Synthesis, Reactions and Antimicrobial Activity of 2-Cyano-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)acetohydrazide Derivatives

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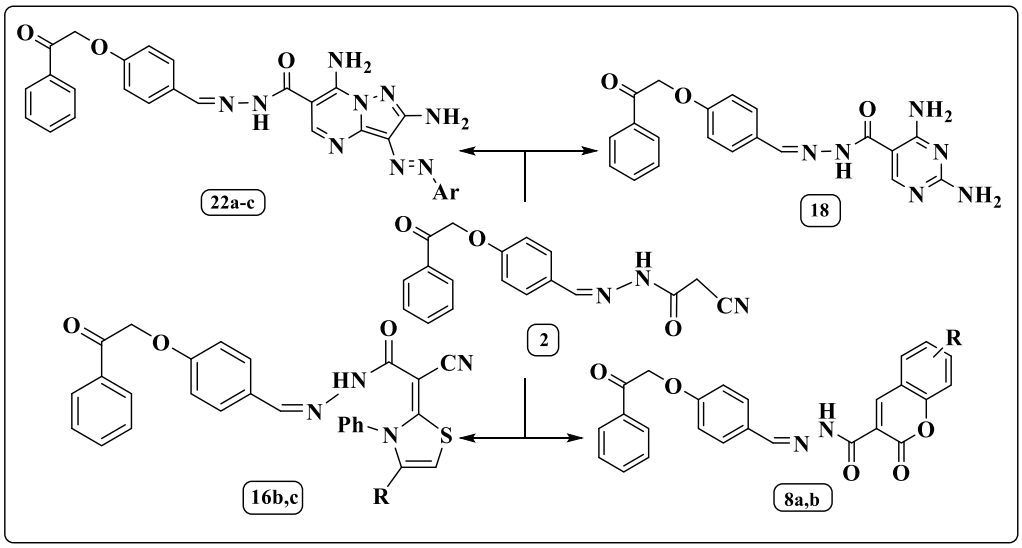
ABSTRACT



Knövenagel condensation of the starting 2-cyano-*N*'-(4-(2-oxo-2-phenylethoxy)-benzylidene)acetohydrazide with different aromatic aldehydes produced the comparable arylidenes derivatives. Else way, 2-cyano-*N*'-(4-(2-oxo-2-phenylethoxy)-benzylidene)-acetohydrazide condensed with *o*-hydroxybenzaldehydes affording the respective chromenes which latter underwent acid hydrolysis giving the oxo-chromenes analogues. Moreover, the reaction of 2-cyano-*N*'-(4-(2-oxo-2-phenylethoxy)benzylidene)acetohydrazide with istain yielded the respective indeno[2,1-*b*]furan derivative that was converted to its oxo-analogue through acid hydrolysis. The treatment of 2-cyano-*N*'-(4-(2-oxo-2-phenylethoxy)benzylidene)acetohydrazide with *α*-halocompounds produced the relevant thiazoles. The enamine 2-cyano-3-(dimethylamino)-*N*'-(4-(2-oxo-2-phenylethoxy)benzylidene)acrylohydrazide underwent nucleophilic substitution reaction with guanidine hydrochloride followed by heterocyclization to get the relative aminopyrimidine. Contrarily, the reaction with various 4-arylazo-3,5-diaminopyrazoles provided the relative

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pyrazolo[1,5-*a*]pyrimidines. The antimicrobial investigation was carried out for some of the newly synthesized compounds using agar well diffusion method.

KEYWORDS: Cyanoacetic hydrazide, Chromenes, Aminopyrazoles, Aminopyrimidines, Pyrazolo[1,5-*a*]pyrimidines.

INTRODUCTION

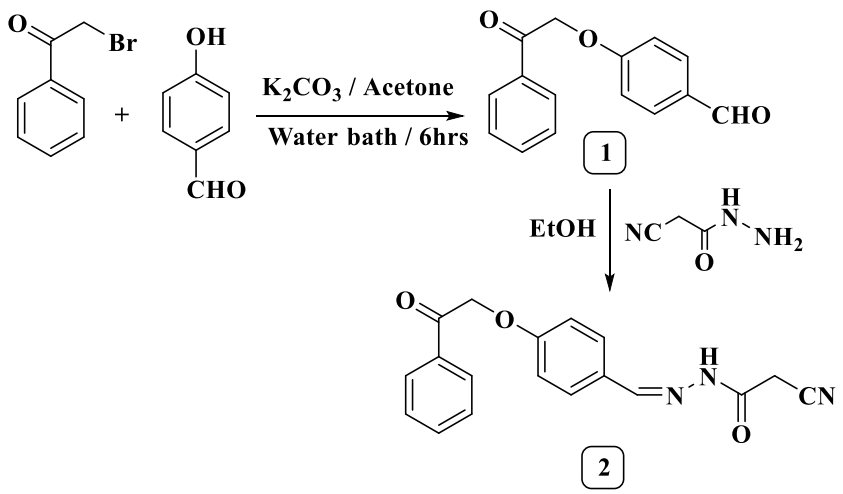
In the last recent ten years, the research programs are aiming to develop new simple procedures and mechanisms for synthesis of some new heterocyclic ring systems with biological applications from available raw starting materials. Derivatives of cyanoacetic acid hydrazide are considered important intermediates and starting materials in the synthesis of many remarkable heterocyclic ring systems as they are highly reactive and polyfunctional compounds owing to having both nucleophilic and electrophilic. Additionally, they have received an excellent attention as pharmaceutical drugs [1,2] and as antibacterial agents [3]. Also, they are applicable within the industrial field in the production of dyes [4,5] and herbicides [6]. Moreover, a lot of heterocyclic ring systems were prepared through cyanoacetic acid hydrazide like pyrazoles [7,8], thiophenes [9-11], thiazoles [12,13], pyrazolopyrimidines [14], pyrimidines [15,16], pyridines [17-20], and others [21-23].

In the view of these observations and as a part of our ongoing research program aimed to the synthesis of biologically active heterocycles [24-35], we report herein the synthesis of some new heterocyclic compounds depending on 2-cyano-*N*'-(4-(2-oxo-2-phenylethoxy)-benzylidene)acetohydrazide **2** as a starting compound that underwent reactions with usual chemical reagents delivering various species of heterocyclic compounds besides that antimicrobial activity assessment has been performed for some selected compounds as a biological application.

RESULTS AND DISCSSION

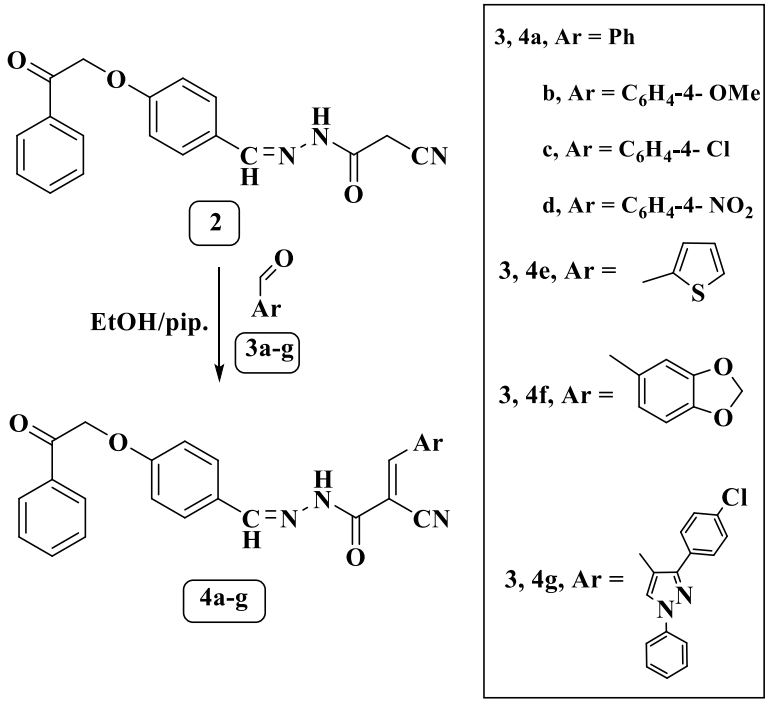
Chemistry. The synthesis of 2-cyano-*N*'-(4-(2-oxo-2-phenylethoxy)-benzylidene)acetohydrazide **2** was achieved through the reaction of cyanoacetic acid hydrazide with 4-(2-oxo-2-phenylethoxy)benzaldehyde **1** [which is prepared by the reaction of phenacyl bromide with *p*-hydroxybenzaldehyde in refluxing dry acetone in the presence of potassium carbonate (Scheme 1)]. The structural formula of compound **2** was approved through spectroscopic data and

elemental analyses. In IR spectrum of **2**, absorption bands appeared at ν_{max} at 3436, 2261, 1712 and 1675 cm^{-1} for the amide, cyano and carbonyl groups, respectively. Its ^{1}H-NMR spectrum showed singlet signals at δ = 4.16 and 5.65 ppm attributed to two CH_2 protons in additionally a *D_2O* exchangeable signal at δ = 11.65 ppm due to –NH- proton. Also, the ^{13}C-NMR spectrum showed characteristic signals at δ = 194.1, 164.5 and 126.6 for two CO and CN groups besides other expected signals. The mass spectrum of compound **2** showed a peak at m/z = 321 (M^+, 13.7%) which is constituent to a molecular formula $C_{18}H_{15}N_3O_3$. The elemental analysis was in agreement with the supposed structure of **2**.



