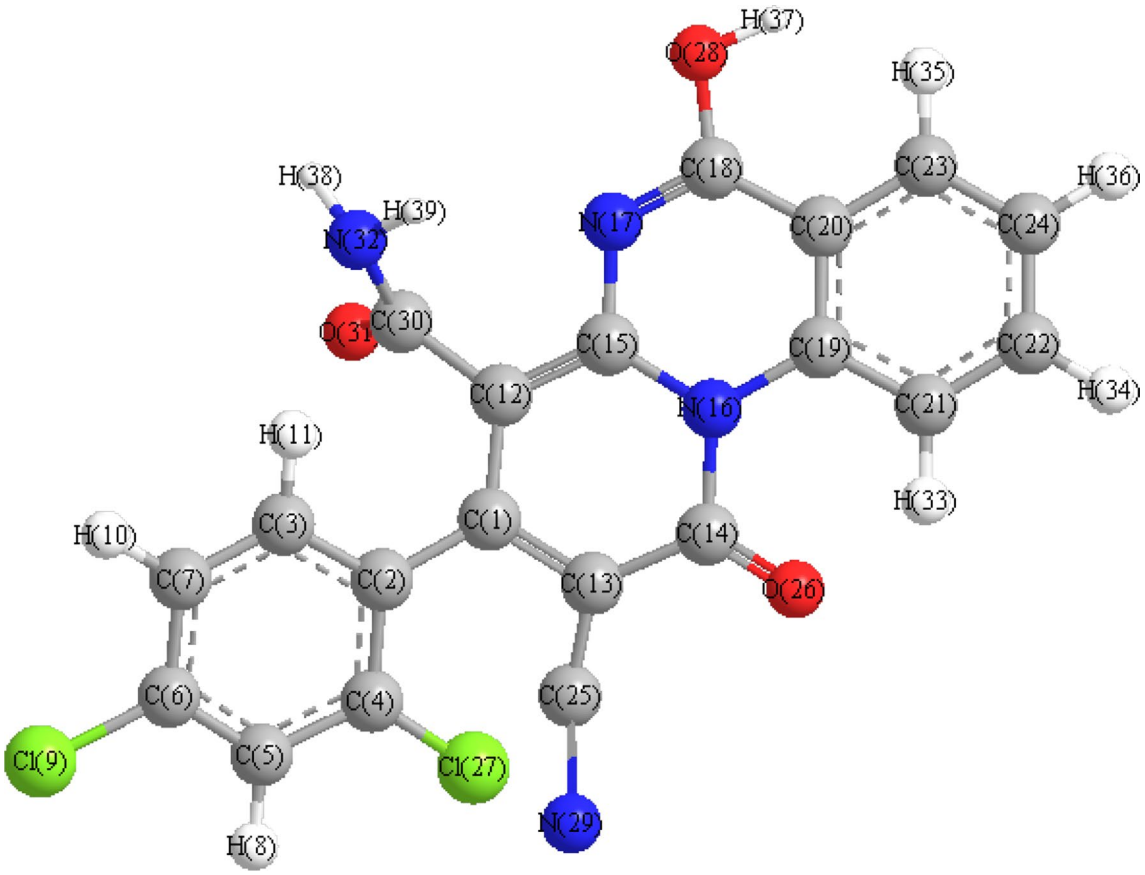



**Fig. 2** The molecular structure of compound **14a** along with the atom numbering scheme

Methyl-2-(6-amino-3,5-dicyano-4-(4-(dimethylamino) phenyl)-2-oxopyri-din-1(2*H*)-yl)benzoate **(6c):** Yellow solid (MeOH); yield 86 %; m.p.: 186–188 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3423, 3180, ($NH_2$), 2218(C≡N) and 1693 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.09 (s, 6H, $N(CH_3)_2$), 3.92 (s, 3H, $OCH_3$), 6.84–8.51(m, 8H, Ar–H), 11.40 (s, 2H, $NH_2$); Anal. Calcd for $C_{23}H_{19}N_5O_3$ (413): C, 66.82; H, 4.63; N, 16.94. Found: C, 66.33; H, 4 0.15 N, 16.50 %.

*General procedure for preparation of **7a–d***

To a solution of either **2a** (2.18 g) or **2b** (2.65 g) (0.01 mmol) in ethanol (30 mL), α-ethoxycarbonyl cinnamonitriles **3** (2.01 g, 0.01 mmol) and piperidine (0.5 mL) were added. The mixture was refluxed for 3 h, cooled and poured into crushed ice acidified with drops of HCl where the solid was filtered off and recrystallized from suitable solvent to give **7a–d**.

