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ORIGINAL ARTICLE

Synthesis of some thiopyrimidine and thiazolopyrimidines starting from 2,6-dibenzylidene-3-methylcyclohexanone and its antimicrobial activities

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2,6-Dibenzylidene-3-methyl-cyclohexanone;
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Abstract A series of novel N-substituted arylidene, pyrazole, thioxopyrimidine and thiazolopyrimidine derivatives **2**–**7** were synthesized by initial reactions of 2-methyl-cyclohexanone with aromatic aldehydes to give 2,6-dibenzylidene-3-methylcyclohexanone **2**. Some of the synthesized compounds were tested as antimicrobial agents. The detailed synthesis, spectroscopic data, and antimicrobial activities of the synthesized compounds were reported.

1. Introduction

Some of the pyrimidine and fused heterocyclic pyrimidine derivatives have provided to be active antiviral, antitumor, analgesic and antimicrobial (Amr et al., 2006; Mohamed et al., 2010; Amr et al., 2009; Said et al., 2009; Mostafa et al., 2008; Abd El-Hafez et al., 2009; Mohamed et al., 2008; El-Gaby et al., 1999; Sayed and Ali, 2008; Mc Guigan and Balzarini, 2006). In addition, pyrimidothiazine, thiazolopyrimidine and oxazolidinione derivatives are antimicrobial agents (Tozkoparan et al., 1999; Leach et al., 2007). Recently, we have found that certain substituted pyrimidine and their heterocyclic derivatives show antimicrobial, anti-inflammatory (Amr et al., 2006; Amr and Abdalla, 2006; Amr et al., 2005) and antitumor activities (Abo-Ghalia et al., 2004; Hammam et al., 2003). On the other hand, thioxopyrimidine and thiazolopyrimidine derivatives have promising biological and anticancer activities (Amr and Abdulla, 2002; Sayed et al., 2007; Hafez et al., 2008; El-Gazzar et al., 2009; Hebat-Allah et al., 2010). In view of these observations and in continuation of our previous work in heterocyclic chemistry, we synthesized some new pyrimidine and thiazolopyrimidine derivatives and tested their antimicrobial activities.

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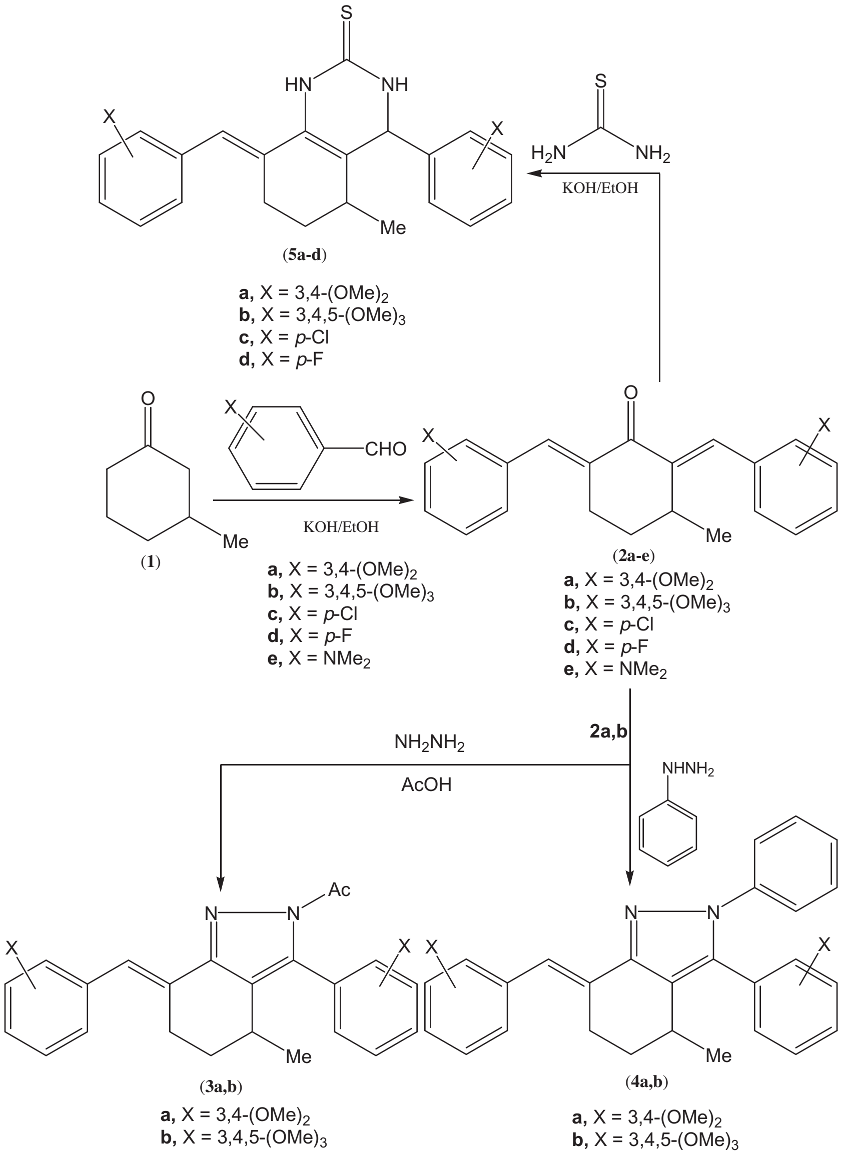
2. Results and discussion

