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Reactivity of Hydrazine, Some Hydrazine derivatives and Diamines toward Ethyl 2,2-Dicyano-1-aryl (or alkyl) vinylcarbamate

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ABSTRACT

A series of pyrimidinone and dipyrimidinone derivatives **2a-c**, **4a-e** and **6a-f** has been synthesized via the reaction between ethyl 2,2-dicyano-1-aryl(or alkyl)vinylcarbamate derivatives **1a-d** and hydrazine derivatives or diamines. The reactivity of compounds **1a-d** toward hydrazine is studied. The result is the formation of triazolones **5a-d** rather than pyrimidinone derivatives.

Indexing terms/Keywords

Hydrazine derivatives; ethyl 2,2-dicyano-1-aryl(or alkyl)vinylcarbamate; pyrimidinones; triazolones

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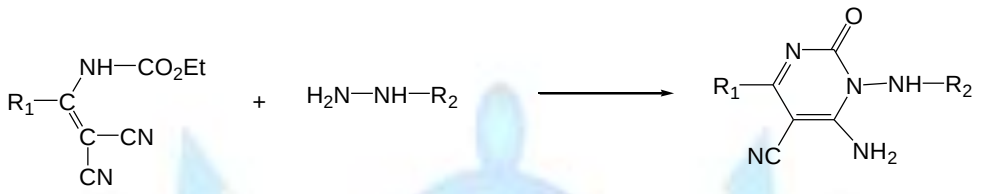
INTRODUCTION

Over the years pyrimidinones derivatives have emerged as an interesting class of heterocycles with an astonishingly wide range of applications in pharmaceutical chemistry [1-4]. It is of great interest that specifically functionalized pyrimidinones may possess specific biological properties. Some are endowed with antiviral activity [5-6], antitumor activity [7-8], anti-inflammatory [9], antioxidant [10]. Many synthetic procedures exist for the synthesis of pyrimidinones derivatives [11-15]. However, the development of simple, easy and efficient methodologies to get pyrimidinones is one of the major aspects in organic synthesis. In fact, the ethyl 2,2-dicyano-1- aryl (or alkyl)vinylcarbamate derivatives are valuable intermediates in a variety of synthetic transformations. In the present study, we report the synthesis of some new pyrimidinones, dipyrimidinones and triazolones derivatives.

RESULTS AND DISCUSSION

Pyrimidine derivatives **2a-c** were synthesized by cyclization, involving the reaction of substrates **1a-c** with phenylhydrazine in chlorobenzene under reflux (scheme 1).



1a-c **2a-c**

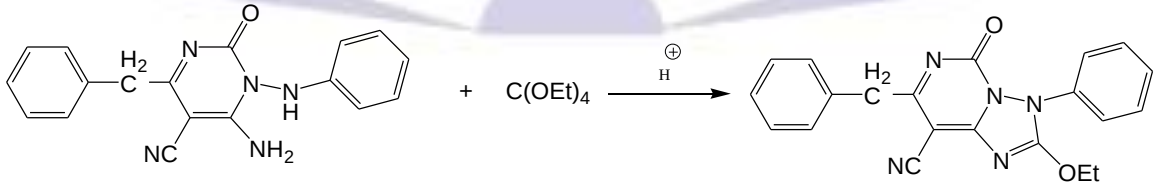
Scheme 1

Table 1: Chemical structure of target compounds **2a-c**.

Composé	R_1	R_2	Yield %
2a	C_6H_5	C_6H_5	63
2b	C_6H_5-CH_2	C_6H_5	60
2c	iPr	C_6H_5	57

The prepared compounds were characterized by spectroscopic techniques. The IR spectra showed the presence of two NH groups stretching at 3420-3241cm^{-1} and CN group stretching at 2220-2210 cm^{-1}. In ^{1}H NMR spectra the most significant information was the disappearance of the triplet and the quadruplet of ethoxy groups of the starting reagent **1a-c**.

