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MULTI-COMPONENT REACTIONS FOR THE SYNTHESIS OF PYRAZOLO [1,5-*a*]QUINOLINE DERIVATIVES TOGETHER WITH THEIR CYTOTOXIC EVALUATIONS

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ABSTRACT. A new approaches for the synthesis of novel pyrazolo[1,5-*a*]quinazoline **8a-f** and pyrazolo[1,5-*a*]quinazolin-6-one **10a-s** and **12a-s** derivatives were obtained using 4-(2-phenylhydrazono)-4*H*-pyrazol-3-amine derivatives **5a-f** via their multi-component reactions. The later pyrazole derivatives were prepared via arylhydrazone derivatives **3a-f**. The structures of the synthesized compounds were established based on their respective analytical data. On the other hand, the cytotoxic effects of the synthesized compounds were obtained against the six cancer cell lines, namely A549, HT-29, MKN-45, U87MG, SMMC-7721 and, H460 utilizing foretinib as the positive control and the standard MTT assay *in vitro*. The obtained results showed that compounds **8c**, **8f**, **10c**, **10i**, **10l**, **10p**, **10s**, **12c**, **12i**, **12l**, **12p** and, **12s** were the most cytotoxic compounds. In most cases the presence of the electronegative Cl group enhanced the cytotoxicity of the tested compound.

KEY WORDS: Multi-component reactions, Pyrazolo[1,5-*a*]quinazoline, Pyrazolo[1,5-*a*]quinazolin-6-one, Cytotoxicity

INTRODUCTION

The multi-component reactions (MCRs) play an important role in the preparation of a desired fused heterocyclic compounds from a simple reagents in a single synthetic method. (MCRs) was considered the most applicable reactions, due to the high selectivity of resultant compounds, high yields, high purity, high atom-economy and the simple reagents which used in the reaction [1-4]. (MCRs) can be proceeded via many traditional synthetic methods [5-10], but the other novel procedures were used widely in the last years to reduce the reaction time, including ultrasound-promoted reaction, microwave-assisted reaction, and metal-catalyzed reaction [11-16]. For significant biological and pharmacological applications, the important quinazoline derivatives containing drugs were represented in Figure 1. The later drugs mainly used as anticancer drugs for non-smal-cell lung carcinoma (gefitnib) [17], for advanced-stage or metastatic breast cancer (lapatinib) [18, 19], erlotinib and afatinib for non-smal-cell lung carcinoma (NSCLC) [20].

The other important ring which presents in the synthesized products was the five-membered heterocyclic ring system pyrazole. The latter ring has a variety of biological activity in many parts of medicinal field [21-26]. Moreover, many non-steroidal anti-inflammatory drugs (NSAID) such as benzydamine, apixaban as anticoagulant and allopurinol as antigout were built based on the pyrazole moiety. Figure 2 represents the important of some pyrazole ring system containing drugs as anticancer agents (axitinib, ruxolitinib and crizotinib).

In the present work, and due to the significant role of the pyrazoles and quinazolines as anticancer agents in many pharmaceutical drugs, a series of novel pyazoloquinazoline derivatives were synthesized. The latter products were obtained by using arylhydrazone derivatives that multi-component reactions, followed be their evaluation toward selected six cancer cell lines compared to the standard reference foretinib.

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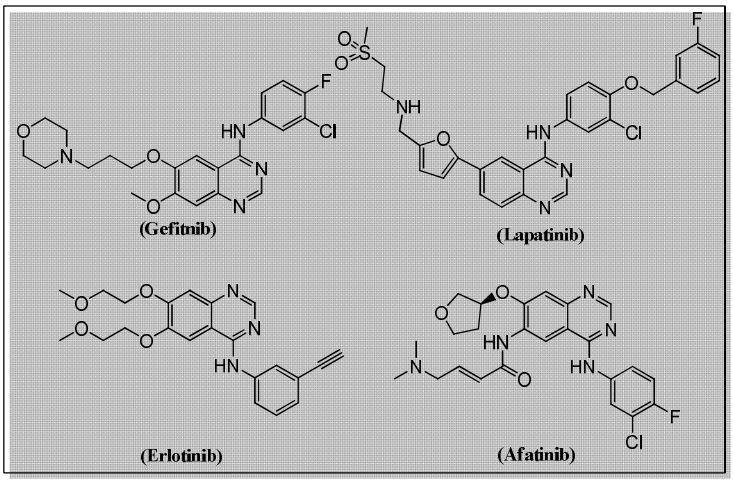


Figure 1. Some significant quinazoline-containing drugs as anticancer agents.

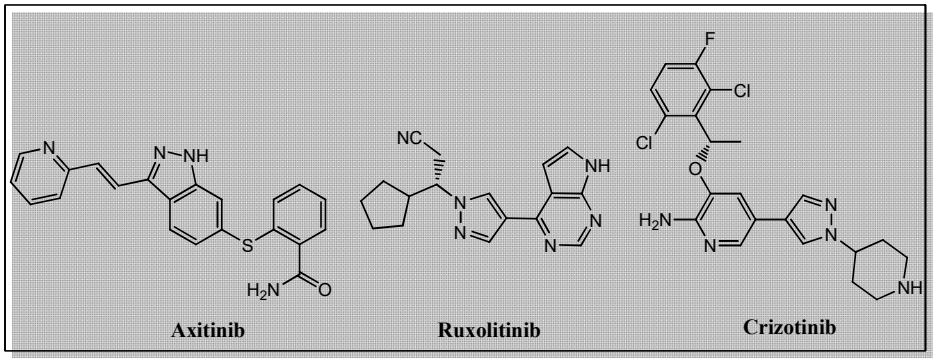
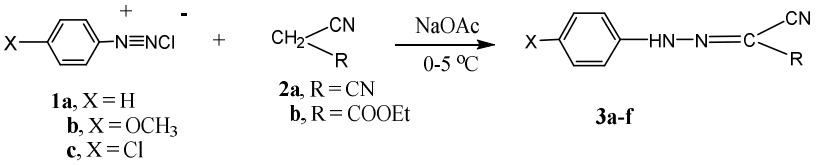


Figure 2. Some notable pyrazole-containing drugs as anticancer agents.

RESULTS AND DISCUSSION

The reaction sequences for the synthesized compounds were demonstrated through Schemes 1-4 starting with arylhydrazone derivatives. Recently, our research group was concerned with different multi-component reactions aiming to produce new heterocyclic compounds characterized by different substituents. This enhanced the use to study plenty of structure activity relationship and thus producing new anti-cancer agents. In continuation of this program we demonstrated in this work the multi-component reactions of some arylhydrazopyrazole derivatives. Thus, the arylhydrazone derivatives **3a-f** were obtained from the reaction of either malononitrile (**2a**) or ethyl cyanoacetate (**2b**) with the aryldiazonium salts **1a-c** in an ice bath (0-5 ºC) and the presence of ethanol together with sodium acetate. The reaction of **3a-f** with hydrazine hydrate (**4**) in ethanol solution and heating under reflux conditions gave the 4-(2-arylhydrazono)-4*H*-pyrazole derivatives **5a-f**, respectively (Scheme 1).

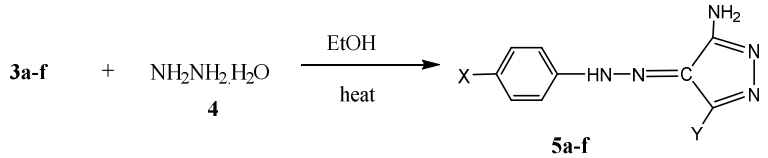


1a, X = H
b, X = OCH_3
c, X = Cl

2a, R = CN
b, R = COOEt

3a-f

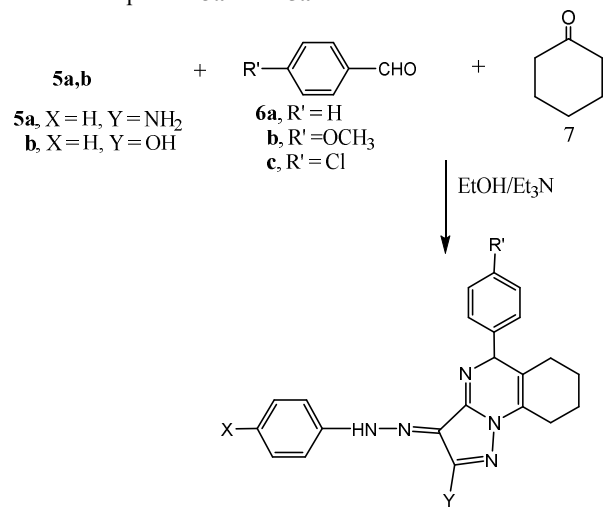
3	a	b	c	d	e	f
X	H	H	OCH_3	OCH_3	Cl	Cl
R	CN	COOEt	CN	COOEt	CN	COOEt



5a-f

5	a	b	c	d	e	f
X	H	H	OCH_3	OCH_3	Cl	Cl
Y	NH_2	OH	NH_2	OH	NH_2	OH

Scheme 1. Synthesis of compounds **3a-f** and **5a-f**.

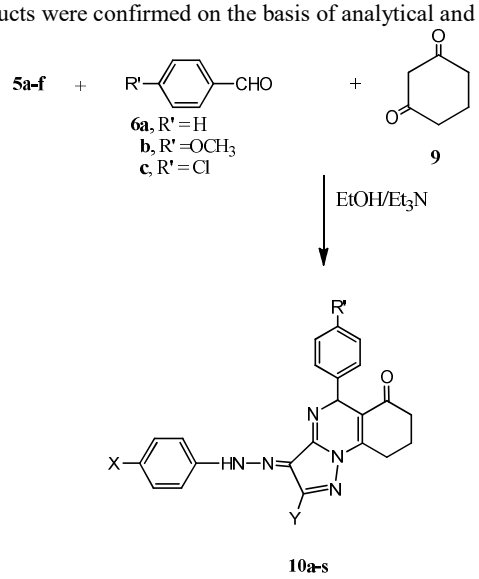


8a-f

8	a	b	c	d	e	f
X	H	H	H	H	H	H
Y	NH_2	NH_2	NH_2	OH	OH	OH
R'	H	OCH_3	Cl	H	OCH_3	Cl

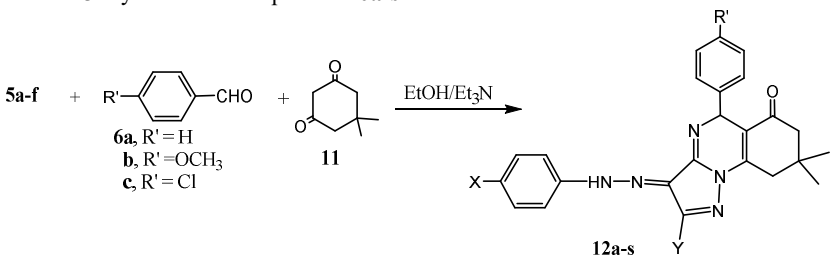
Scheme 2. Synthesis of compounds **8a-f**.

