Tailored-design Synthesis of Sulfapyrimidine Derivatives

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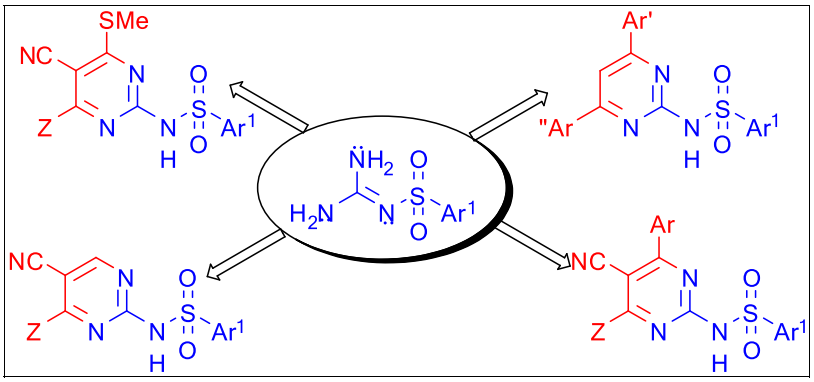

In this paper, we report an efficient and convenient approach for the synthesis of tailored-design target sulfapyrimidine derivatives expected to show remarkable antimicrobial activities. The approach is based on reacting arylsulfonyl guanidine with α,β-unsaturated carbonyl compounds to afford *N*-(4,6-diarylpyrimidin-2-yl)arylsulfonamide or with ylidene derivatives to afford *N*-(6-aryl-5-cyanopyrimidin-2-yl)arylsulfonamide, *N*-(4-amino-5-cyano-6-(methylthio)-pyrimidin-2-yl)-arylsulfonamide, and *N*-(5-cyanopyrimidin-2-yl)arylsulfonamide compounds through Michael addition reaction. The structure of the newly synthesized compounds was confirmed from spectral data and elemental analysis.

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INTRODUCTION

Sulfonamide-substituted heterocyclic compounds exhibit remarkable activities against both Gram-positive and Gram-negative bacteria [1]. Undoubtedly, the efficacy of the sulfonamide groups of this type of compounds, the ease of their oral administration, and its moderately low toxicity distinguish this class of compounds as one of the important antibacterial chemotherapeutic agents. Sulfapyrimidine [2,3], sulfapyridine [4], and sulfathiazole [5] were some of the early representatives of this group of sulfonamides. The unique antimicrobial properties of sulfapyrimidine inspired the further synthesis of a large number of pyrimidine derivatives of the sulfanilamide compounds, many of which with surprising activity and low toxicity characteristics [6]. Similar to other sulfonamides, sulfapyrimidine derivatives were identified as an inhibitor to dihydropteroate synthase enzyme, which some bacteria use to synthesize folic acid [7,8]. Sulfadiazine, a sulfapyrimidine drug (**A**) (Figure 1), is commonly used to treat urinary tract infections and burns. Combination of sulfadiazine and pyrimethamine can be used to treat toxoplasmosis, which is caused by *Toxoplasma gondii* [9,10]. Both sulfamerazine (**B**) and sulfadimidine (**C**) (Figure 1) are used in some acute bacterial infections such as *Escherichia coli* enteritis in veterinary medicine [11], cerebrospinal meningitis, and allergic reaction to penicillins [12]. Sulfapyrimidine drugs with dimethyl groups such as sulfisomidine (**D**) (Figure 1) are used for treatment of urinary infections because of their remarkable solubility in urine and absence of kidney damage [13]. It is commonly used as a sulfa therapy in human serum hemolytic complement system [14]. Sulfadoxine (**E**) (Figure 1) is used in combination with pyrimethamine for treatment of malaria [15]. Sulfadimethoxine (**F**) (Figure 1), a sulfonamide antimicrobial agent, is regularly employed in veterinary medicine because of its enduring half-life of approximately 40 h. It is commonly used to treat several bacterial infections such as respiratory, soft tissue, and urinary tract infections [16]. It can also be administered as a standalone or in combination with some other ormetoprim to widen the spectrum of the target range [17] as well as treating coccidian parasites infections [18].

Different approaches have been reported in the synthesis of sulfapyrimidine derivatives. The condensation reaction of *B*-diketones or *B*-ketocarboxylic esters with arylsulfonyl guanidine is a well-known reaction for the preparation of sulfapyrimidine derivatives [19–21]. Another approach for the synthesis of sulfapyrimidine derivatives is by reacting different 2-aminopyrimidines to

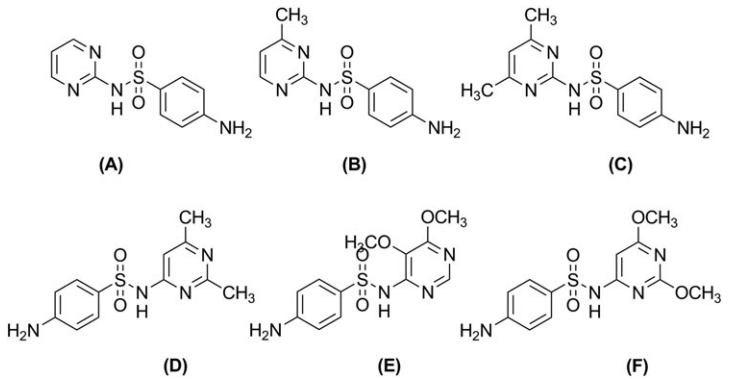


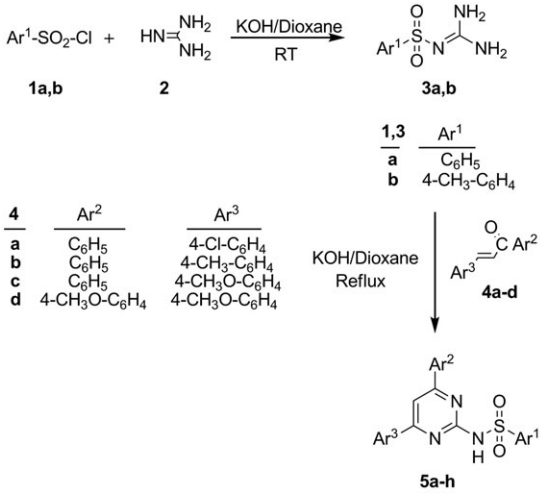
Figure 1. Structure of sulfapyrimidine drugs.

arylsulfonyl chloride [22]. Several derivatives of diphenysulfapyrimidine acetates have also been synthesized by reacting chalcones with sulfaguanidine acetate [23,24]. Our research group has also been involved in synthesizing a variety of substituted heterocyclic derivatives with good biological activities [25–30]. In this paper, we report on a new approach for the synthesis of tailored-design target sulfapyrimidine derivatives expected to show remarkable antimicrobial activities. The approach is based on reacting arylsulfonyl guanidine with α,β-unsaturated carbonyl compounds or with ylidene derivatives of both malononitrile and ethyl cyanoacetate.