A reaction of 3-methylcyclohexanone 1 with aromatic aldehydes, namely, 3,4-dimethoxy-, 3,4,5-trimethoxy-, *p*-chloro-, *p*-flouro-, or *p-N,N*-dimethylaminobenzaldehyde in ethanolic potassium hydroxide gave the corresponding bis-arylmethylene derivatives **2a–e**, respectively (Amr et al., 2006; Hammam et al., 2003). Thioxopyrimidine derivatives **5a–d** were obtained from the reaction of the arylmethylene derivatives **2a–d** with thiourea in refluxing ethanolic potassium hydroxide. Condensation of compound **2a**,**b** with hydrazine hydrate in glacial acetic acid or with phenyl hydrazine in absolute ethanol in the presence of triethylamine as a catalyst afforded the corresponding pyrazole derivatives **3a**,**b** and **4a**,**b**, respectively (Scheme 1).

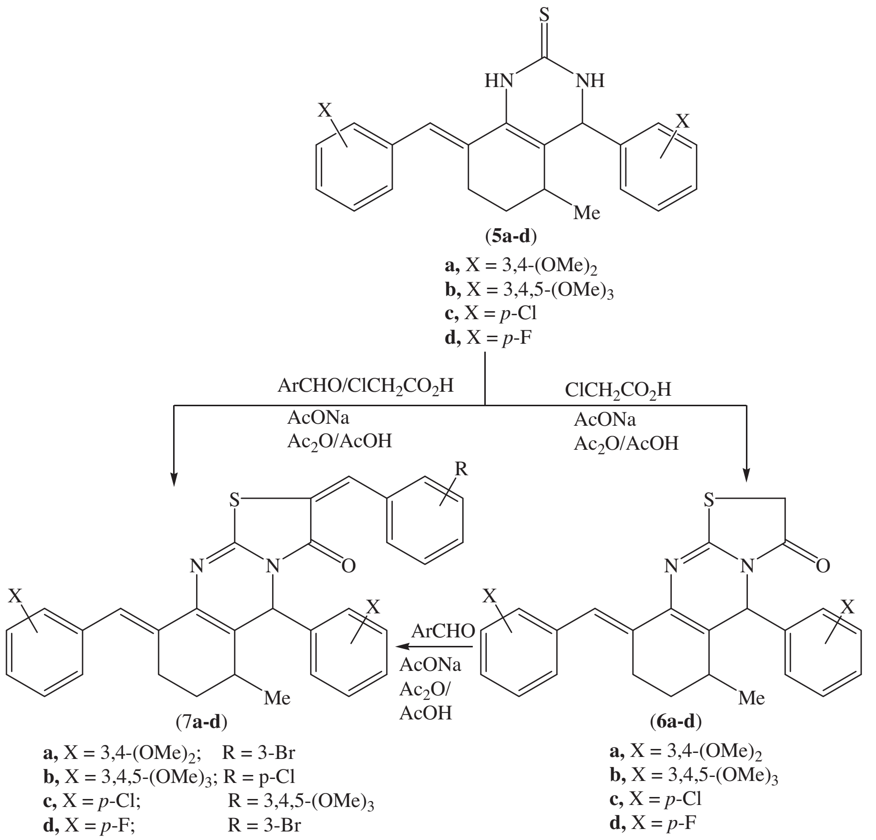
Thioxopyrimidines **5a–d** were condensed with chloroacetic acid in a mixture of acetic acid/acetic anhydride in the presence of anhydrous sodium acetate to yield the corresponding thiazolopyrimidines **6a–d**, which were condensed with aromatic aldehydes, namely, 3-bromo- or *p*-chloro- or 3,4,5-trimethoxy- or 3-bromobenzaldehyde in the presence of anhydrous sodium acetate and glacial acetic acid/acetic anhydride to yield the target arylmethylene thiazolopyrimidine derivatives **7a–d**, respectively. However, the latter compounds were also prepared directly from **5a–d** by the action of chloroacetic acid, aromatic aldehydes, namely, 3-bromo- or *p*-chloro- or 3,4,5-trimethoxy- or 3-bromobenzaldehyde and anhydrous sodium acetate in the presence of an acetic acid/acetic anhydride (Scheme 2).

3. Antimicrobial activity

Preliminary biological activity screening of the synthesized compounds has been performed against microorganisms representing Gram-positive bacteria (*Bacillus subtilis, Bacillus aureus* and *Staphylococcus aureus*), Gram-negative bacteria



Scheme 1 Synthetic routes of compounds 2-5.



Scheme 2 Synthetic routes of compounds **6a–d** and **7a–d**.