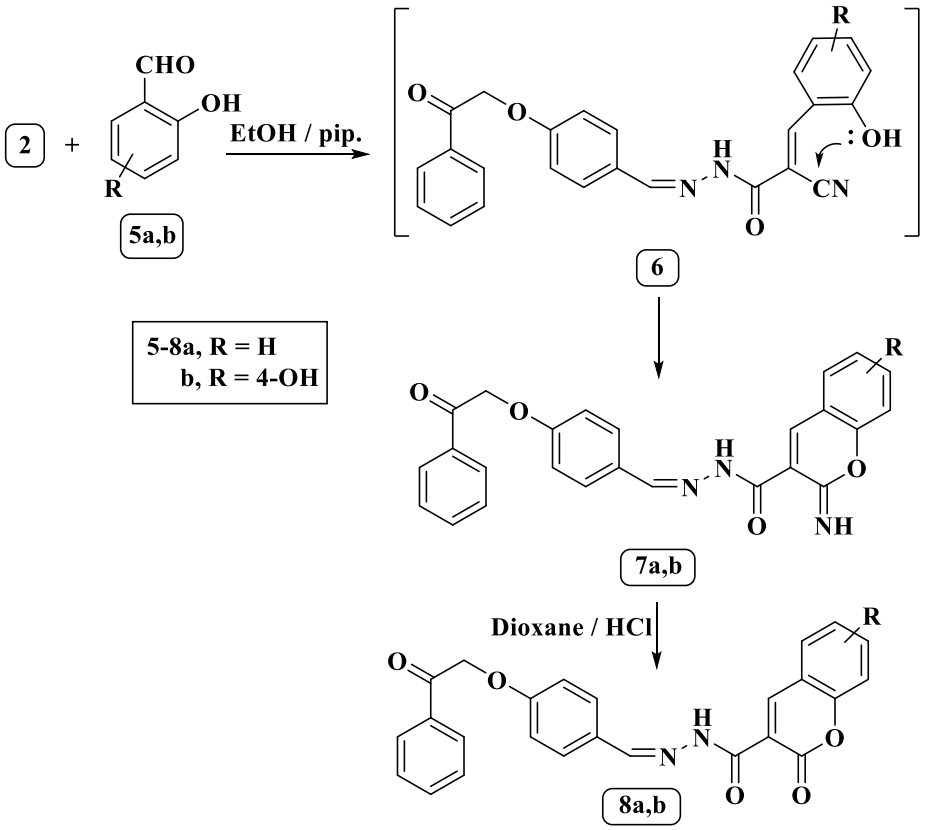
Scheme 1. Synthesis of 4-(2-oxo-2-phenylethoxy)benzaldehyde **1** and 2-cyano-*N*'-(4-(2-oxo-2-phenylethoxy)-benzylidene)acetohydrazide **2**

Knövenagel condensation reaction between compound **2** and the aromatic aldehydes **3a-g** gave the corresponding arymethylene derivatives **4a-g**. The structural formula of these arylmethylenes **4a-g** was affirmed through the data obtained from the elemental and spectral analyses (Scheme 2). The IR spectrum of **4a** displayed bands at ν_{max} = 3423, 2200 and 1689 cm^{-1} due to the NH, CN and CO groups, respectively. In ^{1}H-NMR spectrum of **4a**, a *D_2O* exchangeable singlet appeared at δ = 10.45 ppm owing to NH group along with expecting signals for vinylic and aryl protons. Also, characteristic signals at δ (ppm) = 116.6 (CN), 171.1 (CO) and 185.5 (CO) besides other expected signals appeared in the ^{13}C-NMR spectrum for **4a**. The MS of **4a** demonstrated peak at m/z = 409 (M^+, 2.8%) for the molecular formula $C_{25}H_{19}N_3O_3$ besides other peaks. The IR, ^{1}H-NMR, ^{13}C-NMR and MS data with the elemental analyses supported the proposed structures **4a-g**.



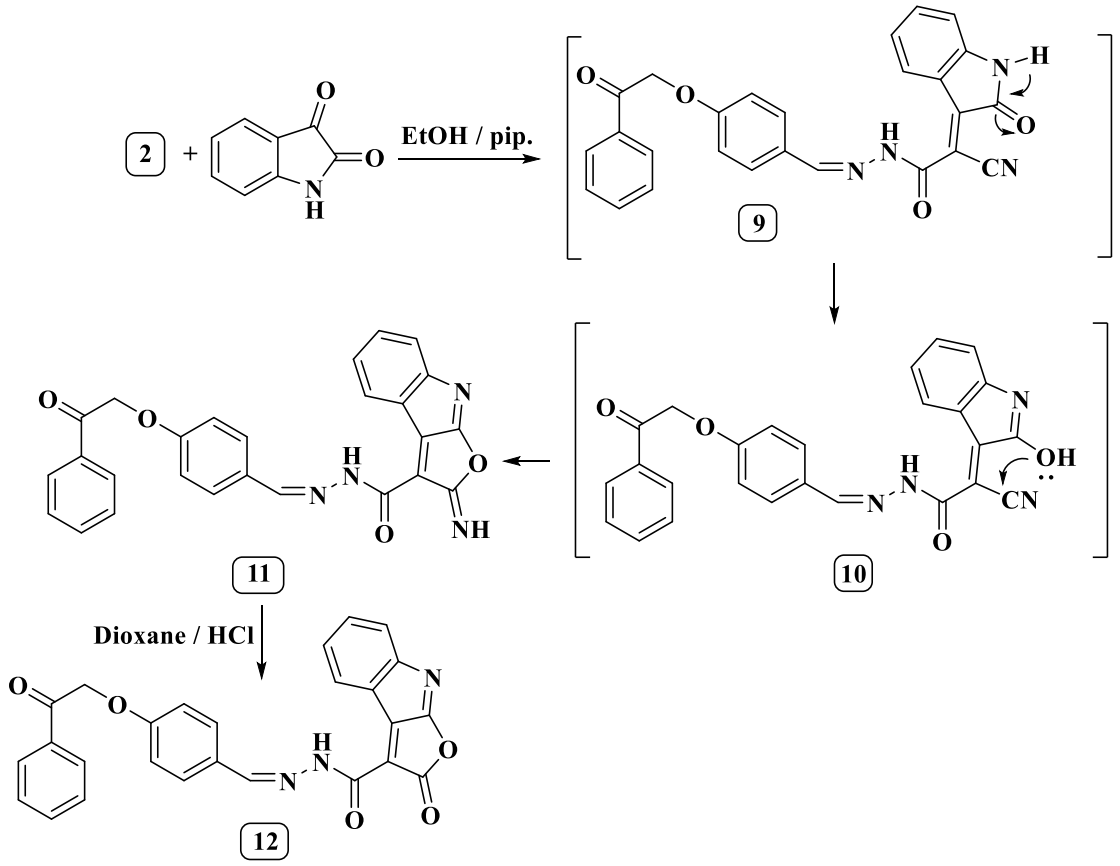
Scheme 2. Synthesis of arylmethylene derivatives **4a-g** of 2-cyano-*N*'-(4-(2-oxo-2-phenylethoxy)-benzylidene)acetohydrazide **2**

