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ARTICLE

Selective cyclization of S-substituted pyrimidinethione: Synthesis and antimicrobial evaluation of novel polysubstituted thiazolopyrimidine and thiazolodipyrimidine derivatives

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Abstract

The synthetic strategy is based on alkylation of 4-aryl-N-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide derivatives **IV a–g**, with some alkyl halides and α-haloketones, namely, methyl iodide, chloroacetonitrile, and phenacyl bromide to give the corresponding S-substituted derivatives **Va–c**. Treatment of **IVa–c** with ethyl bromoacetate in ethanol under reflux in the presence of potassium hydroxide solution led to the formation of N-(4-chlorophenyl)-7-methyl-3-oxo-5-(aryl)-2,3-dihydro-5H-thiazolo [3,2-a]pyrimidine-6-carboxamide derivative **VIII a–c** in a single-step synthesis. On the other hand, compound **IVa** reacted with α-halo carbonitriles, namely, chloro acetonitrile, and monobromo malononitrile, to produce directly thiazolo[3,2-a]pyrimidine derivatives **Xa** and **Xb**, respectively, Compound **Xb** also reacted with each of formic acid, formamide, and ammonium thiocyanate to form thiazolodipyrimidine derivatives **XI–XIII**, respectively. Compound **VIIIa–c** coupled with arenediazonium salts in pyridine to give the corresponding 2-arylhydrazo derivatives **XVIa–e**. Compounds **IV a–g** and **VIIIa–c** were resynthesized under microwave irradiation. Some of the newly synthesized compounds were tested for their antimicrobial activities.

KEYWORDS

alkylation, cyclization, multicomponent, pyrimidinethione, thiazolodipyrimidine

1 | INTRODUCTION

Fused heterocyclic pyrimidine derivatives have received considerable attention over the past years due to their therapeutic and pharmacological properties. Many fused triazolopyrimidines and tetrazolopyrimidines are well known for their antibacterial and antifungal activities.[1–3]

The biological importance of pyrimido [4,5-d] pyrimidines includes their use as fungicides and antioxidants.[4] Meanwhile, pyrimidopurines are famous for their use as inhibitors of spontaneous locomotor activity.[5] Some series of thiazolo[3,2-a]pyrimidine derivatives have been prepared and investigated for their anti-inflammatory[6] and anticancer activities.[7] On the other hand, functionalized 2-thioxopyrimidines are of considerable importance to chemists as excellent precursors for the synthesis of fused pyrimidines. They have been extensively utilized to prepare different fused heterocycles,

including thiazolo-,[8] triazolo-, pyrazolo-,[9] pyridothiazolo-,[10] and imidazothiazolo-pyrimidines.[11,12] Condensed pyrimidine derivatives have also been reported as antimicrobial and hypnotic drugs for the nervous system,[13] with activities including anti-inflammatory,[14] anti-HIV,[15] antiparasitic,[16] and antitumor and have been used as calcium-sensing receptor antagonists,[17] antiulceratives,[18] and antimalarial agents. They are also used as cardiovascular agents[19] and diuretic drugs.[20]

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Prompted by the diverse biological activities associated with fused heterocyclic annulated pyrimidines, this work has been dedicated for the synthesis of some S-substituted and N,S-disubstituted pyrimidine derivatives as precursors for di- and tricyclic fused pyrimidine derivatives. Thus, treatment of 4-chloroacetoacetanilide (**I**), the appropriate aromatic aldehydes **IIa–g** and thiourea in refluxing ethanol containing catalytic amount of concentrated hydrochloric acid, Biginelli type reactions,[21] afforded (**IV a–g**) in a good yield (Scheme 1).[22] The progress of reaction was monitored by TLC. The structures of compounds **IV a–g** were established on the basis of analytical and spectral data (Tables 1 and 2).

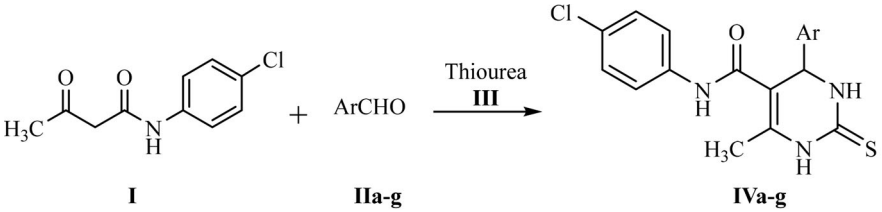
Compounds **IV a–g** were resynthesized under microwave irradiation conditions aiming to increase reaction yields and reduce the reaction times.[23,24] A comparison between MW and thermal reaction techniques is given in Table 3. From Table 3, we find that the use of MW technique improves the yield of the products by 17–23% compared with the conventional methods, and also the reaction times were considerably reduced.

Alkylation of compound **IVa** with some alkyl halides and α-haloketones, namely, methyl iodide, chloroacetonitrile, and phenacyl bromide in refluxing aqueous ethanolic potassium carbonate solution gave the corresponding S-substituted derivatives **Va–c**, respectively (Scheme 2).

The alkylation awarded at S-atom not the N-substituted analogue **VI**. The formation of the S-substituted derivatives **Va–c** could be proved via the evolution of methanethiol when **Va** was treated with hydrazine hydrate, forming the sulfur-free hydrazino derivative **VII** (Scheme 2). Compounds **Va–c** and **VII** gave the expected values in elemental analysis and spectral data (Tables 1 and 2).

Heating IV**a–c,e** derivatives with each of ethyl bromoacetate and chloroacetone under reflux in potassium hydroxide solution led to the formation of **VIIIa–c**, respectively, rather than their isomeric structures **IXa–d** (Scheme 3).

Preferring structure **VIII** over I**X** was based on the comparison of the ^{1}H-NMR spectral data for compounds **IV** and **VIII**. Thus, the ^{1}H-NMR spectrum of **VIIIb**, for example, revealed, in addition to the methyl group, aromatic, and NH proton signals, a singlet (1H) at δ 6.01 assigned to the pyrimidine H-5. The downfield for the pyrimidine H-5 in **VIIIb** compared with the pyrimidine H-4 in **IVb**, which appeared at δ = 5.36 ppm, indicates that the moiety nearby H-5 in **VIIIb** differs from that of H-4 in **IVb**. Therefore, structure **VIII** could be initially assigned for the reaction products. On the other hand, the ^{1}H-NMR spectra for methyl group at C-7 in compound **VIIIb** was not affected; had it been structure **IXb**, the ^{1}H-NMR spectra for methyl group at C-5 in compound **IX** would show a change in the signal position. Actually, the position of the CH_3 group was not affected, which indicates that the two CH_3 groups are not close to each other, which proves the structure of **VIIIb** for the reaction product rather than **IXb**.



I **IIa-g** **IVa-g**

a, Ar = 4-ClC_6H_4
b, Ar = 4-BrC_6H_4
c, Ar = thiophen-2-yl
d, Ar = 4-$NO_2C_6H_4$
e, Ar = 4-$OCH_3C_6H_4$
f, Ar = 4-OHC_6H_4
g, Ar = benzo[d][1,3]dioxol-5-yl

SCHEME 1 Preparation of compounds IV a-g

TABLE 1 Characterization data of compounds **IVa–g, Va–c, VIIIa–d, XIVa–e, and XVIa–e**

Compound	MF (M.Wt.)	Yield %	MP (°C) (solvent)	Color	Analysis Calcd. % C % H % N % Cl % S	Found % C % H % N % Cl % S
IVa	$C_{18}H_{15}Cl_2N_3OS$ (392.30)	63	272–274 (ethanol)	White powder	55.11 3.85 10.71 18.07 8.17	55.01 3.94 10.43 17.83 8.02
IVb	$C_{18}H_{15}BrClN_3OS$ (436.75)	35	258–261 (ethanol)	White powder	49.50 3.46 9.62 8.11 7.34	49.26 3.27 9.41 8.01 7.11
IVc	$C_{16}H_{14}ClN_3OS_2$ (363.88)	48	238–240 (ethanol)	Beige Powder	52.81 3.88 11.55 9.74 17.62	52.66 3.71 11.42 9.55 17.38
IVd	$C_{18}H_{15}ClN_4O_3S$ (402.85)	55	248–250 (ethanol)	Yellow powder	53.67 3.75 13.91 8.79 5.72	53.43 3.62 13.74 8.61 5.55
IVe	$C_{19}H_{18}ClN_3O_2S$ (387.88)	62	241–243 (ethanol)	Pale yellow powder	58.83 4.68 10.83 9.13 8.26	58.71 4.56 10.72 8.67 7.88
IVf	$C_{18}H_{16}ClN_3O_2S$ (373.86)	34	140–142 (ethanol)	White powder	57.83 4.31 11.24 9.48 8.57	57.34 4.10 10.86 9.21 8.24
IVg	$C_{19}H_{16}ClN_3O_3S$ (401.87)	24	253–254 (ethanol)	White powder	56.79 4.01 10.46	56.63 3.85 10.29
Va	$C_{19}H_{17}Cl_2N_3OS$ (406.33)	97	196–198 (ethanol)	Pale yellow powder	56.16 4.22 10.34 17.44 7.89	55.99 4.08 10.15 17.14 7.47
Vb	$C_{20}H_{16}Cl_2N_4OS$ (431.34)	65.3	214–216 (ethanol)	Pale brown powder	55.69 3.74 12.99 16.43 7.43	55.62 3.66 12.90 15.86 7.15

(Continues)

TABLE 1 (Continued)

