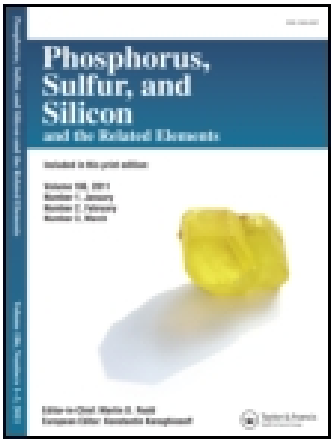

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Synthesis and Antiviral Activity of Some (3,4-Diaryl-3H-thiazol-2-ylidene)pyrimidin-2-yl Amine Derivatives

Gülhan Turan-Zitouni [a] , Ahmet Özdemir [a] & Zafer Asım Kaplancıklı [a]
[a] Faculty of Pharmacy, Department of Pharmaceutical Chemistry , Anadolu University , Eskişehir, Turkey
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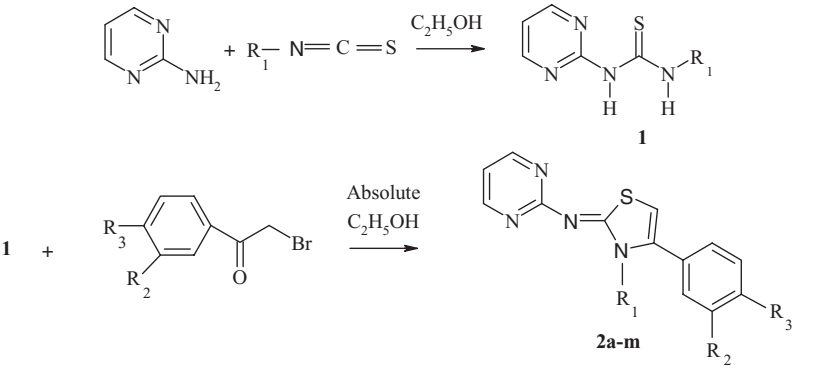
SYNTHESIS AND ANTIVIRAL ACTIVITY OF SOME (3,4-DIARYL-3H-THIAZOL-2-YLIDENE)PYRIMIDIN-2-YL AMINE DERIVATIVES

Gülhan Turan-Zitouni, Ahmet Özdemir, and Zafer Asım Kaplancıklı

Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Anadolu University, Eskişehir, Turkey

GRAPHICAL ABSTRACT



Abstract *Thirteen new (3,4-diaryl-3H-thiazol-2-ylidene)pyrimidin-2-yl amine derivatives were synthesized by reacting 1-aryl-3-pyrimidin-2-yl-thiourea derivatives and phenacyl bromides in absolute ethanol. The solid that separated was filtered and recrystallized from ethanol. The structures of the synthesized compounds were confirmed by elemental analyses and ^{1}H NMR, ^{13}C NMR, and EI-MS spectral data.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Antiviral activity; pyrimidine; thiazole

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The antiviral evaluations were carried out by Dr. Michel Liuzzi (Idenix Senior Director Virology, Laboratorio Cooperativo Idenix–Universita di Cagliari, Italy) and his team. Their contributions, as well as that of Dr. Gilles Gosselin (CNRS Research Director, Senior Scientist Fellow, Idenix Montpellier, France), are gratefully acknowledged.

Address correspondence to Gülhan Turan-Zitouni, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Anadolu University, Eskişehir 26470, Turkey. E-mail: gturan@anadolu.edu.tr

INTRODUCTION

The development of nontoxic selective inhibitors of kinases and polymerases for control of viral diseases has been the focus of intense research.[1] Despite significant progress, there is still a need for novel viral replication inhibitors, particularly for the treatment of infection by human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), influenza virus (FLU), rhino virus (RV), and hepatitis C virus (HCV).

