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Novel approach for the rapid and efficient synthesis of heterocyclic Schiff bases and azetidinones under microwave irradiation

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A series of compounds, viz. 3″-chloro-4″-(substituted phenyl)-1″-[4-(coumarin-3-yl)thiazol-2-yl]-2″-azetidinones **4a-j** have been prepared by the reaction of 2-N-(substituted benzylidene)imino-4-(coumarin-3-yl)thiazoles **3a-j** with chloroacetyl chloride in the presence of triethylamine. The Schiff bases **3a-j** have been prepared by the condensation of 2-amino-4-(coumarin-3-yl)thiazole **1** with different aldehydes **2**. Both the reactions are carried out by conventional and microwave methods. The products are screened for their antibacterial activity against *Staphylococcus aureus, Bacillus subtillis, Escherichia coli* and *Salmonella typhi.*

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A survey of literature reveals that thiazolocoumarins possess a broad spectrum of biological importance. Thiazolocoumarin derivatives are well known biologically active compounds. Coumarin derivatives possess antibacterial[1], anticoagulant[2] and anti-allergic[3] activities. Schiff base has good antimicrobial, fungicidal[4] and pharmacological applications[5] and it can be prepared by the acid catalyzed reaction of amines and ketones or aldehydes. 2-Azetidinone derivatives have been reported to possess anti-inflammatory, antidegenerative, fungicidal[6] and antibiotic[7] activity.

The microwave irradiation is used for carrying out chemical transformations which are pollution free and eco-friendly[8,9]. Herein we wish to present a detailed research work on the synthesis of Schiff bases and azetidinones using N,N-dimethylformamide as a reaction mediator, which absorbs microwave energy efficiently through dipole rotation since it can retain water formed in the reaction thus avoiding the need for a water separator[10]. Commercial microwave oven is used as a convenient source of heat in the laboratory. The microwave assisted organic reactions occur more rapidly, safely and with higher chemical yields[11,12]. These features render the microwave method superior to the conventional one.

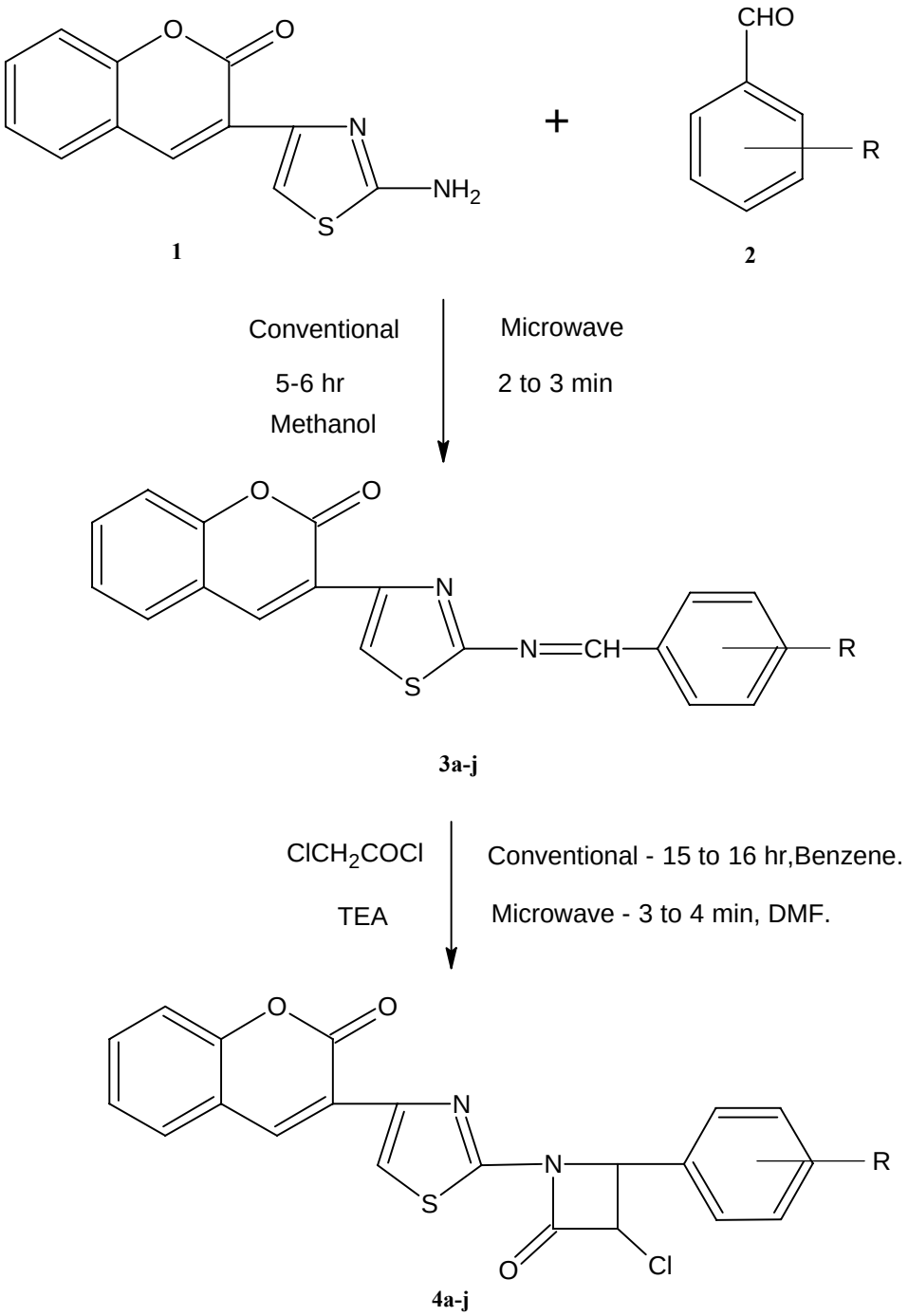
The starting compound namely, the substituted 2-amino-4-(coumarin-3-yl)thiazole **1** was synthesized from the reaction of 3-bromoacetylcoumarin with thiourea[13]. The condensation of **1** with substituted aldehydes **2a-j** was carried out by both conventional and microwave methods to get 2-N-(substituted benzylidene)imino-4-(coumarin-3-yl)thiazoles **3a-j**. In conventional method, the reaction was carried out in methanol and it took 5 to 6 hr. But it took only 2 to 3 min under microwave irradiation[14].