Compound	MF (M.Wt.)	Yield %	MP (°C) (solvent)	Color	Analysis Calcd. % C % H % N % Cl % S	 Found % C % H % N % Cl % S
Vc	$C_{26}H_{21}Cl_2N_3O_2S$ (510.43)	62.8	226–230 (ethanol)	Brown powder	61.18 4.15 8.23 13.89 6.28	61.12 4.03 8.14 13.57 6.11
VII	$C_{18}H_{17}Cl_2N_5OS$ (390.27)	60.1	221–225 (DMF)	Yellow crystals	55.40 4.39 17.95 18.16 8.21	55.11 4.06 17.57 17.79 7.86
VIIIa	$C_{20}H_{15}Cl_2N_3O_2S$ (432.32)	45	223–224 (acetic acid)	Yellow powder	55.57 3.50 9.72 16.39 7.41	55.41 3.39 9.58 15.89 7.13
VIIIb*	$C_{20}H_{15}BrClN_3O_2S$ (476.77)	43	218–220 (acetic acid)	Pale brown Powder	50.38 3.17 8.81 7.43 6.72	50.20 2.87 8.45 7.13 6.23
VIIIc	$C_{18}H_{14}ClN_3O_2S_2$ (403.90)	52	>300 (acetic acid)	Orange powder	53.53 3.49 10.40 8.77 15.87	53.49 3.38 10.21 8.35 15.48
Xa	$C_{20}H_{16}Cl_2N_4OS$ (431.34)	73.4	263–265 (ethanol)	Brown powder	55.69 3.74 12.99 16.43 7.43	55.52 3.52 12.83 16.12 7.32
Xb	$C_{21}H_{15}Cl_2N_5OS$ (456.35)	78.5	223–225 (ethanol)	Pale yellow powder	55.27 3.31 15.35 15.53 7.02	55.08 3.15 15.21 15.34 6.65
XI	$C_{22}H_{15}Cl_2N_5O_2S$ (484.36)	63.36	197–200 (ethanol)	Pale yellow powder	54.56 3.12 14.46 14.63 6.61	54.46 2.93 14.28 14.41 6.33
XII	$C_{22}H_{16}Cl_2N_6OS$ (483.37)	50.1	241–243 (ethanol)	Pale brown powder	54.67 3.34 17.39 14.66 6.63	54.52 3.13 16.89 14.26 6.41

(Continues)

TABLE 1 (Continued)

Compound	MF (M.Wt.)	Yield %	MP (°C) (solvent)	Color	Analysis Calcd. % C % H % N % Cl % S	 Found % C % H % N % Cl % S
XIII	$C_{23}H_{17}Cl_2N_7OS_3$ (574.52)	57.3	210–212 (Dioxane)	Deep brown powder	48.08 2.98 17.07 12.34 16.74	47.38 2.53 16.67 12.13 16.35
XIVa	$C_{27}H_{18}Cl_3N_3O_2S$ (554.87)	70.95	268–270 (acetic acid)	Yellow powder	58.45 3.27 7.57 19.16 5.77	58.40 3.11 7.33 18.84 5.46
XIVb	$C_{28}H_{21}Cl_2N_3O_2S$ (534.46)	73.66	279–280 (acetic acid)	Yellow powder	62.93 3.96 7.86 13.26 5.99	62.82 3.82 7.77 12.97 5.72
XIVc*	$C_{27}H_{18}BrCl_2N_3O_2S$ (599.32)	80.18	276–278 (acetic acid)	Yellow powder	54.11 3.03 7.01 11.83 5.34	53.85 2.87 6.68 11.65 5.16
XIVd*	$C_{28}H_{21}BrClN_3O_2S$ (578.91)	62.18	273–275 (acetic acid)	Yellow powder	58.09 3.66 7.26 6.12 5.53	58.02 3.58 7.15 5.78 5.31
XIVe	$C_{25}H_{17}Cl_2N_3O_2S_2$ (526.45)	55.46	225–226 (acetic acid)	Yellow powder	57.04 3.26 7.98 13.46 12.17	56.86 3.13 7.69 13.25 11.88
XV	$C_{20}H_{17}Cl_2N_3O_3S$ (450.33)	67.8	271–272 (acetic acid)	White crystals	53.34 3.81 9.33 15.74 7.11	53.17 3.64 9.07 15.46 7.03
XVIa	$C_{26}H_{18}Cl_3N_5O_2S$ (570.87)	88.60	243245 –(acetic acid)	Orange powder	54.70 3.18 12.27 18.62 5.61	54.46 2.96 12.02 18.42 5.38

(Continues)

TABLE 1 (Continued)

Compound	MF (M.Wt.)	Yield %	MP (°C) (solvent)	Color	Analysis Calcd. % C % H % N % Cl % S	Found % C % H % N % Cl % S
XVIb	$C_{27}H_{21}Cl_2N_5O_2S$ (550.46)	71.26	185–188 (acetic acid)	Bright orange powder	58.91 3.85 12.72 12.88 5.82	58.82 3.75 12.61 12.67 5.53
XVIc*	$C_{26}H_{18}BrCl_2N_5O_2S$ (615.33)	60.42	184–186 (acetic acid)	Orange powder	50.75 2.95 11.38 11.52 5.21	50.53 2.77 11.22 11.28 5.10
XVId*	$C_{27}H_{21}BrClN_5O_2S$ (594.91)	68.70	194–195 (acetic acid)	Orange powder	54.51 3.56 11.77 5.95 5.38	54.27 3.31 11.57 5.81 5.16
XVIe	$C_{24}H_{17}Cl_2N_5O_2S_2$ (542.45)	65.06	182–186 (acetic acid)	Brown powder	53.14 3.16 12.91 13.07 11.82	52.97 3.02 12.74 12.79 11.58

* **IVb**: Calc; Br, 18.29; found; 18.06.
* **VIIIb**: Calc; Br, 16.75; found; 16.48.
* **XIVc**: Calc; Br, 13.33; found; 13.10.
* XIVd: Calc; Br, 13.80; found; 13.56.
* XVIc: Calc; Br, 12.98; found; 12.59.
* XVId: Calc; Br, 13.43; found; 13.11.

Another conclusive evidence for structure **VIII** has been made, by carrying out earlier studies, which revealed that B3LYP is one of the best functionals that reproduce the experimental geometries among various standard DFT functionals.[25] Formerly, a number of functional properties were studied by B3LYP functional [26–28] and 6-31G** basis set.[29–33] In the current study, the ground-state (S_0) geometries of two representative compounds were optimized at DFT/B3LYP/6-31G** level. The stability calculations of representative compounds **VIIIa** and **IXa** were performed at B3LYP/6-31G* level of theory. The total energy for Compound **VIIIa** was HF = -2,404.431331, while for Compound **IXa,** HF = -2,404.4191378. It was found that Compound **VIIIa** is 31.7 kJ/mol more stable than Compound **IXa**. Also, the charge density distribution of highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMOs) has been illustrated in Figure 1 to understand the intermolecular charge transfer (ICT). The ICT from HOMOs to LUMOs has been observed in both compounds.

Compounds **VIIIa–c** could be resynthesized using microwave-assisted reaction conditions. Comparing compounds produced by the traditional methods with those prepared by the microwave-assisted conditions indicates that the reaction time is reduced to 10 min instead of overnight standing in the latter. Also the reaction yields were improved from 40–53% to 68–85% (Table 3).

On the other hand, Compound **IVa** reacted with α-halo carbonitriles, namely chloro acetonitrile and monobromo malononitrile, in refluxing ethanol containing potassium hydroxide solution to produce directly 3-amino-N,5-bis(4-chlorophenyl)-7-methyl -5H-thiazolo [3,2-a]pyrimidine-6-carboxamide (**Xa**) and 3-amino-N,5-bis(4-chlorophenyl)-2-cyano-7-methyl-5H-thiazolo [3,2-a] pyrimidine-6-carboxamide (**Xb**), respectively (Scheme 4).