Molecules that possess sulfur atoms are common and very significant in living organisms.[2] One important class of heterocycle compound that contains one sulfur atom is known as thiazole. This class is present in many natural and synthetic products with a wide range of pharmacological activities, such as antiviral, anticancer, antibacterial, antifungal, anticonvulsant, antiparkinsonian, and anti-inflammatory activities that can be well illustrated by the large number of drugs in the market containing this function group.[3,4] As examples, the antiviral ritonavir, the antibacterial sulfathiazole, the vitamin B_1, the antiparkinsonian talipexole, the antischistosomal miridazole, the anthelmintic tiabendazole, the anti-ulcer alizatidine, and the anticonvulsant riluzole can be cited.[3,4] In the case of natural products, thiazole is present as a subunit in a large number of terrestrial and marine compounds, with different biological activities that represent a very important field in drug discovery.

On the other hand, the literature survey indicates that a large number of simple, N-bridged, nitrogen- and sulfur-containing heterocyclic compounds carrying a pyrimidine moiety are found to be associated with various biological activities. The chemistry of pyrimidine and its derivatives has been studied for over a century due to their diverse biological activities.[5–8] They possess antiviral,[9–16] antibacterial,[17,18] anticancer,[19,20] and antihypertensive activities.[21,22]

Keeping in view these observations, we decided to undertake the synthesis of some novel heterocycles containing the thiazole and pyrimidine moiety and to evaluate their antiviral activity.

RESULTS AND DISCUSSION

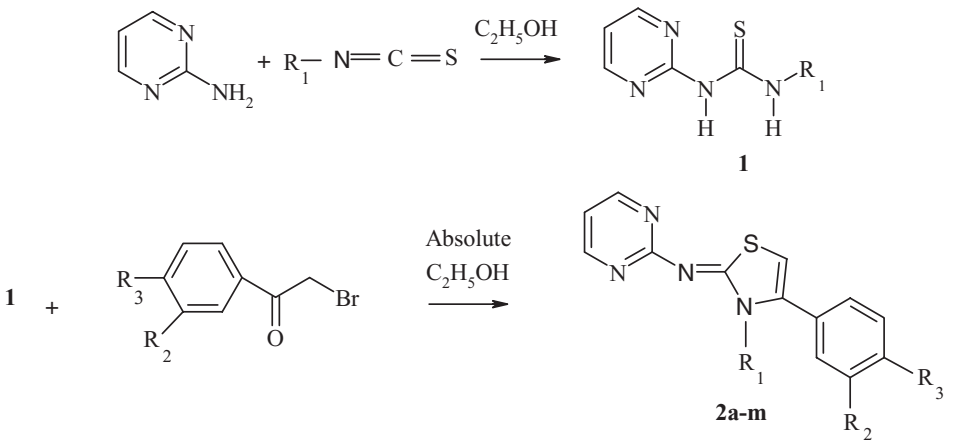
In this study, 13 new compounds were synthesized. 1-Aryl-3-pyrimidin-2-yl-thiourea derivatives (**1**) were prepared by reacting pyrimidin-2-yl amine with *p*-substitutedpheny/benzyl isothiocyanate in accordance with the method described in the literature.[23] The reaction of 1-aryl-3-pyrimidin-2-yl-thiourea derivatives (**1**) and phenacyl bromides gave the (3,4-diaryl-3H-thiazol-2-ylidene)pyrimidin-2-yl amine derivatves (**2a–m**), as shown in Scheme 1. The formulas of compounds **2a–m** were confirmed by ^{1}H NMR, ^{13}C NMR, and EI-MS spectral data. The antiviral activities of the synthesized compounds were screened. The results showed that all of the tested compounds were inactive against the test organism, as shown in Table S1 (Supplemental Materials, available online).