Ethyl-5-cyano-6-hydroxy-1-(2-(methoxycarbonyl) phenyl)-2-oxo-4-*p*-tolyl-1,2-dihydropyridine-3-carboxylate **(7a):** Beige powder (EtOH); yield 77 %; m.p.: 180–182 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3400–3225 (br OH), 2177 (C≡N) and 1723, 1693 (C=O). $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.13 (s, 3H, $CH_3$), 2.26 (s, 3H, $CH_3$), 3.94 (s, 3H, $OCH_3$), 4.36(q, 2H, $CH_2$), 7.25–8.36 (m, 8H, Ar–H), 10.89 (s, 1H, OH); $^{13}$C NMR $\delta$ ppm 13.91, 21.26, 52.29, 62.19, 115.67, 118.50, 120.8 9, 120.93, 121.60, 123.60, 124.02, 124.15, 124.64, 128.60, 129.83, 130.54, 130.87, 132.89, 133.67, 138.82, 144.29, 154.79, 161.91, 167.09; Anal. Calcd for $C_{24}H_{20}N_2O_6$ (432): C, 66.66; H, 4.66; N, 6.48. Found: C, 66.20; H, 4.10 N, 6.70 %.

Ethyl-5-cyano-6-hydroxy-1-(2-(methoxycarbonyl) phenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carboxylate **(7b)**: Yellow crystal (Dioxane); yield 61 %; m.p.: 184–186 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3425–3222 (brOH), 2214(C≡N) and 1710 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.29 (t, 3H, $CH_3$),3.86 (s, 3H, $OCH_3$), 4.33(q, 2H, $CH_2$), 7.13–8.30 (m, 9H, Ar–H), 10.83(s, 1H, OH); Anal. Calcd for $C_{23}H_{18}N_2O_6$ (418): C, 66.02; H, 4.34; N, 6.70. Found: C, 66.20; H, 4.01 N, 6.45 %.

Ethyl-5-cyano-4-(furan-2-yl)-6-hydroxy-1-(2-(methoxycarbonyl)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **(7c):** Beige crystal (AcOH); yield 61 %; m.p.: 178–180 °C.; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3316–3127 (OH), 2220 (C≡N) and 1716 (C=O). $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.09 (s, 3H, $CH_3$), 3.90 (s, 3H, $OCH_3$),