RESULTS AND DISCUSSION

Arylsulfonyl guanidine **3a**,**b** was first synthesized by reacting arylsulfonyl chloride with excess guanidine hydrochloride in the presence of potassium hydroxide in 1,4-dioxane at room temperature. To determine the appropriate reaction conditions for the synthesis of *N*-(4,6-diarylpyrimidin-2-yl)arylsulfonamide **5a**–**h** (Scheme 1), the reaction of 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (1.2 mmol) **4a** and benzenesulfonyl guanidine (1 mmol) **3a** was chosen as a model experiment. Different reaction conditions were evaluated, and the results were all summarized in

Scheme 1. Synthesis of *N*-(4,6-diarylpyrimidin-2-yl)arylsulfonamide.



1,3	Ar^1
a	C_6H_5
b	4-CH_3-C_6H_4

4	Ar^2	Ar^3
a	C_6H_5	4-Cl-C_6H_4
b	C_6H_5	4-CH_3-C_6H_4
c	C_6H_5	4-CH_3O-C_6H_4
d	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4

5	Ar^1	Ar^2	Ar^3
a	C_6H_5	C_6H_5	4-Cl-C_6H_4
b	C_6H_5	C_6H_5	4-CH_3-C_6H_4
c	C_6H_5	C_6H_5	4-CH_3O-C_6H_4
d	C_6H_5	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4
e	4-CH_3-C_6H_4	C_6H_5	4-Cl-C_6H_4
f	4-CH_3-C_6H_4	C_6H_5	4-CH_3-C_6H_4
g	4-CH_3-C_6H_4	C_6H_5	4-CH_3O-C_6H_4
h	4-CH_3-C_6H_4	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4

Table 1. A preliminary screening of catalysts and solvents for the reaction showed that the use of potassium hydroxide and a nonpolar solvent such as 1,4-dioxane under reflux are crucial for this particular cyclic condensation reaction (Table 1, entry 6). Having established the optimal conditions for the condensation reaction, various α,β-unsaturated carbonyl compounds **4a**–**d** (Scheme 1) were allowed to react with benzenesulfonyl **3a** and tosyl guanidine **3b** separately to form *N*-(4,6-diarylpyrimidin-2-yl)arylsulfonamide **5a**–**d** and **5e**–**h**, respectively. The chemical structures of **5a**–**h** were assigned on the basis of its analytical and spectral data. ^{1}H NMR spectrum of compound **5f**, for example, exhibited two singlet signals at δ 2.29 and 2.37 ppm assignable to the protons of two methyl groups as well as four doublet signals at δ 7.16, 7.25, 7.75, and 7.95 ppm for eight protons residing on the two 4-substituted benzene rings. A singlet signal at δ 7.47 ppm was assigned to the proton at C-5 of the pyrimidine ring.

We also attempted to react arylsulfonyl guanidine **3a**,**b** with arylidene-substituted malononitrile derivatives, **6a**–**d**, and arylidene-substituted ethyl cyanoacetate derivatives, **10a**–**d**, through Michael addition reaction (Scheme 2). Different evaluated reaction conditions are summarized in Table 2. The optimal condition for the reaction of benzenesulfonyl guanidine **3a** with 4-chlorobenzylidene malononitrile **6b** incorporated the use of sodium ethoxide in ethanol under reflux (Table 2, entry 4). Applying the same condition to the reaction of benzenesulfonyl guanidine **3a** with 4-chlorobenzylidene ethyl cyanoacetate **10b** to afford 5-cyano-6-oxo-1,6-dihydropyrimidin-2-yl-benzenesulfonamide **13b** resulted in a lower yield. However, employing potassium hydroxide in 1,4-dioxane (Table 2, entry 3) resulted in a higher yield. To explore the scope and limitations of this reaction, we have extended the experimentations to include various substituted benzylidene of both malononitrile **6a**–**d** and ethyl cyanoacetate **10a**–**d** with both benzensulfonyl **3a** and tosyl guanidine **3b** to yield compounds **9a**–**f** and **13a**–**h**, respectively (Scheme 2). The structures of these products were deduced from their

Scheme 2. Synthesis of *N*-(6-aryl-5-cyanopyrimidin-2-yl) arylsulfonamide.

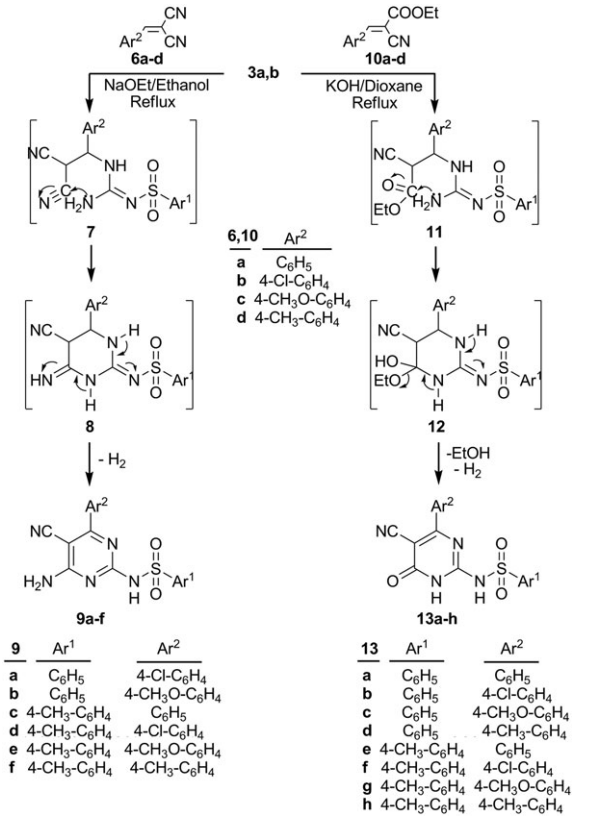
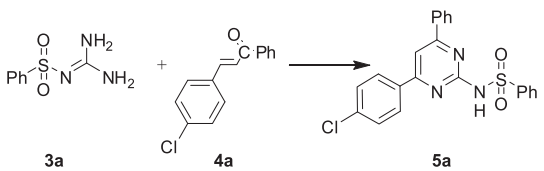


Table 1

Optimization of reaction condition of arylsulfonyl guanidine with α,β-unsaturated carbonyl compounds.

