Bioorganic Chemistry 68 (2016) 80–89

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

# *In silico* binding analysis and SAR elucidations of newly designed benzopyrazine analogs as potent inhibitors of thymidine phosphorylase

Muhammad Taha [a,b,*], Nor Hadiani Ismail [a,b], Syahrul Imran [a,b], Fazal Rahim [d], Abdul Wadood [c], Laode Muhammad Ramadhan Al Muqarrabun [a,b], Khalid Mohammed Khan [e], Mehreen Ghufran [c], Muhammad Ali [f]

[a] *Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor, Malaysia*
[b] *Faculty of Applied Science, Universiti Teknologi MARA (UiTM), 40450 Shah Alam, Selangor, Malaysia*
[c] *Department of Biochemistry, Computational Medicinal Chemistry Laboratory, UCSS, Abdul Wali Khan University Mardan, Pakistan*
[d] *Department of Chemistry, Hazara University, Mansehra 21300, Khyber Pukhtunkhwa, Pakistan*
[e] *H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan*
[f] *Department of Chemistry, COMSATS Institute of Information Technology, University Road, Abbottabad 22060, KPK, Pakistan*

ARTICLE INFO

*Article history:*
Received 4 May 2016
Revised 21 July 2016
Accepted 25 July 2016
Available online 25 July 2016

*Keywords:*
Benzopyrazine
Synthesis
Thymidine phosphorylase inhibition
Molecular docking
SAR

ABSTRACT

Thymidine phosphorylase (TP) is up regulated in wide variety of solid tumors and therefore presents a remarkable target for drug discovery in cancer. A novel class of extremely potent TPase inhibitors based on benzopyrazine (**1–28**) has been developed and evaluated against thymidine phosphorylase enzyme. Out of these twenty-eight analogs eleven (**11**) compounds **1, 4, 14, 15, 16, 17, 18, 19, 20, 24** and **28** showed potent thymidine phosphorylase inhibitory potentials with $IC_{50}$ values ranged between 3.20 ± 0.30 and 37.60 ± 1.15 μM when compared with the standard 7-Deazaxanthine ($IC_{50}$ = 38.68 ± 4.42 μM). Structure-activity relationship was established and molecular docking studies were performed to determine the binding interactions of these newly synthesized compounds. Current studies have revealed that these compounds established stronger hydrogen bonding networks with active site residues as compare to the standard compound 7DX.



## 1. Introduction

Thymidine phosphorylase (EC 2.4.2.4) is an angiogenic factor that exerts its effect by stimulating the endothelial cell migration. Thymidine phosphorylase (TP) enzyme similar to platelet derived endothelial cell growth factor [1–5], catalyzes the reversible phosphorolysis of thymidine to thymine and 2-deoxy-α-D-ribofuranosylphosphate. In contrast to non-neoplastic tissues, high level of TP have been found in ovarian, colorectal, breast, and pancreatic tumors [6,7] and in other hyperproliferative disease states such as rheumatoid arthritis [8] and psoriasis [9]. Abnormal level of thymidine phosphorylase is communicated with various pathological disorders including gastric carcinoma, pancreatic, uterine sarcoma, colon carcinoma, renal carcinoma, uterine leiomyoma, breast and lung cancers, astrocytic tumors, gastric carcinoma, carcinoma of stomach, colon, and bladder, atherosclerosis and numerous inflammatory diseases [10]. The inhibition of TP may result in the reduction of tumor growth and metastasis [11–14].

Physically, the most potent TP inhibitors are pyrimidine derivatives, which were planned to interact with the binding site of thymidine. The most potent inhibitor of TP established so far is the 5-chloro-6-[1-(2-iminopyrrolidinyl)methyl] uracil hydrochloride (TPI) [15] that showed hefty inhibitory potential with $IC_{50}$ value of 0.035 mM [16]. Further some purine derivatives like 7-deazaxanthine (7DX) [9] (Fig. 1) have also been found to exhibit inhibitory potentials against TP. However, 7DX ($IC_{50}$ value = 40 mM [17]) is not as potent as TPI, however, additional structural variations may lead to more potent purine-like TP inhibitors. In addition, some multi-substrate inhibitors designed for interacting with both the thymidine and phosphate-binding site in the literature has been reported [18–20].

Benzopyrazine (quinoxaline) and its analogs are significant nitrogen possessing heterocyclic compounds with numerous pharmaceutical applications. Substituted benzopyrazine derivatives possess broad range of biological potentials that include antibacterial [21,22], anticancer [23], antifungal [24,25], antileishmanial

* Corresponding author at: Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor, Malaysia.
*E-mail addresses:* taha_hej@yahoo.com, muhamm9000@puncakalam.uitm.edu.my (M. Taha).

http://dx.doi.org/10.1016/j.bioorg.2016.07.010
0045-2068/

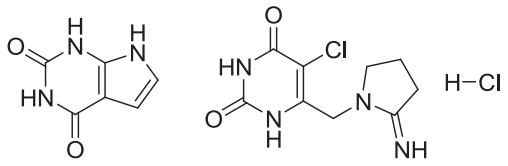



**Fig. 1.** (a) 7DX. (b) TPI.

[26], antitubercular [27], antidepressant activities [28,29] and antimalarial [30,31]. Some of these analogs have also been reported to show antimicrobial [32,33] potent antithrombotic [34], and anti-inflammatory potential [35,36]. The quinoxaline or benzopyrazine is also described as a bioisoster of quinoline, benzothiophene, naphthalene and other aromatic rings such as pyrazine and pyridine. Benzopyrazines have also found application in the field of agriculture as herbicide, fungicide and insecticide [37]. Quinoxaline scaffolds are further present in the structure of several antibiotics such as levomycin, echinomycin, and actinoleutin that inhibit the growth of gram positive bacteria and active against various transplantable tumors [38]. Some of benzopyrazine derivatives have also certain applications in dyes [39].

Literature has revealed that the addition of second ring, *i.e.* pyrrole, in the design of standard inhibitor 7DX creates extra stabilizing interactions by filling the apparent space near the ring of residue Phe210. This modification lead 7DX a novel prototype inhibitor of TPase [40]. Current study involves the designing of new and novel inhibitors based on benzopyrazine nucleus. Benzopyrazine nucleus has replaced 5-membered pyrrole moiety of 7DX with a 6-membered pyrazine heterocyclic moiety; the fact that 7DX contains a second (pyrrole) ring entity in the molecule may open interesting perspectives in the design of new more potent inhibitors. Second, pyrimidine ring in 7DX has been replaced with an unsubstituted benzene ring just to provide a space or cavity filling in the enzyme pocket site. In the newly developed scaffolds; however, the stress has been given on more nitrogen atoms to create extra hydrogen bonding sites. We are currently heterocyclic hybrid molecules [41] and we found that the hybrid compounds are more potent than their individual molecules. We believe that introduction of unsubstituted aromatic moiety together with another fused 6-mebered heterocyclic system instead of 5-membered pyrrole ring should create extra stabilizing interactions by filling the apparent space near the ring of residue Phe210 more effectively. Herein, we report novel benzopyrazine analogs as new leads against TPase and their comparison with the standard inhibitor 7DX with particular reference to molecular docking analysis.

## 2. Results and discussion

### 2.1. Chemistry

In the continuation of our work on heterocyclic hydrazones [42–50]; in this study benzopyrazine derivatives **1–28** (Table 1) were synthesized by reacting benzopyrazine hydrazide (**a**) with various aromatic aldehydes in the presence of catalytic amount of acetic acid (Scheme 1). The structures of the benzopyrazine hydrazones **1–28** were fully characterized by using various spectroscopic techniques such as NMR, MS and were further confirmed using CHN analysis.

### 2.2. Biological activity

The benzopyrazine class of heterocycles should be considered as new lead inhibitors with much more pronounced inhibitory potentials against thymidine phosphorylase and angiogenesis as compared to 7DX. To the best of our knowledge, benzopyrazine analogs are first one to be recognized as efficient inhibitors of the pyrimidine nucleoside phosphorylase, *i.e.* TPase, while these analogs possess the strong and convincing potential in the future design of new TPase inhibitors. The inhibitory potentials noted for benzopyrazine analogs against TPase demonstrated to be at much higher levels in magnitude when compared with 7DX. All synthesized compounds **1–28** were evaluated against thymidine phosphorylase inhibition according to a literature known procedure [51]. The inhibitory potential of compounds were shown in terms of $IC_{50}$ values and were compared with the reference inhibitor, 7-Deazaxanthine, 7DX, ($IC_{50}$ = 38.68 ± 4.42 μM). Out of these twenty-eight analogs eleven (**11**) compounds such as **1, 4, 14, 15, 16, 17, 18, 19, 20, 24** and **28** showed potent thymidine phosphorylase inhibition when compared with the standard. Compound **13** and **21** showed good thymidine phosphorylase inhibition. While compound **2, 3, 5, 6, 12** and **27** exhibit good to moderate inhibition (Table 1).

Structure-activity relationship (SAR) suggested that TP inhibitory potential mainly based on substituent pattern on phenyl ring. We observed during this study that all those analogs having hydroxyl group on phenyl ring showed potent inhibition. Among the hydroxyl containing analogs, those analogs having trihydroxyl functionality such as **18** and **19** are superior to dihydroxy analogs *i.e.* **14**, **15**, and **16** except analog **17**. Further decline in inhibitory potential was observed in monohydroxyl analogs such as **12**, **13**, **20**, **21**, **24** and **28**. The greater potential showed by all these analogs might be due to the hydroxyl groups, which may interact with the enzyme through hydrogen bonding. We observed here that the number and position of hydroxyl group on phenyl ring also affect the inhibitory potential of compounds. The greater potential shown by compound **18** than **17**, which is >**19** on the basis of hydroxyl position 2′ < 4′ < 3′. Similarly compound **14** a 2,3-dihydroxy analog, **15** a 2,4-dihydroxy analog and **16** a 2,5-dihydroxy analog with $IC_{50}$ value 15.40 ± 1.04, 33.40 ± 1.20 and 35.50 ± 1.25 μM respectively showed potent inhibition. The slight activity difference among these analogs showed that position of hydroxyl group on aromatic ring also affects the inhibition. In mono hydroxylated analogs like **12**, a *meta* hydroxyl analog, **13**, a *para* hydroxyl analog, and **28** a *ortho* hydroxyl analog with $IC_{50}$ value 63.20 ± 2.2.1, 48.60 ± 1.17 and 37.16 ± 1.16, it was observed that the position of hydroxyl group also play an important role in this inhibition.