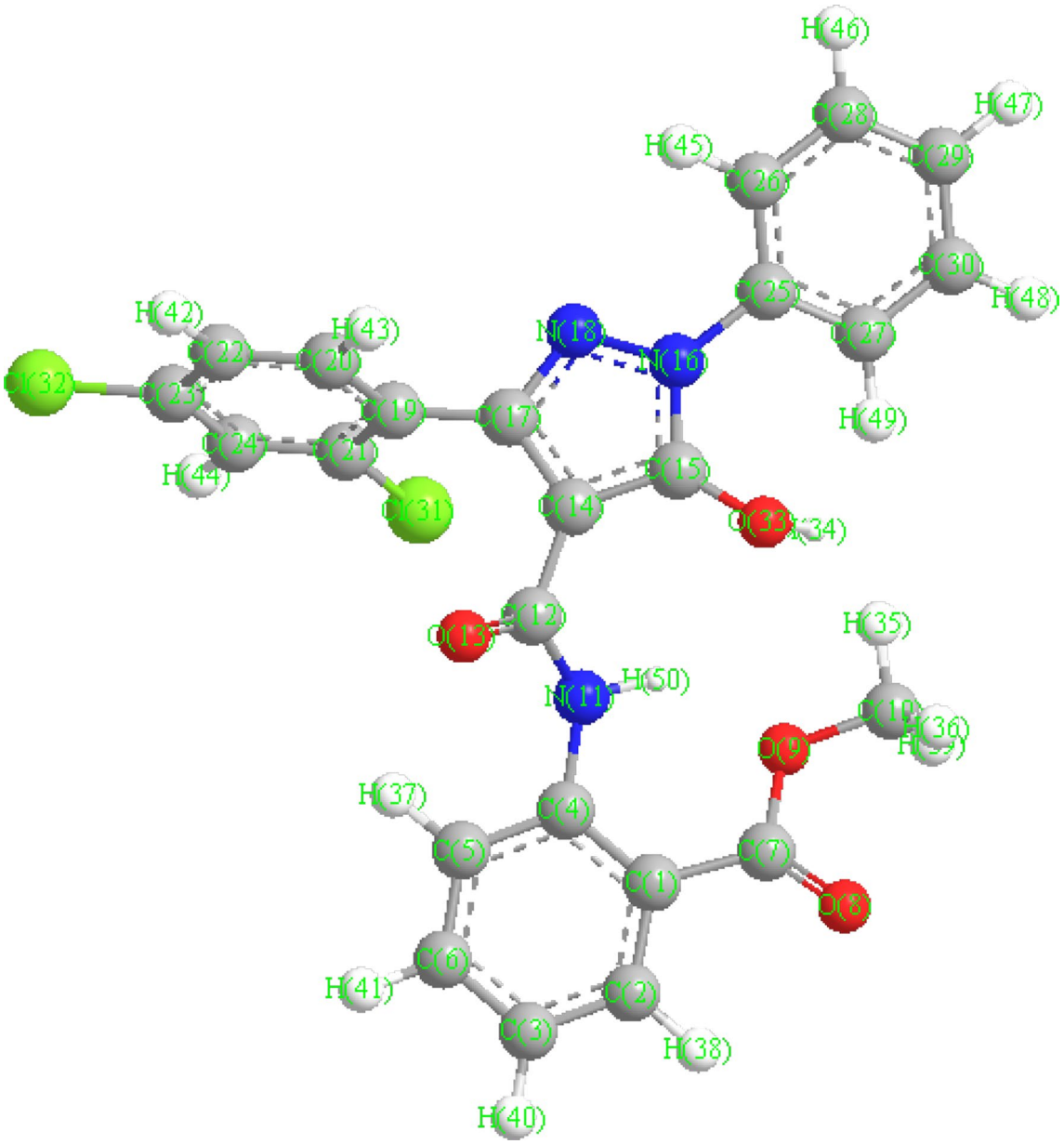



**Fig. 3** The molecular structure of compound **17a** along with the atom numbering scheme

4.37(q, 2H, $CH_2$), 6.91–8.24 (m, 7H, Ar–H), 10.89 (s, 1H, OH). Anal. Calcd for $C_{21}H_{16}N_2O_7$ (408): C, 61.77; H, 3.95; N, 6.86. Found: C, 61.20; H, 4.10 N, 6.30 %.

Methyl-2-(5-cyano-4-(4-(dimethylamino)phenyl)-6-hydroxy-2-oxopyridin-1(2*H*)-yl)benzoate (**7d**): Yellow crystal (MeOH); yield 84 %; m.p.: 176–178 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3396–3141 (OH), 2209 (C≡N) and 1695 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.31 (s, 6H, $N(CH_3)_2$), 3.90 (s, 3H, $OCH_3$), 6.86 (s, 1H, pyridine-H), 7.27–8.24 (m, 8H, Ar–H), 10.88 (s, 1H, OH); Anal. Calcd for $C_{22}H_{19}N_3O_4$ (389): C, 67.86; H, 4.92; N, 10.79. Found: C, 67.80; H, 4.70 N, 11.00 %.

Ethyl-6-amino-5-carbamoyl-4-(furan-2-yl)-1-(2-(methoxycarbonyl)phenyl)-2-oxo-1,2,3,4-tetrahydropyridine-3-carboxylate (**8**): A mixture of compound **2a** (2.18 g, 0.01 mmol), (E)-2-cyano-3-(furan-2-yl)acrylamide **3** (1.62 g, 0.01 mmol) and piperidine (0.05 mL)in ethanol (30 mL) were refluxed for 3 h; the solid product so formed on heating was collected and recrystallized from suitable solvent to give **8**: White powder (EtOH); yield 57 %; m.p.: 178–180 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3422, 3262, ($NH_2$), and 1693, 1686 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.36 (t, 3H, $CH_3$), 3.93 (s, 3H, $OCH_3$),3.70 (d, 1H, pyridine-H3), 3.86 (d, 1H, pyridine-H4), 4.30 (q, 2H, $CH_2$), 7.14–8.22