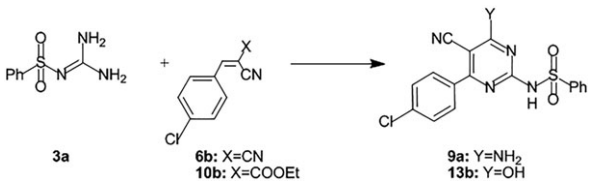


Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield
1	Piperidine	Ethanol	Reflux	8	>10
2	K_2CO_3	Ethanol	Reflux	8	>10
3	NaOEt	Ethanol	RT	24	—
4	NaOEt	Ethanol	Reflux	6	56
5	KOH	1,4-Dioxane	RT	24	25
6	KOH	1,4-Dioxane	Reflux	3	88

RT, room temperature.

Table 2

Optimization of reaction condition of arylsulfonyl guanidine with arylidene derivatives of malononitrile and ethyl cyanoacetate.

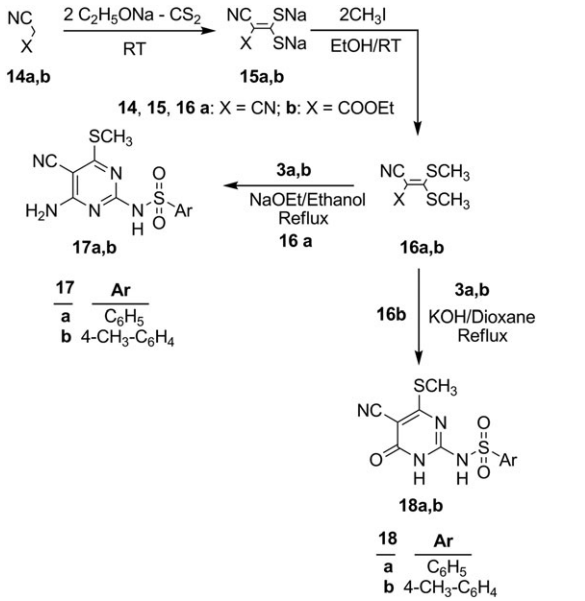


				9a		13b	
Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield	Time	Yield
1	Piperidine	Ethanol	Reflux	8	<20	16	<15
2	K_2CO_3	Ethanol	Reflux	8	30	10	27
3	KOH	1,4-Dioxane	Reflux	5	50	3	88
4	NaOEt	Ethanol	Reflux	3	60	3	71

respective IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. The reaction of arylsulfonyl guanidine **3a**,**b** with arylidene derivatives of both malononitrile and ethyl cyanoacetate is assumed to take place *via* the intermediacy of a non-isolable Michael adducts **7** and **11**, respectively, followed by an intramolecular cyclization to afford the aforementioned compounds. In the case of arylidene malononitrile, this has occurred through the addition of the amino group to one of the cyano groups of the malononitrile, whereas in the case of arylidene ethyl cyanoacetate, the cyclization has occurred through the elimination of an ethanol molecule. The sulfapyrimidine compounds **9a**–**f** and **13a**–**h** were then resulted from the oxidation of non-isolable intermediates **8** and **12**, respectively.

In order to extend the scope of the reaction of arylsulfonyl guanidine with ylidene compounds, we explored the reaction between arylsulfonyl guanidine **3a**, **b** and ketene dithioacetal derivatives **16a**,**b**. The reaction of 2-cyano-3,3-bis(methylthio)acrylonitrile **16a**, prepared elsewhere [31], with arylsulfonyl guanidine in the presence of sodium ethoxide in ethanol under reflux gave *N*-(4-amino-5-cyano-6-(methylthio)pyrimidin-2-yl) arylsulfonamide **17a**,**b** (Scheme 3). Moreover, the reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate **16b** with arylsulfonyl guanidine **3a**,**b** afforded the corresponding *N*-(5-cyano-4-(methylthio)-6-oxo-1,6-dihydropyrimidin-2-yl)benzenesulfonamide **18a**,**b** in good yield using potassium hydroxide in 1,4-dioxane (Scheme 3). The spectral and elemental analyses of compounds **17a**,**b** and **18a**,**b** were consistent with their structures. For example, IR spectrum of compound **17a** displayed absorption bands at υ 33430 and 3348 cm^{-1} for NH and NH_2 groups, respectively, as well as a band at υ 2197 cm^{-1} corresponding to the CN group. In the

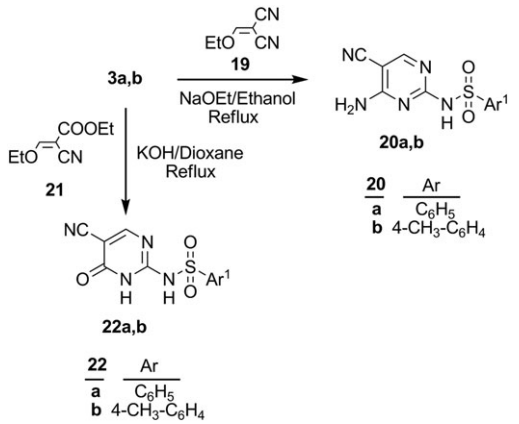
Scheme 3. Synthesis of *N*-(5-cyano-6-(methylthio)pyrimidin-2-yl) arylsulfonamide.



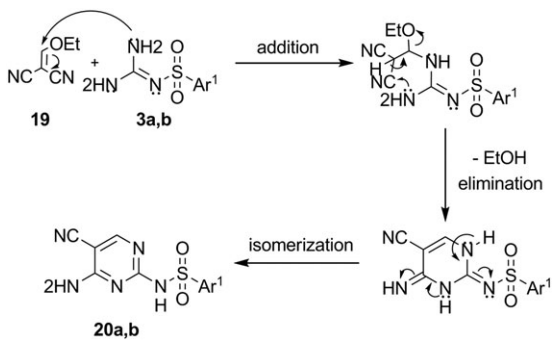
case of compound **18b**, the IR spectra displayed absorption bands at υ 3434, 2206, and 1644 cm^{-1} for NH, CN, and C═O groups, respectively. The ^{1}H NMR spectrum of compound **17a** exhibited one singlet signals at δ 2.12 ppm due to SCH_3 protons in addition to one broad band at δ 6.57 ppm for NH_2 protons while for compound **18b**, it showed two singlet signals at δ 2.16 and 2.33 ppm for SCH_3 and CH_3 protons, respectively. The reaction proceeded *via* Michael addition of one of the amino groups in the arylsulfonyl guanidine to the C═C of the ketene dithioacetal compounds followed by the elimination of CH_3SH molecule and the subsequent intramolecular cyclization.