TABLE 2 Spectral data for compounds IVa-g, Va-c, VIIIa-c, XIVa–e, and XVIa–e

Compound	IR (KBr) cm^{-1}	^{1}H NMR (δ Valeus)	^{13}C NMR (δ Valeus)
IVa	3,300–3,200 (NH), 2,981 (C-H, aliph.), 1,676 (C=O), 1,632 (C=C), 1,241 (C=S)	2.06 (s, 3H, CH_3), 5.37 (s, 1H, CH), 7.25–7.27 (d, 2H, Ar-H, J = 8.5 Hz), 7.31–7.33 (d, 2H, Ar-H, J = 8.9 Hz), 7.43–7.44 (d, 2H, Ar-H, J = 8.5 Hz), 7.56–7.58 (d, 2H, Ar-H, J = 9 Hz), 9.49 (s, 1H, NH, D_2O *exchangeable*), 9.87 (s, 1H, NH, D_2O exchangeable), 10.08 (s, 1H,NH amide, D_2O exchangeable)	16.59 (CH_3), 54.43 (CH), 106.54, 121.25, 127.04, 128.31, 128.55, 128.70, 132.41, 136.38, 137.87, 141.92 (Ar–C), 164.95 (C=O), 174.23 (C=S)
IVb	3,300–3,180 (NH), 3,006 (C-H, aliph.), 1,679 (C=O), 1,636 (C=C), 1,268 (C=S)	2.06 (s, 3H, CH_3), 5.36 (s, 1H, CH), 7.18–7.19 (d, 2H, Ar-H, J = 8.5 Hz), 7.31–7.33 (d, 2H, Ar-H, J = 8.5 Hz), 7.56–7.57 (m, 4H, Ar-H), 9.49 (s, 1H, NH, D_2O exchangeable), 9.87 (s, 1H, NH, D_2O exchangeable), 10.08 (s, 1H, NH, D_2O exchangeable)	16.58 (CH_3), 54.49 (CH), 106.48, 120.95, 121.25, 127.04, 128.54, 128.63, 131.61, 136.35, 137.84142.30 (Ar–C), 164.94 (C=O), 174.22 (C=S)
IVc	3,265–3,180 (NH), 2,989 (C-H aliph.), 1,676 (C=O), 1,636, 1,591, 1,575 (C=C), 1,205 (C=S)	2.10 (s, 3H, CH_3), 5.65 (s, 1H, CH), 6.93–6.97 (d, 1H, Ar-H, J = 3.4 Hz), 6.96–6.98 (dd, 1H, Ar-H, J = 3.57, 1.44 Hz), 7.33–7.32 (d, 2H, Ar-H, J = 8 Hz), 7.42–7.43 (dd, 1H, Ar-H, J = 6.8, 1.7 Hz), 7.60 (d, 2H, Ar-H, J = 8.5 Hz), 9.64 (s, 1H, NH, D_2O exchangeable), 9.85 (s, 1H, NH, D_2O exchangeable), 10.167 (s, 1H, NH amide, D_2O exchangeable)	16.64 (CH_3), 50.33 (CH), 106.81, 121.31, 124.34, 125.73, 126.84, 126.95, 128.49, 137.22, 137.96, 146.91 (Ar–C), 164.65 (C=O), 174.29 (C=S)
IVd	3,300–3,200 (NH str.), 2,900 (C-H aliphatic), 1,682 (C=O), 1,629 (C=C), 1,209 (C=S)	2.09 (s, 3H, CH_3), 5.49 (s, 1H, CH), 7.31–7.32 (d, 2H, Ar-H, J = 8.5 Hz), 7.50–7.52 (d, 2H, Ar-H, J = 8.5 Hz), 7.56–7.57(d, 2H, Ar-H, J = 8.5 Hz), 8.24–8.25 (d, 2H, Ar-H, J = 8.5 Hz), 9.60 (s, 1H, NH, D_2O exchangeable), 9.93 (s, 1H, NH, D_2O exchangeable), 10.20 (s, 1H, NH amide, D_2O exchangeable)	16.70 (CH_3), 54.57 (CH), 105.94, 121.32, 124.07, 127.14, 127.74, 128.56, 137.04, 137.78, 147.04, 149.98 (Ar–C), 164.79 (C=O), 174.54 (C=S)
IVe	3,260–3,100 (NH str.), 3,000 (C-H aliph.), 1,676 (C=O), 1,634 (C=C), 1,245 (C=S)	2.07 (s, 3H, CH_3), 3.33 (s, 3H, OCH_3), 5.34 (s, 1H, CH), 6.88–6.89 (d, 2H, Ar-H, J = 8.7 Hz), 7.15–7.17 (d, 2H, Ar-H, J = 8.7 Hz), 7.29 (d, 2H, Ar-H, J = 9 Hz), 7.57–7.58 (d, 2H, Ar-H, J = 9 Hz), 9.39 (s, 1H, NH, D_2O exchangeable), 9.78 (s, 1H, NH, D_2O exchangeable), 9.95 (s, 1H, NH, D_2O exchangeable)	18.3 (CH3), 53.7 (OCH3), 56.70 (CH), 106.54, 116.4, 121.34, 125.13, 128.14, 129.96, 134.50, 136.04, 156.44 (Ar–C), 163.78 (C=O), 174.52 (C=S)
IVf	3,300–3,188 (NH and OH), 1,663 (C=O), 1,617 (C=C), 1,261 (C=S)	2.05 (s, 3H, CH_3), 5.29 (s, 1H, CH), 6.70–6.72 (d, 2H, Ar-H, J = 8.5 Hz), 7.04–7.06 (d, 2H, Ar-H, J = 8.5 Hz), 7.32–7.33 (d, 2H, Ar-H, J = 8.5 Hz), 7.57–7.58 (d, 2H, Ar-H, J = 8.5 Hz), 9.36 (s, 1H, NH, D_2O exchangeable), 9.44 (s, 1H, OH, D_2O exchangeable), 9.79 (s, 1H, NH, D_2O exchangeable), 9.93 (s, 1H, -NH, D_2O exchangeable)	16.49 (CH_3), 54.62 (CH), 107.24, 115.25, 121.16, 126.86, 127.75, 128.48, 133.55, 135.59, 137.97, 157.0 (Ar–C), 165.15 (C=O), 173.69 (C=S)
IVg	3,430–3,320 (NH), 1,673 (C=O), 1,619 (C=C), 1,250 (C=S), 1,135 (CO)	2.08 (s, 3H, CH_3), 5.322 (d, 1H, CH, J = 3 Hz), 5.99 (s, 2H, CH_2), 6.72–6.73 (dd, 1H, Ar-H, J = 8, 1.5 Hz), 6.78–6.79 (d, 1H, Ar-H, J = 1.5 Hz), 6.87–6.89 (d, 1H, Ar-H, J = 8 Hz), 7.31–7.32 (d, 2H, Ar-H, J = 9 Hz) 7.58–7.60 (d, 2H, Ar-H, J = 9 Hz), 9.41 (s, 1H, NH), 9.81 (s, 1H, NH), 10 (s, 1H, NH amide).	16.93 ppm (CH_3), 55.13 (CH), 101.49, 107.22, 107.33, 108.59, 120.22, 121.58, 127.34, 128.87, 136.45, 137.38, 138.32, 147.21, 147.88 (Ar–C), 165.41 (C=O) and 174.34 (C=S).
Va*	3,500–3,350 (NH), 2,849 (C-H aliph.),	2.18 (s, 3H, CH_3), 2.73 (s, 3H, S-CH_3), 5.85 (s, 1H, CH), 7.32–7.48 (m, 6H, Ar-H), 7.61–7.63 (d, 2H, Ar-H, J = 9 Hz), 10.47 (s, 1H, NH, D_2O	13.98 (CH_3), 16.53 (CH_3), 55.11 (CH), 121.47, 127.63, 128.67, 128.92,

(Continues)

TABLE 2 (Continued)

Compound	IR (KBr) cm^{-1}	^{1}H NMR (δ Valeus)	^{13}C NMR (δ Valeus)
	1,685 (C=O), 1,595 (C=N)	exchangeable), 11.93 (s, 1H, NH, D_2O exchangeable)	129.06, 133.46, 137.33 (Ar–C), 163.60 (C=O)
Vb	3,420–3,340 (NH), 2,849 (C-H aliph.), 2,220 (CN), 1,680 (C=O), 1,595 (C=N)	2.03 (s, 3H, CH_3), 4.11 (s, 2H, S-CH_2), 5.38 (s, 1H, CH), 7.27–7.57 (m, 8H, Ar-H), 8.81 (s, 1H, NH, D_2O exchangeable), 9.70 (s, 1H, NH, D_2O exchangeable)	17.12 (CH_2), 22.86 (CH_3), 54.46 (CH), 114.55, 121.15, 126.75, 128.19, 128.46, 128.51, 128.60, 131.94, 138.10, 139.31, 143.18, 152.30 (Ar–C), 165 (C=O)
Vc	3,396, 3,250 (NH), 1,675 (C=O), 1,632 (C=N)	2.07 (s, 3H, CH_3), 4.10 (s, 2H,S-CH_2), 5.41 (s, 1H, CH), 7.15 (s, 1H, NH, D_2O exchangeable), 7.24–7.52 (m, 6H, Ar-H), 7.84–8.10 (m, 7 H, Ar-H), 9.84 (s, 1H, NH, D_2O exchangeable)	19.22 (CH_3), 32.85 (CH_2), 49.48 (CH), 121.15, 125.33, 126.75, 128.11, 129.46, 132.95, 136.10, 139.73, 152.30 (Ar–C), 164.50 (C=O), 166.21 (CS), 192.10 (C=O)
VII	3,048–2,997 (NH), 2,943 (C-H aliph.), 1,625 (C=O), 1,593 (C=N).	2.07 (s, 3H,CH_3), 5.38 (s, 1H, CH), 7.25–7.58 (m, 8H, Ar-H), 8.72 (s, 2H, NH_2, D_2O exchangeable), 9.50 (s, 1H, NH, D_2O exchangeable), 9.87 (s, 1H, NH, D_2O exchangeable), 10.09 (s, 1H, NH, D_2O exchangeable)	16.57 (CH_3), 54.39 (CH), 106.51, 121.21, 126.99, 128.27, 128.67, 129.12, 130.05, 132.35, 132.61,136.06, 136.36, 137.85, 141.89 (Ar–C), 164.91 (C=O)
VIIIa	3,310 (NH), 1,730, 1,645 (2C=O), 1,586 (C=N)	2.06 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 6.02 (s, 1H, CH), 7.24–7.25 (d, 2H, Ar-H, J = 8.5 Hz), 7.33–7.34 (d, 2H, Ar-H, J = 8.5 Hz), 7.41 7.42 (d, 2H, Ar-H, J = 8.5 Hz), 7.55–7.56 (d, 2H, Ar-H, J = 8.5 Hz), 10.07 (s, 1H, -NH, D_2O exchangeable)	21.24 (CH_3), 31.96 (CH_2), 55.15 (CH), 112.83, 121.25, 127.31, 128.59, 128.81, 128.87, 133.03, 137.53, 138.60, 141.19 (Ar–C), 157.61 (C=N), 165.09, 171.06 (2C=O)
VIIIb*	3,448 (NH), 1,732, 1,646 (2C=O), 1,585 (C=N)	2.06 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 6.01 (s, 1H, CH), 7.17–7.18 (d, 2H, Ar-H, J = 8.5 Hz), 7.33–7.34 (d, 2H, Ar-H, J = 8.5 Hz), 7.54–7.56 (m, 4H, Ar-H), 10.07 (s, 1H, -NH, D_2O exchangeable)	21.24 (CH_3), 31.96 (CH_2), 55.23 (CH), 112.77, 121.25, 121.67, 127.31, 128.59, 129.16, 131.74, 137.53, 139.01, 141.20 (Ar–C), 157.62 (C=N), 165.08, 171.05 (2C=O)
VIIIc	3,287 (NH), 1,733, 1,646 (2C=O), 1,585 (C=N)	2.12 (s, 3H, CH_3), 2.17 (s, 2H, CH_2), 6.41 (s, 1H, CH), 7.01–7.70 (m, 7H, Ar-H), 10.40 (s, 1H, NH, D_2O exchangeable)	21.11 (CH_3), 32.06 (CH_2), 55.20 (CH), 112.86, 121.27, 127.33, 128.59, 128.81, 128.93, 133.07, 137.53, 138.52, 140.89 (Ar–C), 157.9 (C=N), 165, 171 (2C=O)
Xa	3,404 (NH), 3,271–3,105 (NH_2), 1,708 (C=O), 1,650 (C=N),	2.06 (s, 3H, CH_3), 5.49 (s, 1H,CH), 6.01 (s, 1H, CH), 7.22–7.57 (m, 8H, Ar-H), 8.19 (s, 2H, NH_2, D_2O exchangeable), 10.08 (s, 1H, NH, D_2O exchangeable);	19.54 (CH_3), 59.76, 69.97 (2 CH), 121.37, 126.43, 126.45, 128.65, 132.51, 133.89, 136.21, 140.62, 151.62, 156.88, 158.32 (Ar–C), 163.13 (C=O)
Xb	3,338 (NH), 3,150–3,050 (NH_2), 2,206 (CN), 1,643 (C=O), 1,595 (C=N)	2.15 (s, 3H, CH_3), 6.75 (s, 1H, CH), 7.32–7.33 (d, 2H, Ar-H, J = 8.5 Hz), 7.37–7.39 (d, 2H, Ar-H, J = 9 Hz), 7.47–7.48 (d, 2H, Ar-H, J = 8.5 Hz), 7.62–7.65 (d, 2H, Ar-H, J = 9 Hz), 8.01 (s, 2H, NH_2, D_2O exchangeable), 10.24 (s, 1H, NH, D_2O exchangeable)	18.52 (CH_3), 56.76 (CH), 109.93, 112.99, 121.37, 127.65, 128.25, 128.65, 129.18, 133.89, 136.70, 137.22, 151.20 (12 Ar–C), 159.40 (C–NH_2), 163.13 (C=O)
XI	3,286 (NH), 1,691, 1,644 (2C=O), 1,592 (C=N)	2.07 (s, 3H, CH_3), 6.52 (s, 1H, CH), 7.24–7.25 (d, 2H, Ar-H, J = 8.5 Hz), 7.33–7.35 (d, 2H, Ar-H, J = 8.8 Hz), 7.38–7.39 (d, 2H, Ar-H, J = 8.5 Hz), 7.59–7.61 (d, 2H, Ar-H, J = 9 Hz), 8.02 (s, 1H, NH, D_2O exchangeable), 10.08 (s, 1H, NH, D_2O exchangeable), 13.06 (s, 1H, OH, D_2O exchangeable)	21.55 (CH_3), 56.31 (CH), 101.04, 109.93, 121.25, 127.17, 128.14, 128.61, 128.99, 133.01, 137.81, 139.67, 143.03, 150.19 (12 Ar–C), 153.54, 155.51, 158.22 (3C=N), 165.68 (C=O)

