Microwave induced synthesis of some fused thiazoloquinazoline derivatives under solvent free conditions using LiBr as a catalyst

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Síntesis inducida por microondas de algunos derivados fundidos como tiazoloquinazolina en condiciones de ausencia de disolventes y utilizando LiBr como catalizador

Síntesi induïda per microones d'alguns derivats fosos de tiazoloquinazolina en condicions d'absència de dissolvents i utilitzant LiBr com a catalitzador

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RESUMEN

Se presentan dos métodos rápidos y eficientes para la preparación de derivados fundidos de tiazoloquinazolina por reacción de chalconas con hidroxilamina, urea e hidrato de hidrazina en condiciones de ausencia de disolventes y exposición a microondas. El objetivo del presente trabajo es sustituir sustancias químicas tóxicas, peligrosas, y altamente reactivas con bloques de síntesis menos reactivos, menos nocivos pero más selectivos que pueden activar reacciones químicas selectivas mediante una catálisis apropiada, así como sustituir tecnologías anticuadas por otras nuevas caracterizadas por la reducción de subproductos y una separación fácil de los productos.

Palabras clave: LiBr, condiciones de ausencia de disolventes, Chalconas, Isoxazoles, Pirazoles, Pirimidinas.

ABSTRACT

Two rapid and efficient methods for the preparation of fused thiazoloquinazoline derivatives by the reaction of chalcones with hydroxylamine, urea and hydrazine hydrate under solvent free condition and microwave exposure are reported. The aim of present work is to substitute toxic, dangerous, highly reactive chemicals with less reactive, less harmful but more selective building blocks which activate selective chemical reactions by proper catalysis and to replace substituted old technologies to new one characterized by the reduction of by-products and easy separation of products.

Keywords: LiBr, Solvent free condition, Chalcones, Isoxazoles, Pyrazoles, Pyrimidines.

RESUM

Es presenten dos mètodes ràpids i eficients per a la preparació de derivats fosos de tiazoloquinazolina per reacció de calcones amb hidroxilamina, urea i hidrat d'hidrazina en condicions d'absència de dissolvents i exposició a microones. L'objectiu del present treball és substituir substàncies químiques tòxiques, perilloses i altament reactives amb blocs de síntesi menys reactius, menys nocius però més selectius que poden activar reaccions químiques selectives mitjançant una catàlisi apropiada, i també substituir tecnologies antiquades per altres de noves caracteritzades per la reducció de subproductes i una separació fàcil dels productes.

Paraules clau: LiBr, condicions d'absència de dissolvents, Calcones, Isoxazols, Pirazols, Pirimidines.

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INTRODUCTION

"Preventing pollution and minimizing waste generation will gradually clean up sins of the past." In this environmental conscious era, the role of chemistry and chemists[1] involved is to incorporate processes and design products, which can eliminate or minimize the generation of associated pollutants. The increasing environmental consciousness of the chemical community has lead to search for alternative non-polluting media and processes that might reduce pollution at the source for chemical and organic synthesis[2]. Green chemistry[3] is defined as an environmentally benign chemical synthesis, which is the science based and economically driven approach to achieve the goal of environment protection. In recent years, a new technique that is set to revolutionalize organic synthesis has moved to the forefront of Green chemical research. Microwave Assisted Organic Synthesis (MAOS) is sometimes termed as microwave induced organic reaction enhancement (MORE) chemistry[4]. It can also be termed as "e-chemistry" because it is easy, effective, economical and eco-friendly and is believed to be a step towards green chemistry. MORE chemistry techniques are potentially valuable as they reduce the need of organic solvents. As a result, one can reduce the total time for compound production as well as reduce the total cost per compound[5].

The Knoevenagel condensation has been a subject of considerable interest and to effect this condensation efficiently, large number of catalysts have been explored[6,7], e.g. sodium acetate in glacial acetic acid, piperidinium benzoate in refluxing toluene, zeolite, tetrabutyl ammonium bromide, refluxing reactants in toluene at 110 ºC for 3 days, etc. Certainly these processes are not facile as they require long reaction times, high temperature and products are also obtained in low yields. LiBr can potentially replace solvents and conventional corrosive acids in many of their applications [8-11]. LiBr catalyses efficiently the three component condensation reaction of an aldehyde, β-ketoester and urea in refluxing acetonitrile to afford the corresponding dihydropyrimidinones in high yields. It is an improved procedure for the Biginelli reaction[12]. As our interest is to synthesize heterocyclic templates (quinazolinones) capable of bearing some potential pharmacophores which can enhance the inherent biological activity. The systematic propagation of heterocyclic rings in quinazolinones precursors with the installation of biological active heterocyclic units such as isoxazoles, pyrimidines and pyrazoles. Pyrimidines are found to be endowed with potential biological activity such as antitumor[13], antiviral[14], anticancer[15], antibacterial[16] and antimicrobial[17] and many others. Isoxazoles are reported to have bactericidal[18], fungicidal[19] and antimicrobial[20] activity. Pyrazoles display a number of antimicrobial activities like anticancer[21], antidiabetic[22] and antidepressants[23]. The quinazoline moiety is a useful functionality for the development of biologically interesting molecules with a wide portfolio of biological activities[24] such as hypotensive[25], antimalarial and antihypertensive[26] activities. Thus the coupling of this MORE synthesis with solvent free conditions and LiBr is expected to afford an environmentally benign synthesis of biological active compounds.