Compounds **2a–m** were tested for antiviral activity and cytotoxicity in various cell-based assays.[24]

EXPERIMENTAL

Chemistry

All reagents were used as purchased from commercial suppliers without further purification. Melting points were determined by using an Electrothermal 9100 digital



Scheme 1 The synthetic scheme for **2a–m**.

melting point apparatus and were uncorrected. The compounds were checked for purity by TLC on silica gel 60 F_{254}. Spectroscopic data were recorded on the following instruments: elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyzer (Perkin Elmer, Wellesly, MA, USA); ^{1}H NMR and ^{13}C NMR spectra of DMSO-d_6 solutions (TMS as internal standard) were respectively recorded at 400 and 100 MHz with a Bruker apparatus. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Chemical shift (δ) values are given in parts per million and coupling constants (J) in Hz. GC-MS was performed with an Agilent Technologie 6890N GC apparatus (equipped with a 12 m $\times$ 0.20 mm dimethylpolysiloxane capillary column) linked to an Agilent 5973 EIMS mass spectrometer.

General Procedure for Synthesis of the Compounds: Preparation of 1-Aryl-3-pyrimidin-2-yl-thiourea Derivatives (1)

A mixture of pyrimidin-2-yl amine (0.1 mol) and *p*-substitutedpheny/benzyl isothiocyanate (0.1 mol) in ethanol was refluxed for 2 h. The solid that separated upon cooling was filtered, dried, and recrystallized from ethanol.

Preparation of (3,4-Diaryl-3H-thiazol-2-ylidene)pyrimidin-2-yl Amine Derivatives (2a–m)

1-Aryl-3-pyrimidin-2-yl-thiourea derivatives (**1**) (0.001 mol) and the appropriate α-bromoacetophenone (0.001 mol) in absolute ethanol were refluxed for 4–5 h. The solid that separated was filtered and recrystallized from ethanol. Some characteristics of the synthesized compounds are shown in Table 1.

[4-(4-Chlorophenyl)-3-phenyl-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2a). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.01 (1H, t, $J = 7.4$ Hz), 7.22 (1H, t, $J = 4.9$ Hz), 7.35 (2H, t, $J = 8.0$ Hz), 7.44 (2H, d, $J = 8.0$ Hz), 7.67 (2H, d, $J = 7.6$ Hz), 7.72 (2H, d, $J = 8.0$ Hz), 8.63 (2H, d, $J = 4.9$ Hz), 10.60 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 117.6 (2CH), 118.3 (CH), 120.9 (C), 122.1 (CH), 127.4 (2CH), 127.7 (CH), 129.1 (2CH), 131.5 (2CH), 132.8 (C), 134.5 (C), 140.5 (C), 157.1 (2CH), 160.2 (C),

Table 1 Characterization of the title compounds

Compound	R_1	R_2	R_3	Yield (%)	Mp (°C)	Mol. For. (MW)	Elemental Analyses (Calc./Found.) C	H	N
2a	Phenyl	H	Cl	59	216–218	$C_{19}H_{13}ClN_4S$	62.55	3.59	15.36
						364.86	63.10	3.23	14.87
2b	Phenyl	H	CH_3	64	173–174	$C_{20}H_{16}N_4S$	69.74	4.68	16.27
						344.44	69.96	5.36	16.38
2c	Phenyl	H	OCH_3	61	205–207	$C_{20}H_{16}N_4OS$	66.65	4.47	15.54
						360.44	66.85	4.20	15.64
2d	*p*-CH_3-Phenyl	H	Cl	58	274–275	$C_{20}H_{15}ClN_4S$	63.40	3.99	14.79
						378.89	63.73	4.59	15.11
2e	*p*-CH_3-Phenyl	H	NO_2	65	127–128	$C_{20}H_{15}N_5O_2S$	61.68	3.88	17.98
						389.44	61.86	4.38	18.12
2f	*p*-CH_3-Phenyl	H	CH_3	53	202–204	$C_{21}H_{18}N_4S$	70.36	5.06	15.63
						358.47	70.81	5.53	15.94
2g	*p*-CH_3-Phenyl	H	OCH_3	52	241–243	$C_{21}H_{18}N_4OS$	67.36	4.85	14.96
						374.47	67.78	4.72	15.17
2h	*p*-OCH_3-Phenyl	Cl	Cl	67	154–155	$C_{20}H_{14}Cl_2N_4OS$	55.95	3.29	13.05
						429.33	56.24	3.28	13.54
2i	CH_2-Phenyl	H	H	59	169–171	$C_{20}H_{16}N_4S$	69.74	4.68	16.27
						344.44	69.97	4.97	16.41
2j	CH_2-Phenyl	H	Cl	63	242–243	$C_{20}H_{15}ClN_4S$	63.40	3.99	14.79
						378.89	63.76	4.07	14.93
2k	CH_2-Phenyl	H	NO_2	65	193–194	$C_{20}H_{15}N_5O_2S$	61.68	3.88	17.98
						389.44	61.76	4.58	18.11
2l	CH_2-Phenyl	H	CH_3	61	168–170	$C_{21}H_{18}N_4S$	70.36	5.06	15.63
						358.47	70.69	5.18	15.83
2m	CH_2-Phenyl	Cl	Cl	67	213–214	$C_{20}H_{14}Cl_2N_4S$	58.12	3.41	13.55
						413.33	58.37	3.44	13.52