We have also check the effect of other substituents like flouro (analogs **1, 2, 3**) the order of activity was 2-F > 4-F > 3-F. The chloro (analogs **4, 5, 6**) inhibition pattern is observed similar as for flouro analogs 2-Cl > 4-Cl > 3-Cl. The nitro and methyl substituted analogs were found to completely inactive. For the confirmation of the binding interaction, molecular docking analysis was carried out.

### 2.3. Molecular modeling and docking studies

The synthesized compounds were docked into the active site of the target enzyme using MOE with the default parameters i.e. Placement: Triangle Matcher, Rescoring 1: London dG, Refinement: Forcefield, Rescoring 2: London dG. In order to validate the docking protocol, the 3D crystal structure of the thymidine phosphorylase complex with analog of DIDEOXYURIDINE was retrieved from the protein databank PDB ID: 4EAD and redocked in the active site of the enzyme. The ligand binding site for docking was defined as a collection of amino acids enclosed within a sphere of 4.5 Å radius around the coordinates of the ligand, which is the inhibitor molecule present in the binding site of thymidine phosphorylase. For each ligand ten conformations were generated and the top

**Table 1**
Synthesis of various analogs of quinoxaline derivatives **(1–28)** and its thymidine phosphorylase inhibition.

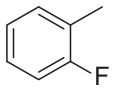
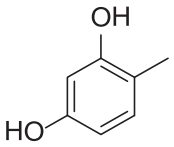
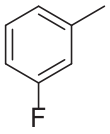
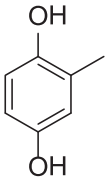
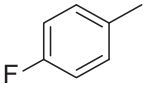
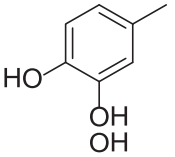
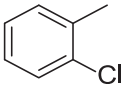
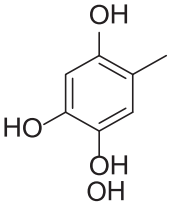
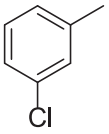
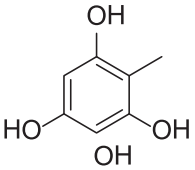
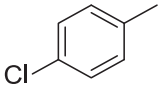
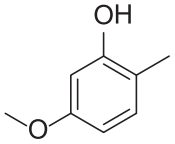
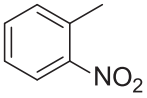
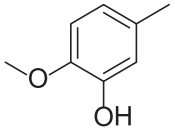
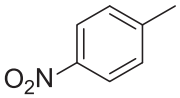
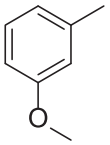
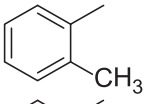
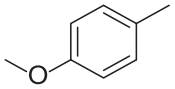
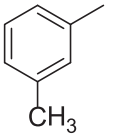
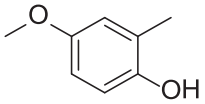
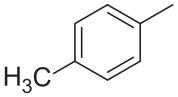
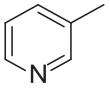
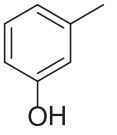
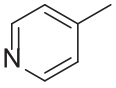
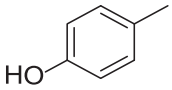
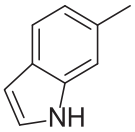
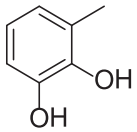
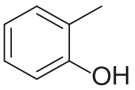
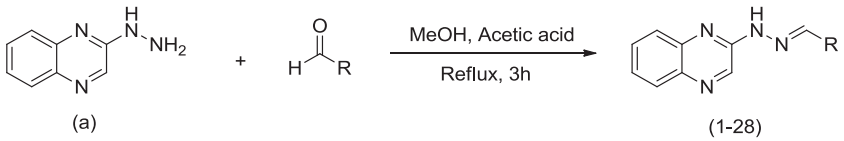
| S. No. | R | $IC_{50}$ (μM ± $SEM_a$) | S. No. | R | $IC_{50}$ (μM ± $SEM_a$) |
|---|---|---|---|---|---|
| 1 |  | 33.60 ± 1.01 | 15 |  | 33.40 ± 1.20 |
| 2 |  | 66.12 ± 2.22 | 16 |  | 35.50 ± 1.25 |
| 3 |  | 58.10 ± 1.10 | 17 |  | 8.60 ± 0.42 |
| 4 |  | 37.60 ± 1.15 | 18 |  | 3.20 ± 0.30 |
| 5 |  | 93.50 ± 2.30 | 19 |  | 9.10 ± 0.44 |
| 6 |  | 73.40 ± 2.28 | 20 |  | 34.40 ± 1.26 |
| 7 |  | N.A. | 21 |  | 46.90 ± 1.14 |
| 8 |  | N.A. | 22 |  | N.A. |
| 9 |  | N.A. | 23 |  | N.A. |
| 10 |  | N.A. | 24 |  | 36.26 ± 1.30 |
| 11 |  | N.A. | 25 |  | N.A. |
| 12 |  | 63.20 ± 2.2.1 | 26 |  | N.A. |

**Table 1** (*continued*)

| S. No. | R | $IC_{50}$ (μM ± $SEM_a$) | S. No. | R | $IC_{50}$ (μM ± $SEM_a$) |
|---|---|---|---|---|---|
| 13 |  | 48.60 ± 1.17 | 27 |  | 84.26 ± 3.20 |
| 14 |  | 15.40 ± 1.04 | 28 |  | 37.16 ± 1.16 |
| 7-Deazaxanthine (7DX) | | | 38.68 ± 4.42 μM | | |




**Scheme 1.** Synthesis of quinoxaline derivatives **(1–28)**.

ranked conformation on the basis of docking score was selected for further studies in molecular docking. The RMSD between docked and co-crystallized ligand was found to be 1.89 Å indicates that the docking method is reliable [41]. The superposition of docked and co-crystallized ligands is shown in Fig. 2. After the molecular docking we analyzed the best poses having polar and π-π interactions by Pymol software.

In order to explore the binding mode of these newly synthesized compounds, molecular docking was performed. The docking results showed that all the compounds well accommodated in the active site of thymidine phosphorylase (Fig. 3a). The predicted docking scores and interactions of these compounds are well correlated with the observed experimental results (Tables 1 and 2) as the most active compounds showed good docking score and good interaction as compare to less active compounds. From the docking conformation of the most active compound, compound **18 ($IC_{50}$ = 3.20 ± 0.30)**, it was observed that this compound established six hydrogen bonds and one arene-arene interactions with active site residues and good docking score (−**13.8359**) as compare to the standard inhibitor (7-Deazaxanthine) having docking score

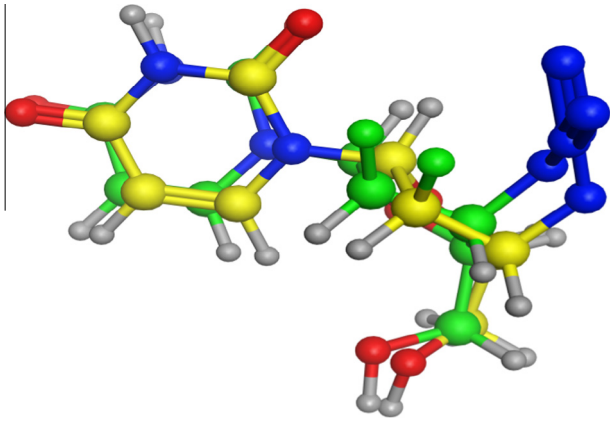


**Fig. 2.** Superposition of docked and co-crystallized ligand, green represents the co crystallized ligand and yellow the re-docked conformation of the ligand.

of −**7.5093** and biological activity with $IC_{50}$ of **38.68 ± 4.42**. The three hydroxyl moieties present at the phenyl ring of the compound formed five hydrogen bonds with His 85, Tyr 168, Arg 171, Ser 186 and Lys 190 respectively. Furthermore, nitrogen atom of the quinoxaline ring formed hydrogen bond with active site residue Gly 88 whereas the phenyl ring of the compound formed arene-arene interaction with phenyl ring of the Tyr 168 (Fig. 3b). This strong bonding network might be one of the reasons for this compound to show good biological activity. The docking conformation of the second most active compound, compound **17** (**$IC_{50}$ = 8.60 ± 0.42**), showed that this compound formed five hydrogen bonds with the active site residues Arg115, Thr 120, Thr 168, Ser 186 and Lys 190 respectively (Fig. 3c) and good docking score **(−10.0389)**. If we compare the structure of compound **17** with the structure of compound **18** the only difference is the presence of one more hydroxyl moiety in compound **18**. The extra hydroxyl moiety might be one the reasons for the good biological activity of compound **18** as compare to compound **17**. The docking results showed that comparatively good interactions were observed for compound **18** than compound **17** (Fig. 3b and c). In case of compounds having only one hydroxyl group (compound **12** and **13**) on phenyl ring showed less biological activities and poor interactions with active site residues. For example, compound **12** has **$IC_{50}$ = 63.20 ± 2.21** and docking score **(−8.8330)**, showed only two hydrogen bonds with active site residues (Fig. 3d). Like the number of hydroxyl moiety the position of hydroxyl moiety also play a role in the activity of these compounds. For example, although compound **19**, the third most active compound in the series has good inhibitory activity with $IC_{50}$ value **9.10 ± 0.44** and docking score i.e. −**9.7813**, have three hydroxyl groups but at different positions as in compound **18**. This different positions of hydroxyl moieties in compounds **19** (Fig. 4a), made this compound to established poor interactions with the active site residues and showed less biological activity as compare to compound **18**. About similar experimental and docking results were observed for compounds **20**, **21** and **24**.

