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One-Pot Three Components Synthesis of Novel 2-Iminoquinazolines and 2-Imino Spiro[indoline-quinazoline/pyrimidine]ones Catalyzed by Sodium Fluoride[1]

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Abstract—Sodium fluoride was determined to be an inexpensive, mild and efficient catalyst in the synthesis of 2-iminoquinazoline and spiro indolinepyrimido[4,5-*d*]pyrimidine derivatives via a three component Biginelli-like reaction of cyclo-β-diketones, aromatic aldehydes or isatin derivatives with guanidine hydrochloride.

Keywords: quinazolines, pyrimido[4,5-*d*]pyrimidine, biginelli reaction, guanidine, sodium fluoride

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INTRODUCTION

Quinazolines and their derivatives demonstrated pronounced antibacterial [1, 2], anti-inflammatory [3–5], antiplasmodial [6–8], antitumor [9–11], antimicrobial, and antioxidant activities [12, 13]. Over the recent years octahydro-quinazolinone derivatives demonstrated potential antibacterial activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and as calcium antagonist [14].

Several methods have been reported for the synthesis of octahydroquinazolin-2,5-diones by the multicomponent Biginelli reaction route involving one pot condensation of cyclic diketones, aromatic aldehydes and urea or thiourea initiated by catalysts such as concentrated HCl in ethanol [15], Nafion-H [16], concentrated H_2SO_4 [17], TMSCl [18], NH_4VO_3 [19], heteropolyacids [20, 21], Bakers' yeast [22], and ionic liquids [23, 24]. Only a limited number of studies [25, 26] has been devoted to guanidine and its derivatives participation in the above processes.

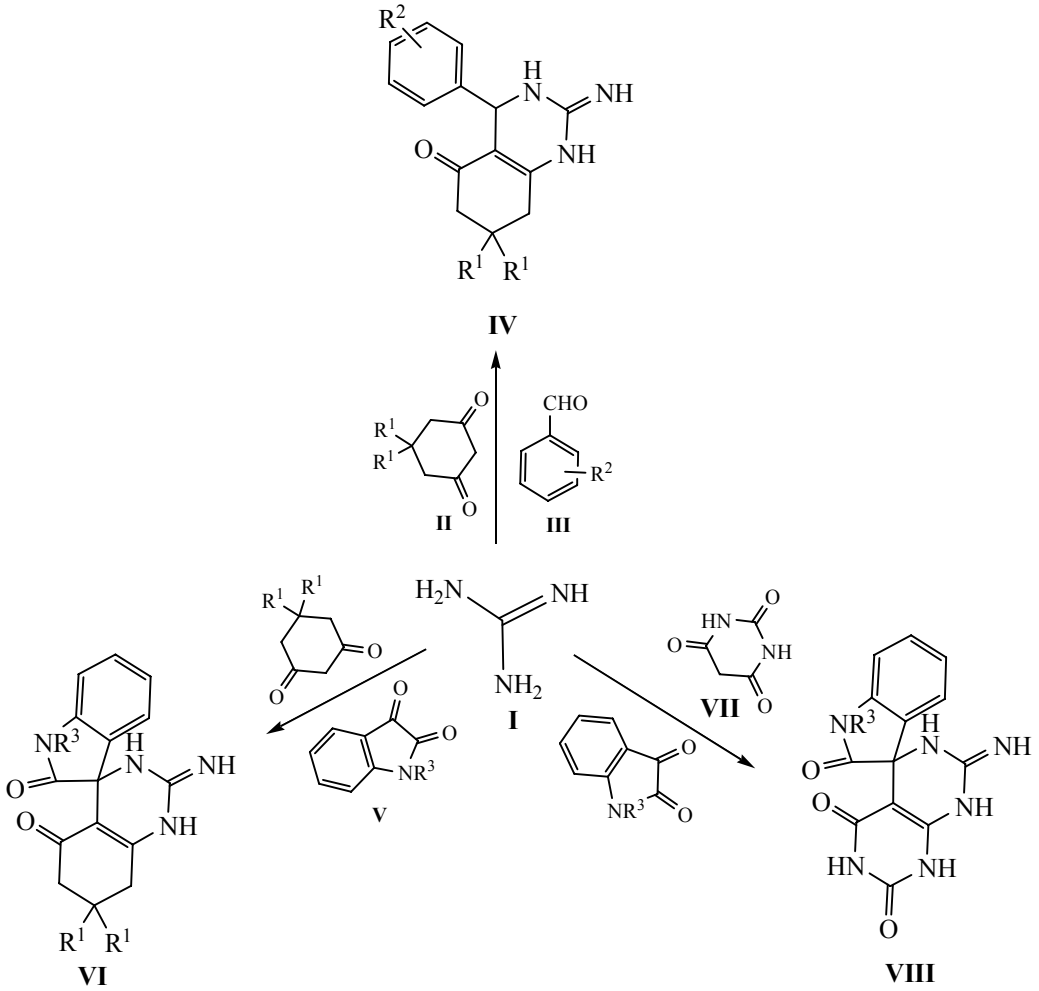
In continuation of our previous studies on the Biginelli reaction [27–31], herein we report, for the first time, a simple approach to novel 2-iminoquinazoline and spiro indolinepyrimido[4,5-*d*]pyrimidine derivatives *via* a new Biginelli-like reaction: a three components cyclocondensation of cyclo-β-diketones, aromatic aldehydes or isatin with guanidine hydrochloride (Scheme 1).

