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MULTI-COMPONENT SYNTHESIS OF PYRAZOLO[1,5-*a*]QUINAZOLINE, THIAZOLE AND THIOPHENE DERIVATIVES AS CYTOTOXIC AGENTS

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ABSTRACT. This study demonstrated the synthesis of a number of pyrazolo[1,5-*a*]quinazoline derivatives about 24 products based on the starting material 4-(2-phenylhydrazono)-4*H*-pyrazol-3-amine derivatives **1a-f**. Moreover, other ring systems including thiophene, pyrazole, thiazole and pyran (16 compounds) were prepared based on another starting compounds 2-(furan-2-ylmethylene)cyclohexane-1,3-dione **10** and 5,5-dimethyl-3-phenyl-2-thioxo-2,3,5,6-tetrahydrobenzo[*d*]thiazol-7(4*H*)-one **18**. The multi-component reaction was used to prepare all the previous compounds. The structures of all the synthesised compounds were confirmed by the analytical and spectral data. Some selected compounds were chosen to test their anticancer activity against 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*. Toward the tested cell lines, nine compounds were the most cytotoxic compounds. The results obtained revealed that the synthesized compounds are good cytotoxic agents and of great impact for future work.

KEY WORDS: Multi-component reactions, Pyrazolo[1,5-*a*]quinazoline, Thiophene, Thiazole, Cytotoxicity

INTRODUCTION

Pyrazolo[1,5-*a*]quinazoline scaffold plays an important role in the preparation of poly heterocyclic systems which have a broad significance in biological activity. The pharmaceutical applications containing the pyrazoloquinazoline system were effective as antimicrobial [1-4], anticancer [5-7], anti-inflammatory [8-9], antiviral [10-12], and SIRT6 activators [13]. In addition, other important ring systems were present in this study such as thiazoles and thiophenes which were considered one of the most effective bioactive rings in many medicinal applications. The multi-component reactions (MCRs) were used herein in our study due to the most important advantages such as high yields, product selectivity, high purity, and simple reactant used [14-16]. The prepared ring systems involved two important and significant heterocyclic rings, pyrazole and quinazoline. Herein some FDA-approved anticancer drugs containing the pyrazole moiety such as Crizotinib, Tozasertib, BPR1P0034, and Ruxolitinib. Moreover, the other anticancer drugs bearing the quinazoline ring were Gefitinib, Eriotiaib, Vandetanib, Lapatinib, and Afatinib. The previous important drugs encourage us to companies, design and synthesize them in one structure.

In this present study, and due to the remarkable role of pyrazolo[1,5-*a*]quinazoline, thiazole, and thiophene as anticancer agents in many pharmaceutical drugs, and in continuation of our interest and according to our previous reports [17-25] a number of novel bioactive systems were synthesized. The later products that were prepared underwent multi-component reactions, followed by their estimation for six cancer cell lines compared to the standard reference Foretinib.

RESULTS AND DISCUSSION

In the present work, we demonstrated the synthesis of pyrazole and thiophene derivatives together with their fused derivatives, the reactions were outlined through Schemes 1-6.

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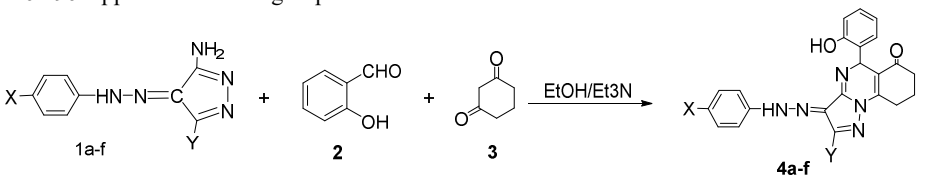
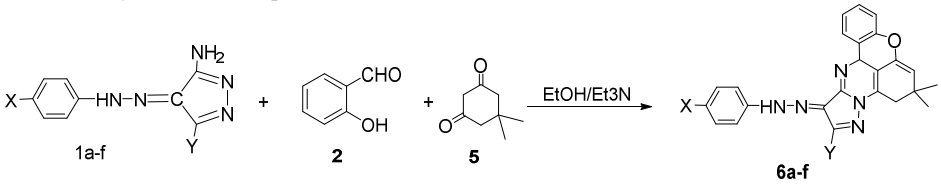
Recently, our research group was concerned with different multi-component reactions aiming to produce new heterocyclic compounds characterized by different substituents. This enhanced us to study plenty of structure activity relationship and thus producing new cytotoxic agents [26-30]. The pyrazole derivatives **1a-f** were synthesized, where such compounds were used as the key starting compounds for the synthesis of new heterocyclic compounds. The multi-component reactions (MCRs) were considered as an elegant and rapid way to synthesize structurally diverse bioactive heterocyclic compounds in a single synthetic operation from simple reagents through. In the field of drug discovery and medicinal chemistry, multi-component reactions were the most applicable reactions. Due to the advantages of multi-component reactions like high atom-economy, simplification of reagents, high yields of products and high selectivity of products many researches were directed through their applications in recent years [31-35]. Compounds **5a-f** were used for a series of multi-component reactions producing new fused heterocyclic compounds that are considered as biologically active target molecules. Thus, the multi-component reactions of compounds **1a-f** with salicylaldehyde (**2**) and cyclohexan-1,3-dione in ethanol solution containing a catalytic amount of triethylamine gave the chromeno[4,3,2-de]pyrazolo[1,5-*a*]quinazoline derivatives **4a,f**; respectively (Scheme 1). Structures of the latter compounds were based on their respective analytical and spectral data. The ^{1}H NMR spectrum of compound **4a** (as an example) revealed signals in the range at δ 1.69-1.72 and 2.90 ppm for the three CH_2 groups of the cyclohexanone moiety and the singlet signal at δ 6.10 ppm for the CH- pyrimidine ring confirmed the formed structure. In addition, the ^{13}C NMR spectrum of compound **4b** showed signals at δ 66.8, 108.9, 115.5, 115.7, 116.6, 121.5, 123.9, 124.7, 125.8, 129.6, 129.8, 130.2, 142.3, 149.9, 150.6, 155.2, 169.7 ppm for the two phenyl moieties, pyrazole and pyrimidine rings and finally at δ 196.2 ppm for the C=O group.



4	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 **4a-f**.

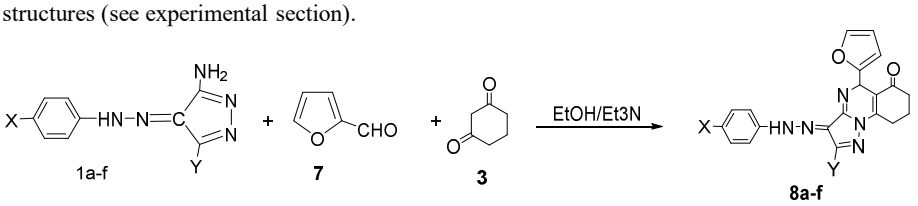


6	a	b	c	d	e	f
X	H	H	OCH_3	OCH_3	Cl	Cl
Y	NH_2	OH	NH_2	OH	NH_2	OH

Scheme 2. Synthesis of compounds **6a-f**.

Similarly, the multi-component reactions of compounds **1a-f** with salicylaldehyde (**2**) and dimedone (**5**) in ethanol solution containing a catalytic amount of triethylamine gave the

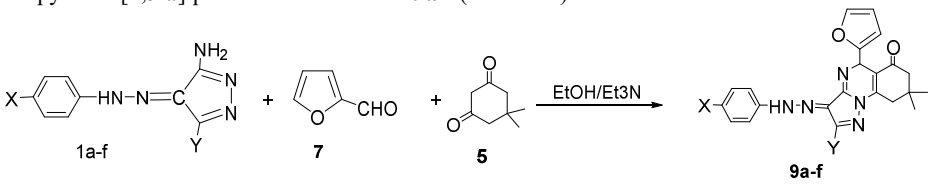
chromeno[4,3,2-de]pyrazolo[1,5-*a*]quinazoline derivatives **6a,f**; respectively (Scheme 2). The high yield obtained in case of the synthesis of compounds **4a-f** and **6a-f** encouraged us to make further multi-component reactions. Thus, the multi-component reactions of **1a-f** with furfural (**7**) and cyclohexan-1,3-dione (**3**) yielded the pyrazolo[1,5-*a*]quinazoline derivatives **8a-f** (Scheme 3). The analytical and spectral data of the latter compounds were in agreement of their respective structures (see experimental section).



8	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 3. Synthesis of compounds **8a-f.**

Moreover, the multi-component reactions of **1a-f** with furfural (**7**) and dimedone (**5**) yielded the pyrazolo[1,5-*a*]quinazoline derivatives **9a-f** (Scheme 4).



9	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

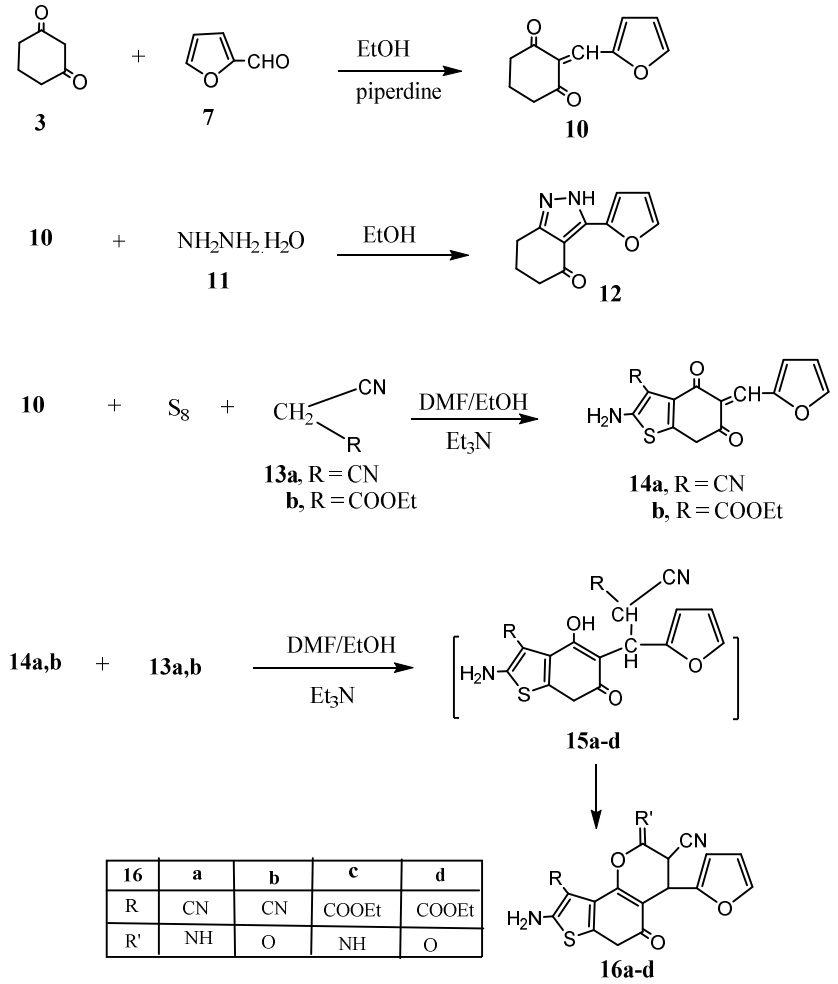
Scheme 4. Synthesis of compounds **9a-f**.

