One- Pot synthesis and reactions of Novel 5-(4-fluoro-phenyl)-3-(8-hydroxyquinolin-5-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile as antimicrobial agents

Shawkat A. Abdelmohsen
Chemistry Department, Faculty of Science, Assiut University, Assiut, 71516, Egypt

Síntesis y reacciones del nuevo 5-(4-fluor-fenil)-3-(8-hidroxiquinolin-5-il)-7-fenil-5H-tiazol[3,2-a] pirimidina-6-carbonitrilo como agente antimicrobiano en un único reactor.

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SUMMARY

The synthesis of 5-(4-fluoro-phenyl)-3-(8-hydroxyquinolin-5-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile **4** was achieved by one-pot three-component synthesis using *p*-TSA (10 mol %) in refluxing CH_3CN. Compound **4** was utilized to synthesize a new series of thiazolo[3,2-*a*]pyrimidines **6-8**, [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **10**, **11a-c** and **12a-c**. Also, derivatives of Schiff bases **13a-c** of compound **9** were obtained by the treatment with some aromatic aldehydes. The latter compounds underwent Mannich reaction with morpholin to afford the *N*-morpholinomethyl- amino derivatives **14a-c**. The structures of the new compounds are supported by FT IR, ^{1}H NMR, ^{13} CNMR, Mass spectroscopy and elemental analysis. All newly synthesized compounds were screened for their antimicrobial activity.

Keywords: One-pot reaction, thiazolo[3,2-*a*]pyrimidines, triazoles, triazolo[3,4-*b*] thiadiazoles, antimicrobial activity.

RESUMEN

La síntesis del 5-(4-flúor-fenil)-3-(8-hidroxiquinolin-5-il)-7-fenil-5*H*-tiazol[3,2-*a*]pirimidina-6-carbonitrilo **4** se conseguía mediante una síntesis de tres componentes en un solo reactor usando *p*-TSA (10 mol %) en el reflujo del CH_3CN. El compuesto **4** se utilizaba para sintetizar una nueva serie de triazol[3,2-*a*] pirimidinas **6-8**, [1,2,4]triazol[3,4-*b*][1,3,4]tiadiazoles **10**, **11a-c** y **12a-c**. Es decir, se obtenían derivados de las bases de Schiff **13a-c** del compuesto **9** mediante el tratamiento con algunos aldehídos aromáticos. Estos últimos compuestos se sometían a una reacción de Mannich con morfolina para dar los derivados *N*-morfolinometil-amino **14a-c**. Las estructuras de los nuevos compuestos son respaldadas por las técnicas de FT IR, ^{1}H NMR, ^{13}CNMR, espectroscopia de masas y análisis elemental. Todos los compuestos recién sintetizados eran sometidos a un screening para su actividad antimicrobiana.

Palabras clave: Reacción en un único reactor; triazol [3,2-*a*] pirimidinas; triazoles; triazol [3,4-*b*] tiadiazoles; actividad antimicrobiana

RESUM

La síntesi del 5-(4-flúor-fenil)-3-(8-hidroxiquinolin-5-il)-7-fenil-5*H*-tiazol[3,2-*a*]pirimidina-6-carbonitrilo **4** s'aconseguia per mitjà d'una síntesi de tres components en un únic reactor fent servir *p*-TSA (10 mol %) en el reflux del CH_3CN. El compost **4** s'utilitzava per sintetitzar una nova sèrie de triazol[3,2-*a*]pirimidinas **6-8**, [1,2,4]triazol[3,4-*b*][1,3,4]tiadiazoles **10**, **11a-c** y **12a-c**. Es a dir, s'obtenien derivats de les bases de Schiff **13a-c** del compost **9** per mitjà d'un tractament amb alguns derivats aromàtics. Aquests últims compostos

***Corresponding author: shawk662001@yahoo.com**

es sotmetien a una reacció de Mannich amb morfolina per donar els derivats *N*-morfolinometil-amino **14a-c**. Les estructures dels nou compostos es troben recolzades per les tècniques de FT IR, ^{1}H NMR, ^{13}CNMR, espectroscòpia de masses i anàlisis elemental. Tots els compostos acabats de sintetitzar es sotmetien a un screening per la seva activitat antimicrobiana.

Paraules clau: Reacció en un únic reactor; triazol [3,2-*a*] pirimidinas; triazoles; triazol[3,4-*b*]tiadiazoles; activitat antimicrobiana