The reaction of arylsulfonyl guanidine with ethoxymethylene compounds to produce new derivatives of sulfapyrimidine was also investigated. Cyclization of compounds arylsulfonyl guanidine **3a**,**b** with ethoxymethylenemalononitrile **19** in the presence of sodium ethoxide and ethanol under reflux afforded the corresponding products **20a**,**b** (Scheme 4). Additionally, the reaction of ethyl (ethoxymethylene)cyanoacetate **21** with arylsulfonyl guanidine **3a**,**b** using KOH in 1,4-dioxane under reflux resulted in the pyrimidine derivatives **22a**,**b** in good yield. All products were characterized by spectral data and elemental analysis. The IR spectrum of compound **22a** was characterized by the presence of absorption bands at υ 3414, 2220, 1669 cm^{-1} corresponding to NH, CN, and C═O groups, respectively. Moreover, its ^1H NMR spectrum revealed the presence of a singlet signal at δ 7.95 ppm for the CH proton of pyrimidine ring and another singlet signal at δ 11.20 ppm for the NH proton of the sulfonamide group. To rationalize the aforementioned results, a possible reaction mechanism is proposed, in which the ethoxymethylene compounds underwent a Michael addition reaction with the arylsulfonyl guanidines that is followed by the elimination of ethanol, intramolecular cyclization, and an isomerization of the resultant molecule to afford the *N*-(5-cyanopyrimidin-2-yl)arylsulfonamide products (Scheme 5).

Scheme 4. Synthesis of *N*-(5-cyanopyrimidin-2-yl)arylsulfonamide.



Scheme 5. Reaction mechanism for the synthesis of *N*-(5-cyanopyrimidin-2-yl)arylsulfonamide.



CONCLUSION

In conclusion, we have described an efficient approach for the preparation of 30 new derivatives of sulfapyrimidines by reacting arylsulfonyl guanidine with α,β-unsaturated carbonyl compounds or with ylidene derivatives such as arylidene-substituted malononitrile, arylidene-substituted ethyl cyanoacetate, 2-cyano-3,3-bis(methylthio)acrylonitrile, ethyl 2-cyano-3,3-bis(methylthio)acrylate, ethoxymethylenemalononitrile, and ethyl (ethoxymethylene)cyanoacetate through Michael addition reaction. The structure of newly synthesized compounds was confirmed spectroscopically and by elemental analysis.

EXPERIMENTAL

All melting points were uncorrected on a Gallenkamp melting point apparatus. IR spectra (KBr discs) were recorded on an FTIR plus 460 or Pye Unicam SP-1000 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance (III)-400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 using Si $(CH_3)_4$ as an internal standard at the Ain Shams University, Cairo, Egypt. Elemental analyses were obtained from the Microanalytical Data Center at Cairo University, Egypt, and were performed on Vario El III Elemental CHNS analyzer. Progress of the reactions and the purity of compounds were monitored and checked by thin-layer chromatography (TLC) aluminum sheets coated with silica gel F254 (Merck), using a mixture of petroleum ether and ethyl acetates as an eluent.

General procedure for the synthesis of 5a–h. A solution of arylsulfonyl guanidine **3a**,**b** (0.01 mol) and chalcone **4a–d** (0.012 mmol) in dry dioxane (20 mL) containing potassium hydroxide (0.015 mol) was heated under reflux for 2–4 h as judged by TLC. The reaction mixture was cooled and poured into ice acidified with HCl. The solid product formed was filtered off, washed by ethyl acetate, and recrystallized from ethanol to give the respective products **5a–h**.

N-(4-(4-Chlorophenyl)-6-phenylpyrimidin-2-yl) benzenesulfonamide 5a. Beige crystals; yield 88%; mp 262–263°C; IR (KBr, cm^{-1}): υ 3433 (NH), 3061 (ArCH), 1562 (C═C), 1353, 1132 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 7.32–8.06 (m, 15H, $2C_6H_5$, C_6H_4 & CH═ pyrimidine). ^{13}C NMR (100 MHz,

DMSO-d_6): δ 101.2 (CH═ pyrimidine), 125.9, 127.1, 127.4, 128.0, 128.9, 129.1, 129.4, 135.0, 137.6, 138.6, 148.1, 148.4, 162.9, 164.5, 165.4 (Ar–C). *Anal.* Calcd. for $C_{22}H_{16}ClN_3O_2S$ (421.90): C% 62.63; H% 3.82; N% 9.96. Found: C% 62.93; H% 3.91; N% 9.72.

N-(4-Phenyl-6-p-tolylpyrimidin-2-yl)benzenesulfonamide 5b. White crystals; yield 86%; mp 306–307°C; IR (KBr, cm^{-1}): υ 3435 (NH), 3056 (ArCH), 1563 (C═C), 1356, 1136 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 7.23–8.00 (m, 15H, $2C_6H_5$, C_6H_4 & CH═ pyrimidine). *Anal.* Calcd. for $C_{23}H_{19}N_3O_2S$ (401.48): C% 68.81; H% 4.77; N% 10.47. Found: C% 68.98; H% 5.06; N% 10.12.

N-(4-(4-Methoxyphenyl)-6-phenylpyrimidin-2-yl) benzenesulfonamide 5c. Beige crystals; yield 90%; mp 295–296°C; IR (KBr, cm^{-1}): υ 3436 (NH), 3059 (ArCH), 1564 (C═C), 1356, 1135 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 6.98 (d, J = 8 Hz, 2H, C_6H_4), 7.31–7.45 (m, 7H, $2C_6H_5$ & CH═ pyrimidine), 7.84–7.87 (m, 2H, C_6H_5), 7.99–8.01 (m, 4H, C_6H_5 & C_6H_4). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9 (OCH_3), 100.5 (CH═ pyrimidine), 114.2, 127.1, 127.3, 127.9, 128.7, 128.8, 129.3, 130.1, 139.2, 148.6, 161.1, 164.1 (Ar–C). *Anal.* Calcd. for $C_{23}H_{19}N_3O_3S$ (417.48): C% 66.17; H% 4.59; N% 10.07. Found: C% 66.50; H% 4.42; N% 10.22.