RESULTS AND DISCUSSION

4-(4-Substituted phenyl)-2-thioxo-1,2,3,4,7,8-hexahydro quinazolin-5(6H)-ones **1(a-c)** were synthesized by LiBr catalyzed cycloaddition of 1,3-cyclohexanedione, substituted benzaldehydes and thiourea under solvent free condition and microwave exposure. The structure of **1(a)** was confirmed by the IR bands at 3335 cm^{-1} due to secondary amino group, 1700 cm^{-1} due to C=O group and 1515 cm^{-1} due to C=S stretching. It is supported by the presence of a broad singlet of 2 NH protons in the region of 9.89 – 9.72 ppm in ^{1}H NMR. The compound **1(a-c)** was treated with chloroacetic acid in the presence of LiBr to give 5-(4-substituted phenyl)-8,9-dihydro-2H-thiazolo[2,3-b] quinazolin-3,6[5H,7H]-diones **2(a-c).** Compound **2(a)** was confirmed by the disappearance of NH stretch in the region of 3330 cm^{-1} in IR spectrum and appearance of an additional band at 1680 cm^{-1} due to C=O stretch of thiazolidinone moiety ^{1}H NMR spectrum of **2(a)** shows the appearance of a singlet of two protons at 3.67 ppm due to CH_2 proton of thiazolidinone nucleus. Compounds **2(a-c)** were easily condensed with 4-chlorobenzaldehyde in the presence of LiBr to furnish 2-(4-chlorobenzylidine)-5-(4-substituted phenyl)-8,9-dihydro-2H-thiazolo[2,3-b] quinazolin-3,6[5H,7H]-dione **3(a-c)**, due to the activity of methylene group of compound **2(a-c)**.

Synthesis of 2-arylmethylene derivatives **3(a-c)** were achieved in a single step by treating **1(a-c)** with chloroacetic acid and 4-chlorobenzaldehyde in the presence of catalytic amount of LiBr. The IR spectrum of compound **3(a)** shows the presence of α, β-unsaturated moiety by the appearance of carbonyl stretch at 1665 cm^{-1} due to conjugation rather than at 1680 cm^{-1} (C=O of thiazolidinone ring). Other prominent peak of C-Cl also appeared at 751 cm^{-1}. ^{1}H NMR spectrum of compound was characterized by the lack of the singlet of two protons of thiazolidinone nucleus at 3.67 ppm and appearance of a new singlet at 6.42 ppm due to arylidine proton (=CH-Ar) of chalcone moiety. Thiazoloquinazolines are convenient starting material for the synthesis of fused thiazoloquinazolines due to their α, β-unsaturated moiety. Firstly, the absence of carbonyl stretching frequency in the region of 1665 cm-1 confirms the formation of products. Isoxazolino derivatives **4(a-c)** were synthesized by the reaction of compound **3(a-c)** with equimolar ratio of hydroxylamine hydrochloride in the presence of LiBr. The structure of **4(a)** was confirmed by appearance of absorption band at 1093 m^{-1} due to C-O stretch and at 940 cm^{-1} due to N-O stretch in IR spectrum. It is supported by the presence of two doublets of two methine protons of isoxazolino moiety at about 4.83 and 3.12 ppm in ^{1}H NMR. Compounds **3(a-c)** treated with hydrazine hydrate in the presence of LiBr as a catalyst yielded 3-(4-chlorobenzylidine)-10-(4-substituted phenyl)-6,7,8-trihydro-3H,3aH,2H-pyrazolo [3'4':4,5]thiazolo [2,3-b]quinazoline-9[10H]-ones **5(a-c)**. Its structure was confirmed by the disappearance of carbonyl stretching frequency in the region of 1665 cm^{-1} in IR spectrum. The methane protons of pyrazoline ring appeared as two doublets centered at 4.98 and 3.43 ppm in its ^{1}H NMR spectrum. Pyrimidino derivatives of compounds **6(a-c)** were synthesized by the reaction of compounds **3(a-c)** with equimolar ratio of urea in the presence of LiBr as a catalyst. The IR spectrum showed a new absorption band in the region of 1687 cm^{-1} was assigned to new carbonyl group (=N-C=O) and in the region of 3327 cm^{-1} due to NH

stretch. A broad signal at 8.84 ppm was observed for the NH proton in the ^{1}H NMR spectrum and it confirms the formation of the product **6(a)**.

Antimicrobial activity

Four compounds were screened *in vitro* for their antimicrobial activities against four strains of bacteria (*Escherichia coli, Bacillus subtilis, Klebsiella pneumoniae, Pseudomonas aeuroginosa*) and two strains of fungi (*Aspergillus fumigatus, Candida albicans*) using the disc diffusion method. Commercial antibacterial ciprofloxacin and antifungal fluconazole were also screened under similar conditions for comparison. The results have been tabulated in the form of inhibition zones and activity index in Table 4.