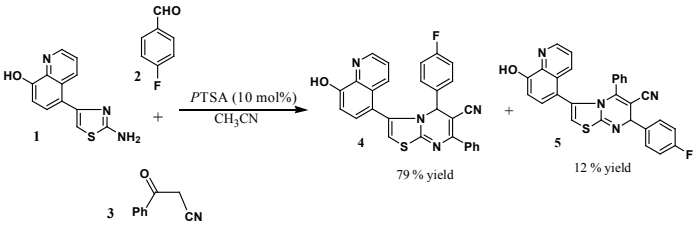
INTRODUCTION

In recent years, increasing interest has been focused on synthesis of thiazolopyrimidines due to their ability to inhibit 2-methylerythritol-2,4-cyclodiphosphate synthase. [1] They have been also used as analgesic, antiparkinsonian agents, [2] anticancer agents, [3-5] phosphate inhibitors [6] and acetylcholinesterase inhibitors.[7] Various condensed thiazolopyrimidines have been reported as antimicrobial substances, [8-10] anti-inflammatory [11] and antiviral activity and as inhibitors of HIV-1 reverse transcriptase.[12] A variety of synthetic methods have been reported for preparation of thiazolopyrimidine derivatives. One of the commonest methods involves cyclization of dihydropyrimidinethiones with 1,2-dielectrophiles such as 2-bromoketones, [13] chloroacetyl chloride,[14] chloroacetic acid, [11, 12, 15] methyl chloroacetate [16] and *N*-aryl-2-chloroacetamides.[17] Most of these methods involve two steps: Biginelli reaction as well as cyclization. To the best of our knowledge, there is no direct route for construction of the thiazolopyrimidine scaffold in a one-pot procedure. Nowadays, multicomponent domino reactions (MDRs), particularly those performed in aqueous media, have become an increasingly useful tool for the synthesis of chemically and biologically important compounds because of their convergence, atom economy, and other suitable characteristics from the point of view of green chemistry. [18–22] With all the above facts in mind and as a part of our program directed towards the synthesis of heterocycles derived from 5-(2-aminothiazol-4-yl)-8-hydroxyquinoline of potential biological interest, [10, 23] we aimed to report herein the one-pot three component synthesis of 5-(4-fluoro-phenyl)-3-(8-hydroxyquinolin-5-yl)-7-phenyl-5*H*-thiazolo[3,2-a] pyrimidine-6-carbonitrile 4 as a conveniently accessible precursor for the synthesis of thiazolo[3,2-a] pyrimidines and other related 1,2,4-triazoles and triazolo[3,4-*b*][1,3,4]thiadiazol systems.

RESULTS AND DISCUSSION

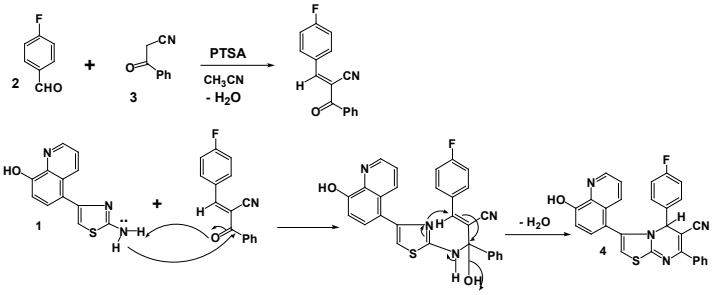
Chemistry

In this paper and as a consequence of our previous work on the green synthesis of heterocyclic compounds of biological interest, [24-26] we investigated a novel green and efficient protocol that was developed for the construction of pyrido[2,3-*d*][1,3] thiazolo[3,2-*a*]pyrimidine moiety **4** *via* the one –pot three component condensation of 5-(2-aminothiazol-4-yl)-8-hydroxyquinoline **1**, 4-fluorobenzaldehyde **2** and benzoylacetonitrile **3** using *p*-toluene sulphonic acid (10 mol%) in refluxing acetonitrile to give the two isomeric mixture of thiazolo[3,2-*a*]pyrimidines **4** and **5** as shown in Scheme 1. In our initial study, we tried to optimize the model procedure mentioned above by detecting the efficiency of different solvent conditions, H_2O, EtOH, MeOH, DCM, $CHCl_3$, THF and CH_3CN as well as, catalyst amount. In each case, the reactants (10 mmol) were allowed together in 10 mL solvent at reflux temperature and in the presence of different amount of *p*-TSA. It was found that CH_3CN was the most suitable solvent for this transformation among others, which afforded the yields of 29-53%. After extensive screening of the mole ratio (5, 10, 15, 20 mol %) of *p*-TSA, we found that 10 mol % was suitable for maximum conversion of product (79% yield) and it was clear that the increase in the mole ratio did not improve neither the yield nor the reaction time (Scheme 1).



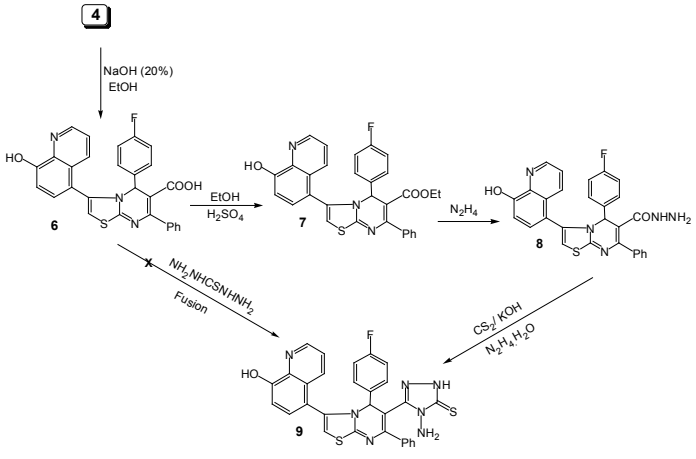
Scheme 1. *Synthetic pathways for the formation of* **4** *and* **5**

The formation of compounds **4** as a major rather than the isomeric **5** was confirmed by the ^{1}H-NMR and ^{13} C-NMR spectra. The chemical shift for the pyrimidine CH-5 and CH-7 for both compounds is markedly affected by the nature of the adjacent nitrogen. [24,27,28] The ^{1}HNMR spectral data of compound **4** showed that δ-values at 4.4 ppm attributed to the pyrimidine CH-5 that near to the sp^3 nitrogen (pyrrole type), differs from δ-values of the pyrimidine CH-7 in compounds **5** that adjacent to sp^2 nitrogen (pyridine type) which appeared at 3.5 ppm. Also, the preference for structures **4** over **5** was shown by ^{13} CNMR spectra. Thus, the ^{13}C-NMR (DMSO-d_6) of **4**, showed a singlet at δ 45.5 ppm that correspond to the pyrimidine CH-5 (pyrrole type). Whereas, ^{13}C-NMR (DMSO-d_6) of **5** displayed a singlet at δ 62.9 ppm, due to the pyrimidine CH-7 (pyridine type), respectively. The plausible mechanism for the formation of **4** was depicted in scheme 2.