In case of compounds having fluoro or chloro phenyl ring, it was observed that when fluorine or chlorine present at *ortho* position of phenyl ring (compound **1** and compound **4**) showed good interactions as compare to compounds having fluorine or chlorine moiety

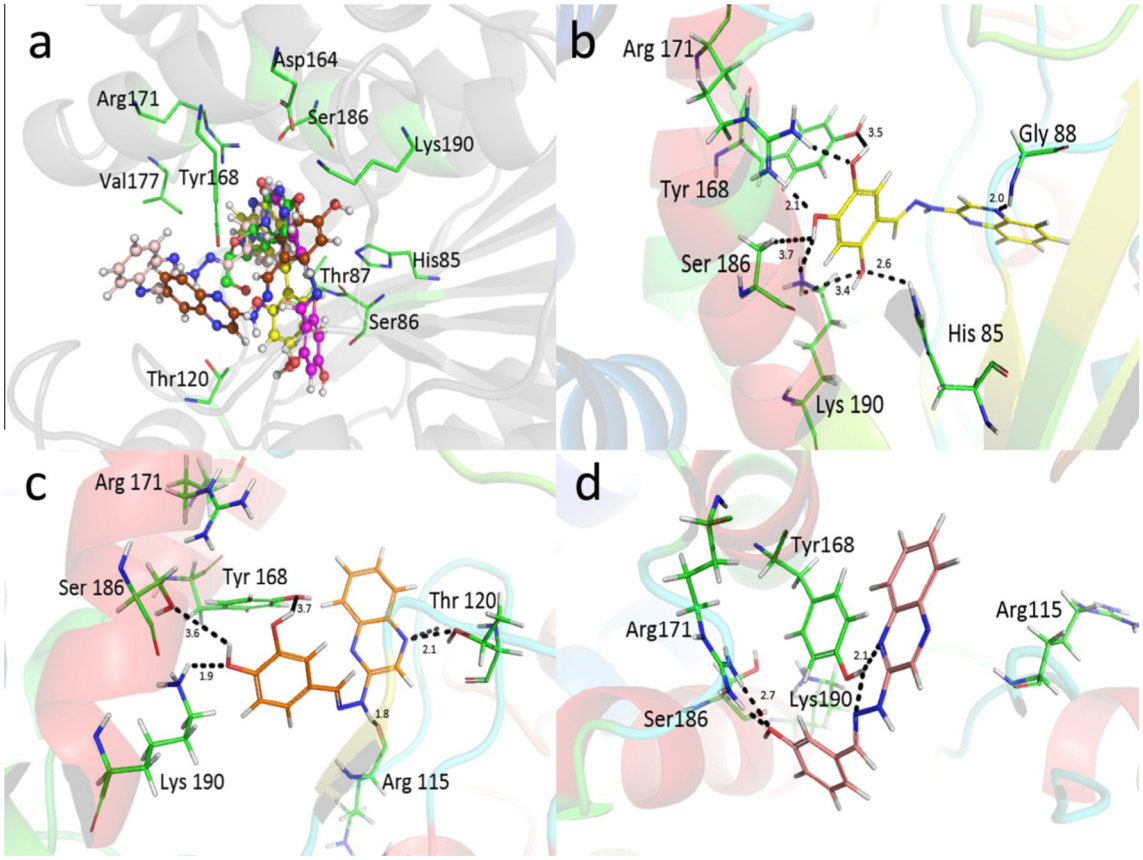



**Fig. 3.** (a) Docking conformations of different ligands, (b) docking conformation of compound **18**, (c) docking conformation of compound **17** and (d) docking conformation of compound **12** in the active site of thymidine phosphorylase.

**Table 2**
Predicted docking scores and interactions of the compounds **1–28**.

| Compound | Docking scores | Number of HBs | No. of arene-arene interactions | No. of arene-cation interactions |
|---|---|---|---|---|
| **1** | −8.6575 | 2 (Tyr168) | – | 1 (Lys190) |
| **2** | −7.9256 | – | – | 1 (Lys190) |
| **3** | −7.9994 | – | – | 1 (Lys190) |
| **4** | −8.0696 | 1 (Lys190) | 1 (Phe210) | 1 (Lys190) |
| **5** | −6.0817 | – | – | 1 (Lys190) |
| **6** | −7.0607 | – | – | 2 (Lys190) |
| **12** | −8.8330 | 2 (Tyr168, Arg171) | – | – |
| **13** | −7.5155 | – | – | 1 (Lys190) |
| **14** | −9.0315 | 2 (Ser86, Tyr168,) | 1 (Phe210) | – |
| **15** | −9.2134 | 1 (Tyr168) | – | 1 (Lys190) |
| **16** | −8.1358 | 1 (Arg115) | – | – |
| **17** | −10.0389 | 5 (Arg115, Thr120, Tyr168, Ser186, Lys 190) | – | – |
| **18** | −13.8359 | 6 (His85, Tyr168, Ser186, Arg171, Lys190) | 1 (Tyr168) | – |
| **19** | −9.7813 | 3 (Gln156, Arg171, (Lys190)) | 1 (Tyr168) | – |
| **20** | −8.1737 | – | 1 (Tyr168) | 1 (Lys190) |
| **21** | −8.0450 | 1 (Tyr168) | 1 (Phe210) | 1 (Lys190) |
| **24** | −8.1296 | 1 (Ser186) | – | – |
| **27** | −6.6362 | – | 1 (Tyr168) | – |
| **28** | −8.0315 | – | – | 1 (Lys190) |

at *meta* or *para* position of phenyl ring (compound **2**, **3**, **5** and **6**). For example, compound **1** has $IC_{50}$ = **33.60 ± 1.01** and docking score of −**8.6575**, showed good interactions with active site residues (Fig. 4b) as compare to compound **2** with $IC_{50}$ of **66.12 ± 2.22** and docking score of −**7.9256** (Fig. 4c). About similar docking results were observed for compound **4**, **5** and **6**. From the docking results of the inactive compounds e.g. compound **22** having no biological activity (Table 1), it was observed that these compounds showed very poor interactions with active site residues (Fig. 4d) and poor docking score. The steric hindrance or low polarizability might be one the reasons for these compounds to show no biological activity.

The binding mode of the standard compound (7-Deazaxanthine; 7DX) showed that this compound established three polar and one arene-arene interaction with active site residues of the enzyme (Fig. 5). If we compare the binding interactions of this compound with most active compounds of the series (**17, 18**, and **19,** etc.) it was observed that these compounds established

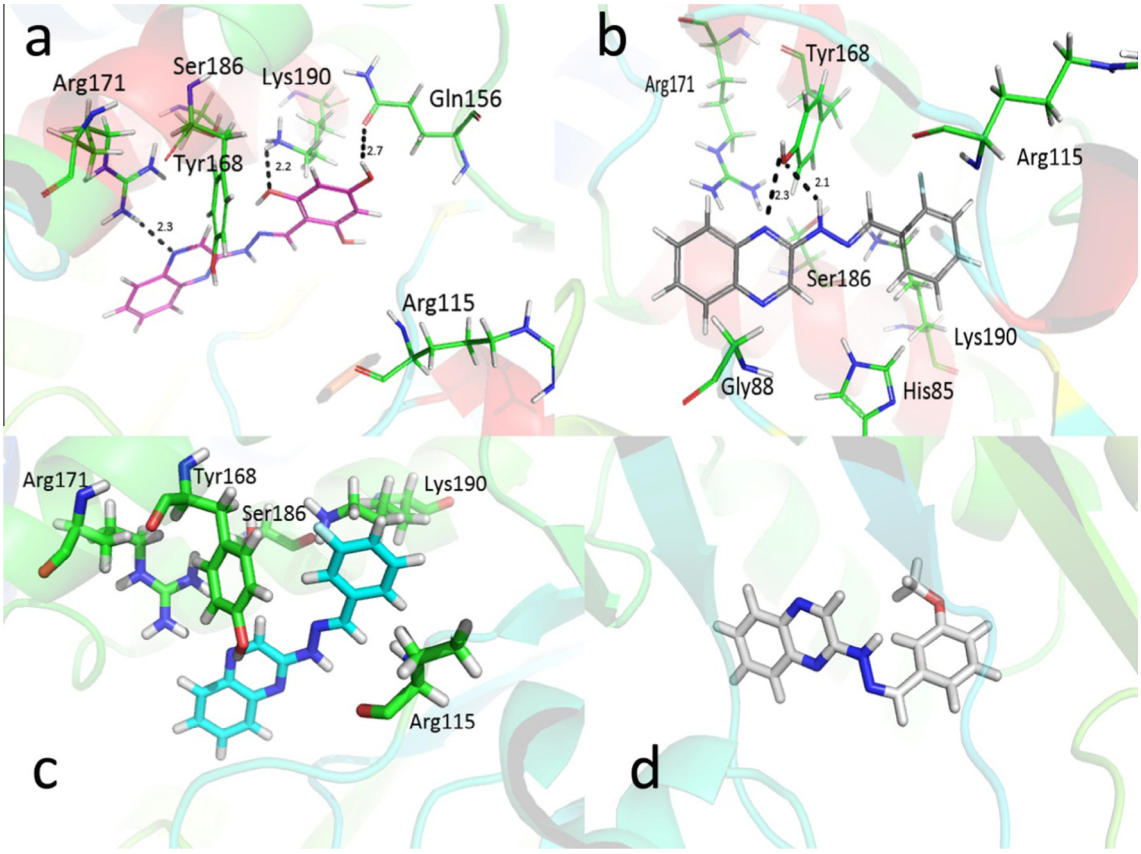



**Fig. 4.** Docking conformation of compound **19** (a), compound **1** (b), **2** (c) and **22** (d) in the active site of thymidine phosphorylase.