N-(4,6-Bis(4-methoxyphenyl)pyrimidin-2-yl) benzenesulfonamide 5d. White crystals; yield 86%; mp 236–237°C; IR (KBr, cm^{-1}): υ 3436 (NH), 3058 (ArCH), 1586 (C═C), 1363, 1164 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 6H, $2OCH_3$), 7.08–7.10 (m, 2H, C_6H_4), 7.54–7.62 (m, 6H, $2C_6H_4$, C_6H_5 & CH═ pyrimidine), 8.07–8.19 (m, 7H, $2C_6H_4$ & C_6H_5), 11.81 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{24}H_{21}N_3O_4S$ (447.51): C% 64.41; H% 4.73; N% 9.39. Found: C% 66.53; H% 4.64; N% 10.21.

N-(4-(4-Chlorophenyl)-6-phenylpyrimidin-2-yl)-4-methylbenzenesulfonamide 5e. White crystals; yield 83%; mp 292–293°C; IR (KBr, cm^{-1}): υ 3435 (NH), 2931 (ArCH), 1563 (C═C), 1357, 1135 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 7.16 (d, J = 8 Hz, 2H, C_6H_4), 7.43–7.53 (m, 6H, $2C_6H_4$, C_6H_5 & CH═ pyrimidine), 7.62–7.65 (m, 2H, $2C_6H_4$ & C_6H_5), 8.02–8.05 (m, 4H, $2C_6H_4$ & C_6H_5). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.3 (CH_3), 101.2 (CH═ pyrimidine), 127.2, 127.4, 128.4, 128.7, 129.2, 130.3, 135.0, 137.6, 138.6, 139.0, 141.4, 145.1, 158.8, 164.5, 165.3 (Ar–C). *Anal.* Calcd. for $C_{23}H_{18}ClN_3O_2S$ (435.93): C% 63.37; H% 4.16; N% 9.64. Found: C% 63.57; H% 4.31; N% 9.52.

4-Methyl-N-(4-phenyl-6-p-tolylpyrimidin-2-yl) benzenesulfonamide 5f. White crystals; yield 80%; mp 289–290°C; IR (KBr, cm^{-1}): υ 3433 (NH), 2918 (ArCH), 1567 (C═C), 1356, 1130 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.16 (d, J = 8 Hz, 2H, C_6H_4), 7.25 (d, J = 8 Hz, 2H, C_6H_4), 7.43–7.44 (m, 3H, C_6H_5), 7.47 (s, 1H, CH═ pyrimidine), 7.75 (d, J = 8 Hz, 2H, C_6H_4), 7.95 (d, J = 8 Hz, 2H, C_6H_4), 8.01–8.04 (m, 2H, C_6H_5). *Anal.* Calcd. for $C_{24}H_{21}N_3O_2S$ (415.51): C% 69.37; H% 5.09; N% 10.11. Found: C% 69.67; H% 5.30; N% 9.88.

N-(4-(4-Methoxyphenyl)-6-phenylpyrimidin-2-yl)-4-methylbenzenesulfonamide 5g. White crystals; yield 86%; mp 275–276°C; IR (KBr, cm^{-1}): υ 3436 (NH), 1561 (C═C), 1356, 1143 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.00 (d, J = 8 Hz, 2H, C_6H_4), 7.17 (d, J = 8 Hz, 2H, C_6H_4), 7.43–7.44 (m, 4H, C_6H_5 & CH═ pyrimidine), 7.75 (d, J = 8 Hz, 2H, C_6H_4), 8.02-8.53 (m, 4H, C_6H_4 & C_6H_5). *Anal.* Calcd. for $C_{24}H_{21}N_3O_3S$ (431.51): C% 66.80; H% 4.91; N% 9.74. Found: C% 67.00; H% 4.80; N% 9.92.

N-(4,6-Bis(4-methoxyphenyl)pyrimidin-2-yl)-4-methylbenzenesulfonamide 5h. White crystals; yield 89%; mp 302–303°C; IR (KBr, cm^{-1}): υ 3438 (NH), 1593 (C═C), 1362, 1168 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.83 (s, 6H, OCH_3), 6.98 (d, J = 8 Hz, 4H, $2C_6H_4$), 7.15 (d, J = 8 Hz, 2H, C_6H_4), 7.38 (s, 1H, CH═ pyrimidine), 7.73 (d, J = 8 Hz, 2H, C_6H_4), 8.00 (d, J = 8 Hz, 4H, $2C_6H_4$). *Anal.* Calcd. for $C_{25}H_{23}N_3O_4S$ (461.53): C% 65.06; H% 5.02; N% 9.10. Found: C% 65.33; H% 5.25; N% 9.20.

General procedure for the synthesis of 9a–f. To a solution of sodium ethoxide in ethanol, prepared from 0.013 mol of sodium added to 10 mL of absolute ethanol, and arylsulfonyl guanidine **3a**,**b** (0.01 mol), arylidene malononitrile **6a–d** (0.012 mol) was added. After heating the mixture under reflux for 2–4 h as judged by TLC, the reaction mixture was cooled and poured into ice acidified with HCl. The solid product was separated by filtration, washed ethanol, and dried under vacuum.

N-(4-Amino-6-(4-chlorophenyl)-5-cyanopyrimidin-2-yl) benzenesulfonamide 9a. Beige crystals; yield 60%; mp >350°C; IR (KBr, cm^{-1}): υ 3442, 3364 (NH, NH_2), 3100 (ArCH), 2209 (CN), 1611 (C═C), 1328, 1145 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34–8.06 (m, 11H, C_6H_5, C_6H_4 & NH_2), 12.05 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.3 (CN), 90.9, 94.5, 128.0, 128.3, 130.2, 130.4, 131.3, 133.9, 135.8, 144.3, 155.1, 160.8 (Ar–C). *Anal.* Calcd. for $C_{17}H_{12}ClN_5O_2S$ (385.83): C% 52.92; H% 3.13; N% 18.15. Found: C% 53.30; H% 3.23; N% 17.85.

N-(4-Amino-5-cyano-6-(4-methoxyphenyl)pyrimidin-2-yl) benzenesulfonamide 9b. White crystals; yield 55%; mp 278–279°C; IR (KBr, cm^{-1}): υ 3445, 3357 (NH, NH_2), 3149 (ArCH), 2210 (CN), 1560 (C═C), 1318, 1158 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 7.06 (d, J = 8 Hz, 2H, C_6H_4), 7.49–7.70 (m, 7H, C_6H_5 & NH_2), 8.04 (d, J = 8 Hz, 2H, C_6H_4), 11.81 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{18}H_{15}N_5O_3S$ (381.41):

C% 56.68; H% 3.96; N% 18.36. Found: C% 56.95; H% 4.10; N% 18.19.