Under the same conditions, brown colored products **7a,b** were obtained through refluxing compound **2** with *o*-hydroxybenzaldehydes **5a,b** in a mixture of absolute ethanol and few drops of piperidine. The imino chromenes **7a,b** were prepared through the non- isolable intermediate **6** that in turn underwent *in situ* heterocyclization to provide the final products (Scheme 3 and see exp.). The IR spectra of **7** revealed the absence of a band near ν_{max} ~ 2180-2300 cm^{-1} ascribed to a CN function instead it showed the appearance of a band near ν_{max} ~ 3400 cm^{-1} as a result, of the generation of a new imino group. Also, the IR spectrum of **7a** displayed bands at ν_{max} = 3338 and 1658 cm^{-1} equivalent to the NH and CO functions, consequently. The 1H-NMR spectrum of **7a** showed two D_2O exchangeable signals at δ = 9.98 and 12.28 ppm assignable to the NH protons alongside another singlet signal at δ = 5.56 ppm assigned to CH_2 group. In addition to, another expected signals for aryl protons were appeared. The supposed structure of the novel products was determined by the spectroscopic and elemental analyses. The acid hydrolysis of imino chromenes **7a,b** in dioxine/hydrochloric acid solution produced the oxo-analogues **8a,b**. The structure of the newly prepared series were approved by ways of physical properties (TLC and m.p) together with spectroscopic data (^{1}H-NMR, IR and MS).



Scheme 3. Preparation of chromene derivatives **7a,b** and oxo-chromene analogues **8a,b**

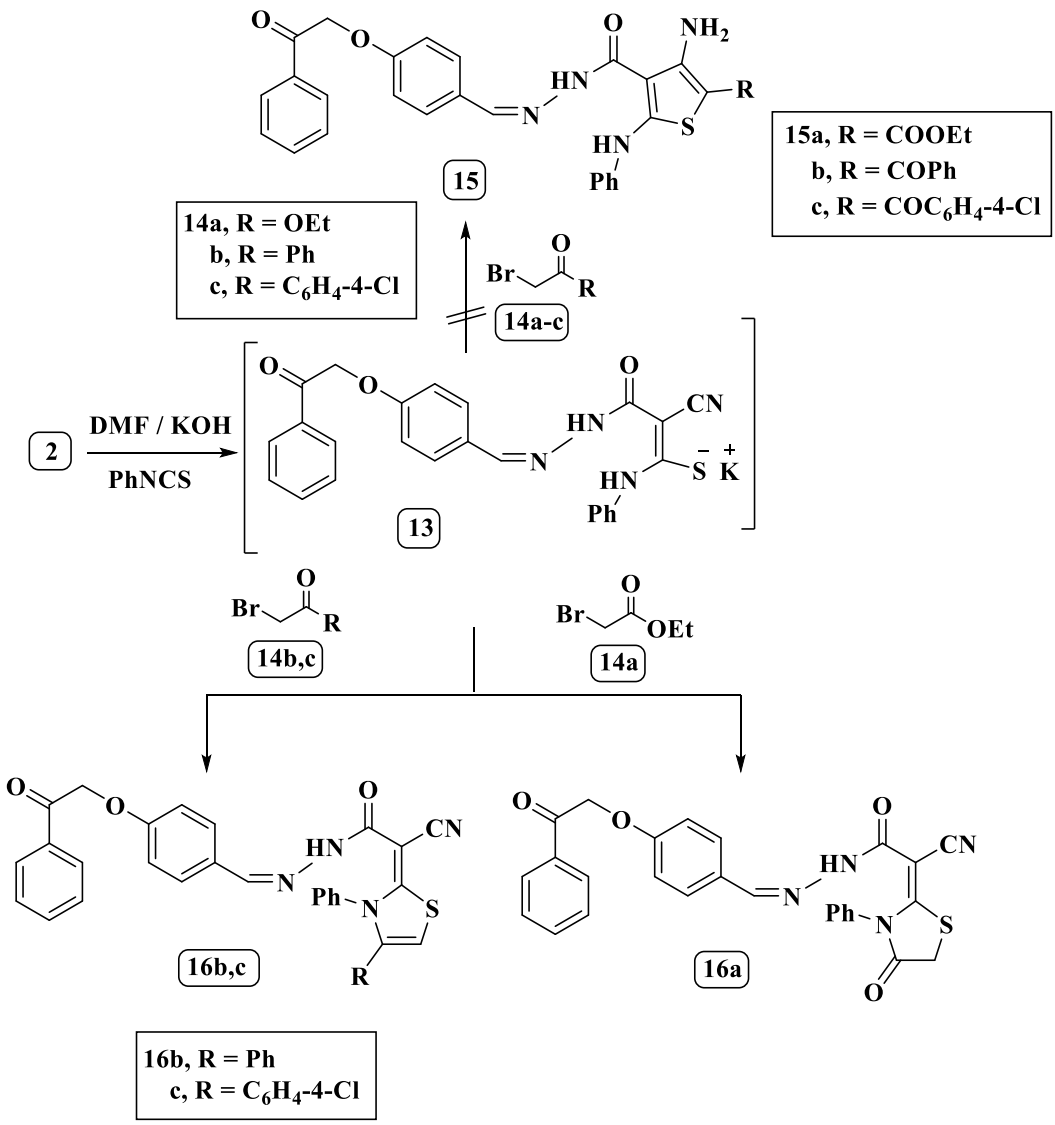
Furthermore, 2-imino-*N*'-(4-(2-oxo-2-phenylethoxy)benzylidene)-2*H*-furo[2,3-*b*]indole-3-carbohydrazide **11** was produced from the treatment of compound **2** with isatin under the same reaction conditions (Scheme 4). The expected mechanism was proceeded through initial tautomerism step in the intermediate **9** affording the intermediate **10** that in turn underwent *in situ* heterocyclization to form the final product **11**. Also, the acid hydrolysis of compound **11** in dioxane/ hydrochloric acid gave the oxo-analogues **12**. The suggested structures of compound **11** and **12** were confirmed by spectroscopic tools (IR, ^{1}H-NMR and MS). As example, the IR spectrum of **11** displayed absorption bands at ν_{max} = 3428 and 1668 cm^{-1} due to imino (NH) and carbonyl (CO) functions while the absorption bands for NH and CO functions in compound **12** appeared bands at ν_{max} = 3405, 1690 and 1634 cm^{-1}. Also, as compared between the ^{1}H-NMR spectra of **11** and **12**, it had been observed that in ^{1}H-NMR spectrum of **11**, two D_2O exchangeable signals were found at chemical shift (δ) = 10.54 and 11.83 ppm for NH protons, while the ^{1}H-NMR spectrum of **12** showed a D_2O exchangeable signal at δ = 10.74 ppm for of NH proton. The elemental data is in agreement with the proposed structures **11** and **12**.



Scheme 4. 2-imino-*N*'-(4-(2-oxo-2-phenylethoxy)benzylidene)-2*H*-furo[2,3-*b*]indole-3-carbo-hydrazide **11** and its oxo-analogous **12**