(Continues)

TABLE 2 (Continued)

Compound	IR (KBr) cm^{-1}	^{1}H NMR (δ Valeus)	^{13}C NMR (δ Valeus)
XII	3,399 (NH), 3,300–3,100 (NH_2), 1,665 (C=O), 1,574 (C=N), 1,470 (C=C)	2.15 (s, 3H, CH_3), 5.38 (s, 1H, CH), 7.26–7.61 (m, 9H, Ar-H), 9.28 (s, 2H, NH_2, D_2O exchangeable), 10.08 (s, 1H, NH, D_2O exchangeable)	16.91 (CH_3), 32.78 (CH), 52.35 (CH), 110.14, 121.24, 127.27, 128.09, 128.54, 128.74, 128.82, 132.67, 134.91, 137.57, 140.75, 156.22 (16 Ar–C), 164.28 (C=O)
XIII	3,399 (NH), 3,300–3,172 (NH_2), 1,664 (C=O), 1,622 (C=N), 1,468 (C=C), 1,333 (C=S)	2.08 (s, 3H, CH_3), 5.40 (s, 1H, CH), 7.27–7.59 (m, 8H, Ar-H), 9.11 (s, 2H, NH_2, D_2O exchangeable), 9.49 (s, 1H, NH, D_2O exchangeable), 9.89 (s, H, NH, D_2O exchangeable), 10.08 (s, 1H, NH, D_2O exchangeable)	16.56 (CH_3), 54.38 (CH), 91.74, 106.48, 121.21, 126.96, 128.28, 128.43, 128.60, 132.31, 136.32, 137.80, 141.84, 151.16 (12 Ar–C), 160.11, 164.88 (C=N), 172.87 (C=O), 174.17, 175.12 (2C=S)
XIVa*	3,306 (NH), 1,715, 1,645 (2C=O), 1,585 (C=N), 1,518 (C=C)	2.12 (s, 3H, CH_3), 6.27 (s, 1H, CH), 7.32–7.35 (d, 2H, Ar-H, $J = 9$ Hz), 7.40–7.41 (d, 2H, Ar-H, $J = 8.5$ Hz), 7.60–7.64 (m, 6H, Ar-H), 7.76 (s, 1H, CH), 10.42 (s, 1H, NH, D_2O exchangeable)	21.27 (CH_3), 55.69 (CH), 114.45, 120.40, 121.34, 127.36, 128.55, 128.71, 128.76, 128.84, 129.02, 129.19, 129.47, 130.78, 131.60, 131.86, 133.19, 135.08, 137.56, 137.99, 140.79 (Ar–C), 152.15 (C=N), 164.21, 164.74 (2C=O)
XIVb*	3,276 (NH), 1,709, 1,646 (2C=O), 1,624 (C=N), 1,586 (C=C)	2.13 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 6.29 (s, 1H, CH), 7.32–7.36 (m, 6H, Ar-H), 7.39–7.40 (d, 2H, Ar-H, $J = 8.5$ Hz), 7.49–7.51 (d, 2H, Ar-H, $J = 9$ Hz), 7.63–7.64 (d, 2H, Ar-H, $J = 8.5$ Hz), 7.72 (s, 1H, CH), 10.46 (s, 1H, NH, D_2O exchangeable)	21.08, 21.26 ($2CH_3$), 55.57 (CH), 114.24, 118.33, 121.32, 126.33, 127.29, 128.47, 128.77, 129.15, 129.98, 130.15, 132.18, 133.12, 137.59, 138.10, 140.87, 140.94, (Ar–C), 152.44 (C=N), 164.36, 164.79 (2C=O)
XIVc	3,303 (NH), 1,715, 1,645 (2C=O), 1,607 (C=N), 1,585 (C=C)	2.13 (s, 3H, CH_3), 6.29 (s, 1H, CH), 7.27–7.28 (d, 2H, Ar-H, $J = 8.5$ Hz), 7.32–7.35 (d, 2H, Ar-H, $J = 9$ Hz), 7.53–7.54 (d, 2H, Ar-H, $J = 8$ Hz), 7.61–7.65 (m, 6H, Ar-H), 7.75 (s, 1H, CH); 10.49 (s, 1H, NH, D_2O exchangeable)	21.25 (CH_3), 55.76 (CH), 114.37, 120.38, 121.34, 121.79, 127.31, 128.48, 129.42, 129.49, 130.73, 131.54, 131.70, 131.83, 135.04, 137.57, 138.36, 140.80 (Ar–C), 152.05 (C=N), 164.15, 164.70 (2C=O)
XIVd*	3,273 (NH), 1,709, 1,645 (2C=O), 1,624 (C=N), 1,586 (C=C)	2.12 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.27 (s, 1H, CH), 7.26–7.27 (d, 2H, Ar-H, $J = 8.5$ Hz), 7.32–7.34 (d, 2H, Ar-H, $J = 9$), 7.35–7.36 (d, 2H, Ar-H, $J = 8$ Hz), 7.49–7.50 (d, 2H, Ar-H, $J = 8$ Hz), 7.53–7.54 (d, 2H, Ar-H, $J = 8.5$ Hz), 7.63–7.65 (d, 2H, Ar-H, $J = 9$ Hz), 7.72 (s, 1H, CH); 10.460 (s, 1H, NH, D_2O exchangeable)	21.59, 21.75 ($2CH_3$), 56.15 (CH), 114.68, 118.82, 121.82, 122.26, 127.79, 128.99, 129.92, 130.50, 130.65, 132.21, 132.71, 138.08, 139.02141.39, 141.42 (Ar–C), 152.96 (C=N), 164.86, 165.28 (2C=O)
XIVe*	3,335 (NH), 1,716, 1,655 (2C=O), 1,606 (C=N), 1,569, 1,517 (C=C)	2.19 (s, 3H, CH_3), 6.60 (s, 1H, CH), 6.96–6.97 (dd, 1H, $J = 5.3$ Hz), 7.15–7.16 (d, 1H, $J = 3$ Hz), 7.34–7.44 (d, 2H, Ar-H, $J = 8.5$ Hz), 7.49–7.51 (dd, 1H, $J = 5$, 1.5 Hz), 7.60–7.70 (m, 6H, Ar-H) 7.86 (s, 1H,CH) 10.53 (s, 1H, NH, D_2O exchangeable)	21.08 (CH_3), 50.64 (CH), 114.09, 120.40, 121.38, 126.98, 127.06, 127.23, 127.27, 128.48, 129.43, 131.13, 131.62, 131.79, 135.13, 137.71, 141.37, 142.28 (Ar–C), 151.77 (C=N), 164.14, 164.69 (2C=O)
XV	3,300–3,100 (OH), 3,224 (NH), 1,717, 1,685 (2C=O)	1.90 (s, 2H, CH_2), 2.06 (s, 3H, CH_3), 5.37–5.38 (d, 1H, CH, $J = 3$ Hz), 7.24–7.32 (m, 4H, Ar-H), 7.41–7.44 (d, 2H, Ar-H, $J = 9$ Hz), 7.55–7.57 (d, 2H, Ar-H, $J = 9$ Hz), 9.83 (s, 1H, NH, D_2O exchangeable), 10.05 (s, 1H, NH, D_2O exchangeable), 11.92 (s, exchangeable) 1H, OH, D_2O	16.59 (SCH_2), 21.11 (CH_3), 54.43 (CH), 106.55, 121.26, 127.05, 128.31, 128.55, 128.70, 132.39, 136.36, 137.85, 141.90 (Ar–C), 164.95, 172.11 (2C=O),174.23 (C-S)