Compounds **2a-c** can be used for the synthesis of heterocyclic compounds. For example we have condensed **2b** with tetraethyl othocarbonate. The result is the formation of 7-benzyl-2-ethoxy-5-oxo-3-phenyl-3,5-dihydro-[1,2,4]triazolo[1,5-f]pyrimidine-8-carbonitrile **3** (scheme 2). Further work is in progress to obtain new structures by condensing compounds **2a-c** with orthoester, tetraethyl othocarbonate, carbon disulfide...



2b **3**

Scheme 2

Furthermore, the reactivity of **1** towards benzohydrazide and acetohydrazide was also investigated as an alternative route to obtain pyrimidinylbezamide derivatives **4a-b** and pyrimidinylacetamide derivatives **4c-e** (scheme 3). The reaction was carried out in ethanol under reflux (benzohydrazide and acetohydrazide are not soluble in chlorobenzene). The intracyclization of compounds **4a-e** is not observed (scheme 3).

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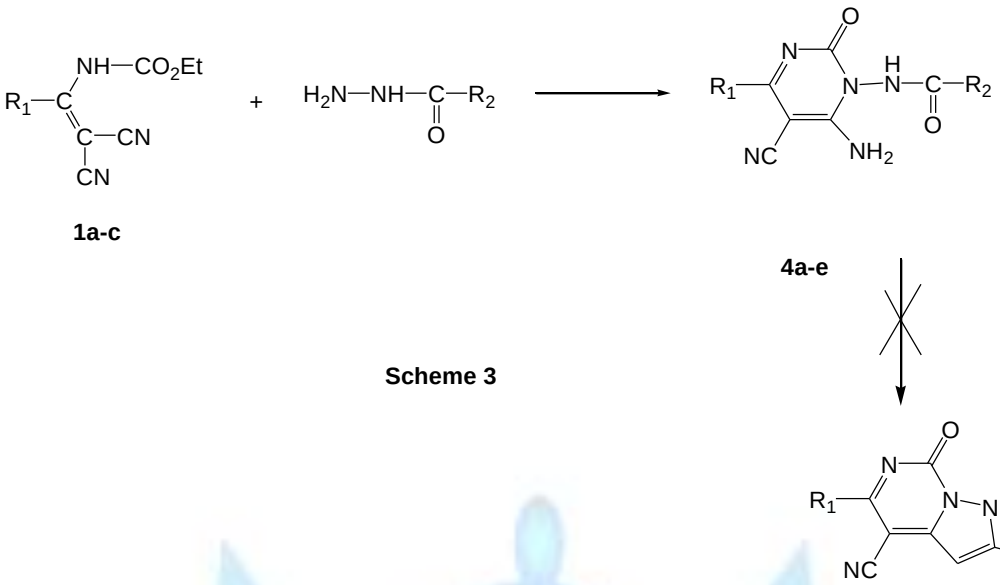