163.4 (C). EI-MS (*m/z*): 366 (32), 365 (52), 364 (M^+, 82%), 363 (100), 327 (2), 285 (6), 272 (6), 260 (6), 245 (11), 227 (6), 193 (5), 164 (16).

[4-(4-Tolyl)-3-phenyl-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2b). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.36 (3H, s), 6.97–7.05 (2H, m), 7.16–7.23 (2H, m), 7.34 (2H, t, $J = 8.0$ Hz), 7.59 (2H, d, $J = 8.0$ Hz), 7.68 (2H, d, $J = 8.0$ Hz), 8.62 (2H, d, $J = 4.9$ Hz), 10.59 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 20.9 (CH_3), 117.5 (2CH), 118.2 (CH), 120.0 (C), 121.9 (CH), 128.0 (2CH), 129.0 (2CH), 129.6 (2CH), 132.9 (CH), 137.5 (C), 140.6 (C), 152.2 (C), 157.0 (2CH), 160.5 (C), 163.1 (C). EIMS (*m/z*): 344 (M^+, 70%), 343 (100), 329 (1), 265 (2), 252 (4), 240 (5), 225 (11), 172 (9).

[4-(4-Methoxyphenyl)-3-phenyl-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2c). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.82 (3H, s), 6.94 (1H, m), 6.96 (1H, m), 7.00 (1H, t, $J = 7.4$ Hz), 7.20 (1H, t, $J = 4.9$ Hz), 7.35 (2H, m), 7.67 (2H, m), 7.69 (2H, m), 8.63 (2H, d, $J = 4.9$ Hz), 10.54 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 55.1 (CH_3), 112.3 (2CH), 117.5 (2CH), 118.1 (CH), 119.4 (C), 121.9 (CH), 127.8 (CH), 129.0 (2CH), 131.1 (2CH), 140.6 (C), 152.0 (C), 157.0 (2CH), 159.3 (C), 160.6 (C), 163.0 (C). EI-MS (*m/z*): 360 (M^+, 86%), 359 (100), 345 (16), 327 (1), 316 (6), 283 (2), 268 (3), 256 (2), 242 (4), 227 (6), 199 (6), 180 (9).

[4-(4-Chlorophenyl)-3-(4-tolyl)-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2d). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.28 (3H, s), 7.18 (2H, d, $J = 7.8$ Hz), 7.27 (1H, m), 7.56 (2H, d, $J = 7.8$ Hz), 7.98 (2H, d, $J = 7.8$ Hz), 8.27 (2H, d, $J = 7.8$ Hz), 8.67 (2H, d, $J = 4.6$ Hz), 10.61 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 20.98 (CH_3), 99.98 (CH), 116.22 (2CH), 118.64 (CH), 122.35 (C), 127.15 (2CH), 129.54 (2CH), 131.17 (2CH), 133.09 (C), 137.798 (C), 142.277 (C), 145.98 (C), 148.98 (C), 157.26 (2CH), 163.80 (C). EI-MS (*m/z*): 378 (M^+, 69%), 377 (100), 363 (4), 346 (27), 345 (15), 284 (9), 267 (7), 253 (2), 228 (6), 182 (11).

