MULTI-COMPONENT REACTIONS OF CYCLOHEXAN-1,3-DIONE TO SYNTHESIZE HETEROCYCLIC DERIVATIVES WITH c-MET ENZYMATIC ACTIVITY, ANTI-PROSTATE, ANTI-PROLIFERATIVE AND TYROSINE KINASE ACTIVITIES

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ABSTRACT. We are aiming in this work to synthesize target molecules not only possess anti-tumor activities but also kinase inhibitors. The target molecules were obtained starting from aryl hydrazones of cyclohexan-1,3-dione followed by its heterocyclization reactions to produce anticancer molecules. The multi-component reactions of the arylhydrazocyclohexan-1,3-dione derivatives 3a-c produced the 1,4,5,6,7,8-hexahydroquinoline derivatives 6a-r and the 4,5,6,8-tetrahydrochromeno[2,3-c]pyrazole derivatives 10a-c. Other multi-component reactions were demonstrated. The anti-proliferative activity of the synthesized compounds toward the six cancer cell lines namely A549, H460, HT-29, MKN-45, U87MG, and SMMC-7721 was studied. In addition the c-Met enzymatic activities and inhibition toward the prostate cancer cell PC-3 were measured. The results obtained in most cases, indicated that the presence of electronegative Cl group through the molecule favour the inhibitions.

KEY WORDS: Multi-component reactions, Cyclohexan-1,3-dione, Chromene, Chromeno[2,3-c]pyrazole, Cytotoxicity

INTRODUCTION

Heterocycles constitute the largest diversity of organic molecules of chemical, biomedical, and industrial significance [1, 2]. They are also among the most frequently encountered scaffolds in numerous drugs and pharmaceutically relevant substances [3-6]. In the past several decades, a significant number of efforts have been made on the discovery and development of more efficient pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers by following well studied natural models and biochemical pathways in living cells [7, 8]. In addition, a series of libraries consisting of heterocycles have been successfully established for the structure activity-relationship studies (SAR) for drug design and synthesis [9]. Meanwhile, the diversity-oriented synthesis (DOS) continues to be an area of importance at the interface of organic synthesis and chemical biology [10-12]. While DOS plays an important role in searching for new bioactive small molecules with functional and stereochemical diversity [13], more efficient multi-component domino reactions (MDRs) for the synthesis of a series of heterocycles, particularly functionalized multi-heterocycles, have been in high demand. In the past several years, the development of new multi-component domino reactions has become an active and challenging topic in modern organic chemistry [14], they can readily provide greater atom-economic access to a diverse spectrum of compounds and their libraries for screening. In addition, hydrazones and their derivatives constitute a versatile class of compounds in organic chemistry. These compounds showed biological properties, such as anti-inflammatory, analgesic, anticonvulsant, antituberculous, antitumor, anti-HIV and antimicrobial activity [15, 16]. Hydrazones are important

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compounds for heterocyclic synthesis due to the presence of C=O, C-N and N-N bonding where
the carbon atom of the hydrazone group has both electrophilic and nucleophilic [17]. Due to
the large mentioned applications of multi-component reactions together with the chemical reactivity
of hydrazones in this context, herein we report on the synthesis and the spectroscopic, structural,
and physicochemical characterization of new heterocyclic derivatives incorporating cyclo-
hexanone moiety starting from the arylhydrazono derivatives of cyclohexan-1,3-diones. The anti-
proliferative activity of the synthesized compounds toward different cancer cell lines was also
explored. This was followed by studying the inhibitions of the most active compounds toward
tyrosine kinases and Pim-1 kinase.

RESULTS AND DISCUSSION
As a continued work through the uses of cyclohexan-1,3-dione to produce heterocyclic
compounds characterized by their high anti-proliferative activities. In the present work, we
demonstrated the use cyclohexan-1,3-dione to synthesis arylhydrazone derivatives. Thus, the
reaction of cyclohexan-1,3-dione (1) with either benzene diazoniumchloride (2a), 4-methyl-
benzene diazonium chloride (2b) or 4-chlorobenzene diazonium chloride (2c) gave the
Corresponding arylhydrazone derivatives 3a-c [18]. Initially 2-arylhydrazonocyclohexan-1,3-
dione was chosen as the model substrate for the synthesis of fused heterocyclic compounds
through studying its multi-component reactions with aromatic aldehydes and cyanoethylene
reagents to give biologically active fused pyridine derivatives. The multi-component reactions of
either 3a, 3b or 3c with either of benzaldehyde (4a), 4-chlorobezaldehyde (4b) or 4-methoxy-
benzaldehyde (4c) and either malononitrile (5a) or ethyl cyanoacetate (5b) in 1,4-dioxane solution
containing ammonium acetate gave the 1,4,5,6,7,8-hexahydroquinoline derivatives 6a-r (Scheme
1). The chemical structures of new compounds were assured by spectral data (IR, 1H, 13C-NMR,
MS). Thus, the 1H NMR spectrum of compound 6a (as an example) showed (beside the expected
signals) a singlet at δ 4.58 (D2O exchangeable) confirming the presence of the NH2 group and a
singlet at δ 5.13 ppm corresponding to the pyridine H-4 In addition, the 13C NMR spectrum showed
signals at δ 38.3, 41.6 for the two CH2 groups, a signal at δ 48.8 for the pyridine C-4, a
signal at δ 117.0 corresponding to the CN group and two signals at δ 166.3, 167.5 equivalent to the
C=N and C=O groups, respectively.

Next, we studied the multi-component reactions of the arylhydrazone derivatives 3a-c with
benzaldehyde (4a) and ethyl benzoylecetate (7) in ethanol solution containing triethylamine gave
the 5,6,7,8-tetrahydro-4H-chromene derivatives 8a-c. Moreover, the multi-component reactions
of the arylhydrazone derivatives 3a-c with benzaldehyde (4a) and 3-methyl-1H-pyrazol-5(4H)-
one (9) in ethanol solution containing triethylamine gave the 4,5,6,8-tetrahydrochroinonen[2,3-
c]pyrazole derivatives 10a-c (Scheme 2). The structures of the latter compounds were based on their
respective analytical and spectral data. Thus the 1H NMR spectrum of compound 10a showed
(beside the expected signals), a singlet at δ 2.80 ppm for the CH3 group and a singlet at δ 5.13
ppm indicating the pyran H-4. Moreover, the 13C NMR spectrum revealed the presence of a signal at
δ 35.8 corresponding for the CH3 group, two signals at δ 37.4, 41.5 corresponding to the two
CH3 groups, a signal at δ 50.7 assigning to the pyran C-4, four signals at δ 130.0, 130.6, 131.4,
132.7 for the pyran carbons and three signals at δ 164.5, 165.2, 168.9 for the two C=N and C=O groups.

The high yields of such multi-component reaction products encouraged us for further reactions using
the arylhydrazone derivatives 3a-c. Thus, the reaction of either compound 3a, 3b or 3c with
benzaldehyde (4a) and 3-oxo-N,3-diphenylpropanamide (11) in 1,4-dioxane containing triethyl
amine gave the 5,6,7,8-tetrahydro-4H-chromene-3-carboxamide derivatives 12a-c. The analytical
and spectral data of 12a-c were in agreement with the proposed structures (see experimental
section). On the other hand, the multi-component reactions of either 3a, 3b or 3c with
benzaldehyde (4a) and either 2-cyanoacetamide (13a) or 2-cyanoethanethioamide (13b) in 1,4-
dioxane solution containing triethylamine gave surprisingly the 1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile derivatives 14a-f not as the expected chromene derivative (Scheme 3).

\[
\begin{array}{cccccccccccccccc}
\text{O} & \begin{array}{c}
\text{2a. } X = H \\
b. X = \text{CH}_3 \\
c. X = \text{Cl}
\end{array} & \begin{array}{c}
\text{N} \\
\text{Cl}
\end{array} & \text{EtOH} & \text{NaoAc} & \begin{array}{c}
\text{O} \\
\text{NH} \\
\text{NH}
\end{array} & \begin{array}{c}
\text{H} \\
\text{CHO}
\end{array} & \begin{array}{c}
\text{H}_3

\end{array}
\end{array}
\]

\[\begin{array}{cccccccccccccccc}
6 & a & b & c & d & e & f & g & h & i & j & k & l & m & n & o & p & q & r \\
X & \text{H} & \text{H} & \text{H} & \text{H} & \text{H} & \text{CH}_3 & \text{CH}_3 & \text{CH}_3 & \text{CH}_3 & \text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} \\
Y & \text{H} & \text{H} & \text{Cl} & \text{Cl} & \text{OCH}_3 & \text{OCH}_3 & \text{H} & \text{H} & \text{Cl} & \text{OCH}_3 & \text{OCH}_3 & \text{H} & \text{H} & \text{Cl} & \text{Cl} & \text{XCH}_3 & \text{OCH}_3 & \text{OCH}_3 \\
R' & \text{NH}_2 & \text{OH} & \text{NH}_2 & \text{OH} & \text{NH}_2 & \text{OH} & \text{NH}_2 & \text{OH} & \text{NH}_2 & \text{OH} & \text{NH}_2 & \text{OH} & \text{NH}_2 & \text{OH} & \text{NH}_2 & \text{OH} & \text{NH}_2 & \text{OH} \\
\end{array}\]

Scheme 1. Synthesis of compounds 3a-c and 6a-r.

\[
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{NNH} \\
\text{N}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{3a. } X = H \\
b. X = \text{CH}_3 \\
c. X = \text{Cl}
\end{array}
\end{array}
\]

Scheme 2. Synthesis of compounds 8a-c and 10a-c.