1a-c **4a-e**

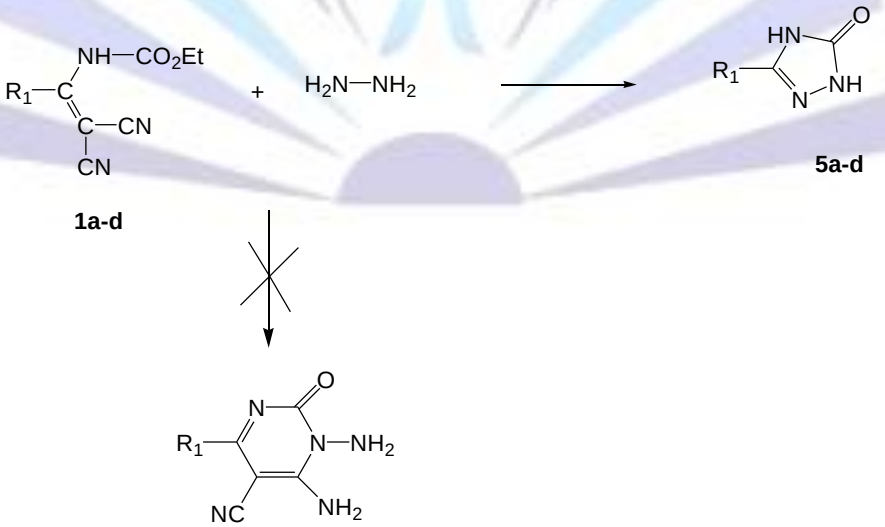
Scheme 3

Table 2: Chemical structure of target compounds **4a-e**.

Composé	R_1	R_2	Yield %
4a	C_6H_5	C_6H_5	68
4b	iPr	C_6H_5	69
4c	C_6H_5	CH_3	72
4d	C_6H_5-CH_2	CH_3	52
4e	iPr	CH_3	62

The structures of compounds **4a-e** are in accordance with their spectroscopic data. These new products were assigned by IR, NMR and mass spectroscopy. The IR spectra showed bands (NH), (CN), and (2C=O). In the ^{1}HNMR spectra of compounds **4c-e** we have noticed the appearance of the singlet of methyl groups at around 2ppm.

In addition, heating **1a-d** with hydrazine hydrate in chlorobenzene furnished trizol-3-one derivatives **5a-d** rather than pyrimidinone derivatives **5'a-d** (scheme 4).



1a-d **5a-d**

5'a-d

Scheme 4

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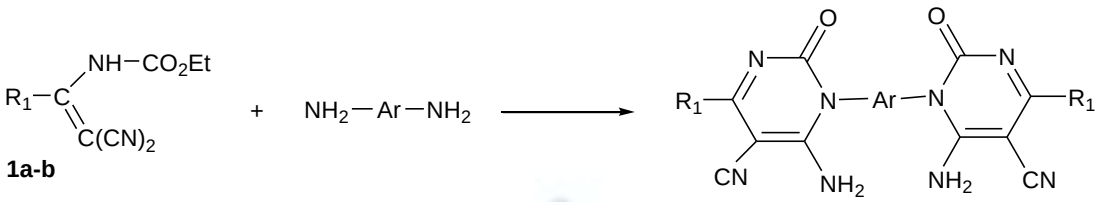
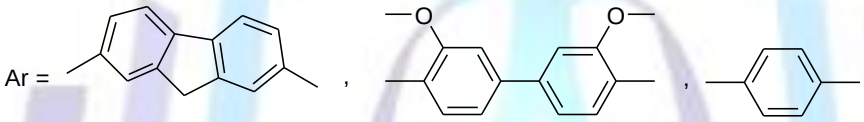
The reaction products were confirmed on the basis of their spectral data and mass spectroscopy (**5a-b**). The IR spectra of the isolated products showed the absence of cyano groups. It also showed absorption bands due to (NH) and (C=O). Besides, the mass spectra displayed the respective $[M + H]^+$ peaks.

Hydrazine hydrate reacts with its two nucleophilic centers (NH_2 groups) but hydrazine derivatives (phenylhydrazine, benzohydrazide and acetohydrazide) react with one of their nucleophilic centers (NH_2 and not NH). This may be due to the conjugation of NH with carbonyl or phenyl groups.

To further explore the synthetic potential of enamine **1**, the condensation of **1a-b** with diamine (2,7-diam inofluorene, orthodianisidine and 1,4-benzenediamine) was investigated. Thus, refluxing ethyl 2,2-dicyano-1-arylvinylcarbamate derivatives **1a-b** with diamine in chlorobenzene afforded dipyrimidinone derivatives **6a-f** (scheme 5).





Scheme 5

The structure of compounds **6a-f** was proved on the basis of spectral data and mass spectroscopy. The IR spectra of **6a-f** indicated the presence of NH group stretching at 3328-3132 cm^{-1}, CN group stretching at 2207-2210 cm^{-1} and C=O group stretching at 1660-1676 cm^{-1}. The ^{1}HNMR spectra of compounds **6a-b** indicated a singlet at δ 3.74-3.79 due to CH_2 group. Also, the mass spectra showed the respective $[M + H]^+$ peaks.