(*Escherichia coli*), yeast (*Candida albicans*) and fungi (*Aspergillus niger*), using the bioassay technique of antibiotics (Abou-Zeid and Shehata, 1969) specified in US pharmacopeia at 50 µg/ml. The most active compounds are: **3b**, **4b**, **5c**, **6a**, 7a and **7d** (*Bacillus subtilis*), **2e**, **3a**, **4a**, **5b**, 6c and **7b** (*Bacillus aureus*), **2b**, **2e**, **4b**, **5d**, 6d and **7c** (*Staphylococcus aureus*), **2d**, **3b**, 6b and **7b** (*Escherichia coli*), **2c**, **3a**, **6a**, 7a and **7c** (*Candida albicans*), **2c**, **4a**, **5a**, **5d**, 6c and **7b** (*Aspergillus niger*). Ampicillin and chloramphenicol were used as standards. The results obtained are summarized in Table 1.

4. Conclusion

From the obtained results, we can conclude that thiazolopyrimidine and substituted thiazolopyrimidine moieties fused to 3-methycyclohexane ring are essential for antimicrobial activities. Additionally, the difference in activity between the compounds which is due to the presence of substituents in the phenyl group of the molecule.

5. Experimental section

Melting points were determined on open glass capillaries using an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Elemental analyses were performed on the Elementar, Vario EL, Micro-analytical Unit, National Research Centre, Cairo, Egypt and were found within ±0.4% of the theoretical values. Infrared spectra were recorded on the Carlzeise Spectrophotometer model "UR 10" spectrophotometer using the KBr disc technique. ^{1}H NMR spectra were recorded on the Varian Gemini 270 MHz spectrometer (DMSO-d$_6$) and the chemical shifts are given in δ (ppm) which used TMS as an internal standard. The mass spectra were measured using a Finnigan SSQ 7000 mass spectrometer. Follow-up of the reactions and checking of the purity of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60 F$_{254}$, Merck, Darmstadt, Germany). Compounds 2,6-bis-(3,4-dimethoxy-benzylidene)-3-methylcyclohexanone **2a** and 2,6-bis-(p-chlorobenzylidene)-3-methylcyclohexanone **2c** were reported before in the previous literatures (Vorlander, 1925; Nerdel and Kreseze, 1955).

*5.1. Synthesis of 2,6-bisarylmethylene-3-methylcyclohexanones (**2a–e**)*

5.1.1. Method A

A mixture of 3-methylcyclohexanone 1 (1.12 g, 10 mmol) and aromatic aldehydes, namely, 3,4-dimethoxy-, 3,4,5-trimethoxy-, p-chloro- or p-fluoro-, p-*N,N*-dimethylaminobenzaldehyde (20 mmol) in MeOH (50 mL) in the presence of sodium methoxide (10 mmol) was left for 14 days at room temperature. The obtained solid was filtered off, dried and crystallized from the proper solvent to give the corresponding arylmethylene derivatives **2a–e**, respectively.

5.1.2. Method B

To a mixture of 3-methylcyclohexanone 1 (1.12 g, 10 mmol), the appropriate aromatic aldehydes, namely, 3,4-dimethoxy-, 3,4,5-trimethoxy-, p-chloro-, p-fluoro- or p-*N,N*-dimethyl aminobenzaldehyde (20 mmol) in ethanol (50 mL), potassium hydroxide (10 mmol) in 5 mL H$_2$O was added. The reaction

Table 1 Antimicrobial activity of the newly synthesized compounds.

Comp. No.	Inhibition zones (cm)					
	Gram-positive bacteria			Gram-negative bacteria	Yeast	Fungi
	Bacillus subtilis	*Bacillus aureus*	*Staphylococcus aureus*	*Escherichia coli*	*Candida albicans*	*Aspergillus niger*
2a	1.05	1.35	1.20	–	–	1.75
b	1.00	1.55	1.85	0.65	–	0.90
c	0.95	1.25	–	0.45	0.65	2.10
d	0.75	–	0.95	0.70	–	–
e	1.15	1.95	1.85	0.55	–	0.85
3a	1.55	2.05	1.10	0.60	0.70	–
b	1.95	–	–	0.70	–	1.50
4a	1.40	1.85	1.00	–	–	1.95
b	1.75	1.15	1.90	0.50	–	1.60
5a	0.95	1.05	–	–	–	2.05
b	0.90	2.00	1.05	0.50	–	1.55
c	1.90	1.55	0.90	–	–	–
d	1.05	1.65	1.95	0.45	–	2.00
6a	1.85	1.70	0.95		0.55	–
b	0.95	–	0.90	0.75	–	1.65
c	0.90	2.00	0.85	0.60	–	2.10
d	1.10	1.75	1.85	–	–	1.45
7a	1.85	1.60	1.05	–	0.80	–
b	0.90	2.05	1.00	0.65	–	2.05
c	0.80	1.75	1.90	0.55	0.70	–
d	1.90	1.60	1.15	–	–	1.70
Ampicillin	1.15	2.50	1.30	0.75	–	2.30
Chloramphinicol	2.00	2.10	2.00	0.95	–	2.10

mixture was stirred at room temperature for 2 h, the solid formed was collected by filtration and crystallized from the proper solvent to give the corresponding arylmethylene derivatives **2a**–**e**, respectively.