The multi-component reactions of compounds **5a,b** with each of aromatic aldehydes namely benzaldehyde (**6a**), 4-methoxybenzaldehyde (**6b**) and 4-chlorobenzaldehyde (**6c**) and cyclohexanone (**7**) in ethanol containing triethylamine gave the 3,5,6,7,8,9-hexahydro-pyrazolo[1,5-*a*]quinazoline derivatives **8a-f**, respectively (Scheme 2). The structures of the latter products were confirmed on the basis of analytical and spectral data.



10	a	b	c	d	e	f	g	h	i
X	H	H	H	H	H	H	OCH_3	OCH_3	OCH_3
Y	NH_2	NH_2	NH_2	OH	OH	OH	NH_2	NH_2	NH_2
R'	H	OCH_3	Cl	H	OCH_3	Cl	H	OCH_3	Cl
10	**k**	**l**	**m**	**n**	**o**	**p**	**q**	**r**	**s**
X	OCH_3	OCH_3	OCH_3	Cl	Cl	Cl	Cl	Cl	Cl
Y	OH	OH	OH	NH_2	NH_2	NH_2	OH	OH	OH
R'	H	OCH_3	Cl	H	OCH_3	Cl	H	OCH_3	Cl

Scheme 3. Synthesis of compounds **10a-s**.



12	a	b	c	d	e	f	g	h	i
X	H	H	H	H	H	H	OCH_3	OCH_3	OCH_3
Y	NH_2	NH_2	NH_2	OH	OH	OH	NH_2	NH_2	NH_2
R'	H	OCH_3	Cl	H	OCH_3	Cl	H	OCH_3	Cl
12	**k**	**l**	**m**	**n**	**o**	**p**	**q**	**r**	**s**
X	OCH_3	OCH_3	OCH_3	Cl	Cl	Cl	Cl	Cl	Cl
Y	OH	OH	OH	NH_2	NH_2	NH_2	OH	OH	OH
R'	H	OCH_3	Cl	H	OCH_3	Cl	H	OCH_3	Cl

Scheme 4. Synthesis of compounds **12a-s**.

Similarly, the multi-component reaction of compounds **5a-f** and aromatic aldehydes namely benzaldehyde (**6a**), 4-methoxybenzaldehyde (**6b**) and 4-chlorobenzaldehyde (**6c**) and cyclohexan-1,3-dione (**9**) in ethanol containing triethylamine gave the 5,7,8,9-tetrahydro-pyrazolo[1,5-*a*]quinazolin-6(3*H*)-one derivatives **10a-s**, respectively (Scheme 3). The analytical and spectral data of the products were in agreement of their proposed structures (see experimental section).

In addition The multi-component reaction of of compounds **5a-f** and aromatic aldehydes namely benzaldehyde (**6a**), 4-methoxybenzaldehyde (**6b**) and 4-chlorobenzaldehyde (**6c**) and dimedone (**11**) in ethanol containing triethylamine gave the 8,8-dimethy5,7,8,9-tetrahydro-pyrazolo[1,5-*a*]quinazolin-6-one derivatives **12a-s**, respectively (Scheme 4). ^{1}H NMR and ^{13}C NMR spectra were the basics of their structural elucidation (see experimental section).

Cell proliferation assay of 37 samples

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 [27-30]. 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 ºC 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 ºC 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. 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 substituents within the heterocyclic moiety together with the heterocycle ring being attached have a notable influence on the anti-proliferative activity.

Structure activity relationship

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 using the standard MTT assay in vitro, with foretinib as the positive control. 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 substituents within the aryl moiety together with the heterocycle ring being attached have a notable influence on the anti-proliferative activity. For the 3,5,6,7,8,9-hexahydropyrazolo[1,5-*a*]quinazoline derivatives **8a-f**, it was clear that compounds **8c** (Y = NH_2, R′ = Cl) and **8f** (Y = OH, R′ = Cl) showed the highest inhibitions through these six of compounds. Such high inhibitions of **8c** and **8f** was attributed to the presence of the Cl substituent at the aryl moiety. However, in compounds **8b** and **8e** the presence of the electron donating OCH_3 group resists the inhibitions. Considering the 5,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazoline derivatives **10a-s** it was obvious that compounds **10c** (X = H, Y= NH_2, R′ = Cl), **10f** (X = H, Y= OH, R′ = Cl), **10i** (X = OCH_3, Y = NH_2, R′ = Cl), **10l** (X = OCH_3, Y= OH, R′ = OCH_3), **10p** (X = Cl, Y = NH_2, R′ = Cl), and **10s** (X = Cl, Y= OH, R′ = Cl) exhibited the highest inhibitions among such

large series of compounds. Compound **10n** exhibited moderate inhibitions and the rest of compounds exhibited low inhibitions.

Similarly for the 8,8-dimethyl-5,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazoline derivatives **12a-s**, it was clear that compounds **12c** (X = H, Y= NH_2, R′ = Cl), **12i** (X = OCH_3, Y = NH_2, R′= Cl), **12l** (X = OCH_3, Y = OH, R′ = OCH_3), **12p** (X = Cl, Y = NH_2, R′ = Cl) and **12s** (X = Cl, Y = OH, R′ = Cl) exhibited the highest inhibitions among such series of compounds. However, compounds **12m** and **12q** exhibited moderate inhibitions and the rest of compounds showed low inhibitions. Through the tested compounds it was clear that compounds **8c**, **8f**, **10c**, **10i**, **10l**, **10p**, **10s**, **12c**, **12i**, **12l**, **12p** and **12s** showed the highest inhibitions among all tested compounds.

Table 1. In vitro growth inhibitory effects IC_{50} ± SEM (μM) of the newly synthesized compounds against cancer cell lines.

Compound No	IC_{50} ± SEM (μM)					
	A549	H460	HT29	MKN-45	U87MG	SMMC-7721
8a	6.45±1.32	7.41± 0.82	6.53± 1.29	8.28 ± 2.18	6.25±1.33	7.23± 2.35
8b	5.24 ± 1.18	6.31 ± 2.70	8.48 ± 2.41	7.23 ± 1.86	6.34 ± 1.53	7.40 ± 1.84
8c	0.36 ±0.14	0.31 ±0.16	0.41±0.12	0.29 ± 0.15	0.36±0.28	0.52 ±0.28
8d	10.41±2.68	9.54±2.70	7.52±3.27	10.68±2.70	8.49±2.37	8.90±2.41
8e	9.39 ±2.31	8.75±2.37	8.90 ±2.53	7.47 ±2.39	6.73 ±1.27	8.32 ±2.15
8f	0.42 ± 0.32	0.15 ± 0.08	0.36 ± 0.16	0.45 ± 0.08	0.28 ± 0.11	0.48 ± 0.26
10a	6.67± 1.56	7.31 ±1.48	8.43 ± 2.35	9.63 ± 2.59	8.90 ±2.41	8.45 ±2.33
10b	6.70±1.56	7.18±2.32	8.53±2.52	8.42±2.51	9.70±2.62	8.81±2.63
10c	0.23± 0.08	0.26 ± 0.13	0.53 ± 0.32	0.39 ± 0.25	0.63 ± 0.22	0.45± 0.26
10d	8.52± 2.39	7.93 ± 1.40	8.58 ± 2.36	9.03±2.41	8.36± 2.76	5.09 ± 1.36
10f	0.32 ± 2.39	6.43 ± 2.30	8.52 ± 3.52	7.58 ± 3.73	9.83 ± 3.62	5.81±1.32
10g	7.28±2.15	8.16±2.19	5.23±1.13	6.28±1.18	7.33±1.42	8.46±2.24
10h	8.43±2.25	7.26±2.15	8.39 ± 2.15	6.28 ± 1.15	7.33 ± 1.17	8.39±2.17
10i	0.16 ± 0.02	0.25 ±0.08	0.36 ±0.12	0.19±0.07	0.26±0.16	0.25±0.14
10k	5.21±1.59	8.32 ±2.37	6.41 ± 1.53	7.38 ±2.32	5.64 ±1.42	6.36 ± 1.57
10l	0.41±0.25	0.63±0.28	0.81±0.52	0.16±0.08	0.37±0.29	0.42±0.23
10m	8.45±2.33	6.52±2.60	5.83±2.36	7.43±3.58	8.96±2.37	4.20±1.32
10n	2.58 ± 0.79	3.68 ± 1.73	1.73± 0.86	1.94 ± 0.94	1.13 ± 0.89	2.53 ± 1.18
10o	7.48 ± 2.42	6.27 ± 2.31	8.23 ± 2.31	5.68 ± 1.28	7.33 ± 2.15	5.85 ± 1.72
10p	0.35±0.12	0.26±0.15	0.23±3.19	0.26±0.08	0.39±0.23	0.39±0.21
10q	5.26 ± 1.32	6.38±1.83	7.48± 1.32	8.29±2.36	7.26±1.78	5.83±1.73
10r	4.32± 1.28	6.28 ± 1.43	7.12± 2.39	6.38 ± 1.68	7.38 ± 1.56	6.53± 1.25
10s	0.23 ±0.12	0.40 ± 0.25	0.22± 0.13	0.41 ±0.26	0.23 ±0.10	0.46 ± 02.24
12a	7.83± 1.53	8.28± 2.15	8.26± 2.19	7.42 ± 1.80	8.26± 2.39	7.68± 1.38
12b	6.94 ± 1.38	8.24 ± 2.19	7.58±1.36	5.34± 1.58	8.61 ± 2.28	6.28 ± 1.62
12c	0.41 ±0.14	0.28±0.06	0.31±0.18	0.30±0.16	0.43±0.21	0.29±0.13
12g	8.12±2.35	7.14±1.26	8.93±2.59	6.83±1.72	5.79±1.86	7.92±2.58
12h	6.48± 2.56	5.72± 2.14	8.65± 3.72	7.53±1.29	8.93±2.52	8.56± 3.19
12i	0.18±0.05	0.34±0.26	0.49±0.29	0.63±0.36	0.52±0.27	0.44±0.35
12k	6.83± 1.21	7.63 ±2.75	8.39 ± 2.49	8.75 ± 2.38	8.73 ±2.69	8.27 ±2.90
12l	0.35 ±0.17	0.29±0.17	0.22 ±0.09	0.42 ±0.27	0.52 ±0.26	0.48 ±0.21
12m	2.89 ± 1.02	3.69 ± 1.49	2.75 ± 1.13	3.72 ± 1.08	2.59 ± 1.17	3.76 ± 1.27
12n	8.72± 2.43	8.55 ± 2.73	7.68 ± 2.42	8.67±2.23	9.56 ± 2.82	7.33 ± 2.53
12p	0.43±0.21	0.39±0.27	0.27±0.16	0.37±0.25	0.42±0.25	0.59±0.32
12q	4.25± 1.69	5.73 ± 1.82	7.92 ± 1.69	5.08 ± 1.54	4.74 ± 1.02	8.43± 1.39
12r	6.25±1+.38	7.36± 2.55	7.90± 1.42	8.59 ± 2.39	6.48±1.52	7.68± 2.19
12s	0.84±0.37	0.20±0.16	0.52±0.27	0.64±0.33	0.83±0.51	0.49±0.21
Foretinib	0.08 ± 0.01	0.18 ± 0.03	0.15 ± 0.023	0.03±0.0055	0.90 ± 0.13	0.44 ± 0.062