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Scheme 3. Synthesis of compounds 12a-c and 14a-f.

Cell proliferation assay

The anti-proliferative activities of the newly synthesized compounds (Table 1) were evaluated against the six cancer cell lines A549, HT-29, MKN-45, U87MG, and SMMC-7721 and H460 using the standard MTT assay in vitro, with foretinib as the positive control [19-21]. The cancer cell lines were cultured in minimum essential medium (MEM) supplemented with 10% fetal bovine serum (FBS). Approximate 4 x 10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37 °C for 24 h. The compounds tested at the indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 µg/mL, and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 µL of DMSO each well, and the absorbency at 492 nM (for absorbance of MTT formazan) and 630 nM (for the reference wavelength) was measured with an ELISA reader. All of the compounds were tested three times in each cell line and the results expressed as IC_{50} (inhibitory concentration 50%) were the averages of three determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

The mean values of three independent experiments, expressed as IC_{50} values, were presented in Table 1. Most of the synthesized compounds exhibited potent anti-proliferative activity with IC_{50} values less than 30 µM. Generally, the variations of substituent’s within the heterocyclic ring being attached have a notable influence on the anti-proliferative activity.

Structure activity relationship

Table 1 showed the cytotoxicity of most of the synthesized compounds toward the six cancer cell lines A549, H460, HT-29, MKN-45, U87MG, and SMMC-7721. The reaction of cyclohexan-1,3-
Table 1. In vitro growth inhibitory effects IC₅₀ ± SEM (µM) of the newly synthesized compounds against cancer cell lines.

| Compound No. | A549 | H460 | HT29 | MKN-45 | U87MG | SMMC-7721 |
|--------------|------|------|------|--------|-------|-----------|
| 3a           | 6.26 ± 2.86 | 8.36 ± 3.24 | 5.69 ± 1.39 | 6.58 ± 1.37 | 9.62 ± 3.15 | 0.43 ± 2.25 |
| 3b           | 0.28 ± 0.12 | 0.33 ± 0.18 | 0.53 ± 0.13 | 0.33 ± 0.17 | 0.61 ± 0.28 | 0.52 ± 0.16 |
| 3c           | 0.43 ± 0.31 | 0.51 ± 0.25 | 0.49 ± 0.28 | 0.63 ± 0.39 | 0.82 ± 0.27 | 0.93 ± 0.39 |
| 6b           | 1.36 ± 0.89 | 1.61 ± 0.85 | 0.63 ± 0.25 | 2.46 ± 0.93 | 1.53 ± 0.68 | 1.36 ± 0.27 |
| 6c           | 7.72 ± 2.67 | 8.25 ± 3.86 | 6.63 ± 2.34 | 9.04 ± 1.92 | 8.62 ± 2.23 | 9.68 ± 3.25 |
| 6d           | 0.40 ± 0.26 | 0.36 ± 0.19 | 0.64 ± 0.28 | 0.33 ± 0.23 | 0.23 ± 0.53 | 0.36 ± 0.13 |
| 6f           | 0.62 ± 0.28 | 0.83 ± 0.38 | 0.65 ± 0.26 | 0.59 ± 0.28 | 0.62 ± 0.29 | 0.26 ± 0.28 |
| 6g           | 8.54 ± 2.42 | 9.56 ± 3.67 | 7.38 ± 2.42 | 8.47 ± 2.42 | 7.28 ± 2.25 | 8.48 ± 3.82 |
| 6h           | 0.25 ± 0.13 | 0.30 ± 0.09 | 0.52 ± 0.17 | 0.37 ± 0.19 | 0.34 ± 0.21 | 0.53 ± 0.17 |
| 6i           | 0.42 ± 0.35 | 0.60 ± 0.29 | 0.39 ± 0.28 | 0.42 ± 0.26 | 0.64 ± 0.23 | 0.57 ± 0.23 |
| 6l           | 0.82 ± 0.40 | 0.77 ± 0.68 | 0.83 ± 0.26 | 0.59 ± 0.29 | 0.53 ± 0.17 | 0.46 ± 0.18 |
| 6m           | 1.32 ± 0.60 | 1.15 ± 0.08 | 2.39 ± 1.02 | 1.52 ± 0.86 | 2.28 ± 1.21 | 1.26 ± 0.84 |
| 6n           | 5.48 ± 1.28 | 6.79 ± 1.05 | 5.84 ± 1.69 | 7.49 ± 2.64 | 8.09 ± 2.36 | 6.94 ± 1.68 |
| 6o           | 0.40 ± 0.23 | 0.32 ± 0.15 | 0.42 ± 0.20 | 0.30 ± 0.19 | 0.73 ± 2.14 | 0.32 ± 0.19 |
| 6p           | 0.23 ± 0.15 | 0.33 ± 0.12 | 0.25 ± 0.19 | 0.25 ± 0.13 | 0.42 ± 0.18 | 0.33 ± 0.21 |
| 6q           | 8.41 ± 2.28 | 6.35 ± 1.28 | 9.41 ± 2.16 | 8.50 ± 2.38 | 7.42 ± 2.26 | 8.53 ± 2.29 |

**dione (1) with the arylidiazonium salts 2a-c produced the arylhydrazono derivatives 3a-c, respectively. The two compounds 3b (X = CH₂) and 3e (X = Cl) showed the highest cytotoxicity among the three compounds toward the six cancer cell lines. The multi-component reactions of either of 3a-c with either of the arylaldehydes 4a-c and either malononitrile or ethyl cyanoacetate to give the 1,4,5,6,7,8-hexahydroquinoline derivatives 6a-r, respectively. Thirty-one compounds were selected from such series to be tested toward the six cancer cell lines where these showed**

*Multi-component reactions of cyclohexan-1,3-dione to synthesize heterocyclic derivatives* [132]

**Table 1. In vitro growth inhibitory effects IC₅₀ ± SEM (µM) of the newly synthesized compounds against cancer cell lines.**
Cl group within both compounds. Considering the 5,6,7,8-tetrahydro-4H-chromene-3-carboxamide derivatives 12a-c where compound 12e exhibited the highest inhibition. Surprisingly the inhibitions of the 1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile derivatives 14a-f through such series compounds 14b, 14c and 14d exhibited moderate inhibitions while compounds 14e (X = Cl, Y' = OH) and 14f (X = Cl, Y' = SH) exhibited the highest inhibitions. It clear from Table 1 that compounds 3b, 3c, 6b, 6d, 6f, 6h, 6i, 6o, 6p, 8c, 10c, 12c, 14e and 14f were the most cytototoxic among the tested compounds toward the six cancer cell line.

**HTRF kinase assay**

The c-Met kinase activity of all compounds was evaluated using homogeneous time-resolved fluorescence (HTRF) assay as previously reported [22, 23]. In addition, the most active compounds were further evaluated against other five tyrosine kinase (c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR) using the same screening method. The experimental procedure applied for the HTRF kinase tests were as reported procedure [24].

**In vitro enzymatic assays**

All the newly synthesized quinoline and chromene derivatives were evaluated for their inhibitions toward c-Met enzyme using a homogeneous time-resolved fluorescence (HTRF) assay. Taking foretinib as the positive control, the results expressed as IC$_{50}$ were summarized in Table 2. The IC$_{50}$ values are the average of at least three independent experiments. As illustrated in Table 1, all the tested compounds displayed potent c-Met enzymatic activity with IC$_{50}$ values ranging from 0.03 to 18.29 nM. Compared with foretinib (IC$_{50}$ = 1.16 nM), seventeen of them (3c, 6c, 6e, 6f, 6j, 6n, 6r, 6c, 10c, 12e, 14a, 14b, 14c, 14d, 14e and 14f) exhibited equivalent or higher potency with IC$_{50}$ values less than 1.30 nM. On the other hand, compounds 3a, 3b, 3c, 6b, 6c, 6d, 6e, 6f, 6h, 6j, 6n, 6o, 6p, 6r, 6c, 10a, 10b, 10c, 12b, 12c and 14a-f showed higher inhibitions toward the PC-3 cell line than the reference SGI-1776 (IC$_{50}$ 4.86 nM). Analyzing the data demonstrated through Table 2 revealed that many compounds displayed potent c-Met enzymatic activity and inhibitions toward the prostate cancer cell line PC-3. Considering the arylhydrazone derivatives 3a-c, compound 3c exhibited the highest inhibitions toward c-Met and PC-3 with IC$_{50}$'s 0.03 and 0.02 nM. For the 1,4,5,6,7,8-hexahydroquinoline derivatives 6a-r, where compounds 6b, 6c, 6d, 6f, 6j, 6n and 6r exhibited the highest inhibitions toward c-Met and PC-3. It was found that compounds 6e and 6h showed high inhibitions toward c-Met with IC$_{50}$ 1.02, 1.42 nM but low inhibitions toward PC-3 cell line with IC$_{50}$ 3.42 and 3.53 nM, respectively. On the other side, compound 6p expressed high inhibition toward PC-3 cell line with IC$_{50}$ 0.02 nM but decline inhibition toward c-Met IC$_{50}$ 2.40 nM. For the 5,6,7,8-tetrahydro-4H-chromene derivatives 8a-c and the 4,5,6,8-tetrahydrochromeno[2,3-c]pyrazole derivatives 10a-c where compounds 8c and 10c showed the highest inhibitions toward c-Met and PC-3 but compounds 10a and 10b exhibited higher inhibitions than that of 8a and 8b. On the other hand for compounds 12a-c, compound 12e exhibited the highest inhibitions toward c-Met kinase and PC-3 cell line. Surprisingly, the five compounds 14a, 14e, 14d, 14e and 14f exhibited high inhibitions toward c-Met kinase and PC-3 cell line.