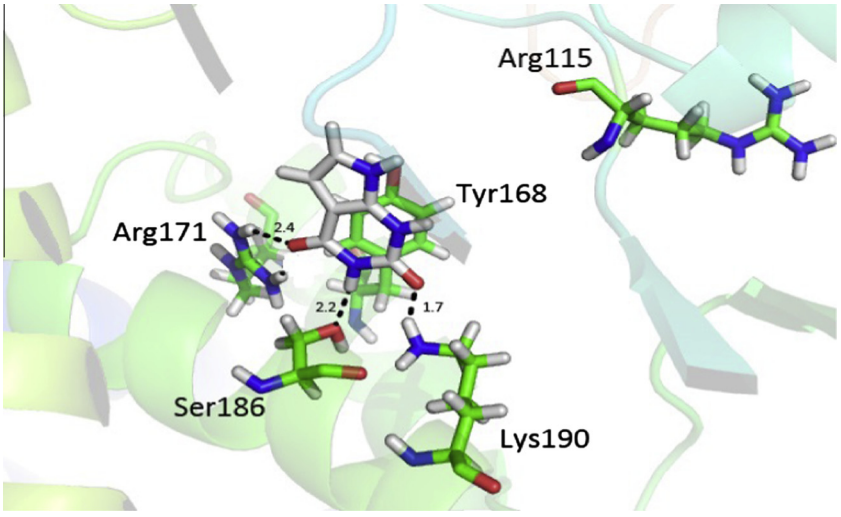



**Fig. 5.** Docking conformation of standard inhibitor (7-Deazaxanthine) in the active site of thymidine phosphorylase.

strong hydrogen bonding network with active site residues as compare to the standard compound (Figs. 3b, 3c, 4a and 5). These strong bonding interactions might be one of the reasons for these compounds to be more active as compare to the standard compound.

Over all the docking results showed that the number as well as positions of hydroxyl moiety on phenyl ring of these newly synthesized compounds plays a key role in their biological activities.

## 3. Conclusion

In conclusion we have synthesized benzopyrazine analogs **1–28**, characterized by EI-MS and $^{1}$H NMR and checked for thymidine phosphorylase inhibitory potentials. Eleven compounds were identified as potent thymidine phosphorylase inhibitor. Compounds **1, 4, 14, 15, 16, 17, 18, 19, 20, 24** and **28** showed potent thymidine phosphorylase inhibition. Subsequent molecular

docking studies were performed to determine the binding interaction of the compounds. These analogs offer the possibility of convenient further modifications that could give rise to further optimized lead structures with improved pharmacokinetic properties and selectivity towards the enzyme.

## 4. Material and methods

NMR experiments were performed on Avance Bruker AM 300 MHz machine. CHN Analysis was performed on a Carlo Erba Strumentazion-Mod-1106, Italy. Ultraviolet (UV) spectra were recorded on Perkin–Elmer Lambda-5 UV/vis spectrophotometer in MeOH. Infrared (IR) spectra were recorded on JASCO IR-A-302 spectrometer as KBr (disc). Electron impact mass spectra (EI MS) were recorded on a Finnigan MAT-311A (Germany) mass spectrometer. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm.

### 4.1. Preparation of ligands

All the twenty-eight synthesized inhibitors of the thymidine phosphorylase were built in MOE (Molecular Operating Environment) software. The synthesized ligands were energy minimized by using the default parameters of the MOE i.e. gradient: 0.05, Force Field: MMFF94X and saved all the ligands in mdb file for further assessment in molecular docking.

### 4.2. Preparation of protein

The 3D crystal structure of the thymidine phosphorylase was retrieved from the protein databank PDB ID: 4EAD. All the water molecules and ions from the target protein were removed. The energy minimization was carried out after the 3D protonation by the default parameters of the MOE for the stability of the protein.

### 4.3. Thymidine phosphorylase assay

Since human TP is not easily to get, we used commercially available recombinant *E. coli* TP. Main sequence of TP is frequently preserved throughout evolution as mammalian TP is reported to share 39% sequence resemblance with the TP of *E. coli*. The mammalian enzyme as well shared up to 70% resemblance with the active site residues, and three dimensional structure of *E. coli* TP enzyme. The Thymidine phosphorylase/PD-ECGF (*E. coli*) activity was determined by measuring the absorbance at 290 nm spectrophotometrically. In brief, total reaction mixture of 200 μL contained 145 μL of potassium phosphate buffer (pH 7.4), 30 μL of enzyme (*E. coli*) at concentration 0.05 and 0.002 U, respectively, were incubated with 5 μL of test materials for 10 min at 25 °C in microplate reader. After incubation, pre read at 290 nm was taken to deduce the absorbance of substrate particles. Substrate (20 μL, 1.5 mM), was dissolved in potassium phosphate buffer, was immediately added to plate and continuously read after 10, 20, and 30 min in microplate reader (spectra max, molecular devices, CA, USA). All assays were performed in triplicate.

#### 4.3.1. Calculations

Reactions for above mentioned biological activities were carried out in triplicate. Results were then processed using SoftMax Pro 4.8 software (Molecular Devices, CA, USA) and then by Microsoft Excel. Percent inhibition for above mentioned biological activities was calculated by following formula:

$$\text{Percent Inhibition} = 100 - (\text{OD}_{\text{test compound}}/\text{OD}_{\text{control}}) \times 100$$

### 4.4. General procedure for the synthesis of compounds **1–28**

Equimolar quantities (1 mmol) of compound **5** and substituted benzaldehydes (1 mmol) in methanol (25 mL) were refluxed for 3 h, in the presence of catalytic amount of glacial acetic acid. The resulting solid was filtered and recrystallized from methanol in good yields.

#### 4.4.1. (E)-2-(2-(2-fluorobenzylidene)hydrazinyl)quinoxaline (**1**)

Yield: 94%. m.p.: 239–241 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.83 (s, 1H), 9.13 (s, 1H), 8.35 (s, 1H), 8.09 (t, $J$ = 7.6 Hz, 1H), 7.94 (d, $J$ = 8.2 Hz, 1H), 7.76–7.64 (m, 2H), 7.59–7.40 (m, 2H), 7.35–7.24 (m, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 163.7; 161.3; 150.2; 140.8; 138.0; 137.3; 136.4; 130.8; 130.3; 128.8; 126.2; 125.3; 122.9; 115.9; 112.4. HREI-MS: $m/z$ calcd for $C_{15}H_{11}FN_4$ [M]+ 266.0968; Found 266.0972; Anal. Calcd for $C_{15}H_{11}FN_4$, C, 67.66; H, 4.16; N, 21.04; Found C, 67.67; H, 4.15; N, 21.05. IR (cm$^{-1}$, KBr): 3460 (NH); 1582 (C=N).

#### 4.4.2. (E)-2-(2-(3-fluorobenzylidene)hydrazinyl)quinoxaline (**2**)

Yield: 71%. m.p.: 239–240 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.81 (s, 1H), 9.16 (s, 1H), 8.14 (s, 1H), 7.93 (d, $J$ = 8.1 Hz, 1H), 7.70 (dt, $J$ = 6.6, 3.9 Hz, 2H), 7.65 (d, $J$ = 10.2 Hz, 1H), 7.59 (d, $J$ = 7.7 Hz, 1H), 7.54–7.46 (m, 2H), 7.22 (td, $J$ = 8.3, 2.3 Hz, 1H); 7.28 (2H, m, H2′) and (H4′ or H6′). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 161.2; 159.2; 150.1; 140.8; 138.0; 136.3; 134.3; 131.0; 130.4; 128.8; 126.2; 125.4; 124.9; 122.2; 115.8 ppm. HREI-MS: $m/z$ calcd for $C_{15}H_{11}FN_4$ [M]+ 266.0968; Found 266.0961; Anal. Calcd for $C_{15}H_{11}FN_4$, C, 67.66; H, 4.16; N, 21.04; Found C, 67.64; H, 4.17; N, 21.03. IR (cm$^{-1}$, KBr): 3443 (NH); 1580 (C=N).

#### 4.4.3. (E)-2-(2-(4-fluorobenzylidene)hydrazinyl)quinoxaline (**3**)

Yield: 87%. m.p.: 217–219 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.68 (s, 1H), 9.11 (s, 1H), 8.15 (s, 1H), 7.92 (d, $J$ = 8.2 Hz, 1H), 7.84 (dd, $J$ = 8.4, 5.8 Hz, 2H), 7.76–7.63 (m, 2H), 7.61–7.46 (m, 1H), 7.28 (t, $J$ = 8.8 Hz, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 162.35, 146.39, 143.94, 143.79, 141.92, 139.04, 131.58, 130.53, 130.53, 130.10, 129.21, 127.32, 115.42, 115.42, 115.12. HREI-MS: $m/z$ calcd for $C_{15}H_{11}FN_4$ [M]+ 266.0968; Found 266.0974; Anal. Calcd for $C_{15}H_{11}FN_4$, C, 67.66; H, 4.16; N, 21.04; Found C, 67.64; H, 4.18; N, 21.06. IR (cm$^{-1}$, KBr): 1583 (C=N).

#### 4.4.4. (E)-2-(2-(2-chlorobenzylidene)hydrazinyl)quinoxaline (**4**)

Yield: 79%. m.p.: 210–211 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.92 (s, 1H), 9.13 (s, 1H), 8.53 (s, 1H), 8.17 (dd, $J$ = 7.5, 1.8 Hz, 1H), 7.94 (d, $J$ = 8.2 Hz, 1H), 7.76–7.65 (m, 2H), 7.60–7.48 (m, 2H), 7.48–7.37 (m, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.1; 140.8; 138.0; 137.6; 136.4; 132.2; 131.9; 130.5; 130.3; 129.8; 128.8; 127.5; 126.6; 126.3; 125.4 ppm. HREI-MS: $m/z$ calcd for $C_{15}H_{11}ClN_4$ [M]+ 282.0672; Found 282.0678; Anal. Calcd for $C_{15}H_{11}ClN_4$, C, 63.72; H, 3.92; N, 19.82; Found C, 63.74; H, 3.91; N, 19.83. IR (cm$^{-1}$, KBr): 1584 (C=N).