CONCLUSION

In conclusion, in this work we have tested the reactivity of ethyl 2,2-dicyano-1-aryl(or alkyl)vinylcarbamate derivatives toward phenylhydrazine, benzohydrazide, acetohydrazide, hydrazine and some diamine (2,7-diaminofluorene, orthodianisidine and 1,4-benzenediamine). Results demonstrate that hydrazine and its derivatives react differently to the compound **1a-d** even though they have the same nucleophilic centre.

EXPERIMENTAL

Melting points are recorded in degrees Celsius on a Kofler apparatus. All reactions were followed by TLC (E. Merck Kieselgel 60 F-254), with UV detection at 254 nm. The IR spectra were recorded in the solid state as KBr discs on a Perkin-Elmer PARAGON 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR were determined in solution in DMSO-d_6 with an AC Bruker spectrometer at 300 MHz using TMS as an internal standard. The mass spectra were recorded on an ion trap mass spectrometer (Finnigan LCQ Deca XP Max) using electrospray as an ionization source. The purity of all compounds was determined by LC-PDA-MS methods and was found to be in the range between 96-99%.

GENERAL EXPERIMENTAL PROCEDURE

General procedure for the preparation of 2a-c , 4a-e and 6a-f.

To a magnetically stirred solution of the ethyl 2,2-dicyanolvinylcarbamate derivatives **1a-d** (1 mmol) in chlorobenzene or ethanol (10 mL), the appropriate hydrazine derivatives or diamine (1.2 mmol) were added and the reaction mixture stirred under reflux. The progress of the reaction was monitored by TLC (mobile phase, ethyl acetate: dichloromethane; 70/30;v/v). The resulting mixture was allowed to cool at room temperature. The precipitate formed was isolated by filtration and washed with diethyl ether to obtain the pure product.

General procedure for the preparation of 3

A mixture of **2b** (1mmole), tetraethyl othocarbonate (5ml) and few drops of acetic acid was heated under reflux for 24 hr. The progress of the reaction was monitored by TLC (mobile phase, diethyl ether: hexane; 60/40;v/v). The solvent was removed in vacuo. Column chromatography purification using diethyl ether/ hexane as eluent gave the product **3**.

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Spectral Data of New Compounds

***6-amino-2-oxo-4-phenyl-1-(phenylamino)-1,2-dihydropyrimidine-5-carbonitrile 2a* :** Yield = 63% ; mp =212°C ; IR (KBr) v = 3420 - 3319 (NH), 2236 (CN), 1694 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 6.88- 7.99 (m, 13H); ^{13}C-NMR (DMSO-d6): δ = 72.8(C5), 118.5 (**C**N), 153.4(C2) , 160.5(C4), 175.1(C6), 125.4-145.2(C_{arom}).

***6-amino-4-benzyl-2-oxo-1-(phenylamino)-1,2-dihydropyrimidine-5-carbonitrile 2b* :**Yield = 60% ;mp =178°C ; IR (KBr) v = 3410 - 3241 (NH), 2220 (CN),1674 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 3.86 (s, 2H), 6.62-7.33 (m, 10H), 8.63 (s,2H, NH_2), 8.76 (s,1H, NH); ^{1}H-NMR (DMSO-d6): 43.4 (**C**H_2), 73.5(C5), 116.1 (**C**N), 153.0(C2) , 160.4(C4), 174.9(C6), 121.3-146.2(C_{arom}).