RESULTS AND DISCUSSION

The optimum conditions of the process were determined in the study of the reaction of 1,3-cyclohexadione (2.5 mmol), 4-bromobenzaldeyde (2.5 mmol) and guanidine hydrochloride (5 mmol) that led to the synthesis of 4-(4-bromophenyl)-2-imino-1,2,3,4,7,8-hexahydroquinazoline-5-(6*H*)-one (**IVa**) (Scheme 1). The reaction mixture was refluxed in EtOH media in the presence of 0.5 mmol of various catalysts such as Na_2CO_3, NH_4Cl, tetrabutylammonium chloride (TBACl), tetrabutylammonium bromide (TBABr), tetrabutylammonium fluoride (TBAF), and other fluorides (Table 1). It was determined that all fluorides promoted the reaction more efficiently than the other catalysts. Product **IVa** was obtained in high yields in 30 min (Table 1, entries 5–8). The best result was achieved in the reaction catalyzed by NaF. This might be explained by the strength of the H–F bond and electrophilicity of the carbonyl group of aromatic aldehyde enhanced by coordination of the carbonyl oxygen with Na^+. According to the accumulated data (Table 1) the amount of NaF 0.65 mmol led to the highest yield (90%).

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 2-amino quinazoline derivatives.



The scope and limitations of the reaction were studied by extending it to various substituted aldehydes and 1,3-diketones with guanidine hydrochloride in the presence of NaF. In all cases the reaction proceeded smoothly to give the corresponding products **IVa–IVf** in good to excellent yields (Table 2). Similarly, the optimized conditions were applied to the reaction of isatin used instead of aromatic aldehyde. The corresponding spiro-indolinequinazoline **VI** was synthesized with high yield (Scheme 1, Table 2). The reaction of barbituric acid as a cyclic 1,3-dicarbonyl compound and isatin derivatives with guanidine hydrochloride in the presence of NaF gave spiro-(indoline-3,4'-pyrimido[4,5-*d*]pyrimidine) derivatives **VIIIa–VIIIc** (Scheme 1, Table 2).