The reaction of cyclohexan-1,3-dione (**3**) with furfural (**7**) in ethanol solution containing piperidine gave the yilidene derivative **10**. The latter compound reacted with hydrazine hydrate **11** to yield the 3-(furan-2-yl)-6,7-dihydro-2*H*-indazol-4(5*H*)-one (**12**). Compound **10** underwent the Gewald's thiophene [36-38] reaction to produce fused thiophene derivatives **14a,b**. The analytical and spectral data of the latter products were in agreement with their respective structures. Thus, the ^{1}H NMR spectrum of **14a** showed signal at δ 6.83 ppm for the NH_2 group which elucidate the formed structure. Compounds **14a,b** underwent the Michael addition reactions when reacted with either malononitrile (**13a**) or ethyl cyanoacetate (**13b**) in DMF/ethanol solution containing triethylamine to give the thieno[2,3-*h*]chromene derivatives **16a-d**, respectively (Scheme 5).

The reaction of dimedone (**5**) with elemental sulfur and phenylisothiocyanate gave the tetrahydrobenzo[*d*]thiazole derivative **18**. The reaction of the latter compound with elemental sulfure and either malononitrile or ethyl cyanoacetate afforded the thieno[3',2':3,4]benzo[1,2-*d*]thiazole derivatives **19a** and **19b**, respectively. Analytical and spectral data of compounds **18** and **19a,b** were in agreement with their respective structures (see experimental section). Compound **18** underwent multi-component reactions with malononitrile (**13a**) and either

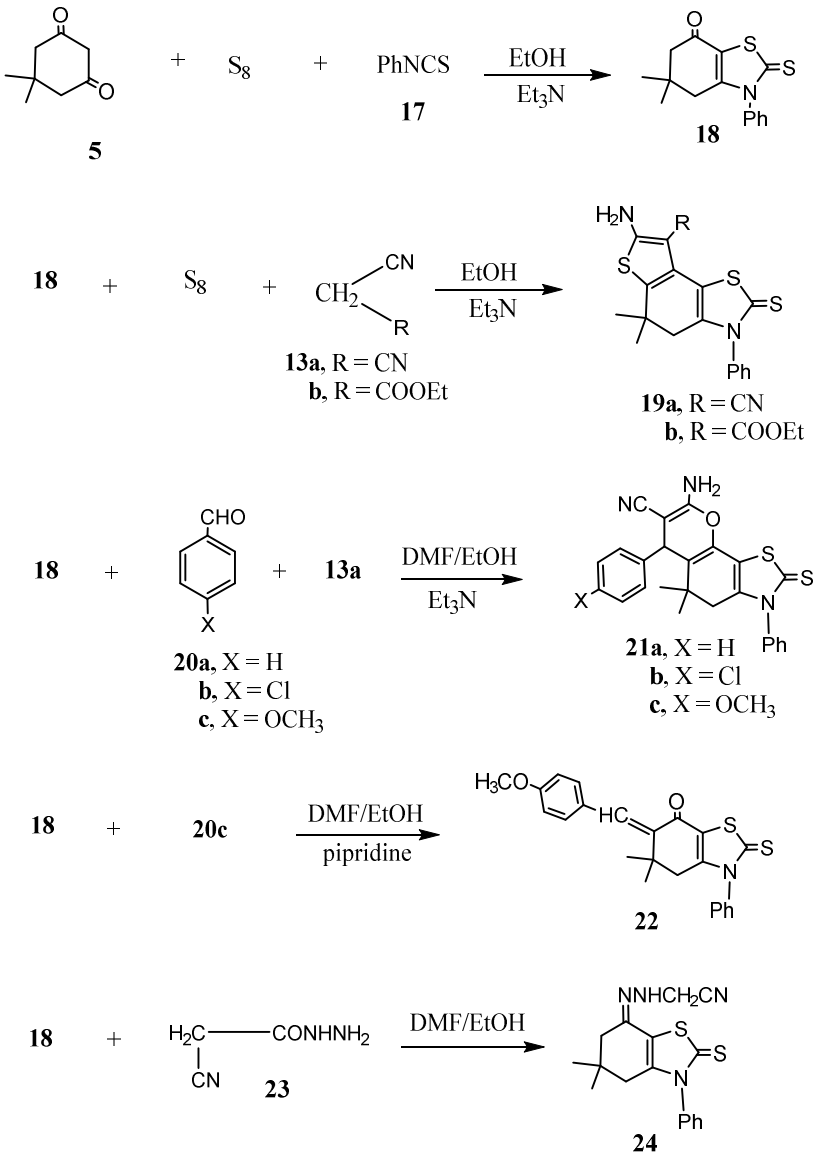
benzaldehyde (**20a**), 4-chlorobenzaldehyde (**20b**) or 4-methoxybenzaldehyde (**20c**) to give the chromeno[7,8-*d*]thiazole derivatives **2a1-c**, respectively. On the other hand, the reaction of **18** with 4-methoxybenzaldehyde (**20c**) in dimethylformamide solution containing ethanol and in the presence of a catalytic amount of piperidine gave the arylidine derivative **22**.

A number of hydrazide–hydrazone derivatives have been claimed to possess interesting bioactivity such as antibacterial–antifungal, anticonvulsant, antiinflammatory, antimalarial, analgesic, antiplatelets, antituberculosis and anticancer activities [39-46]. Due to such interest of bioactive properties of hydrazide-hydrazone derivatives compound **18** was suitable for the synthesis of such group of compounds. Thus compound **18** reacted with cyanoacetylhydrazine **23** in dimethylformamide solution containing ethanol to give the hydrazide-hydrazone derivative **24** (Scheme 6).



16	a	b	c	d
R	CN	CN	COOEt	COOEt
R'	NH	O	NH	O

Scheme 5. Synthesis of compounds **10**, **12a,b** and **16a-d**.



Scheme 6. Synthesis of compounds **18**, **19a,b**; **21**, **22** and **24**.

Structure activity relationship

The cytotoxic 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. Most of the synthesized compounds exhibited potent anti-proliferative activity with IC_{50} values less than 10 μM. The most active compounds towards all the used anticancer cell lines were **4c**, **4d**, **4e**, **6c**, **6e**. **8c**, **14b**, **18** and **24**.

This result indicate that the compounds which having the ethoxy group OCH_3 were the most active compounds **4c**, **4d**, **6c** and **8c**. Moreover, the presence of the Cl group with the NH_2 moiety enhance the activity such as in compounds **4e** and **6e**. In addition, compound **14b** which including the ethoxy moiety beside the thiophene and furan ring systems exhibit a high effects for all the cancer cell lines used. Compounds **18** and **24**, where the thiazole ring system with the phenyl moiety present in their structures revealed potent cytotoxic effect towards all the tested cell lines used. Generally, all the tested cancer cell lines indicate moderate effect for all the novel prepared compounds. But, the two cancer cell lines U87MG and SMMC-7721 showed high effect for most of the selected tested products. For U87MG cancer cell line, compounds **4c**, **4d**, **4e**, **4f**, **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **8c**, **8d**, **12**, **14a**, **14b**, **18** and **24** showed most active effect among all the other compounds. Also, compounds **4a**, **4c**, **4d**, **4e**, **4f**, **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **8a**, **8b**, **8c**, **8e**, **12**, **14a**, **14b**, **18** and **24** revealed high anticancer effect for SMMC-7721 cancer cell line. The series **4a-f** was the most active one among the other tested series **6a-f**, **8a-f** and **9a-f**.