6-amino-4-isopropyl-2-oxo-1-(phenylamino)-1,2-dihydropyrimidine-5-carbonitrile 2c:Yield = 57%; mp =148°C; IR (KBr) v = 3385 – 3275 (NH), 2212 (CN), 1690 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 1.07 (d, 6H), 2.48 (m, 1H), 6.63-7.23 (m, 5H), 8.52 (s, 2H, NH_2), 8.76 (s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ = 20.7(**C**H_3), 34.9 (**C**H), 72.3 (C5), 115.9 (**C**N), 153.3(C2) , 160.4(C4), 181.0(C6), 121.2-146.3(C_{arom}).

7-benzyl-2-ethoxy-5-oxo-3-phenyl-3,5-dihydro-[1,2,4]triazolo[1,5-f]pyrimidine-8-carbonitrile 3: Yield = 20%; IR (KBr) v = 2216 (CN), 1684 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 0.93 (t, 3H), 3.62 (s, 2H), 4.11 (q, 2H), 7.21- 7.93 (m, 10H); ^{13}C-NMR (DMSO-d6): δ = 13.9 (**C**H_3), 31.7 (**C**H_2), 36.7 (**C**H_2), 74.4 (C8), 118.0 (**C**N), 138.3(C7) , 147.2(C5), 153.0(C2), 124.0-129.6(C_{arom}).

N-(6-amino-5-cyano-2-oxo-4-phenylpyrimidin-1(2H)-yl)benzamide 4a : Yield =68% ; mp =256°C; IR (KBr) v = 3361-3253 (NH), 2216 (CN), 1746 (C=O), 1682(C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 7.44 – 7.99 (m ,10H), 9.2 (s, 2H, NH_2), 10.60 (s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ = 72.5 (C5), 118.5 (**C**N), 156.8(C2) , 160.7(C4), 166.9(C6), 171.8 (**C**O), 125.2-137.1(C_{arom}).

N-(6-amino-5-cyano-4-isopropyl-2-oxopyrimidin-1(2H)-yl)benzamide 4b: Yield =69% ; mp =196°C; IR (KBr) v = 3348 - 3221 (NH), 2212 (CN), 1733 (C=O), 1681(C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 1.14 (d, 6H), 3.01(m, 1H), 7.39 – 7.97 (m ,5H), 8.5 (s, 2H, NH_2), 11.11 (s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ = 20.8 (**C**H_3), 35.0(**C**H), 72.3 (C5), 115.7 (**C**N), 152.4(C2) , 159.9 (C4), 166.9(C6), 181.5 (**C**O), 127.5-133.0(C_{arom}).

N-(6-amino-5-cyano-2-oxo-4-phenylpyrimidin-1(2H)-yl)acetamide 4c: Yield =72% ; mp =248 °C ; IR (KBr) v = 3373 - 3249 (NH), 2213 (CN), 1724 (C=O), 1688(C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 2.03 (s,3 H), 7.50 – 7.76 (m ,5H), 8.65 (s, 2H, NH_2), 10.73 (s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ=72.4 (C5), 116.5 (**C**N), 151.9(C2) , 160.4 (C4), 168.5(C6), 171.7 (**C**O), 128.7-137.2 (C_{arom}).

N-(6-amino-4-benzyl-5-cyano-2-oxopyrimidin-1(2H)-yl)acetamide 4d: Yield = 52%; mp = 226°C; IR (KBr) v = 3491-3224 (NH), 2226 (CN), 1735 (C=O), 1687(C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 1.98 (s, 3H), 3.82 (s, 2H), 7.24- 7.30 (m, 5H), 8.58 (s,2H, NH_2), 10.60 (s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ= 43.4 (**C**H_2), 20.9 (**C**H_3), 72.2 (C5), 116.0 (**C**N), 152.5(C2) , 159.7 (C4), 168.4(C6), 170.2 (**C**O), 127.3-136.9 (C_{arom}).