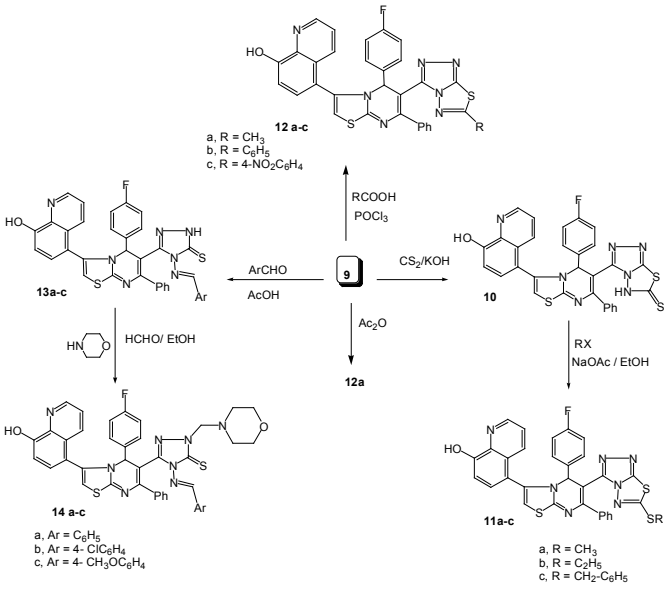
Scheme 2. *One –pot three component mechanistic pathway for the formation of* **4**

A further confirmation of structure **4** could be obtained by the alkaline hydrolysis of the cyano group in compound **4** to yield the corresponding 5-(4-fluoro phenyl_-3-(8-hydroxyquniolin-5-yl)-7-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-carboxylic acid **6**. IR spectra of **6** showed the absence of absorption band at 2220 cm^{-1} for CN function in compound **4** and gave a broad band at 3020-2790 and 1710 cm^{-1} attributed to OH and C=O of carboxylic group, respectively. Esterification of compound **6** with absolute ethanol in presence of conc H_2SO_4, afforded the corresponding 6-ethyl carboxylate derivative **7**. IR spectrum of compound **7**, showed an absorption band at 1747 cm^{-1} due to C=O ester group. Hydrazonolysis of **7** by treatment with hydrazine hydrate gave the acid hydrazide derivative **8**. In the IR spectrum of **8**, N-H function was observed at 3336-3257 cm^{-1}, which was absent in precursor **7**. In the ^{1}H NMR spectrum, the characteristic proton of the CONH group was observed at δ 9.25 ppm as a singlet. The reaction of **8** with carbon disulphide and potassium hydroxide followed by the treatment with hydrazine hydrate, furnished 4-amino-5-[5-(4-fluorophenyl)-7-phenyl-3-(8-hydroxyquinolin-5-yl)-5*H*-[1,3]thiazolo[3,2-*a*] pyrimidin-6-yl]-4*H*-1,2,-triazole-3-thiol **9**. Alternatively, the triazole **9** could not be synthesized *via* the fusion of **6** with thiocarbohydrazide due to its high melting point (233 °C) in which the thiocarbohydrazide undergoes decomposition (169-174 °C). The IR spectra of compound **9** showed absorption bands at 3360, 3270, 3160 and 1210 cm^{-1} attributed to NH_2, NH and C=S groups, respectively. Its ^{1} HNMR spectra displayed two characteristic singlets at 11.3 and 5.85 ppm corresponding to NH and NH_2, respectively (Scheme 3). The amino and mercapto groups are ready-made nucleophilic centers for the synthesis of condensed heterocyclic rings. Thus, the ring closure of s-triazole **9** with carbon disulphide in methanolic potassium hydroxide formed 5-[5-(4-fluorophenyl)-6-(6-mercapto-[1,2,4]triazolo[3,4-*b*]-3-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinoline-8-ol **10**, which when treated with methyl iodide, ethyl iodide and benzyl bromide afforded the s-alkylating products **11a-c**, in good yields. A one-step preparation of 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles **12a-c**, from the corresponding 4-aminotriazole **9** and carboxylic acids by prolonged heating with phosphoryl chloride was achieved.



Scheme 3. *Synthetic pathways for the formation of* **6**-**9**

It is worthy to note that compound **12a** (R = CH_3) could be obtained, in a rather better yield: (88 %), directly by the reaction of **9** with acetic anhydride. The IR spectrum of **12a** showed no NH bands and the ^{1}H NMR spectrum showed a singlet at 2.66 ppm corresponding to the methyl substituent at position 6 (Scheme 4). The desired triazole Schiff bases **13a-c**, were prepared by heating compound **9** and appropriate aldehydes in glacial acetic acid. The ^{1}H NMR spectrum of **13a-c**, displayed the characteristic peaks at 9.3-9.45 and 10.96-11.20 ppm attributed to the imine and triazole NH protons. Mass spectrum of compound **13b** as an example showed a peak analogous to the molecular ion at m/z 688.17 (M^+, 62%). Mannich base formation can take place at the triazole NH protons in compounds **13a-c** by condensing with formaldehyde and morpholine to give the corresponding *N*-morpholinomethyl products **14a-c**. The ^{1}H-NMR spectra of compounds **14a-c** showed the absence of triazole NH proton signals and displayed characteristic >N-CH_2-N< signals at around δ 4.48-4.52 ppm , beside to broad singlets at 2.50-2.58 and 3.30-3.38 ppm due to the $N(CH_2)_2$ and $O(CH_2)_2$ of the morpholine moiety, reinforced the formation of compounds **14a-c** (Scheme 4).