Though the exact mechanism of formation of compounds **IV**, **VI** and **VIII** was not established, a possible one is presented in Scheme 2 for the product **IVa**. According to it F^- ions activate the nitrogen groups of guanidine hydrochloride and induces nucleophilic addition of nitrogen to the carbonyl group of aldehyde producing the intermediate **IX**. The following Michael addition of 1,3-cyclohexadione (tautomeric form) to intermediate **IX,** the intermolecular cyclization, loss of water and tautomerization give the product **IV**.

In conclusion, a new class of three components Biginelli-like reaction based on cyclo-β-diketones, aromatic aldehydes or isatin derivatives and guanidine hydrochloride in the presence of NaF as an efficient and inexpensive catalyst was introduced. The reaction is an efficient and convenient method for some novel 2-iminoquinazoline and spiro[indoline-quinazoline/pyrimidine]ones. The method was applicable to all three components containing a variety of substituents denoting its potential in combinatorial chemistry

related to quinazolines, pyrimidines and spiro oxindoles of potent biological importance.

EXPERIMENTAL

All reagents were purchased from Merck and Fluka and used without further purification. Melting points were measured on an Electro-thermal IA 9100 apparatus. IR spectra were recorded as KBr discs on a Shimadzu FT-IR 8600 spectrophotometer. ^{1}H and ^{13}C NMR spectrum spectra were measured in DMSO-d_6 on a Bruker 400 DRX Avance instrument at 400 and 100 MHz.

General procedure for the compounds IV, VI, and VIII. A mixture of 1,3-cyclic diketone (2.5 mmol), aromatic aldehyde or isatin derivative (2.5 mmol), guanidine hydrochloride (5 mmol), and NaF (0.65 mmol) in EtOH (5 mL) was refluxed on an oil bath for the appropriate time (Table 2). Upon completion of the process, as indicated by TLC, the reaction mixture was poured on crashed ice. The precipitate was filtered off and dried. The solid product was washed four times with cold EtOH.

4-(4-Bromophenyl)-2-imino-1,2,3,4,7,8-hexahydroquinazoline-5(6*H*)-one (IVa). mp 248–250°C, IR spectrum, ν, cm^{-1}: 3332, 3022, 2954, 1720, 1602, 1286, 1033. ^{1}H NMR spectrum spectrum (500 MHz), δ_H, ppm: 1.86–2.09 m (2H), 2.10–2.18 m (2H), 2.35–2.50 m (2H), 3.44 br (3H, NH), 4.28 s (1H), 7.15 d (2H, J = 8.0 Hz), 7.32 d (2H, J = 8.0 Hz). ^{13}C NMR spectrum spectrum (125 MHz), δ_C, ppm: 20.1, 32.6, 37.0, 59.9, 100.4, 115.7, 118.6, 130.6, 131.2, 145.1, 168.3, 195.9. Found, %: C 53.13; H 4.96; N 12.29. $C_{14}H_{14}BrN_3O$. Calculated, %: C 52.52; H 4.41; N 13.12.

Table 1. Influence of the nature and amounts of catalysts on the synthesis of **IVa**[a]

Entry no.	Catalyst, mmol	*t,* min	Yield, %
1	Na_2CO_3, 0.5	50	62
2	NH_4Cl, 0.5	50	Traces
3	TBACl, 0.5	50	Traces
4	TBABr, 0.5	40	45
5	NH_4F, 0.5	30	68
6	TBAF, 0.5	30	64
7	CsF, 0.5	30	72
8	NaF, 0.5	30	82
9	NaF, 0.65	30	90
10	NaF, 0.85	30	90
11	NaF, 1.0	30	90

[a] Reaction conditions: 1,3-cyclohexadione (2.5 mmol), 4-bromobenzaldeyde (2.5 mmol), guanidine hydrochloride (5 mmol), EtOH, reflux.