*5.1.3. 2,6-Bis-(3,4-dimethoxybenzylidene)-3-methylcyclohexanone (**2b**)*

Yield 95% [A], 82% [B]; mp 157–159 °C (EtOH); IR (KBr, cm^{-1}): 1680, 1660; ^{1}H NMR: 7.72 and 7.65 (2s, 2H, benzylic proton), 7.54 and 7.33 (2s, 4H, ArH), 3.83, 3.75, 3.61 (3s, 18H, 6OCH$_3$), 3.28 (m, 1H, CH), 1.92–1.54 (m, 4H, cyclohexene protons), 1.24 (d, J = 6.8 Hz, 3H, CH$_3$); MS (EI): m/z 468 [M$^+$] (100), 453 [M$^+$-CH$_3$] (65), 285 [453-Ph(OCH$_3$)$_3$, H] (54); Anal. Calcd for $C_{27}H_{32}O_7$: C, 69.21; H, 6.88. Found: C, 69.18; H, 6.84.

*5.1.4. 2,6-Bis-(p-fluorobenzylidene)-3-methylcyclohexanone (**2d**)*

Yield 85% [A], 78% [B]; mp 103–105 °C (EtOH); IR (KBr, cm^{-1}): 1658, 1598; ^{1}H NMR: 7.70 and 7.68 (2s, 2H, benzylic protons), 7.54–7.33 (m, 8H, ArH), 3.51 (m, 1H, CH), 2.92–1.85 (m, 4H, cyclohexene protons), 1.26 (d, J = 6.8 Hz, 3H, CH$_3$); MS (EI): m/z 324 [M$^+$] (100), 296 [M$^+$-C=O] (38), 281 [296-CH$_3$] (37); Anal. Calcd for $C_{21}H_{18}F_2O$: C, 77.76; H, 5.59. Found: C, 77.73; H, 5.57.

*5.1.5. 2,6-Bis-(p-N-dimethylbenzylidene)-3-methylcyclohexanone (**2e**)*

Yield 80% [A], 65% [B]; mp 123–125 °C (EtOH); IR (KBr, cm^{-1}): 1681, 1663; ^{1}H NMR: 7.54 and 7.32 (2s, 2H, benzylic protons), 7.28–6.87 (m, 8H, ArH), 2.94, 2.81 (2s, 12H, 4-NCH$_3$), 3.45 (m, 1H, CH), 2.86–1.64 (m, 4H, cyclohexene protons), 1.18 (d, J = 6.80 Hz, 3H, CH$_3$); MS (EI): m/z 374 [M$^+$] (100), 359 [M$^+$-CH$_3$] (65), 239 [359-Ph-N-CH$_3$)$_2$]; Anal. Calcd for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 80.07; H, 8.00; N, 7.42.

*5.2. Synthesis of **3a**,**b** and **4a**,**b***

To a solution of compounds **2a**,**b** (5 mmol) in acetic acid (50 mL), hydrazine hydrate or phenylhydrazine (5 mmol) was added. The reaction mixture was refluxed for 3 h, after cooling; the mixture was poured onto cold water. The obtained solid was collected by filtration, dried and crystallized from the proper solvent to give the corresponding indazole derivatives **3a**,**b** and **4a**,**b**, respectively.

*5.2.1. 2-Acetyl-7-(34-dimethoxybenzylidene)-3-(3,4-dimethoxyphenyl)-4-methyl-3,3a,4,5,6,7-hexahydro-2H-indazole (**3a**)*

Yield 55%; mp: 161–163 °C (EtOH); IR (KBr, cm^{-1}): 1627, 1673; ^{1}H NMR: 7.53–6.68 (m, 7H, ArH + CH-benzylic), 4.58 (d, J = 7.20 Hz, 1H, CH), 3.92, 3.88 (2s, 12H, 4OCH$_3$), 3.32 (m, 1H, CH), 2.74 (m, 2H, CH$_2$), 2.51 (s, 3H, COCH$_3$), 1.89 (m, 1H, CH), 1.65 (m, 2H, CH$_2$), 1.42 (d, J = 6.76 Hz, 3H, CH$_3$); MS (EI): m/z 464 [M$^+$] (100), 284 [M$^+$-dimethoxy-benzyl-idene] (45); Anal. Calcd for $C_{27}H_{32}N_2O_5$: C, 69.81; H, 6.94; N, 6.03. Found: C, 69.76; H, 6.90; N, 5.95.