Scheme 4. *Synthetic pathways for the formation of* **10**-**14a-c**

PHARMACOLOGICAL STUDIES

Antimicrobial Activity

In *vitro* antimicrobial activity was carried out by using the agar well-diffusion method. [29] All of the newly synthesized compounds **4-14a-c** was initially evaluated for their antibacterial activity against *Staphylococcus aureus* (AUMC B.54), *Bacillus cereus* (AUMC B.52) as a Gram positive bacteria and *Escherichia coil* (AUMC B.53), *and Pseudomonas aeruginosa* (AUMC B. 73) as Gram negative bacteria using chloramphenicol as control. The antifungal activity was investigated against Candida albicans (AUMC No. 418) and Aspergillus

flavus (AUMC No. 1276) using Clotrimazole as control. The results were recorded for each tested compound as the mean diameter of inhibition zone of bacteria or fungal growth around the discs in mm in Table 1. It was observed that compounds **9**, **10**, **12b** and **14c** exhibited the highest activity against *S.aureus* and *E. coli.* Compound **11b** displayed an equipotent to chloramphenicol in inhibiting the growth of *S.aureus* and *B cereus.* Whereas, Compound **13b** showed a remarkable activity against *B. cereus* and *P. aeruginosa*. On the other hand, compound **14c** gave the highest antifungal activity against both of tested fungi species *C.albicans* and *A flavus.* While, compounds **11c** and **13b** were almost equipotent to clotrimazole in inhibiting the growth of *C.albicans* only. Other compounds exhibited weak activity against *C. albicans* and *A flavus* as compared to standard Clotrimazole (Table 1).

Table 1. *Antimicrobial activity of the newly thiazolo[3,2-a] pyrimidines*

Compound No.	Mean zone inhibition (in mm)[a,b]					
	Gram (+) bacteria		Gram (-) bacteria		Fungi	
	S.aureus	*B. cereus*	*E.coli*	*P. aeruginosa*	*C.albicans*	*A flavus*
4	11	10	10	-	13	-
6	8	15	13	9	-	-
7	10	-	13	-	-	-
8	14	-	-	19	-	-
9	31	-	29	19	12	10
10	33	18	26	12	7	18
11a	14	-	-	-	-	-
11b	28	26	-	-	18	-
11c	15	16	17	12	26	18
12a	-	-	-	-	8	-
12b	36	20	28	-	-	17
12c	15	11	-	-	-	-
13a	6	-	16	33	10	11
13b	-	30	-	33	25	-
13c	13	17	9	13	-	-
14a	-	15	14	-	-	-
14b	18	-	-	-	9	13
14c	29	25	25	-	34	44
Chlorampenicol	28	26	20	32	-	-
Clotrimazole	-	-	-		26	40

[a] Values are mean (n= 3)

[b] All the test and the standard drug were tested at the concentration of 20 mg/ml

'–' indicates no sensitivity or mean inhibition zone diam eter lower than 7 mm

CONCLUSION

It is concluded that the present work provides a convenient and efficient route for the preparation of new thiazolo [3,2-*a*] pyrimidines, **4**, **6**, **7** and **8** and their derived *N*-aminotriazole thiols **9**, Schiff bases **13a-c**, Mannich products **14a-c** and triazolo[3,4-*b*] thiadiazoles, **10**, **11a-c** and **12a-c**. All of the newly synthesized compounds have been screened for their antimicrobial activities. Compounds **9**, **10**, **12b** and **14c** exhibited the highest activity against *S.aureus* and *E. coli.* Compound **13b** showed a remarkable activity against *B. cereus* and *P. aeruginosa*. Compounds **11c** and **13b** exihibited an equipotent activity against *C.albicans* only. Other compounds exhibited no or weak activity against the tested microorganisms. This results may serve as a ready reference for the researchers to take advantage of proficient procedure applied for the synthesis of novel series of derivatives and further plausible modifications which will augment the therapeutic potential of thiazolo [3,2-*a*] pyrimidine derivatives.

EXPERIMENTAL

Melting points are uncorrected and determined using a Gallenkamp melting point apparatus. IR spectra were recorded on a Pye-Unicam SP 3-100 spectrophotometer using the KBr Wafer technique. ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer and on GNM-LA (400 MHz) in DMSO-d_6 as a solvent and TMS as internal standard. Chemical shifts are expressed in ppm. ^{13}C NMR spectra were measured on a Varian EM-200, 100 MHz spectrometer. Mass spectra were determined on a JEOL JMS-600 spectrometer. Elemental analyses were carried out in the Microanalytical Unit at the at Assiut University (Egypt). Compound **1** was synthesized using reported procedure. [23]

General procedure for the Synthesis of 3-(8-hydroxyquinolin-5-yl)-thiazolo[3,2-*a*] pyrimidine-6-carbonitriles 4 and 5 A mixture of 5-(2-Aminothiazol-4-yl)-8-hydroxyquinoline **1** (2.43 g, 10 mmol), 4-fluorobenzaldehyde **2** (1.24 g, 10 mmol), benzoylacetonitrile **3** (1.45 g, 10 mmol), and *PTSA* (2.47 g, 20.00 mmol) was dissolved in acetonitrile (30 mL) and the resulting solution was refluxed for 3 h. After the completion of reaction the reaction mixture was cooled to room temperature and extracted with $CHCl_3$ (3 X 25 mL), washed successively with water (2 x 25 mL), 2% dilute HCl solution and dried over anhydrous Na_2SO_4. The residue was purified by preparative layer chromatography (PLC) [silica gel (F254) powder; petroleum ether–ethyl acetate (10:2)]. The solvent was removed under reduced pressure and the products were obtained.