4-(3-Bromophenyl)-2-imino-1,2,3,4,7,8-hexahydroquinazoline-5(6*H*)-one (IVb). mp 239–241°C, IR spectrum, ν, cm^{-1}: 3327, 3068, 2948, 1716, 1600, 1288, 1033. ^{1}H NMR spectrum (500 MHz), δ_H, ppm: 1.81–1.91 m (2H), 2.07–2.20 m (2H), 2.35–2.46 m (2H), 3.41 br (3H, NH), 4.31 s (1H), 7.11 (1H, J = 8.0Hz, t) 7.18 d (1H, J = 8.0 Hz), 7.21–7.24 m (1H), 7.35 s (1H). ^{13}C NMR spectrum (125 MHz), δ_C, ppm: 20.1, 32.9, 37.0, 59.7, 100.5, 115.5, 121.1, 127.9, 128.6, 130.0, 131.7, 148.5, 168.5, 196.0. Found, %: C

Scheme 2. Proposed mechanism for the synthesis of 2-iminoquinazolines **IV**.

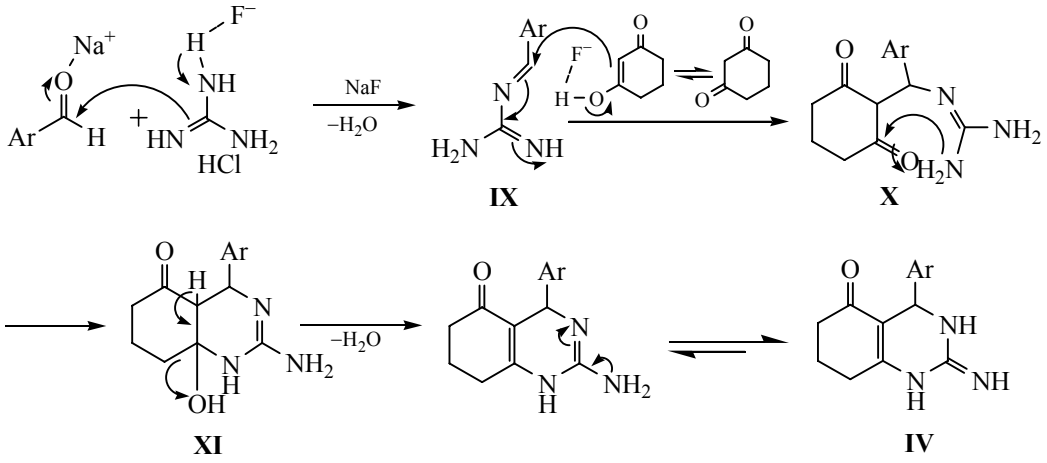
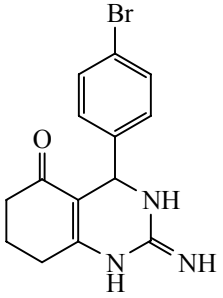
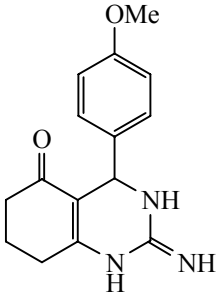
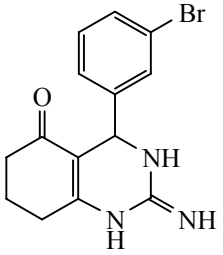
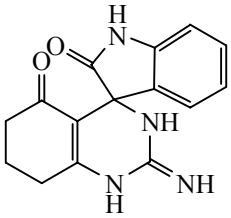
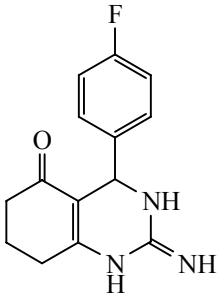
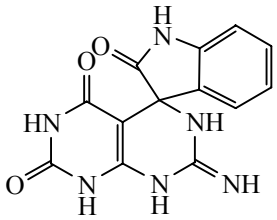
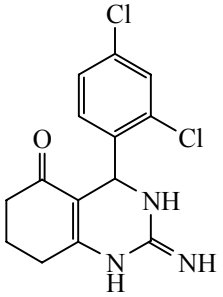
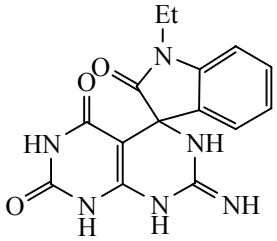
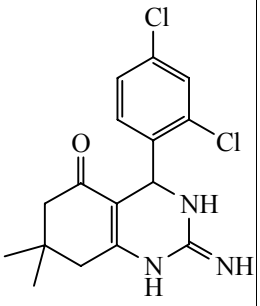
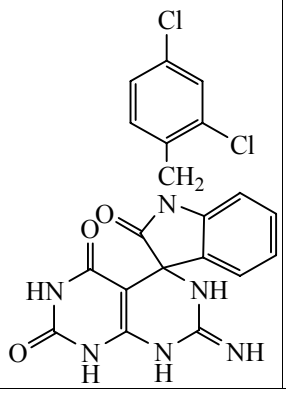