EXPERIMENTAL

All melting points were determined on an Electro-thermal digital meting point apparatus and are uncorrected. IR Spectra (KBr discs) were recorded on a FITR plus 460 or Pye Unicam SP-1000 spectrophotometer. ^{1}H-NMR spectra were recorded with Varian Gemini-200 (200 MHZ) (Cairo University) and Jeol AS 500 MHz (National Research Center) instruments in DMSO-d6 as solvent using TMS as internal standard and chemical shifts are expressed as δ ppm. The mass spectra were recorded with Hewlett Packard 5988 AGC/MS system and GCMS-QP1000 Ex shimadzu instruments. Analytical data were obtained from the Micro Analytical Data Unit at Cairo University and were performed on Vario El III Elemental CHNS analyzer.

*General procedure for the synthesis of phenylcarbonohydrazonoyl cyanide derivatives (**3a-f**)*

To a cold solution (0-5 °C) of compound **2a** malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate **2b**, in ethanol (20 mL) containing sodium acetate (1.00 g), any of benzenediazonium chloride (0.01 mol), 4-meyhoxybenzenediazonium chloride (0.01 mol) or 4-chlorobenzene-diazonium chloride (0.01 mol) [prepared by the addition of sodium nitrite (0.70 g, 0.01 mol) to a cold solution (0-5 °C) of any of aniline (0.93 g, 0.01 mol), 4-methoxyaniline (1.23 g, 0.01 mol) or 4-chloroaniline (1.27 g, 0.01 mol) in concentrated hydrochloric acid (12 mL, 18 M) with continuous stirring] was gradually added with continuous stirring. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water and crystallized from absolute alcohol.

*Phenylcarbonohydrazonoyl dicyanide (**3a**)*. Faint brown crystals, m.p. 132-135 °C, yield: 1.54 g (90%). Elemental analysis calculated for $C_9H_6N_4$ (170.17): C, 63.52; H, 3.55; N, 32.92%. Found: C, 63.76; H, 3.77; N, 32.70%. IR (ν, cm^{-1}): 3194, 3132 (NH), 3060 (CH-aromatic), 2231, 2212 (2CN), 1604, 1468 (C=C), 1541 (C=N). ^{1}H NMR (*δ*, ppm): 7.19-7.48 (m, 5H, C_6H_5), 12.99 (s, 1H, D_2O exchangeable, NH). EIMS: m/e [M^+] = 170 (56%).

*Ethyl 2-cyano-2-(2-phenylhydrazono)acetate (**3b**)*. Yellow crystals, m.p. 112-115 °C, yield: 1.91 g (88%). Elemental analysis calculated for $C_{11}H_{11}N_3O_2$ (217.22): C, 60.82; H, 5.10; N, 19.34%. Found: C, 60.52; H, 5.00; N, 19.60%. IR (ν, cm^{-1}): 3226-3134 (NH), 3064 (CH-aromatic), 2975-2878 (CH_2, CH_3), 2211 (CN), 1732 (C=O ester), 1603, 1477 (C=C), 1545 (C=N). ^{1}H NMR (*δ*, ppm): 1.27-1.39 (t, 3H, CH_3), 4.26-4.37 (q, 2H, CH_2), 7.14-7.53 (m, 5H, C_6H_5), 12.21 (s, 1H, D_2O exchangeable, NH). EIMS: m/e [M^+] = 217 (43%).

*(4-Methoxyphenyl)carbonohydrazonoyl dicyanide (**3c**)*. Brown crystals, m.p. 107-110 °C, yield: 1.98 g (99%). Elemental analysis calculated for $C_{10}H_8N_4O$ (200.20): C, 59.99; H, 4.03; N, 27.99%. Found: C, 60.20; H, 4.25; N, 27.70%. IR (ν, cm^{-1}): 3224-3128 (NH), 3056 (CH-aromatic), 2979-2844 (CH_3), 2224 (CN), 1596, 1445 (C=C), 1544 (C=N). ^{1}H NMR (*δ*, ppm): 3.76 (s, 3H, OCH_3), 6.96-7.41 (m, 4H, C_6H_4), 12.80 (s, 1H, D_2O exchangeable, NH). EIMS: m/e [M^+] = 200 (50%).

*Ethyl 2-cyano-2-(2-(4-methoxyphenyl)hydrazono)acetate (**3d**)*. Green crystals, m.p. 82-85 °C, yield: 2.4 g (97%). Elemental analysis calculated for $C_{12}H_{13}N_3O_3$ (247.25): C, 58.29; H, 5.30; N, 16.99%. Found: C, 58.40; H, 5.61; N, 16.70%. IR (ν, cm^{-1}): 3231-3140 (NH), 2994-2839 (CH_2, CH_3), 2210 (CN), 1732 (C=O ester), 1613, 1474 (C=C), 1512 (C=N). ^{1}H NMR (*δ*, ppm): 1.25-1.33 (t, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.21-4.32 (q, 2H, CH_2), 6.95-7.49 (m, 4H, C_6H_4), 12.20 (s, 1H, D_2O exchangeable, NH). EIMS: m/e [M^+] = 247 (60%).

*(4-Chlorophenyl)carbonohydrazonoyl dicyanide (**3e**)*. Dark yellow crystals, m.p. 167-170 °C, yield: 1.82 g (89%). Elemental analysis calculated for $C_9H_5ClN_4$ (204.62): C, 52.83; H, 2.46; N, 27.38%. Found: C, 52.60; H, 2.25; N, 27.70%. IR (ν, cm^{-1}): 3444-3127 (NH), 3105, 3060 (CH-

aromatic), 2227, 2212 (2CN), 1603, 1460 (C=C), 1542 (C=N). ^{1}H NMR (δ, ppm): 7.47-7.49 (m, 4H, C_6H_4), 12.10 (s, 1H, D_2O exchangeable, NH). EIMS: m/e [M^+] = 204 (68%).

*Ethyl 2-(2-(4-chlorophenyl)hydrazono)-2-cyanoacetate (**3f**)*. Yellow crystals, m.p. 112-115 °C, yield: 2.39 g (95%). Elemental analysis calculated for $C_{11}H_{10}ClN_3O_2$ (251.67): C, 52.50; H, 4.01; N, 16.70%. Found: C, 52.70; H, 4.31; N, 16.50%. IR (ν, cm^{-1}): 3216-3130 (NH), 3065 (CH-aromatic), 2975, 2933 (CH_2, CH_3), 2215 (CN), 1677 (C=O), 1603, 1480 (C=C), 1539 (C=N). ^{1}H NMR (δ, ppm): 1.26-1.32 (t, 3H, CH_3), 4.27-4.30 (q, 2H, CH_2), 7.46-7.48 (m, 4H, C_6H_4), 12.30 (s, 1H, D_2O exchangeable, NH). EIMS: m/e [M^+] = 251 (55%).

*General procedure for the synthesis of 4-(2-phenylhydrazono)-4H-pyrazol-3-amine derivatives (**5a-f**)*

To a solution of either of compounds **3a** (1.70 g, 0.01 mol), **3b** (2.17 g, 0.01 mol), **3c** (2.00 g, 0.01 mol), **3d** (2.47 g, 0.01 mol), **3e** (2.04 g, 0.01 mol) or **3f** (2.51 g, 0.01 mol) in absolute ethanol (25 mL), hyrazinhydrate (**4**) (1.06 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 1 hour. The solid product formed, in each case, upon pouring onto an ice/water mixture was collected by filtration and crystallized from absolute ethanol.

*4-(2-Phenylhydrazono)-4H-pyrazole-3,5-diamine (**5a**)*. Yellow crystals, m.p. 227-230 °C, yield: 1.98 g (98%). Elemental analysis calculated for $C_9H_{10}N_6$ (202.22): C, 53.46; H, 4.98; N, 41.56%. Found: C, 53.62; H, 4.71; N, 41.80%. IR (ν, cm^{-1}): 3462-3130 (NH_2, NH), 3062 (CH-aromatic), 1612, 1493 (C=C), 1558 (C=N). ^{1}H NMR (δ, ppm): 4.95, 5.80 (s, 4H, D_2O exchangeable, $2NH_2$), 7.18-7.67 (m, 5H, C_6H_5), 10.70 (s, 1H, D_2O exchangeable, NH). EIMS: m/e [M^+] = 202 (55%).

*5-Amino-4-(2-phenylhydrazono)-4H-pyrazol-3-ol (**5b**)*. Dark red crystals, m.p. 232-235 °C, yield: 1.97 g (97%). Elemental analysis calculated for $C_9H_9N_5O$ (203.20): C, 53.20; H, 4.46; N, 34.47%. Found: C, 53.50; H, 4.66; N, 34.10%. IR (ν, cm^{-1}): 3536-3197 (OH, NH_2, NH), 3056 (CH-aromatic), 1588, 1477 (C=C), 1562 (C=N). ^{1}H NMR (δ, ppm): 4.57 (s, 2H, D_2O exchangeable, NH_2), 7.09-7.54 (m, 7H, C_6H_5), 10.52 (s, 1H, D_2O exchangeable, NH), 12.93 (s, 1H, D_2O exchangeable, OH). EIMS: m/e [M^+] = 203 (60%).

*4-(2-(4-Methoxyphenyl)hydrazono)-4H-pyrazole-3,5-diamine (**5c**)*. Dark red crystals, m.p. 112-115 °C, yield: 2.02 g (86%). Elemental analysis calculated for $C_{10}H_{12}N_6O$ (232.24): C, 51.72; H, 5.21; N, 36.19%. Found: C, 51.90; H, 4.99; N, 36.30%. IR (ν, cm^{-1}): 3444 (OH), 3395, 3290 ($2NH_2$), 3194-3130 (NH), 3061 (CH-aromatic), 1598, 1496 (C=C), 1549 (C=N). ^{1}H NMR (δ, ppm): 3.84 (s, 3H, OCH_3), 4.63, 5.72 (2s, 4H, D_2O exchangeable, $2NH_2$), 6.92-7.70 (m, 4H, C_6H_4), 10.40 (s, 1H, D_2O exchangeable, NH). EIMS: m/e [M^+] = 232 (65%).