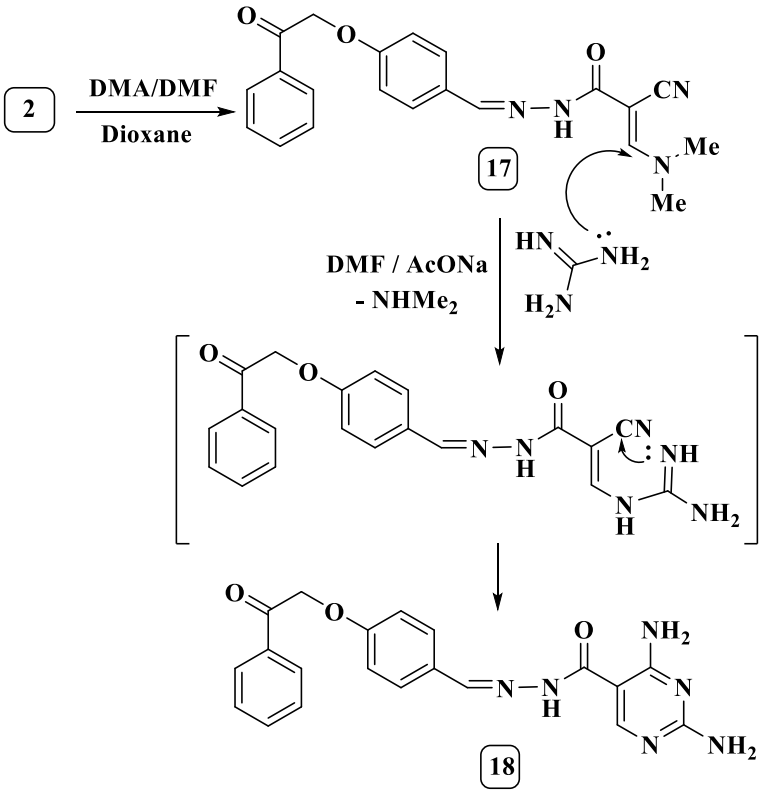
The reaction of 2-cyano-*N*'-(4-(2-oxo-2-phenylethoxy)-benzylidene)acetohydrazide **2** with phenyl isothiocyanate in a mixture of dry *N*,*N*-dimethylformamide and solid potassium hydroxide at room temperature afforded the non-isolable potassium salt **13** followed by the addition of ethyl bromoacetate **14a** giving thiazole derivative **16a** instead of the expected thiophene **15**. The structure of **16a** was confirmed through spectroscopic and elemental tools. The IR spectrum of **16a** showed absorption bands at ν_{max} 3425, 2203, 1695 and 1666 cm^{-1} corresponding to the NH, CN and CO functional groups, respectively. Moreover, its ^{1}H-Nuclear magnetic resonance spectrum deduced signals at δ = 11.28 and 4.10 ppm relative to NH and CH_2 protons of thiazole ring besides signals for aryl protons. In MS spectrum of **16a**, a peak was identified at m/z = 496 (M^+, 67.7%) that was found to be consistent with the molecular formula $C_{27}H_{20}N_4O_4S$ of the compound **16a** (Scheme 5).

Also, under the same conditions of the above reaction, compound **2** reacted with phenacyl chlorides **14b,c** to get the corresponding thiazoles **16b,c** rather than expected thiophenes **15**. The IR spectrum of **16c** revealed bands at ν_{max} 3426, 2197 and 1688 cm^{-1} referred to NH, CN and CO groups, respectively. It`s ^1H NMR displayed a D_2O exchangeable signal at δ = 11.26 ppm due to the presence of NH proton and another signal at δ = 5.61 ppm relative to CH_2 protons besides signals for aryl and CH protons. The representative spectroscopic data with elemental analysis together indicated the formation of thiazole **16** and ruled out the formation of thiophene **15** (Scheme 5 and see exp.).



Scheme 5. Synthesis of thiazoles derivatives **16a-c**

Compound **2** reacted with *N*,*N*-dimethylformamide/dimethylacetal (DMF/DMA) to afford the respective enamine 2-cyano-3-(dimethylamino)-*N*'-(4-(2-oxo-2-phenylethoxy)benzylidene) acrylohydrazide **17** (Scheme 6). The IR spectrum of **17** exhibited absorption bands at ν_{max} 3294, 2184, 1702 and 1658 cm^{-1} assignable to NH, CN and CO groups, respectively. Its ^{1}H-NMR spectrum showed two new singlet signals at δ = 3.21 and 3.30 ppm for two methyl protons of the amino group, additionally, it appeared signals at δ = 5.65 ppm for CH_2 protons and multiplet signals at δ = 7.54 – 7.72 ppm for aryl protons besides a D_2O exchangeable singlet signal at δ = 10.76 ppm for amide proton. Additionally, it revealed signals at δ = 7.00 and 8.01 ppm as doublet signal with *J* = 8.4 and 7.2 Hz, respectively for aryl protons. The reaction of compound **17** with guanidine hydrochloride gave the corresponding diaminopyrimidine **18**. The structure of compound **18** was established by elemental analysis and spectroscopic data (Scheme 6). The IR spectrum of **18** showed disappearance of absorption band at ν_{max} = 2254 cm^{-1} for CN group, instead it showed a broad band at ν_{max} 3442 cm^{-1} equivalent to NH_2 and NH groups. Also, its ^{1}H-NMR spectrum revealed absence of two singlet signals at δ = 3.21 ppm of the two methyl protons of dimethylamino function in addition to three D_2O exchangeable signals at δ = 10.49, 6.79 and 6.82 ppm respective to NH and two NH_2 protons. The suggested reaction mechanism was assumed to start out with initial displacement of dimethylamine moiety followed by nucleophilic addition of the NH_2 nitrogen atom to the nitrile function then tautomeric conversion of imino (=NH) group to the amino (NH_2) group to develop the target product **18** (Scheme 6 and see exp.).

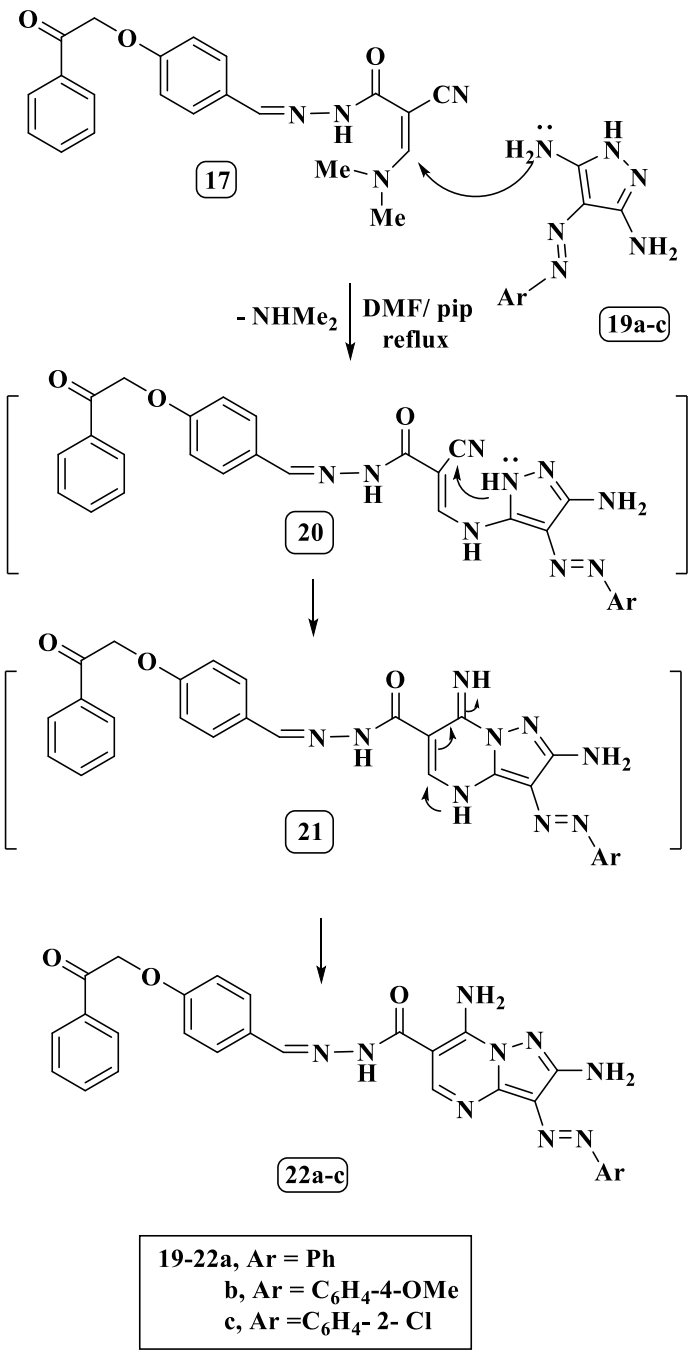


Scheme 6

Scheme 6. Synthetic route of 2,4-diamino pyrimidine derivative **18**

The reaction of compound **17** with 4-arylazo-3,5-diaminopyrazoles **19a-c** afforded the relative pyrazolo[1,5-*a*]pyrimidine derivatives **22a-c**. The presumed structure for the products was proved by spectral and elemental data. The IR spectrum of compound **22a**, as a typical example of the prepared series, revealed absence of an absorption band at ν_{max} = 2254 cm^{-1} relative to a cyano group and appearance of a broad absorption band at ν_{max} = 3400 cm^{-1} for NH_2 and NH groups besides other bands for carbonyl groups at ν_{max} = 1668 and 1658 cm^{-1}. The H^1-NMR spectrum of compound **22a** revealed two *D_2O* exchangeable broad signals for amino protons at δ = 6.35 and 6.77 ppm, besides a *D_2O* exchangeable signal at δ = 10.89 ppm for NH proton. The suggested structure of the newly obtained products **22a-c** was affirmed by their elemental analysis and physical properties (m.p. and TLC) together with the spectroscopic data. The suggested mechanism for the synthesis of **22** was proceeded through initial substitution of NMe_2 by a nucleophilic addition achieved by the amino group of the substrate **19** to yield non-isolable intermediate **20,** then followed by intramolecular heterocyclization producing the non-

isolable intermediate **21**. Finally, a tautomeric step was occurred giving the final product **22** (Scheme 7 and see exp.).