Table 2. Synthesis of 2-iminoquinazolines and 2-iminospiro[indoline-3,4'-pyrimido[4,5-*d*]pyrimidine] derivatives[a]

Comp. no.	Structure	*t*, min	Yield, %	mp, °C	Comp. no.	Structure	*t*, min	Yield, %	mp, °C
IVa		30	90	248–250	**IVf**		85	72	207–209
IVb		45	89	239–241	**VI**		150	71	290–292
IVc		50	74	251–253	**VIIIa**		120	89	321–323
IVd		60	79	237–239	**VIIIb**		140	81	314–316
IVe		80	76	205–207	**VIIIc**		150	75	327–329

[a] Reaction conditions: 1,3-diketone (2.5 mmol), aromatic aldehydes or isatin derivatives (2.5 mmol), and Guanidine hydrochloride (5 mmol), NaF (0.65 mmol), EtOH, reflux.

52.98; H 4.81; N 11.85. $C_{14}H_{14}BrN_3O$. Calculated, %: C 52.52; H 4.41; N 13.12.

4-(4-Fluorophenyl)-2-imino-1,2,3,4,7,8-hexahydroquinazoline-5(6*H*)-one (IVc). mp 251–253°C, IR spectrum, ν, cm^{-1}: 3317, 2958, 2825, 1720, 1629, 1292, 1035. ^1H NMR spectrum (500 MHz), δ_H, ppm: 1.85–1.88 m (2H), 2.09–2.17 m (2H), 2.35–2.44 m (2H), 3.40 br (3H, NH), 4.30 s (1H), 6.95 t (2H, *J* = 17.2 Hz), 7.19–7.21 d.d (2H, *J* = 8.5, 5.7 Hz). ^{13}C NMR spectrum (125 MHz), δ_C, ppm: 20.1, 32.3, 37.1, 60.1, 100.5, 111.4, 114.3, 116.0, 130.5, 141.5, 168.1, 196.0. Found, %: C 63.45; H 5.78; N 16.95. $C_{14}H_{14}FN_3O$. Calculated, %: C 64.85; H 5.44; N 16.21.

4-(2,4-Dichlorophenyl)-2-imino-1,2,3,4,7,8-hexahydroquinazoline-5(6*H*)-one (IVd). mp 237–239°C, IR spectrum, ν, cm^{-1}: 3361, 3097, 2945, 1714, 1612, 1294, 1062. ^1H NMR spectrum (500 MHz), δ_C, ppm: 1.83–1.86 m (2H), 1.96–2.08 m (2H), 2.14–2.28 m (2H), 3.40 br (3H, NH), 4.59 s (1H), 7.10 d (1H, *J* = 8.0 Hz), 7.17 d (1H, *J* = 8.0 Hz), 7.46 d (1H, *J* = 2.0 Hz). ^{13}C NMR spectrum (125 MHz), δ_C, ppm: 20.5, 28.9, 37.1, 59.5, 101.6, 110.6, 126.4, 128.2, 130.9, 133.0, 133.3, 140.6, 170.5, 196.3. Found, %: C 55.16; H 4.82; N 12.31. $C_{14}H_{13}Cl_2N_3O$. Calculated, %: C 54.21; H 4.22; N 13.55.