*5-Amino-4-(2-(4-methoxyphenyl)hydrazono)-4H-pyrazol-3-ol (**5d**)*. Dark green crystals, m.p. 172-175 °C, yield: 2.27 g (97%). Elemental analysis calculated for $C_{10}H_{11}N_5O_2$ (233.23): C, 51.50; H, 4.75; N, 30.03%. Found: C, 51.79; H, 4.98; N, 29.80%. IR (ν, cm^{-1}): 3442 (OH), 3420, 3336 (NH_2), 3228-3153 (NH), 1609, 1593 (C=C), 1538 (C=N). ^{1}H NMR (δ, ppm): 3.76 (s, 3H, OCH_3), 4.68 (s, 2H, D_2O exchangeable, NH_2), 6.95-7.50 (m, 4H, C_6H_4), 10.50 (s, 1H, D_2O exchangeable, NH), 12.0 (s, 1H, D_2O exchangeable, OH). EIMS: m/e [M^+] = 233 (65%).

*4-(2-(4-Chlorophenyl)hydrazono)-4H-pyrazole-3,5-diamine (**5e**)*. Pale yellow crystals, m.p. 217-220 °C, yield: 2.35 g (99%). Elemental analysis calculated for $C_9H_9ClN_6$ (236.66): C, 45.68; H, 3.83; N, 35.51%. Found: C, 45.88; H, 4.01; N, 35.81%. IR (ν, cm^{-1}): 3442 (OH), 3401, 3292 ($2NH_2$), 3190 (NH), 3084 (CH-aromatic), 1613, 1511 (C=C), 1560 (C=N). ^{1}H NMR (δ, ppm):

4.68, 5.49 (2s, 4H, D_2O exchangeable, $2NH_2$), 7.40-7.70 (m, 8H, C_6H_4), 10.80 (s, 1H, D_2O exchangeable, NH). EIMS: m/e [M^+] = 236 (70%).

5-Amino-4-(2-(4-chlorophenyl)hydrazono)-4H-pyrazol-3-ol ***(5f)***. Reddish brown crystals, m.p. 187-190 ºC, yield: 2.33 g (98%). Elemental analysis calculated for $C_9H_8ClN_5O$ (237.65): C, 45.49; H, 3.39; N, 29.47%. Found: C, 45.85; H, 3.60; N, 29.21%. IR (ν, cm^{-1}): 3465 (OH), 3401, 3350, 3293 (NH_2), 3175 (NH), 1634, 1485 (C=C), 1571 (C=N). ^{1}H NMR (δ, ppm): 5.32 (s, 2H, D_2O exchangeable, NH_2), 7.41-7.59 (m, 6H, C_6H_4), 10.20 (s, 1H, D_2O exchangeable, NH), 10.52 (s, 1H, D_2O exchangeable, OH). EIMS: m/e [M^+] = 237 (58%).

General procedure for the synthesis of 5-phenyl-3-(2-phenylhydrazono)-3,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazoline ***(8a-f)***

To a solution of either of compounds **5a** (2.02 g, 0.01 mol), **5b** (2.03 g, 0.01 mol), **5c** (2.32 g, 0.01 mol), **5d** (2.33 g, 0.01 mol), **5e** (2.36 g, 0.01 mol) or **5f** (2.37 g, 0.01 mol) in absolute ethanol (25 mL) and triethylamine, either benzaldehyde (**6a**) (1.06 g, 0.01 mol), *p*-methoxy benzaldehyde (**6b**) (1.08 g, 0.01 mol) or *p*-chloro benzaldehyde (**6c**) (1.40 g, 0.01 mol) was added with cyclohexanone (**7**) (0.98 g, 0.01 mol). The reaction mixture was heated under reflux for 1 hour. The solid products formed, in each case; upon pouring onto an ice/water/drops HCl mixture were collected by filtration and crystallized from absolute ethanol.

5-Phenyl-3-(2-phenylhydrazono)-3,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolin-2-amine ***(8a)***. Yellow crystals, m.p. 197-200 ºC, yield: 2.99 g (81%). Elemental analysis calculated for $C_{22}H_{22}N_6$ (370.45): C, 71.33; H, 5.99; N, 22.69%. Found: C, 71.24; H, 5.72; N, 22.80%. IR (ν, cm^{-1}): 3389-3178 (NH), 3062 (CH-aromatic), 2896 (CH_2), 1612, 1451 (C=C), 1557 (C=N). ^{1}H NMR (δ, ppm): 2.48-2.50 (m, 8H, $4CH_2$), 4.80 (s, 2H, D_2O exchangeable, NH_2), 7.18-7.62 (m, 11H, 2 C_6H_5, pyrimidine-H), 10.69 (s, 1H, D_2O exchangeable, NH).

5-(4-Methoxyphenyl)-3-(2-phenylhydrazono)-3,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolin-2-amine ***(8b)***. Orange crystals, m.p. 200-203 ºC, yield: 3.66 g (82%). Elemental analysis calculated for $C_{23}H_{24}N_6O$ (400.48): C, 68.98; H, 6.04; N, 20.99%. Found: C, 68.82; H, 5.91; N, 20.73%. IR (ν, cm^{-1}): 3390-3175 (NH_2, NH), 3063 (CH-aromatic), 2896, 2848 (CH_2, CH_3), 1612, 1452 (C=C), 1556 (C=N). ^{1}H NMR (δ, ppm): 2.47-2.51 (m, 8H, $4CH_2$), 3.87 (s, 3H, OCH_3), 4.80 (s, 2H, D_2O exchangeable, NH_2), 7.09-7.94 (m, 10H, C_6H_5, C_6H_4, pyrimidine-H), 10.69 (s, 1H, D_2O exchangeable, NH).

5-(4-Chlorophenyl)-3-(2-phenylhydrazono)-3,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolin-2-amine ***(8c)***. Dark yellow crystals, m.p. 207-210 ºC, yield: 3.07 g (76%). Elemental analysis calculated for $C_{22}H_{21}ClN_6$ (404.90): C, 65.26; H, 5.23; N, 20.76%. Found: C, 65.52; H, 5.46; N, 20.50%. IR (ν, cm^{-1}): 3390-3182 (NH_2, NH), 3063 (CH-aromatic), 2896 (CH_2, CH_3), 1613, 1452 (C=C), 1557 (C=N). ^{1}H NMR (δ, ppm): 2.45-2.52 (m, 8H, $4CH_2$), 4.83 (s, 2H, D_2O exchangeable, NH_2), 7.18-8.02 (m, 10H, C_6H_5, C_6H_4, pyrimidine-H), 10.69 (s, 1H, D_2O exchangeable, NH).

5-Phenyl-3-(2-phenylhydrazono)-3,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolin-2-ol ***(8d)***. Dark orange crystals, m.p. 182-185 ºC, yield: 3.22 g (87%). Elemental analysis calculated for $C_{22}H_{21}N_5O$ (371.44): C, 71.14; H, 5.70; N, 18.85%. Found: C, 71.44; H, 5.59; N, 18.69%. IR (ν, cm^{-1}): 3506-3232 (OH, NH), 3078 (CH-aromatic), 2943, 2915 (CH_2, CH_3), 1600, 1484 (C=C), 1554 (C=N). ^{1}H NMR (δ, ppm): 2.48-2.53 (m, 8H, $4CH_2$), 7.12-7.93 (m, 11H, $2C_6H_5$, pyrimidine-H), 8.28 (s, 1H, D_2O exchangeable, NH)., 10.02 (s, 1H, D_2O exchangeable, OH).

5-(4-Methoxyphenyl)-3-(2-phenylhydrazono)-3,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolin-2-ol ***(8e)***. Orange crystals, m.p. 188-190 ºC, yield: 3.08 g (77%). Elemental analysis calculated for $C_{23}H_{23}N_5O_2$ (401.46): C, 68.81; H, 5.77; N, 17.44%. Found: C, 68.66; H, 5.59; N, 17.60%. IR (ν, cm^{-1}): 3479-3199 (OH, NH), 3057 (CH-aromatic), 1635, 1483 (C=C), 1561 (C=N). ^{1}H NMR (*δ*, ppm): 2.44-2.50 (m, 8H, $4CH_2$), 3.86 (s, 3H, OCH_3), 6.93-7.97 (m, 10H, C_6H_5, C_6H_4, pyrimidine-H), 8.49 (s, 1H, D_2O exchangeable, NH_2), 10.53 (s, 1H, D_2O exchangeable, OH).

5-(4-Chlorophenyl)-3-(2-phenylhydrazono)-3,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolin-2-ol ***(8f)***. Red crystals, m.p. 127-130 ºC, yield: 3.24 g (80%). Elemental analysis calculated for $C_{22}H_{20}ClN_5O$ (405.88): C, 65.10; H, 4.97; N, 17.25%. Found: C, 65.32; H, 5.01; N, 17.40%. IR (ν, cm^{-1}): 3524-3220 (OH, NH), 3055 (CH-aromatic), 1610, 1485 (C=C), 1551 (C=N). ^{1}H NMR (*δ*, ppm): 2.47-2.50 (m, 8H, $4CH_2$), 7.12-8.05 (m, 10H, C_6H_5, C_6H_4, pyrimidine-H), 8.39 (s, 1H, D_2O exchangeable, NH), 10.01 (s, 1H, D_2O exchangeable, NH).

General procedure for the synthesis of 5-phenyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one ***(10a-s)***

To a solution of either of compounds **5a** (2.02 g, 0.01 mol), **5b** (2.03 g, 0.01 mol), **5c** (2.32 g, 0.01 mol), **5d** (2.33 g, 0.01 mol), **5e** (2.36 g, 0.01 mol) or **5f** (2.37 g, 0.01 mol) in absolute ethanol (25 mL) and triethylamine, either benzaldehyde (**6a**) (1.06 g, 0.01 mol), *p*-methoxy benzaldehyde (**6b**) (1.08 g, 0.01 mol) or *p*-chloro benzaldehyde (**6c**) (1.40 g, 0.01 mol) was added with cyclohexane-1,3-dione (**9**) (1.12 g, 0.01 mol). The reaction mixture was heated under reflux for 1 hour. The solid products formed, in each case; upon pouring onto ice/water/drops HCl mixture were collected by filtration and crystallized from absolute ethanol.