**Structures of the most active compounds toward Inhibition against c-Met kinase**

![Structures](image-url)
Table 2. c-Met enzymatic activity of the newly synthesized compounds.

| Compound No. | X     | Y/Y'  | R'    | IC<sub>50</sub> (nM) c-Met | IC<sub>50</sub> (nM) PC-3 |
|--------------|-------|-------|-------|-----------------------------|--------------------------|
| 3a           | H     | -     | -     | 1.89 ± 0.76                 | 2.39 ± 1.06              |
| 3b           | CH<sub>3</sub> | -     | -     | 4.37 ± 1.28                 | 3.52 ± 1.32              |
| 3c           | Cl    | -     | -     | 0.03 ± 0.006                 | 0.02 ± 0.01              |
| 6a           | H     | H     | NH<sub>2</sub> | 6.80 ± 2.49                 | 5.72 ± 2.39              |
| 6b           | H     | Cl    | OH    | 1.32 ± 0.64                 | 1.63 ± 0.89              |
| 6c           | H     | Cl    | NH<sub>2</sub> | 0.52 ± 0.29                 | 0.32 ± 0.22              |
| 6d           | H     | Cl    | OH    | 0.90 ± 0.36                 | 0.69 ± 0.41              |
| 6e           | H     | OCH<sub>3</sub> | NH<sub>2</sub> | 1.02 ± 0.39                 | 3.42 ± 0.69              |
| 6f           | H     | OCH<sub>3</sub> | OH    | 0.92 ± 0.43                 | 0.62 ± 0.15              |
| 6g           | CH<sub>3</sub> | H     | NH<sub>2</sub> | 3.72 ± 1.14                 | 6.42 ± 2.49              |
| 6h           | CH<sub>3</sub> | H     | OH    | 1.42 ± 0.88                 | 3.53 ± 1.29              |
| 6i           | CH<sub>3</sub> | Cl    | NH<sub>2</sub> | 5.27 ± 1.83                 | 7.33 ± 2.82              |
| 6j           | CH<sub>3</sub> | Cl    | OH    | 0.23 ± 0.17                 | 0.36 ± 0.15              |
| 6l           | CH<sub>3</sub> | OCH<sub>3</sub> | NH<sub>2</sub> | 15.31 ± 4.26                | 12.42 ± 4.28             |
| 6m           | Cl    | H     | NH<sub>2</sub> | 4.28 ± 1.53                 | 6.82 ± 2.41              |
| 6n           | Cl    | H     | OH    | 0.29 ± 0.15                 | 0.49 ± 0.26              |
| 6o           | Cl    | Cl    | NH<sub>2</sub> | 1.83 ± 0.67                 | 2.66 ± 1.56              |
| 6p           | Cl    | Cl    | OH    | 2.40 ± 0.53                 | 0.02 ± 0.04              |
| 6q           | Cl    | OCH<sub>3</sub> | NH<sub>2</sub> | 12.56 ± 4.70                | 8.38 ± 4.72              |
| 6r           | Cl    | OCH<sub>3</sub> | OH    | 1.28 ± 0.98                 | 2.80 ± 1.63              |
| 8a           | H     | -     | -     | 12.32 ± 4.72                 | 8.29 ± 3.52              |
| 8b           | CH<sub>3</sub> | -     | -     | 18.29 ± 6.31                 | 10.17 ± 3.69             |
| 8c           | Cl    | -     | -     | 0.39 ± 0.25                 | 0.21 ± 0.13              |
| 10a          | H     | -     | -     | 1.28 ± 0.52                 | 2.27 ± 0.84              |
| 10b          | CH<sub>3</sub> | -     | -     | 3.61 ± 1.80                 | 2.13 ± 0.89              |
| 10c          | Cl    | -     | -     | 0.13 ± 0.06                 | 0.32 ± 0.16              |
| 12a          | H     | -     | -     | 8.35 ± 2.71                 | 12.52 ± 3.82             |
| 12b          | CH<sub>3</sub> | -     | -     | 10.40 ± 2.64                | 1.63 ± 0.92              |
| 12c          | Cl    | -     | -     | 0.24 ± 0.15                 | 0.22 ± 0.13              |
| 14a          | H     | OH    | -     | 0.98 ± 0.41                 | 0.84 ± 0.36              |
| 14b          | H     | SH    | -     | 1.23 ± 0.53                 | 3.62 ± 1.62              |
| 14c          | CH<sub>3</sub> | OH    | -     | 0.96 ± 0.42                 | 0.70 ± 0.31              |
| 14d          | CH<sub>3</sub> | SH    | -     | 1.16 ± 0.68                 | 1.38 ± 0.92              |
| 14e          | Cl    | OH    | -     | 0.21 ± 0.04                 | 0.13 ± 0.06              |
| 14f          | Cl    | SH    | -     | 0.59 ± 0.23                 | 0.48 ± 0.21              |
| **Foretinib**| -     | -     | -     | 1.16 ± 0.17                 | 4.86 ± 0.16              |

Inhibitions of the most active compounds towards tyrosine kinases

The most active compounds 3c, 6c, 6d, 6e, 6f, 6j, 6n, 6r, 8c, 10a, 10c, 12c, 14a, 14b, 14c, 14d, 14e and 14f towards c-Met enzymatic activity were further evaluated against the five tyrosine kinases (c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR) using the same screening method (Table 3). These receptor tyrosine kinases (RTKs) have been implicated in vascular development by affecting the proliferation and migration of endothelial cells or pericytes. Among them, VEGF is a major regulator of tumor angiogenesis via endothelial cell proliferation and blood vessel permeability [25, 26]. It is clear from Table 3 that compounds 3c, 6c, 6e, 6f, 6j, 6n, 6r, 8c, 10c, 12c, 14c, 14d, 14e and 14f were the most potent towards the five tyrosine kinases. Compound 6n showed high potency towards the four kinases VEGFR-2 with IC<sub>50</sub> 0.72 nM, while it showed

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moderate inhibition towards c-Kit, Flt-3 and EGFR kinases with IC\textsubscript{50}’s 1.07, 1.25 and 1.83 nM. Compound 14b showed moderate inhibitions toward c-Kit and Flt-3 kinases with IC\textsubscript{50}’s 1.68 and 1.29 nM, respectively, while it showed high inhibitions toward VEGFR-2, EGFR and PDGFR kinases with IC\textsubscript{50}’s 0.51, 0.26 and 0.38 nM, respectively. It is clear that compounds 6j and 14e exhibited the highest inhibitions among the tested compounds.

| Table 3. Inhibitions toward tyrosine kinases [Enzyme IC\textsubscript{50} (nM)] of selected compounds. |
|---------------------------------|--------------------------------|-----------------|-----------------|-----------------|-----------------|
| Compound | c-Kit IC\textsubscript{50} (nM) | Flt-3 IC\textsubscript{50} (nM) | VEGFR-2 IC\textsubscript{50} (nM) | EGFR IC\textsubscript{50} (nM) | PDGFR IC\textsubscript{50} (nM) |
| 3c | 0.21 | 0.34 | 0.23 | 0.46 | 0.29 |
| 6c | 0.30 | 0.26 | 0.31 | 0.28 | 0.34 |
| 6e | 0.30 | 0.26 | 0.41 | 0.53 | 0.19 |
| 6f | 0.28 | 0.23 | 0.31 | 0.38 | 0.41 |
| 6j | 0.14 | 0.21 | 0.54 | 0.39 | 0.21 |
| 6n | 1.07 | 1.25 | 0.72 | 1.83 | 2.50 |
| 8c | 0.32 | 0.29 | 0.38 | 0.26 | 0.33 |
| 6c | 0.25 | 0.24 | 0.19 | 0.31 | 0.35 |
| 10c | 1.26 | 1.84 | 2.63 | 1.52 | 1.26 |
| 12c | 0.23 | 0.38 | 0.14 | 0.37 | 0.51 |
| 14b | 1.68 | 1.29 | 0.51 | 0.26 | 0.38 |
| 14c | 0.42 | 0.26 | 0.31 | 0.24 | 0.53 |
| 14d | 0.52 | 0.21 | 0.53 | 0.80 | 0.46 |
| 14e | 0.19 | 0.28 | 0.27 | 0.31 | 0.28 |
| 14f | 0.33 | 0.24 | 0.19 | 0.32 | 0.25 |

