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Synthesis of Schiff's bases of 8-methyl-tetrazolo[1,5-*a*]quinoline as potential anti-inflammatory and antimicrobial agents

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A series of 4-substituted–imino-methyltetrazolo[1,5-*a*]quinoline derivatives reported have been synthesized by condensation of 4-formyl-8-methyltetrazolo[1,5-*a*]quinoline with appropriate aromatic amine by refluxing in dioxane. All the compounds have been characterized by IR, ^{1}H NMR and mass spectroscopy and have been evaluated for their anti-inflammatory and antimicrobial activities.

Keywords: 8-Methyltetrazolo[1,5-*a*]quinoline, Schiff's bases, antimicrobial, anti-inflammatory

Quinoline derivatives have been reported to possess antimicrobial[1] and anti-inflammatory[2] activities besides wide range of pharmacological activities. Moreover fusion of tetrazole, which is considered as planar acidic heterocyclic analogue of carboxylic function[3,4], have ability to increase potency[5,6] and improve bioavailability[7]. Similarly Schiff's bases have been reported to possess antimicrobial[8,9] apart from other biological activities. These observations led to the conception that Schiff's bases of tetrazolo[1,5-*a*]quinoline possess potential antimicrobial and anti-inflammatory activities. In the present study a new series of Schiff's bases of tetrazolo[1,5-*a*]quinoline has been synthesized successfully.

The reaction sequence for the title compound is outlined in **Scheme I**. Vilsmeier-Haack formylation[10] of *m*-methylacetanilide gave 2-chloro-3-formyl-7-methylquinoline **1**, which on treatment with sodium azide in dimethylsulphoxide at 40°C gave 4–formyl-8-methyltetrazolo[1,5-*a*]quinoline **2** in good yield as a key intermediate. Subsequent condensation of **2** with various aromatic amines in dioxane gave the title compounds

3a-m. Purity of the compound was checked by TLC and structure of the compound was deduced on the basis of their IR, ^{1}H NMR and mass spectroscopy. The characterization data of compounds **3a-m** is given in **Table I**

Antimicrobial activity

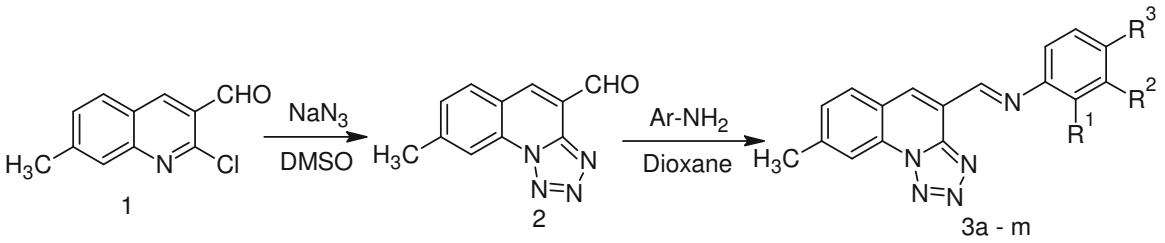
The compounds **3a-m** were screened for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* at concentration of 50µg/mL and 100µg/mL using ofloxacin as standard and antifungal activity against *Candida albicans* at concentration of 50µg/mL and 100µg/mL using ketoconozole as standard. DMF was used as solvent control, nutrient agar was used as culture medium and the method employed was cup plate method[11]. The zones of inhibition formed was measured in mm and is shown in **Table II**. It was observed that tetrazolo[1, 5-*a*]quinoline derivatives having electron withdrawing groups like F, Cl, Br, NO_2 and Cl & F groups in the phenyl ring showed good activity whereas rest of the compounds showed moderate activity against bacterial strains. These compounds were found to be inactive against *Candida albicans.*

Anti-inflammatory activity

The Anti-inflammatory activity of the synthesized compounds **3a, 3b, 3d, 3e, 3f** and **3g** was evaluated *in vivo* using the carrageenan-induced paw edema bioassay[12] in rats taking indomethacin as reference standard. The results showed that compounds **3e** and **3d** gave 57.8 and 53.0% protection against inflammation. Compounds **3a** and **3g** exhibited 45.0 and 44.5% protection against inflammation. The remaining two compounds **3b** and **3f** showed 32.0 and 28.9% protection respectively against carrageenan induced inflammation when compared to indomethacin which gave 78.9% protection against rat paw edema.

Experimental Section

Melting points were determined in open glass capillaries using Kjeldahl flask containing liquid paraffin and are uncorrected. Purity of the compounds was checked on TLC. The infrared spectra of compounds were recorded on a Bio-rad FT-IR spectrophotometer using KBr disc technique. ^{1}H NMR was recorded on a Bruker 300 MHz instrument in DMSO-d_6 using TMS as an internal standard and mass spectra on a Jeol SX 102/DA-6000 mass spectrometer. Satisfactory C, H, N, analysis was recorded for all the compounds.