(Continues)

TABLE 2 (Continued)

Compound	IR (KBr) cm^{-1}	^1H NMR (δ Valeus)	^{13}C NMR (δ Valeus)
XVIa*	3,408 (NH), 2,920 (C-H aliph.), 1,738, 1,676 (2C=O), 1,640, 1,569 (C=N), 1,519 (C=C)	2.11 (s, 3H, CH_3), 6.17 (s, 1H, CH), 7.22–7.24 (d, 2H, Ar-H, J = 8.57 Hz), 7.29–7.31 (d, 2H, Ar-H, J = 9.35 Hz), 7.34–7.44 (d, 2H, Ar-H, J = 8.57 Hz), 7.36–7.38 (d, 2H, Ar-H, J = 9.35 Hz), 7.42–7.44 (d, 2H, Ar-H, J = 9 Hz), 7.56–7.57 (d, 2H, Ar-H, J = 9 Hz), 10.16 (s, 1H, NH, D_2O exchangeable), 10.96 (s, 1H, NH, D_2O exchangeable)	20.91 (CH_3), 55.28 (CH), 114.72, 115.73, 121.07, 121.34, 126.03, 127.41, 128.54, 128.80, 129.05, 129.17, 133.17, 137.43, 138.04, 140.20, 142.12, 151.47 (Ar–C), 160.34, 164.54 (2C=O)
XVIb	3,401 (NH), 2,900 (C-H aliph.), 1,767, 1,654 (2C=O), 1,616, 1,593 (C=N)	2.31 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 6.14 (s, 1H, CH), 7.23–7.42 (m, 10 H, Ar-H), 7.76–7.77 (d, 2H, Ar-H, J = 9 Hz), 9.78 (s, 1H, NH, D_2O exchangeable), 11.36 (s, 1H, NH, D_2O exchangeable)	21.32 (CH_3), 59.53 (CH), 115.67, 121.41, 124.35, 126.44, 127.38, 128.64, 129.63, 131.77, 132.81, 136.41, 140.67, 142.11, 151.93, 155.45 (Ar–C), 163.78, 168.64 (2C=O)
XVIc	3,404 (NH), 1,685, 1,654 (2C=O), 1,591, 1,573 (C=N), 1,490 (C=C)	2.11 (s, 3H, CH_3), 6.164 (s, 1H, CH), 7.18–7.58 (m, 12H, Ar-H), 10.20 (s, 1H, NH, D_2O exchangeable), 11.04 (s, 1H, NH, D_2O exchangeable)	21.21 (CH_3), 55.33 (CH), 115.72, 121.13, 121.38, 121.47, 126.03, 127.38, 127.50, 128.66, 129.30, 131.76, 131.83, 137.46, 138.62, 138.92, 140.73, 142.17, 150.93 (Ar–C), 164.74, 165 (2C=O)
XVId	3,404 (NH), 2,900 (C-H aliph.), 1,750, 1,690 (2C=O), 1,654, 1,593 (C=N), 1,529 (C=C)	2.31 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 6.14 (s, 1H, CH), 7.20–7.23 (d, 2H, Ar-H, J = 8.54 Hz), 7.41–7.43 (d, 2H, Ar-H, J = 9.33 Hz), 7.45–7.46 (d, 2H, Ar-H, J = 8.54 Hz), 7.49–7.50 (d, 2H, Ar-H, J = 9.33 Hz), 7.84–7.86 (d, 2H, Ar-H, J = 9 Hz), 7.86–7.88 (d, 2H, Ar-H, J = 9 Hz), 9.77 (s, 1H, NH, D_2O exchangeable), 11.34 (s, 1H, NH, D_2O exchangeable)	21.53 (CH_3), 60.52 (CH), 116.67, 121.45, 125.43, 126.41, 127.78, 128.77, 130.52, 131.76, 133.68, 136.41, 141.35, 142.14, 152.96, 155.44 (Ar–C), 163.74, 169.21 (2C=O)
XVIe	3,422 (NH), 3,100 (C-H aliph.), 1,719, 1,685 (2C=O), 1,654, 1,594 (C=N), 1,569 (C=C)	2.17 (s, 3H, CH_3), 6.50 (s, 1H, CH), 7.25–7.63 (m, 11H, Ar-H), 10.24 (s, 1H, NH, D_2O exchangeable), 11.05 (s, 1H, NH, D_2O exchangeable)	21.32 (CH_3), 50.22 (CH), 114.46, 115.80, 121.37, 121.44, 126.54, 126.83, 127.10, 127.24, 128.61, 128.65, 129.31, 137.61, 141.67, 142.05, 142.12, 142.32, 150.54 (Ar–C), 164.7, 165 (2C=O)

* Va: MS (m/z; %), 408 (M^{+2}; 6.5), 406 (M + H; 9.1), 360 (1.5), 318 (0.5).
* VIIIb: MS (m/z; %), 479 (M^{+4}; 2.51), 477 (M^{+2}; 8.40), 475 (M^+; 6.18), 351 (M^{+2} - 126; 100), 349 (M^+ − 126; 98.42), 323 (M^{+2}–154; 7.76), 321 (M^+ − 154; 7.65)
* Xb: MS (m/z), 459 (M^{+4}; 2.89%), 457 (M^{+2}; 12.59%), 455 (M^+; 18.14%), 331 (M^{+2}–126; 36.71%), 329 (M^+-126; 98.36%), 318 (M^{+2}–139; 20.43%), 316 (M^+; 30.75%), 165 (100%)
* XIVa: MS (m/z; %), 559 (M^{+6}; 0.43), 557 (M^{+4}; 2.61), 555 (M^{+2}; 6.70), 553 (M^+; 6.57), 429 (M^{+2}–126; 69.34), 427 (M^+-126; 100), 165 (M^{+2}–390; 13.82), 163 (M^+-390; 37.53), 67 (28.93)
* **XIVb:** MS (m/z; %), 537 (M^{+4}; 1.04), 535 (M^{+2}; 4.44), 533 (M^+; 5.92), 409 (M^{+2}–126; 41.10), 407 (M^+-126; 100), 165 (M^{+2}–370; 17.88), 163 (M^+-370; 50.43), 67 (38.86)
* **XIVd:** MS (m/z; %), 581 (M^{+4}; 2.74), 579 (M^{+2}; 8.71), 577 (M^+; 6.37), 453 (M^{+2}–126; 100),451 (M^+ − 126; 94.10), 209 (M^{+2}–370; 32.40), 207 (M^+-370; 31.63), 128 (15.89), 67 (27.48)
* **XIVe:** MS (m/z; %), 529 (M^{+4}; 1.86), 527 (M^{+2}; 7.32), 525 (M^+; 9.35), 401 (M^{+2}–126; 44.62), 399 (M^+-126; 99.46), 135 (100), 67 (56.65)
* **XVIa:** MS (m/z; %), 575 (M^{+6}; 0.77), 573 (M^{+4}; 4.48), 571 (M^{+2}; 11.77), 569 (M^+; 11.51), 447 (M^{+4}–126; 15.74), 445 (M^{+2}–126; 72.96), 443 (M^+-126; 100), 359 (M^{+2}212; 9.71), 357 (M^+-212; 14.43), 67 (58.20)

Compound **Xa** could also be synthesized stepwise by refluxing **Vb** in ethanol in the presence of sodium ethoxide solution. Compounds **Xa** and **b** gave the expected values in elemental analyses and spectral data (Tables 1 and 2).

Compound **Xb**, as typical enaminonitriles, allowed heterocyclic annelations performing access to more fused pyrimidines. They could be used as precursors for the preparation of thiazolodipyrimidine, pyrazolothiazolo-

TABLE 3 The difference in the outcome of the MW-assisted and thermal reactions for the synthesis of compounds **IVa–g** and **VIIIa–c**

	Reaction yield %		Reaction time/min	
Compound	**Microwave**	**Conventional method**	**Microwave**	**Conventional method**
IVa	88	63	11	1,440
IVb	74	35	14	180
IVc	87	48	10	360
IVd	83	55	15	1,440
IVe	82	62	15	1,500
IVf	76	34	13	1,440
IVg	55	24	15	2,540
VIIIa	88	45	10	1,440
VIIIb	74	43	14	1,440
VIIIc	87	52	9	1,440

pyrimidine, and pyridothiazolopyrimidine derivatives. Thus, a mixture of **Xb** with each of formic acid, formamide in formic acid/DMF mixture and an excess of ammonium thiocyanate in acetic acid to yield N,9-bis (4-chlorophenyl)-7-methyl-4-oxo-1,4-dihydro-9H-thiazolo [3,2-a:4,5-d']dipyrimi-dine-8-carboxamide **(XI),** 4-amino-N,9-bis(4-chlorophenyl)-7-methyl-9H-thiazolo[3,2-a:4,5-d'] dipyrimidine-8-carboxamide derivative(**XII**) and N,9-bis (4-chloro- phenyl)-7-methyl-4-thioureido-2-thioxo-1,2-dihydro-9H-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carboxamide (**XIII**), respectively (Scheme 5). Compounds **XI**, **XII,** and **XIII** gave the expected values in elemental analyses and spectral data (Tables 1 and 2).

An extension of alkylation and cycloalkylation, Compounds **IVa–c** were heated under reflux with a mixture of chloroacetic acid, aromatic aldehyde and fused sodium acetate in acetic acid/acetic anhydride solution to give 5-(Aryl)-N-(4-chlorophenyl)-7-methyl-2-(Arylidene)-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxamide **XIVa–e**, in good yields (Scheme 6). Compounds **XIVa–e** gave the expected values in elemental analyses and spectral data (Tables 1 and 2).