The results revealed that all tested compounds exhibit moderate to strong activity against both fungi and E. coli. Compounds 4(a), 5(a) and 6(a) show considerable potency against A. fumigatus while against C. albicans, they are moderately active. Similarly, compound 6(a) was found to show strong activity against K. pneumonae and P. aeurogenosa. 5(a) was found to show excellent activity against K. pneumonae while against P. aeurogenosa, it exhibited moderate activity.

Table 1 *: Physical data of synthesized compounds*
a = Conventional, b = Microwave + Solvent, c = Microwave + LiBr (solvent free) under microwave irradiation

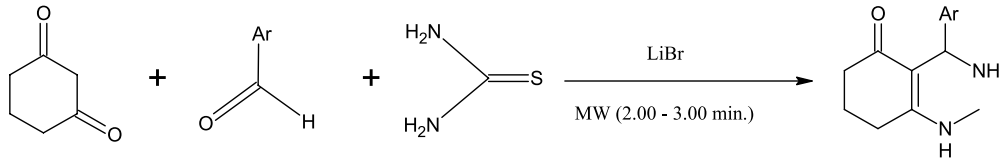
Compd.	Ar	Ar'	Mol. Formula	Mol. Weight	M.P. (°C)	Yield [a] % [Time] (hr.)	Yield [b] % [Time] (min.)	Yield [c]% [Time] (min.)
1a	4-FC_6H_4	-	C14H13N2OSF	276	275	66 [16]	69 [6]	76 [4]
1b	4-$OCH_3C_6H_4$	-	C15H16N2O2S	288	270	65 [6]	86 [5]	80 [3]
1c	-C_6H_5	-	C14H14N2OS	258	264	68 [6]	72 [4.5]	89 [2.5]
2a	4-FC_6H_4	-	C16H13N2O2SF	316	224	73 [6]	75 [4.5]	87 [3]
2b	4-$OCH_3C_6H_4$	-	C17H16N2O3S	328	220	70 [6]	76 [4.5]	87 [3]
2c	-C_6H_5	-	C16H14N2OS	298	214	68 [8]	72 [6]	86 [5]
3a	4-FC_6H_4	4-ClC6H4	C23H16N3O2SFCl	438	230	69 [8]	72 [5.5]	88 [4]
3b	4-$OCH_3C_6H_4$	4-ClC6H4	C24H19N3O3ClS	450	231	68 [6]	70 [6]	80 [5]
3c	-C_6H_5	4-ClC6H4	C23H17N2O2ClS	420	228	68 [8]	70 [6]	86 [5]
4a	4-FC_6H_4	4-ClC6H4	C23H16N3O2SFCl	452	251	79 [3]	82 [6]	90 [5]
4b	4-$OCH_3C_6H_4$	4-ClC6H4	C24H19N3O3ClS	464	239	65 [3]	80 [6]	87 [5]
4c	-C_6H_5	4-ClC6H4	C23H17N3O2ClS	434	242	61 [3]	68 [7]	75 [4.5]
5a	4-FC_6H_4	4-ClC6H4	C25H19N4O2SFCl	493	265	65 [14]	70 [7]	87 [6]
5b	4-$OCH_3C_6H_4$	4-ClC6H4	C26H22N4O3ClS	505	247	65 [14]	77 [6]	85 [6]
5c	-C_6H_5	4-ClC6H4	C25H20N4O2ClS	475	251	70 [14]	76 [6]	81 [6.5]
6a	4-FC_6H_4	4-ClC6H4	C24H16N4O2SFCl	478	215	68 [12]	75 [8]	92 [7]
6b	4-$OCH_3C_6H_4$	4-ClC6H4	C25H19N4O3ClS	490	213	64 [12]	70 [8]	87 [7]
6c	-C_6H_5	4-ClC6H4	C24H17N4O2ClS	460	221	66 [12]	74 [9]	89 [7.5]

Table 2 *: Analytical data of synthesized compounds*

Compd.	Calculated / Found (%)			
	C	H	N	S
1a	60.86 / 60.84	4.71 / 4.69	10.14 / 10.00	11.59 / 11.57
1b	62.50 / 62.48	5.55 / 5.58	9.72 / 9.68	11.11 / 10.99
1c	65.11 / 65.13	5.42 / 5.38	10.85 / 10.79	12.40 / 12.38
2a	60.75 / 60.79	2.82 / 2.83	19.61 / 19.60	10.12 / 9.90
2b	62.19 / 62.01	3.91 / 3.88	8.43 / 8.40	9.75 / 9.68
2c	64.42 / 64.36	4.69 / 4.65	8.53 / 8.58	10.73 / 10.68
3a	63.01 / 62.97	3.65 / 3.61	6.39 / 6.27	7.30 / 7.27
3b	64.00 / 64.06	4.22 / 4.16	6.22 / 6.15	7.11 / 7.07
3c	65.71 / 65.67	4.04 / 3.97	6.66 / 6.61	7.61 / 7.59
4a	61.06 / 60.98	3.53 / 3.49	9.29 / 9.27	7.07 / 7.10
4b	62.06 / 62.01	4.09 / 4.11	9.05 / 8.98	6.89 / 6.81
4c	63.59 / 63.51	3.91 / 3.94	9.67 / 9.54	7.37 / 7.28
5a	60.85 / 60.78	3.85 / 3.87	11.35 / 11.31	6.49 / 6.43
5b	61.78 / 61.72	4.35 / 4.29	11.08 / 10.98	6.33 / 6.28
5c	63.15 / 63.05	4.21 / 4.17	11.78 / 11.72	6.73 / 6.69
6a	60.25 / 60.17	3.34 / 3.36	11.71 / 11.69	6.69 / 6.63
6b	61.22 / 61.18	3.87 / 3.78	11.42 / 11.29	6.53 / 6.56
6c	62.60 / 62.55	3.69 / 3.61	12.17 / 12.09	6.95 / 6.90