#### 4.4.5. (E)-2-(2-(3-chlorobenzylidene)hydrazinyl)quinoxaline (**5**)

Yield: 82%. m.p.: 235 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.87 (s, 1H), 9.16 (s, 1H), 8.92 (s, 1H), 8.57 (d, $J$ = 4.4 Hz, 1H), 8.23 (d, $J$ = 7.9 Hz, 1H), 8.18 (s, 1H), 7.94 (d, $J$ = 8.2 Hz, 1H), 7.70 (q, $J$ = 8.4 Hz, 2H), 7.52 (t, $J$ = 6.8 Hz, 1H), 7.48 (dd, $J$ = 7.9, 4.8 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.2; 140.8; 140.2; 138.0; 137.0; 136.5; 133.7; 130.6; 130.3; 128.8; 127.1; 126.2; 125.7; 125.3; 125.2 ppm. HREI-MS: $m/z$ calcd for $C_{15}H_{11}ClN_4$ [M]+ 282.0672; Found 282.0679; Anal. Calcd for $C_{15}H_{11}ClN_4$, C, 63.72; H, 3.92; N, 19.82; Found C, 63.73; H, 3.93; N, 19.80. IR (cm$^{-1}$, KBr): 1587 (C=N).

*4.4.6. (E)-2-(2-(3-chlorobenzylidene)hydrazinyl)quinoxaline (**6**)*

Yield: 89%. m.p.: 249–250 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.76 (s, 1H), 9.11 (s, 1H), 8.13 (s, 1H), 7.92 (d, $J$ = 8.1 Hz, 1H), 7.80 (d, $J$ = 8.5 Hz, 2H), 7.73–7.65 (m, 2H), 7.55–7.47 (m, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.2; 140.8; 140.4; 138.0; 136.4; 133.6; 133.5; 130.3; 128.8; 128.7; 128.1; 126.2; 125.2 ppm. HREI-MS: $m/z$ calcd for $C_{15}H_{11}ClN_4$ [M]+ 282.0672; Found 282.06774; Anal. Calcd for $C_{15}H_{11}ClN_4$, C, 63.72; H, 3.92; N, 19.82; Found C, 63.74; H, 3.91; N, 19.81. IR (cm$^{-1}$, KBr): 1578 (C=N).

*4.4.7. (E)-2-(2-(2-nitrobenzylidene)hydrazinyl)quinoxaline (**7**)*

Yield: 81%. m.p.: 220–221 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.05 (s, 1H), 9.09 (s, 1H), 8.52 (s, 1H), 8.26 (d, $J$ = 7.7 Hz, 1H), 8.03 (d, $J$ = 8.1 Hz, 1H), 7.94 (d, $J$ = 8.1 Hz, 1H), 7.78 (t, $J$ = 7.6 Hz, 1H), 7.72 (dd, $J$ = 7.8, 7.2 Hz, 1H), 7.68 (d, $J$ = 7.5 Hz, 1H), 7.61 (t, $J$ = 7.5 Hz, 1H), 7.52 (t, $J$ = 7.4 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.0; 147.6; 140.7; 138.2; 136.5; 136.3; 133.3; 130.4; 129.6; 128.8; 128.7; 127.9; 126.4; 125.6; 124.5 ppm. HREI-MS: $m/z$ calcd for $C_{15}H_{11}N_5O_2$ [M]+ 293.0913; Found 293.0919; Anal. Calcd for $C_{15}H_{11}N_5O_2$, C, 61.43; H, 3.78; N, 23.88; Found C, 61.44; H, 3.76; N, 23.86. IR (cm$^{-1}$, KBr): 3489 (NH); 1580 (C=N); 1512 and 1344 ($NO_2$).

*4.4.8. (E)-2-(2-(4-nitrobenzylidene)hydrazinyl)quinoxaline (**8**)*

Yield: 85%. m.p.: 270–271 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.08 (s, 1H), 9.18 (s, 1H), 8.28 (d, $J$ = 8.3 Hz, 2H), 8.23 (s, 1H), 8.04 (d, $J$ = 8.4 Hz, 2H), 7.96 (d, $J$ = 8.2 Hz, 1H), 7.78–7.66 (m, 2H), 7.54 (t, $J$ = 7.3 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.0; 147.1; 141.2; 140.7; 139.1; 138.2; 136.4; 130.4; 128.8; 127.2; 126.4; 125.7; 124.0 ppm. HREI-MS: $m/z$ calcd for $C_{15}H_{11}N_5O_2$ [M] + 293.0913; Found 293.0906; Anal. Calcd for $C_{15}H_{11}N_5O_2$, C, 61.43; H, 3.78; N, 23.88; Found C, 61.42; H, 3.76; N, 23.85. IR (cm$^{-1}$, KBr): 3412 (NH); 1578 (C=N); 1510 and 1340 ($NO_2$).

*4.4.9. (E)-2-(2-(2-methylbenzylidene)hydrazinyl)quinoxaline (**9**)*

Yield: 91%. m.p.: 162–163 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.65 (s, 1H), 9.08 (s, 1H), 8.42 (s, 1H), 7.92 (d, $J$ = 8.4 Hz, 2H), 7.68 (q, $J$ = 8.0 Hz, 2H), 7.49 (t, $J$ = 7.0 Hz, 1H), 7.39–7.12 (m, 3H), 2.47 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.3; 140.9; 140.9; 137.9; 136.4; 136.0; 132.6; 130.9; 130.3; 128.9; 128.8; 126.5; 126.2; 126.0; 125.1; 19.4. HREI-MS: $m/z$ calcd for $C_{16}H_{14}N_4$ [M]+ 262.1218; Found 262.1225; Anal. Calcd for $C_{16}H_{14}N_4$, C, 73.26; H, 5.38; N, 21.36; Found C, 73.27; H, 5.36; N, 21.34. IR (cm$^{-1}$, KBr): 1591 (C=N).

*4.4.10. (E)-2-(2-(3-methylbenzylidene)hydrazinyl)quinoxaline (**10**)*

Yield: 78%. M.P.: 194–195 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.67 (s, 1H), 9.11 (s, 1H), 8.12 (s, 1H), 7.92 (d, $J$ = 8.2 Hz, 1H), 7.74–7.64 (m, 2H), 7.60 (s, 1H), 7.55 (d, $J$ = 7.6 Hz, 1H), 7.49 (t, $J$ = 7.2 Hz, 1H), 7.34 (t, $J$ = 7.6 Hz, 1H), 7.21 (d, $J$ = 7.4 Hz, 1H), 2.38 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.3; 142.0; 140.9; 138.0; 137.9; 136.4; 134.6; 130.2; 129.9; 128.7; 128.6; 126.9; 126.1; 125.0; 123.8; 20.9 ppm. HREI-MS: $m/z$ calcd for $C_{16}H_{14}N_4$ [M]+ 262.1218; Found 262.1223; Anal. Calcd for $C_{16}H_{14}N_4$, C, 73.26; H, 5.38; N, 21.36; Found C, 73.27; H, 5.36; N, 21.35. IR (cm$^{-1}$, KBr): 3445 (NH); 1595 (C=N).

*4.4.11. (E)-2-(2-(4-methylbenzylidene)hydrazinyl)quinoxaline (**11**)*

Yield: 81%. m.p.: 220–221 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.61 (s, 1H), 9.09 (s, 1H), 8.12 (s, 1H), 7.92 (d, $J$ = 8.1 Hz, 1H), 7.74–7.59 (m, 4H), 7.49 (ddd, $J$ = 8.2, 6.1, 2.2 Hz, 1H), 7.27 (d, $J$ = 7.9 Hz, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.3; 142.0; 141.0; 138.9; 137.8; 136.4; 132.0; 130.3; 129.4; 129.4; 128.8; 126.5; 126.5; 126.1; 125.0; 21.0. HREI-MS: $m/z$ calcd for $C_{16}H_{14}N_4$ [M]+ 262.1218; Found 262.1213; Anal. Calcd for $C_{16}H_{14}N_4$, C, 73.26; H, 5.38; N, 21.36; Found C, 73.27; H, 5.39; N, 21.34. IR (cm$^{-1}$, KBr): 1581 (C=N).

*4.4.12. (E)-3-((2-(quinoxalin-2-yl)hydrazono)methyl)phenol (**12**)*

Yield: 86%. m.p.: 269–270 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.64 (s, 1H), 9.58 (s, 1H), 9.05 (s, 1H), 8.07 (s, 1H), 7.92 (d, $J$ = 7.9 Hz, 1H), 7.73–7.63 (m, 2H), 7.49 (ddd, $J$ = 8.3, 6.3, 2.0 Hz, 1H), 7.25 (t, $J$ = 7.8 Hz, 1H), 7.21–7.19 (m, 1H), 7.15 (d, $J$ = 7.7 Hz, 1H), 6.81 (dd, $J$ = 8.0, 2.4 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 157.7; 150.3; 142.1; 141.0; 137.9; 136.3; 136.0; 130.3; 129.9; 128.8; 126.2; 125.1; 118.0; 116.6; 112.3. HREI-MS: $m/z$ calcd for $C_{15}H_{12}N_4O$ [M]+ 264.1011; Found 264.1018; Anal. Calcd for $C_{15}H_{12}N_4O$, C, 68.17; H, 4.58; N, 21.20; Found C, 68.18; H, 4.56; N, 21.18. IR (cm$^{-1}$, KBr): 1574 (C=N).

*4.4.13. (E)-4-((2-(quinoxalin-2-yl)hydrazono)methyl)phenol (**13**)*

Yield: 95%. m.p.: 257–258 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.46 (s, 1H), 9.82 (s, 1H), 9.05 (s, 1H), 8.06 (s, 1H), 7.90 (d, $J$ = 8.3 Hz, 1H), 7.68–7.63 (m, 2H), 7.60 (d, $J$ = 8.5 Hz, 2H), 7.46 (ddd, $J$ = 8.2, 5.6, 2.7 Hz, 1H), 6.84 (d, $J$ = 8.5 Hz, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 158.7; 150.4; 142.4; 141.1; 137.7; 136.4; 130.2; 128.7; 128.2; 128.2; 126.0; 125.7; 124.7; 115.7; 115.7. HREI-MS: $m/z$ calcd for $C_{15}H_{12}N_4O$ [M]+ 264.1011; Found 264.1017; Anal. Calcd for $C_{15}H_{12}N_4O$, C, 68.17; H, 4.58; N, 21.20; Found C, 68.18; H, 4.59; N, 21.18. IR (cm$^{-1}$, KBr): 3489 (OH); 1599 (C=N).