**Table 3** Selected bond lengths and Angles (°) of **17a** compound

| Atoms | Actual bond lengths (angles) (Å) | Optimal bond lengths (angles) (Å) |
|---|---|---|
| C(27)–H(49) | 1.101 | 1.100 |
| C(17)–N(18) | 1.358 | 1.358 |
| C(26)–H(45) | 1.098 | 1.100 |
| C(15)–O(33) | 1.358 | 1.355 |
| C(24)–H(44) | 1.096 | 1.100 |
| C(22)–H(42) | 1.096 | 1.100 |
| C(29)–C(30) | 1.392 | 1.420 |
| C(28)–H(46) | 1.096 | 1.100 |
| C(14)–C(17) | 1.429 | 1.420 |
| C(12)–O(13) | 1.217 | 1.208 |
| C(10)–H(35) | 1.099 | 1.111 |
| N(11)–H(50) | 1.007 | 1.012 |
| C(7)–O(8) | 1.215 | 1.208 |
| C(6)–H(41) | 1.095 | 1.100 |
| C(5)–H(37) | 1.098 | 1.100 |
| C(3)–H(40) | 1.095 | 1.100 |
| C(3)–C(6) | 1.392 | 1.420 |
| C(2)–H(38) | 1.098 | 1.100 |
| H(48)–C(30)–C(29) | 119.953 | 120.000 |
| H(48)–C(30)–C(27) | 119.769 | 120.000 |
| H(47)–C(29)–C(30) | 119.954 | 120.000 |
| H(47)–C(29)–C(28) | 120.037 | 120.000 |
| H(46)–C(28)–C(29) | 119.97 | 120.000 |
| H(46)–C(28)–C(26) | 119.524 | 120.000 |
| H(49)–C(27)–C(30) | 119.447 | 120.000 |
| H(49)–C(27)–C(25) | 120.971 | 120.000 |
| H(45)–C(26)–C(28) | 119.635 | 120.000 |
| C(27)–C(25)–C(26) | 120.307 | 120.000 |
| C(27)–C(25)–N(16) | 119.994 | 120.000 |
| C(26)–C(25)–N(16) | 119.698 | 120.000 |
| H(44)–C(24)–C(23) | 120.564 | 120.000 |
| H(44)–C(24)–C(21) | 120.365 | 120.000 |
| H(42)–C(22)–C(23) | 119.879 | 120.000 |
| H(42)–C(22)–C(20) | 120.575 | 120.000 |
| Cl(31)–C(21)–C(24) | 118.383 | 118.800 |
| C(24)–C(21)–C(19) | 120.584 | 120.000 |
| H(43)–C(20)–C(22) | 119.976 | 120.000 |
| H(43)–C(20)–C(19) | 119.764 | 120.000 |
| C(21)–C(19)–C(20) | 119.511 | 120.000 |
| C(14)–C(12)–O(13) | 124.456 | 123.000 |
| C(14)–C(12)–N(11) | 113.322 | 112.740 |
| O(13)–C(12)–N(11) | 122.155 | 122.600 |
| H(36)–C(10)–H(35) | 109.851 | 109.000 |
| H(41)–C(6)–C(5) | 119.726 | 120.000 |
| H(41)–C(6)–C(3) | 119.941 | 120.000 |
| H(37)–C(5)–C(6) | 119.098 | 120.000 |
| H(37)–C(5)–C(4) | 120.454 | 120.000 |
| N(11)–C(4)–C(5) | 119.485 | 120.000 |
| N(11)–C(4)–C(1) | 120.951 | 120.000 |
| C(5)–C(4)–C(1) | 119.365 | 120.000 |

**Table 3** continued

| Atoms | Actual bond lengths (angles) (Å) | Optimal bond lengths (angles) (Å) |
|---|---|---|
| H(40)–C(3)–C(6) | 120.169 | 120.000 |
| H(40)–C(3)–C(2) | 120.018 | 120.000 |
| H(38)–C(2)–C(3) | 119.491 | 120.000 |
| H(38)–C(2)–C(1) | 119.554 | 120.000 |
| C(4)–C(1)–C(2) | 119.089 | 120.000 |

(m, 9H, Ar–H + $NH_2$),10.88 (s, 2H, $CONH_2$); MS: 353 (M–$HCO_2Et$, 0.5 (40 %)); Anal. Calcd for $C_{15}H_{13}N_3O_3$ (427): C, 59.01; H, 4.95; N, 9.83. Found: C, 58.80; H, 4.75 N, 9.61 %.

Methyl-2-(6-amino-5-cyano-4-methyl-2-oxopyridin-1(2*H*)-yl)benzoate (**9**): A mixture of compound either **2a** or **2b** (0.01 mmol), acetaldehyde (0.01 mmol), malononitrile (0.01 mmol) and piperidine (0.05 mL) in ethanol (30 mL) were refluxed for 3 h; the solid product so formed on heating was collected and recrystallized from suitable solvent to give **9:** Brown powder (EtOH); yield 77 %; m.p.: 180–182 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3337, 3242 ($NH_2$), 2200(C≡N) and 1670 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 2.18 (s, 3H, $CH_3$), 3.85 (s, 3H, $OCH_3$), 6.25 (s, 1H, pyridine-H3), 7.20–8.30 (m, 6H, Ar–H + $NH_2$). MS: 283 (0.29 %). Anal. Calcd for $C_{15}H_{13}N_3O_3$ (283): C, 63.60; H, 4.63; N, 14.83. Found: C, 63.20; H, 4.15 N, 14.60 %.

*General procedure for preparation of **10a, b***

A mixture of compound either **2a** or **2b** (0.01 mmol), ethyl 2-cyano-3-ethoxyacrylate (0.01 mol) and piperidine (0.05 mL) in ethanol (30 mL) were refluxed for 6 h; the solid product was collected and recrystallized from suitable solvent to give **10a**, **b**.