5-(4-Fluoro-phenyl)-3-(8-hydroxyqinolin-5-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (4). Orange solid, yield 79% (3.76 g), m.p. 208-210 °C. IR (KBr) : 2220 (CN), 1625 (C=N) cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.09- 8.60 (m, 15 H, Ar-H), 6.55 (s, 1H, thiazole H-2), 4.40 (s, 1H, pyrimidine H-5). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.43, 161.57, 158.43 (d, J_{F-C} = 243.2 Hz, C_{Ar-F}), 153.28, 150.77, 145.33, 142.46, 138.22, 135.01 (2C), 133.25, 131.40, 129.58, 128.51 (2C), 126.43 (2C), 125.71, 124.19, 122.24, 122.11, 116.27, 112.55 (2C), 111.34, 95.07, 86.25, 45.40. MS: *m/e* 476.3 (M^+, 23%). Anal. Calculated for $C_{28}H_{17}FN_4OS$ (476.52): C, 70.57; H, 3.60; N, 11.76; S, 6.73. Found: C, 70.75; H, 3.83; N, 11.92; S 7.06.

7-(4-Fluoro-phenyl)-3-(8-hydroxyqinolin-5-yl)-5-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (5). Orange solid, yield 12% (0.57 g), m.p. 268-270 °C. IR (KBr): 2225 (CN), 1630 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.95-8.80 (m, 15 H, Ar-H), 6.58 (s, 1H, thiazole H-2), 3.50 (s, 1H, pyrimidine H-7). ^{13}C NMR (100 MHz, DMSO-d_6): δ =163.46, 160.33, 158.51 (d, J_{F-C} = 244.4 Hz, C_{Ar-F}), 153.29, 151.11, 148.17, 143.49, 139.34, 135.11 (2C), 133.63, 130.29, 129.52, 128.77 (2C), 126.38 (2C), 125.92, 123.60, 122.44, 121.16, 117.23, 112.81 (2C), 111.70, 98.11, 88.13, 62.90. Anal. Calculated for $C_{28}H_{17}FN_4OS$ (476.52): C 70.57, H 3.60, N 11.76, S 6.73; found: C 70.85, H 3.49, N 11.43, S 7.11.

Synthesis of 5-(4-fluoro-phenyl)-3-(8-hydroxyqinolin-5-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*] pyrimidine-6-carboxylic acid (6)

A mixture of **4** (1.425 g, 3 mmol) and aqueous sodium hydroxide (15 mL 10%) in ethanol (20 mL) was heated under reflux for 3 h, then neutralized with diluted HCl. The solid precipitate that formed was filtered off, washed with water and crystallized from dioxane to give **6** as pale yellow needles, yield 69% (1.02 g), m.p. 233-235 °C. IR (KBr): 3020-2790 (br, OH), 1710 (C=O), 1628 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.90- 8.55 (m, 15 H, Ar-H), 6.65 (s, 1H, thiazole H-2), 4.65 (s, 1H, pyrimidine H-5). Anal. Calculated for $C_{28}H_{18}FN_3O_3S$ (495.52): C 67.87, H 3.66, N 8.48, S 6.47; Found: C 67.48, H 3.44, N 8.86, S 6.72.

Synthesis of ethyl-5-(4-fluoro-phenyl)-3-(8-hydroxyqinolin-5-yl)-7-phenyl-5*H*-thiazolo [3,2-*a*]pyrimidine-6-carboxylate (7)

A mixture of **6** (2.47 g, 5 mmol) and H_2SO_4 (15 mL) in ethanol (40 mL) was heated under reflux for 5 h, then left to cool. The yellow crystals that formed were filtered off, washed with water and crystallized from ethanol to give **7** as yellow needles, yield 66% (1.73 g), m.p. 195-197 °C. IR (KBr): 1747 (C=O), 1633 (C=N) cm^{-1}, ^1H NMR(400 MHz, DMSO-d_6): δ = 6.99- 8.68 (m, 15 H, Ar-H), 6.70 (s, 1H, thiazole H-2), 4.70 (s, 1H, pyrimidine H-5), 4.25 (q, *J* = 6.9 Hz, 2H, CH_2), 1.35 (t, *J* =7.8 Hz, 3H, CH_3). Anal. Calculated for $C_{30}H_{22}FN_3O_3S$ (523.58): C 68.82, H 4.24, N 8.03, S 6.12; Found: C 69.13, H 4.45, N 7.89, S 6.38.

Synthesis of 5-(4-fluoro-phenyl)-3-(8-hydroxyqinolin-5-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*] pyrimidine-6-carbohydrazide (8)

A mixture of **7** (1.57 g, 3 mmol) and hydrazine hydrate (7 mL, 80%) in ethanol (30 mL) was heated under reflux for 1 h. The solid precipitate that formed was filtered off, washed with water and crystallized from ethanol to give **8** as yellow needles, yield 71% (1.08 g), m.p. 215-217 °C. IR(KBr): 3336, 3257 (NH, NH_2), 1710 (C=O), 1621 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.25 (s, 1H, NH), 6.90- 8.55 (m, 15 H, Ar-H), 6.69 (s, 1H, thiazole H-2), 4.77 (s, 1H, pyrimidine H-5), 4.28 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.13, 161.41, 159.11 (d, J_{F-C} = 240.7 Hz, C_{Ar-F}), 157.91, 153.33, 150.32, 146.29, 143.88, 138.36, 135.16 (2C), 132.93, 131.44, 129.00, 127.76 (2C), 125.88 (2C), 125.04, 123.77, 121.91, 120.22, 117.66, 114.62 (2C), 113.55, 101.19, 49.30. Anal. Calculated for $C_{28}H_{20}FN_5O_2S$ (509.55): C 66.00, H 3.96, N 13.74, S 6.29; Found: C 66.37, H 4.19, N 13.63, S 6.09.