*4.4.14. (E)-3-((2-(quinoxalin-2-yl)hydrazono)methyl)benzene-1,2-diol (**14**)*

Yield: 82%. m.p.: 240–241 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.70 (s, 1H), 10.08 (s, 1H), 9.35 (s, 1H), 8.85 (s, 1H), 8.43 (s, 1H), 7.91 (d, $J$ = 8.2 Hz, 1H), 7.68 (d, $J$ = 2.7 Hz, 2H), 7.49 (ddd, $J$ = 8.2, 5.3, 3.0 Hz, 1H), 7.16 (d, $J$ = 7.6 Hz, 1H), 6.82 (dd, $J$ = 7.8, 1.3 Hz, 1H), 6.73 (t, $J$ = 7.8 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 149.5; 145.6; 145.0; 142.2; 141.1; 137.8; 136.7; 130.3; 128.7; 126.2; 125.0; 120.4; 119.2; 117.9; 116.3. HREI-MS: $m/z$ calcd for $C_{15}H_{12}N_4O_2$ [M]+ 280.0960; Found 280.0953; Anal. Calcd for $C_{15}H_{12}N_4O_2$, C, 64.28; H, 4.32; N, 19.99; Found C, 64.29; H, 4.30; N, 20.01. IR (cm$^{-1}$, KBr): 1584 (C=N).

*4.4.15. (E)-4-((2-(quinoxalin-2-yl)hydrazono)methyl)benzene-1,3-diol (**15**)*

Yield: 95%. m.p.: 280–281 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.49 (s, 1H), 10.70 (s, 1H), 9.80 (s, 1H), 8.79 (s, 1H), 8.32 (s, 1H), 7.88 (d, $J$ = 8.1 Hz, 1H), 7.70–7.59 (m, 2H), 7.55–7.40 (m, 2H), 6.36 (dd, $J$ = 6.6, 2.1 Hz, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 160.0; 158.2; 149.5; 142.7; 141.2; 137.6; 136.8; 130.2; 129.1; 128.7; 126.1; 124.7; 111.7; 107.7; 102.5 ppm. HREI-MS: $m/z$ calcd for $C_{15}H_{12}N_4O_2$ [M]+ 280.0960; Found 280.0968; Anal. Calcd for $C_{15}H_{12}N_4O_2$, C, 64.28; H, 4.32; N, 19.99; Found C, 64.26; H, 4.30; N, 19.98. IR (cm$^{-1}$, KBr): 3435 (NH); 1584 (C=N).

*4.4.16. (E)-2-((2-(quinoxalin-2-yl)hydrazono)methyl)benzene-1,4-diol (**16**)*

Yield: 91%. m.p.: 271–272 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.64 (s, 1H), 9.72 (s, 1H), 8.90 (d, $J$ = 9.9 Hz, 2H), 8.37 (s, 1H), 7.91 (d, $J$ = 8.1 Hz, 1H), 7.78–7.55 (m, 2H), 7.55–7.38 (m, 1H), 7.17 (d, $J$ = 2.5 Hz, 1H), 6.75 (d, $J$ = 8.6 Hz, 1H), 6.68 (dd, $J$ = 8.6, 2.3 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.0; 149.8; 149.2; 141.1; 140.8; 137.8; 136.5; 130.3; 128.7; 126.2; 125.0; 120.5; 118.0; 116.9; 111.8 ppm. HREI-MS: $m/z$ calcd for $C_{15}H_{12}N_4O_2$ [M]+ 280.0960; Found 280.0951; Anal. Calcd for $C_{15}H_{12}N_4O_2$, C, 64.28; H, 4.32; N, 19.99; Found C, 64.31; H, 4.31; N, 20.00. IR (cm$^{-1}$, KBr): 3454 (O-H); 1589 (C=N).

*4.4.17. (E)-4-((2-(quinoxalin-2-yl)hydrazono)methyl)benzene-1,2-diol (**17**)*

Yield: 85%. m.p.: 263–264 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.43 (s, 1H), 9.33 (s, 1H), 9.18 (s, 1H), 8.99 (s, 1H), 7.98 (s, 1H), 7.89 (d, $J$ = 8.3 Hz, 1H), 7.66 (d, $J$ = 3.3 Hz, 2H), 7.63–7.40 (m, 1H), 7.24 (s, 1H), 6.97 (d, $J$ = 8.1 Hz, 1H), 6.79 (d, $J$ = 8.0 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.3; 147.3; 145.7; 142.8; 141.1; 137.7; 136.4; 130.2; 128.7; 126.2; 126.0; 124.7; 119.5; 115.6; 112.5 ppm. HREI-MS: $m/z$ calcd for $C_{15}H_{12}N_4O_2$ [M]+ 280.0960; Found 280.0964; Anal. Calcd for $C_{15}H_{12}N_4O_2$, C, 64.28; H, 4.32; N, 19.99; Found C, 64.30; H, 4.35; N, 19.97. IR (cm$^{-1}$, KBr): 3500 (OH); 3464 (NH); 1591 (C=N).

*4.4.18. (E)-5-((2-(quinoxalin-2-yl)hydrazono)methyl)benzene-1,2,4-triol (**18**)*

Yield: 87%. m.p.: 263–264 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.41 (s, 1H), 9.87 (s, 1H), 9.37 (s, 1H), 8.80 (s, 1H), 8.50 (s, 1H), 8.28 (s, 1H), 7.88 (d, $J$ = 7.7 Hz, 1H), 7.64 (s, 2H), 7.45 (s, 1H), 7.07 (s, 1H), 6.36 (s, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 153.88, 150.83, 145.73, 143.97, 143.89, 141.98, 140.21, 139.09, 131.88, 129.32, 129.27, 127.36, 117.27, 112.91, 102.80. HREI-MS: $m/z$ calcd for $C_{15}H_{12}N_4O_3$ [M]+ 296.0909; Found 296.0916; Anal. Calcd for $C_{15}H_{12}N_4O_3$, C, 60.81; H, 4.08; N, 18.91; Found C, 60.82; H, 4.09; N, 18.89. IR (cm$^{-1}$, KBr): 3500 (OH); 3464 (NH); 1591 (C=N).

*4.4.19. (E)-5-((2-(quinoxalin-2-yl)hydrazono)methyl)benzene-2,4,6-triol (**19**)*

Yield: 93%. m.p.: 274–276 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.53 (s, 1H), 10.93 (s, 2H), 9.76 (s, 1H), 8.58 (s, 1H), 8.50 (s, 1H), 7.87 (d, $J$ = 8.1 Hz, 1H), 7.65 (d, $J$ = 3.8 Hz, 2H), 7.46 (dt, $J$ = 8.2, 4.0 Hz, 1H), 5.88 (s, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 163.29, 161.49, 161.49, 143.87, 143.92, 142.94, 141.92, 139.89, 131.58, 129.31, 129.25, 127.16, 106.63, 95.78, 95.78. HREI-MS: $m/z$ calcd for $C_{15}H_{12}N_4O_3$ [M]+ 296.0909; Found 296.0901; Anal. Calcd for $C_{15}H_{12}N_4O_3$, C, 60.81; H, 4.08; N, 18.91; Found C, 60.82; H, 4.09; N, 18.90. IR (cm$^{-1}$, KBr): 3467 (OH); 3264 (NH); 1592 (C=N).

*4.4.20. (E)-5-methoxy-2-((2-(quinoxalin-2-yl)hydrazono)methyl) phenol (**20**)*

Yield: 91%. m.p.: 252–255 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.57 (s, 1H), 10.87 (s, 1H), 8.82 (s, 1H), 8.36 (s, 1H), 7.89 (d, $J$ = 7.9 Hz, 1H), 7.67 (s, 2H), 7.61 (d, $J$ = 8.5 Hz, 1H), 7.47 (s, 1H), 6.53 (dd, $J$ = 8.6, 2.3 Hz, 1H), 6.49 (d, $J$ = 2.3 Hz, 1H), 3.77 (s, 4H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 162.00, 161.23, 147.11, 143.97, 143.89, 141.98, 139.09, 131.88, 130.82, 129.32, 129.27, 127.36, 113.95, 107.29, 102.05, 56.03. HREI-MS: $m/z$ calcd for $C_{16}H_{14}N_4O_2$ [M]+ 294.1117; Found 294.1125; Anal. Calcd for $C_{16}H_{14}N_4O_2$, C, 65.30; H, 4.79; N, 19.04; Found C, 65.31; H, 4.81; N, 19.06. IR (cm$^{-1}$, KBr): 3515 (OH); 3354 (NH); 1583 (C=N).

*4.4.21. (E)-2-methoxy-5-((2-(quinoxalin-2-yl)hydrazono)methyl) phenol (**21**)*

Yield: 81%. m.p.: 243–244 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.50 (s, 1H), 9.22 (s, 1H), 9.02 (s, 1H), 8.01 (s, 1H), 7.90 (d, $J$ = 8.1 Hz, 1H), 7.74–7.63 (m, 2H), 7.47 (ddd, $J$ = 8.3, 5.7, 2.6 Hz, 1H), 7.30 (d, $J$ = 2.0 Hz, 1H), 7.08 (dd, $J$ = 8.3, 2.0 Hz, 1H), 6.97 (d, $J$ = 8.3 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 149.90, 146.65, 145.38, 143.97, 143.89, 141.98, 139.09, 131.88, 129.56, 129.32, 129.27, 127.36, 120.35, 115.24, 115.11, 56.78. HREI-MS: $m/z$ calcd for $C_{16}H_{14}N_4O_2$ [M]+ 294.1117; Found 294.1126; Anal. Calcd for $C_{16}H_{14}N_4O_2$, C, 65.30; H, 4.79; N, 19.04; Found C, 65.28; H, 4.77; N, 19.01. IR (cm$^{-1}$, KBr): 3428 (OH); 3451 (NH); 1624 (C=N).