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
4 a	1.28±0.89	0.86±0.46	0.69±0.35	1.38±0.76	1.89±0.76	0.64±0.52
4 b	1.38±0.75	1.29±0.14	2.33± 1.06	1.36 ±0.80	2.41 ±0.96	1.60 ±0.83
4 c	0.38±0.13	0.49±0.15	0.68±0.32	0.57±0.25	0.66±0.31	0.72±0.347
4 d	0.76±0.23	0.64±0.25	0.57±0.26	0.82±0.24	0.78±0.26	0.67±0.37
4 e	0.26± 0.14	0.35± 0.16	0.38± 0.14	0.56 ± 0.28	0.48 ± 0.25	0.37 ± 0.18
4 f	1.18±0.78	1.92 ±0.31	0.69±0.35	0.71±0.19	0.38±0.23	0.79±0.33
6 a	1.76± 1.04	0.68 ± 0.27	0.42± 0.24	0.52± 0.29	0.53± 0.31	0.39±0.24
6 b	1.43±0.69	0.69 ± 0.25	0.63 ±0.30	0.72 ± 0.41	0.53 ±0.29	0.81 ±0.26
6 c	0.26±0.14	0.37±0.22	0.63±0.41	0.56±0.31	0.92 ± 0.64	0.71 ± 0.33
6 d	1.45 ± 0.83	0.49 ±0.24	0.29 ± 0.14	0.34 ± 0.26	0.76 ± 0.38	0.56 ± 0.19
6 e	0.96±0.43	0.68±0.38	0.48±0.19	0.72±0.32	0.69±0.27	0.57±0.21
6 f	1.23 ±0.64	0.89± 0.58	0.73 ± 0.32	0.80± 0.39	0.64± 0.32	0.57±0.24
8 a	0.53±0.20	0.69 ±0.28	0.67 ± 0.24	0.49 ±0.22	1.57 ±0.82	0.83 ± 0.47
8 b	1.32±0.69	2.80±1.03	1.69±0.88	1.65±0.93	1.29±0.70	0.58±0.28
8 c	0.84 ± 0.51	0.69 ± 0.32	0.72±0.30	0.94± 0.27	0.80 ± 0.35	0.79 ± 0.41
8 d	0.85± 0.36	1.09± 0.48	0.94± 0.39	1.93 ± 0.68	0.79± 0.37	1.15± 0.65
8 e	1.54 ± 1.18	0.92 ± 0.61	0.83 ± 0.46	1.37 ± 0.79	1.07± 0.48	0.96 ± 0.35
8 f	1.28 ±0.72	1.49 ± 0.84	2.51± 0.96	1.28 ±0.70	0.63 ±0.32	1.49± 0.69
9 a	5.22±2.39	4.56±1.63	2.70±1.16	3.40±1.23	5.83±1.79	2.48±1.15
9 b	5.60±1.70	3.69±1.27	4.59±1.37	3.93±1.09	4.72±1.53	2.70±1.36
9 c	6.20± 1.46	6.39 ±1.72	4.26 ± 1.36	4.88±1.06	5.36 ±1.58	5.60±1.26
9 d	3.48 ±1.28	2.40±1.27	3.62±1.37	2.92±1.13	1.84±0.75	1.27±0.79
9 e	4.38 ±1.82	5.38 ±1.27	6.73±1.73	4.26 ± 1.39	5.68±1.52	6.82 ±2.53
9 f	5.73± 1.35	4.80 ± 1.62	3.75± 1.80	3.69 ± 1.38	2.68 ± 1.03	3.79 ± 1.04
10	7.29 ±2.50	6.88 ±1.49	5.90±1.37	4.93±1.76	3.90±1.42	6.90±1.52
12	0.84±0.36	0.95±0.40	1.37 ± 0.78	0.67 ± 0.22	0.29 ± 0.15	0.65±0.33
14 a	0.85±0.30	0.76±0.29	2.70±1.07	1.83±0.95	0.65±0.33	0.52±0.28
14 b	0.49 ± 0.15	0.52 ± 0.21	0.62± 0.25	0.79 ± 0.31	0.53 ± 0.21	0.78 ± 0.31
18	0.45 ± 0.31	0.52 ± 0.27	0.29 ± 0.17	0.65 ± 0.25	0.32 ± 0.18	0.41 ± 0.25
19 a	1.31±0.72	1.18±0.85	0.89±0.42	1.12±0.52	1.26±0.80	1.24±0.72
21 a	2.63±1.08	1.87±1.17	2.52± 1.31	1.87 ±0.95	1.19 ±0.93	0.95 ±0.32
21 c	7.93±2.41	6.54 ±1.73	5.93±1.37	4.90±1.39	2.79±1.05	1.93±0.84
22	8.23± 2.64	7.05± 2.73	8.92± 2.63	7.49 ± 2.31	9.53 ± 2.62	8.09 ± 2.41
24	0.73±0.29	0.72±0.38	0.83±0.59	0.32±0.25	0.38±0.29	0.55±0.31
Foretinib	0.08 ± 0.01	0.18 ± 0.03	0.15 ± 0.02	0.03±0.005	0.90 ± 0.13	0.44 ± 0.062

EXPERIMENTAL

All the 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-d_6 as solvent using TMS as internal standard and chemical shifts are expressed as 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 CHNNS analyzer.

*General procedure for the synthesis of 5-(2-hydroxyphenyl)-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one derivatives (**4a-f**)*

To a solution of compounds **1a** (2.02 g, 0.01 mol), **1b** (2.03 g, 0.01 mol), **1c** (2.32 g, 0.01 mol), **1d** (2.33 g, 0.01 mol), **1e** (2.36 g, 0.01 mol), **1f** (2.37 g, 0.01 mol), in ethanol (20 mL) containing triethylamine (0.50 mL), salicylaldehyde **2** (1.22 g, 0.01 mol) and cyclohexane-1,3-dione **3** (1.12 g, 0.01 mol) were added. The solid product formed in each case, upon cooling in an ice-bath was collected by filtration, washed with water and crystallized from absolute alcohol.

*2-Amino-5-(2-hydroxyphenyl)-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one (**4a**)*. Yellow crystals, m.p. 132-135 ºC, yield: 3.2 2 g (80%). Elemental analysis for $C_{22}H_{20}N_6O_2$ (400.43), (% calcd/found): 65.99/66.11 (C), 5.03/5.20 (H), 20.99/20.70 (N). IR (ν, cm^{-1}): 3663 (OH), 3382, 3293 (NH, NH_2), 3179 (CH-aromatic), 2950 (CH_2), 1720 (C=O), 1606, 1454 (C=C). ^{1}H NMR (*δ*, ppm): 1.69-1.72 (s, 4H, 2CH_2), 2.90 (s, 2H, CH_2), 5.79 (s, 1H, OH), 6.10 (s, 1H, CH-pyrimidine), 6.72-7.77 (m, 11H, C_6H_4, C_6H_5, NH_2), 9.50 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 21.2, 23.8, 36.6, 53.7, 109.7, 113.7, 115.7, 116.2, 121.3, 121.5, 124.7, 127.1, 129.2, 129.3, 129.9, 150.5, 151.9, 155.4, 155.6, 194.2

*2-Hydroxy-5-(2-hydroxyphenyl)-3-(2-phenylhydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (**4b**)*. Dark red crystals, m.p. 113-115 ºC, yield: 3.17 g (79%). Elemental analysis for $C_{22}H_{19}N_5O_3$ (401.42), (% calcd/found): 65.83/65.99 (C), 4.77/4.50 (H), 17.45/17.70 (N). IR (ν, cm^{-1}): 3616, 3408, 3307 (2OH, NH), 3055 (CH-aromatic), 2945 (CH_2), 1721 (C=O), 1622, 1456 (C=C), 1556 (C=N). ^{1}H NMR (*δ*, ppm): 1.65-1.90 (s, 4H, 2CH_2), 2.37 (s, 2H, CH_2), 5.80 (s, 1H, OH), 6.19 (s, 1H, CH-pyrimidine), 6.99-7.56 (m, 9H, C_6H_4, C_6H_5), 10.50 (s, 1H, NH), 12.20 (s, 1H, OH).

*2-Amino-5-(2-hydroxyphenyl)-3-(2-(4-methoxyphenyl)hydrazono)-5,7,8,9-tetrahydro-pyrazolo-[1,5-a]quinazolin-6(3H)-one (**4c**)*. Faint Brown crystals, m.p. 132-135 ºC, yield: 4.23 g (98%). Elemental analysis for $C_{23}H_{22}N_6O_3$ (430.46), (% calcd/found): 64.17/64.30 (C), 5.15/5.30 (H), 19.52/19.30 (N). IR (ν, cm^{-1}): 3507, 3452, 3272 (OH, NH, NH_2), 3067 (CH-aromatic), 2945, 2835 (CH_2, CH_3), 1721 (C=O), 1597, 1440 (C=C). ^{1}H NMR (*δ*, ppm): 1.60-1.80 (s, 4H, 2CH_2), 2.47 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 5.80 (s, 1H, OH), 6.10 (s, 1H, CH-pyrimidine), 6.95-7.99 (m, 10H, 2C_6H_4, NH_2), 9.60 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 20.8, 24.1, 37.1, 48.4, 55.8, 107.5, 114.7, 114.7, 114.9, 115.7, 115.9, 122.5, 123.8, 124.7, 127.3, 129.3, 147.5, 150.1, 153.1, 155.3, 159.7, 196.6.

*2-Hydroxy-5-(2-hydroxyphenyl)-3-(2-(4-methoxyphenyl)hydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]quinazolin-6(3H)-one (**4d**)*. Dark orange crystals, m.p. 98-100 ºC, yield: 3.67 g (85%). Elemental analysis for $C_{23}H_{21}N_5O_4$ (431.44), (% calcd/found): 64.03/64.30 (C), 4.91/5.22 (H), 16.23/16.00 (N). IR (ν, cm^{-1}): 3676, 3442, 3338 (2OH, NH), 3100 (CH-aromatic), 2947-2836 (CH_2, CH_3), 1720 (C=O), 1600, 1456 (C=C), 1553 (C=N). ^{1}H NMR (*δ*, ppm): 1.70-1.90 (s, 4H,

$2CH_2$), 2.37 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 5.90 (s, 1H, OH), 6.18 (s, 1H, CH-pyrimidine), 6.95-7.52 (m, 8H, $2C_6H_4$), 9.60 (s, 1H, NH), 10.50 (s, 1H, OH). ^{13}C NMR (δ, ppm): 20.8, 24.1, 36.3, 48.6, 55.8, 109.0, 115.1, 115.1, 115.7, 118.1, 118.1, 121.7, 124.7, 125.7, 127.2, 129.9, 136.0, 149.9, 150.6, 155.5, 157.1, 157.4, 196.