Synthesis of 5-[6-(4-amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-5-(4-fluoro-phenyl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (9)

A mixture of **8** (2.03 g, 4 mmol), potassium hydroxide (0.22 g, 4 mmol), carbon disulphide (8 mL) and ethanol (25 mL) was heated under reflux until the evolution of H_2S ceases. The reaction mixture was concentrated, dissolved in water and acidified with HCl. The resulting product is treated with hydrazine hydrate (20 mL) in ethanol under reflux condition for 7-8 hrs. After completion of reaction, the contents were poured into ice cold water which on neutralization by glacial acetic acid. The resulting product was filtered, dried and crystallized from ethanol to give **9** as orange crystals, yield 66% (1.50 g), m.p. 320-322 °C. IR (KBr): 3360, 3270, 3160 (NH, NH_2), 1621 (C=N), 1210 (C=S) cm^{-1}. ^1H NMR (90 MHz, DMSO-d_6): δ = 11.30 (s, 1H, NH), 6.85- 8.67 (m, 15 H, Ar-H), 6.65 (s, 1H, thiazole H-2), 5.70 (s, 2H, NH_2), 4.60 (s, 1H, pyrimidine H-5). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.12, 160.09, 158.17 (d, J_{F-C} = 240.4 Hz, C_{Ar-F}), 153.49, 150.30, 146.40 (2C), 139.81, 137.63, 135.05, 134.72, 132.66, 130.15 (2C), 129.11 (2C), 128.22, 127.54, 126.98, 126.33, 125.65 (2C), 123.71, 121.90, 115.33 (2C), 111.54, 84.90, 48.60. MS: *m/e* 565.65 (M^+, 47%). Anal. Calculated for $C_{29}H_{20}FN_7OS_2$ (565.64): C 61.58, H 3.56, N 17.33, S 11.34; Found: C 61.88, H 3.42, N 17.09, S 1.69.

Synthesis of 5-[5-(4-fluorophenyl)-6-(6-mercapto-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl] -quinolin-8-ol (10)

To a solution of **9** (2.82 g, 4 mmol) in methanol (40 mL), KOH (2.5 g) and CS_2 (8 mL) were added and the reaction mixture was refluxed for 2 h. The solvent was removed under reduced pressure, and then the residue was poured into an ice-water mixture with stirring. The solid product obtained was washed with water, filtered and recrystallized from ethanol to give **10** as yellow crystals, yield 80% (1.90 g), m.p. 177-179 °C. IR (KBr): 3190 (NH), 1631 (C=N), 1217 (C=S) cm^{-1}. ^1H NMR (90 MHz, DMSO-d_6): δ = 11.25 (s, 1H, NH), 6.88- 8.77 (m, 15 H, Ar-H),

6.68 (s, 1H, thiazole H-2), 4.55 (s, 1H, pyrimidine H-5). MS: *m/e* 606.21 (M^+, 63%). Anal. Calculated for $C_{30}H_{18}FN_7OS_3$ (607.70): C 59.29, H 2.99, N 16.13, S 15.83; Found: C 59.64, H 2.83, N 15.88, S 16.08.

General procedure for the synthesis of 5-[5-(4-Fluorophenyl)-6-(6-substitued thio-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadzol-3-yl)-7phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (11a-c)

A mixture of **10** (1.82 g, 3 mmol), methyl iodide, ethyl iodide and/or benzyl bromide (3 mmol) in etha-

nol (50 mL) was refluxed in the presence of anhydrous sodium acetate (1.5 g) for 4 h. The solid product separated from the hot mixture was filtered off, washed with water and recrystallized from dioxane.

5-[5-(4-Fluorophenyl)-6-(6-methyltio-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-7-phnyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (11a). Yellow crystals, yield 73% (1.36 g), m.p. 146-148°C. IR (KBr): 2980 (CH-aliphatic), 1627(C=N), 1170 (C-S) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.85- 8.69 (m, 15 H, Ar-H), 6.70 (s, 1H, thiazole H-2), 5.11 (s, 1H, pyrimidine H-5), 2.55 (s, 3H, CH_3). %). ^{13}C NMR (100 MHz, DMSO-d_6): δ =161.44, 155.37 (d, J_{F-C} = 244.6 Hz, C_{Ar-F}), 151.36, 149.22, 144.87 (2C), 138.55, 136.69, 135.18, 134.66, 132.19, 131.85 (2C), 130.14 (2C), 128.87, 128.00, 127.11, 126.13, 125.66 (2C), 122.91, 120.24, 114.79 (2C), 113.49 (2C), 110.45, 88.76, 51.93, 19.66. Anal. Calculated for $C_{31}H_{20}FN_7OS_3$ (621.73): C 59.89, H 3.24, N 15.77, S 15.47; Found: C 60.25, H 3.37, N 15.39, S 15.08.

5-[5-(4-Fluorophenyl)-6-(6-ethylthio-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-7-phnyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (11b). Yellow crystals, yield 67% (1.3 g), m.p. 116-118 °C. IR(KBr): 2995 (CH-aliphatic), 1622 (C=N), 1163 (C-S) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.09- 8.57 (m, 15 H, Ar-H), 6.55 (s, 1H, thiazole H-2), 4.75 (s, 1H, pyrimidine H-5), 4.15 (q, *J* = 7.4 Hz, 2H, CH_2), 1.27 (t, *J* = 7.4 Hz, 3H, CH_3). Anal. Calculated for $C_{32}H_{22}FN_7OS_3$ (635.76): C 60.45, H 3.49, N 15.42, S 15.13; Found: C 60.13, H 3.82, N 15.68, S 14.79.

5-[5-(4-Fluorophenyl)-6-(6-benzylthio-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (11c). Yellow crystals, yield 61%, m.p. 161-163 °C. IR (KBr): 2998 (CH-aliphatic), 1626 (C=N), 1177 (C-S) cm^{-1}. ^1H NMR(400 MHz, DMSO-d_6): δ = 6.88- 8.80 (m, 15 H, Ar-H), 6.57 (s, 1H, thiazole H-2), 4.60 (s, 1H, pyrimidine H-5), 4.20 (s, 2H, CH_2). Anal. Calculated for $C_{37}H_{24}FN_7OS_3$ (697.83): C 63.68, H 3.47, N 14.05, S 13.78; Found: C 63.90, H 3.58, N 14.33, S 13.44.