*4.4.22. (E)-2-(2-(3-methoxybenzylidene)hydrazinyl)quinoxaline (**22**)*

Yield: 75%. m.p.: 179–180 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.71 (s, 1H), 9.13 (s, 1H), 8.12 (s, 1H), 7.92 (d, $J$ = 8.0 Hz, 1H), 7.73–7.47 (m, 3H), 7.41 (dd, $J$ = 55.1, 4.5 Hz, 1H), 7.32 (dd, $J$ = 9.7, 2.2 Hz, 2H), 6.99–6.82 (m, 1H), 3.82 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 159.6; 150.3; 141.7; 140.9; 137.9; 136.4; 136.1; 130.3; 129.8; 128.8; 126.1; 125.1; 119.2; 115.3; 110.9; 55.2 ppm. HREI-MS: $m/z$ calcd for $C_{16}H_{14}N_4O$ [M]+ 278.1168; Found 278.1172; Anal. Calcd for $C_{16}H_{14}N_4O$, C, 69.05; H, 5.07; N, 20.13; Found C, 69.07; H, 5.05; N, 20.12. IR (cm$^{-1}$, KBr): 3453 (NH); 1582 (C=N).

*4.4.23. (E)-2-(2-(4-methoxybenzylidene)hydrazinyl)quinoxaline (**23**)*

Yield: 89%. m.p.: 220–222 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.55 (s, 6H), 9.07 (s, 6H), 8.10 (s, 6H), 7.90 (d, $J$ = 8.1 Hz, 7H), 7.71 (d, $J$ = 8.7 Hz, 12H), 7.66 (d, $J$ = 6.4 Hz, 9H), 7.47 (s, 5H), 7.01 (d, $J$ = 8.6 Hz, 13H), 3.81 (s, 17H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 160.2; 150.3; 141.8; 141.0; 137.8; 136.4; 130.2; 128.7; 128.0; 127.3; 126.0; 124.8; 114.3; 55.2 ppm. HREI-MS: $m/z$ calcd for $C_{16}H_{14}N_4O$ [M]+ 278.1168; Found 278.1161; Anal. Calcd for $C_{16}H_{14}N_4O$, C, 69.05; H, 5.07; N, 20.13; Found C, 69.03; H, 5.04; N, 20.14. IR (cm$^{-1}$, KBr): 3451 (NH); 1612 (C=N).

*4.4.24. (E)-4-methoxy-2-((2-(quinoxalin-2-yl)hydrazono)methyl) phenol (**24**)*

Yield: 91%. m.p.: 258–261 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.69 (s, 1H), 9.98 (s, 1H), 8.97 (s, 1H), 8.42 (s, 1H), 7.91 (d, $J$ = 8.2 Hz, 1H), 7.71–7.65 (m, 2H), 7.49 (ddd, $J$ = 8.2, 6.2, 2.1 Hz, 1H), 7.31 (s, 1H), 6.86 (d, $J$ = 1.6 Hz, 2H), 3.77 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 154.41, 154.30, 145.73, 143.97, 143.89, 141.98, 139.09, 131.88, 129.32, 129.27, 127.36, 121.70, 116.57, 116.33, 112.80, 56.03; HREI-MS: $m/z$ calcd for $C_{16}H_{14}N_4O_2$ [M]+ 294.1117; Found 294.1117; Anal. Calcd for $C_{16}H_{14}N_4O_2$, C, 65.30; H, 4.79; N, 19.04; Found C, 65.29; H, 4.77; N, 19.06. IR (cm$^{-1}$, KBr): 1589 (C=N).

*4.4.25. (E)-2-(2-(pyridin-3-ylmethylene)hydrazinyl)quinoxaline (**25**)*

Yield: 86%. m.p.: 236–238 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.97 (s, 1H), 9.13 (s, 1H), 8.47 (s, 1H), 8.18 (d, $J$ = 8.6 Hz, 1H), 7.94 (d, $J$ = 8.0 Hz, 1H), 7.74–7.67 (m, 3H), 7.53 (dd, $J$ = 8.1, 1.6 Hz, 1H), 7.50 (dd, $J$ = 8.6, 1.8 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 149.85, 146.31, 143.97, 143.89, 141.98, 141.65, 139.09, 135.66, 133.80, 131.88, 129.32, 129.27, 127.36, 124.41. HREI-MS: $m/z$ calcd for $C_{14}H_{11}N_5$ [M]+ 249.1014; Found 249.1019; Anal. Calcd for $C_{14}H_{11}N_5$, C, 67.46; H, 4.45; N, 28.10; Found C, 67.47; H, 4.43; N, 28.11. IR (cm$^{-1}$, KBr): 3524 (NH); 1621 (C=N).

*4.4.26. (E)-2-(2-(pyridin-4-ylmethylene)hydrazinyl)quinoxaline (**26**)*

Yield: 92%. m.p.: 256–257 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 12.02 (s, 1H), 9.18 (s, 1H), 8.63 (d, $J$ = 6.0 Hz, 2H), 8.11 (s, 1H), 7.96 (d, $J$ = 7.9 Hz, 1H), 7.77–7.68 (m, 4H), 7.57–7.52 (m, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 150.19, 146.30, 143.94, 143.82, 141.92, 140.73, 139.19, 131.85, 129.39, 129.17, 127.48, 122.25, 122.25; HREI-MS: $m/z$ calcd for $C_{14}H_{11}N_5$ [M]+ 249.1014; Found 249.1019; Anal. Calcd for $C_{14}H_{11}N_5$, C, 67.46; H, 4.45; N, 28.10; Found C, 67.47; H, 4.43; N, 28.08; IR (cm$^{-1}$, KBr): 1578 (C=N).

*4.4.27. (E)-2-(2-((1H-indol-3-yl)methylene)hydrazinyl)quinoxaline (**27**)*

Yield: 96%. m.p.: 256–257 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.52 (s, 1H), 11.33 (s, 1H), 9.10 (s, 1H), 8.37 (s, 1H), 8.33–8.27 (m, 1H), 7.89 (d, $J$ = 8.3 Hz, 1H), 7.80 (s, 1H), 7.65 (d, $J$ = 3.7 Hz, 2H), 7.50–7.42 (m, 2H), 7.27–7.20 (m, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 143.97, 143.89, 141.98, 139.09, 134.84, 134.81, 134.47, 131.88, 129.32, 129.27, 127.36, 127.11, 121.32, 120.74, 118.38, 113.20, 105.66. HREI-MS: $m/z$ calcd for $C_{17}H_{13}N_5$ [M]+ 287.1171; Found 287.1178; Anal. Calcd for $C_{17}H_{13}N_5$, C, 71.06; H, 4.56; N, 24.37; Found C, 71.07; H, 4.54; N, 24.35. IR (cm$^{-1}$, KBr): 1618 (C=N).

*4.4.28. (E)-2-((2-(quinoxalin-2-yl)hydrazono)methyl)phenol (**28**)*

Yield: 95%. m.p.: 256–257 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 11.69 (s, 1H), 10.54 (s, 1H), 8.91 (s, 1H), 8.45 (s, 1H), 7.91 (d, $J$ = 8.2 Hz, 1H), 7.74 (d, $J$ = 7.5 Hz, 1H), 7.68 (q, $J$ = 8.3 Hz, 2H), 7.57–7.45 (m, 1H), 7.30–7.21 (m, 1H), 6.92 (dd, $J$ = 16.1, 7.9 Hz, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 156.3; 149.7; 141.1; 141.0; 137.8; 136.7; 130.5; 130.3; 128.8; 127.1; 126.2; 125.1; 120.2; 119.4; 116.2. HREI-MS: $m/z$ calcd for $C_{15}H_{12}N_4O$ [M]+ 264.1011; Found 264.1002; Anal. Calcd for $C_{15}H_{12}N_4O$, C, 68.17; H, 4.58; N, 21.20; Found C, 68.18; H, 4.56; N, 21.18. IR (cm$^{-1}$, KBr): 3491 (OH); 1580 (C=N).

## Acknowledgements

The author (Dr. M. Taha) would like to acknowledge Universiti Teknologi MARA – Malaysia for the financial support under the Research Intensive Faculty grant scheme with reference number UiTM 600-RMI/DANA 5/3/LESTARI (54/2015) and The author (Dr. M.A.) is grateful to Higher Education Commission of Pakistan for providing research grant vide No. 20-1933/NRPU/R&D/HEC/12/5017.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bioorg.2016.07.010.