Table 3*: Spectral data of synthesized compounds*

Compd.		Spectral Data
1a	IR (KBr cm^{-1}):	3067 (C-H str., Ar-H), 3335 (NH str.), 2921, 2842 (CH str., CH_2), 1700 (C=O str.), 1605, 1525 (C=C str.), 1515, 1231 (C=S amide II and amide I), 1182 (C-F str.) and 835 (Ar-H bend, 1,4-disubs.)
	^{1}H NMR δ:	9.89 – 9.72 (s, 2H, NH), 2.86 – 1.62 (m, 6H, -CH_2), 5.02 (s, 1H, CH-Ar) and 7.97 - 7.15 (m, 4H, Ar-H).
1b	IR (KBr cm^{-1}):	3062 (C-H str., Ar-H), 3328 (NH str.), 2933, 2851 (CH str., CH_2), 1710 (C=O str.), 1612, 1519 (C=C str.), 1516, 1225 (C=S amide II and amide I), 1093 (C-O str.) and 843 (Ar-H bend, 1,4-disubs.)
	^{1}H NMR δ:	9.95 – 9.62 (bs, 2H, NH), 2.90 – 1.63 (m, 6H, -CH_2), 5.09 (s, 1H, CH-Ar) and 7.93 - 7.05 (m, 4H, Ar-H).
1c	IR (KBr cm^{-1}):	3055 (C-H str., Ar-H), 3337 (NH str.), 2926, 2852 (CH str., CH_2), 1709 (C=O str.), 1607, 1527 (C=C str.) and 1524, 1222 (C=S amide II and amide I str.),
	^{1}H NMR δ:	9.83 – 9.57 (bs, 2H, NH), 2.90 – 1.63 (m, 6H, -CH_2), 5.08 (s, 1H, CH-Ar) and 7.96 - 7.03 (m, 5H, Ar-H).
2a	IR (KBr cm^{-1}):	3057 (C-H str., Ar-H), 2932, 2835 (CH str., CH_2), 1695 (C=O str.), 1680 (C=O, thiazolidinone ring), 1610 (C=N str.), 1600, 1530 (C=C str.), 1195 (C-F str.), 1115 (C-N str.), 841(Ar-H bend, 1,4-disubs.) and 695 (C-S-C str.).
	^{1}H NMR δ:	7.86 - 7.17 (m, 4H, Ar-H), 5.96 (s, 1H, CH-Ar), 3.67 (s, 2H, -CH_2, thiazolidinone ring) and 2.90 – 1.66 (m, 6H, -CH_2).
2b	IR (KBr cm^{-1}):	3047 (C-H str., Ar-H), 2918, 2845 (CH str., CH_2), 1697 (C=O str.), 1678 (C=O, thiazolidinone ring), 1611 (C=N str.), 1618, 1539 (C=C str.), 1082 (C-O str.), 1108 (C-N str.), 835 (Ar-H bend, 1,4-disubs.) and 689 (C-S-C str.).
	^{1}H NMR δ:	7.91- 7.07 (m, 4H, Ar-H), 5.93 (s, 1H, CH-Ar), 3. 55 (s, 2H, -CH_2, thiazolidino-ne ring), 3.84 (s, 3H, -OCH_3) and 2. 83 – 1.59 (m, 6H, -CH_2).
2c	IR (KBr cm^{-1}):	3049 (C-H str., Ar-H), 2925, 2842 (CH str., CH_2), 1699 (C=O str.), 1682 (C=O, thiazolidino-ne ring), 1608 (C=N str.), 1612, 1541 (C=C str.), 1101 (C-N str.) and 699 (C-S-C str.).
	^{1}H NMR δ:	7.73- 7.02 (m, 5H, Ar-H), 5.90 (s, 1H, CH-Ar), 3. 61 (s, 2H, -CH_2, thiazolidinone ring) and 2. 87 – 1.58 (m, 6H, -CH_2).
3a	IR (KBr cm^{-1}):	3075 (C-H str., Ar-H), 2954, 2851 (CH str., CH_2), 1694 (C=O str.), 1665 (C=C-C=O, chalcone carbonyl str.), 1620 (C=N str.), 1607, 1513 (C=C str.), 1175 (C-F str.), 751 (C-Cl str.), 1116 (C-N str.), 843 (Ar-H bend, 1,4-disubs.) and 681 (C-S-C str.).
	^{1}H NMR δ:	7.73 - 7.01 (m, 8H, Ar-H), 6.32 (s, 1H, =CH-Ar'), 5.59 (s, 1H, CH-Ar) and 2.89 – 1.53 (m, 6H, -CH_2).
3b	IR (KBr cm^{-1}):	3056 (C-H str., Ar-H), 2929, 2850 (CH str., CH_2), 1690 (C=O str.), 1662 (C=C-C=O, chalco-ne carbonyl str.), 1617 (C=N str.), 1616, 1503 (C=C str.), 1182 (C-O str.), 749 (C-Cl str.), 1115 (C-N str.), 749 (C-Cl str.), 842 (Ar-H bend, 1,4-disubs.) and 674 (C-S-C str.).
	^{1}H NMR δ:	7.79 - 7.07 (m, 8H, Ar-H), 6.40 (s, 1H, =CH-Ar'), 5.54 (s, 1H, CH-Ar), 3.74 (s, 3H, -OCH_3) and 2.81– 1.56 (m, 6H, -CH_2).
3c	IR (KBr cm^{-1}):	3064 (C-H str., Ar-H), 2923, 2849 (CH str., CH_2), 1701 (C=O str.), 1664 (C=C-C=O, chalcone carbonyl str.), 1628 (C=N str.), 1627, 1507 (C=C str.), 749 (C-Cl str.), 1114 (C-N str.), 747 (C-Cl str.), 839 (Ar-H Bend, 1,4-disubs.) and 684 (C-S-C str.).
	^{1}H NMR δ:	7.83 - 7.02 (m, 9H, Ar-H), 6. 34 (s, 1H, =CH-Ar'), 5.63 (s, 1H, CH-Ar) and 2.85– 1. 63 (m, 6H, -CH_2).