Inhibitions of the selected compounds towards Pim-1 kinase

Compounds 3c, 6c, 6e, 6f, 6j, 6n, 6r, 8c, 10c, 12c, 14c, 14d, 14e and 14f were selected to examine their Pim-1 kinase inhibition activity at a range of 10 concentrations and the IC\textsubscript{50} values were calculated (Table 4). Compounds 3c, 6c, 6e, 6f, 6j, 6r, 8c and 14d were the most potent to inhibit Pim-1 activity with IC\textsubscript{50} values of 0.24, 0.56, 0.23, 0.23, 0.40, 0.48, 0.22 and 0.38 \(\mu\)M, respectively. On the other hand, compounds 6n, 10c, 12c, 14c, 14e and 14f were less effective (IC\textsubscript{50} > 10 \(\mu\)M). SGI-1776 was used as the positive control with IC\textsubscript{50} 0.048 \(\mu\)M in the assay. These profiles in combination with cell growth inhibitions data of the selected compounds listed in Table 4 indicated that Pim-1 kinase was a potential target of these compounds.

| Table 4. The inhibitor activity of selected compounds towards Pim-1 kinase. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Compound No | Inhibition ratio At 10 \(\mu\)M | IC\textsubscript{50} (\(\mu\)M) |
| 3c | 94 | 0.24 |
| 6c | 84 | 0.56 |
| 6e | 95 | 0.23 |
| 6f | 96 | 0.23 |
| 6j | 90 | 0.40 |
| 6n | 28 | >10 |
| 6r | 88 | 0.48 |
| 8c | 97 | 0.22 |
| 10c | 24 | >10 |
| 12c | 16 | >10 |
| 14c | 24 | >10 |
| 14d | 89 | 0.38 |
| 14e | 36 | >10 |
| 14f | 28 | >10 |
| SGI-1776 | - | 0.048 ± 0.019 |
**EXPERIMENTAL**

Chemistry

Newly synthesized compounds showed melting points that were uncorrected. For all compounds the IR spectra (KBr discs) were measured using a FTIR plus 460 or Pye Unicam SP-1000 spectrophotometer. The spectra 1HNMR were measured using Varian Gemini-300 (300 MHz) and Jeol AS 500 MHz instruments spectra were performed in DMSO-d$_6$ as solvent using TMS as internal standard and chemical shifts are expressed as $\delta$ ppm. The spectra MS (EI) were measured using Hewlett Packard 5988 A GC/MS system and GCMS-QP 1000 Ex Shimadzu instruments. The microanalytical data CHN were obtained from the Micro-analytical Data Unit at Cairo University and were performed on Vario EL III Elemental analyzer. Screening of compounds against the cancer cell lines and tyrosine kinases were performed through The National Cancer Institute at Cairo University. Compounds 3a-c were prepared according to our reported work [18].

General procedure for the synthesis of the 1,4,5,6,7,8-hexahydroquinoline derivatives 6a-r. Each of either benzaldehyde (1.06 g, 0.01 mol), 4-chlorobenzaldehyde (1.40 g, 0.01 mol) or 4-methoxybenzaldehyde (1.36 g, 0.01 mol) and either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) were added to a solution of either 2a (2.16 g, 0.01 mol), 2b (2.30 g, 0.01 mol) or 3e (2.50 g, 0.01 mol) in 1,4-dioxane (50 mL) containing ammonium acetate (2.00 g). The whole reaction mixture was heated under reflux for 2 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

2-Amino-7-oxo-4-phenyl-8-(2-phenylhydrazono)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6a). Pale brown crystals from 1,4-dioxane, yield (2.41 g, 60%), Mp $>300 \degree$ C. IR (KBr) u max cm$^{-1}$: 3463-3359 (NH$_2$, NH), 3055 (CH, aromatic), 2221 (CN), 1694 (C=O), 1640 (C=N), 1636 (C=C); 1H NMR (DMSO-d$_6$, 300 MHz): $\delta$ = 2.81-2.99 (2t, 4H, 2CH$_2$), 4.58 (s, 2H, D$_2$O exchangeable NH$_2$), 5.13 (s, 1H, pyridine H-4), 7.26-7.43 (m, 10H, 2C$_6$H$_5$), 8.29, 8.32 (2s, 2H, D$_2$O exchangeable, 2NH); 13C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 38.4, 41.6 (2CH$_3$), 48.8 (pyridine C-4), 117.0 (CN), 120.1, 120.7, 121.3, 123.8, 124.2, 125.6 (2C$_6$H$_5$), 129.1, 129.3, 130.2, 133.8 (pyridine C), 166.3 (C=N), 167.5 (C=O). Anal. calcd. for C$_{22}$H$_{19}$N$_2$O: C, 71.53; H, 5.18; N, 18.96%. Found: C, 71.70; H, 5.25; N, 19.14%. MS: m/z 369 (M$^+$, 35%).

2-Hydroxy-7-oxo-4-phenyl-8-(2-phenylhydrazono)-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile (6b). Pale brown from 1,4-dioxane, yield (2.70 g, 73%), Mp 145-147 \degree C. IR (KBr) u max cm$^{-1}$: 3552-3371 (OH, NH), 3055 (CH, aromatic), 2222 (CN), 1697 (C=O), 1643 (C=N), 1630 (C=C); 1H NMR (DMSO-d$_6$, 300 MHz): $\delta$ = 2.80-3.02 (2t, 4H, 2CH$_2$), 5.16 (s, 1H, pyridine H-4), 7.23-7.42 (m, 10H, 2C$_6$H$_5$), 8.29, 8.33 (2s, 2H, D$_2$O exchangeable, 2NH), 10.40 (s, 1H, D$_2$O exchangeable, OH); 13C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 37.6, 42.5 (2CH$_3$), 48.1 (pyridine C-4), 116.7 (CN), 120.1, 120.4, 121.7, 121.9, 123.4, 124.7, 125.2, 125.6 (2C$_6$H$_5$), 128.5, 129.6, 130.8, 132.8 (pyridine C), 166.6 (C=N), 168.8 (C=O). Anal. calcd. for C$_{22}$H$_{19}$N$_2$O: C, 71.34; H, 4.90; N, 15.13%. Found: C, 71.60; H, 4.87; N, 15.28%. MS: m/z 370 (M$^+$, 44%).

2-Amino-4-(4-chlorophenyl)-7-oxo-8-(2-phenylhydrazono)-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile (6c). Brown crystals from 1,4-dioxane, yield (2.41 g, 60%), Mp 120-122 \degree C. IR (KBr) u max cm$^{-1}$: 3484-3339 (NH$_2$, NH), 3055 (CH, aromatic), 2222 (CN), 1693 (C=O), 1642 (C=N), 1633 (C=C); 1H NMR (DMSO-d$_6$, 300 MHz): $\delta$ = 2.80-2.99 (2t, 4H, 2CH$_2$), 4.94 (s, 2H, D$_2$O exchangeable NH$_2$), 5.16 (s, 1H, pyridine H-4), 7.23-7.57 (m, 9H, C$_6$H$_5$, C$_6$H$_4$), 8.36, 8.46 (2s, 2H, D$_2$O exchangeable, 2NH); 13C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 37.2, 41.7 (2CH$_3$), 48.9 (pyridine C-4), 117.8 (CN), 120.3, 120.6, 121.8, 121.9, 122.3, 123.6, 124.7, 126.1 (C$_6$H$_5$, C$_6$H$_4$), 128.6, 129.2, 130.5, 132.2 (pyridine C), 166.3 (C=N), 167.3 (C=O). Anal. calcd. for C$_{22}$H$_{19}$ClN$_2$O: C, 65.43; H, 4.49; N, 17.34%. Found: C, 65.39; H, 4.28; N, 17.57%. MS: m/z 403 (M$^+$, 68%).

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4-(4-Chlorophenyl)-2-hydroxy-7-oxo-8-(2-phenylhydrazono)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6d). Red crystals from 1,4-dioxane, yield (2.68 g, 66%), Mp 148-150 °C. IR (KBr) ν max cm⁻¹: 3561-3373 (OH, NH), 3056 (CH, aromatic), 2222 (CN), 1697 (C=O), 1643 (C=N), 1631 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.80-2.99 (2t, 4H, 2CH₂), 5.15 (s, 1H, pyridine H-4), 7.25-7.58 (m, 9H, C₆H₅), 8.28, 8.42 (2s, 2H, D₄O exchangeable, 2NH), 10.49 (s, 1H, D₄O exchangeable, OH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 37.8, 41.5 (2CH₂), 48.8 (pyridine C-4), 117.2 (CN), 120.1, 120.8, 121.7, 122.4, 124.2, 125.2, 125.8 (C₆H₅), 128.3, 129.5, 130.5, 132.6 (pyridine C), 166.9 (C=N), 168.4 (C=O). Anal. calcd. for C₂₉H₂₁ClN₂O₆: C, 62.7%; H, 4.23; N, 13.84%. Found: C, 65.53; H, 4.26; N, 14.02%. MS: m/z 404 (M⁺, 48%).