N-(6-amino-5-cyano-4-isopropyl-2-oxopyrimidin-1(2H)-yl)acetamide 4e : Yield = 62%; mp =240°C; IR (KBr) v = 3370 - 3230 (NH), 2231 (CN), 1745 (C=O), 1688 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 1.11 (d, 6H), 1.99 (s, 3H), 2.96 (m, 1H), 8.49 (s, 2H, NH_2), 10.58 (s, 1H, NH); ^{13}C-NMR (DMSO-d6): δ= 20.8(**C**H_3), 34.9(**C**H), C_7 20.9 (**C**H_3), 72.2 (C5), 115.7 (**C**N), 152.3(C2) , 158.5 (C4), 159.7(C6), 170.2 (**C**O), 127.5-133.0 (C_{arom}).

5-phenyl-2H-1,2,4-triazol-3(4H)-one 5a: Yield = 55% ; mp = 276°C ; IR (KBr) v = 3450 - 3189 (NH), 1748 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6): δ= 7.43 – 7.75 (m, 5H), 11.69 (s, 2H, 2NH); ^{13}C-NMR (DMSO-d6): δ= 145.5 (C5), 156.8 (C3), 125.2-130.3 (C_{arom}); MS-(+)ESI: *m/z* (%):162 ([M+H]$^+$, 100).

5-p-tolyl-2H-1,2,4-triazol-3(4H)-one 5b: Yield = 60%, mp= 269°C; IR (KBr) v= 3438–3180 (NH), 1713 (C=O); ^{1}H-NMR: (DMSO-d6): δ = 2.34 (s, 3H, CH_3), 7.30(d, 2H, J=6.0), 7.70(d, 2H, J=6.0), 11.65 (s,2H, 2NH); ^{13}C-NMR (DMSO-d6): δ = 20.8 (**C**H_3), 145.1 (C5), 156.3 (C3), 124.3-139.3(C_{arom}); MS-(+)ESI: *m/z* (%):190 ([M+H]$^+$, 100).

5-benzyl-2H-1,2,4-triazol-3(4H)-one 5c: Yield = 44% ; mp = 212°C ; IR (KBr) v= 3453 -3189 (NH), 1767 (C=O) cm^{-1} ; ^{1}H-NMR (DMSO-d6) : δ= 3.70 (s, 2H), 7.21 – 7.32 (m, 5H), 11.21 (s,2H, 2NH); ^{13}C-NMR (DMSO-d6): δ= 32.9 (**C**H_2), 146.7 (C5), 156.7 (C3), 127.2-136.7 (C_{arom}).

5-isopropyl-2H-1,2,4-triazol-3(4H)-one 5d: Yield = 48%; mp = 220°C ; IR (KBr) v= 3382 - 3181 (NH), 1733 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d6) : δ= 1.13 (d, 6H), 2.94 (m, 1H), 11.32 (s, 2H, 2NH), ^{13}C-NMR (DMSO-d6): δ= 20.7 (**C**H_3), 35.0(**C**H), 146.3 (C5), 156.8 (C3).

***6-amino-1-(7-(6-amino-5-cyano-2-oxo-4-phenylpyrimidin-1(2H)-yl)-9H-fluoren-2-yl)-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carbonitrile* 6a**: yield = 48%; $C_{35}H_{22}N_8O_2$, M=586g.mol^{-1}, mp= 294°C; IR (KBr) v: 3315–3197 (NH2), 2208 (CN), 1676 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 3.79 (s, 2H, CH_2), 6.62–7.84 (m,20H, Ar-H + $2NH_2$); ^{13}C-NMR (DMSO-d6): δ = 36.8 (**C**H_2), 72.7 (C5), 117.1 (**C**N), 154.3 (C6), 160.8 (C2), 171.7 (C4), 119.5-145.6(C_{arom}); MS-(+)ESI: *m/z* (%):587 ([M+H]$^+$, 100)**.**