4a	IR (KBr cm^{-1}):	3095 (C-H str., Ar-H), 2922, 2836 (CH str., CH_2), 1703 (C=O str.), 1625 (C=N str.), 1609, 1505 (C=C str.), 1162 (C-F str.), 1093 (C-O str.), 940 (N-O str.), 816 (Ar-H bend, 1,4-disubs.), 745 (C-Cl str.), 1116 (C-N str.) and 683 (C-S-C str.).
	^{1}H NMR δ:	7.96 - 7.13 (m, 8H, Ar-H), 5.30 (s, 1H, CH-Ar), 4.83 (d, 1H, -CH-Ar' isoxazoli-ne ring), 3.12 (d, 1H, -CH-S) and 2.90 – 1.73 (m, 6H, -CH_2).
4b	IR (KBr cm^{-1}):	3080 (C-H str., Ar-H), 2918, 2849 (CH str., CH_2), 1699 (C=O str.), 1628 (C=N str.), 1617, 1510 (C=C str.), 1080 (C-O str.), 930 (N-O str.), 820 (Ar-H bend, 1,4-disubs.), 755 (C-Cl str.), 1115 (C-N str.), and 676 (C-S-C str.).
	^{1}H NMR δ:	7.61 - 7.03 (m, 8H, Ar-H), 5.28 (s, 1H, CH-Ar), 4.81 (d, 1H, -CH-Ar' isoxazoline ring), 3.82 (s, 3H –OCH_3), 3.08 (d, 1H, -CH-S) and 2.78 – 1.53 (m, 6H, -CH_2).
4c	IR (KBr cm^{-1}):	3076 (C-H str., Ar-H), 2925, 2851 (-CH str., CH_2), 1700 (C=O str.), 1630 (C=N str.), 1619, 1500 (C=C str.), 1091 (C-O str.), 943 (N-O str.), 810 (Ar-H bend, 1,4-disubs.), 749 (C-Cl str.) and 671 (C-S-C str.).
	^{1}H NMR δ:	7.81 - 7.11 (m, 9H, Ar-H), 5.27 (s, 1H, CH-Ar), 4.80 (d, 1H, -CH-Ar' isoxazoli-ne ring), 3.08 (d, 1H, -CH-S) and 2.87 – 1.61 (m, 6H, -CH_2).
5a	IR (KBr cm^{-1}):	3083 (C-H str., Ar-H), 2965, 2843 (CH str., CH_2), 1700 (C=O str.), 1627 (C=N str.), 1610, 1495 (C=C str.), 1172 (C-F str.), 824 (Ar-H bend, 1,4-disubs.), 732 (C-Cl str.), 1115 (C-N str.), and 682 (C-S-C str.).
	^{1}H NMR δ:	7.73 - 7.01 (m, 8H, Ar-H), 5.32 (s, 1H, CH-Ar), 4.98 (d, 1H, -CH-Ar' pyrazoli-ne ring), 3.43 (d, 1H, -CH-S) and 2.93 – 1.62 (m, 6H, -CH_2).
5b	IR (KBr cm^{-1}):	3080 (C-H str., Ar-H), 2954, 2847 (CH str., CH_2), 1705 (C=O str.), 1620 (C=N str.), 1611, 1505 (C=C str.), 1083 (C-O str.), 837 (Ar-H bend, 1,4-disubs.), 741 (C-Cl str.), 1114 (C-N str.), and 674 (C-S-C str.).
	^{1}H NMR δ:	7.73 – 7.01 (m, 8H, Ar-H), 5.29 (s, 1H, CH-Ar), 5.01 (d, 1H, -CH-Ar' pyrazoline ring), 3.80 (s, 3H, -OCH_3), 3.37 (d, 1H, -CH-S) and 2.87 – 1.59 (m, 6H, -CH_2).
5c	IR (KBr cm^{-1}):	3074 (C-H str., Ar-H), 2959, 2852 (CH str., CH_2), 1703 (C=O str.), 1628 (C=N str.), 1602, 1515 (C=C str.), 830 (Ar-H bend, 1,4-disubs.), 730 (C-Cl str.), 1115 (C-N str.) and 678 (C-S-C str.).
	^{1}H NMR δ:	7.69 – 7.01 (m, 9H, Ar-H), 5.26 (s, 1H, CH-Ar), 4.93 (d, 1H, -CH-Ar' pyrazoli-ne ring), 3.31 (d, 1H, -CH-S) and 2.89– 1.63 (m, 6H, -CH_2).
6a	IR (KBr cm^{-1}):	3327 (NH str.), 3015 (CH str., Ar-H), 2911, 2831 (CH str. CH_2), 1710, 1687 (C=O str.), 1620 (C=N str.), 1607, 1527 (C=C str.), 1182 (C-F str.), 730 (C-Cl str.), 841 (Ar-H bend, 1, 4-disubs.) and 678 (C-S-C str.)
	^{1}H NMR δ:	8.94 (s, 1H, NH), 7.68-7.09 (m, 8H, Ar-H), 5.23 (s, 1H, CH-Ar) and 2.86-1.61 (m, 6H, -CH_2)
6b	IR (KBr cm^{-1}):	3324(NH str.), 3025 (CH str., Ar-H), 2921, 2842 (CH str., CH_2), 1705, 1681 (C=O str.), 1630 (C=N str.), 1603, 1499 (C=C str.), 741 (C-Cl str.), 1079 (C-O str.), 837 (Ar-H bend, 1, 4-disubs.) and 669 (C-S-C str.)
	^{1}H NMR δ:	8.80 (s, 1H, NH), 7.61-7.07 (m, 8H, Ar-H), 5.25 (s, 1H, CH-Ar), 3.78 (s, 3H –OCH_3) and 2.81-1.53 (m, 6H, -CH_2)
6c	IR (KBr cm^{-1}):	3327(NH str.), 3028 (CH str., Ar-H), 2925, 2837 (CH str., CH_2), 1710, 1685 (C=O str.), 1628 (C=N str.), 1614, 1502 (C=C str.), 745 (C-Cl str.), 832 (Ar-H bend, 1, 4-disubs.) and 673 (C-S-C str.).
	^{1}H NMR δ:	8.92 (s, 1H, NH), 7.51-7.01 (m, 8H, Ar-H), 5.19 (s, 1H, CH-Ar) and 2.82-1.61 (m, 6H, -CH_2).