N-(4-Amino-5-cyano-6-phenylpyrimidin-2-yl)-4-methylbenzenesulfonamide 9c. White crystals; yield 75%; mp 248–249°C; IR (KBr, cm^{-1}): υ 3400, 3340 (NH, NH_2), 3246 (ArCH), 2215 (CN), 1556 (C═C), 1327, 1159 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 7.36 (d, J = 8 Hz, 2H, C_6H_4), 7.51–7.59 (m, 3H, C_6H_5), 7.69 (d, J = 8 Hz, 2H, C_6H_5), 7.95 (d, J = 8 Hz, 2H, C_6H_4), 11.74 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.5 (CH_3), 116.6 (CN), 81.4, 128.8, 128.9, 129.5, 131.5, 137.8, 143.8, 157.5, 164.8 (Ar–C). *Anal.* Calcd. for $C_{18}H_{15}N_5O_2S$ (365.41): C% 59.16; H% 4.14; N% 19.17. Found: C% 59.39; H% 4.02; N% 19.32.

N-(4-Amino-6-(4-chlorophenyl)-5-cyanopyrimidin-2-yl)-4-methylbenzenesulfonamide 9d. White crystals; yield 78%; mp 293–294°C; IR (KBr, cm^{-1}): υ 3408, 3346 (NH, NH_2), 3161 (ArCH), 2215 (CN), 1554 (C═C), 1333, 1160 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 7.36 (d, J = 11 Hz, 2H, C_6H_4), 7.62 (d, J = 11 Hz, 2H, C_6H_4), 7.72 (d, J = 11 Hz, 2H, C_6H_4), 7.93 (d, J = 11 Hz, 2H, C_6H_4), 11.75 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{18}H_{14}ClN_5O_2S$ (399.85): C% 54.07; H% 3.53; N% 17.51. Found: C% 54.45; H% 3.25; N% 17.72.

N-(4-Amino-5-cyano-6-(4-methoxyphenyl)pyrimidin-2-yl)-4-methylbenzenesulfonamide 9e. Off white crystals; yield 80%; mp 290–291°C; IR (KBr, cm^{-1}): υ 3418, 3350 (NH, NH_2), 3149 (ArCH), 2214 (CN), 1567 (C═C), 1321, 1159 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 7.08 (d, J = 8 Hz, 2H, C_6H_4), 7.35 (d, J = 8 Hz, 2H, C_6H_4), 7.73 (d, J = 8 Hz, 2H, C_6H_4), 7.94 (d, J = 8 Hz, 2H, C_6H_4), 11.67 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4 (CH_3), 55.9 (OCH_3), 117.0 (CN), 66.8, 80.2, 128.4, 129.5, 130.7, 138.1, 143.6, 162.0, 165.0 (Ar–C). *Anal.* Calcd. for $C_{19}H_{17}N_5O_3S$ (395.43): C% 57.71; H% 4.33; N% 17.71. Found: C% 57.95; H% 4.48; N% 17.92.

N-(4-Amino-5-cyano-6-*p*-tolylpyrimidin-2-yl)-4-methylbenzenesulfonamide 9f. White crystals; yield 80%; mp 289–290°C; IR (KBr, cm^{-1}): υ 3417, 3347 (NH, NH_2), 3163 (ArCH), 2214 (CN), 1567 (C═C), 1321, 1158 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.32–7.37 (m, 4H, 2 C_6H_4), 7.61 (d, J = 8 Hz, 2H, C_6H_4), 7.94 (d, J = 8 Hz, 2H, C_6H_4), 11.66 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{19}H_{17}N_5O_2S$ (379.44): C% 60.14; H% 4.52; N% 18.46. Found: C% 60.47; H% 4.37; N% 18.25.

General procedure for the synthesis of 13a–h. A solution of arylsulfonyl guanidine **3a**,**b** (0.01 mol) and arylidene ethyl cyanoacetate **10a–d** (0.012 mmol) in dry dioxane (20 mL) containing potassium hydroxide (0.015 mol) was heated under reflux for 2–4 h as judged by TLC. The reaction mixture was cooled and poured into ice acidified with HCl. The solid product formed was filtered off, washed by ethyl acetate, and recrystallized from ethanol to give the respective products **13a–h**.

N-(5-Cyano-6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl) benzenesulfonamide 13a. Off white crystals; yield 85%; mp >350°C; IR (KBr, cm^{-1}): υ 3431 (NH), 3053 (ArCH), 2210 (CN), 1650 (C═O), 1563 (C═C), 1350, 1142 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 3.57 (s, 1H, NH), 7.41–7.79 (m, 10H, $2C_6H_5$), 11.32 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{17}H_{12}N_4O_3S$ (352.37): C% 57.95; H% 3.43; N% 15.90. Found: C% 58.30; H% 3.58; N% 16.11.

N-(4-(4-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyrimidin-2-yl)benzenesulfonamide 13b. Beige crystals; yield 88%; mp >350°C; IR (KBr, cm^{-1}): υ 3438 (NH), 3057 (ArCH), 2207 (CN), 1650 (C═O), 1564 (C═C), 1348, 1143 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 3.57 (s, 1H, NH), 7.42–7.51 (m, 7H, C_6H_5 & C_6H_4), 7.76–7.78 (m, 2H, C_6H_5), 11.34 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 118.7 (CN), 83.9, 127.3, 128.3, 128.4, 130.9, 130.7, 135.5, 136.5, 145.7, (Ar–C), 168.2 (CO). *Anal.* Calcd. for $C_{17}H_{11}ClN_4O_3S$ (386.81): C% 52.79; H% 2.87; N% 14.48. Found: C% 53.08; H% 2.70; N% 14.73.

N-(5-Cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-2-yl)benzenesulfonamide 13c. Beige crystals; yield 87%; mp >350°C; IR (KBr, cm^{-1}): υ 3432 (NH), 3053 (ArCH), 2212 (CN), 1645 (C═O), 1554 (C═C), 1346, 1142 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 3.57 (s, 1H, NH), 3.82 (s, 3H, OCH_3), 6.96 (d, J = 8 Hz, 2H, C_6H_4), 7.42–7.47 (m, 3H, C_6H_5), 7.52 (d, J = 8 Hz, 2H, C_6H_4), 7.78–7.80 (m, 2H, C_6H_5), 11.19 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{18}H_{14}N_4O_4S$ (382.39): C% 56.54; H% 3.69; N% 14.65. Found: C% 56.90; H% 3.54; N% 14.94.