***6-amino-1-(7-(6-amino-5-cyano-2-oxo-4-p-tolylpyrimidin-1(2H)-yl)-9H-fluoren-2-yl)-2-oxo-4-p-tolyl-1,2-dihydropyrimidine-5-carbonitrile* 6b**: Yield = 53%; $C_{37}H_{26}N_8O_2$, M=614g.mol^{-1}, mp= 209°C; IR (KBr) v: 3327–3132 (NH2), 2209 (CN), 1660 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 2.36 (s, 6H, $2CH_3$), 3.74 (s, 2H, CH_2), 6.62–7.90 (m,18H, Ar-H + $2NH_2$); ^{13}C-NMR (DMSO-d6): δ = 21.5 (**C**H_3), 36.8 (**C**H_2), 72.6 (C5), 117.2 (**C**N), 154.3 (C6), 160.8 (C2), 171.4 (C4), 120.1-144.6(C_{arom}); MS-(+)ESI: *m/z* (%):615 ([M+H]$^+$, 100).

Compound *6c*: Yield = 39%; $C_{36}H_{26}N_8O_4$, M=634g.mol^{-1}, mp= 270°C; IR (KBr) v: 3319–3196 (NH2), 2206 (CN), 1673 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 3.95 (s, 6H, 2O-CH_3), 7.33–8.35 (m,20H, Ar-H + 2NH_2); ^{13}C-NMR (DMSO-d6): δ = 56.0 (O-**C**H_3), 72.0 (C5), 117.1 (**C**N), 154.8 (C6), 159.9 (C2), 171.9 (C4), 119.5-142.9(C_{arom}); MS-(+)ESI: *m/z* (%):635 ([M+H]$^+$, 100).

Compound *6d*: Yield = 41%; $C_{38}H_{30}N_8O_4$, M=662g.mol^{-1}, mp= 265°C; IR (KBr) v: 3328–3200 (NH_2), 2210 (CN), 1666 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 2.41 (s, 6H, 2CH_3), 4.02 (s, 6H, 2 O-CH_3),7.35–7.79 (m,18H, Ar-H + 2NH_2); ^{13}C-NMR (DMSO-d6): δ = 21.5 (**C**H_3), 56.5 (O-**C**H_3), 72.1 (C5), 117.1 (**C**N), 155.5 (C6), 160.5 (C2), 171.9 (C4), 119.6-143.3(C_{arom}); MS-(+)ESI: *m/z* (%):663 ([M+H]$^+$, 100).

***6-amino-1-(4-(6-amino-5-cyano-2-oxo-4-phenylpyrimidin-1(2H)-yl)phenyl)-2-oxo-4-phenyl-1,2-dihydro pyrimidine-5-carbonitrile* 6e**: Yield = 62%; $C_{28}H_{18}N_8O_2$, M=498g.mol^{-1}, mp= 255°C; IR (KBr) v: 3312–3212 (NH2), 2208 (CN), 1673 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 6.49–7.95 (m,18H, Ar-H + 2NH_2); ^{13}C-NMR (DMSO-d6): δ = 72.8 (C5), 117.1 (**C**N), 154.5 (C6), 160.9 (C2), 171.3 (C4), 120.9-137.4(C_{arom}); MS-(+)ESI: *m/z* (%):499 ([M+H]$^+$, 100).

***6-amino-1-(4-(6-amino-5-cyano-2-oxo-4-p-tolylpyrimidin-1(2H)-yl)phenyl)-2-oxo-4-p-tolyl-1,2-dihydro pyrimidine-5-carbonitrile* 6f**: Yield = 65%; $C_{30}H_{22}N_8O_2$, M=526g.mol^{-1}, mp= 270°C; IR (KBr) v: 3314–3207 (NH2), 2207 (CN), 1674 (C=O) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 2.39 (s, 6H, 2CH_3), 6.66–7.95 (m,16H, Ar-H + 2NH_2); ^{13}C-NMR (DMSO-d6): δ = 21.5 (**C**H_3), 73.3 (C5), 117.26 (**C**N), 154.5 (C6), 161.0 (C2), 171.2 (C4), 122.1-141.4(C_{arom}); MS-(+)ESI: *m/z* (%):527 ([M+H]$^+$, 100).

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