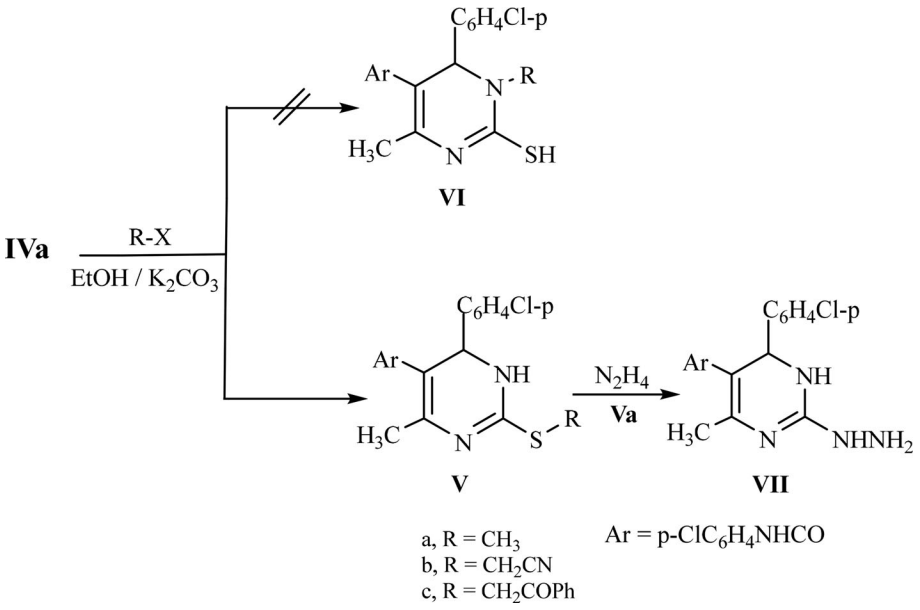
In support of structure **XIV**, compound **XIVa**, as an example, could be synthesized step wisely. Thus, when compound **IVa** was heated under reflux with chloroacetic acid and fused sodium acetate in acetic acid, it gave the 2-carboxymethylthio derivative **XV**. The latter compound could be cyclized by heating with acetic acid/acetic anhydride solution at 100°C to give Compound **VIIIa** (Scheme 7), which could also be obtained from **IVa** in one step by heating under reflux with a mixture of chloroacetic acid and fused sodium acetate in acetic acid / acetic anhydride solution. Compound **VIIIa** condensed with p-chloro benzaldehyde in refluxing acetic acid/acetic anhydride solution and gave **XIVa,** which was identical in all aspects with **XIVa** produced by one-pot synthesis.

Compound **XV** gave the expected values in elemental analyses and spectral data (Tables 1 and 2). Furthermore, Compounds **VIIIa–c** coupled with arenediazonium salts in pyridine to give the corresponding 2-arylhydrazo derivatives **XVIa–e** (Scheme 8). Compounds **XVI** gave agreeable values in elemental analyses and spectral data (Tables 1 and 2).

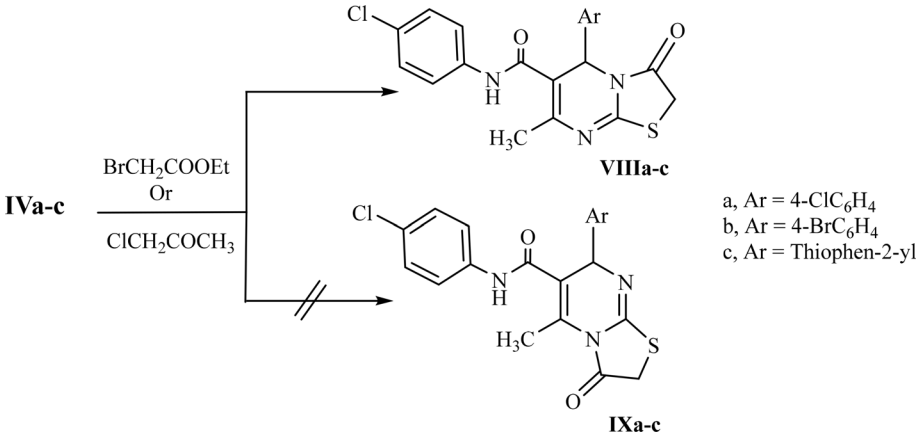
2.2 | Antimicrobial evaluation

Most of the newly synthesized compounds were screened for their in vitro antimicrobial activity against different microorganisms representing gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*, and *Staphylococcus mutants*) and gram-negative bacteria (*Enterobacter cloacae*, *Proteus vulgaris*, and *Escherichia coli*) using the standard antibiotic gentamycin (4 μg/ml) as reference drugs and fungi (*Aspergillus fumigates*, *Aspergillus flavus*, and *Candida albicans*) using the standard antibiotic ketoconazole (100 μg/ml). The compounds were tested for their activities with the same concentration of the standard using inhibition zone diameter (in millimeters) as a criterion for the antimicrobial activity,[34,35] and the results are shown in (Table 4).

The antimicrobial activity of the synthesized compounds was carried out by the mean zone of inhibition method. The ketoconazole was the antifungal control of this study with a concentration of 100 μg/ml, while gentamycin was used as gram-positive and gram-negative control with a concentration of 4 μg/ml, while the synthesized compounds were used with the same concentration as the control compounds. The antifungal activity of the newly synthesized compounds was tested against *Aspergillus flavus*, *Aspergillus fumigatus*, and *Candida albicans*. The inhibition activities showed that five of the tested compounds exhibited antifungal activity more than the ketoconazole.



SCHEME 2 Alkylation of compound IV a



SCHEME 3 Synthesis of compounds VIII a-c

The active antifungal compounds from the highest to the lowest against *Aspergillus flavus* were **XIVb, XVIb, VIIIb**, **XVIe**, and **IVb,** respectively. Furthermore, compounds **VIIIb**, **XVIa**, and **XVIe,** respectively, had the highest activity against *Aspergillus fumigates*, while the activity of tested compounds against *Candida albicans* ranged from moderate to undetectable.

Compound **Xb** had inhibition activity against *Aspergillus fumigatus* and *Streptococcus mutants* similar to ketoconazole and gentamycin activities, respectively. The inhibition activity of Compound **Va** against the *Streptococcus mutants* (gram-positive) and the *Proteus vulgaris* (gram-negative) was similar to the inhibition activity of gentamycin. All of the synthesized compounds that exerted high antifungal or antibacterial activity were mostly due to the presence of pyrimidine and carboxamide units (**XIVb, XVIb, VIIIb, XVIc, and IVb**). Compounds **(Xb, VIIIb, XVIe, XIVb and XVIa)** containing thiazol moiety beside the pyrimidine and carboxamide groups were with higher inhibition activity of some fungi and bacteria compared with the broad specificity antifungal (ketoconazole) and antibacterial drugs (gentamycin). The highest inhibition activity that exceeds the inhibition activity of the control drugs may be due to the presence of pyrimidine, carboxamide, and thiazole groups, which are well known to act as antibacterial and antifungal drugs. [36–38]

2.3 | Experimental

All melting points were determined with a Stuart Digital Melting Point apparatus SMP10 and are uncorrected. The elemental analyses were performed on a Perkin-Elmer 240 microanalyzer, PE 2400 Series II CHNS/O Analyzer, carried out at the regional center for mycology and biotechnology, Al-Azhar University, Egypt. IR spectra were determined as KBr pellets on a Thermo Nicolet apparatus (Thermo Scientific, Madison, WI) at Postgraduate campus for Girls at Lassan, King Khalid University, Abha. The NMR spectra were recorded on a Varian Mercury 300 MHz NMR spectrometer at Faculty of Science, Cairo

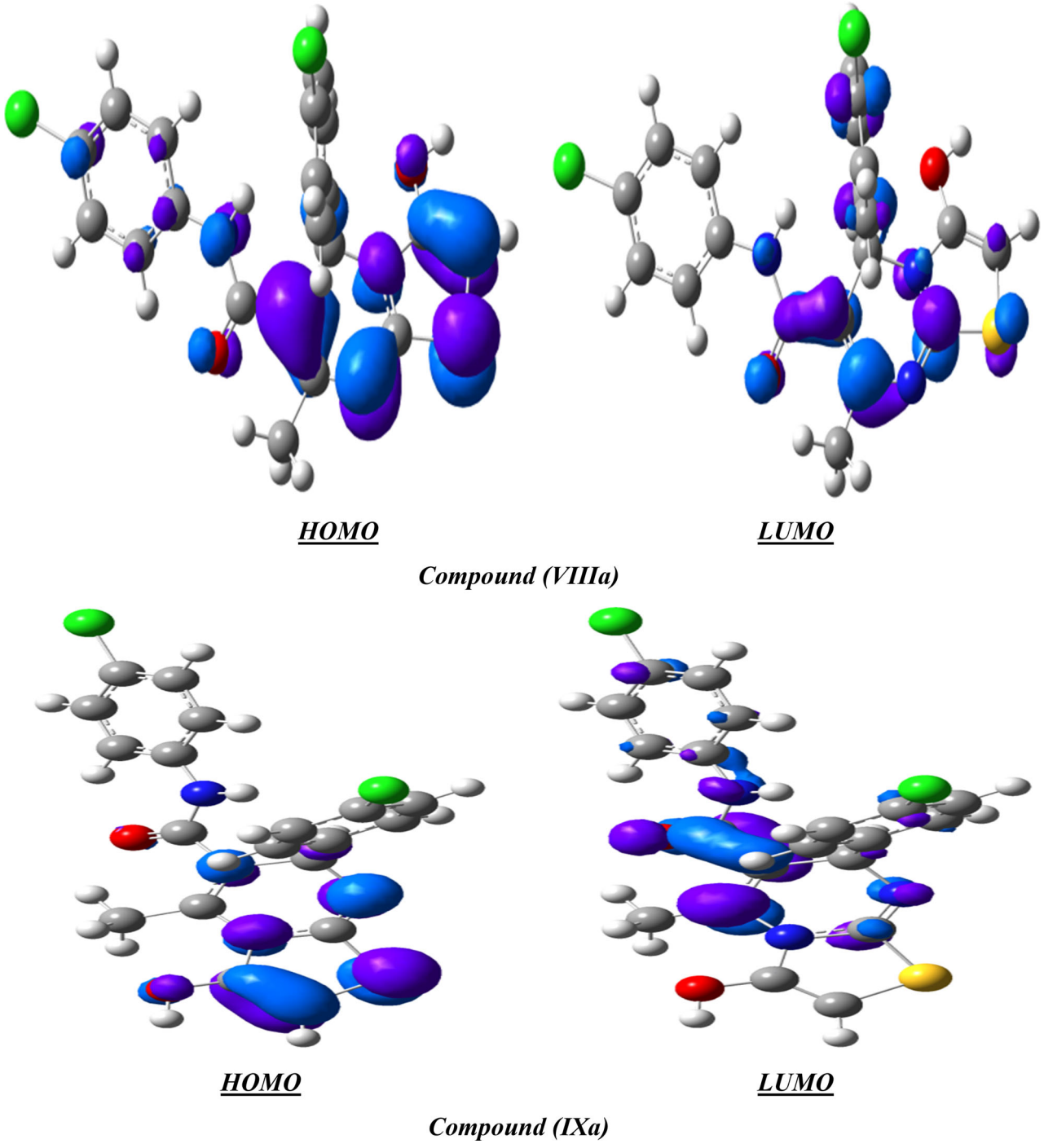
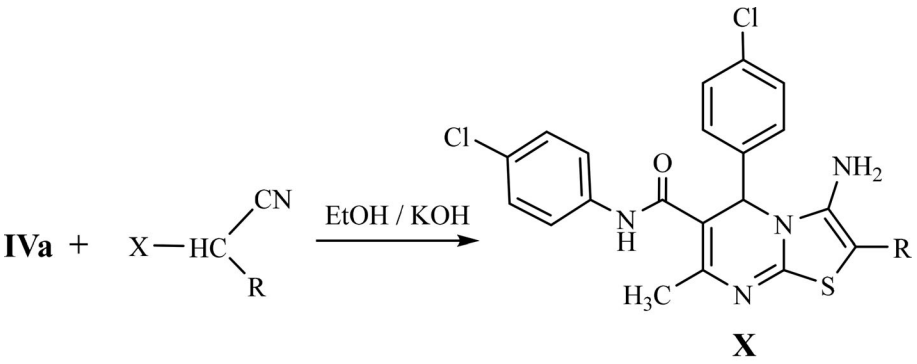