2-Amino-4-(4-methoxyphenyl)-7-oxo-8-(2-phenylhydrazono)-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile (6e). Pale brown crystals from 1,4-dioxane, yield (2.40 g, 66%), Mp > 300 °C. IR (KBr) ν max cm⁻¹: 3459-3324 (NH₂, NH), 3055 (CH, aromatic), 2220 (CN), 1697 (C=O), 1646 (C=N), 1632 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.80-2.99 (2t, 4H, 2CH₂), 3.68 (s, 3H, OCH₃), 4.88 (s, 2H, D₄O exchangeable NH₂), 5.05 (s, 1H, pyridine H-4), 7.25-7.58 (m, 9H, C₆H₅), 8.30, 8.41 (2s, 2H, D₄O exchangeable, 2NH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 36.6, 40.8 (2CH₂), 50.6 (OCH₃), 50.8 (pyridine C-4), 116.8 (CN), 120.1, 121.4, 122.2, 122.6, 123.7, 124.6, 125.5, 126.2 (C₆H₅), 128.6, 129.08, 130.7, 133.5 (pyridine C), 166.4 (C=N), 167.6 (C=O). Anal. calcd. for C₂₉H₂₁N₂O₆: C, 69.16; H, 5.30; N, 17.53%. Found: C, 69.31; H, 5.26; N, 17.42%. MS: m/z 399 (M⁺, 42%).

2-Hydroxy-4-(4-methoxyphenyl)-7-oxo-8-(2-phenylhydrazono)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6f). Pale brown crystals from 1,4-dioxane, yield (2.80 g, 70%), Mp 143-145 °C. IR (KBr) ν max cm⁻¹: 3568-3341 (OH, NH), 3055 (CH, aromatic), 2222 (CN), 1698 (C=O), 1641 (C=N), 1632 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.84-3.03 (2t, 4H, 2CH₂), 3.72 (s, 3H, OCH₃), 5.16 (s, 1H, pyridine H-4), 7.21-7.54 (m, 9H, C₆H₅), 8.29, 8.43 (2s, 2H, D₄O exchangeable, 2NH), 10.36 (s, 1H, D₄O exchangeable, OH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 37.2, 41.6 (2CH₂), 50.6 (OCH₃), 50.8 (pyridine C-4), 116.8 (CN), 120.1, 120.3, 121.5, 123.8, 124.6, 124.8, 125.1, 126.3 (C₆H₅), 128.6, 129.8, 130.2, 132.3 (pyridine C), 166.5 (C=N), 168.2 (C=O). Anal. calcd. for C₂₉H₂₃N₂O₆: C, 68.99; H, 5.03; N, 13.99%. Found: C, 68.63; H, 4.92; N, 14.25%. MS: m/z 400 (M⁺, 40%).

2-Amino-7-oxa-4-phenyl-8-(2-p-tolyldihydrazono)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6g). Brown crystals from 1,4-dioxane, yield (2.29 g, 60%), Mp > 300 °C. IR (KBr) ν max cm⁻¹: 3488-3372 (NH₂, NH), 3055 (CH, aromatic), 2223 (CN), 1697 (C=O), 1643 (C=N), 1630 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.61-3.02 (2t, 4H, 2CH₂), 2.78 (s, 3H, CH₃), 4.89 (s, 2H, D₄O exchangeable NH₂), 5.16 (s, 1H, pyridine H-4), 7.22-7.49 (m, 9H, C₆H₅), 8.28, 8.46 (2s, 2H, D₂O exchangeable, 2NH), 10.36 (s, 1H, D₂O exchangeable, OH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 36.3, 40.9 (2CH₂), 35.6 (CH₃), 50.8 (pyridine C-4), 117.0 (CN), 120.1, 121.3, 122.2, 122.8, 123.1, 124.6, 124.8, 125.5 (C₆H₅), 131.9, 129.6, 130.5, 131.8 (pyridine C), 166.2 (C=N), 167.4 (C=O). Anal. calcd. for C₂₉H₂₃N₂O: C, 72.04; H, 5.52; N, 18.26%. Found: C, 71.92; H, 5.72; N, 18.33%. MS: m/z 383 (M⁺, 60%).

2-Hydroxy-7-oxa-4-phenyl-8-(2-p-tolyldihydrazono)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile(6h). Pale brown crystals from 1,4-dioxane, yield (2.64 g, 69%), Mp > 300 °C. IR (KBr) ν max cm⁻¹: 3558-3373 (OH, NH), 3055 (CH, aromatic), 2222 (CN), 1698 (C=O), 1642 (C=N), 1630 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.80-3.21 (2t, 4H, 2CH₂), 2.76 (s, 3H, CH₃), 5.08 (s, 1H, pyridine H-4), 7.24-7.52 (m, 9H, C₆H₅), 8.32, 8.44 (2s, 2H, D₂O exchangeable, 2NH), 10.41 (s, 1H, D₂O exchangeable, OH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 37.5, 41.6 (2CH₂), 36.8 (CH₃), 50.7 (pyridine C-4), 116.2 (CN), 120.3, 120.6, 121.8, 122.2, 123.7, 124.2, 125.8, 126.2 (C₆H₅), 128.3, 129.1, 132.3, 132.6 (pyridine C), 166.7 (C=N), 168.5 (C=O).

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Anal. calcd. for C_{32}H_{24}N_{2}O_{2}: C, 71.86; H, 5.24; N, 14.57%. Found: C, 71.61; H, 5.36; N, 14.70%. MS: m/z 384 (M^+, 28%).

2-Amino-4-(4-chlorophenyl)-7-oxo-8-(2-p-tolyl)hydrazono)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6i). Pale brown crystals from 1,4-dioxane, yield (21.6 g, 76%). IR (KBr) v max cm\(^{-1}\): 3480-3360 (NH, NH), 3055 (CH, aromatic), 2223 (CN), 1694 (C=O), 1643 (C=C), 1632 (C=C); \(^1\)H NMR (DMSO-d_6, 300 MHz): \(\delta = 2.68-3.17\) (2t, 4H, 2CH_2), 2.72 (s, 3H, CH_3), 4.68 (s, 2H, D,O exchangeable NH), 5.09 (s, 1H, pyridine H-4), 7.25-7.58 (m, 8H, 2C_6H_5), 8.31, 8.49 (2s, 2H, D,O exchangeable, 2NH); \(^1^3\)C NMR (DMSO-d_6, 75 MHz): \(\delta = 36.2, 41.6\) (2CH_2), 36.5 (CH_3), 50.9 (pyridine C-4), 116.8 (CN), 120.3, 120.5, 122.5, 122.8, 123.1, 123.6, 125.8, 126.3 (2C_6H_5), 127.8, 128.8, 130.2, 131.6 (pyridine C), 166.3 (C=C), 168.6 (C=O). Anal. calcd. for C_{32}H_{23}ClN_{2}O: C, 66.10; H, 4.82; N, 16.76%. Found: C, 65.91; H, 4.63; N, 16.82%. MS: m/z 417 (M^+, 55%).

4-(4-Chlorophenyl)-2-hydroxy-7-oxo-8-(2-p-tolyl)hydrazono)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6j). Yellow crystals from 1,4-dioxane, yield (24.1 g, 55%), Mp 131-133 °C. IR (KBr) v max cm\(^{-1}\): 3539-3342 (OH, NH), 3055 (CH, aromatic), 2221 (CN), 1692 (C=O), 1645 (C=C), 1631 (C=C); \(^1\)H NMR (DMSO-d_6, 300 MHz): \(\delta = 2.83-2.96\) (2t, 4H, 2CH_2), 2.72 (s, 3H CH_3), 5.11 (s, 1H, pyridine H-4), 7.21-7.47 (m, 8H, 2 C_6H_5), 8.26, 8.42 (2s, 2H, D,O exchangeable, 2NH), 10.31 (s, 1H, D,O exchangeable, OH); \(^1^3\)C NMR (DMSO-d_6, 75 MHz): \(\delta = 38.4, 42.8\) (2CH_2), 36.2 (CH_3), 51.2 (pyridine C-4), 117.6 (CN), 120.0, 120.6, 122.8, 123.2, 125.0, 125.2, 126.0, 126.5 (2 C_6H_5), 130.2, 132.8, 134.8, 136.5 (pyridine C), 166.8 (C=C), 168.5 (C=O). Anal. calcd. for C_{32}H_{23}ClN_2O_2: C, 65.81; H, 4.29; N, 9.82%. Found: C, 65.54; H, 4.51; N, 9.68%. MS: m/z 418 (M^+, 50%).

2-Amino-4-(4-methoxyphenyl)-7-oxo-8-(2-p-tolyl)hydrazono)-1,4,5,6,7,8-hexahydro-4H-quinoline-3-carbonitrile (6k). Brown crystals from 1,4-dioxane, yield (3.22 g, 78%), Mp > 300 °C. IR (KBr) v max cm\(^{-1}\): 3482-3348 (NH, NH), 3055 (CH, aromatic), 2222 (CN), 1696 (C=O), 1643 (C=C), 1631 (C=C); \(^1\)H NMR (DMSO-d_6, 300 MHz): \(\delta = 2.62-3.19\) (2t, 4H, 2CH_2), 2.78 (s, 3H CH_3), 3.69 (s, 3H OCH_3), 4.52 (s, 2H, D,O exchangeable NH), 5.06 (s, 1H, pyridine H-4), 7.21-7.50 (m, 8H, 2C_6H_5), 8.34, 8.41 (2s, 2H, D,O exchangeable, 2NH); \(^1^3\)C NMR (DMSO-d_6, 75 MHz): \(\delta = 36.3, 40.7\) (2CH_2), 36.8 (CH_3), 50.2 (OCH_3), 51.3 (pyridine C-4), 116.9 (CN), 119.6, 120.2, 122.6, 123.2, 124.2, 125.0, 125.2, 126.3 (2 C_6H_5), 128.7, 130.1, 130.2, 132.5 (pyridine C), 164.6 (C=C), 168.6 (C=O). Anal. calcd. for C_{32}H_{24}N_2O_2: C, 69.72; H, 5.61; N, 16.94%. Found: C, 69.58; H, 5.76; N, 17.17%. MS: m/z 413 (M^+, 66%).