2.*2-Amino-3-(2-(4-chlorophenyl)hydrazono)-5-(2-hydroxyphenyl)-5,7,8,9-tetrahydro-pyrazolo-[1,5-a]quinazolin-6(3H)-one (**4e**)*. Yellow crystals, m.p. 113-115 °C, yield: 4.23 g (96%). Elemental analysis for $C_{22}H_{19}ClN_6O_2$ (434.88), (% calcd/found): 60.76/60.99 (C), 4.40/4.60 (H), 19.32/19.00 (N). IR (ν, cm^{-1}): 3506, 3449, 3295 (OH, NH, NH_2), 3152 (CH-aromatic), 2947 (CH_2), 1721 (C=O), 1607, 1455 (C=C). ^{1}H NMR (δ, ppm): 1.70-1.80 (s, 4H, $2CH_2$), 2.37 (s, 2H, CH_2), 5.78 (s, 1H, OH), 6.15 (s, 1H, CH-pyrimidine), 6.70-7.82 (m, 10H, $2C_6H_4$, NH_2), 9.50 (s, 1H, NH). ^{13}C NMR (δ, ppm): 21.2, 24.1, 36.3, 53.8, 107.5, 115.7, 116.0, 116.2, 121.7, 124.7, 126.2, 127.3, 128.1, 129.7, 132.5, 151.8, 152.2, 155.5, 155.7, 195.5.

*3-(2-(4-Chlorophenyl)hydrazono)-2-hydroxy-5-(2-hydroxyphenyl)-5,7,8,9-tetrahydro-pyrazolo-[1,5-a]quinazolin-6(3H)-one (**4f**)*. Orange crystals, m.p. 128-130 °C, yield: 3.5481 g (87%). Elemental analysis for $C_{22}H_{18}ClN_5O_3$ (435.86), (% calcd/found): 60.62/60.89 (C), 4.16/4.40 (H), 16.07/15.80 (N). IR (ν, cm^{-1}): 3505, 3296 (2OH, NH), 3042 (CH-aromatic), 2948 (CH_2), 1695 (C=O), 1617, 1454 (C=C). ^{1}H NMR (δ, ppm): 1.70-1.90 (s, 4H, $2CH_2$), 2.38 (s, 2H, CH_2), 5.20 (s, 1H, OH), 6.20 (s, 1H, CH-pyrimidine), 6.92-7.47 (m, 8H, $2C_6H_4$), 10.30 (s, 1H, NH), 12.20 (s, 1H, OH). ^{13}C NMR (δ, ppm): 21.3, 24.1, 36.3. 62.1, 111.2, 115.7, 118.1, 118.3, 120.5, 124.7, 126.7, 127.3, 129.5, 129.6, 130.0, 132.5, 141.3, 149.9, 150.1, 154.6, 161.2, 196.9.

*General procedure for the synthesis of 6,6-dimethyl-1-(2-phenylhydrazono)-1,5,6,12b-tetrahydrochromeno[4,3,2-de]pyrazolo[1,5-a]quinazoline derivatives (**6a-f**)*

To a solution of compounds **1a** (2.02 g, 0.01 mol), **1b** (2.03 g, 0.01 mol), **1c** (2.32 g, 0.01 mol), **1d** (2.33 g, 0.01 mol), **1e** (2.36 g, 0.01 mol), **1f** (2.37 g, 0.01 mol), in ethanol (20 mL) containing triethylamine (0.50 mL), salicylaldehyde (1.22 g, 0.01 mol) and 5,5-dimethylcyclohexane-1,3-dione (1.40 g, 0.01 mol) were added. The solid product formed in each case, upon cooling in an ice-bath was collected by filtration, washed with water, and crystallized from absolute alcohol.

*6,6-Dimethyl-1-(2-phenylhydrazono)-1,5,6,12b-tetrahydrochromeno-[4,3,2-de]pyrazolo[1,5-a]-quinazolin-2-amine (**6a**)*. Yellow crystals, m.p. 173-175 °C, yield: 3.17 g (77%). Elemental analysis for $C_{24}H_{22}N_6O$ (410.47), (% calcd/found): 70.23/70.49 (C), 5.40/5.60 (H), 20.47/20.10 (N). IR (ν, cm^{-1}): 3392, 3290 (NH_2), 3181 (NH), 3043 (CH-aromatic), 2961-2870 (CH_2, $2CH_3$), 1607, 1469 (C=C), 1520 (C=N). ^{1}H NMR (δ, ppm): 0.97, 1.04 (s, 6H, $2CH_3$), 2.04 (s, 2H, CH_2), 5.04 (s, 1H, CH-pyran), 5.80 (s, 1H, CH), 6.96-7.67 (m, 9H, C_6H_4, C_6H_5), 9.40 (s, 2H, NH_2), 10.23 (s, 1H, NH). ^{13}C NMR (δ, ppm): 28.1, 29.5, 32.0, 41.1, 50.8, 111.2, 117.3, 117.6, 119.8, 122.5, 122.6, 126.0, 127.3, 129.3, 129.6, 130.3, 134.2, 137.1, 150.0, 153.4, 153.8, 160.9.

*6,6-Dimethyl-1-(2-phenylhydrazono)-1,5,6,12b-tetrahydrochromeno-[4,3,2-de]pyrazolo[1,5-a]-quinazolin-2-ol (**6b**)*. Faint Brown crystals, m.p. 168-170 °C, yield: 3.83 g (93%). Elemental analysis for $C_{24}H_{21}N_5O_2$ (411.46), (% calcd/found): 70.06/70.29 (C), 5.14/5.30 (H), 17.02/16.80 (N). IR (ν, cm^{-1}): 3403, 3271, 3198 (OH, NH), 2953-2869 (CH_2, $2CH_3$), 1591, 1459 (C=C). ^{1}H NMR (δ, ppm): 0.98, 1.04 (s, 6H, $2CH_3$), 2.05 (s, 2H, CH_2), 5.10 (s, 1H, CH-pyran), 5.78 (s, 1H, CH), 6.94-7.53 (m, 9H, C_6H_4, C_6H_5), 10.20 (s, 1H, NH), 10.50 (s, 1H, OH). ^{13}C NMR (δ, ppm): 28.3, 29.1, 32.6, 41.1, 55.4, 61.8, 111.1, 115.0, 115.4, 117.3, 118.2, 118.6, 124.3, 126.0, 127.3, 128.7, 150.3, 157.6.

*1-(2-(4-Methoxyphenyl)hydrazono)-6,6-dimethyl-1,5,6,12b-tetrahydrochromeno[4,3,2-de]pyrazolo[1,5-a]quinazolin-2-amine (**6c**)*. Reddish Brown crystals, m.p. 138-140 °C, yield: 4.23 g

(96%). Elemental analysis for $C_{25}H_{24}N_6O_2$ (440.50), (% calcd/found): 68.17/68.29 (C), 5.49/5.70 (H), 19.08/18.80 (N). IR (ν, cm^{-1}): 3498, 3408 (NH_2), 3296 (NH), 3076 (CH-aromatic), 2954, 2835 (CH_2, $3CH_3$), 1595, 1440 (C=C). ^{1}H NMR (*δ*, ppm): 1.03-1.12 (s, 6H, $2CH_3$), 2.06 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 5.05 (s, 1H, CH-pyran), 5.75 (s, 1H, CH), 6.85-8.00 (m, 10H, $2C_6H_4$, NH_2), 10.26 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 27.9, 28.1, 32.4, 41.1, 50.9, 55.8, 114.6, 115.1, 115.7, 117.7, 119.2, 119.9, 122.8, 124.6, 126.1, 127.3, 129.3, 136.9, 155.5, 159.8, 161.1.

1-(2-(4-Methoxyphenyl)hydrazono)-6,6-dimethyl-1,5,6,12b-tetrahydro-chromeno[4,3,2-de]pyrazolo[1,5-a]quinazolin-2-ol ***(6d)***. Brown crystals, m.p. 178-180 ºC, yield: 4.24 g (96%). Elemental analysis for $C_{25}H_{23}N_5O_3$ (441.48), (% calcd/found): 68.01/68.30 (C), 5.25/5.50 (H), 15.86/15.60 (N). IR (ν, cm^{-1}): 3443-3200 (OH, NH), 2961-2837 (CH_2, $3CH_3$), 1575, 1461 (C=C), 1550 (C=N). ^{1}H NMR (*δ*, ppm): 1.05-1.28 (s, 6H, $2CH_3$), 2.00 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 5.05 (s, 1H, CH-pyran), 5.70 (s, 1H, CH), 6.92-7.50 (m, 8H, $2C_6H_4$), 10.40 (s, 1H, NH), 11.80 (s, 1H, OH). ^{13}C NMR (*δ*, ppm): 28.2, 29.6, 32.1. 41.1, 55.8, 61.8, 111.3, 115.1, 115.8, 117.2, 118.1, 118.2, 124.6, 126.1, 127.3, 128.9, 150.1, 157.1.

1-(2-(4-Chlorophenyl)hydrazono)-6,6-dimethyl-1,5,6,12b-tetrahydro-chromeno[4,3,2-de]pyrazolo [1,5-a]quinazolin-2-amine ***(6e)***. Canary yellow crystals, m.p. 168-170 ºC, yield: 4.23 g (95%). Elemental analysis for $C_{24}H_{21}ClN_6O$ (444.92), (% calcd/found): 64.79/64.99 (C), 4.76/4.50 (H), 18.89/18.70 (N). IR (ν, cm^{-1}): 3401, 3304 (NH_2), 3188 (NH), 3044 (CH-aromatic), 2956, 2870 (CH_2, $2CH_3$), 1606, 1469 (C=C), 1523 (C=N). ^{1}H NMR (*δ*, ppm): 1.03-1.07 (s, 6H, $2CH_3$), 2.00 (s, 2H, CH_2), 5.05 (s, 1H, CH-pyran), 5.70 (s, 1H, CH), 6.95-7.78 (m, 10H, $2C_6H_4$, NH_2), 9.42 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 28.1, 29.6, 32.1, 41.1, 50.9, 111.3, 115.8, 117.3, 122.9, 126.1, 127.3, 128.9, 129.2, 129.5, 130.8, 132.7, 132.9, 134.1, 150.1, 152.3, 152.9, 161.1, 165.2.