General procedure for the synthesis of 5-[5-(4-Fluorophenyl)-6-(6-alkyl/aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-7-phnyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (12a-c)

Method A: A mixture of **9** (1.13 g, 3 mmol) and aliphatic and/ or aromatic acids (3 mmol) in phosphoryl chloride (10 mL) was heated under reflux for 5 h. After cooling, the solvent was removed under reduced pressure and an ice-water mixture was added to the residue with stirring. The reaction mixture was neutralized with ammonium hydroxide and the solid precipitate formed was filtered and recrystallized from ethanol to give **12a-c**.

Method B: A mixture of **9** (0.56 g, 1 mmol) and acetic anhydride (10 mL) was heated under reflux for 2 h. After cooling, an ice-water mixture was added to the residue with stirring and the solid precipitate formed was filtered and recrystallized from ethanol to give **12a**. Yield 88% (0.49 g), m.p. and mixed m.p. with a sample obtained by the above procedure are identical.

5-[5-(4-Fluorophenyl)-6-(6-methyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (12a). Yellow crystals, yield 73% 044 g), m.p. 211-213 °C. IR (KBr): 2880 (CH-aliphatic), 1633 (C=N) cm^{-1}. ^1H NMR (90 MHz, DMSO-d_6): δ = 6.89- 8.77 (m, 15 H, Ar-H), 6.69 (s, 1H, thiazole H-2), 4.67 (s, 1H, pyrimidine H-5), 2.35 (s, 3H, CH_3). Anal. Calculated for $C_{31}H_{20}FN_7OS_2$(589.67): C 63.14, H 3.42, N 16.63, S 10.88; Found: C 63.45, H 3.73, N 16.41, S 10.59.

5-[5-(4-Fluorophenyl)-6-(6-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (12b).Yellow crystals, yield 57% (0.32 g), m.p. 271-273 °C. IR (KBr): 3010 (CH-aromatic, 2890 (CH-aliphatic), 1630 (C=N) cm^{-1}. ^1H NMR(90 MHz, DMSO-d_6): δ = 6.95- 8.80 (m, 20 H, Ar-H), 6.55 (s, 1H, thiazole H-2), 4.58 (s, 1H, pyrimidine H-5). Anal. Calculated for $C_{36}H_{22}FN_7OS_2$ (651.73): C 66.34, H 3.40, N 15.04, S 9.84; Found: C 66.72, H 3.70, N 15.36, S 9.62.

5-[5-(4-Fluorophenyl)-6-(6-(4-nitrophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (12c).Yellow crystals, yield 65% (0.36 g), m.p. 305-307 °C. IR (KBr): 3055 (CH-aromatic, 2895 (CH-aliphatic), 1629 (C=N) cm^{-1} ^1H NMR(400 MHz, DMSO-d_6): δ = 6.99- 8.87 (m, 19 H, Ar-H), 6.62 (s, 1H, thiazole H-2), 4.50 (s, 1H, pyrimidine H-5). Anal. Calculated for $C_{36}H_{21}FN_8O_3S_2$ (696.73): C 62.06, H 3.04, N 16.08, S 9.20; Found: C 62.39, H 2.79, N 16.76, S 9.55.

General procedure for the synthesis of 5-[6-[4-(substituted benzylidene amino)-5-mercapto-4*H*-(1,2,4) triazole-3-yl]-5-(4-fluoro-phenyl)-7-phenyl-5*H*-thiazolo[3,2-*a*]-pyrimidin-3-yl]-quinolin-8-ol (13a-c)

Equimolar amounts of **9** and appropriate aromatic aldehydes (2 mmol) in glacial acetic acid (5 mL) were heated under reflux for 2 h. The mixture was then cooled to room temperature, filtered and washed with water. The obtained solids were recrystallized from ethanol to afford the Schiff bases **13a-c**.

5-[6-[4-(Benzylidene-amino)-5-mercapto-4*H*-(1,2,4)triazole-3-yl]-5-(4-fluoro-phenyl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (13a). Yellow crystals, yield 66% (0.86 g), m.p. 229-231°C. IR (KBr): 3390 (NH), 3020 (CH-aromatic), 1631 (C=N) cm^{-1}. ^1H NMR (90 MHz, DMSO-d_6): δ = 10.96 (s, 1H, NH), 9.30 (s, 1H, N=CH), 6.95- 8.80 (m, 20 H, Ar-H), 6.67 (s, 1H, thiazole H-2), 4.49 (s, 1H, pyrimidine H-5). Anal. Calculated for $C_{36}H_{24}FN_7OS_2$ (653.75): C 66.14, H 3.70, N 15.00, S 9.81; Found: C 65.77, H 3.96, N 15.39, S 10.02.

5-[6-[4-(4-Chlorobenzylidene-amino)-5-mercapto-4H-(1,2,4)triazole-3-yl]-5-(4-fluoro-phenyl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl]-quinolin-8-ol (13b). Yellow crystals, yield 71% (0.96 g), m.p. 154-156°C. IR (KBr): 3377 (NH), 3010 (CH-aromatic), 1623 (C=N) cm^{-1}. ^1H NMR (90 MHz, DMSO-d_6): δ = 11.15 (s, 1H, NH), 9.38 (s, 1H, N=CH), 6.97- 8.86 (m, 19 H, Ar-H), 6.60 (s, 1H, thiazole H-2), 4.53 (s, 1H, pyrimidine H-5). MS: *m/e* 688.17.65 (M^+, 62%). Anal. Calculated for $C_{36}H_{23}ClFN_7OS_2$ (688.20): C 62.83, H 3.37, Cl 5.15, N 14.25, S 9.32; Found: C 63.08, H 3.52, Cl 4.91, N 14.58, S 8.96.