Reaction of the Schiff bases **3a-j** with chloroacetyl chloride in the presence of triethylamine was carried out by conventional method in benzene as a solvent to yield 3″-chloro-4″-(substituted phenyl)-1″-[4-(coumarin-3-yl)thiazol-2-yl]-2″-azetidinones **4a-j**. It took 15-16 hr, while under microwave irradiation using DMF as a solvent the reaction was completed in 3 to 4 min (**Scheme I**).

A comparative study in terms of yield and reaction period is shown in **Table I** and **Table II**.

Experimental Section

All the melting points were determined on a PMP-DM scientific melting point apparatus and are uncorrected. The purity of compounds was checked by TLC on silica gel 'G' coated glass plates. IR spectra were recorded with KBr on a Shimatzu FT-IR 8300 spectrophotometer; ^{1}H NMR spectra on a Brucker DRX-300 in $CDCl_3$ at 200 MHz using TMS as an internal standard. Microwave assisted reactions were carried out in a "QPro-M Modified Microwave System" made in Canada.



3,4	R	3,4	R
a	3-OCH_3, 4-OH	**f**	2-Cl
b	3,4,5-$(OCH_3)_3$	**g**	2-OCH_3
c	4-$N(CH_3)_2$	**h**	4-OCH_3
d	2-OH	**i**	2,4-$(Cl)_2$
e	4-Cl	**j**	2-NO_2

Scheme I

Table I — Characterization data of compounds **3a-j**

Compd	m.p. °C	Yield (%) (period/hr) Conventional method	Yield (%) (period/min) Microwave method	Mol. formula (Mol. wt)	Found (Calcd) (%) C	H	N	^{1}H NMR ($CDCl_3$) (δ, ppm)
3a	131	82(5.0)	89(2.0)	$C_{20}H_{14}N_2O_4S$ (378.402)	63.48 (63.45	3.73 3.72	7.40 7.43)	6.80-7.88 (4H, m, Ar-H), 5.20 (1H, s, >C=CH-), 4.44 (1H, s, -N=CH-), 6.58 (3H, m, Ar-H), 3.89 (3H, d, $-OCH_3$)
3b	123	76(5.0)	80(2.0)	$C_{22}H_{18}N_2O_5S$ (422.455)	62.55 (62.57	4.29 4.30	6.63 6.66)	6.72-7.80 (4H, m, Ar-H), 5.10 (1H, s, >C=CH-), 4.42 (1H, s, -N=CH-), 6.30 (2H, d, Ar-H)
3c	138	74(5.5)	83(2.0)	$C_{21}H_{17}N_3O_2S$ (375.445)	67.18 (67.18	4.56 4.50	11.19 11.19)	6.75-7.89 (4H, m, Ar-H), 5.30 (1H, s, >C=CH-), 4.45 (1H, s, -N=CH-), 6.45 (4H, m, Ar-H), 2.89 (6H, m, $-N(CH_3)_2$)
3d	110	80(5.5)	88(1.5)	$C_{19}H_{12}N_2O_3S$ (348.367)	65.50 (65.54	3.47 3.48	8.04 8.07)	—
3e	118	71(5.0)	77(2.5)	$C_{19}H_{11}N_2O_2SCl$ (366.822)	62.21 (62.18	3.02 3.04	7.64 7.60)	—
3f	113	68(6.0)	75(2.5)	$C_{19}H_{11}N_2O_2SCl$ (366.822)	62.21 (62.24	3.02 3.05	7.64 7.67)	—
3g	112	78(5.5)	86(2.0)	$C_{20}H_{14}N_2O_3S$ (362.403)	66.28 (66.31	3.89 3.89	7.73 7.75)	—
3h	117	81(6.0)	90(1.5)	$C_{20}H_{14}N_2O_3S$ (362.403)	66.28 (66.33	3.89 3.87	7.73 7.72)	—
3i	125	72(6.5)	81(2.5)	$C_{19}H_{10}N_2O_2Cl_2S$ (401.266)	56.87 (56.82	2.51 2.46	6.98 6.96)	6.80-7.92 (4H, m, Ar-H), 5.10 (1H, s, >C=CH-), 4.39 (1H, s, -N=CH-), 7.13 (3H, m, Ar-H)
3j	141	70(6.0)	78(2.5)	$C_{19}H_{11}N_3O_4S$ (377.374)	60.47 (60.50	2.94 2.94	11.13 11.11)	6.83-7.90 (4H, m, Ar-H), 5.30 (1H, s, >C=CH-), 4.46 (1H, s, -N=CH-), 8.21 (4H, m, Ar-H)