1-(2-(4-Chlorophenyl)hydrazono)-6,6-dimethyl-1,5,6,12b-tetrahydro-chromeno[4,3,2-de]pyrazolo[1,5-a]quinazolin-2-ol ***(6f)***. Faint brown crystals, m.p. 170-172 ºC, yield: 4.24 g (95%). Elemental analysis for $C_{24}H_{20}ClN_5O_2$ (445.90), (% calcd/found): 64.65/64.89 (C), 4.52/4.70 (H), 15.71/15.40 (N). IR (ν, cm^{-1}): 3447, 3294 (OH, NH), 3139 (NH), 2961-2870 (CH_2, $2CH_3$), 1556, 1485 (C=C). ^{1}H NMR (*δ*, ppm): 1.03-1.05 (s, 6H, $2CH_3$), 2.06 (s, 2H, CH_2), 5.05 (s, 1H, CH-pyran), 5.80 (s, 1H, CH), 6.92-7.59 (m, 8H, $2C_6H_4$), 10.20 (s, 1H, NH), 10.70 (s, 1H, OH). ^{13}C NMR (*δ*, ppm): 28.0, 29.2, 32.6, 41.1, 55.3, 61.1, 111.4, 115.0, 115.2, 117.6, 118.5, 119.6, 124.8, 126.1, 127.1, 128.9, 150.2, 157.2.

General procedure for the synthesis of 5-(furan-2-yl)-3-(2-phenyl-hydrazono)-5,7,8,9-tetrahydropyrazolo[1,5-a]quinazolin-6(3H)-one derivatives ***(8a-e)***

To a solution of compounds **1a** (2.02 g, 0.01 mol), **1b** (2.03 g, 0.01 mol), **1c** (2.32 g, 0.01 mol), **1d** (2.33 g, 0.01 mol), **1e** (2.36 g, 0.01 mol), **1f** (2.37 g, 0.01 mol), in ethanol (20 mL) containing triethylamine (0.50 mL), furan-2-carbaldehyde **7** (0.96 g, 0.01 mol) and cyclohexane-1,3-dione **3** (1.12 g, 0.01 mol) were added. The solid product formed in each case, upon cooling in an ice-bath was collected by filtration, washed with water and crystallized from absolute alcohol.

2-Amino-5-(furan-2-yl)-3-(2-phenylhydrazono)-5,7,8,9-tetrahydro-pyrazolo[1,5-a]quinazolin-6-(3H)-one ***(8a)***. Brown crystals, m.p. 213-215 ºC, yield: 3.60 g (96%). Elemental analysis for $C_{20}H_{18}N_6O_2$ (374.40), (% calcd/found): 64.16/64.30 (C), 4.85/4.60 (H), 22.45/22.10 (N). IR (ν, cm^{-1}): 3305, 3204 (NH_2), 3118 (NH), 2944 (CH_2), 1660 (C=O), 1600, 1478 (C=C), 1557 (C=N). ^{1}H NMR (*δ*, ppm): 1.80, 2.32, 2.88 (m, 6H, $3CH_2$), 6.00 (s, 1H, CH-pyrimidine), 6.20, 6.40 (s, 2H, CH-furan), 7.18-7.95 (m, 8H, C_6H_5, NH_2, CH-furan), 10.40 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 28.6, 29.8, 31.2, 41.1, 55.3, 61.5, 111.4, 115.2, 115.5, 118.5, 119.8, 124.8, 126.6, 127.4, 128.3, 150.2, 155.6.

*5-(Furan-2-yl)-2-hydroxy-3-(2-phenylhydrazono)-5,7,8,9-tetrahydro-pyrazolo[1,5-a]quinazolin-6(3H)-one (**8b**)*. Brown crystals, m.p. 223-225 ºC, yield: 3.19 g (85%). Elemental analysis for $C_{20}H_{17}N_5O_3$ (375.38), (% calcd/found): 63.99/64.20 (C), 4.56/4.70 (H), 18.66/16.40 (N). IR (ν, cm^{-1}): 3686, 3271 (OH, NH), 3014 (CH-aromatic), 2945, 2874 (CH_2), 1660 (C=O), 1592, 1454 (C=C). ^{1}H NMR (*δ*, ppm): 1.82-1.95, 2.89 (m, 6H, $3CH_2$), 5.20 (s, 1H, CH-pyrimidine), 5.80, 6.10 (s, 2H, CH-furan), 7.16-7.95 (m, 6H, C_6H_5, CH-furan), 10.50 (s, 1H, NH), 10.70 (s, 1H, OH). ^{13}C NMR (*δ*, ppm): 28.3, 29.3, 31.2, 41.6, 55.3, 61.8, 111.4, 115.6, 115.3, 118.4, 119.6, 124.2, 126.4, 127.4, 128.1, 150.6, 153.8.

*2-Amino-5-(furan-2-yl)-3-(2-(4-methoxyphenyl)hydrazono)-5,7,8,9-tetrahydropyrazolo-[1,5-a]-quinazolin-6(3H)-one (**8c**)*. Faint brown crystals, m.p. 208-210 ºC, yield: 4.04 g (90%). Elemental analysis for $C_{21}H_{20}N_6O_3$ (404.42), (% calcd/found): 62.37/62.60 (C), 4.98/5.20 (H), 20.78/20.90 (N). IR (ν, cm^{-1}): 3449, 3324 (NH2), 3118 (NH), 2944, 2836 (CH_2, CH_3), 1670 (C=O), 1597, 1496 (C=C). ^{1}H NMR (*δ*, ppm): 1.80-1.95, 2.89 (m, 6H, $3CH_2$), 3.82 (s, 3H, OCH_3), 5.97 (s, 1H, CH-pyrimidine), 6.10, 6.30 (s, 2H, CH-furan), 6.94-7.79 (m, 7H, C_6H_4, NH_2, CH-furan), 10.80 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 28.3, 29.3, 31.2, 41.6, 55.3, 61.8, 111.4, 115.6, 115.3, 118.4, 119.6, 124.2, 126.4, 127.4, 128.1, 150.6, 153.8.

*5-(Furan-2-yl)-2-hydroxy-3-(2-(4-methoxyphenyl)hydrazono)-5,7,8,9-tetrahydro-pyrazolo[1,5-a]quinazolin-6(3H)-one (**8d**)*. Dark orange crystals, m.p. 178-180 ºC, yield: 3.81 g (94%). Elemental analysis for $C_{21}H_{19}N_5O_4$ (405.41), (% calcd/found): 62.22/62.40 (C), 4.72/4.90 (H), 17.27/17.50 (N). IR (ν, cm^{-1}): 3394-3209 (OH, NH), 3040 (CH-aromatic), 2896 (CH_2, CH_3), 1649 (C=O), 1604, 1504 (C=C), 1543 (C=N). ^{1}H NMR (*δ*, ppm): 1.90-2.10, 2.80 (m, 6H, $3CH_2$), 3.82 (s, 3H, OCH_3), 5.30 (s, 1H, CH-pyrimidine), 6.20, 6.30 (s, 2H, CH-furan), 6.91-7.63 (m, 5H, C_6H_4, CH-furan), 9.80 (s, 1H, NH), 10.60 (s, 1H, OH). ^{13}C NMR (*δ*, ppm): 28.1, 29.2, 31.7, 41.2, 55.1, 61.3, 111.4, 114.3, 115.0, 118.3, 119.6, 124.2, 126.4, 127.1, 128.5, 150.6, 154.3.

*2-Amino-3-(2-(4-chlorophenyl)hydrazono)-5-(furan-2-yl)-5,7,8,9-tetrahydropyrazolo-[1,5-a]-quinazolin-6(3H)-one (**8e**)*. Brown crystals, m.p. 178-180 ºC, yield: 3.27 g (80%). Elemental analysis for $C_{20}H_{17}ClN_6O_2$ (408.84), (% calcd/found): 58.75/58.95 (C), 4.19/4.30 (H), 20.56/20.30 (N). IR (ν, cm^{-1}): 3564-3152 (NH, NH_2), 2945, 2888 (CH_2), 1670 (C=O), 1589, 1455 (C=C), 1513 (C=N). ^{1}H NMR (*δ*, ppm): 1.80-2.00, 2.70 (m, 6H, $3CH_2$), 5.20 (s, 1H, CH-pyrimidine), 6.00, 6.40, 7.00 (s, 3H, CH-furan), 7.40-7.70 (m, 6H, C_6H_4, NH_2), 10.40 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 28.3, 29.5, 31.7, 41.6, 55.1, 61.0, 112.1, 114.3, 115.6, 118.0, 119.3, 124.2, 126.4, 127.3, 128.5, 150.4, 156.6.

*3-(2-(4-Chlorophenyl)hydrazono)-5-(furan-2-yl)-2-hydroxy-5,7,8,9-tetrahydropyrazolo-[1,5-a]-quinazolin-6(3H)-one (**8f**)*. Faint brown crystals, m.p. 143-145 ºC, yield: 3.36 g (82%). Elemental analysis for $C_{20}H_{16}ClN_5O_3$ (409.83), (% calcd/found): 58.61/58.85 (C), 3.94/4.20 (H), 17.09/16.80 (N). IR (ν, cm^{-1}): 3410-3153 (OH, NH), 2946, 2874 (CH_2), 1671 (C=O), 1573, 1485 (C=C). ^{1}H NMR (*δ*, ppm): 1.80-1.95, 2.89 (m, 6H, $3CH_2$), 5.84 (s, 1H, CH-pyrimidine), 6.50, 7.00 (s, 2H, CH-furan), 7.41-7.59 (m, 5H, C_6H_4, CH-furan), 10.50 (s, 1H, NH), 12.80 (s, 1H, OH). ^{13}C NMR (*δ*, ppm): 28.1, 29.3, 31.7, 41.8, 55.2, 61.3, 112.4, 114.6, 115.4, 118.0, 119.6, 125.4, 126.4, 127.6, 128.5, 150.1, 155.8.

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

To a solution of compounds **1a** (2.02 g, 0.01 mol), **1b** (2.03 g, 0.01 mol), **1c** (2.32 g, 0.01 mol), **1d** (2.33 g, 0.01 mol), **1e** (2.36 g, 0.01 mol), **1f** (2.37 g, 0.01 mol), in ethanol (20 mL) containing triethylamine (0.50 mL), furan-2-carbaldehyde **7** (0.96 g, 0.01 mol) and 5,5-dimethylcyclohexane-1,3-dione **5** (1.40 g, 0.01 mol) were added. The solid product formed in each case, upon

cooling in an ice-bath was collected by filtration, washed with water and crystallized from absolute alcohol.