*5.2.2. 2-Acetyl-7-(3,4,5-trimethoxybenzylidene)-3-(3,4,5-trimethoxyphenyl)-4-methyl-3,3a,4,5,6,7-hexahydro-2H-indazole (**3b**)*

Yield 52%; mp 208–210 °C (Dioxane); IR (KBr, cm^{-1}): 1625, 1670; ^{1}H NMR: 7.12–6.65 (m, 5H, ArH + benzylic proton), 4.68 (d, J = 7.18 Hz, 1H, CH), 3.82, 3.73, 3.65 (3s, 18H, 6OCH$_3$), 3.45 (m, 1H, CH), 2.82 (m, 2H, CH$_2$), 2.43 (s, 3H, COCH$_3$), 2.12 (m, 1H, CH), 1.87 (m, 2H, CH$_2$), 1.34 (d, J = 6.75 Hz, 3H, CH$_3$); MS (EI): m/z 524 [M$^+$] (57), 481 [M$^+$-COCH$_3$] (100), 313 [481-trimethoxy-benzilidine, H] (74), 287 [313-CN]; Anal. Calcd for $C_{29}H_{36}N_2O_7$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.32; H, 6.86; N, 5.28.

*5.2.3. 7-(3,4-Dimethoxybenzylidene)-3-(3,4-dimethoxyphenyl)-2-phenyl-4-methyl-3,3a,4,5,6,7-hexahydro-2H-indazole (**4a**)*

Yield 65%; mp 127–129 °C (MeOH); IR (KBr, cm^{-1}): 1650; ^{1}H NMR: 7.71–6.68 (m, 12H, ArH + benzylic proton), 4.58 (d, J = 7.25 Hz, 1H, CH), 3.95, 3.93 (2s, 12H, 4OCH$_3$), 3.32 (m, 1H, CH), 2.74 (m, 2H, CH$_2$), 1.89 (m, 1H, CH), 1.65 (m, 2H, CH$_2$), 1.42 (d, J = 6.75 Hz, 3H, CH$_3$); MS (EI): m/z 498 [M$^+$] (15), 408 [M$^+$-PhNH] (100), 285 [408-4OCH$_3$ -H] (74), 257 [285- N,CH$_2$] (54); Anal. Calcd for $C_{31}H_{34}N_2O_4$: C, 74.67; H, 6.87; N, 5.62. Found: C, 74.60; H, 6.81; N, 5.56.

*5.2.4. 7-(3,4,5-Trimethoxybenzylidene)-3-(3,4,5-trimethoxyphenyl)-2-phenyl-4-methyl-3,3a,4,5,6,7-hexa-hydro-2H-indazole (**4b**)*

Yield 60%; mp 133–135 °C (EtOH); IR (KBr, cm^{-1}): 1656; ^{1}H NMR: 7.34–6.62 (m, 10H, ArH + CH-benzylic), 4.58 (d, J = 7.30 Hz, 1H, CH), 3.93, 3.88, 3.82 (3s, 18H, 6OCH$_3$), 3.32 (m, 1H, CH), 2.80 (d, 2H, CH$_2$), 1.94 (m, 1H, CH), 1.62 (m, 2H, CH$_2$), 1.27 (d, J = 6.82 Hz, 3H, CH$_3$); MS (EI): m/z 558 [M$^+$] (100), 377 [M$^+$-trimethoxybenzylidene] (25), 255 [377-PhNN, OCH$_3$] (18); Anal. Calcd for $C_{33}H_{38}N_2O_6$: C, 70.95; H, 6.86; N, 5.01. Found: C, 70.90; H, 6.80; N, 4.95.

*5.3. Synthesis of 8-(substituted-benzylidene)-4-(substituted-phenyl)-5-methyl-3,4,5,6,7,8-hexahydro-1H-quinazoline-2-thione (**5a–d**)*

A mixture of compound **2a–d** (10 mmol) and thiourea (0.76 g, 10 mmol) in ethanolic potassium hydroxide (2 g in 100 mL ethanol) was refluxed for 3 h. The reaction mixture was poured onto cold water acidified with hydrochloric acid (1N); the obtained precipitate was filtered off, washed with water, dried and crystallized from the proper solvent to give the corresponding thioxopyrimidine derivatives **5a–d**, respectively.

*5.3.1. 8-(3,4-Dimethoxybenzylidene)-4-(3,4-dimethoxyphenyl)-5-methyl-3,4,5,6,7,8-hexahydro-1H-quina-zoline-2-thione (**5a**)*

Yield 85%; mp 204–206 °C (EtOH); IR (KBr, cm^{-1}): 3400–3320, 1600, 1250; ^{1}H NMR: 8.89, 9.15 (2s, 2H, 2NH exchangeable with D$_2$O), 7.19–7.03 (m, 7H, ArH + benzylic proton), 5.42 (d, J = 7.32 Hz, 1H, CH), 3.85, 3.78 (2s, 12H, 4OCH$_3$), 3.48 (m, 1H, CH), 2.98–1.80 (m, 4H, 2CH$_2$), 1.31 (d, J = 6.68 Hz, 3H, CH$_3$); MS (EI): m/z 466 [M$^+$] (68.6), 382 [M$^+$-C=S, 2NH] (100), 205 [414-CH$_2$-C=CH-Ph(OCH$_3$)$_2$] (54); Anal. Calcd for $C_{26}H_{30}N_2O_4S$: C, 66.92; H, 6.48; N, 6.00; S, 6.87. Found: C, 66.90; H, 6.46; N, 5.99; S, 6.85.