5-[6-[4-(4-Methoxybenzylidene-amno) -5-mercapto-4*H*-(1,2,4)triazole-3-yl]-5-(4-fluoro-phenyl)-7-phenyl-5*H*-thiazolo[3,2-*a*] pyrimidin-3-yl]-quinolin-8-ol (13c).

Yellow crystals, yield 59% (0.8 g), m.p. 261-263°C. IR (KBr): 3325 (NH), 3018 (CH-aromatic), 1635 (C=N), 1210 (C-O) cm^{-1}. ^1H NMR (90 MHz, DMSO-d_6): δ = 11.20 (s, 1H, NH), 9.45 (s, 1H, N=CH), 6.79- 8.90 (m, 19 H, Ar-H), 6.54 (s, 1H, thiazole H-2), 4.60 (s, 1H, pyrimidine H-5), 3.35 (s, 3H, CH_3). Anal. Calculated for $C_{37}H_{26}FN_7O_2S_2$ (683.78): C 64.99, H 3.83, N 14.34, S 9.38; Found: C 64.63, H 4.09, N 14.13, S 9.77.

General procedure for the synthesis of 4-(substituted benzylidene-amino)-5-[5-(4-fluoro-phenyl)—3-(8-hydroxyquniolin-5-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]-2-morpholin-4yl-methyl-[1,2,4] triazole-3-thione (14a-c)

Formalin 40% (1 mL) was added to a stirred solution of **13a-c** (5 mmol) in absolute ethanol (40 mL). An ethanolic solution (10 mL) of morpholin (5 mmol) was added portionwise to the reaction mixture, stirred for 3 h at room temperature, and left overnight in a refrigerator. The precipitate formed was filtered, washed with cold ethanol, dried, and crystallized from ethanol to afford compounds **14a-c**.

4-(Benzylidene-amino)-5-[5-(4-fluoro-phenyl)-3-(8-hydroxyquniolin-5-yl)-7-Phenyl--5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]-2-morpholin-4ylmethyl-[1,2,4]triazole-3-thione (14a). Yellow crystals, yield 73% (2.37 g), m.p. 187-189°C. IR (KBr): 2990, 2885 (CH-aliphatic), 1618 (C=N), 1377 (C=S) cm^{-1}. ^1H NMR(400 MHz, DMSO-d_6): δ = 9.30 (s, 1H, N=CH), 6.81- 8.99 (m, 20 H, Ar-H), 6.69 (s, 1H, thiazole H-2), 4.65 (s, 1H, pyrimidine H-5), 4.48 (s, 2H, N-CH_2-N), 3.30 (brs, 4H, 2CH_2-O), 2.50 (brs, 4H, 2CH_2-N). Anal. Calculated for $C_{41}H_{33}FN_8O_2S_2$ (752.88): C 65.41, H 4.42, N 14.88, S 8.52; Found: C 65.80, H 4.73, N 15.23, S 8.26.

4-(4-Chlorobenzylidene-amino)-5-[5-(4-fluoro-phenyl)—3-(8-hydroxyquniolin-5-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]-2-morpholin-4ylmethyl-[1,2,4] triazole-3-thione (14b). Yellow crystals, yield 59% (2.0 g), m.p. 199-201°C. IR (KBr): 2989, 2890 (CH-aliphatic), 1622 (C=N), 1371 (C=S) cm^{-1}. ^1H NMR (90 MHz, DMSO-d_6): δ = 9.55 (s, 1H, N=CH), 6.90- 8.99 (m, 19 H, Ar-H), 6.55 (s, 1H, thiazole H-2), 4.72 (s, 1H, pyrimidine H-5), 4.50 (s, 2H, N-CH_2-N), 3.35 (brs, 4H, 2CH_2-O), 2.58 (brs, 4H, 2CH_2-N). ^{13}C NMR (100 MHz, DMSO-d_6): δ =

162.03 (d, J_{F-C} = 240.9 Hz, C_{Ar-F}), 154.44, 150.67, 146.25, 141.35 (2C), 138.29, 137.11, 135.63, 133.26, 132.77 (2C), 131.81 (2C), 129.06, 128.19, 127.45, 126.22 (2C), 123.15, 119.55, 113.39 (2C), 111.12, 91.34, 78.66, 73.19 (2C), 55.11 (2C), 51.93, 46.32. Anal. Calculated for $C_{41}H_{32}ClFN_8O_2S_2$ (787.33): C 62.55, H 4.10, Cl 4.50, N 14.23, S 8.15; Found: C 62.88, H 4.44, Cl 4.21, N 14.42, S 8.54.

4-(4-Methoxybenzylidene-amino)-5-[5-(4-fluoro-phenyl)—3-(8-hydroxyquniolin-5-yl)-7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]-2-morpholin-4ylmethyl-[1,2,4] triazole-3-thione (14c). Yellow crystals, yield 66% (2.24 g), m.p. 233-235°C. IR (KBr): 2985, 2895 (CH-aliphatic), 1628 (C=N), 1369 (C=S), 1215 (C-O) cm^{-1}. ^1H NMR(90 MHz, DMSO-d_6): δ = 9.45 (s, 1H, N=CH), 6.95- 9.02 (m, 19 H, Ar-H), 6.58 (s, 1H, thiazole H-2), 4.68 (s, 1H, pyrimidine H-5), 4.52 (s, 2H, N-CH_2-N), 3.54 (s, 3H, CH_3), 3.38 (brs, 4H, 2CH_2-O), 2.55 (brs, 4H, 2CH_2-N). Anal. Calculated for $C_{42}H_{35}FN_8O_3S_2$ (782.91): C 64.43, H 4.51, N 14.31, S 8.19; Found: C 64.79, H 4.32, N 14.27, S 8.43.

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