[4-(4-Nitrophenyl)-3-(4-tolyl)-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2e). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.27 (3H, s), 7.16 (2H, d, $J = 7.8$ Hz), 7.25 (1H, m), 7.53 (2H, d, $J = 7.8$ Hz), 7.96 (2H, d, $J = 7.8$ Hz), 8.24 (2H, d, $J = 7.8$ Hz), 8.64 (2H, d, $J = 4.6$ Hz), 10.58 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 20.4 (CH_3), 99.5 (CH), 117.9 (2CH), 118.6 (CH), 122.3 (C), 122.7 (2CH), 129.5 (2CH), 131.0 (2CH), 131.3 (C), 137.9 (C), 142.3 (C), 146.9 (C), 149.6 (C), 157.2 (2CH), 163.8 (C). EI-MS (*m/z*): 390 (27), 389 (M^+, 100%), 388 (58), 359 (6), 358 (7), 343 (8), 342 (18), 310 (7), 226 (15), 171 (16).

[3,4-Di-(4-tolyl)-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2f). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.26 (3H, s), 2.36 (3H, s), 7.13–7.21 (5H, m), 7.50–7.60 (4H, m), 8.61 (2H, d, $J = 4.9$ Hz), 10.46 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 20.38 (CH_3), 20.95 (CH_3), 117.74 (2CH), 118.04 (CH), 119.64 (C), 126.06 (CH), 127.96 (2CH), 129.44 (2CH), 129.56 (2CH), 130.97 (C), 132.87 (C), 137.51 (C), 152.24 (C), 156.98 (2CH), 160.55 (C), 163.41 (C). EI-MS (*m/z*): 358 (M^+, 76%), 357 (100), 279 (3), 267 (2), 252 (4), 240 (5), 225 (11), 179 (6).

[4-(4-Methoxyphenyl-)3-(4-tolyl)-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2g). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.29 (3H, s), 3.67 (3H, s), 7.14–7.23 (5H, m), 7.52–7.61 (4H, m), 8.63 (2H, d, $J = 4.9$ Hz), 10.53 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 20.4 (CH_3), 55.8 (CH_3), 118.0 (2CH), 118.1 (CH), 119.7 (C), 126.2 (CH), 127.9 (2CH), 128.9 (2CH), 129.4 (2CH), 130.8 (C), 131.1 (C), 138.0 (C), 152.8 (C), 156.7 (2CH), 161.2 (C), 164.2 (C). EI-MS (*m/z*): 374 (M^+, 72%), 358 (100), 277 (5), 253 (8), 240 (7), 223 (15), 180 (6).

[4-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)-3H-thiazol-2-ylidene] pyrimidin-2-yl amine (2h). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.74 (3H, s), 6.94 (1H, m), 6.96 (1H, m), 7.21 (1H, t, $J = 4.9$ Hz), 7.53 (1H, m), 7.55 (1H, m), 7.63 (1H, d, $J = 8.4$ Hz), 7.68 (1H, dd, $J = 8.4$, 1.9 Hz), 7.92 (1H, d, $J = 1.9$ Hz), 8.62 (2H, d, $J = 4.9$ Hz), 10.42 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 55.2 (CH_3), 114.4 (2CH), 118.3 (CH), 120.0 (2CH), 120.9 (C), 129.6 (CH), 130.0 (CH), 130.1 (C), 130.6 (C), 131.5 (CH), 133.7 (CH), 136.3 (C), 149.4 (C), 154.9 (C), 157.1 (2CH), 160.0 (C), 164.4 (C). EI-MS (*m/z*): 430 (M^+, 71%), 428 (M^+, 100%), 427 (28), 415 (34), 413 (49), 393 (2), 377 (2), 349 (3), 306 (2), 281 (8), 246 (14), 196 (16).