Table II — Characterization data of compounds **4a-j**

Compd	m.p. °C	Yield (%) (period/hr) Conventional method	Yield (%) (period/min) Microwave method	Mol. formula (Mol. wt)	Found (Calcd) (%) C	H	N	^{1}H NMR ($CDCl_3$) (δ, ppm)
4a	107	70(15.0)	79(4.0)	$C_{22}H_{15}N_2O_5SCl$ (454.884)	58.09 (58.12	3.32 3.33	6.16 6.19)	6.85-7.98 (4H, m, Ar-H), 5.5 (1H, s, >C=CH-), 6.68 (4H, m, Ar-H), 5.10 (1H, s, -OH), 2.80 (1H, s, $>CH-NR_2$)
4b	128	66(15.0)	74(3.5)	$C_{24}H_{19}N_2O_6SCl$ (498.936)	57.77 (57.79	3.84 3.83	5.61 5.59)	6.81-7.96 (4H, m, Ar-H), 5.2 (1H, s, >C=CH-), 6.70 (4H, m, Ar-H), 5.0 (1H, s, -OH), 2.80 (1H, s, $>CH-NR_2$)
4c	157	60(16.0)	78(3.5)	$C_{23}H_{18}N_3O_3SCl$ (451.926)	61.13 (61.09	4.01 4.02	9.30 9.32)	6.79-7.99 (4H, m, Ar-H), 5.4 (1H, s, >C=CH-), 6.66 (4H, m, Ar-H), 5.10 (1H, s, -OH), 2.90 (1H, s, $>CH-NR_2$)

— Contd

Table II — Characterization data of compounds **4a-j** — *Contd*

Compd	m.p. °C	Yield (%) (period/hr) Conventional method	Yield (%) (period/min) Microwave method	Mol. formula (Mol. wt)	Found (Calcd) (%) C	H	N	^{1}H NMR ($CDCl_3$) (δ, ppm)
4d	150	69(15.0)	80(3.5)	$C_{21}H_{13}N_2O_4SCl$ (424.858)	59.37 (59.40	3.08 3.04	6.59 6.62)	—
4e	143	65(15.0)	77(3.0)	$C_{21}H_{12}N_2O_3SCl_2$ (443.303)	56.90 (56.91	2.73 2.73	6.32 6.29)	—
4f	153	60(16.0)	70(3.5)	$C_{21}H_{12}N_2O_3SCl_2$ (443.303)	56.90 (56.86	2.73 2.74	6.32 6.34)	—
4g	171	68(16.0)	75(3.5)	$C_{22}H_{15}N_2O_4SCl$ (438.884)	60.21 (60.23	3.44 3.39	6.38 6.40)	—
4h	178	71(15.0)	81(3.0)	$C_{22}H_{15}N_2O_4SCl$ (438.884)	60.21 (60.21	3.44 3.40	6.38 6.36)	—
4i	146	64(15.0)	70(4.0)	$C_{22}H_{11}N_2O_3SCl_3$ (477.748)	52.79 (52.83	2.32 2.32	5.86 5.84)	6.82-7.93 (4H, m, Ar-H), 5.3 (1H, s, >C=CH-), 6.67 (4H, m, Ar-H), 5.0 (1H, s, -OH), 2.85 (1H, s, >CH-NR_2)
4j	181	62(16.0)	70(4.0)	$C_{21}H_{12}N_3O_5SCl$ (453.856)	55.57 (55.54	2.67 2.62	9.26 9.29)	6.80-7.95 (4H, m, Ar-H), 5.6 (1H, s, >C=CH-), 6.61 (4H, m, Ar-H), 5.10 (1H, s, -OH), 2.71 (1H, s, >CH-NR_2)