4-(2,4-Dichlorophenyl)-7,7-dimethyl-2-imino-1,2,3,4,7,8-hexahydroquinazoline-5(6*H*)-one (IVe). mp 205–207°C, IR spectrum, ν, cm^{-1}: 3415, 2954, 1722, 1606, 1290, 1068. ^1H NMR spectrum (500 MHz), δ_H, ppm: 1.03 s (3H), 1.09 s (3H), 2.03–2.09 m (2H), 2.24–2.50 m (2H), 3.37 br (3H, NH), 4.52 s (1H), 7.09 d (1H, *J* = 8.6 Hz), 7.18 d.d (1H, *J* = 8.6, 2.1 Hz), 7.48 d (1H, *J* = 2.1 Hz). ^{13}C NMR spectrum (125 MHz), δ_C, ppm: 26.1, 26.3, 31.3, 42.1, 50.2, 52.6, 108.6, 125.9, 127.8, 128.4, 130.5, 132.3, 132.8, 140.0, 167.7, 195.6. Found, %: C 55.03; H 5.81; N 13.12. $C_{16}H_{17}Cl_2N_3O$. Calculated, %: C 56.82; H 5.07; N 12.42.

4-(4-Methoxyphenyl)-2-imino-1,2,3,4,7,8-hexahydroquinazoline-5(6*H*)-one (IVf). mp 207–209ºC, IR spectrum, ν, cm^{-1}: 3388, 3026, 2954, 1722, 1604, 1298, 1238 cm^{-1}. ^1H NMR spectrum (500 MHz), δ_H, ppm: 1.83–1.86 m (2H), 1.93–1.99 m (2H), 2.25–2.30 m (2H), 3.97 br (6H, 3NH, OCH_3), 4.52 s (1H), 6.76 d (2H, *J* = 8.4 Hz), 7.08 d (2H, *J* = 8.4 Hz). ^{13}C NMR spectrum (125 MHz), δ_C, ppm: 19.9, 26.4, 29.9, 36.4, 54.9, 113.3, 115.7, 128.9, 136.7, 157.5, 157.6, 164.6, 196.3. Found, %: C 65.82; H 7.12; N 14.81. $C_{15}H_{17}N_3O_2$. Calculated, %: C 66.40; H 6.32; N 15.49.

2'-Imino-2',3',7',8'-tetrahydro-1'*H*-spiro[indoline-3,4'-quinazoline]2,5'(6'*H*)-dione (VI). mp 290–292ºC, IR spectrum, ν, cm^{-1}: 3342, 3269, 3057, 2941, 1722, 1687, 1600, 1481 ^1H NMR spectrum (500 MHz), δ_H, ppm: 1.83–1.87 m (2H), 2.04–2.09 m (2H), 2.39–2.45 m (2H), 6.79 d (1H, *J* = 7.6 Hz), 6.83 t (1H, *J* = 7.6 Hz), 6.90 d (1H, *J* = 7.2 Hz), 7.10 t (1H, *J* = 7.2 Hz), 7.35 s (1H, NH), 8.82 s (1H, NH), 10.28 s (1H, NH), 11.00 s (1H, NH). ^{13}C NMR spectrum (125 MHz), δ_C, ppm: 20.5, 29.5, 35.6, 47.1, 100.9, 109.7, 112.9, 121.7, 121.9, 127.9, 133.7, 144.8, 170.5, 194.8. Found, %: C 64.53; H 4.66; N 20.05. $C_{15}H_{14}N_4O_2$. Calculated, %: C 63.82; H 5.00; N 19.85..