[4-Phenyl- 3-benzyl-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2i). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 5.44 (2H, s), 6.90–7.70 (12H, m), 8.79 (2H, d, $J = 5.0$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 49.1 (CH_2), 107.4 (CH), 112.5 (CH), 125.5 (CH), 126.5 (2CH), 127.3 (CH), 128.3 (2CH), 128.6 (2CH), 129.3 (2CH), 129.5 (CH), 130.1 (C), 136.2 (C), 139.3 (C), 157.3 (CH), 157.4 (C), 164.6 (C). EI-MS (*m/z*): 344 (M^+, 75%), 328 (2), 312 (25), 311 (100), 297 (1), 284 (1), 265 (19), 250 (11), 240 (6), 226 (5), 184 (16), 134 (32), 91 (48).

[4-(4-Chlorophenyl)-3-benzyl-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2j). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 5.46 (2H, s), 6.88–7.27 (11H, m), 8.83

(2H, d, $J = 5.1$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 49.4 (CH_2), 107.9 (CH), 112.3 (CH), 125.4 (CH), 126.3 (2CH), 127.2 (CH), 128.4 (2CH), 129.0 (2CH), 129.5 (2CH), 129.9 (C), 130.0 (C), 136.3 (C), 139.2 (C), 157.5 (CH), 157.8 (C), 164.8 (C). EI-MS (*m/z*): 380 (23), 378 (M^+, 62%), 362 (2), 347 (29), 346 (21), 345 (85), 299 (16), 284 (9), 252 (9), 184 (25), 182 (11), 168 (27), 91 (100).

[4-(4-Nitrophenyl)-3-benzyl-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2k). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 5.47 (2H, s), 6.92–7.32 (11H, m), 8.82 (2H, d, $J = 5.2$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 48.6 (CH_2), 107.9 (CH), 113.5 (CH), 123.7 (2CH), 126.3 (2CH), 127.2 (CH), 128.5 (2CH), 130.3 (2CH), 136.5 (C), 136.7 (C), 137.1 (C), 147.6 (C), 157.5 (2CH), 162.4 (C), 163.5 (C). EI-MS (*m/z*): 390 (25), 389 (M^+, 65%), 388 (55), 360 (5), 358 (7), 344 (8), 300 (15), 285 (10), 184 (26), 168 (25), 91 (100).

[4-(4-Tolyl)-3-benzyl-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2l). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.35 (3H, s), 5.44 (2H, s), 6.90–7.30 (11H, m), 8.82 (2H, d, $J = 5.1$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 20.9 (CH_3), 49.2 (CH_2), 107.74 (CH), 112.2 (CH), 125.4 (CH), 126.4 (2CH), 127.0 (C), 127.3 (CH), 128.2 (CH), 128.4 (2CH), 129.2 (2CH), 129.3 (CH), 136.1 (C), 139.3 (C), 139.6 (C), 157.3 (CH), 158.1 (C), 165.0 (C). EI-MS (*m/z*): 359 (18), 358 (M^+, 68%), 357 (16), 326 (27), 325 (100), 279 (15), 267 (11), 252 (5), 240 (7), 184 (13), 162 (9), 147 (21), 91 (30).

[4-(3,4-Dichlorophenyl-)3-benzyl-3H-thiazol-2-ylidene]pyrimidin-2-yl amine (2m). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 5.48 (2H, s), 6.91–7.32 (10H, m), 8.85 (2H, d, $J = 5.1$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 47.8 (CH_2), 107.5 (CH), 112.4 (CH), 124.0 (CH), 126.5 (2CH), 127.2 (CH), 128.2 (2CH), 130.0 (2CH), 130.4 (C), 136.4 (C), 137.0 (2C), 148.2 (C), 157.0 (2CH), 162.4 (C), 163.2 (C). EI-MS (*m/z*): 413 (M^+, 64%), 360 (2), 347 (29), 345 (22), 344 (87), 298 (19), 283 (7), 253 (8), 185 (25), 183 (12), 169 (28), 91 (100).

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