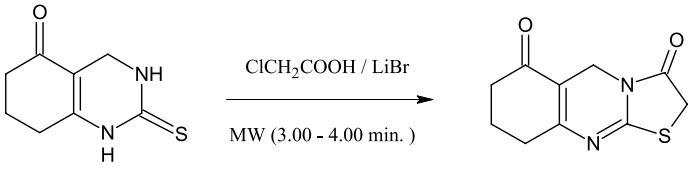
1 (a - c)

Ar = (a) 4- FC_6H_4

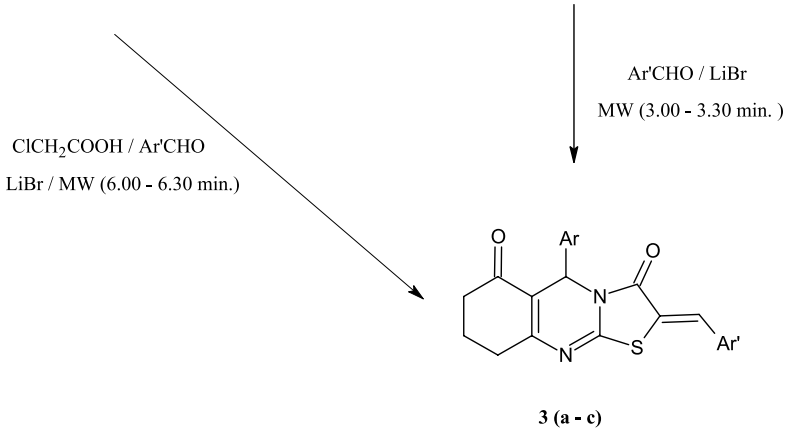
(b) 4- $OCH_3C_6H_4$

(c) -C_6H_5

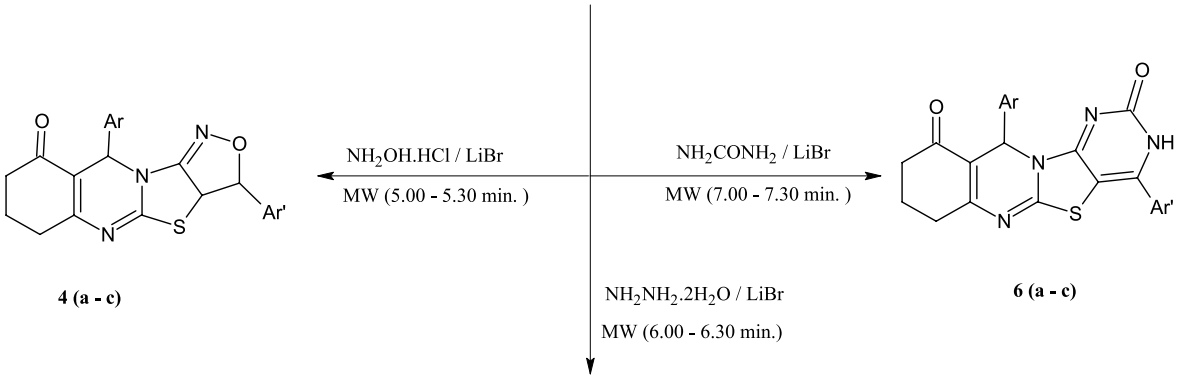
Reaction Scheme 1



1 (a - c) **2 (a - c)**



3 (a - c)