N-(5-Cyano-6-oxo-4-*p*-tolyl-1,6-dihydropyrimidin-2-yl) benzenesulfonamide 13d. Beige crystals; yield 85%; mp >350°C; IR (KBr, cm^{-1}): υ 3431 (NH), 3052 (ArCH), 2206 (CN), 1651 (C═O), 1562 (C═C), 1347, 1140 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 3.57 (s, 1H, NH), 7.21 (d, J = 8 Hz, 2H, C_6H_4), 7.39–7.46 (m, 5H, C_6H_5 & C_6H_4), 7.79 (d, J = 8 Hz, 2H, C_6H_5). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.3 (CH_3), 118.7 (CN), 83.9, 127.5, 128.3, 128.7, 128.8, 130.9, 137.6, 140.7, 142.7, 156.7, 163.7 (Ar–C), 169.7 (CO). *Anal.* Calcd. for $C_{18}H_{14}N_4O_3S$ (366.39): C% 59.01; H% 3.85; N% 15.29. Found: C% 59.35; H% 4.05; N% 15.04.

N-(5-Cyano-6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)-4-methylbenzenesulfonamide 13e. White crystals; yield 81%; mp >350°C; IR (KBr, cm^{-1}): υ 3434 (NH), 3051 (ArCH), 2209 (CN), 1651 (C═O), 1564 (C═C), 1349, 1142 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 3.58 (s, 1H, NH), 7.24 (d, J = 13.6 Hz, 2H, C_6H_4), 7.42–7.52 (m, 5H, C_6H_5), 7.68 (d, J = 11.2 Hz, 2H, C_6H_4), 11.24 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{18}H_{14}N_4O_3S$ (366.39): C% 59.01; H% 3.85; N% 15.29. Found: C% 59.38; H% 3.98; N% 15.42.

N-(4-(4-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyrimidin-2-yl)-4-methylbenzenesulfonamide 13f. Beige crystals; yield 88%; mp >350°C; IR (KBr, cm^{-1}): υ 3436 (NH), 3047 (ArCH), 2206 (CN), 1649 (C=O), 1565 (C=C), 1348, 1141 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 3.57 (s, 1H, NH), 7.24 (d, J = 8 Hz, 2H, C_6H_4), 7.50–7.55 (m, 4H, $2C_6H_4$), 7.67 (d, J = 8 Hz, 2H, C_6H_4). *Anal.* Calcd. for $C_{18}H_{13}ClN_4O_3S$ (400.84): C% 53.94; H% 3.27; N% 13.98. Found: C% 54.24; H% 3.03; N% 14.22.

N-(5-Cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-2-yl)-4-methylbenzenesulfonamide 13g. White crystals; yield 87%; mp >350°C; IR (KBr, cm^{-1}): υ 3432 (NH), 3195 (ArCH), 2212 (CN), 1646 (C=O), 1557 (C=C), 1345, 1140 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.98 (d, J = 8 Hz, 2H, C_6H_4), 7.24 (d, J = 8 Hz, 2H, C_6H_4), 7.57 (d, J = 8 Hz, 2H, C_6H_4), 7.68 (d, J = 8 Hz, 2H, C_6H_4), 11.19 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d_6):δ 21.3 (CH_3), 55.8 (OCH_3), 119.0 (CN), 83.0, 113.7, 127.5, 128.7, 129.8, 130.7, 140.7, 142.7, 156.5, 161.6, 163.9 (Ar–C), 168.9 (CO). *Anal.* Calcd. for $C_{19}H_{16}N_4O_4S$ (396.42): C% 57.57; H% 4.07; N% 14.13. Found: C% 57.92; H% 4.28; N% 13.97.

N-(5-Cyano-6-oxo-4-p-tolyl-1,6-dihydropyrimidin-2-yl)-4-methylbenzenesulfonamide 13h. White crystals; yield 82%; mp >350°C; IR (KBr, cm^{-1}): υ 3438 (NH), 3027 (ArCH), 2206 (CN), 1651 (C=O), 1573 (C=C), 1346, 1146 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.21–7.30 (m, 4H, $2C_6H_4$), 7.41 (d, J = 8 Hz, 2H, C_6H_4), 7.66 (d, J = 8 Hz, 2H, C_6H_4), 11.19 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.3, 21.4 ($2CH_3$), 118.8 (CN), 83.6, 126.0, 127.5, 128.7, 129.4, 134.8, 140.6, 140.8, 142.7, 157.6, 163.7 (Ar–C), 169.6 (CO). *Anal.* Calcd. for $C_{19}H_{16}N_4O_3S$ (380.42): C% 59.99; H% 4.24; N% 14.73. Found: C% 60.30; H% 4.03; N% 14.97.

General procedure for the synthesis of 17a,b. To a solution of sodium ethoxide in ethanol, prepared from 0.013 mol of sodium added to 10 mL of absolute ethanol, and arylsulfonyl guanidine **3a**,**b** (0.01 mol), **16a** (0.012 mol) was added. After heating the mixture under reflux for 2–4 h as judged by TLC, the reaction mixture was cooled and poured into ice acidified with HCl. The solid product was separated by filtration, washed ethanol, and dried under vacuum.

N-(4-Amino-5-cyano-6-(methylthio)pyrimidin-2-yl) benzenesulfonamide 17a. Yellow crystals; yield 65%; mp 228–229°C; IR (KBr, cm^{-1}): υ 3430, 3348 (NH, NH_2), 3242 (ArCH), 2197 (CN), 1555 (C=C), 1403, 1132 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.12 (s, 3H, SCH_3), 6.57 (s, 2H, NH_2), 7.36–7.37 (m, 3H, C_6H_5), 7.77–7.79 (m, 2H, C_6H_5). *Anal.* Calcd. for $C_{12}H_{11}N_5O_2S_2$ (321.38): C% 44.85; H% 3.45; N% 21.79. Found: C% 45.10; H% 3.62; N% 22.00.

N-(4-Amino-5-cyano-6-(methylthio)pyrimidin-2-yl)-4-methylbenzenesulfonamide 17b. Yellow crystals; yield 55%; mp 262–263°C; IR (KBr, cm^{-1}): υ 3435, 3340 (NH, NH_2), 3246 (ArCH), 2207 (CN), 1558 (C=C), 1409, 1136 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, SCH_3), 2.30 (s, 3H, CH_3), 6.48 (s, 2H, NH_2), 7.22 (d, J = 8 Hz, 2H, C_6H_4), 7.65 (d, J = 8 Hz, 2H, C_6H_4). *Anal.* Calcd. for $C_{13}H_{13}N_5O_2S_2$ (335.40): C% 46.55; H% 3.91; N% 20.88. Found: C% 46.87; H% 4.18; N% 20.55.