2-Amino-5-phenyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one ***(10a)***. Faint brown crystals, m.p. 112-115 ºC, yield: 3.81 g (99%). Elemental analysis calculated for $C_{22}H_{20}N_6O$ (384.43): C, 68.73; H, 5.24; N, 21.86%. Found: C, 68.93; H, 5.41; N, 21.50%. IR (ν, cm^{-1}): 3338-3306 (NH_2, NH), 2947 (CH_2), 1636 (C=O), 1597, 1423 (C=C), 1576 (C=N). ^{1}H NMR (*δ*, ppm): 1.80-1.90 (m, 4H, $2CH_2$), 2.65 (m, 2H, CH_2), 4.88 (s, 2H, D_2O exchangeable, NH_2), 5.91 (s, 1H, pyrimidine-H), 7.18-7.82 (m, 10H, $2C_6H_5$,), 10.90 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (*δ*, ppm): 21.1, 26.6, 36.8, 57.1, 108.4, 113.6 (2), 121.9, 126.6 (2), 127.5, 128.4 (2), 129.4, 129.5, 137.5, 142.2, 145.0, 147.1, 151.2. 153.1, 196.8.

2-Amino-5-(4-methoxyphenyl)-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one ***(10b)***. Yellow crystals, m.p. 157-160 ºC, yield: 3.27 g (79%). Elemental analysis calculated for $C_{23}H_{22}N_6O_2$ (414.46): C, 66.65; H, 5.35; N, 20.28%. Found: C, 66.90; H, 5.61; N, 19.90%. IR (ν, cm^{-1}): 3330, 3231 (NH_2, NH), 3067 (CH-aromatic), 2946, 2871 (CH_2, CH_3), 1719 (C=O), 1596, 1491 (C=C). ^{1}H NMR (*δ*, ppm): 1.86-1.902 (m, 4H, $2CH_2$), 2.64 (m, 2H, CH_2), 3.57 (s, 3H, OCH_3), 4.85 (s, 2H, D_2O exchangeable, NH_2), 5.90 (s, 1H, pyrimidine-H), 6.89-7.95 (m, 9H, C_6H_5, C_6H_4), 10.01 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (δ, ppm): 21.2, 26.7, 36.8, 56.7, 59.9, 107.8, 113.9 (2), 115.5, 115.7, 121.6, 129.0, 129.4, 130.1, 130.3, 135.3, 139.9, 141.6, 144.6, 151.4, 153.5, 165.4, 196.8.

2-Amino-5-(4-chlorophenyl)-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one ***(10c)***. Yellow crystals, m.p. 102-105 ºC, yield: 3.27 g (78%). Elemental analysis calculated for $C_{22}H_{19}ClN_6O$ (418.88): C, 63.08; H, 4.57; N, 20.06%. Found: C, 63.20; H, 4.71; N, 19.81%. IR (ν, cm^{-1}): 3430, 3237 (NH_2, NH), 3064 (CH-aromatic), 2946, 2871 (CH_2, CH_3), 1730 (C=O), 1580, 1439 (C=C), 1556 (C=N). ^{1}H NMR (*δ*, ppm): 1.85 (m, 4H, $2CH_2$), 2.72 (m, 2H, CH_2), 4.88 (s, 2H, D_2O exchangeable, NH_2), 5.86 (s, 1H, pyrimidine-H), 6.81-7.86 (m, 9H, C_6H_5, C_6H_4), 10.80 (s, 1H, D_2O exchangeable, NH).

2-Hydroxy-5-phenyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (***10d***). Dark orange crystals, m.p. 122-125 °C, yield: 2.89 g (75%). Elemental analysis calculated for $C_{22}H_{19}N_5O_2$ (385.42): C, 68.56; H, 4.97; N, 18.17%. Found: C, 68.83; H, 5.21; N, 17.90%. IR (ν, cm^{-1}): 3418-3246 (OH, NH), 3054 (CH-aromatic), 2944 (CH_2), 1719 (C=O), 1594, 1491 (C=C), 1556 (C=N). ^{1}H NMR (*δ*, ppm): 1.90-1.94 (m, 4H, $2CH_2$), 2.85 (m, 2H, CH_2), 5.81 (s, 1H, pyrimidine-H), 6.99-7.65 (m, 10H, $2C_6H_5$), 10.00 (s, 1H, D_2O exchangeable, NH), 13.10 (s, 1H, D_2O exchangeable, OH).

2-Hydroxy-5-(4-methoxyphenyl)-3-(2-phenylhydrazono)-5,7,8,9-tetrahydro-pyrazolo[1,5-a]-quinazolin-6(3H)-one (***10e***). Orange crystals, m.p. 152-155 °C, yield: 3.61 g (87%). Elemental analysis calculated for $C_{23}H_{21}N_5O_3$ (415.44): C, 66.49; H, 5.09; N, 16.86%. Found: C, 66.70; H, 5.31; N, 16.50%. IR (ν, cm^{-1}): 3529-3197 (OH, NH), 2958, 2836 (CH_2, CH_3), 1721 (C=O), 1632, 1484 (C=C), 1591 (C=N). ^{1}H NMR (*δ*, ppm): 1.84-1.90 (m, 4H, $2CH_2$), 2.35 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3), 5.80 (s, 1H, pyrimidine-H), 6.84-7.65 (m, 9H, C_6H_5, C_6H_4), 10.52 (s, 1H, D_2O exchangeable, NH), 13.01 (s, 1H, D_2O exchangeable, OH).

5-(4-Chlorophenyl)-2-hydroxy-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]-quinazolin-6(3H)-one (***10f***). Orange crystals, m.p. 112-115 °C, yield: 3.23 g (77%). Elemental analysis calculated for $C_{22}H_{18}ClN_5O_2$ (419.86): C, 62.93; H, 4.32; N, 16.68%. Found: C, 63.20; H, 4.61; N, 16.30%. IR (ν, cm^{-1}): 3507-3337 (OH, NH), 2958, 2886 (CH_2), 1719 (C=O), 1631, 1489 (C=C), 1597 (C=N). ^{1}H NMR (*δ*, ppm): 1.86-1.94 (m, 4H, $2CH_2$), 2.65 (m, 2H, CH_2), 5.80 (s, 1H, pyrimidine-H), 6.89-7.25 (m, 9H, C_6H_5, C_6H_4), 10.00 (s, 1H, D_2O exchangeable, NH), 13.00 (s, 1H, D_2O exchangeable, OH). ^{13}C NMR (δ ppm): 20.9, 26.9, 36.8, 59.9, 100.5, 115.6, 115.7, 116.4, 127.6, 127.7, 128.3, 128.8, 130.1, 130.3, 130.8, 131.2, 131.6, 144.0, 165.4, 168.3, 196.8.

2-Amino-3-(2-(4-methoxyphenyl)hydrazono)-5-phenyl-5,7,8,9-tetrahydropyrazolo-[1,5-a]-quinazolin-6(3H)-one (***10g***). Dark red crystals, m.p. 152-155 °C, yield: 2.94 g (71%). Elemental analysis calculated for $C_{23}H_{22}N_6O_2$ (414.46): C, 66.65; H, 5.35; N, 20.28%. Found: C, 66.80; H, 5.62; N, 19.90%. IR (ν, cm^{-1}): 3250, 3304 (NH_2), 3210 (NH), 3024 (CH-aromatic), 2947, 2836 (CH_2, CH_3), 1719 (C=O), 1597, 1494 (C=C). ^{1}H NMR (δ, ppm): 1.86-1.98 (m, 4H, $2CH_2$), 2.65 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.96 (s, 2H, D_2O exchangeable, NH_2), 5.90 (s, 1H, pyrimidine-H), 6.98-7.80 (m, 9H, C_6H_5, C_6H_4), 10.75 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (*δ* ppm): 21.0, 26.9, 36.9, 55.9, 114.6, 115.2, 116.0, 116.2, 123.1, 125.6, 126.7, 128.4, 145.0, 145.7, 147.6, 165.3, 167.9, 196.8.

2-Amino-5-(4-methoxyphenyl)-3-(2-(4-methoxyphenyl)hydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (***10h***). Brown crystals, m.p. 122-125 °C, yield: 3.33 g (75%). Elemental analysis calculated for $C_{24}H_{24}N_6O_3$ (444.49): C, 64.85; H, 5.44; N, 18.91%. Found: C, 65.10; H, 5.62; N, 18.69%. IR (ν, cm^{-1}): 3380, 3250 (NH_2), 3200 (NH), 2955-2836 (CH_2, CH_3), 1720 (C=O), 1599, 1508 (C=C). ^{1}H NMR (*δ*, ppm): 1.91-1.95 (m, 4H, $2CH_2$), 2.61 (m, 2H, CH_2), 3.69-3.87 (s, 6H, $2OCH_3$), 4.94 (s, 2H, D_2O exchangeable, NH_2), 5.82 (s, 1H, pyrimidine-H), 6.74-7.76 (m, 8H, $2C_6H_4$), 9.87 (s, 1H, D_2O exchangeable, NH).

2-Amino-5-(4-chlorophenyl)-3-(2-(4-methoxyphenyl)hydrazono)-5,7,8,9-tetrahydro-pyrazolo-[1,5-a]quinazolin-6(3H)-one (***10i***). Orange crystals, m.p. 152-155 °C, yield: 2.24 g (50%). Elemental analysis calculated for $C_{23}H_{21}ClN_6O_2$ (448.90): C, 61.54; H, 4.72; N, 18.72%. Found: C, 61.73; H, 4.90; N, 18.49%. IR (ν, cm^{-1}): 3451, 3293 (NH, NH_2), 3067 (CH-aromatic), 2945-2836 (CH_2, CH_3), 1718 (C=O), 1596, 1491 (C=C). ^{1}H NMR (*δ*, ppm): 1.92-1.95 (m, 4H, $2CH_2$), 2.64 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.91 (s, 2H, D_2O exchangeable, NH_2), 5.90 (s, 1H, pyrimidine-H), 7.01-7.95 (m, 8H, $2C_6H_4$), 10.01 (s, 1H, D_2O exchangeable, NH).