## References

[1] R. Nencka, in: F.R.S. Atta-ur-Rahman, M. Iqbal Choudhary (Eds.), Thymidine Phosphorylase Inhibitors in Anti-Angiogenesis Drug Discovery and Development, Bentham Science Publishers, 2011, p. 116.
[2] A. Moghaddam, R. Bicknell, Biochemistry 31 (1992) 12141.
[3] T. Furukawa, A. Yoshimura, T. Sumizawa, M. Haraguchi, S.-I. Akiyama, K. Fukui, M. Ishizawa, Y. Yamada, Nature 356 (1992) 668.
[4] N.S. Brown, A. Jones, C. Fujiyama, A.L. Harris, R. Bicknell, Cancer Res. 60 (2000) 6298.
[5] K. Usuki, J. Saras, J. Waltenberger, K. Miyazono, G. Pierce, A. Thomason, C.H. Heldin, Biochem. Biophys. Res. Commun. 184 (1992) 1311.
[6] M.J. Pérez-Pérez, E.M. Priego, A.I. Hernández, M.J. Camarasa, J. Balzarini, S. Liekens, Mini-Rev. Med. Chem. 5 (2005) 1113.
[7] A. Moghaddam, H.T. Zhang, T.P. Fan, D.E. Hu, V.C. Lees, H. Turley, S.B. Fox, K.C. Gatter, A.L. Harris, R. Bicknell, Proc. Nat. Acad. Sci. USA 92 (1995) 998.
[8] M. Takeuchi, T. Otsuka, N. Matsui, K. Asai, T. Hirano, A. Moriyama, I. Isobe, Y.Z. Eksioglu, K. Matsukawa, T. Kato, T. Tada, Arthritis Rheum. 37 (1994) 662.
[9] D. Creamer, R. Jaggar, M. Allen, R. Bicknell, J. Barker, Brit. J. Dermatol. 137 (1997) 851.
[10] F. Focher, S. Spadari, Curr. Cancer Drug Targets 1 (2001) 141.
[11] J. Folkman, New. Engl. J. Med. 285 (1971) 1182.
[12] J. Folkman, J. Natl. Cancer Inst. 82 (1990) 4.
[13] S. Matsushita, T. Nitanda, T. Furukawa, T. Sumizawa, A. Tani, K. Nishimoto, S. Akiba, K. Miyadera, M. Fukushima, Y. Yamada, H. Yoshida, T. Kanzaki, S. Akiyama, Cancer Res. 59 (1999) 1911.
[14] F. Focher, S. Spadari, Curr. Cancer Drug. Targets 1 (2001) 141.
[15] M. Fukushima, N. Suzuki, T. Emura, S. Yano, H. Kazuno, Y. Tada, Y. Yamada, T. Asao, Biochem. Pharmacol. 59 (2000) 1227.
[16] S. Yano, H. Kazuno, T. Sato, N. Suzuki, T. Emura, K. Wierzba, J.-I. Yamashita, Y. Tada, Y. Yamada, M. Fukushima, T. Asao, Bioorg. Med. Chem. Lett. 12 (2004) 3443.
[17] J. Balzarini, A.E. Gamboa, R. Esnouf, S. Liekens, J. Neyts, E. De Clercq, M.-J. Camarasa, M.-J. Pérez-Pérez, FEBS Lett. 438 (1998) 91.
[18] A. Esteban-Gamboa, J. Balzarini, R. Esnouf, E. De Clercq, M.-J. Camarasa, M.-J. Pérez-Pérez, J. Med. Chem. 43 (2000) 971.
[19] A.L. Allan, P.L. Gladstone, M.L.P. Price, S.A. Hopkins, J.C. Juarez, F. Doñate, R.J. Ternansky, D.E. Shaw, B. Ganem, Y. Li, W. Wang, S. Ealick, J. Med. Chem. 49 (2006) 7807.
[20] S.A. Diab, S.C. De, M. Muzard, R. Plantier-Royon, E. Pfund, T. Lequeux, J. Med. Chem. 55 (2012) 2758.
[21] H.M. Refaat, A.A. Moneer, O.M. Khalil, Arch. Phram. Res. 27 (2004) 1093.
[22] S.A. El-Hawash, N.S. Habib, N.H. Fanaki, Pharmazie 54 (1999) 808.
[23] A. Monge, F.J. Martinez-Crespo, A.L. Cerain, J.A. Palop, S. Narro, V. Senador, A. Marin, Y. Sainz, M. Gonzalez, E. Hamilton, A.J. Barker, J. Med. Chem. 38 (1995) 4488.
[24] V.K. Tandon, D.B. Yadav, H.K. Maurya, A.K. Chaturvedi, P.K. Shukla, Bioorg. Med. Chem. 14 (2006) 6120.
[25] P. Sanna, A. Carta, M. Loriga, S. Zanetti, L. Sechi, Part 3: II Farmaco 54 (1999) 1169.
[26] J. Guillon, I. Forfar, M.M. Matsuda, V. Desplat, M. Saliege, D. Thiolat, Bioorg. Med. Chem. Lett. 15 (2007) 194.
[27] A. Jaso, B. Zarranz, I. Aldana, A. Monge, Eur. J. Med. Chem. 38 (2003) 791.
[28] S.Y. Hassan, S.N. Khattab, A.A. Bekhit, A. Amer, Bioorg. Med. Chem. Lett. 16 (2006) 1753.
[29] R. Sarges, H.R. Howard, R.G. Browne, L.A. Lebel, P.A. Seymour, B.K. Koe, J. Med. Chem. 33 (1990) 2240.
[30] J.B. Rangisetty, C.N.V.H.B. Gupta, A.L. Prasad, P. Srinivas, N. Sridhar, P. Parimoo, A. Veeranjaneyulu, J. Pharm. Pharmacol. 53 (2001) 1409.
[31] A.F. Crowther, F.H.S. Curd, D.G. Davey, G.J. Stacey, J. Chem. Soc. (1949) 1260.
[32] M.M. Ali, M.M.F. Ismail, M.S.A. El-Gaby, M.A. Zahran, Y.A. Ammar, Molecules 5 (2000) 864.
[33] C.A. Obafemi, D.A. Akinpelu, Phosphorus, Sulfur, Silicon, Relat. Elem. 180 (2005) 1795.
[34] U.J. Ries, H.W. Priekpe, N.H. Havel, S. Handschuh, G. Mihm, J.M. Stassen, W. Wienen, H. Nar, Bioorg. Med. Chem. Lett. 13 (2003) 2297.
[35] G.R. Wendt, K.W. Ledig, U.S. Patent, 3,431,262, Chem. Abstr. 70 (1969) 106512.
[36] D.S. Su, M.G. Bock, US Patent. Appl. 2005, (20050020591).
[37] G. Sakata, K. Makino, Y. Karasawa, Heterocycles 27 (1988) 2481.
[38] (a) A. Dell, D.H. William, H.R. Morris, G.A. Smith, J. Feeney, G.C.K. Roberts, J. Am. Chem. Soc. 97 (1975) 2497;
(b) M.M. Heravi, K. Bakhtiari, M.H. Tehrani, N.M. Javadi, H.A. Oskooie, ARKIVOC (xvi) (2006) 16;
(c) S.A. Raw, C.D. Wilfred, R.J.K. Taylor, Chem. Commun. 18 (2003) 2286.
[39] (a) A. Kumar, S. Kumar, A. Saxena, A. De, S. Mozumdar, Catal. Commun. (2008) 778;
(b) J.Y. Jaung, Dyes Pigm. 71 (2006) 45.
[40] J. Balzarini, A.E. Gamboa, R. Esnouf, S. Liekens, J. Neyts, E. De Clercq, C. Maria-José, Maria-Jesus Pérez-Pérez, FEBS Lett. 91 (1998) 438.
[41] (a) N.K.N.A. Zawawi, M. Taha, N. Ahmat, A. Wadood, N.H. Ismail, F. Rahim, S.S. Azam, N. Abdullah, Bioorg. Chem. 64 (2016) 29;
(b) M. Taha, N.H. Ismail, S. Imran, M. Selvaraj, F. Rahim, RSC Adv. 6 (2016) 3276;
(c) S. Imran, M. Taha, N.H. Ismail, S.M. Kashif, F. Rahim, W. Jamil, H. Wahab, K. M. Khan, Chem. Biol. Drug. Des. 87 (2015) 361;
(d) M. Taha, N.H. Ismail, S. Imran, A. Wadood, F. Rahim, K.M. khan, M. Riaz, Bioorg. Chem. 66 (2016) 80;
(f) M. Taha, N.H. Ismail, S. Imran, A. Wadood, M. Ali, F. Rahim, A.A. Khan, M. Riaz, RSC Adv. 6 (2016) 33733;
M. Taha, N.H. Ismail, S. Imran, A. Wadood, F. Rahim, S.M. Saad, K.M. Khan, A. Nasir, Bioorg. Chem. 66 (2016) 117;
(f) M. Taha, N.H. Ismail, S. Imran, A. Wadood, F. Rahim, M. Ali, A.U. Rehman, Med. Chem. Comm. 6 (2015) 1826.
[42] M. Taha, N.H. Ismail, S. Imran, E.H. Anouar, M. Ali, W. Jamil, N. Uddin, S.M. Kashif, RSC Adv. 6 (2016) 3003–3012.
[43] M. Taha, N.H. Ismail, S. Lalani, M.Q. Fatmi, Atia-tul-Wahab, S. Siddiqui, K.M. Khan, S. Imran, M.I. Choudhary, Eur. J. Med. Chem. 92 (2015) 387–400.
[44] M. Taha, N.H. Ismail, S. Imran, M.Q.B. Rokei, S.M. Saad, K.M. Khan, Bioorg. Med. Chem. 23 (2015) 4155–4162.
[45] M. Taha, N.H. Ismail, A. Khan, S.A.A. Shah, A. Anwar, S.A. Halim, M.Q. Fatmi, S. Imran, F. Rahim, K.M. Khan, Bioorg. Med. Chem. Lett. 25 (2015) 3285–3289.
[46] M. Taha, K.A.A. Alkadi, N.H. Ismail, S. Imran, A. Adam, S.M. Kashif, S.A.A. Shah, W. Jamil, S. Sidiqqui, K.M. Kha, Antiglycation and antioxidant potential of novel imidazo[4,5-b]pyridine benzohydrazones, Arab. J. Chem. (2015), http://dx.doi.org/10.1016/j.arabjc.2015.08.004.
[47] M. Taha, S.A.A. Shah, A. Khan, F. Arshad, N.H. Ismail, M. Afifi, S. Imran, M.I. Choudhary, Arab. J Chem. (2015), http://dx.doi.org/10.1016/j.arabjc.2015.06.036.
[48] S. Imran, M. Taha, N.H. Ismail, S.M. kashif, F. Rahim, W. Jamil, M. Hariono, M. Yusuf, H. Wahab, Eur. J. Med Chem. 105 (2015) 156–170.
[49] M. Taha, N.H. Ismail, S. Imran, M. Selvaraj, A. Rahim, M. Ali, S. Siddiqui, F. Rahim, K.M. Khan, Bioorg. Med. Chem. 23 (2015) 7394–7404.
[50] M. Taha, N.H. Ismail, W. Jamil, H. Rashwan, S.M. Kashif, A.A. Sain, M.I. Adenan, E.H. Anouar, M. Ali, F. Rahim, K.M. Khan, Eur. J. Med. Chem. 84 (2014) 731–738.
[51] J. Boström, J.R. Greenwood, J. Gottfries, J. Mol. Graph. Model 21 (2003) 449.