Scheme 7. Reaction pathway to afford the relative pyrazolo[1,5-*a*]pyrimidines **22a-c**

ANTIMICROBIAL ACTIVITY INVESTIGATION

The antimicrobial activity of some of the newly synthesized products was investigated against fungal strain (Candida *albicans*), Gram positive bacterial strain (Staphylococcus *aureus*) and Gram negative bacterial strain (Escherichia *coli* and Klebsiella *pneumonia*) using nutrient agar medium diffusion method [36]. Nystatin was used as a standard antifungal drug for Candida *albicans*, while Ampicilin and Gentamicin are used as standard antibiotics for Gram positive and Gram negative bacterial strains. The investigation`s results varied form no antimicrobial activity for the tested compounds in most of the microbial strains to moderate or even very strong antimicrobial activity in specific microbial strains while most of the tested compounds showed no antifungal activity except few of them showed very strong activity (Table 1).

For Antifungal Activity: Most of the tested compounds have no activity against Candida *albicans* except compound **4b** which showed weak antifungal activity with the mean inhibition zone = 10.3 ± 0.5 mm while compounds **22c** and **4c** showed moderate activity with the mean inhibition zone = 16.3 ± 0.5 mm. The presence of 4-methoxyphenyl moiety in **4b**, 4-chlorophenyl moiety in **4c** and 4-phenyl azo pyrazolo[1,5-*a*]pyrimidine moiety in **22c** enhanced the antifungal activity for these compounds and the presence of electron withdrawing group in **4c** and **22c** increased the antifungal activity more than the presence of electron donating group in **4b**. In comparison with Nystatin, compounds **18** and **4d** showed very strong antifungal activity relative to that of nystatin with mean inhibition zone = 20.6 ± 0.6 and 20.3 ± 0.5 mm, respectively while that of nystatin = 21.0 ± 0.5 mm. The presence of aminopyrimidine moiety and 4-nitrophenyl moiety in compounds **18** and **4d** respectively, improved the antifungal activity against the Candida *albicans*.

For Antibacterial Activity*:*

In **Staphylococcus *aureus:*** all the tested compounds have no antibacterial activity against that strain.

In **Escherichia *coli:*** compounds **4f** and **7b** showed moderate activity with mean inhibition zone = 12.3 ± 0.5 mm hence the standard drug gentamicin showed 27 ± 0.6 mm. The Antibacterial

activity for these compounds may be due to the presence of pipronyl moiety and hydroxychromene rings in **4f** and **7b**, respectively.

In **Klebsiella *pneumonia*:** the starting compounds **1** and **2** have moderate antibacterial activity with mean inhibition zone = 14.3 ± 0.5 mm compared with that of gentamicin = 25 ± 0.5 mm. Introducing indeno[2,1-*b*]furan and 4-chlorophenylthiazole moieties in compounds **11** and **16c**, respectively quietly decreased the antibacterial activity with mean inhibition zone = 10.3 ± 0.5 and 11.3 ± 0.5 mm, respectively.

***Table 1*: The antimicrobial results for the tested selected compounds against different strains**

Antimicrobial strains	Staphylococcus *aureus*	Escherichia *coli*	Klebsiella *pneumonia*	Candida *albican*
St. Drug	Ampicillin 22 ± 0.5 mm	Gentamicin 27 ± 0.6 mm	Gentamicin 25 ± 0.5 mm	Nystatin 21 ± 0.5 mm
1	NA	NA	14.3 ± 0.5	NA
2	NA	NA	14.3 ± 0.5	NA
4b	NA	NA	NA	10.3 ± 0.5
4c	NA	NA	NA	16.3 ± 0.5
4d	NA	NA	NA	20.3 ± 0.5
4f	NA	12.3 ± 0.5	NA	NA
7a	NA	NA	NA	NA
7b	NA	12.3 ± 0.5	NA	NA
11	NA	NA	10.3 ± 0.5	NA

16a	NA	NA	NA	NA
16b	NA	NA	NA	NA
16c	NA	NA	11.3 ± 0.5	NA
18	NA	NA	NA	20.6 ± 0.6
22c	NA	NA	NA	16.3 ± 0.5

EXPERIMENTAL SECTION

I. General chemistry.

Melting points were determined in (^{o}C) on an electrothermal (9100) apparatus (Kleinfled, Gehrden, Germany) and are uncorrected. IR spectra were recorded as KBr pellets on a Nicolet 205 spectrophotometer (Nicolet, Madison, WI, USA). The ^{1}H-NMR (300 MHz) spectra and ^{13}C-NMR spectra (75 MHz) were obtained on a Varian EM-300 MHz spectrometer and DMSO-d_6 is used to dissolve the tested compounds besides, tetramethylsilane as an internal standard sand the results are obtained as δ value (Varian Inc., Palo Alto, CA, USA). Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (Shimadzu, Kyoto, Japan; 70 eV). Elemental analyses and spectral measurements were carried out by the microanalytic center at Cairo University. The procedure for the synthesis of cyanoacetic acid hydrazide and **3g** were prepared according to literature [37, 38].

Synthesis of 4-(2-oxo-2-phenylethoxy)benzaldehyde (1).

4-Hydroxybenzaldehyde (10 mmol) was added to phenacyl bromide (10 mmol) and potassium carbonate (10 mmol) in dry acetone (10 ml). The reaction mixture was heated to refluxing for 12 hrs in water bath at 30 ^{o}C. Yellowish brown solid was formed, filtered off, washed well with water, dried and recrystallized from ethanol.

Yellowish brown crystals, yield (60%), m.p 129-130 ^{o}C; IR (KBr) ν/cm^{-1}: 2980 (HC=O), 1745 (C=O) and 1698 (C=O); ^{1}H NMR (*DMSO-d*$_6$); δ = 5.76 (s, 2H, CH_2), 7.16 (d, 2H, *J* = 8.7 Hz, Ar), 7.56 (d, 2H, *J* = 7.2 Hz, Ar), 7.68 (d, 2H, *J* = 7.2 Hz, Ar), 7.85-8.05 (m, 3H, Ar), 9.87 (s, 1H, aldehydic H). ^{13}C NMR (*DMSO-d*$_6$) δ = 70.3, 115.1 (2C), 127.8 (2C), 128.8 (2C), 129.9 (2C), 131.6 (2C), 133.8, 134.1, 162.9, 191.2, 193.7. Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.16; H, 5.22%.

Synthesis of 2-cyano-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)acetohydrazide (2)

Compound **1** (10 mmol) and cyanoacetic acid hydrazide (10 mmol) was heated in absolute ethanol (10 ml) for 4 hrs. The product was collected, filtered off and recrystallized from an ethanol/dioxane.