*5.3.2. 8-(3,4,5-Timethoxybenzylidene)-4-(3,4,5-trimethoxyphenyl)-5-methyl-3,4,5,6,7,8-hexahydro-1H-quinazoline-2-thione (**5b**)*

Yield 90%; mp 152–154 °C (MeOH); IR (KBr, cm^{-1}): 3368–3312, 1610, 1248; ^{1}H NMR: 9.30, 9.10 (2s, 2H, 2NH exchangeable with D$_2$O), 7.43 (s, 1H, benzylic proton), 6.94, 6.86 (2s, 4H, ArH), 5.21 (d, J = 7.29 Hz, 1H, CH), 3.44 (m, 1H, CH), 2.4–1.80 (m, 4H, 2CH$_2$), 1.23 (d, J = 6.68 Hz, 3H, CH$_3$); MS (EI): m/z 526 [M$^+$] (68.6), 348 [M$^+$-trimethoxybenzlidine] (100), 181 [348-trimethoxyphenyl, 3H] (62); Anal. Calcd for $C_{28}H_{34}N_2O_6S$: C, 63.85; H, 6.50; N, 5.32; S, 6.08. Found: C, 63.87; H, 6.47; N, 5.31; S, 6.05.

*5.3.3. 8-(p-Chlorobenzylidene)-4-(p-chlorophenyl)-5-methyl-3,4,5,6,7,8-hexahydro-1H-quinazoline-2-thione (**5c**)*

Yield 85%; mp: 230–232 °C (EtOH); IR (KBr, cm^{-1}): 3350–3255, 1605, 1252; ^{1}H NMR: 9.50, 9.20 (2s, 2H, 2NH exchangeable with D$_2$O), 7.60–7.20 (m, 9H, ArH + CH-benzylic), 5.34 (d, J = 7.48 Hz, 1H, CH), 3.20 (m, 1H, CH), 2.40–1.80 (m, 4H, 2CH$_2$), 1.18 (d, J = 6.72 Hz, 3H, CH$_3$); MS (EI): m/z 414 [M$^+$] (68), 413 [M$^+$-H] (100), 303 [414- *p*-Cl-Ph] (54), 176 [303- *p*-Cl-Ph, CH$_3$, H] (43); Anal. Calcd for $C_{22}H_{20}Cl_2N_2S$: C, 63.61; H, 4.85; Cl, 17.07; N, 6.74; S, 7.72. Found: C, 63.67; H, 4.82; Cl, 17.00; N, 6.72; S, 7.73.

*5.3.4. 8-(p-Fluorobenzylidene)-4-(p-fluorophenyl)-5-methyl-3,4,5,6,7,8-hexahydro-1H-quinazoline-2-thione (**5d**)*

Yield 87%; mp 173–175 °C (MeOH); IR (KBr, cm^{-1}): 3380–3290, 1602, 1245; ^{1}H NMR: 9.70, 9.40 (2s, 2H, 2NH exchangeable with D$_2$O), 7.74–7.36 (m, 9H, ArH + CH-benzylic), 5.28 (d, J = 7.25 Hz, 1H, CH), 3.29 (m, 1H, CH), 2.78–1.96 (m, 4H, 2CH$_2$), 1.19 (d, J = 6.80 Hz, 3H, CH$_3$); MS (EI): m/z 382 [M$^+$] (100), 287 [M$^+$-(*p*-F-Ph)] (65), 146 [287-(*p*-F-Ph), SH] (54); Anal. Calcd for $C_{22}H_{20}F_2N_2S$: C, 69.08; H, 5.27; N, 7.32; S, 8.38. Found: C, 69.05; H, 5.30; N, 7.31; S, 8.34.

*5.4. Synthesis of 9-(substituted-benzylidene)-5-(substituted-phenyl)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazolin-3-one (**6a–d**)*

A mixture of compound **5a–d** (2 mmol), chloroacetic acid ($\sim$0.1 g, 2 mmol), sodium acetate anhydrous (25 g) glacial acetic acid and acetic anhydride (40 mL, 3:1) was refluxed for 3 h. After cooling, the reaction mixture was poured gradually with stirring onto cold water, the solid formed was filtered off, washed with water, dried and crystallized from proper solvent to give the corresponding thiazolopyrimidine derivatives **6a–d**, respectively.