FIGURE 1 Ground state frontier molecular orbitals (HOMOs) and (LUMOs) of Compounds **VIIIa** and **IXa**, contour value 0.05

University, Egypt; Bruker NMR spectrometer 500 MHz at King Khalid University, Abha and Bruker NMR spectrometer 850 MHz, at King Abdul-Aziz, Jeddah, respectively, using tetramethyl silane as internal standard (TMS) in DMSO-d_6, as solvent. The chemical shifts were recorded in (δ) units. Mass spectra on GC/MS-QP5 spectrometer and the antimicrobial activity were measured at regional center for mycology and biotechnology, Al-Azhar University, Egypt.

2.4 | General procedures for the synthesis of N-(4-chlorophenyl)-4-(aryl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide IVa–g

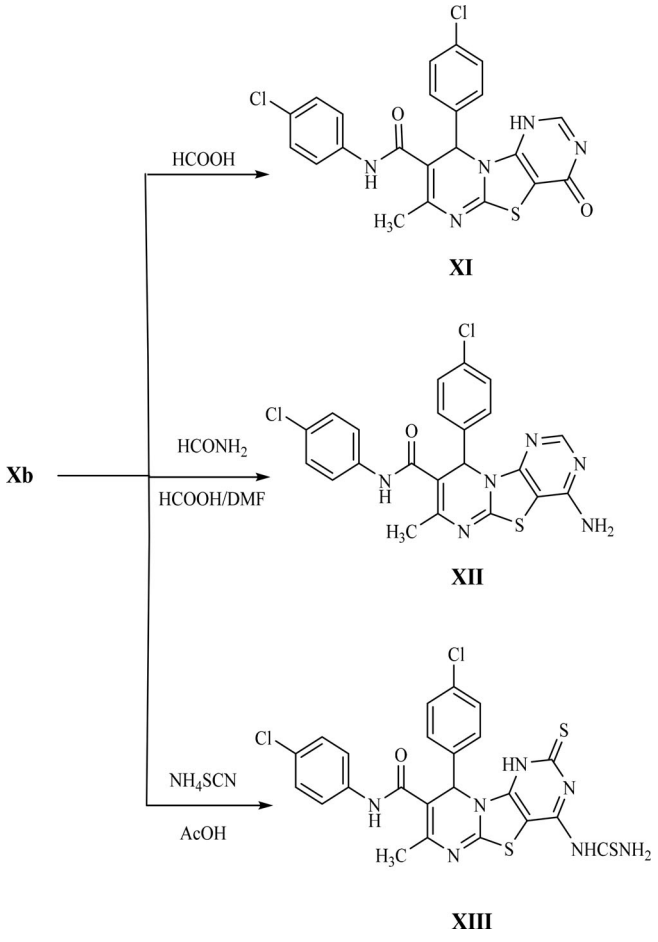
A mixture of thiourea **III** (0.01 mol, 0.76 g), *p*-chloro Acetoacetanilide **I** (0.01 mol, 2.11 g) and aromatic aldehyde derivatives **IIa–g** (0.01 mol) in ethanol in the



SCHEME 4 Synthesis of compounds Xa,b

Scheme **4**

presence of catalytic amount of HCl was refluxed (monitored by TLC), The precipitate that formed after cooling was filtered off, then dried, and recrystallized from ethanol to afford **IVa–g**.



SCHEME 5 Preparation of compounds XI, XII and XIII

2.5 | General procedures for the synthesis of N,6-bis(4-chlorophenyl)-4-methyl-2-(alkylthio)-1,6-dihydropyrimidine-5-carboxamide Va–c

In alcoholic potassium carbonate (0.28 g) **IVa** was added (5 mmol, 2 g) after 1 hr of reflux (5 mmol) the alkyl halide was added, the mixture continued to reflux and was monitored by TLC. The reaction was cooled and poured onto ice-water acidified by drops of HCl, the formed precipitate was filtered, washed with water repeatedly, dried, and recrystallized from ethanol.

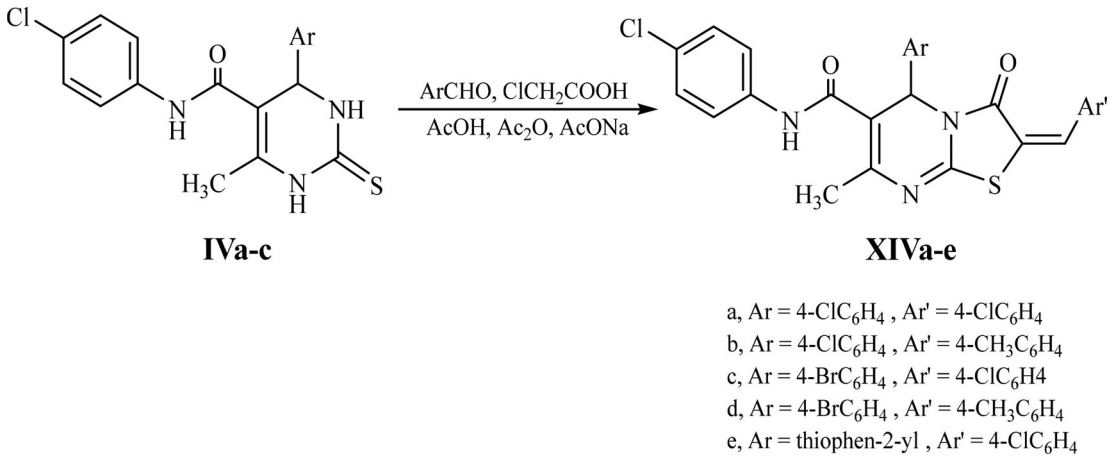
2.6 | Synthesis of N,6-Bis (4-chlorophenyl)-2-hydrazineyl-4-methyl-1,6-dihydropyrimidine-5-carboxamide VII

A mixture of **Va** (2.4 mmol, 1 g) and hydrazine hydrate (3 ml) in 15 ml dioxane was refluxed for 5 hr. The reaction mixture was left to cool to room temperature and then poured onto ice water, the formed precipitate was filtered off, washed thoroughly with water, dried, and recrystallized from DMF.

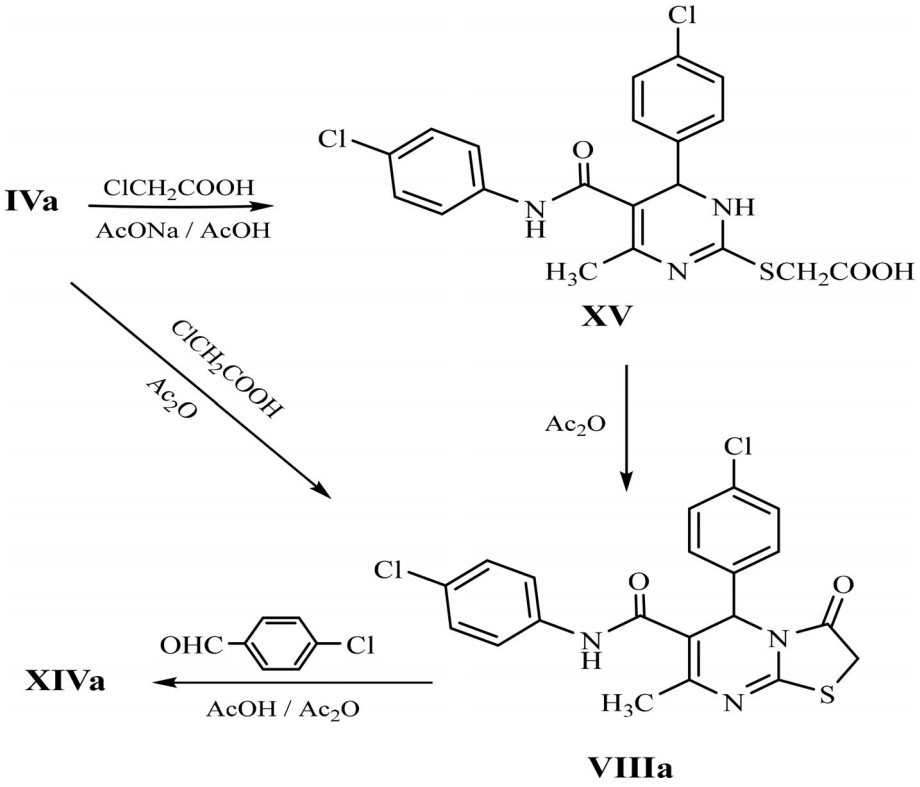
2.7 | Synthesis of N-(4-Chlorophenyl)-5-(4-methoxyphenyl)-3,7-dimethyl-5H-thiazolo[3,2-a] pyrimidine-6-carboxamide VIIIa-c