2-Hydroxy-4-(4-methoxyphenyl)-7-oxo-8-(2-p-tolyl)hydrazono)-1,4,5,6,7,8-hexahydro-4H-quinoline-3-carbonitrile (6l). Orange crystals from 1,4-dioxane, yield (2.98 g, 72%), Mp 175-177 °C. IR (KBr) v max cm\(^{-1}\): 3573-3347 (OH, NH), 3054 (CH, aromatic), 2222 (CN), 1696 (C=O), 1640 (C=C), 1634 (C=C); \(^1\)H NMR (DMSO-d_6, 300 MHz): \(\delta = 2.79-3.13\) (2t, 4H, 2CH_2), 2.69 (s, 3H CH_3), 3.70 (s, 3H OCH_3), 5.05 (s, 1H, pyridine H-4), 7.24-7.49 (m, 8H, 2 C_6H_5), 8.30, 8.45 (2s, 2H, D,O exchangeable, 2NH), 10.34 (s, 1H, D,O exchangeable, OH); \(^1^3\)C NMR (DMSO-d_6, 75 MHz): \(\delta = 37.5, 40.9\) (2CH_2), 36.7 (CH_3), 50.3 (OCH_3), 50.5 (pyridine C-4), 116.5 (CN), 120.1, 120.4, 121.8, 122.6, 123.5, 124.8, 125.6, 125.9 (2 C_6H_5), 128.3, 129.6, 130.7, 131.3 (pyridine C), 166.9 (C=C), 168.3 (C=O). Anal. calcd. for C_{32}H_{24}N_2O: C, 69.55; H, 5.35; N, 13.52%. Found: C, 69.68; H, 5.47; N, 13.80%. MS: m/z 414 (M^+, 32%).

2-Amino-8-(2-(4-chlorophenyl)hydrazono)-7-oxo-4-phenyl-1,4,5,6,7,8-hexahydropyridine-3-carbonitrile (6m). Orange crystals from 1,4-dioxane, yield (2.21 g, 55%), Mp > 300 °C. IR (KBr) v max cm\(^{-1}\): 3479-3341 (NH, NH), 3055 (CH, aromatic), 2222 (CN), 1694 (C=O), 1646 (C=C), 1635 (C=C); \(^1\)H NMR (DMSO-d_6, 300 MHz): \(\delta = 2.64-3.02\) (2t, 4H, 2CH_2), 4.87 (s, 2H, D,O

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exchangable NH$_2$), 5.08 (s, 1H, pyridine H-4), 7.22-7.53 (m, 9H, C$_6$H$_5$, C$_6$H$_4$), 8.33, 8.42 (2s, 2H, D$_2$O exchangeable, 2NH); $^1$H NMR (DMSO-d$_6$, 75 MHz): $\delta$ 36.3, 41.8 (2CH$_2$), 50.8 (pyridine C-4), 117.0 (CN), 120.1, 120.4, 121.3, 122.7, 122.8, 123.9, 124.6, 125.7 (C$_6$H$_5$, C$_6$H$_4$), 129.3, 129.7, 130.3, 131.8 (pyridine C), 167.6 (C=N), 168.2 (C=O). Anal. calcd. for C$_5$H$_3$ClN$_2$O: C, 65.43; H, 4.49; N, 17.34%. Found: C, 65.72; H, 4.39; N, 17.52%. MS: m/z 403 (M$^+$, 48%).

8-(2-(4-Chlorophenyl)hydrazono)-2-hydroxy-7-axo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6a). Yellow crystals from 1,4-dioxane, yield (2.42 g, 60%), Mp 162-164 °C. IR (KBr) v max cm$^{-1}$: 3528-3358 (OH, NH), 3054 (CH, aromatic), 2222 (CN), 1697 (C=O), 1640 (C=N), 1633 (C=C); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 2.83-3.32 (2t, 4H, 2CH$_2$), 5.08 (s, 1H, pyridine H-4), 7.25-7.49 (m, 9H, C$_6$H$_5$, C$_6$H$_4$), 8.30, 8.42 (2s, 2H, D$_2$O exchangeable, 2NH), 10.41 (s, 1H, D$_2$O exchangeable, OH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 37.2, 41.3 (2CH$_2$), 50.3 (pyridine C-4), 117.3 (CN), 120.2, 121.2, 121.8, 122.9, 123.4, 124.4, 125.1, 125.8 (C$_6$H$_5$, C$_6$H$_4$), 128.7, 128.8, 130.8, 131.9 (pyridine C), 167.0 (C=N), 168.9 (C=O). Anal. calcd. for C$_9$H$_7$ClN$_2$O: C, 65.27; H, 4.23; N, 13.84%. Found: C, 65.14; H, 4.40; N, 14.21%. MS: m/z 404 (M$^+$, 35%).

2-Amino-4-(4-chlorophenyl)-8-(2-(4-chlorophenyl)hydrazono)-7-axo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6b). Orange crystals from 1,4-dioxane, yield (3.32 g, 76%), Mp 185-187 °C. IR (KBr) v max cm$^{-1}$: 3473-3352 (NH, NH), 3053 (CH, aromatic), 2222 (CN), 1696 (C=O), 1641 (C=N), 1635 (C=C); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 2.63-3.13 (2t, 4H, 2CH$_2$), 4.89 (s, 2H, D$_2$O exchangeable NH$_2$), 5.08 (s, 1H, pyridine H-4), 7.24-7.53 (m, 9H, 2CH$_2$), 8.33, 8.42 (2s, 2H, D$_2$O exchangeable, 2NH); $^{13}$N NMR (DMSO-d$_6$, 75 MHz): $\delta$ 36.7, 41.2 (2CH$_2$), 50.8 (pyridine C-4), 117.1 (CN), 120.2, 120.7, 122.4, 122.6, 123.8, 124.3, 125.3, 126.4 (2CH$_2$), 128.8, 129.5, 130.4, 131.6 (pyridine C), 167.3 (C=N), 168.8 (C=O). Anal. calcd. for C$_9$H$_7$ClN$_2$O: C, 60.29; H, 3.91; N, 15.98%. Found: C, 60.37; H, 3.78; N, 15.25%. MS: m/z 438 (M$^+$, 48%).

4-(4-Chlorophenyl)-8-(2-(4-chlorophenyl)hydrazono)-2-hydroxy-7-axo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6p). Pale yellow crystals from 1,4-dioxane, yield (2.97 g, 68%), Mp 171-173 °C. IR (KBr) v max cm$^{-1}$: 3538-3349 (OH, NH), 3055 (CH, aromatic), 2220 (CN), 1701 (C=O), 1646 (C=N), 1632 (C=C); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 2.83-3.21 (2t, 4H, 2CH$_2$), 5.05 (s, 1H, pyridine H-4), 7.23-7.59 (m, 9H, 2CH$_2$), 8.26, 8.43 (2s, 2H, D$_2$O exchangeable, 2NH), 10.35 (s, 1H, D$_2$O exchangeable, OH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 37.8, 41.5 (2CH$_2$), 51.4 (pyridine C-4), 117.2 (CN), 120.3, 120.8, 121.5, 121.9, 123.6, 124.8, 125.1, 125.6 (2CH$_2$), 129.2, 129.8, 130.3, 132.4 (pyridine C), 166.6 (C=N), 168.9 (C=O). Anal. calcd. for C$_8$H$_7$ClN$_2$O: C, 60.15; H, 3.67; N, 12.75%. Found: C, 60.26; H, 3.59; N, 12.92%. MS: m/z 439 (M$^+$, 48%).

2-Amino-8-(2-(4-chlorophenyl)hydrazono)-4-(4-methoxyphenyl)-7-axo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6q). Orange crystals from 1,4-dioxane, yield (3.03 g, 70%), Mp 300 °C. IR (KBr) v max cm$^{-1}$: 3483-3239 (NH, NH), 3055 (CH, aromatic), 2220 (CN), 1687 (C=O), 1641 (C=N), 1633 (C=C); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 2.58-3.14 (2t, 4H, 2CH$_2$), 3.64 (s, 3H, OCH$_3$), 4.86 (s, 2H, D$_2$O exchangeable NH$_2$), 5.13 (s, 1H, pyran H-4), 7.26-7.55 (m, 8H, 2CH$_2$), 8.32, 8.42 (2s, 2H, D$_2$O exchangeable, 2NH); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 37.3, 41.8 (2CH$_2$), 50.1 (OCH$_3$), 51.6 (pyran C-4), 117.0 (CN), 120.3, 120.5, 121.8, 122.9, 124.3, 124.6, 125.1, 126.0 (2CH$_2$), 128.1, 129.6, 130.2, 131.3 (pyran C), 165.4 (C=N), 168.9 (C=O). Anal. calcd. for C$_9$H$_7$O$_2$N$_2$: C, 63.67; H, 4.65; N, 16.14%. Found: C, 63.92; H, 4.59; N, 16.26%. MS: m/z 433 (M$^+$, 66%).