Diethyl-6-amino-1-(2-(methoxycarbonyl)phenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarboxylate **(10a)**: Brown powder (MeOH); yield 72 %; m.p.: 178–180 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3402–3317 (br $NH_2$) and 1690 (C=O); $^1$HNMR (200 MHz, DMSO-$d_6$): $\delta$ 3.80 (s, 3H, $OCH_3$), 1.10, 1.29 (2t, 6H, $2CH_3$), 4.20, 4.29 (2q, 4H, $2CH_2$), 7.20–8.45 (m, 5H, Ar–H + pyridine-H); MS: 388 (6.35 %); Anal. Calcd for $C_{19}H_{20}N_2O_7$ (388): C, 58.76; H, 5.19; N, 7.21. Found: C, 58.19; H, 4.80; N, 7.50 %.

Ethyl-2-amino-5-cyano-1-(2-(methoxycarbonyl) phenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate **(10b)**: Yellow crystals (EtOH); yield 77 %; m.p.: 162–164 °C. IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3402–3317 (br $NH_2$), 2229 (C≡N) and 1670 (C=O); $^1$HNMR (200 MHz, DMSO-$d_6$): $\delta$ 1.10 (t, 3H, $CH_3$), 4.29 (q, 2H, $CH_2$), 3.80 (s, 3H, $OCH_3$), 7.11–8.57 (m, 5H, Ar–H + pyridine-H), 10.99 (s, 2H, $NH_2$); Anal. Calcd for $C_{17}H_{15}N_3O_5$ (341): C, 59.82; H, 4.43; N, 12.31. Found: C, 58.70; H, 4.27 N, 12.50 %.

Ethyl-2′-amino-3′-cyano-6′-hydroxy-1′-(2-(methoxycarbonyl)phenyl)-3-oxo-2,3-dihydro-1′H-spiro[indene-1,4′-pyridine]-5′-carboxylate **(12):** A mixture of compound **2b** (0.01 mmol), and 2-(3-oxo-2,3-dihydro-1*H*-inden-1-ylidene) malononitrile (0.01 mmol) and piperidine (0.05 mL) in ethanol (30 mL) were refluxed for 3 h; the solid product so formed on heating was collected and recrystallized from suitable solvent to give **12**. Brown powder (Dioxan); yield 65 %; m.p.: 184–186 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3355–3144 (br $NH_2$), 2202 (C≡N) and 1670 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.07 (t, 3H, $CH_3$) 2.74 (s, 2H, $CH_2$) 3.80 (s, 3H, $OCH_3$), 4.03 (q, 2H, $CH_2$) 7.27–8.24 (m, 10H, Ar–H + $NH_2$), 12.19 (s, 1H, OH); Anal. Calcd for $C_{25}H_{21}N_3O_6$ (459): C, 65.35; H, 4.61; N, 9.15. Found: C, 65.00; H, 4.77; N, 9.10 %.

*General procedure for preparation of **14a–e***

A mixture of compound **2b** (0.01 mmol), α-substituted cinnamonitriles **3** (0.01 mmol), and piperidine (0.05 mL) in DMF (30 mL) were refluxed for 6 h, then cooled and poured into crushed ice acidified with drops of HCl where the solid was filtered off and recrystallized from suitable solvent to give **14a–e**.

2-cyano-3-(2,4-dichlorophenyl)-6-hydroxy-1-oxo-1*H*-pyrido[1,2-a]quinazoline-4-carboxamide **(14a):** Yellow crystals (EtOH); yield 71 %; m.p.: 158–160 °C; IR (KBr): $V_{max}$ $cm^{-1}$ 3423–3352 (br $NH_2$), 2219 (C≡N) and 1657 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 7.17–8.01 (m, 9H, Ar–H + $CONH_2$), 11.99 (s, 1H, OH); Anal. Calcd for $C_{20}H_{10}Cl_2N_4O_3$ (424): C, 56.49; H, 2.37; N, 13.18. Found: C, 56.78; H, 2.07 N, 13.00 %.

3-(4-chlorophenyl)-2-cyano-6-hydroxy-1-oxo-1*H*-pyrido[1,2-a]quinazoline-4-carboxamide **(14b):** Beige crystals (EtOH); yield 63 %; m.p.: 156–158 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3423–3111 (br $NH_2$), 2219 (C≡N) and 1697 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 7.17–8.01 (m, 10H, Ar–H + $CONH_2$), 11.40 (s, 1H, OH); Anal. Calcd for $C_{20}H_{11}ClN_4O_3$ (390): C, 61.47; H, 2.84; N, 14.34; Found: C, 61.30; H, 2.70; Cl, 8.90; N, 14.11 %.

2-cyano-3-(4-(dimethylamino)phenyl)-6-hydroxy-1-oxo-1*H*-pyrido[1,2-a]quinazoline-4-carboxamide **(14c):** Brown crystals (MeOH); yield 65 %; m.p.: 170–172 °C.

IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3423–3221 (br $NH_2$), 2209 (C≡N) and 1650 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.04 (s, 6H, N $(CH_3)_2$) 6.79–8.51 (m, 10H, Ar–H + $CONH_2$), 11.70 (s, 1H, OH); Anal. Calcd for $C_{22}H_{17}N_5O_3$ (399): C, 66.16; H, 4.29; N, 17.53. Found: C, 66.00; H, 4.10 N, 17.30 %.

Ethyl 3-(2-chlorophenyl)-2-cyano-6-hydroxy-1-oxo-1*H*-pyrido[1,2-a] quinazoline-4-carboxylate **(14d)**: Green powder (EtOH); yield 51 %; m.p.: 182–184 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3370–3237 (br OH), 2223 (C≡N) and 1728 (C=O). $^1$HNMR (200 MHz, DMSO-$d_6$): $\delta$ 1.25 (t, 3H, $CH_3$), 4.38 (q, 2H, $CH_2$), 7.54–8.12 (m, 8H, Ar–H), 9.53 (s, 1H, OH); 11.70. Anal. Calcd for $C_{22}H_{14}ClN_3O_4$ (419): C, 62.94; H, 3.36; N, 10.01. Found: C, 62.75; H, 3.16 N, 9.85 %.

Ethyl-2-cyano-3-(4-(dimethylamino)phenyl)-6-hydroxy-1-oxo-1H-pyrido-[1,2-a]quinazoline-4-carboxylate **(14e):** Yellow powder (EtOH); yield 59 %; m.p.: 176–178 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3438–3312 (br OH), 2213 (C≡N) and 1698 (C=O). $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.24 (t, 3H, $CH_3$), 427 (q, 2H, $CH_2$), 3.05 (s, 6H, $N(CH_3)_2$) 6.76–8.04 (m, 8H, Ar–H), 11.72 (s, 1H, OH); $^{13}$C NMR: $\delta$ 14.09, 40.33, 61.35, 86.31, 92.05, 111.56, 114.02, 115.12, 115.87, 117.34, 118.24, 120. 85, 121.88, 123.94, 133.54, 133.66, 139.62, 153.59, 154.00, 160.82, 163.38, 169.56; Anal. Calcd for $C_{24}H_{20}N_4O_4$ (428): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.10; H, 4.50; N, 12.70 %.

*General procedure for preparation of **15a–d***

To a solution of either **2a** (2.18 g) or **2b** (2.65 g) (0.01 mmol) in ethanol (30 mL), a mixture of aromatic aldehyde (0.01 mmol) and piperidine (0.5 mL) were added. The mixture was refluxed for 3 h, cooled and poured into crushed ice, acidified with drops of HCl where the solid was filtered off and recrystallized from suitable solvent to give **15a–d**.

(Z)-Methyl-2-(3-(2,4-dichlorophenyl)-2-(ethoxycarbonyl) acrylamido)-benzoate **(15a):** White powder (AcOH); yield 76 %; m.p.: 140–142 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3082 (NH) and 1651 (C=O);$^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.29 (t, 3H, $CH_3$), 3.90 (s, 3H, $OCH_3$), 4.35 (q, 2H, $CH_2$), 6.70–8.23 (m, 8H,Ar–H + methine-H), 11.90 (s, 1H, NH); Anal. Calcd for $C_{20}H_{17}Cl_2NO_5$ (421): C, 56.89; H, 4.06; N, 3.32. Found: C, 56.45; H, 4.00 N, 3.10 %.

(Z)-Methyl-2-(3-(2-chlorophenyl)-2-ethoxycarbonyl) acrylamido)benzoate**(15b):** White powder (EtOH); yield 54 %; m.p.: 144–146 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3082 (NH), and 1651 (C=O); MS: 387 (2.79 %); Anal. Calcd for $C_{20}H_{18}ClNO_5$ (387): C, 61.94; H, 4.68; N, 3.61. Found: C, 61.55; H, 4.50 N, 3.40 %.

(E)-Methyl-2-(2-cyano-3-(2,4-dichlorophenyl)acrylamido)benzoate **(15c):** White powder (EtOH); yield 76 %; m.p.: 132–134 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3082 (NH), 2201 (C≡N) and 1693 (C=O); MS: 374 (22.39 %). Anal. Calcd for $C_{18}H_{12}Cl_2N_2O_3$ (374): C, 57.62; H, 3.22; N, 7.47. Found: C, 57.13; H, 3.00 N, 7.10 %.