Yellowish brown crystals, yield (96%), m.p 215-217 ^{o}C; IR (KBr) ν/cm^{-1}: 3436 (NH), 2261 (CN), 1712 (C=O) and 1675 (C=O); ^{1}H NMR (*DMSO-d*$_6$); δ = 4.16 (s, 2H, CH_2), 5.65 (s, 2H, CH_2), 7.01 (d, 2H, *J* = 8.7 Hz, Ar), 7.55 (d, 2H, *J* = 7.2 Hz, Ar), 7.61-7.64 (m, 3H, Ar), 7.67 (d, 2H, *J* = 7.5 Hz, Ar), 7.94 (s, 1H, CH), 11.65 (s, 1H, NH); ^{13}C NMR (*DMSO-d*$_6$) δ = 66.3, 70.1, 114.9 (2C), 116.1, 126.6, 127.8 (2C), 128.5 (2C), 128.7, 128.8, 133.8, 134.2, 144.1, 159.5, 164.5, 194.1; MS: m/z = 322 (M^++1, 2.9%), 321 (M^+, 13.7%), 313 (0.1%), 299 (0.1%), 281 (0.1%), 278 (0.1%), 254 (0.7%), 238 (0.8%), 224 (0.35%), 213 (0.23%), 203 (0.26%), 185 (0.27%), 167 (0.2%), 152 (0.4%), 133 (0.68%), 105 (100%), 91 (12.8%), 83 (3.4%), 77 (31.5%). Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.47; H, 4.89; N, 13.32 %.

Synthesis of compounds 4a-g.

A mixture of compound **2** (10 mmol) and aromatic aldehydes **3a-g** (10 mmol) was heated in ethanol (10 ml) containing drops of piperdine for 4 hrs. The products **4a-g** was collected by filtration and recrystallized from acetic acid.

2-Cyano-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-3-phenylacrylohydrazide (4a)

Yellow crystals, yield (89%), m.p 253-255 ^{o}C; IR (KBr) ν/cm^{-1}: 3423 (NH), 2200 (CN) and 1689 (C=O); ^{1}H NMR (*DMSO-d*$_6$); δ = 5.48 (s, 2H, CH_2), 6.91- 8.02 (m, 15H, Ar and CH), 8.45 (s, 1H, CH), 10.45 (s, 1H, NH); MS: *m/z* = 409 (M^+, 2.8%), 395 (0.9%), 393 (1.5%), 367 (2.7%), 353 (1.4%), 342 (2.9%), 321 (8%), 304 (2.6%), 287 (35%), 275 (13%), 258 (3.3%), 239 (4.1%),

230 (10.1%), 207 (4%), 187 (23.2%), 172 (3%), 146 (5.7%), 119 (15.1%), 105 (91%), 91 (99.7%), 77 (100%), 73 (16.7%), 69 (34.6%). Anal. Calcd. for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26. Found: C, 73.52; H, 4.85; N, 10.49 %.

2-Cyano-3-(4-methoxyphenyl)-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)acrylohydrazide (4b)

Yellowish brown crystals, yield (76%), m.p 238-240 ^oC; IR (KBr) ν/cm^{-1}: 3438 (NH), 2180 (CN) and 1688 (CO); ^1H NMR (*DMSO-d_6*); δ = 3.86 (s, 3H, OCH_3), 5.42 (s, 2H, CH_2), 6.96 - 8.00 (m, 14H, Ar & CH), 8.43 (s, 1H, CH), 10.34 (s, 1H, NH). Anal. Calcd. for $C_{26}H_{21}N_3O_4$: C, 71.06; H, 4.82; N, 9.56. Found: C, 71.23; H, 5.01; N, 9.79 %.

3-(4-Chlorophenyl)-2-cyano-N'-(4-(2-oxo-2-phenylethoxy) benzylidene)acrylohydrazide (4c)

Yellowish brown crystals, yield (90%), m.p 260-261 ^oC; IR (KBr) ν/cm^{-1}: 3423 (NH), 2361 (CN) and 1696 (CO); ^1H NMR (*DMSO-d_6*); δ = 5.61 (s, 2H, CH_2), 7.43 – 8.33 (m, 15H, Ar and 2CH), 10.67 (s, 1H, NH); MS: m/z = 444 (M^++1, 24.5%), 443 (M^+, 39.8%), 431 (12.5%), 429 (19.5%), 411 (10.7%), 402 (6.6%), 394 (6.1%), 376 (15.4%), 350 (6.1%), 344 (35.4%), 336 (12.5%), 321 (28.2%), 320 (97.8%), 303 (20.5%), 280 (3.5%), 263 (7.6%), 242 (3.3%), 224 (6.1%), 124 (6.4%), 88 (22.7%), 76 (100%), 68 (20.5%). Anal. Calcd. for $C_{25}H_{18}ClN_3O_3$: C, 67.65; H, 4.09; Cl, 7.99; N, 9.47. Found: C, 67.81; H, 4.26; N, 9.70 %.

2-Cyano-3-(4-nitrophenyl)-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)acrylohydrazide (4d)

Brown crystals, yield (87%), m.p 266-270 ^oC; IR (KBr) ν/cm^{-1}: 3423 (NH), 2197 (CN) and 1678 (C=O); ^1H NMR (*DMSO-d_6*); δ = 5.34 (s, 2H, CH_2), 7.42-8.38 (m, 15H, Ar and 2CH), 10.81 (s, 1H, NH); MS: *m/z* = 454 (M^+, 0.4%), 416 (0.7%), 395 (0.8%), 368 (7.4%), 353 (2.5%), 339 (1.33%), 313 (2.8%), 299 (1.5%), 285 (1.9%), 271 (2.1%), 261 (5.4%), 251 (6.8%), 236 (2.5%), 213 (3.1%), 183 (4.9%), 161 (3.4%), 139 (3.6%), 129 (7.9%), 111 (13.4%), 97 (25.0%), 84 (45.9%), 71 (40.1%), 67 (25.2%), 57 (100%), 55 (81.2%). Anal. Calcd. for $C_{25}H_{18}N_4O_5$: C, 66.08; H, 3.99; N, 12.33. Found: C, 66.25; H, 4.18; N, 12.56 %.

2-Cyano-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-3-(thiophen-2-yl)acrylohydrazide (4e)

Brown crystals, yield (96%), m.p 240-242 ^oC; IR (KBr) ν/cm^{-1}: 3417 (NH), 2223 (CN) and 1670 (C=O); ^1H NMR (*DMSO-d_6*); δ = 5.55 (s, 2H, CH_2), 7.21-8.40 (m, 14H, Ar and 2CH), 10.73 (s,

1H, NH); MS: m/z = 415 (M^+, 18.3%), 410 (9.05%), 399 (16.8%), 388 (14.07%), 381 (10.7%), 373 (26.9%), 360 (23.1%), 337 (7.7%), 321 (10.3%), 308 (11.1%), 303 (11.3%), 292 (100%), 280 (10.7%), 270 (8.9%), 240 (1.8%), 106 (9.9%), 104 (36.4%), 90 (13.1%), 83 (19.5%), 76 (79%). Anal. Calcd. for $C_{23}H_{17}N_3O_3S$: C, 66.49; H, 4.12; N, 10.11; S, 7.72. Found: C, 66.67; H, 4.28; N, 10.34; S, 7.90 %.

3-(Benzo[d][1,3]dioxol-5-yl)-2-cyano-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)acrylo-hydrazide (4f)

Brown crystals, yield (89%), m.p 279-280 ^oC; IR (KBr) ν/cm^{-1}: 3406 (NH), 2204 (CN) and 1696 (C=O); ^1H NMR (*DMSO-d_6*); δ = 5.49 (s, 2H, CH_2), 6.27 (s, 2H, CH_2), 7.67-8.21 (m, 13H, Ar and CH), 8.46 (s, 1H, CH), 10.48 (s, 1H, NH). Anal. Calcd. for $C_{26}H_{19}N_3O_5$: C, 68.87; H, 4.22; N, 9.27. Found: C, 69.25; H, 4.39; N, 9.48%.

3-(4-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-3-yl)-2-cyano-N'-(4-(2-oxo-2-phenyl-ethoxy)-benzylidene)acrylohydrazide (4g)

Yellow crystals, yield (59%), m.p 266-268 ^oC; IR (KBr) ν/cm^{-1}: 3424 (NH), 2300 (CN) and 1648 (C=O); ^1H NMR (*DMSO-d_6*); δ = 5.58 (s, 2H, CH_2), 7.33-7.87 (m, 19H, Ar and CH), 8.62 (s, 1H, CH), 9.28 (s, 1H, CH), 10.52 (s, 1H, NH). Anal. Calcd. for $C_{34}H_{24}ClN_5O_3$: C, 69.68; H, 4.13; Cl, 6.05; N, 11.95. Found: C, 69.84; H, 4.31; N, 12.18 %.