2-Amino-5-(furan-2-yl)-8,8-dimethyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydro-pyrazolo[1,5-a] quinazolin-6(3H)-one (***9a***). Brown crystals, m.p. 208-210 ºC, yield: 3.39 g (84%). Elemental analysis for $C_{22}H_{22}N_6O_2$ (402.45), (% calcd/found): 65.66/65.85 (C), 5.51/5.70 (H), 20.88/21.10 (N). IR (ν, cm^{-1}): 3509, 3306 (NH_2), 3118 (NH), 3066 (CH-aromatic), 2955-2870 (CH_2, CH_3), 1671 (C=O), 1601, 1478 (C=C), 1559 (C=N). ^{1}H NMR (*δ*, ppm): 0.99, 1.02 (s, 6H, $2CH_3$), 2.20, 2.30 (s, 4H, $2CH_2$), 5.30 (s, 1H, CH-pyrimidine), 5.80, 6.20 (s, 2H, CH-furan), 7.20-7.65 (m, 8H, C_6H_5, CH-furan, NH_2), 8.20 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 28.5, 30.2, 31.4, 41.2, 61.8, 112.4, 118.0, 119.4, 125.4, 126.4, 127.6, 128.3, 139.3, 140.2, 152.4, 155.3.

5-(Furan-2-yl)-2-hydroxy-8,8-dimethyl-3-(2-phenylhydrazono)-5,7,8,9-tetrahydro-pyrazolo[1,5-a]quinazolin-6(3H)-one (***9b***). Brown crystals, m.p. 163-165 ºC, yield: 3.22 g (80%). Elemental analysis for $C_{22}H_{21}N_5O_3$ (403.43), (% calcd/found): 65.50/65.85 (C), 5.25/5.50 (H), 17.36/17.10 (N). IR (ν, cm^{-1}): 3409-3200 (OH, NH), 3012 (CH-aromatic), 2955, 2871 (CH_2, CH_3), 1670 (C=O), 1581, 1451 (C=C). ^{1}H NMR (*δ*, ppm): 0.99, 1.01 (s, 6H, $2CH_3$), 2.10, 2.27 (s, 4H, $2CH_2$), 5.20 (s, 1H, CH-pyrimidine), 5.80, 6.20 (s, 2H, CH-furan), 7.10-7.51 (m, 6H, C_6H_5, CH-furan), 8.10 (s, 1H, NH), 10.50 (s, 1H, OH). ^{13}C NMR (*δ*, ppm): 28.2, 30.4, 31.6, 42.8, 112.4, 118.4, 119.4, 125.4, 126.4, 127.6, 128.6, 139.3, 140.2, 142.3, 152.4, 155.3.

2-Amino-5-(furan-2-yl)-3-(2-(4-methoxyphenyl)hydrazono)-8,8-dimethyl-5,7,8,9-tetrahydropyr-azolo[1,5-a]quinazolin-6(3H)-one (***9c***). Faint brown crystals, m.p. 213-215 ºC, yield: 4.23 g (98%). Elemental analysis for $C_{23}H_{24}N_6O_3$ (432.48), (% calcd/found): 63.88/64.10 (C), 5.59/5.70 (H), 19.43/19.10 (N). IR (ν, cm^{-1}): 3556 (NH), 3409, 3308 (NH_2), 2955-2836 (CH_2, CH_3), 1672 (C=O), 1598, 1466 (C=C), 1561 (C=N). ^{1}H NMR (*δ*, ppm): 0.99, 1.03 (s, 6H, $2CH_3$), 3.79 (s, 3H, OCH_3), 2.20, 2.29 (s, 4H, $2CH_2$), 5.20 (s, 1H, CH-pyrimidine), 5.70, 6.20 (m, 2H, CH-furan), 6.94-7.65 (m, 7H, C_6H_4, CH-furan, NH_2), 8.20 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 28.1, 30.3, 31.9, 42.8, 112.6, 118.4, 119.4, 125.4, 126.4, 127.6, 128.5, 139.3, 140.3, 142.1, 1522, 155.6.

5-(Furan-2-yl)-2-hydroxy-3-(2-(4-methoxyphenyl)hydrazono)-8,8-dimethyl-5,7,8,9-tetrahydro-pyrazolo[1,5-a]quinazolin-6(3H)-one (***9d***). Dark orange crystals, m.p. 218-220 ºC, yield: 3.81 g (88%). Elemental analysis for $C_{23}H_{23}N_5O_4$ (433.46), (% calcd/found): 63.73/63.90 (C), 5.35/5.70 (H), 16.16/15.80 (N). IR (ν, cm^{-1}): 3443-3202 (OH, NH), 3037 (CH-aromatic), 2840 (CH_2, CH_3), 1680 (C=O), 1630, 1444 (C=C), 1561 (C=N). ^{1}H NMR (*δ*, ppm): 0.99, 1.02 (s, 6H, $2CH_3$), 3.79 (s, 3H, OCH_3), 2.10, 2.28 (s, 4H, $2CH_2$), 5.20 (s, 1H, CH-pyrimidine), 6.20, 6.40 (m, 2H, CH-furan), 6.94-7.53 (m, 5H, C_6H_4, CH-furan), 9.80 (s, 1H, NH), 10.60 (s, 1H, OH). ^{13}C NMR (*δ*, ppm): 28.2, 30.4, 31.6, 42.8, 112.4, 118.4, 119.4, 125.4, 126.4, 127.6, 128.6, 139.3, 140.2, 142.3, 152.4, 155.3.

2-Amino-3-(2-(4-chlorophenyl)hydrazono)-5-(furan-2-yl)-8,8-dimethyl-5,7,8,9-tetrahydropyra-zolo[1,5-a]quinazolin-6(3H)-one (***9e***). Brown crystals, m.p. 198-200 ºC, yield: 4.24 g (97%). Elemental analysis for $C_{22}H_{21}ClN_6O_2$ (436.89), (% calcd/found): 60.48/60.70 (C), 4.84/5.10 (H), 19.24/19.01 (N). IR (ν, cm^{-1}): 3323-3117 (NH_2, NH), 2958-2871 (CH_2, CH_3), 1685 (C=O), 1592, 1469 (C=C). ^{1}H NMR (*δ*, ppm): 0.99, 1.01 (s, 6H, $2CH_3$), 2.12, 2.29 (s, 4H, $2CH_2$), 5.20 (s, 1H, CH-pyrimidine), 5.83, 6.27 (m, 2H, CH-furan), 7.38-7.79 (m, 7H, C_6H_4, CH-furan, NH_2), 8.40 (s, 1H, NH). ^{13}C NMR (*δ*, ppm): 28.5, 30.4, 31.8, 42.8, 112.6, 118.9, 119.2, 125.4, 126.1, 127.6, 128.3, 139.3, 140.2, 142.3, 152.8, 156.5.

3-(2-(4-Chlorophenyl)hydrazono)-5-(furan-2-yl)-2-hydroxy-8,8-dimethyl-5,7,8,9-tetrahydropyr-azolo[1,5-a]quinazolin-6(3H)-one (***9f***). Brown crystals, m.p. 213-215 ºC, yield: 3.51 g (80%). Elemental analysis for $C_{22}H_{20}ClN_5O_3$ (437.88), (% calcd/found): 60.34/60.60 (C), 4.60/4.85 (H),

15.99/15.65 (N). IR (ν, cm^{-1}): 3519-3164 (OH, NH), 3118 (CH-aromatic), 2957-2870 (CH_2, CH_3), 1666 (C=O), 1591, 1469 (C=C). ^{1}H NMR (δ, ppm): 0.99, 1.01 (s, 6H, $2CH_3$), 2.28, 2.29 (s, 4H, $2CH_2$), 5.83 (s, 1H, CH-pyrimidine), 6.20, 6.50, 7.00 (m, 3H, CH-furan), 7.41-7.59 (m, 4H, C_6H_4), 8.50 (s, 1H, NH), 10.50 (s, 1H, OH). ^{13}C NMR (δ, ppm): 29.2, 30.6, 31.2, 41.2, 112.3, 118.9, 119.8, 125.2, 126.5, 127.6, 128.1, 139.1, 140.2, 142.1, 152.6, 155.2.

*Synthesis of 2-(furan-2-ylmethylene)cyclohexane-1,3-dione (**10**)*

To a solution of compound **3** (2.02 g, 0.01 mol), in ethanol (20 mL) containing piperdine (0.50 mL), furan-2-carbaldehyde **7** (0.96 g, 0.01 mol) was added. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water and crystallized from absolute alcohol. Brown crystals, m.p. 218-220 °C, yield: 1.60 g (84%). Elemental analysis for $C_{11}H_{10}O_3$ (190.20), (% calcd/found): 69.46/69.61 (C), 5.30/5.01 (H). IR (ν, cm^{-1}): 2944, 2873 (CH, CH_2), 1771, 1680 (2C=O), 1586, 1454 (C=C), 1506 (C=N). ^{1}H NMR (δ, ppm): 1.64, 2.99, 3.01 (s, 6H, $2CH_2$), 5.20, 7.60, 8.10 (m, 3H, CH-furan), 6.40 (s, 1H, =CH). ^{13}C NMR (δ, ppm): 30.2, 30.8, 31.7, 118.0, 118.9, 119.8, 125.2, 126.2, 127.8, 128.1, 139.5, 140.6, 142.7, 150.6, 154.8.