2'-Imino-2',3'-dihydro-1'*H*-spiro[indoline-3,4'-pyrimido[4,5-*d*]pyrimidine]-2,5',7'-(6'*H*,8'*H*)-trione (VIIIa). mp 321–323ºC, IR spectrum, ν, cm^{-1}: 3419, 3364, 3296, 3253, 3205, 3097, 1745, 1685, 1569, 1436. ^1H NMR spectrum (500 MHz), δ_H, ppm: 6.04 s (1H, NH), 6.49 d (1H, *J* = 7.6 Hz), 6.71 t (1H, *J* = 7.2 Hz), 6.92 t (1H, *J* = 7.6 Hz), 7.59 d (1H, *J* = 7.2 Hz), 9.72 br (3H, NH), 9.85 s (1H, NH). ^{13}C NMR spectrum (125 MHz), δ_C, ppm: 57.1, 108.2, 118.2, 120.8, 125.1, 126.5, 135.8, 138.7, 141.7, 151.8, 158.2, 165.8, 178.1. Found, %: C 51.91; H 4.42; N 27.16. $C_{13}H_{10}N_6O_3$. Calculated, %: C 52.35; H 3.38; N 28.18.

1-Ethyl-2'-imino-2',3'-dihydro-1'*H*-spiro[indoline-3,4'-pyrimido[4,5-*d*]pyrimidine-2,5',7'(6'*H*,8'*H*)-trione (VIIIb). mp 314–316ºC, IR spectrum, ν, cm^{-1}: 3330, 3195, 3085, 1704, 1608, 1423. ^1H NMR spectrum (500 MHz), δ_H, ppm: 1.01 t (3H, *J* = 7.2 Hz), 3.57–3.62 m (2H), 5.08 s (1H, NH), 6.93–6.98 m (2H), 7.18 d (1H, *J* = 7.2 Hz), 7.25 t (1H, *J* = 7.6 Hz), 11.20–11.38 m (4H, NH). ^{13}C NMR spectrum (125 MHz), δ_C, ppm: 12.1, 34.6, 53.0, 108.8, 122.4, 123.5, 124.5, 128.0, 129.0, 138, 144.0, 150.6, 153.0, 168.2, 174.0. Found, %: C 56.29; H 4.79; N 24.71. $C_{15}H_{14}N_6O_3$. Calculated, %: C 55.21; H 4.32; N 25.75.

1-(2,4-Dichlorobenzyl)-2'-imino-2',3'-dihydro-1'*H*-spiro[indoline-3,4'-pyrimido[4,5-*d*]primidine]-2,5',7'-(6'*H*,8'*H*)-trione (VIIIc). mp 327–329ºC, IR spectrum, ν, cm^{-1}: 3371, 3193, 1710, 1666, 1469, 1573. ^1H NMR spectrum (500MHz), δ_H, ppm: 4.75 d (1H, *J* = 17.2 Hz), 4.90 d (1H, *J* = 17.2 Hz), 6.09 s (1H, NH), 6.61 d (1H, *J* = 7.6 Hz), 6.91–6.95 m (2H), 7.07 t (1H, *J* = 7.6 Hz), 7.25 d (1H, *J* = 7.6 Hz), 7.38 d.d (1H, *J* = 8.4, 2.0 Hz), 7.66 d (1H, *J* = 2.0 Hz), 9.12 (1H, NH), 9.17 s (1H, NH), 10.4 s (1H, NH), 10.62 s (1H, NH). ^{13}C NMR spectrum (125 MHz), δ_C, ppm: 48.5, 50.0, 108.0, 122.2, 126.4, 127.2, 128.3, 129.2,

132.9, 151.8, 152.1, 158.2, 164.3, 164.8, 168.2, 168.5, 170.8, 172.7, 175.7. Found, %: C 53.16; H 3.76; N 17.60. $C_{20}H_{14}Cl_2N_6O_3$. Calculated, %: C 52.51; H 3.06; N 18.38.

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