Synthesis of compounds 7a,b.

Compound **2 (**10 mmol) was reacted with *o*-hydroybenzaldehyde derivatives **5a,b** (10 mmol) in ethanol (10 ml) containing few drops of piperdine for 4 hrs. The products **7a,b** were collected by filtration, dried and recrystallized from *N*,*N*-dimethylformamide.

2-Imino-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-2H-chromene-3-carbohydrazide (7a)

Brown crystals, yield (67%), m.p 248-250 ^oC; IR (KBr) ν/cm^{-1}: 3338 (NH) and 1658 (C=O); ^1H NMR (*DMSO-d_6*); δ = 5.56 (s, 2H, CH_2), 6.95-8.01 (m, 13H, Ar), 8.44 (s, 1H, CH), 8.64 (s, 1H, CH), 9.98 (s, 1H, NH), 12.28 (s, 1H, NH); MS: m/z = 425 (M^+, 16.4%), 421 (24.4%), 410 (17.3%), 395 (9.6%), 393 (10.8%), 369 (10.1%), 358 (41.9%), 355 (15.9%), 342 (10.2%), 341 (26.1%), 328 (21.5%), 313 (21.72%), 303 (46.6%), 287 (10.6%), 246 (7.74%), 104 (47.4%), 83

(46.1%), 76 (100%), 71 (41.6%). Anal. Calcd. for $C_{25}H_{19}N_3O_4$: C, 70.58; H, 4.50; N, 9.88. Found: C, 70.71; H, 4.65; N, 10.12 %.

7-Hydroxy-2-imino-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-2H-chromene-3-carbohydrazide (7b)

Brown crystals, yield (75%), m.p > 300 ^oC; IR (KBr) ν/cm^{-1}: 3422 (OH and NH) and 1653 (C=O); ^1H NMR (*DMSO-d_6*); δ = 5.27 (s, 2H, CH_2), 6.93-8.01 (m, 12H, Ar), 8.41 (s, 1H, CH), 8.62 (s, 1H, CH), 10.48 (s, 1H, NH), 10.56 (s, 1H, OH), 11.78 (s, 1H, NH); MS: m/z = 442 (M^++1, 0.25%), 441 (M^+, 0.3%), 431 (0.37%), 411 (0.35%), 401 (1.75%), 368 (1.8%), 353 (0.7%), 331 (0.57%), 316 (1.1%), 305 (0.8%), 291 (0.8%), 271 (1.1%), 256 (1.26%), 237 (1.45%), 221 (1.0%), 213 (1.59%), 193 (1.44%), 165 (2.58%), 149 (4.3%), 137 (5.0%), 111 (17.8%), 95 (21.4%), 83 (36.2%), 69 (52.3%), 57 (100%), 55 (66.4%). Anal. Calcd. for $C_{25}H_{19}N_3O_5$: C, 68.02; H, 4.34; N, 9.52. Found: C, 68.18; H, 4.53; N, 9.75 %.

Synthesis of ompounds 8a,b.

Compounds **7a,b** (10 mmol) were heated for 3 hrs in a mixture of dioxane (5 ml) and concentrated hydrochloric acid (5 drops) (1:1). The formed solids were collected, filtrated off, dried and recrystallized from *N*,*N*-dimethylformamide.

2-Oxo-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-2H-chromene-3-carbohydrazide (8a)

Brown crystals, yield (56%), m.p 270-275 ^oC; IR (KBr) ν/cm^{-1}: 3277 (NH) 1700 (C=O) and 1645 (C=O); ^1H NMR (*DMSO-d_6*); δ = 5.44 (s, 2H, CH_2), 7.38-8.47 (m, 14H, Ar and CH), 8.54 (s, 1H, CH), 10.67 (s, 1H, NH); MS: m/z = 426 (M^+, 6.33%), 425 (16.47%), 421(24.49%), 409 (17.72%), 393 (10.86%), 369 (10.12%), 358 (41.98%), 341 (26.15%), 328 (21.50%), 313 (21.72%), 303 (46.67%), 287 (10.66%), 246 (7.74%), 104 (47.47%), 83 (46.19%), 76 (100%). Anal. Calcd. for $C_{25}H_{18}N_2O_5$: C, 70.42; H, 4.25; N, 6.57. Found: C, 70.63; H, 4.44; N, 6.79 %.

7-Hydroxy-2-oxo-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-2H-chromene-3-carbohydrazide (8b)

Brown crystals, yield (70%), m.p > 300 ^oC; IR (KBr) ν/cm^{-1}: 3389 (OH and NH), 1679 (C=O) and 1643 (C=O); ^1H NMR (*DMSO-d_6*); δ = 5.56 (s, 2H, CH_2), 7.48 – 8.45 (m, 13H, Ar and CH),

9.07 (s, 1H, CH), 10.53 (s, 1H, OH), 10.73 (s, 1H, NH). Anal. Calcd. for $C_{25}H_{18}N_2O_6$: C, 67.87; H, 4.10; N, 6.33. Found: C, 68.04; H, 4.26; N, 6.56 %.

Synthesis of 2-imino-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-2H-furo[2,3-b]indole-3-carbohydrazide (11)

Compound **2** (10 mmol) was heated with isatin (10 mmol) in absolute ethanol (10 ml) in presence of few drops of piperidine for 3 hrs. The solid product was collected by filtration and recrystallized from *N*,*N*-dimethylformamide.

Brown crystals, yield (54%), m.p > 300 ^{o}C; IR (KBr) ν/cm^{-1}: 3428 (NH) and 1668 (C=O); ^{1}H NMR (*DMSO-d*$_6$); δ = 5.66 (s, 2H, CH_2), 7.68-8.42 (m, 13H, Ar and CH), 8.60 (s, 1H, CH), 10.54 (s, 1H, NH), 11.83 (s, 1H, NH). Anal. Calcd. for $C_{26}H_{18}N_4O_4$: C, 69.33; H, 4.03; N, 12.44. Found: C, 69.48; H, 4.20; N, 12.62 %.

Synthesis of 2-oxo-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-2H-furo[2,3-b]indole-3-carbohydrazide (12) the same procedure for synthesis of (8a,b)

Compounds **7a,b** (10 mmol) were heated for 3 hrs in a mixture of dioxane (5 ml) and concentrated hydrochloric acid (5 drops) (1:1). The formed solids were collected, filtrated off, dried and recrystallized from *N*,*N*-dimethylformamide.

Brown crystals, yield (60%), m.p > 300 ^{o}C; IR (KBr) ν/cm^{-1}: 3405 (NH), 1690 (CO) and 1634 (C=O); ^{1}H NMR (*DMSO-d*$_6$); δ = 5.41 (s, 2H, CH_2), 7.16-7.69 (m, 12H, Ar), 8.48 (s, 1H, CH), 8.52 (s, 1H, CH), 10.74 (s, 1H, NH). Anal. Calcd. for $C_{26}H_{17}N_3O_5$: C, 69.18; H, 3.80; N, 9.31. Found: C, 69.34; H, 3.97; N, 9.54 %.

Synthesis of compounds 16a-c.

Dissolved compound **2** (10 mmol) in *N*,*N*'-dimethylformamide (DMF) (10 ml), then add potassium hydroxide (10 mmol). The mixture was stirred at room temperature till complete dissolution of potassium hydroxide then phenyl isothiocyanate (10 mmol) was added with completing the stirring for 3 hrs. The *α*-haloketones **14a-c** (10 mmol) were added with stirring for overnight. Then, it was quenched into water and acidified with 10% hydrochloric acid and obtained products **16a-c** were collected by filtration and recrystallized from acetic acid.

2-oxo-2-phenylethoxy)benzylidene)-2-(4-oxo-3-phenylthiazolidin-2-ylidene)acetohydrazide (16a)

Brown crystals, yield (89%), m.p 258-260 ^{o}C; IR (KBr) ν/cm^{-1}: 3425 (NH), 2203 (CN), 1695 (C=O) and 1666 (C=O); ^{1}H NMR (*DMSO-d*$_6$); δ = 4.10 (s, 2H, CH_2), 5.66 (s, 2H, CH_2), 7.05 (d, 2H, *J* = 7.2 Hz, Ar), 7.38 – 7.70 (m, 12H, Ar), 8.62 (s, 1H, CH), 11.28 (s, 1H, NH); MS: m/z = 496 (M^+, 67.7%), 416 (59%), 410 (57.9%), 374 (100%), 300 (61.7%), 238 (100%), 236 (83.6%), 203 (96.7%), 198 (60.1%), 173 (97.2%), 121 (70.4%), 61 (100%). Anal. Calcd. for $C_{27}H_{20}N_4O_4S$: C, 65.31; H, 4.06; N, 11.28; S, 6.46. Found: C, 65.49; H, 4.23; N, 11.49; S, 6.64 %.