8-(2-(4-Chlorophenyl)hydrazono)-2-hydroxy-4-(4-methoxyphenyl)-7-axo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6r). Pale yellow crystals from 1,4-dioxane, yield (3.38 g, 78%), Mp 171-
Multi-component reactions of cyclohexan-1,3-dione to synthesize heterocyclic derivatives

173 °C. IR (KBr) v max cm⁻¹: 3573-3532 (OH, NH), 3055 (CH, aromatic), 2220 (CN), 1688 (C=O), 1641 (C=N), 1633 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.78-3.12 (2t, 4H, 2CH₂), 3.76 (s, 3H, OCH₃), 5.07 (s, 1H, pyridine H-4), 7.21-7.53 (m, 8H, 2 CH₃), 8.26, 8.42 (2s, 2H, D₂O exchangeable, 2NH), 10.36 (s, 1H, D₂O exchangeable, OH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 38.2, 41.5 (2CH₂), 50.4 (OCH₃), 50.8 (pyridine C-4), 116.7 (CN), 120.3, 120.8, 121.2, 122.9, 123.0, 123.7, 125.2, 126.5 (2 CH₃), 128.4, 129.4, 130.2, 131.6 (pyridine C), 164.3 (C=N), 168.8 (C=O). Anal. calcd. for C₂₃H₂₁N₄O₂: C, 63.52; H, 4.40; N, 12.88%. Found: C, 63.63; H, 4.52; N, 13.05%. MS: m/z 434 (M⁺, 86%).

General procedure for the synthesis of the 5,6,7,8-tetrahydro-4H-chromene derivatives 8a-c. Each of benzaldehyde (1.06 g, 0.01 mol) and ethyl benzoylacetate (1.92 g, 0.01 mol) were added to a solution of either 3a (2.16 g, 0.01 mol), 3b (2.30 g, 0.01 mol) or 3e (2.5 g, 0.01 mol) in absolute ethanol (50 mL) containing triethylamine (2.00 mL). The whole reaction mixture was heated under reflux for 2 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

Ethyl 7-oxo-4,5-diphenyl-8-(2-phenyldihyrazono)-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (8a). Orange crystals from ethanol, yield (3.15 g, 66%), Mp 142-144 °C. IR (KBr) v max cm⁻¹: 3439-3333 (NH), 3055 (CH, aromatic), 1699, 1688 (C=O), 1641 (C=N), 1632 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 1.13 (t, 3H, J = 7.22 Hz, OCH₃), 2.63-3.20 (2t, 4H, 2CH₂), 4.21 (q, 2H, J = 7.22 Hz, OCH₂CH₃), 5.11 (s, 1H, pyran H-4), 7.24-7.53 (m, 15H, 3CH₃), 8.31 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 16.8 (OCH₃), 37.2, 41.8 (2CH₂), 50.1 (pyran C-4), 50.8 (OCH₂CH₃), 120.3, 120.6, 121.0, 121.7, 122.5, 122.8, 123.1, 123.4, 123.7, 125.2, 126.6 (3CH₃), 130.3, 130.5, 131.6, 133.8 (pyran C), 165.8 (C=N), 166.3, 168.7 (C=O). Anal. calcd. for C₂₃H₂₁N₄O₂: C, 75.30; H, 5.48; N, 5.85%. Found: C, 75.51; H, 5.62; N, 5.73%. MS: m/z 478 (M⁺).

Ethyl 7-oxo-4,5-diphenyl-8-(2-p-tolyl)dihyrazono)-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (8b). Orange crystals from ethanol, yield (3.64 g, 74%), Mp 186-188 °C. IR (KBr) v max cm⁻¹: 3469-3336 (NH), 3055 (CH, aromatic), 1694, 1689 (C=O), 1643 (C=N), 1630 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 1.12 (t, 3H, J = 7.59 Hz, OCH₃), 2.72 (s, 3H, CH₃), 2.63-3.20 (2t, 4H, 2CH₂), 4.21 (q, 2H, J = 7.59 Hz, OCH₂CH₃), 5.13 (s, 1H, pyran H-4), 7.21-7.58 (m, 14H, 2CH₃, C₆H₅), 8.32 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 16.8 (OCH₃), 34.2 (CH₃), 36.5, 40.6 (2CH₂), 50.3 (pyran C-4), 50.8 (OCH₂CH₃), 120.1, 120.5, 122.3, 122.5, 123.8, 123.9, 124.0, 124.1, 124.8, 125.1, 125.3, 126.9 (2CH₃, C₆H₅), 130.6, 131.7, 133.2, 133.9 (pyran C), 165.2 (C=N), 166.6, 168.9 (C=O). Anal. calcd. for C₂₃H₂₂N₄O₂: C, 75.59; H, 5.73; N, 5.69%. Found: C, 75.31; H, 5.49; N, 5.82%. MS: m/z 492 (M⁺).

Ethyl 8-(2-(4-chlorophenyl)dihyrazono)-7-oxo-4,5-diphenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (8c). Orange crystals from ethanol, yield (3.68 g, 72%), Mp 173-175 °C. IR (KBr) v max cm⁻¹: 3469-3336 (NH), 3055 (CH, aromatic), 1694, 1689 (C=O), 1643 (C=N), 1630 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 1.12 (t, 3H, J = 6.80 Hz, OCH₃), 2.61-3.23 (2t, 4H, 2CH₂), 4.23 (q, 2H, J = 6.80 Hz, OCH₂CH₃), 5.12 (s, 1H, pyran H-4), 7.24-7.62 (m, 14H, 2CH₃, C₆H₅), 8.32 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 16.8 (OCH₂CH₃), 36.2, 39.1 (2CH₂), 50.4 (pyran C-4), 51.0 (OCH₂CH₃), 120.4, 120.8, 122.2, 123.0, 123.6, 123.8, 124.2, 124.6, 125.0, 125.7, 126.2, 126.7 (2CH₃, C₆H₅), 130.4, 131.6, 132.8, 133.3 (pyran C), 165.7 (C=N), 166.2, 168.5 (C=O). Anal. calcd. for C₂₃H₂₀ClN₄O₂: C, 70.24; H, 4.91; N, 5.46%. Found: C, 70.37; H, 5.16; N, 5.72%. MS: m/z 512 (M⁺, 32%).

General procedure for the synthesis of the 4,5,6,7-tetrahydrochroemo[2,3-c]pyrazole derivatives 10a-c. Each of benzaldehyde (1.06 g, 0.01 mol) and 3-methyl-1H-pyrazol-5(4H)-one
(0.98 g, 0.01 mol) were added to a solution of either 3a (2.16 g, 0.01 mol), 3b (2.30 g, 0.01 mol) or 3c (2.50 g, 0.01 mol) in absolute ethanol (50 mL) containing triethylamine (2.00 mL). The whole reaction mixture was heated under reflux for 2 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

3-Methyl-4-phenyl-8-(2-phenylhydrazono)-4,5,6,8-tetrahydrochromeno[2,3-c]pyrazol-7(1H)-one (10a). Orange crystals from ethanol, yield (2.30 g, 60%), Mp 135-137 °C. IR (KBr) υ max cm⁻¹: 3453-3329 (NH), 3055 (CH, aromatic), 1699 (C=O), 1641 (C=N), 1632 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.80 (s, 3H, CH₃), 2.63-3.29 (2t, 4H, 2CH₂), 5.13 (s, 1H, pyran H-4), 7.26-7.45 (m, 10H, 2C₆H₅). ¹³C NMR (DMSO-d₆, 75 MHz): δ = 35.8 (CH₃), 37.1, 41.2 (2CH₃), 8.24, 8.43 (2s, 2H, D₂O exchangeable, 2NH); ¹⁵N NMR (DMSO-d₆, 75 MHz): δ = 32.3, 35.6 (2CH₃), 37.1, 41.2 (2CH₃), 50.5 (pyran C-4), 120.3, 120.8, 121.2, 121.8, 122.5, 124.6, 125.0, 125.7 (2C₆H₅), 130.2, 130.3, 131.1, 132.2 (pyran C), 164.8, 165.7 (2C=O), 168.5 (C=O). Anal. calcd. for C₂₃H₂₃N₂O: C, 77.36; H, 5.76; N, 14.05%. Found: C, 77.45; H, 5.75; N, 14.05%. MS: m/z 384 (M⁺, 38%).

8-(2-(4-Chlorophenyl)hydrazono)-3-methyl-4-phenyl-4,5,6,8-tetrahydrochromeno[2,3-c]pyrazol-7(1H)-one (10c). Pale brown crystals from ethanol, yield (2.29 g, 55%), Mp 159-162 °C. IR (KBr) υ max cm⁻¹: 3471-3332 (NH), 3055 (CH, aromatic), 1701 (C=O), 1644 (C=N), 1630 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.83 (s, 3H, CH₃), 2.62-3.15 (2t, 4H, 2CH₂), 5.12 (s, 1H, pyran H-4), 7.22-7.54 (m, 9H, C₆H₅, C₆H₄), 8.31, 8.42 (2s, 2H, D₂O exchangeable, 2NH); ¹³C NMR (DMSO-d₆, 75 MHz): δ = 34.3 (CH₃), 37.1, 41.9 (2CH₃), 50.5 (pyran C-4), 120.3, 120.8, 121.2, 121.8, 122.5, 124.6, 125.0, 125.7 (C₆H₅, C₆H₄), 130.2, 130.3, 131.1, 132.2 (pyran C), 164.8, 165.7 (2C=O), 168.6 (C=O). Anal. calcd. for C₂₃H₂₁ClN₂O: C, 65.95; H, 4.57; N, 13.38%. Found: C, 66.15; H, 4.70; N, 13.52%. MS: m/z 418 (M⁺, 21%).