*5.4.1. 9-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo [2,3-b]quinazolin-3-one (**6a**)*

Yield 70%; mp 104–106 °C (EtOH); IR (KBr, cm^{-1}): 1718, 1639; ^{1}H NMR: 7.52 (s, 1H, benzylic proton), 7.48–7.32 (m, 6H, ArH), 5.54 (s, 1H, CH), 3.82 (s, 2H, CH$_2$, thiazole), 2.89 (m, 2H, CH$_2$), 2.46 (m, 1H, CH), 1.76 (m, 2H, CH$_2$), 1.10 (d, J = 6.74 Hz, 3H, CH$_3$); MS (EI): m/z 466 [M$^+$] (68), 382 [M$^+$-C=S, CHCH$_2$CH$_3$, 2H], 205 [382-3,4-dimethoxybenzlidene, CH$_2$]; Anal. Calcd for $C_{28}H_{30}N_2O_5S$: C, 66.38; H, 5.96; N, 5.53; S, 6.33. Found: C, 66.35; H, 5.99; N, 5.50; S, 6.31.

*5.4.2. 9-(3,4,5-Trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazolin-3-one (**6b**)*

Yellow solid, yield 65%; mp: 135–137 °C (MeOH); IR (KBr, cm^{-1}): 1724, 1626; ^{1}H NMR: 7.48 (s, 1H, benzylic proton), 7.41, 7.32 (2s, 4H, ArH), 5.49 (s, 1H, CH), 3.79 (s, 2H, CH$_2$, thiazole), 2.88 (m, 2H, CH$_2$), 2.35 (m, 1H, CH), 1.69 (m, 2H, CH$_2$), 1.00 (d, J = 6.68 Hz, 3H, CH$_3$); MS (EI): m/z 566 [M$^+$] (68), 565 [M$^+$-H] (100), 506 (45), 369 (16), 233

(75); Anal. Calcd for $C_{30}H_{34}N_2O_7S$: C 63.59, H 6.05, N 4.94, S 5.66, found: C 63.52, H 5.98, N 4.88, S 5.60.

5.4.3. *9-(p-Chlorobenzylidene)-5-(p-chlorophenyl)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]-quinazolin-3-one (**6c**)*

Yellow solid, yield 80%; mp: 158–160 °C (EtOH); IR (KBr, cm^{-1}): 1724, 1622; ^1H NMR: 7.58 (s, 1H, benzylic proton), 7.76–7.23 (m, 8H, ArH), 5.53 (s, 1H, CH), 3.79 (s, 2H, CH_2, thiazole), 2.68 (m, 2H, CH_2), 2.35 (m, 1H, CH), 1.98 (m, 2H, CH_2), 1.12 (d, J = 6.69 Hz, 3H, CH_3); MS (EI): m/z 454 [M^+-1] (83), 343 [M^+-(*p*-chlorophenyl)] (100), 217 [343-(*p*-chlorophenyl), CH_3] (54); Anal. Calcd for $C_{24}H_{20}Cl_2N_2OS$: C 63.29, H 4.42, N 6.15, S 7.04, found: C 63.25, H 4.40, N 6.12, S 7.06.

5.4.4. *9-(p-Fluorobenzylidene)-5-(p-fluorophenyl)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]-quina-zolin-3-one (**6d**)*

Yellow solid, yield 75%; mp: 198–200 °C (MeOH); IR (KBr, cm^{-1}): 1730, 1615; ^1H NMR: 7.53 (s, 1H, benzylic proton), 7.42–6.95 (m, 8H, ArH), 5.50 (s, 1H, CH), 3.72 (s, 2H, CH_2, thiazole), 2.70 (m, 2H, CH_2), 2.30 (m, 1H, CH), 1.50 (m, 2H, CH_2), 1.15 (d, J = 6.66 Hz, 3H, 6-CH_3); MS (EI): m/z 422 [M^+] (100), 327 [M^+-(*p*-fluorophenyl)], 299 [327-C=O]; Anal. Calcd for $C_{24}H_{20}N_2F_2OS$: C 68.22, H 4.77, N 6.63, S 7.59. Found: C 68.20, H 4.79, N 6.60, S 7.55.

5.5. *Synthesis of 2,9-bi(substituted-benzylidene)-5-(substituted-phenyl)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazolin-3-one (**7a–d**)*

5.5.1. *Method A*

A mixture of compounds **5a–d** (2 mmol), chloroacetic acid (2 mmol), sodium acetate anhydrous (2 g) in glacial acetic acid and acetic acid anhydride (40 mL, 3:1) was refluxed for 12 min., then equimolecular amount of the appropriate aromatic aldehydes, namely, 3-bromo- or *p*-chloro- or 3,4,5-trimethoxy- or 3-bromobenzaldehyde (2 mmol) was added. The reaction mixture was refluxed for 2 h, allowed to cool, poured onto cold water; the formed precipitate was filtered off, dried and crystallized from proper solvent to give the corresponding arylmethylene thiazolopyrimidine derivatives **7a–d**, respectively.