2-Cyano-2-(3,4-diphenylthiazol-2(3H)-ylidene)-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-acetohydrazide (16b)

Brown crystals, yield (52%), m.p 276-278 ^{o}C; IR (KBr) ν/cm^{-1}: 3418 (NH), 2226 (CN) and 1675 (C=O); ^{1}H NMR (*DMSO-d*$_6$); δ = 5.67 (s, 2H, CH_2), 7.04-8.03 (m, 20H, Ar and CH), 8.50 (s, 1H, CH), 11.76 (s, 1H, NH). Anal. Calcd. for $C_{33}H_{24}N_4O_3S$: C, 71.21; H, 4.35; N, 10.07; S, 5.76. Found: C, 71.44; H, 4.54; N, 10.31; S, 5.93 %.

2-(4-(4-Chlorophenyl)-3-phenylthiazol-2(3H)-ylidene)-2-cyano-N'-(4-(2-oxo-2-phenylethoxy)-benzylidene)acetohydrazide (16c)

Yellowish brown crystals, yield (55%), m.p 278-280 ^{o}C; IR (KBr) ν/cm^{-1}: 3426 (NH), 2197 (CN) and 1688 (C=O); ^{1}H NMR (*DMSO-d*$_6$); δ = 5.61 (s, 2H, CH_2), 6.64-8.01 (m, 19H, Ar and CH), 8.58 (s, 1H, CH), 11.26 (s, 1H, NH). Anal. Calcd. for $C_{33}H_{23}ClN_4O_3S$: C, 67.06; H, 3.92; Cl, 6.00; N, 9.48; S, 5.42. Found: C, 67.22; H, 4.06; N, 9.70; S, 5.61%.

Synthesis of 2-cyano-3-(dimethylamino)-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)acrylo-hydrazide (17)

Compound **2** (10 mmol) was reacted with (DMF-DMA) (10 mmol) in dry dioxane (10 ml) for 6 hrs. The product was collected by filtration, dried and recrystallized from an ethanol/dioxane.

Brown crystals, yield (86%), m.p 224-226 ^{o}C; IR (KBr) ν/cm^{-1}: 3294 (NH), 2184 (CN), 1702 (C= O) and 1658 (C=O); ^{1}H NMR (*DMSO-d*$_6$); δ = 3.21 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 5.65 (s,

2H, CH_2), 7.00 (d, 2H, *J* = 8.4 Hz, Ar), 7.54-7.72 (m, 5H, Ar), 7.81 (s, 1H, CH), 8.01 (d, 2H, *J* = 7.2 Hz, Ar), 8.27 (s, 1H, CH), 10.76 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 67.24; H, 5.54; N, 15.12 %.

Synthesis of 2,4-diamino-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)pyrimidine-5-carbo-hydrazide (18)

Compound **17** (10 mmol) was mixed with guanidine hydrochloride (10 mmol) and sodium carbonate (10 mmol) in *N*,*N*-dimethylformamide (10 ml). The reaction mixture was heated for 6 hrs. The product was collected by filtration, washed off with water and ethanol and recrystallized from *N*,*N*-dimethylformamide.

Brown crystals, yield (53%), m.p > 300 ^oC; IR (KBr) ν/cm^{-1}: 3442 (NH_2 and NH), 1681 (C=O) and 1642 (C=O); ^1H NMR (*DMSO-d*$_6$); δ = 5.47 (s, 2H, CH_2), 6.79 (broad, 2H, NH_2), 6.82 (broad, 2H, NH_2), 7.41-8.17 (m, 9H, Ar), 8.46 (s, 1H, CH), 9.23 (s, 1H, CH), 10.49 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{18}N_6O_3$: C, 61.53; H, 4.65; N, 21.53. Found: C, 61.68; H, 4.81; N, 21.77%.

Synthesis of compounds 22a-c.

Compound **17** (10 mmol) was reacted with compounds **22a-c** (10 mmol) in *N*,*N*-dimethylformamide (10 ml) containing few drops of piperidine (3 drops), and heated for 6 hrs. The solid products **17a-c** were collected by filletration, washed with ethanol, dried and recrystallized from *N*,*N*-dimethylformamide.

2,7-Diamino-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-3-(phenyldiazenyl)pyrazolo[1,5-a]-pyrimidine-6-carbohydrazide (22a)

Brownish orange crystals, yield (56%), m.p > 300 ^oC; IR (KBr) ν/cm^{-1}: 3400 (NH), 1668 (C=O) and 1658 (C=O); ^1H NMR (*DMSO-d*$_6$); δ = 5.60 (s, 2H, CH_2), 6.35 (broad, 2H, NH_2), 6.77 (broad, 2H, NH_2), 7.34-8.26 (m, 15H, Ar and CH), 8.54 (s, 1H, CH), 10.89 (s, 1H, NH). Anal. Calcd. for $C_{28}H_{23}N_9O_3$: C, 63.03; H, 4.35; N, 23.63. Found: C, 63.15; H, 4.53; N, 23.87 %.

2,7-Diamino-3-((4-methoxyphenyl)diazenyl)-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-pyrazolo[1,5-a]pyrimidine-6-carb-hydrazide (22b)

Brown crystals, yield (56%), m.p > 300 ^{o}C; IR (KBr) ν/cm^{-1}: 3412 (NH_2 and NH), 1670 (C=O) and 1644 (C=O); ^{1}H NMR (*DMSO-d_6*); δ = 3.86 (s, 3H, OCH_3), 5.68 (s, 2H, CH_2), 6.73 (broad, 2H, NH_2), 7.24 (broad, 2H, NH_2), 7.33-8.18 (m, 13H, Ar), 8.44 (s, 1H, CH), 8.50 (s, 1H, CH), 10.58 (s, 1H, NH). Anal. Calcd. for $C_{29}H_{25}N_9O_4$: C, 61.80; H, 4.47; N, 22.37. Found: C, 61.96; H, 4.64; N, 22.62 %.

2,7-Diamino-3-((2-chlorophenyl)diazenyl)-N'-(4-(2-oxo-2-phenylethoxy)benzylidene)-pyrazolo[1,5-a]pyrimidine-6-carbohydrazide (22c)

Brown crystals, yield (89%), m.p > 300 ^{o}C; IR (KBr) ν/cm^{-1}: 3396 (NH), 1676 (C=O) and 1638 (C=O); ^{1}H NMR (*DMSO-d_6*); δ = 5.62 (s, 2H, CH_2), 6.72 (broad, 2H, NH_2), 6.99 (broad, 2H, NH_2), 7.19-8.03 (m, 13H, Ar), 8.16 (s, 1H, CH), 8.35 (s, 1H, CH), 11.05 (s, 1H, NH). Calcd. Anal. for $C_{28}H_{22}ClN_9O_3$: C, 59.21; H, 3.90; Cl, 6.24; N, 22.19. Found: C, 59.39; H, 4.06; N, 22.42%.

Antimicrobial activity investigation:

Agar well diffusion method

The sterilized media were poured into the sterilized petri dishes (20-25 ml, each petri dish) and allowed to solidify at room temperature. The microbial suspension was prepared in sterilized saline equivalent to McFarland 0.5 standard solution (1.5 x 105 CFU ml-1) and its turbidity was adjusted to OD = 0.13 using spectrophotometer at 625 nm. After 15 min, a sterile cotton swab was dipped into the adjusted suspension and was flooded on the dried agar surface then allowed to dry for 15 min with lid in place. With a sterile borer, wells of 6 mm diameter were made in the solidified media. 100 µl of the solution of the tested compound was added to each well with the help of micropipette. The plates were incubated at 37 ^{o}C for 24 hrs in case of antibacterial activity and the experiment was carried out three times and the inhibition zones were measured in mm scale.

Supporting information:

Supplementary file

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