(E)-Methyl-2-(3-(2-chlorophenyl)-2-cyanoacrylamido) benzoate **(15d):** White powder (EtOH); yield 62 %; m.p.: 128–130 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3216 (NH), 2204 (C≡N) and 1693 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.90 (s, 3H, OCH3), 7.29–8.61 (m, 9H, Ar–H + methine-H), 11.90 (s, 1H, NH); Anal. Calcd for $C_{18}H_{13}ClN_2O_3$ (340): C, 63.44; H, 3.85; N, 8.22. Found: C, 63.11; H, 3.21; N, 8.00 %.

*General procedure for preparation of **16, 17a, b, d** and **18a–c***

To a solution of **3a–d** (0.01 mmol) in ethanol (30 mL), and hydrazine hydrate or phenyl hydrazine (0.01 mmol) was added. The mixture was refluxed for 3 h, cooled and filtered off and recrystallized from suitable solvent to give **16, 17a**, **b**, **d and 18a–c.**

Methyl 2-(3-amino-5-(2-chlorophenyl)-1*H*-pyrazole-4-carboxamido)-benzoate **(16):** Brown powder (MeOH); yield 76 %; m.p.: 178–180 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3424, 3312, 3122 ($NH_2$, NH), and 1651 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.66 (s, 2H, $NH_2$), 3.90 (s, 3H, $OCH_3$), 6.51–7.71 (m, 10H, Ar–H + 2NH); Anal. Calcd for $C_{18}H_{15}ClN_4O_3$ (370): C, 58.31; H, 4.08; N, 15.11. Found: C, 58.10; H, 4.00; N, 15.42 %.

Methyl2-(3-(2,4-dichlorophenyl)-5-hydroxy-1-phenyl-1*H*-pyrazole-4-carboxamido)benzoate **(17a):** Yellow powder (EtOH); yield 51 %; m.p.: 194–196 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3200 (br NH), and 1688 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.90 (s, 3H, $OCH_3$), 6.78–8.23 (m, 13H, Ar–H + NH), 10.84 (s, 1H, OH); MS: 464 (M–OH, 3.20 %). Anal. Calcd for $C_{24}H_{17}Cl_2N_3O_4$ (481): C, 59.77; H, 3.55; Cl, 14.70; N, 8.71. Anal. Found: C, 59.50; H, 3.30; N, 8.40 %.

Methyl2-(3-(2-chlorophenyl)-5-hydroxy-1-phenyl-1*H*-pyrazole-4-carbox-amido)benzoate **(17b):** Brown powder (Dioxan); yield 51 %; m.p.: 196–198 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3298 (br NH), and 1692 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.75 (s, 3H, $OCH_3$), 6.75–8.18 (m, 14H, Ar–H + NH), 10.72 (s, 1H, OH); Anal. Calcd for $C_{24}H_{18}ClN_3O_4$ (447): C, 64.36; H, 4.05; N, 9.38. Found: C, 64.01; H, 4.00; N, 9.11 %.

Methyl-2-(5-amino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbox-amido)benzoate **(17d):** White powder (EtOH); yield 62 %; m.p.: 174–176 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3400–3100 (br $NH_2$, NH), 1690 (C=O); $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 3.85 (s, 3H, $OCH_3$), 7.18–8.14 (m, 15H, Ar–H + $NH_2$), 11.40 (s, 1H, NH); MS: 446(2.20 %); Anal. Calcd for $C_{24}H_{19}ClN_4O_3$ (446): C, 64.50; H, 4.29; N, 12.54. Found: C, 64.10; H, 4.20; N, 12.30 %.

3-Amino-2-(5-(2,4-dichlorophenyl)-3-hydroxy-1*H*-pyrazol-4-yl)quinazolin-4(3*H*)-one **(18a):** White powder (MeOH); yield 52 %; m.p.: 188–190 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3400–3100 (br, $NH_2$, NH), and 1648 (C=O); $^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$ 7.17–7.7.99 (m, 10H, Ar–H + $NH_2$ + NH), 11.38(s, 1H, OH); Anal. Calcd for $C_{17}H_{11}Cl_2N_5O_2$ (387): C, 52.60; H, 2.86; N, 18.04. Found: C, 53.11; H, 2.62; N, 17.80 %.

3-Amino-2-(5-(2-chlorophenyl)-3-hydroxy-1*H*-pyrazol-4-yl)quinazolin-4(3*H*)-one **(18b)**: Yellow powder (EtOH); yield 52 %; m.p.: 200–202 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3400–3100 (br, $NH_2$, NH), 1648 (C=O);$^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$ 7.23–8.17 (m, 10H, Ar–H + $NH_2$), 8.97 (s, 1H, NH), 11.30 (s, 1H, OH); MS: (353, 0.60 %); Anal. Calcd for $C_{17}H_{12}ClN_5O_2$ (353): C, 57.72; H, 3.42; N, 19.80. Found: C, 57.21; H, 3.10; N, 19.40 %.