5.5.2. *Method B*

A mixture of compounds **6a–d** (2 mmol), equimolecular amount of appropriate aromatic aldehydes, namely, 3-bromo- or *p*-chloro- or 3,4,5-trimethoxy- or 3-bromobenzaldehydes (2 mmol) in amixtur of acetic acid and acetic anhydride (40 mL, 1:3 ratio) was refluxed for 1.5 h. After cooling, the reaction mixture was poured onto cold water; the formed solid was collected by filtration and crystallized from the proper solvent to give the corresponding arylmethylene thiazolopyrimidine derivatives **7a–d**, respectively. The products were identified by their m.p. and R_f-values in comparison with authentic samples previously obtained by method A. The yield from method A was better than from method B.

5.5.3. *9-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-2-(3-bromobenzylidene)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazolin-3-one (**7a**)*

Yellow solid, yield 76% [A] and 68% [B]; mp: 188–190 °C (EtOH); IR (KBr): 1708 cm^{-1}; ^1H NMR: 7.75, 7.68 (2s, 2H, benzylic protons), 7.40–6.61 (m, 10H, ArH), 5.63 (s, 1H, CH), 3.75, 3.73 (2s, 12H, $4OCH_3$), 2.70 (m, 2H, CH_2), 2.30 (m, 1H, CH), 1.50 (m, 2H, CH_2), 1.16 (d, J = 6.82 Hz, 3H, CH_3); MS (EI): m/z 672 [M^+] (58), 421 [M^+- (dimethoxy-benzlidine, $2OCH_3$, C=O, CH_3)] (100), 165 [421-(3-bromobenzylidene, CH=Ph)] (21); Anal. Calcd for $C_{35}H_{33}BrN_2O_5S$: C 62.40, H 4.93, N 4.15, S 4.75, found: C 62.36, H 4.90, N 4.11, S 4.72.

5.5.4. *9-(3,4,5-Trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-2-(p-chlorobenzylidene)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazolin-3-one (**7b**)*

Orange crystals, yield 60% [A] and 55% [B]; mp: 210–212 °C (EtOH); IR (KBr): 1706 cm^{-1}; ^1H NMR: 7.84, 7.73 (2s, 2H, benzylic protons), 7.44–6.92 (m, 8H, ArH), 5.53 (s, 1H, CH-), 3.82, 3.79, 3.72 (3s, 18H, $6OCH_3$), 2.70 (m, 2H, CH_2), 2.30 (m, 1H, CH), 1.50 (m, 2H, CH_2), 1.18 (d, J = 6.72 Hz, 3H, CH_3); MS (EI): m/z 688 [M^+] (24), 521 [M^+-(*p*-chlorophenyl), H] (24), 343 [521-(trimethoxybenzylidene), C=O] (100), 269 [343-thiourea]; Anal. Calcd for $C_{37}H_{37}ClN_2O_7S$: C 64.47, H 5.41, N 4.06, S 4.65, found: C 64.40, H 5.35, N 4.00, S 4.59.

5.5.5. *9-(p-Chlorobenzylidene)-5-(p-chlorophenyl)-2-(3,4,5-trimethoxybenzylidene)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazolin-3-one (**7c**)*

Yellow powder, yield 70% [A] and 65% [B]; mp: 147–149 °C (MeOH); IR (KBr): ν = 1706 cm^{-1}; ^1H NMR: 7.72, 7.50 (2s, 2H, benzylic protons), 7.48–6.97 (m, 10H, ArH), 5.56 (s, 1H, CH), 3.86 (s, 9H, $3OCH_3$), 2.70 (m, 2H, CH_2), 2.30 (m, 1H, CH), 1.50 (m, 2H, CH_2), 1.20 (d, J = 6.77 Hz, 3H, CH_3); MS (EI): m/z 633 [M^+] (46), 521 [M^+-(*p*-chlorophenyl), H] (100), 299 [521-(trimethoxybenzylidene), C=O], 209 [299-thiourea, CH_3, H]; Anal. Calcd for $C_{34}H_{30}Cl_2N_2O_4S$: C 64.45, H 4.77, N 4.42, S 5.06, found: C 64.40, H 4.72, N 4.40, S 5.00.

5.5.6. *9-(p-Fluorobenzylidene)-5-(p-fluorophenyl)-2-(3-bromobenzylidene)-6-methyl-6,7,8,9-tetrahydro-5H-thiazolo[2,3-b]quinazolin-3-one (**7d**)*

Red solid, yield 72% [A] and 64% [B]; mp: 247–249 °C (EtOH); IR (KBr): ν = 1704 cm^{-1}; ^1H NMR: 7.80, 7.60 (2s, 2H, benzylic protons), 7.70–7.60 (m, 12H, ArH), 5.8 (s, 1H, CH), 3.60 (b, 1H, CH), 2.40–1.80 (m, 4H, $2CH_2$), 1.16 (d, J = 6.67 Hz, 3H, CH_3); MS (EI): m/z 589 [M^+] (73), 493 [M^+-(*p*-fluorophenyl), H] (100), 465 [493-C=O], 251 [465-(3-bromobenzylidene), C=O, 2H]; Anal. Calcd for $C_{31}H_{23}BrF_2N_2OS$: C 63.16, H 3.93, N 4.75, S 5.43, found: C 63.10, H 3.88, N 4.70, S 5.38.

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