4 (a - c) **6 (a - c)**

5 (a - c)

Ar = (a) 4-FC_6H_4

(b) 4-$OCH_3C_6H_4$

(c) -C_6H_5

Ar' = 4-ClC_6H_4

Reaction Scheme II

Table 4 *: Antimicrobial activity of some synthesized compounds (500 ppm)*

Compd.	Antifungal activity (Activity index)		Antibacterial activity (Activity index)			
	A. fumigatus	*C. albicans*	*E.coli*	*B.subtilis*	*P.aeuroginosa*	*K.pneumoniae*
4a	20	19 (0.63)	17 (0.50)	15 (0.43)	24 (0.54)	13 (0.34)
5a	24	20 (0.66)	12 (0.35)	11 (0.31)	14 (0.32)	34 (0.89)
6a	22	23 (0.76)	17 (0.50)	16 (0.46)	27 (0.61)	28 (0.73)
C_1	Nil	30	-	-	-	-
C_2	-	-	34	35	44	38
[a] Activity index = Inhibition area of the sample / inhibition area of the standard.						
Standard: C_1 = Fluconazole, C_2 = Ciprofloxacin.						

EXPERIMENTAL SECTION

General Procedure

All reactions were carried out in a domestic microwave oven (Kenstar, Model No. OM-26 EGO). Melting points are uncorrected and determined in open capillaries. Reactions were monitored by thin layer chromatography using silica gel-G as adsorbent using ethyl acetate : n-hexane (7 : 3) as eluent and products were detected by iodine vapors. IR spectra (KBr pellets) were recorded on Perkin-Elmer 1800 (FTIR) spectrometer. ^{1}H NMR spectra (DMSO-d_6) were taken on a Bruker DRX spectrometer (300 MHz FT NMR) using TMS as internal standard and chemical shift were expressed in δ. Mass spectra were taken on a JEOL SX-102/PA-6000 (EI) spectrometer and elemental analysis was carried out on C, H, N analyzer (Elemental Vario Carlo Alba 1108). The results were found to be in good agreement with the calculated values (± 0.2%). The starting compounds were prepared according to reported method.

Microwave induced synthesis of 4-(4-substituted phenyl)-2-thioxo-1,2,3,4,7,8-hexahydro quinazolin-5(6H)-ones 1(a - c):

A mixture of thiourea (0.01 mole), aromatic aldehydes (0.01 mole), 1,3-cyclohexadione (0.01 mole) and LiBr (10 mole %) was mixed with a glass rod and placed in small conical flask at room temperature. The mixture was then exposed to microwave radiations at 80 % power for 2-3 minutes. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and it was stirred for 5 minutes. The solid thus obtained was filtered, dried and recrystallized from ethanol.

Conventional synthesis of 4-(4-substituted phenyl)-2-thioxo-1,2,3,4,7,8-hexahydro quinazolin-5(6H)-ones 1(a-c):

A mixture of thiourea (0.01 mole), aromatic aldehydes (0.01 mole), 1,3-cyclohexadione (0.01 mole), absolute alcohol (25 mL) and 36% HCl (1 mL) was refluxed for about 5 hr on a water bath. The solvent was removed and residue was recrystallized from ethanol to yield compound **1(a – c).**

Microwave induced synthesis of 5-(4-substituted phenyl)-8, 9-dihydro-2H-thiazolo [2, 3-b] quinazolin-3, 6[5H,7H]-diones 2(a-c):

Compound **1(a-c)** (0.01 mole), chloroacetic acid (0.01 mole) and LiBr (10 mole %) was placed in small conical flask and mixed with a glass rod at room temperature. The mixture was then exposed to microwave radiations at 60 % power for 3-4 minutes. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and it was stirred for 5 minutes. The solid thus obtained was filtered, dried and recrystallized from ethanol.

Conventional synthesis of 5-(4-substituted phenyl)-8,9-dihydro-2H-thiazolo[2,3-b]quinazolin-3,6[5H,7H]-diones 2(a-c):

Compound **1(a-c)** (0.01 mole), chloroacetic acid (0.01 mole) and fused CH_3COONa (0.5 g) in acetic acid (10 mL) was refluxed for about 7 hr on a heating mantle. After cooling, the reaction mixture was poured into ice cold water. The solid separated was filtered off and recrystallized from ethanol to obtain compounds **2(a-c)**.