*Synthesis of 3-(furan-2-yl)-6,7-dihydro-2H-indazol-4(5H)-one (**12**)*

To a solution of compound **10** (1.90 g, 0.01 mol), in ethanol (20 mL), hydrazine hydrate **11** (0.50 g, 0.01 mol) was added. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water and crystallized from absolute alcohol. Brown crystals, m.p. 208-210 °C, yield: 1.60 g (79%). Elemental analysis for $C_{11}H_{10}N_2O_2$ (202.21), (% calcd/found): 65.34/65.60 (C), 4.98/5.20 (H), 13.85/13.60 (N). IR (ν, cm^{-1}): 3213 (NH), 2943, 2882 ($3CH_2$), 1681 (C=O), 1590, 1469 (C=C), 1506 (C=N). ^{1}H NMR (δ, ppm): 1.91, 2.73, 2.89 (s, 6H, $2CH_2$), 5.20, 7.81, 7.90 (s, 3H, CH-furan), 10.40 (s, 1H, NH). ^{13}C NMR (δ, ppm): 30.5, 30.8, 31.7, 118.2, 118.4, 119.9, 122.3, 123.6, 125.2, 126.1, 127.5, 128.7, 139.2, 140.3, 144.6, 153.3, 156.2.

*General procedure for the synthesis of 2-amino-5-(furan-2 ylmethylene)benzo [b] thiophene-4,6(5H,7H)-dione derivatives (**14a-b**)*

To a solution of compound **10** (1.90 g, 0.01 mol), in ethanol/DMF (20/10 mL) and triethylamine (0.50 mL), malononitrile **13a** (0.66 g, 0.01 mol) or ethyl cyanoacetate **13b** (1.13 g, 0.01 mol) in the presence of an equimolar amount of elemental sulfur were added. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water and crystallized from absolute alcohol.

*2-Amino-5-(furan-2-ylmethylene)-4,6-dioxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (**14a**)*. Brown crystals, m.p. 243-245 °C, yield: 2.50 g (88%). Elemental analysis for $C_{14}H_8N_2O_3S$ (284.29), (% calcd/found): 59.15/59.30 (C), 2.84/3.10 (H), 9.85/9.65 (N), 11.28/11.01 (S). IR (ν, cm^{-1}): 3377, 3309 (NH_2), 3130 (CH-aromatic), 2971 (CH_2), 2202 (CN), 1655, 1612 (2C=O), 1568, 1454 (C=C). ^{1}H NMR (δ, ppm): 3.33 (s, 2H, CH_2), 6.50, 7.95, 8.10 (m, 3H, CH-furan), 6.83 (s, 2H, NH_2), 7.30 (s, 1H, =CH). ^{13}C NMR (δ, ppm): 30.1, 30.8, 31.6, 116.8, 118.4, 119.4, 122.5, 123.6, 125.1, 126.1, 127.3, 128.7, 139.0, 140.2, 144.6, 153.1, 156.6.

*Ethyl 2-amino-5-(furan-2-ylmethylene)-4,6-dioxo-4,5,6,7-tetrahydrobenzo[b]thio-phene-3-carboxylate (**14b**)*. Faint brown crystals, m.p. 188-190 °C, yield: 2.88 g (87%). Elemental analysis for $C_{16}H_{13}NO_5S$ (331.34), (% calcd/found): 58.00/58.30 (C), 3.95/4.20 (H), 4.23/4.05 (N), 9.68/9.41 (S). IR (ν, cm^{-1}): 3210, 3151 (NH_2), 3117 (CH-aromatic), 2945, 2873 (CH, CH_2, CH_3), 1715, 1680, 1660 (3C=O), 1597, 1453 (C=C), 1506 (C=N). ^{1}H NMR (δ, ppm): 1.15-1.22 (t, 3H, CH_3), 4.00 (s, 2H, CH_2), 4.10 (q, 2H, CH_2), 6.40, 7.95, 8.10 (m, 3H, CH-furan), 6.90 (s, 2H, NH_2), 7.32 (s, 1H, =CH). ^{13}C NMR (δ, ppm): 20.3, 30.2, 31.7, 116.5, 118.4, 119.4, 122.5, 123.4, 125.3, 126.8, 127.3, 128.7, 139.2, 140.3, 144.5, 154.4, 155.8.

*General procedure for the synthesis of 8-amino-4-(furan-2-yl)-5-oxo-3,4,5,6-tetrahydro-2H-thieno[2,3-h]chromene-3-carbonitrile derivatives (**16a-d**)*

To a solution of compounds **14a** (2.84 g, 0.01 mol) or **14b** (3.31 g, 0.01 mol), in ethanol/DMF (20/10 mL) and triethylamine (0.50 mL), malononitrile **13a** (0.66 g, 0.01 mol) or ethyl cyanoacetate **13b** (1.13 g, 0.01 mol) were added. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water and crystallized from absolute alcohol.

*8-Amino-4-(furan-2-yl)-2-imino-5-oxo-3,4,5,6-tetrahydro-2H-thieno[2,3-h]chromene-3,9-dicarbonitrile (**16a**)*. Brown crystals, m.p. 178-180 ºC, yield: 2.63 g (75%). Elemental analysis for $C_{17}H_{10}N_4O_3S$ (350.35), (% calcd/found): 58.28/58.50 (C), 2.88/3.10 (H), 15.99/15.75 (N), 9.15/8.80 (S). ^{1}H NMR (δ, ppm): 2.96 (d, 1H, CH-pyran), 3.85 (d, 1H, CH-pyran), 3.99 (s, 2H, CH_2), 6.51, 6.83, 7.53 (m, 3H, CH-furan), 7.99 (s, 2H, NH_2), 11.99 (s, 1H, NH). ^{13}C NMR (δ, ppm): 50.6, 116.7, 116.9, 117.2, 118.3, 119.6, 122.5, 123.2, 125.8, 126.5, 127.6, 128.7, 139.6, 140.0, 142.1, 154.6, 170.3.

*8-Amino-4-(furan-2-yl)-2,5-dioxo-3,4,5,6-tetrahydro-2H-thieno[2,3-h]chromene-3,9-dicarbonitrile (**16b**)*. Brown crystals, m.p. 208-210 ºC, yield: 2.81 g (80%). Elemental analysis for $C_{17}H_9N_3O_4S$ (351.34), (% calcd/found): 58.12/58.40 (C), 2.58/2.70 (H), 11.96/11.70 (N), 9.13/8.81 (S). ^{1}H NMR (δ, ppm): 2.89 (d, 1H, CH-pyran), 3.45 (d, 1H, CH-pyran), 3.99 (s, 2H, CH_2), 6.84, 6.96, 7.30 (m, 3H, CH-furan), 7.95 (s, 2H, NH_2).

*Ethyl 8-amino-3-cyano-4-(furan-2-yl)-2-imino-5-oxo-3,4,5,6-tetrahydro-2H-thieno[2,3-h]chromene-9-carboxylate (**16c**)*. Brown crystals, m.p. 198-200 ºC, yield: 3.07 g (77%). Elemental analysis for $C_{19}H_{15}N_3O_5S$ (397.40), (% calcd/found): 57.42/57.60 (C), 3.80/4.00 (H), 10.57/10.30 (N), 8.07/7.80 (S). ^{1}H NMR (δ, ppm): 1.13-1.18 (t, 3H, CH_3), 2.89 (d, 1H, CH-pyran), 3.71 (d, 1H, CH-pyran), 3.87 (s, 2H, CH_2), 4.30 (q, 2H, CH_2), 6.83, 7.14, 7.86 (m, 3H, CH-furan), 7.95 (s, 2H, NH_2), 9.90 (s, 1H, NH).

*Ethyl 8-amino-3-cyano-4-(furan-2-yl)-2,5-dioxo-3,4,5,6-tetrahydro-2H-thieno[2,3-h]chromene-9-carboxylate (**16d**)*. Faint brown crystals, m.p. 213-215 ºC, yield: 3.19 g (80%). Elemental analysis for $C_{19}H_{14}N_2O_6S$ (398.39), (% calcd/found): 57.28/57.55 (C), 3.54/3.20 (H), 7.03/7.35 (N), 8.05/7.82 (S). ^{1}H NMR (δ, ppm): 1.14-1.29 (t, 3H, CH_3), 2.89 (d, 1H, CH-pyran), 3.48 (d, 1H, CH-pyran), 3.99 (s, 2H, CH_2), 4.10 (q, 2H, CH_2), 6.85, 7.15, 7.60 (m, 3H, CH-furan), 7.95 (s, 2H, NH_2). ^{13}C NMR (δ, ppm): 16.8, 20.3, 50.6, 116.8, 116.3, 117.8, 118.2, 119.5, 121.3, 124.4, 125.6, 126.7, 127.2, 128.3, 139.6, 140.0, 142.1, 154.4, 165.8.

*Synthesis of 5,5-dimethyl-3-phenyl-2-thioxo-2,3,5,6-tetrahydrobenzo[d]thiazol-7(4H)-one (**18**)*

To a solution of compounds **5** (1.40 g, 0.01 mol) in ethanol (20 mL) and triethylamine (0.50 mL), phenylisothiocyanate **17** (1.35 g, 0.01 mol) in the presence an equimolar amount of elemental sulfur was added. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water, and crystallized from absolute alcohol. Off white crystals, m.p.148-150 ºC, yield: 2.81 g (97%). Elemental analysis for $C_{15}H_{15}NOS_2$ (289.42), (% calcd/found): 62.25/62.00 (C), 5.22/5.44 (H), 4.84/5.10 (N), 22.16/21.80 (S). IR (ν, cm^{-1}): 3013 (CH-aromatic), 2961-2871 ($2CH_2$, $2CH_3$), 1598 (C=O), 1545, 1462 (C=C), 1398, 1291 (C=S). ^{1}H NMR (δ, ppm): 0.96-1.06 (s, 6H, $2CH_3$), 2.27, 2.40 (2s, 4H, $2CH_2$), 7.18, 7.21, 7.97, 7.99 (m, 5H, C_6H_5). ^{13}C NMR (δ, ppm): 27.8 (2), 31.9, 39.3, 40.1, 108.1, 124.1, 124.9, 128.9, 130.4, 139.9, 180.1, 190.5.

*General procedure for the synthesis of 7-amino-5,5-dimethyl-3-phenyl-4,5-dihydrothieno[3',2':3,4]benzo[1,2-d]thiazole-2(3H)-thione derivatives (**19a-b**)*

To a solution of compounds **18** (2.89 g, 0.01 mol) in ethanol (20 mL) and triethylamine (0.50

mL), malononitrile **13a** (0.66 g, 0.01 mol) or ethyl cyanoacetate **13 b** (1.13 g, 0.01 mol) in the presence an equimolar amount of elemental sulfur were added. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water and crystallized from absolute alcohol.