*2-Hydroxy-3-(2-(4-methoxyphenyl)hydrazono)-5-phenyl-5,7,8,9-tetrahydro-pyrazolo[1,5-a]-quinazolin-6(3H)-one (**10k**)*. Dark orange crystals, m.p. 162-165 °C, yield: 3.45 g (83%). Elemental analysis calculated for $C_{23}H_{21}N_5O_3$ (415.44): C, 66.49; H, 5.09; N, 16.86%. Found: C, 66.69; H, 5.40; N, 16.50%. IR (ν, cm^{-1}): 3509-3305 (OH, NH), 3054-3023 (CH-aromatic), 2961-2836 (CH_2, CH_3), 1720 (C=O), 1595, 1493 (C=C), 1538 (C=N). ^{1}H NMR (*δ*, ppm): 1.86-1.96 (m, 4H, $2CH_2$), 2.63 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 5.75 (s, 1H, pyrimidine-H), 6.98-7.75 (m, 9H, C_6H_4, C_6H_5), 10.02 (s, 1H, D_2O exchangeable, NH), 12.20 (s, 1H, D_2O exchangeable, OH).

*2-Hydroxy-5-(4-methoxyphenyl)-3-(2-(4-methoxyphenyl)hydrazono)-5,7,8,9-tetrahydropyrazo-lo[1,5-a]quinazolin-6(3H)-one (**10l**)*. Faint brown crystals, m.p. 147-150 °C, yield: 3.25 g (73%). Elemental analysis calculated for $C_{24}H_{23}N_5O_4$ (445.47): C, 64.71; H, 5.20; N, 15.72%. Found: C, 64.93; H, 5.60; N, 15.39%. IR (ν, cm^{-1}): 3731-3255 (OH, NH), 3029 (CH-aromatic), 2917, 2837 (CH_2, CH_3), 1720 (C=O), 1601, 1509 (C=C). ^{1}H NMR (*δ*, ppm): 1.84-1.98 (m, 4H, $2CH_2$), 2.60 (m, 2H, CH_2), 3.68-3.87 (s, 6H, $2OCH_3$), 5.70 (s, 1H, pyrimidine-H), 6.74-7.89 (m, 8H, $2C_6H_4$), 9.87 (s, 1H, D_2O exchangeable, NH), 13.00 (s, 1H, D_2O exchangeable, OH).

*5-(4-Chlorophenyl)-2-hydroxy-3-(2-(4-methoxyphenyl)hydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (**10m**)*. Faint orange crystals, m.p. 152-155 °C, yield: 4.46 g (99%). Elemental analysis calculated for $C_{23}H_{20}ClN_5O_3$ (449.89): C, 61.40; H, 4.48; N, 15.57%. Found: C, 61.63; H, 4.70; N, 15.20%. IR (ν, cm^{-1}): 3437-3246 (OH, NH), 3045 (CH-aromatic), 2945-2837 (CH_2, CH_3), 1718 (C=O), 1601, 1444 (C=C), 1547 (C=N). ^{1}H NMR (*δ*, ppm): 1.92-1.95 (m, 4H, $2CH_2$), 2.64 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 5.70 (s, 1H, pyrimidine-H), 7.00-7.36 (m, 8H, $2C_6H_4$), 10.00 (s, 1H, D_2O exchangeable, NH), 12.20 (s, 1H, D_2O exchangeable, OH).

*2-Amino-3-(2-(4-chlorophenyl)hydrazono)-5-phenyl-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazo-lin-6(3H)-one (**10n**)*. Yellow crystals, m.p. 112-115 °C, yield: 3.39 g (81%). Elemental analysis calculated for $C_{22}H_{19}ClN_6O$ (418.88): C, 63.08; H, 4.57; N, 20.06%. Found: C, 63.39; H, 4.70; N, 19.80%. IR (ν, cm^{-1}): 3541 (NH), 3434, 3307 (NH_2), 3054-3023 (CH-aromatic), 2945, 2921 (CH_2), 1720 (C=O), 1590, 1479 (C=C). ^{1}H NMR (*δ*, ppm): 1.85-1.97 (m, 4H, $2CH_2$), 2.60 (m, 2H, CH_2), 4.91 (s, 2H, D_2O exchangeable, NH_2), 5.90 (s, 1H, pyrimidine-H), 7.18-7.84 (m, 9H, C_6H_4, C_6H_5), 10.00 (s, 1H, D_2O exchangeable, NH).

*2-Amino-3-(2-(4-chlorophenyl)hydrazono)-5-(4-methoxyphenyl)-5,7,8,9-tetrahydro-pyrazolo-[1,5-a]quinazolin-6(3H)-one (**10o**)*. Faint orange crystals, m.p. 122-125 °C, yield: 3.59 g (80%). Elemental analysis calculated for $C_{23}H_{21}ClN_6O_2$ (448.90): C, 61.54; H, 4.72; N, 18.72%. Found: C, 61.79; H, 4.95; N, 18.40%. IR (ν, cm^{-1}): 3520 (NH), 3382, 3306 (NH_2), 2957-2836 (CH_2, CH_3), 1720 (C=O), 1601, 1439 (C=C), 1509 (C=N). ^{1}H NMR (*δ*, ppm): 1.80-1.93 (m, 4H, $2CH_2$), 2.61 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3), 4.91 (s, 2H, D_2O exchangeable, NH_2), 5.60 (s, 1H, pyrimidine-H), 6.47-7.49 (m, 8H, $2C_6H_4$), 9.90 (s, 1H, D_2O exchangeable, NH).

*2-Amino-5-(4-chlorophenyl)-3-(2-(4-chlorophenyl)hydrazono)-5,7,8,9-tetrahydro-pyrazolo[1,5-a]quinazolin-6(3H)-one (**10p**)*. Canary yellow crystals, m.p. 147-150 °C, yield: 4.44 g (98%). Elemental analysis calculated for $C_{22}H_{18}Cl_2N_6O$ (453.32): C, 58.29; H, 4.00; N, 18.54%. Found: C, 58.49; H, 4.35; N, 18.20%. IR (ν, cm^{-1}): 3717, 3346 (NH, NH_2), 2946, 2873 (CH_2, CH_3), 1718 (C=O), 1594, 1491 (C=C). ^{1}H NMR (*δ*, ppm): 1.91-1.95 (m, 4H, $2CH_2$), 2.62 (m, 2H, CH_2), 4.93 (s, 2H, D_2O exchangeable, NH_2), 5.91 (s, 1H, pyrimidine-H), 7.18-7.95 (m, 8H, $2C_6H_4$), 10.00 (s, 1H, D_2O exchangeable, NH).

*3-(2-(4-Chlorophenyl)hydrazono)-2-hydroxy-5-phenyl-5,7,8,9-tetrahydropyrazolo-[1,5-a]quin-azolin-6(3H)-one (**10q**)*. Orange crystals, m.p.127-130 °C, yield: 3.86 g (92%). Elemental analysis calculated for $C_{22}H_{18}ClN_5O_2$ (419.11): C, 62.93; H, 4.32; N, 16.68%. Found: C, 63.20; H, 4.62;

N, 16.30%. IR (ν, cm^{-1}): 3685-3234 (OH, NH), 2952 (CH_2), 1719 (C=O), 1632, 1485 (C=C), 1590 (C=N). ^{1}H NMR (δ, ppm): 1.92-1.94 (m, 4H, $2CH_2$), 2.65 (m, 2H, CH_2), 5.90 (s, 1H, pyrimidine-H), 6.98-7.71 (m, 9H, C_6H_4, C_6H_5), 10.00 (s, 1H, D_2O exchangeable, NH), 13.00 (s, 1H, D_2O exchangeable, OH).

*3-(2-(4-Chlorophenyl)hydrazono)-2-hydroxy-5-(4-methoxyphenyl)-5,7,8,9-tetra-hydropyrazolo[1,5-a]quinazolin-6(3H)-one (**10r**)*. Brown crystals, m.p. 157-160 ºC, yield: 4.45 g (99%). Elemental analysis calculated for $C_{23}H_{20}ClN_5O_3$ (449.89): C, 61.40; H, 4.48; N, 15.57%. Found: C, 61.70; H, 4.72; N, 15.20%. IR (ν, cm^{-1}): 3459-3178 (OH, NH), 2960-2837 (CH_2, CH_3), 1720 (C=O), 1601, 1445 (C=C), 1510 (C=N). ^{1}H NMR (δ, ppm): 1.91-1.95 (m, 4H, $2CH_2$), 2.63 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 5.70 (s, 1H, pyrimidine-H), 6.74-7.70 (m, 8H, $2C_6H_4$), 10.50 (s, 1H, D_2O exchangeable, NH), 13.00 (s, 1H, D_2O exchangeable, OH).

*5-(4-Chlorophenyl)-3-(2-(4-chlorophenyl)hydrazono)-2-hydroxy-5,7,8,9-tetrahydro-pyrazolo-[1,5-a]quinazolin-6(3H)-one (**10s**)*. Faint orange crystals, m.p. 132-135 ºC, yield: 3.41 g (75%). Elemental analysis calculated for $C_{22}H_{17}Cl_2N_5O_2$ (454.31): C, 58.16; H, 3.77; N, 15.42%. Found: C, 58.30; H, 3.99; N, 15.10%. IR (ν, cm^{-1}): 3450, 3138 (OH, NH), 3068 (CH-aromatic), 2946, 2873 (CH_2), 1719 (C=O), 1593, 1486 (C=C). ^{1}H NMR (δ, ppm): 1.87-1.95 (m, 4H, $2CH_2$), 2.64 (m, 2H, CH_2), 5.70 (s, 1H, pyrimidine-H), 7.18-7.95 (m, 8H, $2C_6H_4$), 10.00 (s, 1H, D_2O exchangeable, NH), 12.30 (s, 1H, D_2O exchangeable, OH).

*General procedure for the synthesis of 8,8-dimethyl-5-phenyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one (**12a-s**)*

To a solution of either of compounds **5a** (2.02 g, 0.01 mol), **5b** (2.03 g, 0.01 mol), **5c** (2.32 g, 0.01 mol), **5d** (2.33 g, 0.01 mol), **5e** (2.36 g, 0.01 mol) or **5f** (2.37 g, 0.01 mol) in absolute ethanol (25 mL) and triethylamine, either benzaldehyde (**6a**) (1.06 g, 0.01 mol), *p*-methoxy benzaldehyde (**6b**) (1.08 g, 0.01 mol) or *p*-chloro benzaldehyde (**6c**) (1.40 g, 0.01 mol) was added with 5,5-dimethylcyclohexane-1,3-dione (**11**) (1.40 g, 0.01 mol). The reaction mixture was heated under reflux for 1 hour. The solid products formed, in each case; upon pouring onto ice/water/drops HCl mixture were collected by filtration and crystallized from absolute ethanol.