Microwave induced synthesis of 2-(4-chlorobenzylidine)-5-(4-substituted phenyl)-8,9-dihydro-2H-thiazolo[2,3-b]quinazolin-3,6[5H,7H]-diones 3(a-c):

Method – 1

Compound **2(a-c)** (0.01 mole), 4-chlorobenzaldehyde (0.01 mole) and LiBr (10 mole %) were mixed with mortar-pestle and placed in small conical flask at room temperature. The mixture was then exposed to microwave radiations at 50% power for 3-3.30 minutes. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and it was stirred for 5 minutes. The solid thus obtained was filtered, dried and recrystallized from ethanol.

Method – 2

Compound **1(a-c)** (0.01mole), chloroacetic acid (0.01 mole), 4-chlorobenzaldehyde (0.01 mole) and LiBr (10 mole %) were placed in small conical flask and mixed with a glass rod at room temperature. The mixture was then exposed to microwave radiations at 50% power for 6-6.30 minutes. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture, stirred for

5 minutes. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compounds **3(a-c)**.

Conventional synthesis of 2-(4-Chlorobenzylidine)-5-(4-substituted phenyl)-8,9-dihydro-2H-thiazolo[2,3-b]quinazolin-3,6[5H,7H]-diones 3(a-c):
Compound **2(a-c)** (0.01 mole), 4-chlorobenzaldehyde (0.01 mole) and 2-3 drops of glacial acetic acid in ethanol (25 mL) was refluxed on heating mantle for about 6 hr. The solvent was removed and residue was recrystallized from ethanol.

Microwave induced synthesis of 3-(4-chlorobenzylidine)-10-(4-substituted phenyl)-6,7,8-trihydro-3H,3aH-isoxazolo [3'4':4,5]thiazolo [2,3-b]quinazoline-9[10H]-ones 4(a-c)
Compound **3(a-c)** (0.01 mole), hydroxylamine hydrochloride (0.012 mole) and LiBr (10 mole %) were mixed with mortar - pestle and placed in a small conical flask at room temperature. The mixture was then exposed to microwave radiations at 60% power for 5-5.30 minutes. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and it was stirred for 5 minutes. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compounds **4(a-c)**.

Conventional synthesis of 3-(4-chlorobenzylidinel)-10-(4-substituted phenyl)-6,7,8-trihydro-3H,3aH-isoxazolo [3'4':4,5]thiazolo [2,3-b] quinazoline-9[10H]-ones 4(a-c)
To a mixture of compound **3(a-c)** (0.01 mole) and hydroxylmine hydrochloride (0.012 mole) in absolute ethanol, (0.01 mole), a solution of sodium acetate (0.012 mole) in acetic acid (5 mL) was added. The reaction mixture was refluxed on heating mantle for 12 hr. The reaction mixture was concentrated, kept overnight and poured into ice water. The resulting solid was filtered, washed with water and recrystallized from acetic acid.

Microwave induced synthesis of 3-(4-chlorobenzylidine)-10-(4-fluorophenyl)-6,7,8-trihydro-3H,3aH,2H-pyrazolo [3'4':4,5]thiazolo [2,3-b]quinazoline-9[10H]-ones 5(a-c)
Compound **3(a-c)** (0.01 mole), hydrazine hydrate (0.02 mole) and LiBr (10 mole %) were placed in a small conical flask and mixed with a glass rod at room temperature. The mixture was then exposed to microwave radiations at 60% power for 6-6.30 minutes. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and it was stirred for 5 minutes. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford compounds **5(a-c)**.

Conventional synthesis of 3-(4-chlorobenzylidine)-10-(4-substituted phenyl)-6,7,8-trihydro-3H,3aH,2H-pyrazolo [3'4':4,5]thiazolo [2,3-b] quinazoline-9[10H]-ones 5(a-c)
A solution of compound **3(a-c)** (0.01 mole) in abso lute ethanol (30 mL) was treated with hydrazine hydrate in excess (0.02 mole) and refluxed on heating mantle in the presence of glacial acetic acid as a catalyst for 14 hr. The reaction mixture was concentrated, kept overnight and poured into ice water. The resulting solid was filtered, washed with water and recrystallized from absolute ethanol to afford compounds **5(a-c)**.

Microwave induced synthesis of 4-(4-chlorophenyl)-11-(4-substituted phenyl)-7,8,9-trihydro-2H-pyrimido [4'5':4,5]thiazolo [2,3-b]quinazoline-2,10 [3H,11H]-diones 6(a-c)
Compound **3(a-c)** (0.01 mole), urea (0.01 mole) and LiBr (10 mole %) were placed in small conical flask and mixed with a glass rod at room temperature. The mixture was then exposed to microwave radiations at 60% power for 7-7.30 minutes. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. 15 mL of water was then added to reaction mixture and it was stirred for 5 minutes. The solid thus obtained was filtered, dried and recrystallized from ethanol.

Conventional synthesis of 4-(4-Chlorophenyl)-11-phenyl-7,8,9-trihydro-2H-pyrimido[4'5':4,5]thiazolo [2,3-b]quinazoline-2,10 [3H,11H]-diones 6(a-c)
A solution of compound **3(a-c)** (0.01 mole) in absolute ethanol (30 mL) was treated with urea (0.01 mole). A few drops of conc. HCl were added and refluxed on a heating mantle for 12 hr. The reaction mixture was concentrated, kept overnight, poured into ice water and neutralized with 5N NaOH solution. The solid product was colleced, washed several times with water and recrystallized from absolute ethanol.

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