General procedure for the synthesis of 18a,b. A solution of arylsulfonyl guanidine **3a**,**b** (0.01 mol) and **16b** (0.012 mmol) in dry dioxane (20 mL) containing potassium hydroxide (0.015 mol) was heated under reflux for 2–4 h as judged by TLC. The reaction mixture was cooled and poured into ice acidified with HCl. The solid product formed was filtered off, washed by ethyl acetate, and recrystallized from ethanol to give the respective products **18a**,**h**.

N-(5-Cyano-4-(methylthio)-6-oxo-1,6-dihydropyrimidin-2-yl) benzenesulfonamide 18a. Pale yellow crystals; yield 80%; mp >350°C; IR (KBr, cm^{-1}): υ 3448 (NH), 3043 (ArCH), 2213 (CN), 1653 (C=O), 1556 (C=C), 1472, 1144 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.10 (s, 3H, SCH_3), 7.44–7.48 (m, 3H, C_6H_5), 7.74–7.76 (m, 2H, C_6H_5), 11.12 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6 (SCH_3), 117.1 (CN), 81.5, 126.6, 128.6, 130.9, 145.5, 155.1, 174.3 (Ar–C), 162.8 (C=O). *Anal.* Calcd. for $C_{12}H_{10}N_4O_3S_2$ (322.36): C% 44.71; H% 3.13; N% 17.38. Found: C% 44.97; H% 3.00; N% 17.64.

N-(5-Cyano-4-(methylthio)-6-oxo-1,6-dihydropyrimidin-2-yl)-4-methylbenzenesulfonamide 18b. Yellow crystals; yield 87%; mp >350°C; IR (KBr, cm^{-1}): υ 3434 (NH), 3045 (ArCH), 2206 (CN), 1644 (C=O), 1558 (C=C), 1464, 1144 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ 2.16 (s, 3H, SCH_3), 2.33 (s, 3H, CH_3), 7.24 (d, J = 8 Hz, 2H, C_6H_4), 7.62 (d, J = 8 Hz, 2H, C_6H_4), 11.03 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6 (SCH_3), 21.3 (CH_3), 117.4 (CN), 81.3, 126.7, 129.0, 140.7, 142.8, 155.2, 174.1 (Ar–C), 161.7 (C=O). *Anal.* Calcd. for $C_{13}H_{12}N_4O_3S_2$ (336.39): C% 46.42; H% 3.60; N% 16.66. Found: C% 46.88; H% 3.45; N% 16.87.

General procedure for the synthesis of 20a,b. To a solution of sodium ethoxide in ethanol, prepared from 0.013 mol of sodium added to 10 mL of absolute ethanol, and arylsulfonyl guanidine **3a**,**b** (0.01 mol), **19** (0.012 mol) was added. After heating the mixture under reflux for 2–4 h as judged by TLC, the reaction mixture was cooled and poured into ice acidified with HCl. The solid product was separated by filtration, washed ethanol, and dried under vacuum.

N-(4-Amino-5-cyanopyrimidin-2-yl)benzenesulfonamide 20a. Off white crystals; yield 50%; mp 210–211°C; IR (KBr, cm^{-1}): υ 3406, 3323 (NH, NH_2), 3219 (ArCH), 2218 (CN), 1555 (C=C), 1414, 1134 (SO_2). ^1H NMR

(400 MHz, DMSO-d_6): 7.43 (s, 2H, NH_2), 7.51–7.53 (m, 3H, C_6H_5), 7.82–7.83 (m, 2H, C_6H_5), 8.32 (s, 1H, CH═ pyrimidine), 14.51 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{11}H_9N_5O_2S$ (275.29): C% 47.99; H% 3.30; N% 25.44. Found: C% 48.33; H% 3.52; N% 25.17.

N-(4-Amino-5-cyanopyrimidin-2-yl)-4-methylbenzenesulfonamide 20b. Off white crystals; yield 60%; mp 208–209°C; IR (KBr, cm^{-1}): υ 3438, 3351 (NH, NH_2), 3230 (ArCH), 2109 (CN), 1527 (C═C), 1409, 1132 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 7.31 (d, J = 8 Hz, 2H, C_6H_4), 7.92 (d, J = 8 Hz, 2H, C_6H_4), 8.37 (s, 1H, CH═ pyrimidine). *Anal.* Calcd. for $C_{12}H_{11}N_5O_2S$ (289.31): C% 49.82; H% 3.83; N% 24.21. Found: C% 50.17; H% 3.60; N% 24.57.

General procedure for the synthesis of 22a,b. A solution of arylsulfonyl guanidine **3a,b** (0.01 mol) and **21** (0.012 mmol) in dry dioxane (20 mL) containing potassium hydroxide (0.015 mol) was heated under reflux for 2–4 h as judged by TLC. The reaction mixture was cooled and poured into ice acidified with HCl. The solid product formed was filtered off, washed by ethyl acetate, and recrystallized from ethanol to give the respective products **22a,b**.

N-(5-Cyano-6-oxo-1,6-dihydropyrimidin-2-yl) benzenesulfonamide 22a. Off white crystals; yield 73%; mp >350°C; IR (KBr, cm^{-1}): υ 3414 (NH), 3065 (ArCH), 2220 (CN), 1669 (C═O), 1534 (C═C), 1361, 1144 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39–7.46 (m, 3H, C_6H_5), 7.77–7.79 (m, 2H, C_6H_5), 7.95 (s, 1H, CH═ pyrimidine), 11.20 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{11}H_8N_4O_3S$ (276.27): C% 47.82; H% 2.92; N% 20.28. Found: C% 48.14; H% 2.71; N% 20.66.

N-(5-Cyano-6-oxo-1,6-dihydropyrimidin-2-yl)-4-methylbenzenesulfonamide 22b. Beige crystals; yield 75%; mp >350°C; IR (KBr, cm^{-1}): υ 3420 (NH), 3061 (ArCH), 2208 (CN), 1665 (C═O), 1544 (C═C), 1365, 1145 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 7.21 (d, J = 8 Hz, 2H, C_6H_4), 7.67 (d, J = 8 Hz, 2H, C_6H_4), 7.94 (s, 1H, CH═ pyrimidine), 11.09 (s, 1H, $NHSO_2$). *Anal.* Calcd. for $C_{12}H_{10}N_4O_3S$ (290.30): C% 49.65; H% 3.47; N% 19.30. Found: C% 49.89; H% 3.54; N% 19.10.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.