2.7.1 | Method (A)

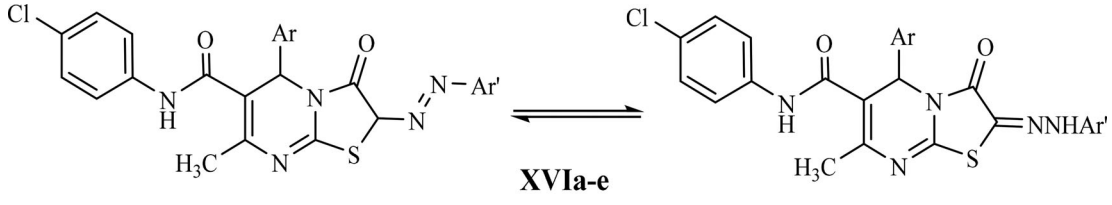
A solution of 2-thioxopyrimidine derivatives **IVa–c** (5 mmol, 1.93 g) and each of chloroacetone (5 mmol, 0.5 ml), ethyl bromoacetate (5 mmol, 0.56 ml), in ethanol (30 ml) in the presence of potassium hydroxide (5 mmol, 0.34 g) was refluxed for 2 hr. The reaction mixture was left to cool to room temperature, poured onto ice water,



SCHEME 6 Preparation of compounds XIVa-e



SCHEME 7 The step wise synthesis of compound VIIIa



a, Ar = 4-ClC6H4 , Ar' = 4-ClC6H4
b, Ar = 4-ClC6H4 , Ar' = 4-CH3C6H4
c, Ar = 4-BrC6H4 , Ar' = 4-ClC6H4
d, Ar = 4-BrC6H4 , Ar' = 4-CH3C6H4
e, Ar = C4H3S , Ar' = 4-ClC6H4

SCHEME 8 Tautomeric form of compounds XVIa-e

TABLE 4 Inhibition zone in (mm) as a criterion of antimicrobial activity of some newly synthesized compounds compared to the broad-spectrum antibiotics

Microorganism inhibition zone diameter (mm)									
	Gram +ve bacteria			Gram −ve bacteria			Fungi		
Compound no.	*Staphylococcus aureus*	*Bacillus subtilis*	*Strepotococcus mutans*	*Escherichia coli*	*Enterobacter cloacae*	*Proteus vulgaris*	*Aspergillus fumigates*	*Aspergillus flavus*	*Candida albicans*
Iva	NA	NA	NA	NA	NA	9	NA	11	NA
IVb	NA	NA	NA	NA	NA	10	NA	18	NA
IVc	10	12	NA	11	12	13	15	14	NA
IVd	13	12	NA	14	NA	13	NA	NA	NA
IVe	NA	12	NA	NA	11	10	NA	NA	NA
IVf	14	20	15	20	15	18	13	NA	NA
Va	14	21	20	16	20	25	13	15	13
VIIIa	NA	10	12	NA	13	16	15	9	NA
VIIIb	11	11	14	12	19	16	20	23	14
VIIIc	13	12	11	10	12	15	NA	NA	NA
Xb	12	20	19	15	19	18	17	NA	10
XI	13	15	17	16	17	16	13	12	11
XII	13	NA	NA	13	NA	NA	NA	NA	NA
XIVa	11	10	NA	11	10	11	NA	NA	NA
XIVb	11	10	NA	8	12	10	NA	25	13
XIVc	12	11	NA	9	11	12	NA	13	12
XIVd	NA	NA	NA	NA	NA	NA	NA	NA	NA
XIVe	NA	NA	NA	NA	NA	NA	14	NA	NA
XV	NA	9	10	13	NA	10	NA	NA	NA
XVIa	14	13	14	15	13	14	18	12	13
XVIb	10	15	8	10	15	12	NA	24	NA
XVIc	10	12	9	12	21	14	13	20	9
XVId	10	13	11	12	17	13	14	15	NA
XVIe	9	10	NA	NA	NA	NA	18	NA	10
Gentamycin	24	26	20	30	27	25	-	-	-
Ketoconazol	-	-	-	-	-	-	17	16	20

Note: NA, not active; diameter of hole = 6 mm; data are expressed as mean ± *SD*.

and acidified with HCl. The formed precipitate was filtered off, washed with water, dried, and recrystallized from the proper solvent.

2.7.2 | Method (B)

A mixture of 2-thioxopyrimidine derivatives **IVa–c** (5 mmol), fused sodium acetate (5 mmol, 0.41 g) and chloroacetic acid (5 mmol, 0.47 g) in 30 ml AcOH and 15 ml Ac_2O was refluxed for 12 hr. The reaction mixture was left to cool, poured onto ice-water; the formed precipitate was filtered off, washed thoroughly with water, dried, and recrystallized from acetic acid to afford compounds **VIIIa–c**.

2.8 | General procedures for the synthesis of 3-amino-N,5-bis (4-chlorophenyl)-2-alkyl-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxamide Xa,b

A mixture of 2-thioxopyrimidine derivative **IVa** (2.5 mmol, 2 g), chloro acetonitrile or monobromo malononitrile (2.5 mmol) in ethanolic potassium hydroxide solution was refluxed for 1 hr. The precipitate was collected by filtration, washed with cold ethanol, dried, and recrystallized from ethanol.

2.9 | Synthesis of N,9-bis (4-chlorophenyl)-7-methyl-4-oxo-1,4-dihydro-9H-thiazolo[3,2-a:4,5-d'] dipyrimidine-8-carboxamide XI

A mixture of thiazolo[3,2-a]pyrimidine-6-carboxamide **Xb** (2 mmol, 1.0 g) and formic acid (20 ml) was refluxed for 20 hr. The reaction mixture was left to cool and poured onto ice water, and the separated precipitate was filtered off, washed with water, dried, and recrystallized.

2.10 | Synthesis of 4-amino-N,9-bis (4-chlorophenyl)-7-methyl-9H-thiazolo [3,2-a:4,5-d']dipyrimidine-8-carboxamide XII

A mixture of **Xb** (1 mmol, 0.5 g), formic acid (5 ml), formamide (10 ml), and DMF (5 ml) was refluxed for 6 hr, left to cool, poured onto ice water, the formed precipitate was filtered off, washed with water, dried, and recrystallized.

2.11 | Synthesis of N,9-bis (4-chlorophenyl)-7-methyl-4-thioureido-2-thioxo-1,2-dihydro-9H-thiazolo [3,2-a:4,5-d']dipyrimidine-8-carboxamide XIII

A mixture of **Xb** (2 mmol, 1 g), Acetic Acid (10 ml) and excess ammonium thiocyanate (0.5 g) was refluxed overnight then left to cool, poured onto ice water, the formed precipitate was filtered off, dried, and recrystallized.

2.12 | General procedures for the synthesis of 5-(aryl)-N-(4-chlorophenyl)-7-methyl-2-(Arylidene)-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxamide XIVa–e

Equimolar amounts of **IVa–c** (5 mmol), an aromatic aldehyde (5 mmol), fused sodium acetate (5 mmol, 0.41 g) and chloroacetic acid (5 mmol, 0.47 g) in 30 ml of AcOH and 15 ml Ac_2O were refluxed for (5–12 hr) then left to cool and poured onto ice water. The separated precipitate formed was filtered off, washed with water, dried, and recrystallized from AcOH.

2.13 | Synthesis of 2-((6-(4-chlorophenyl)-5-((4-chlorophenyl) carbamoyl)-4-methyl-1,6-dihydropyrimidin-2-yl)thio)acetic acid XV

A mixture of **IVa** (6 mmol, 2 g), fused sodium acetate (6 mmol, 0.5 g) and chloroacetic acid (6 mmol, 0.56 g) in 30 ml of AcOH were refluxed for 6 hr. The reaction mixture left to cool, poured onto cold water. The precipitate formed was filtered off, washed with water, dried, and recrystallized.

2.14 | General procedures for the synthesis of N-(4-chlorophenyl)-2-(2-(aryl) hydrazineylidene)-7-methyl-3-oxo-5-(aryl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxamide XVI a–e

The appropriate aromatic amine (2.5 mmol) was dissolved in 10 ml of concentrated HCl the solution was then cooled to 0–5°C in an ice bath. A solution of sodium nitrite (2.5 mmol, 0.1 g) in water (5 ml) was then added drop wise with continues stirring. The diazonium solution was added portion wise to a solution prepared by mixing a suspension of **VIIIa–c** (2.5 mmol) in 10 ml of ethanol with sodium acetate (0.12 g), the temperature was maintained at 0–5°C

with continues stirring for a few hours, the mixture was then kept cold overnight, poured onto ice-water, the precipitated crude dyes were collected by filtration, washed with water repeatedly, and dried.

3 | CONCLUSIONS

The antifungal and antibacterial activities of the synthesized compounds may be due to the pyrimidine, carboxamide, and thiazol groups. Addition of methylbenzylidene to the compound containing pyrimidine carboxamide and thiazol ring boosted its antifungal activity. More over the presence of chlorophenyl diazenyl and thiophen-2-yl to the pyrimidine carboxamide and thiazol ring decreased their antifungal activity.

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