2-N-(3′-Methoxy-4′-hydroxybenzylidene)imino-4-(coumarin-3-yl)thiazole 3a (conventional method). A mixture of 2-amino-4-(coumarin-3-yl)thiazole (0.01 mole, 2.44 g) and 3-methoxy-4-hydroxybenzaldehyde (0.01 mole, 1.52 g) was taken in a R.B. flask fitted with a Deanstark apparatus. Then 50 mL of methanol was added to it and refluxed for 5-6 hr. After the completion of reaction, the solvent was removed by vacuum distillation. The Schiff base was filtered, dried and recrystallised from absolute alcohol.

2-N-(3′-Methoxy-4′-hydroxybenzylidene)imino-4-(coumarin-3-yl)thiazole 3a (microwave method). A mixture of 2-amino-4-(coumarin-3-yl)thiazole (0.01 mole, 2.44 g) and 3-methoxy-4-hydroxybenzaldehyde (0.01 mole, 1.52 g) was taken in R.B. flask. Then 20 mL of methanol was added. The mixture was irradiated inside a QPro-M Modified Microwave System (200 W) for about 2-3 min. It was then diluted with ice-cold water. The Schiff base formed was filtered, dried and recrystallised from ethanol.

Following the same procedure, compounds **3b-j** were prepared. The characterization data of **3a-j** are recorded in **Table I**.

3″-Chloro-4″-(3′-hydroxy-4′-methoxyphenyl)-1″-[4-(coumarin-3-yl) thiazol-2-yl]-2″-azetidinone 4a (conventional method). The Schiff base **3** (0.01 mole, 3.78 g) in benzene was taken in a 50 mL flat bottom flask. To it chloroacetyl chloride (0.01 mole, 1.12 g) and triethylamine (0.01 mole, 1.01 g) in benzene were added slowly. The mixture was refluxed for 15-16 hr. The triethylamine hydrochloride was removed and the benzene was distilled off to get the product. The solid product was filtered, dried and recrystallised from ethanol.

3″-Chloro-4″-(3′-hydroxy-4′-methoxyphenyl)-1″-[4-(coumarin-3-yl)-thiazol-2-yl]-2″-azetidinone 4a (microwave method). The Schiff base **3** (0.01 mole, 3.78 g) in DMF was taken in R.B. flask. To it chloroacetyl chloride (0.01 mole, 1.12 g) and triethylamine (0.01 mole, 1.01 g) were added slowly. Then it was irradiated in a microwave oven for 3-4 min. It was then diluted with ice-cold water. The solid product formed was filtered, dried and recrystallised from ethanol.

Following the same procedure, the compounds **4b-j** were prepared. The characterization data of **4a-j** are recorded in **Table II**.

Antibacterial activity

The compounds were tested for their antibacterial activity by measuring the zone of inhibition on agar plates (diffusimetric method)[15] with *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and

Table III — Zone of inhibition (mm) of compounds **3a-j** and **4a-j**

Compd	*S.aureus.*	*B.subtllis*	*E.coli.*	*S.typhi*
3a	8.0	12.0	7.0	12.0
3b	9.0	8.0	10.0	10.0
3c	11.0	9.0	8.0	9.0
3d	9.0	7.0	10.0	8.0
3e	8.0	9.0	7.0	9.0
3f	7.0	11.0	9.0	9.0
3g	14.0	7.0	12.0	10.0
3h	13.0	12.0	12.0	11.0
3i	12.0	10.0	11.0	7.0
3j	7.0	8.0	6.0	9.0
4a	9.0	9.0	7.0	12.0
4b	8.0	12.0	9.0	10.0
4c	7.0	7.0	10.0	9.0
4d	11.0	9.0	9.0	8.0
4e	9.0	10.0	8.0	9.0
4f	8.0	10.0	7.0	9.0
4g	13.0	9.0	11.0	10.0
4h	14.0	11.0	12.0	11.0
4i	11.0	10.0	12.0	7.0
4j	8.0	9.0	7.0	9.0
Ampicillin	12	14	11	13
Penicilline	13	16	12	14
Tetracycline	15	13	16	17

Salmonella typhi as test organisms. The compounds possess moderate to good activity against all stains in comparison with ampicillin, penicillin and tetracycline (**Table III**).

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