General procedure for the synthesis of the 5,6,7,8-tetrahydro-4H-chromene derivatives 12a-c. Each of benzaldehyde (1.06 g, 0.01 mol) and 3-oxo-N,3-diphenylpropanamide (2.39 g, 0.01 mol) were added to a solution of either 3a (2.16 g, 0.01 mol), 3b (2.30 g, 0.01 mol) or 3c (2.50 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (2.00 mL). The whole reaction mixture was heated under reflux for 5 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

7-Oxo-N,2,4-triphenyl-8-(2-phenylhydrazinylidene)-5,6,7,8-tetrahydro-4H-chromene-3-carboxamide (12a). Orange crystals from 1,4-dioxane, yield (3.67 g, 70%), Mp 180-182 °C. IR (KBr) υ max cm⁻¹: 3478-3339 (NH), 3055 (CH, aromatic), 1689 (C=O), 1641 (C=N), 1632 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.61-3.23 (2t, 4H, 2CH₂), 5.15 (s, 1H, pyran H-4), 7.21-7.56 (m, 20H, 4C₆H₅), 8.23, 8.33 (2s, 2H, D₂O exchangeable, 2NH); ¹³C NMR (DMSO-d₆, 75 MHz): δ = 37.4, 41.6 (2CH₃), 50.1 (pyran C-4), 119.8, 120.1, 120.8, 121.2, 121.5, 122.3, 122.5, 123.0, 123.6, 124.2, 124.6, 124.8, 125.2, 125.8, 126.2, 126.9 (4C₆H₅), 130.3, 130.5, 131.6, 133.8 (pyran C), 164.5, 164.7 (2C=O), 168.4 (C=O). Anal. calcd. for C₇₁H₅₃N₂O: C, 77.01; H, 5.30; N, 14.19%. Found: C, 77.10; H, 5.32; N, 14.20%. MS: m/z 1338 (M⁺, 20%).
7-Oxo-N,2,4-triphenyl-8-(2-(p-tolyl)hydrazineylidene)-5,6,7,8-tetrahydro-4H-chromene-3-carboxamide (12b). Yellow crystals from 1,4-dioxane, yield (2.50 g, 0.01 mol) in 1,4-dioxane, yield (3.80 g, 68%), Mp 135-137 °C. IR (KBr) ν max cm⁻¹: 3495-3346 (NH), 3054 (CH, aromatic), 1695, 1688 (C=O), 1641 (C=N), 1630 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.78 (s, 3H, CH₃), 2.61-3.24 (2t, 4H, 2CH₂), 5.16 (s, 1H, pyran H-4), 7.25-7.56 (m, 19H, 3C₆H₅, C₆H₄), 8.25, 8.32 (2s, 2H, D₂O exchangeable, 2NH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 36.2, 39.5 (2CH₃), 50.4 (pyridine C-4), 116.7 (CN), 119.6, 120.1, 122.0, 122.3, 123.0, 123.8, 124.2, 124.6, 125.2, 125.5, 126.0, 126.3 (3C₆H₅, C₆H₄), 130.1, 131.2, 132.4, 133.1 (pyridine C), 165.4 (C=N), 166.2, 168.7 (C=O). Anal. calcd. for C₃₈H₂₆N₆O₇: C, 77.90; H, 5.42; N, 7.79%. Found: C, 78.21; H, 5.36; N, 7.80%. MS: m/z 539 (M⁺, 34%).

8-(2-(4-Chlorophenyl)hydrazineylidene)-7-oxo-N,2,4-triphenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxamide (12c). Orange crystals from 1,4-dioxane, yield (0.84 g, 0.01 mol) in 1,4-dioxane, yield (2.77 g, 75%), Mp 165-166 °C. IR (KBr) ν max cm⁻¹: 3490-3339 (NH), 3055 (CH, aromatic), 1695, 1688 (C=O), 1640 (C=N), 1630 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.63-3.25 (2t, 4H, 2CH₂), 5.09 (s, 1H, pyran H-4), 7.21-7.58 (m, 19H, 3C₆H₅, C₆H₄), 8.25, 8.31 (2s, 2H, D₂O exchangeable, 2NH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 36.2, 39.1 (2CH₃), 50.7 (pyridine C-4), 119.3, 120.1, 120.5, 121.3, 121.6, 121.9, 122.2, 123.0, 123.8, 124.2, 124.6, 125.2, 125.5, 126.0, 126.3 (3C₆H₅, C₆H₄), 130.1, 131.2, 132.4, 133.1 (pyridine C), 165.4 (C=N), 166.2, 168.7 (C=O). Anal. calcd. for C₃₈H₂₆ClN₆O₇: C, 72.92; H, 4.68; N, 7.50%. Found: C, 73.26; H, 4.72; N, 7.74%. MS: m/z 560 (M⁺, 36%).

**General procedure for the synthesis of the 1,4,5,6,7,8-hexahydroquinoline derivatives 14a-f.** Each of benzaldehyde (1.06 g, 0.01 mol) and either 2-cyanoacetamide (0.84 g, 0.01 mol) or 2-cyanoethanethioamide (1.00 g, 0.01 mol) were added to a solution of either 3a (2.16 g, 0.01 mol), 3b (2.30 g, 0.01 mol) or 3c (2.50 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (2.00 mL). The whole reaction mixture was heated under reflux for 2 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

**2-Hydroxy-7-oxo-4-phenyl-8-(2-phenylhydrazineylidene)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (14a).** Yellow crystals from 1,4-dioxane, yield (2.77 g, 75%), Mp 170-172 °C. IR (KBr) ν max cm⁻¹: 3564-3372 (OH, NH), 3055 (CH, aromatic), 2220 (CN), 1689 (C=O), 1640 (C=N), 1630 (C=C); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.60-3.28 (2t, 4H, 2CH₂), 5.13 (s, 1H, pyridine H-4), 7.25-7.48 (m, 10H, 2C₆H₅, 2C₆H₄), 8.28, 8.34 (2s, 2H, D₂O exchangeable, 2NH), 10.23 (s, 1H, D₂O exchangeable, OH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 36.2, 39.5 (2CH₃), 50.4 (pyridine C-4), 117.6 (CN), 119.6, 120.1, 122.3, 123.0, 123.8, 124.6, 124.6 (2CH₂C₆H₅), 130.3, 131.6, 132.1, 133.8 (pyridine C), 165.6 (C=N) 168.9 (C=O). Anal. calcd. for C₂₃H₁₈N₂O: C, 71.34; H, 4.90; N, 15.13%. Found: C, 71.59; H, 4.78; N, 15.08%. MS: m/z 370 (M⁺, 48%).

**2-Mercapto-7-oxo-4-phenyl-8-(2-phenylhydrazineylidene)-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile (14b).** Yellow crystals from 1,4-dioxane, yield (2.54 g, 66%), Mp 180-184 °C. IR (KBr) ν max cm⁻¹: 3487-3339 (NH), 3055 (CH, aromatic), 2222 (CN), 1688 (C=O), 1640 (C=N), 1630 (C=C), 1205 (SH); ¹H NMR (DMSO-d₆, 300 MHz): δ = 2.62-3.27 (2t, 4H, 2CH₂), 5.15 (s, 1H, pyridine H-4), 7.22-7.52 (m, 10H, 2C₆H₅, 2C₆H₄), 8.26, 8.38 (2s, 2H, D₂O exchangeable, 2NH), 10.41 (s, 1H, D₂O exchangeable, SH); ¹³C NMR (DMSO-d₆, 75 MHz): δ 36.2, 39.5 (2CH₃), 50.6 (pyridine C-4), 116.9 (CN), 119.4, 120.5, 121.8, 122.7, 123.6, 124.0, 124.6, 124.8 (2CH₂C₆H₅), 130.0, 131.7, 132.5, 133.3 (pyridine C), 165.4 (C=N) 168.5 (C=O). Anal. calcd. for C₂₃H₁₈N₂S: C,
measurements were carried out to evaluate the target molecules as anticancer agents. Seven components reactions. Different measurements were carried out to evaluate the target molecules as anticancer agents. Seven

CONCLUSION

In this work the adopted synthesis of heterocyclic compounds starting from arylhydrazone derivatives of cyclohexan-1,3-dione through different multi-component reactions. Different measurements were carried out to evaluate the target molecules as anticancer agents. Seven...
Multi-component reactions of cyclohexan-1,3-dione to synthesize heterocyclic derivatives were the most common potent compounds toward the cancer cell lines, c-Met kinase, PC-3 cell line, tyrosine kinases. Whereas, eight compounds were the most common potent compounds toward Pim-1 kinase. The results obtained in this work encourage further work in the future since many compounds were considered as promising anticancer agents.

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