*7-Amino-5,5-dimethyl-3-phenyl-2-thioxo-2,3,4,5-tetrahydrothieno[3',2':3,4]benzo-[1,2-d]thiazole-8-carbonitrile (**19a**)*. Grey crystals, m.p. 153-155 °C, yield: 3.30 g (89%). Elemental analysis for $C_{18}H_{15}N_3S_3$ (369.53), (% calcd/found): 58.51/58.80 (C), 4.09/4.34 (H), 11.37/11.10 (N), 26.03/25.80 (S). ^{1}H NMR (δ, ppm): 0.96-1.05 (s, 6H, $2CH_3$), 2.40 (s, 2H, CH_2), 7.12-7.50 (m, 7H, C_6H_5, NH_2). ^{13}C NMR (δ, ppm): 20.6, 116.2, 117.6, 119.3, 119.3, 121.3, 123.8, 125.8, 126.2, 127.2, 127.3, 128.6, 140.5, 141.2, 150.8, 165.6.

*Ethyl 7-amino-5,5-dimethyl-3-phenyl-2-thioxo-2,3,4,5-tetrahydrothieno[3',2':3,4]-benzo[1,2-d]thiazole-8-carboxylate (**19b**)*. Off white crystals, m.p. 98-100 °C, yield: 3.41 g (82%). Elemental analysis for $C_{20}H_{20}N_2O_2S_3$ (416.58), (% calcd/found): 57.66/57.88 (C), 4.84/4.95 (H), 6.72/6.50 (N), 23.09/22.82 (S). IR (ν, cm^{-1}): 3205, 3185 (NH_2), 3047, 3015 (CH-aromatic), 2961-2871 (CH_2, $3CH_3$), 2220 (CN), 1715 (C=O), 1611, 1495 (C=C), 1399, 1246 (C=S). ^{1}H NMR (δ, ppm): 0-91-1-09 (s, 6H, $2CH_3$), 1.29-1.34 (t, 3H, CH_3), 2.40 (s, 2H, CH_2), 4.50-4.52 (q, 2H, CH_2), 7.12-7.50 (m, 7H, C_6H_5, NH_2). ^{13}C NMR (δ, ppm): 14.5, 27.9, 27.9, 31.9. 46.2, 108.1, 124.1, 124.5, 126.4, 128.9, 128.9, 130.0, 130.0, 130.4, 170.5.

*General procedure for the synthesis of 8-amino-5,5-dimethyl-3,6-diphenyl-2-thioxo-3,4,5,6-tetrahydro-2H-chromeno[7,8-d]thiazole-7-carbonitrile derivatives (**21a-c**)*

To a solution of compounds **18** (2.89 g, 0.01 mol) in ethanol/DMF (15/5 mL) and triethylamine (0.50 mL), malononitrile **13a** (0.66 g, 0.01 mol) and benzaldehyde **20a** (1.06 g, 0.01 mol), *p*-chlorobenzaldehyde **20b** (1.40 g, 0.01 mol) or *p*-methoxybenzaldehyde **20b** (1.36 g, 0.01 mol) were added. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water, and crystallized from absolute alcohol.

*8-Amino-5,5-dimethyl-3,6-diphenyl-2-thioxo-3,4,5,6-tetrahydro-2H-chromeno[7,8-d]thiazole-7-carbonitrile (**21a**)*. Faint Brown crystals, m.p. 183-185 °C, yield: 3.86 g (87%). Elemental analysis for $C_{25}H_{21}N_3OS_2$ (443.58), (% calcd/found): 67.69/67.90 (C), 4.77/4.96 (H), 9.47/9.20 (N), 14.46/14.22 (S). ^{1}H NMR (δ, ppm): 0.96-1.04 (s, 6H, $2CH_3$), 2.23 (s, 2H, CH_2), 4.17 (s, 1H, CH-pyran), 6.96-7.31 (m, 10H, $2C_6H_5$), 8.50 (s, 2H, NH_2).

*8-Amino-6-(4-chlorophenyl)-5,5-dimethyl-3-phenyl-2-thioxo-3,4,5,6-tetrahydro-2H-chromeno-[7,8-d]thiazole-7-carbonitrile (**21b**)*. Brown crystals, m.p. 98-100 °C, yield: 4.40 g (92%). Elemental analysis for $C_{25}H_{20}ClN_3OS_2$ (478.03), (% calcd/found): 62.81/63.10 (C), 4.22/4.44 (H), 8.79/8.50 (N), 13.42/13.12 (S). IR (ν, cm^{-1}): 3375, 3309 (NH_2), 3179 (CH-aromatic), 2960 ($3CH_3$), 2188 (CN), 1601, 1490 (C=C), 1365, 1249 (C=S). ^{1}H NMR (δ, ppm): 0.95-1.03 (s, 6H, $2CH_3$), 2.22 (s, 2H, CH_2), 4.20 (s, 1H, CH-pyran), 7.03-7.58 (m, 9H, C_6H_5, C_6H_4), 8.52 (s, 2H, NH_2).

*8-Amino-6-(4-methoxyphenyl)-5,5-dimethyl-3-phenyl-2-thioxo-3,4,5,6-tetrahydro-2H-chromeno [7,8-d]thiazole-7-carbonitrile (**21c**)*. Off white crystals, m.p. 175-177 °C, yield: 3.85 g (81%). Elemental analysis for $C_{26}H_{23}ClN_3O_2S_2$ (473.61), (% calcd/found): 65.94/66.20 (C), 4.89/5.10 (H), 8.87/8.55 (N), 13.54/13.22 (S). IR (ν, cm^{-1}): 3450, 3330 (NH_2), 3014 (CH-aromatic), 2962 (CH_2, $3CH_3$), 2222 (CN), 1608, 1564 (C=C), 1397, 1246 (C=S). ^{1}H NMR (δ, ppm): 0.96-1.05 (s, 6H, $2CH_3$), 2.27 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 5.19 (s, 1H, CH-pyran), 7.18-7.99 (m, 9H, C_6H_5, C_6H_4), 8.40 (s, 2H, NH_2). ^{13}C NMR (δ, ppm): 20.3, 27.3, 30.8, 31.4, 46.2, 108.1, 124.3, 124.5, 126.7, 128.6, 1285, 130.3, 130.0, 130.5, 170.2.

*Synthesis of 6-(4-methoxybenzylidene)-5,5-dimethyl-3-phenyl-2-thioxo-2,3,5,6-tetrahydro-benzo[d]thiazol-7(4H)-one (**22**)*. To a solution of compounds **18** (2.89 g, 0.01 mol) in ethanol/DMF (15/5 mL) and piperidine (0.50 mL), **19a** (3.69 g, 0.01 mol) was added. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water, and crystallized from absolute alcohol. Yellow crystals, m.p. 98-100 ºC, yield: 3.30 g (81%). Elemental analysis for $C_{23}H_{21}NO_2S_2$ (407.55), (% calcd/found): 67.78/67.99 (C), 5.19/5.40 (H), 3.44/3.11 (N), 15.74/15.50 (S). IR (ν, cm^{-1}): 2955-2869 (CH_2, $3CH_3$), 1680 (C=O), 1610, 1531 (C=C), 1375, 1336 (C=S). ^{1}H NMR (δ, ppm): 0.95-1.05 (s, 6H, $2CH_3$), 2.22 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.77 (s, 1H, =CH), 7.04-7.99 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (δ, ppm): 22.2, 26.9, 27.9, 43.9, 56.2, 115.0, 115.1, 128.1, 129.2, 129.4, 129.8, 130.1, 130.1, 132.3, 132.3, 132.9, 164.7, 191.8.

*Synthesis of 2-(2-(5,5-dimethyl-3-phenyl-2-thioxo-2,3,5,6-tetrahydrobenzo[d]thiazol-7(4H)-ylidene)hydrazinyl)acetonitrile (**24**)*. To a solution of compounds **18** (2.89 g, 0.01 mol) in ethanol/DMF (15/5 mL), 2-cyanoacetohydrazide **23** (0.99 g, 0.01 mol) was added. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water, and crystallized from absolute alcohol. Faint brown crystals, m.p. 137-140 ºC, yield: 2.75 g (80%). Elemental analysis for $C_{17}H_{18}N_4S_2$ (342.48), (% calcd/found): 59.62/59.92 (C), 5.30/5.60 (H), 16.36/16.01 (N), 18.73/18.52 (S). IR (ν, cm^{-1}): 3254 (NH_2), 2220 (CN), 2956-2871 ($3CH_2$, $2CH_3$), 1538, 1494 (C=C), 1385, 1314 (C=S). ^{1}H NMR (δ, ppm): 1.03-1.05 (s, 6H, $2CH_3$), 1.30 (s, 2H, CH_2), 2.10 (s, 2H, CH_2), 3.88 (s, 2H, CH_2), 7.27-7.56 (m, 5H, C_6H_4), 8.30 (s, 1H, NH). ^{13}C NMR (δ, ppm): 27.2, 27.6, 33.0, 34.9, 39.3, 39.9, 116.4, 117.3, 128.6, 129.3, 129.3, 130.0, 130.4, 138.8, 156.2, 160.1, 161.4.

Cell proliferation assay 31 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. 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 hetero cycle ring being attached have a notable influence on the anti-proliferative activity.

CONCLUSION

A series of novel pyrazolo[1,5-*a*]quinazoline derivatives were obtained from the multi-component reaction of 4-(2-phenylhydrazono)-4*H*-pyrazol-3-amine derivatives **1a-f**. About six cancer cell lines such as A549, HT-29, MKN-45, U87MG, SMMC-7721 and, H460 were used to evaluate the cytotoxic effect of some selected of the novel products. Compounds, **4d**, **4e**, **6c**, **6e**. **8c**, **14b**,

18 and **24** were the most potent compounds among the other novel prepared products. The work succeeded in demonstrating new heterocyclic compounds as cytotoxic agents which has great impact for future work.

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