*2-Amino-8,8-dimethyl-5-phenyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (**12a**)*. Yellow crystals, m.p. 112-115 ºC, yield: 3.51 g (85%). Elemental analysis calculated for $C_{24}H_{24}N_6O$ (412.49): C, 69.88; H, 5.86; N, 20.37%. Found: C, 69.60; H, 5.99; N, 20.01%. IR (ν, cm^{-1}): 3417, 3319 (NH_2, NH), 3042 (CH-aromatic), 2956-2868 (CH_2, CH_3), 1670 (C=O), 1590, 1451 (C=C). ^{1}H NMR (δ, ppm): 0.95-1.01 (s, 6H, $2CH_3$), 2.30 (m, 4H, $2CH_2$), 4.93 (s, 2H, D_2O exchangeable, NH_2), 5.90 (s, 1H, pyrimidine-H), 7.16-7.68 (m, 10H, $2C_6H_5$), 10.00 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (δ, ppm): 27.2 (2), 32.6, 39.3, 50.3, 57.5, 107.2, 113.9, 121.6, 125.3, 126.6, 128.6 (2), 129.6, 130.0, 142.7, 149.2, 153.5, 193.5.

*2-Amino-5-(4-methoxyphenyl)-8,8-dimethyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one (**12b**)*. Faint yellow crystals, m.p. 152-155 ºC, yield: 3.19 g (72%). Elemental analysis calculated for $C_{25}H_{26}N_6O_2$ (442.51): C, 67.86; H, 5.92; N, 18.99%. Found: C, 67.99; H, 6.20; N, 18.66%. IR (ν, cm^{-1}): 3404 (NH), 3270, 3188 (NH_2), 3064 (CH-aromatic), 2957-2837 (CH_2, CH_3), 1675 (C=O), 1605, 1454 (C=C), 1551 (C=N). ^{1}H NMR (δ, ppm): 0.90-1.03 (s, 6H, $2CH_3$), 2.09-2.32 (m, 4H, $2CH_2$), 3.87 (s, 3H, OCH_3), 4.93 (s, 2H, D_2O exchangeable, NH_2), 5.85 (s, 1H, pyrimidine-H), 6.75-7.89 (m, 9H, C_6H_5, C_6H_4), 9.87 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (δ, ppm): 26.9, 27.3, 32.4, 39.3, 50.5, 55.5, 56.1, 113.8, 113.9, 114.4, 114.9, 121.8, 129.3, 129.4, 130.1, 132.3, 136.9, 147.7, 153.4, 158.0, 159.2, 163.2, 196.6.

*2-Amino-5-(4-chlorophenyl)-8,8-dimethyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (**12c**)*. Dark yellow crystals, m.p. 122-125 ºC, yield: 3.17 g (71%). Elemental analysis calculated for $C_{24}H_{23}ClN_6O$ (446.93): C, 64.50; H, 5.19; N, 18.80%. Found: C, 64.79; H, 5.30; N, 18.56%. IR (ν, cm^{-1}): 3545 (NH), 3307, 3172 (NH_2), 2956-2868 (CH_2, CH_3), 1670 (C=O), 1588, 1489 (C=C). ^{1}H NMR (*δ*, ppm): 0.95-1.19 (s, 6H, $2CH_3$), 2.19-2.27 (m, 4H, $2CH_2$), 4.93 (s, 2H, D_2O exchangeable, NH_2), 6.03 (s, 1H, pyrimidine-H), 6.96-8.02 (m, 9H, C_6H_5, C_6H_4), 10.00 (s, 1H, D_2O exchangeable, NH).

*2-Hydroxy-8,8-dimethyl-5-phenyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydro-pyrazolo[1,5-a]-quinazolin-6(3H)-one (**12d**)*. Orange crystals, m.p. 172-175 ºC, yield: 4.01 g (97%). Elemental analysis calculated for $C_{24}H_{23}N_5O_2$ (413.47): C, 69.72; H, 5.61; N, 16.94%. Found: C, 69.99; H, 5.30; N, 16.66%. IR (ν, cm^{-1}): 3457-3185 (OH, NH), 3032 (CH-aromatic), 2957-2868 (CH_2, CH_3), 1666 (C=O), 1557, 1448 (C=C). ^{1}H NMR (*δ*, ppm): 1.04-1.05 (s, 6H, $2CH_3$), 2.30-2.31 (m, 4H, $2CH_2$), 5.80 (s, 1H, pyrimidine-H), 6.88-7.65 (m, 10H, $2C_6H_5$), 10.50 (s, 1H, D_2O exchangeable, NH), 13.00 (s, 1H, D_2O exchangeable, OH).

*2-Hydroxy-5-(4-methoxyphenyl)-8,8-dimethyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazo-lo[1,5-a]quinazolin-6(3H)-one (**12e**)*. Red crystals, m.p. 137-140 ºC, yield: 3.86 g (87%). Elemental analysis calculated for $C_{25}H_{25}N_5O_3$ (443.50): C, 67.70; H, 5.68; N, 15.79%. Found: C, 67.90; H, 5.90; N, 15.50%. IR (ν, cm^{-1}): 3451-3180 (OH, NH), 3034 (CH-aromatic), 2954, 2836 (CH_2, CH_3), 1672 (C=O), 1632, 1492 (C=C), 1564 (C=N). ^{1}H NMR (*δ*, ppm): 1.00-1.04 (s, 6H, $2CH_3$), 2.16-2.30 (m, 4H, $2CH_2$), 3.87 (s, 3H, OCH_3), 5.80 (s, 1H, pyrimidine-H), 6.88-7.54 (m, 9H, C_6H_5, C_6H_4), 10.50 (s, 1H, D_2O exchangeable, NH), 13.10 (s, 1H, D_2O exchangeable, OH).

*5-(4-Chlorophenyl)-2-hydroxy-8,8-dimethyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (**12f**)*. Reddish brown crystals, m.p. 122-125 ºC, yield: 3.23 g (72%). Elemental analysis calculated for $C_{24}H_{22}ClN_5O_2$ (447.92): C, 64.35; H, 4.95; N, 15.64%. Found: C, 64.60; H, 5.20; N, 15.30%. IR (ν, cm^{-1}): 3406-3183 (OH, NH), 3118 (CH-aromatic), 2954-2866 (CH_2, CH_3), 1666 (C=O), 1621, 1485 (C=C), 1555 (C=N). ^{1}H NMR (*δ*, ppm): 0.97-1.03 (s, 6H, $2CH_3$), 2.18-2.30 (m, 4H, $2CH_2$), 5.80 (s, 1H, pyrimidine-H), 6.92-7.54 (m, 9H, C_6H_5, C_6H_4), 10.50 (s, 1H, NH), 13.10 (s, 1H, D_2O exchangeable, OH).

*2-Amino-3-(2-(4-methoxyphenyl)hydrazono)-8,8-dimethyl-5-phenyl-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (**12g**)*. Brown crystals, m.p. 137-140 ºC, yield: 4.38 g (99%). Elemental analysis calculated for $C_{25}H_{26}N_6O_2$ (442.51): C, 67.86; H, 5.92; N, 18.99%. Found: C, 68.01; H, 6.20; N, 18.66%. IR (ν, cm^{-1}): 3528-3307 (NH, NH_2), 3079 (CH-aromatic), 2997-2930 (CH_2, CH_3), 1670 (C=O), 1592, 1450 (C=C). ^{1}H NMR (*δ*, ppm): 0.96-1.09 (s, 6H, $2CH_3$), 2.30-2.49 (m, 4H, $2CH_2$), 3.84 (s, 3H, OCH_3), 4.90 (s, 2H, D_2O exchangeable, NH_2), 5.95 (s, 1H, pyrimidine-H), 6.96-7.97 (m, 9H, C_6H_5, C_6H_4), 10.02 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (δ, ppm): 28.3, 32.6, 39.3, 47.1, 55.8, 66.8, 114.5, 114.6, 115.0, 123.8, 125.5, 126.4, 128.3, 128.6, 135.0, 141.4, 193.7.

*2-Amino-5-(4-methoxyphenyl)-3-(2-(4-methoxyphenyl)hydrazono)-8,8-dimethyl-5,7,8,9-tetra-hydropyrazolo[1,5-a]quinazolin-6(3H)-one (**12h**)*. Brown crystals, m.p. 97-100 ºC, yield: 3.45 g (73%). Elemental analysis calculated for $C_{26}H_{28}N_6O_3$ (472.54): C, 66.09; H, 5.97; N, 17.78%. Found: C, 66.31, H, 6.30; N, 17.58%. IR (ν, cm^{-1}): 3425-3317 (NH, NH_2), 2954-2835 (CH_2, CH_3), 1675 (C=O), 1591, 1497 (C=C). ^{1}H NMR (δ, ppm): 0.98-1.09 (s, 6H, $2CH_3$), 2.22-2.49 (m, 4H, $2CH_2$), 3.76-3.86 (s, 6H, $2OCH_3$), 4.94 (s, 2H, D_2O exchangeable, NH_2), 5.83 (s, 1H, pyrimidine-H), 6.76-7.97 (m, 8H, $2C_6H_4$), 9.87 (s, 1H, D_2O exchangeable, NH).

2-Amino-5-(4-chlorophenyl)-3-(2-(4-methoxyphenyl)hydrazono)-8,8-dimethyl-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one (***12i***). Dark red crystals, m.p. 137-140 ºC, yield: 3.58 g (75%). Elemental analysis calculated for $C_{25}H_{25}ClN_6O_2$ (476.96): C, 62.95; H, 5.28; N, 17.62%. Found: C, 63.21; H, 5.60; N, 17.48%. IR (ν, cm^{-1}): 3369-3297 (NH, NH_2), 3009 (CH-aromatic), 2955-2869 (CH_2, CH_3), 1673 (C=O), 1591, 1492 (C=C), 1554 (C=N). ^{1}H NMR (*δ*, ppm): 0.94-1.08 (s, 6H, $2CH_3$), 2.28-2.30 (m, 4H, $2CH_2$), 3.83 (s, 3H, OCH_3), 4.96 (s, 2H, D_2O exchangeable, NH_2), 5.95 (s, 1H, pyrimidine-H), 6.96-7.95 (m, 8H, $2C_6H_4$), 10.00 (s, 1H, D_2O exchangeable, NH).

2-Hydroxy-3-(2-(4-methoxyphenyl)hydrazono)-8,8-dimethyl-5-phenyl-5,7,8,9-tetrahydro-pyrazolo[1,5-a]quinazolin-6(3H)-one (***12k***). Dark orange crystals, m.p. 97-100 ºC, yield: 3.46 g (78%). Elemental analysis calculated for $C_{25}H_{25}N_5O_3$ (443.50): C, 67.70; H, 5.68; N, 15.79%. Found: C, 67.90; H, 5.80; N, 15.47%. IR (ν, cm^{-1}): 3444-3204 (OH, NH), 3022 (CH-aromatic), 2960-2837 (CH_2, CH_3), 1675 (C=O), 1589, 1492 (C=C). ^{1}H NMR (*δ*, ppm): 0.95-1.09 (s, 6H, $2CH_3$), 2.27-2.37 (m, 4H, $2CH_2$), 3.78 (s, 3H, OCH_3), 5.93 (s, 1H, pyrimidine-H), 6.80-7.61 (m, 9H, C_6H_4, C_6H_5), 10.00 (s, 1H, D_2O exchangeable, NH), 13.20 (s, 1H, D_2O exchangeable, OH).