3-Amino-2-(3-amino-5-(2,4-dichlorophenyl)-1*H*-pyrazol-4-yl)quinazolin-4(3*H*)-one **(18c)**: Yellow powder (EtOH); yield 57 %; m.p.: 188–190 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3400–3100(br, $NH_2$, NH), 1614 (C=O); $^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$ 7.368.16–8.17 (m, 11H, Ar–H + $2NH_2$), 8.95 (s, H, NH); $^{13}C$ NMR: $\delta$ ppm 120.70, 120.72, 120.74, 120.77, 120.83, 127.12, 127 0.67, 128.14, 128.61, 130.10, 130.46, 130.52, 131.57, 133.08, 134.59, 158.10; Anal. Calcd for $C_{17}H_{12}Cl_2N_6O$ (386): C, 52.73; H, 3.12; Cl, 18.31; N, 21.70. Found: C, 52.23; H, 3.00; N, 21.30 %.

*General procedure for preparation of **19a–d***

To a solution of **15a–d** (0.01 mmol) in ethanol (30 mL), semicarbazide (0.75 g, 0.01 mmol) was added. The mixture was refluxed for 3 h, cooled, filtered off and recrystallized from suitable solvent to give **19a–d**.

3-(2,4-Dichlorophenyl)-5-hydroxy-4-(4-oxo-3-ureido-3,4-dihydroquinazolin-2-yl)-1*H*-pyrazole-1-carboxamide**(19a):**White powder (AcOH); yield 51 %; m.p.: 198–200 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3400–3200 (br $NH_2$, NH), 1711, 1646 (C=O); $^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.58 (s, 1H, NH),7.39–8.15 (m, 11H, Ar–H + $2CONH_2$), 10.50 (s, 1H, OH); Anal. Calcd for $C_{19}H_{13}Cl_2N_7O_4$ (473): C, 48.12; H, 2.76; N, 20.67. Found: C, 48.10; H, 2.30; N, 20.23 %.

3-(2-Chlorophenyl)-5-hydroxy-4-(4-oxo-3-ureido-3,4-dihydroquinazolin-2-yl)-1*H*-pyrazole-1-carboxamide **(19b):** Yellow powder (EtOH); yield 51 %; m.p.: 190–92 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3400–3200 (br $NH_2$, NH), 1637 (C=O). $^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.60 (s, 1H, NH), 6.65–8.20 (m, 12H, Ar–H + $2CONH_2$), 10.62 (s, 1H, OH); Anal. Calcd for $C_{19}H_{14}ClN_7O_4$ (439): C, 51.89; H, 3.21; N, 22.29. Found: C, 51.60; H, 3.00; N, 22.00 %.

5-Amino-3-(2,4-dichlorophenyl)-4-(4-oxo-3-ureido-3,4-dihydroquinazolin-2-yl)-1*H*-pyrazole-1-carboxamide **(19c):** Yellow powder (MeOH); yield 55 %; m.p.: 166–68 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3400–3200 (br $NH_2$, NH), 1610 (C=O); $^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.60 (s, 1H, NH), 6.00 (s, 2H, $NH_2$), 7.00–8.15 (m, 11H, Ar–H + $2CONH_2$); Anal. Calcd for $C_{19}H_{14}Cl_2N_8O_3$ (472): C, 48.22; H, 2.98; Cl, 14.98; N, 23.68 Found: C, 48.00; H, 2.50; N, 23.40 %.

5-Amino-3-(2-chlorophenyl)-4-(4-oxo-3-ureido-3,4-dihydroquinazolin-2-yl)-1*H*-pyrazole-1-carboxamide **(19d):** White powder (EtOH); yield 51 %; m.p.: 190–92 °C; IR (KBr, $\bar{\nu}$, $cm^{-1}$): 3400–3200 (br $NH_2$, NH), 1727 (C=O); $^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.64 (s, 1H, NH), 6.55 (s, 2H, $NH_2$) 7.33–8.23 (m, 12H, Ar–H + $2CONH_2$); Anal. Calcd for $C_{19}H_{15}ClN_8O_3$ (438): C, 52.00; H, 3.45; N, 25.53. Found: C, 51.70; H, 3.20; N, 25.10 %.

## Molecular modeling studies

An attempt to gain a better insight into the molecular structure of the synthesized compounds, geometric optimization and conformation analysis were performed using semi-empirical method PM3 as implemented in HyperChem 7.5 [51]. The structures of synthesized reported compounds were optimized with semi-empirical method PM3 (Parametric Method-3). A gradient of 0.01 kcal $Å^{-1}$ was set as a convergence criterion in all the molecular mechanics and quantum calculations. The lowest energy structure was used for each molecule to calculate physicochemical properties.

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