2-Hydroxy-5-(4-methoxyphenyl)-3-(2-(4-methoxyphenyl)hydrazono)-8,8-dimethyl-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one (***12l***). Greenish brown crystals, m.p. 117-120 ºC, yield: 3.50 g (74%). Elemental analysis calculated for $C_{26}H_{27}N_5O_4$ (473.52): C, 65.95; H, 5.75; N, 14.79%. Found: C, 66.20; H, 5.90; N, 14.47%. IR (ν, cm^{-1}): 3366-3218 (OH, NH), 3098-3049 (CH-aromatic), 2957, 2837 (CH_2, CH_3), 1679 (C=O), 1596, 1509 (C=C). ^{1}H NMR (*δ*, ppm): 0.94-1.09 (s, 6H, $2CH_3$), 2.12-2.35 (m, 4H, $2CH_2$), 3.67-3.82 (s, 6H, $2OCH_3$), 5.84 (s, 1H, pyrimidine-H), 6.69-7.60 (m, 8H, $2C_6H_4$), 10.00 (s, 1H, D_2O exchangeable, NH), 13.00 (s, 1H, D_2O exchangeable, OH).

5-(4-Chlorophenyl)-2-hydroxy-3-(2-(4-methoxyphenyl)hydrazono)-8,8-dimethyl-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one (***12m***). Dark red crystals, m.p. 102-105 ºC, yield: 3.44 g (72%). Elemental analysis calculated for $C_{25}H_{24}ClN_5O_3$ (477.94): C, 62.82; H, 5.06; N, 14.65%. Found: C, 63.10; H, 5.30; N, 14.37%. IR (ν, cm^{-1}): 3483-3202 (OH, NH), 2958-2837 (CH_2, CH_3), 1670 (C=O), 1551, 1498 (C=C). ^{1}H NMR (*δ*, ppm): 0.94-1.06 (s, 6H, $2CH_3$), 2.29-2.30 (m, 4H, $2CH_2$), 3.75 (s, 3H, OCH_3), 5.95 (s, 1H, pyrimidine-H), 6.89-7.92 (m, 8H, $2C_6H_4$), 9.97 (s, 1H, NH), 13.10 (s, 1H, D_2O exchangeable, OH).

2-Amino-3-(2-(4-chlorophenyl)hydrazono)-8,8-dimethyl-5-phenyl-5,7,8,9-tetrahydro-pyrazolo-[1,5-a]quinazolin-6(3H)-one (***12n***). Canary yellow crystals, m.p. 112-115 ºC, yield: 3.31 g (74%). Elemental analysis calculated for $C_{24}H_{23}ClN_6O$ (446.93): C, 64.50; H, 5.19; N, 18.80%. Found: C, 64.90; H, 5.30; N, 18.65%. IR (ν, cm^{-1}): 3200, 3181 (NH, NH_2), 3065-3025 (CH-aromatic), 2960, 2871 (CH_2, CH_3), 1670 (C=O), 1586, 1492 (C=C). ^{1}H NMR (*δ*, ppm): 0.89-1.09 (s, 6H, $2CH_3$), 2.23-2.33 (m, 4H, $2CH_2$), 4.89 (s, 2H, D_2O exchangeable, NH_2), 5.93 (s, 1H, pyrimidine-H), 6.96-7.31 (m, 9H, C_6H_4, C_6H_5), 10.02 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (δ, ppm): 27.0, 32.7, 39.4, 50.8, 58.1, 110.1, 114.9, 125.5, 125.6, 126.9, 127.7, 128.3, 128.4, 129.3, 129.4, 130.0, 135.0, 141.3, 144.8, 165.8, 167.2, 196.2.

2-Amino-3-(2-(4-chlorophenyl)hydrazono)-5-(4-methoxyphenyl)-8,8-dimethyl-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one (***12o***). Dark yellow crystals, m.p. 92-95 ºC, yield: 4.29 g (90%). Elemental analysis calculated for $C_{25}H_{25}ClN_6O_2$ (476.96): C, 62.95; H, 5.28; N, 17.62%. Found: C, 63.20; H, 5.58; N, 17.35%. IR (ν, cm^{-1}): 3524-3310 (NH, NH_2), 2955-2836 (CH_2, CH_3), 1675 (C=O), 1588, 1467 (C=C), 1508 (C=N). ^{1}H NMR (*δ*, ppm): 0.96-1.09 (s, 6H, $2CH_3$), 2.10-2.31 (m, 4H, $2CH_2$), 3.87 (s, 3H, CH_3), 4.93 (s, 2H, D_2O exchangeable, NH_2), 5.83 (s, 1H, pyrimidine-H), 6.76-7.89 (m, 8H, $2C_6H_4$), 9.87 (s, 1H, D_2O exchangeable, NH).

*2-Amino-5-(4-chlorophenyl)-3-(2-(4-chlorophenyl)hydrazono)-8,8-dimethyl-5,7,8,9-tetrahydro-pyrazolo[1,5-a]quinazolin-6(3H)-one (**12p**)*. Yellow crystals, m.p. 97-100 °C, yield: 4.72 g (98%). Elemental analysis calculated for $C_{24}H_{22}Cl_2N_6O$ (481.38): C, 59.88; H, 4.61; N, 17.46%. Found: C, 60.10; H, 4.81; N, 17.16%. IR (ν, cm^{-1}): 3450-3316 (NH, NH_2), 3066 (CH-aromatic), 2956, 2869 (CH_2, CH_3), 1737 (C=O), 1588, 1489 (C=C), 1508 (C=N). ^{1}H NMR (*δ*, ppm): 0.94-1.09 (s, 6H, $2CH_3$), 2.31-2.32 (m, 4H, $2CH_2$), 4.93 (s, 2H, D_2O exchangeable, NH_2), 5.94 (s, 1H, pyrimidine-H), 6.94-7.77 (m, 8H, $2C_6H_4$), 10.00 (s, 1H, D_2O exchangeable, NH).

*3-(2-(4-Chlorophenyl)hydrazono)-2-hydroxy-8,8-dimethyl-5-phenyl-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (**12q**)*. Dark orange crystals, m.p. 107-110 °C, yield: 3.31 g (74%). Elemental analysis calculated for $C_{24}H_{22}ClN_5O_2$ (447.92): C, 64.35; H, 4.95; N, 15.64%. Found: C, 64.60; H, 5.21; N, 15.36%. IR (ν, cm^{-1}): 3509-3308 (OH, NH), 3030 (CH-aromatic), 2960-2871 (CH_2, CH_3), 1663 (C=O), 1587, 1485 (C=C). ^{1}H NMR (*δ*, ppm): 0.95-1.09 (s, 6H, $2CH_3$), 2.32-2.33 (m, 4H, $2CH_2$), 5.93 (s, 1H, pyrimidine-H), 6.97-7.70 (m, 9H, C_6H_4, C_6H_5), 8.70 (s, 1H, D_2O exchangeable, NH), 10.10 (s, 1H, D_2O exchangeable, OH). ^{13}C NMR (δ, ppm): 27.1, 27.4, 32.7, 39.4, 47.0, 66.8, 114.9, 118.0, 125.5, 126.8, 127.7, 128.3, 128.9, 129.6, 130.0, 135.0, 141.3,196.2.

*3-(2-(4-Chlorophenyl)hydrazono)-2-hydroxy-5-(4-methoxyphenyl)-8,8-dimethyl-5,7,8,9-tetra-hydropyrazolo[1,5-a]quinazolin-6(3H)-one (**12r**)*. Brown crystals, m.p. 92-95 °C, yield: 3.82 g (80%). Elemental analysis calculated for $C_{25}H_{24}ClN_5O_3$ (477.94): C, 62.82; H, 5.06; N, 14.65%. Found: C, 63.10; H, 5.31; N, 14.35%. IR (ν, cm^{-1}): 3413-3153 (OH, NH), 3016 (CH-aromatic), 2958- 2810 (CH_2, CH_3), 1665 (C=O), 1585, 1485 (C=C), 1508 (C=N). ^{1}H NMR (*δ*, ppm): 0.94-1.09 (s, 6H, $2CH_3$), 2.31-2.35 (m, 4H, $2CH_2$), 3.84 (s, 3H, OCH_3), 5.84 (s, 1H, pyrimidine-H), 6.69-7.66 (m, 8H, $2C_6H_4$), 9.87 (s, 1H, D_2O exchangeable, NH), 13.00 (s, 1H, D_2O exchangeable, OH).

*5-(4-Chlorophenyl)-3-(2-(4-chlorophenyl)hydrazono)-2-hydroxy-8,8-dimethyl-5,7,8,9-tetra-hydropyrazolo[1,5-a]quinazolin-6(3H)-one (**12s**)*. Brown crystals, m.p. 132-135 °C, yield: 3.62 g (75%). Elemental analysis calculated for $C_{24}H_{21}Cl_2N_5O_2$ (482.36): C, 59.76; H, 4.39; N, 14.52%. Found: C, 60.01; H, 4.61; N, 14.34%. IR (ν, cm^{-1}): 3420-3189 (OH, NH), 3153 (CH-aromatic), 2956- 2840 (CH_2, CH_3), 1671 (C=O), 1629, 1484 (C=C), 1584 (C=N). ^{1}H NMR (*δ*, ppm): 0.89-1.08 (s, 6H, $2CH_3$), 2.33-2.38 (m, 4H, $2CH_2$), D_2O exchangeable, 5.93 (s, 1H, pyrimidine-H), 6.93-7.95 (m, 8H, $2C_6H_4$), 10.00 (s, 1H, D_2O exchangeable, NH), 13.00 (s, 1H, D_2O exchangeable, OH).

CONCLUSION

In this work, the multi-component reaction of 3-amino pyrazole derivatives **5a-f** was used to produce novel pyrazoloquinazolines **8a-f**, **10a-s** and **12a-s**. The cytotoxicity of some of the prepared obtained products was examined against the six cancer cell lines namely, A549, HT-29, MKN-45, U87MG, SMMC-7721 and, H460. The results were promising and showed that many of the prepared compounds were the most active products for all the tested cancer cell lines. The presence of the Cl group in the most potent compounds **8c**, **8f**, **10c**, **10i**, **10l**, **10p**, **10s**, **12c**, **12i**, **12l**, **12p** and, **12s** was responsible for their activity.

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