2-Chloro-3-formyl-7-methylquinoline **1**

Scheme I

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

Compd	m. p. °C	Yield%	Mol. formula (Mol. Wt.)	Elemental analysis Found (Calcd) (%)		
				C	H	N
3a	173	72	$C_{17}H_{13}N_5$	70.97	4.52	24.31
			(287.31)	(71.06	4.56	24.37)
3b	197	69	$C_{18}H_{15}N_5$	71.67	5.01	23.17
			(301.34)	(71.74	5.02	23.24)
3c	219	71	$C_{17}H_{12}N_5F$	66.81	3.93	22.89
			(305.30)	(66.88	3.96	22.94)
3d	213	68	$C_{17}H_{12}N_5Cl$	63.41	3.72	21.71
			(321.76)	(63.46	3.76	21.77)
3e	221	71	$C_{17}H_{12}N_5Br$	55.67	3.28	19.09
			(366.21)	(55.75	3.30	19.12)
3f	226	65	$C_{17}H_{12}O_2N_6$	61.37	3.62	25.26
			(332.31)	(61.44	3.64	25.29)
3g	229	73	$C_{18}H_{15}O_2N_5$	68.06	4.75	22.03
			(317.34)	(68.13	4.76	22.07)
3h	193	64	$C_{18}H_{15}N_5$	71.64	5.01	23.19
			(301.34)	(71.74	5.02	23.24)
3i	198	68	$C_{19}H_{17}N_5$	72.29	5.41	22.18
			(315.37)	(72.36	5.43	22.21)
3j	191	63	$C_{18}H_{15}N_5$	71.67	5.05	23.19
			(301.34)	(71.74	5.02	23.24)
3k	220	81	$C_{17}H_{12}N_5Cl$	63.40	3.74	21.74
			(321.76)	(63.46	3.76	21.77)
3l	223	61	$C_{17}H_{12}N_5Cl$	63.37	3.73	21.71
			(321.76)	(63.46	3.76	21.77)
3m	231	58	$C_{17}H_{11}N_5ClF$	60.02	3.24	20.57
			(339.75)	(60.10	3.26	20.61)

N, N-Dimethylformamide (0.125 mole) was cooled to 0ºC in flask equipped with a drying tube and phosphoryl chloride (0.35 mole) was added drop-wise with stirring. To this solution was added m-methylacetanilide (0.05 mole) and after 5 min the solution was heated under reflux for 6 hr at 75ºC. The reaction mixture was cooled and poured into ice-water (300 mL) and stirred for 30 min at 0-10ºC. The precipitate formed was filtered off, washed with cold water, dried and recrystallized from ethylacetate.

Table II — Antibacterial and anti-inflammatory activities of compounds **3a-m**

Compd	Antibacterial activity (zone of inhibition in mm)				Anti-inflammatory activity
	Staphylococcus aureus		*Escherichia coli*		% Inhibition of oedema
	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	
3a	6	8	6	9	45.0
3b	7	8	7	8	32.0
3c	9	12	9	10	---
3d	8	11	7	9	53.0
3e	10	12	9	12	57.8
3f	9	13	6	10	28.9
3g	6	9	5	8	44.5
3h	6	8	6	7	---
3i	7	9	6	8	---
3j	7	8	6	9	---
3k	7	8	6	8	---
3l	7	10	7	10	---
3m	12	15	10	12	---
Ofloxacin	19	22	24	27	---
Indomethacin	---	---	---	---	78.9

Yield 62%, m.p. 145-147ºC. Anal. Calcd for $C_{11}H_8ONCl$: C, 64.25; H, 3.32; N, 6.81. Found: C, 64.17; H, 3.30; N, 6.79 %; IR (KBr): 1688 (C=O), 1579 (C=C), 755 cm^{-1} (C-Cl); ^1H NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3), 7.52 (d, 1H, H-6, *J*=7.5 Hz), 7.75 (s, 1H, H-8), 8.07 (d, 1H, H-5, *J*=7.3 Hz), 8.78 (s, 1H, H-4), 10.35 (s, 1H, CHO).

4–Formyl-8-methyltetrazolo[1,5-*a*]quinoline 2

To a solution of **1** (0.02 mole) in dimethylsulphoxide (200 mL) and acetic acid (4 mL), a solution of sodium azide (0.03 mole) in water (10 mL) was added portion wise. The reaction mixture was stirred at 40ºC for 3 hr. Stirring was continued further for 5 days at ambient temperature. The white precipitate formed was filtered, washed with water and recrystallized from DMF. Yield 72%, m. p. 258-260ºC. Anal. Calcd for $C_{11}H_8ON_4$: C, 62.26; H, 3.80; N, 26.40. Found : C, 62.19; H, 3.79; N, 26.38 %; IR (KBr): 1703 (C=O), 1556, (C=C), 1480 cm^{-1}(C-N); ^1H NMR (DMSO-d_6): δ 2.64 (s, 3H, CH_3), 7.69 (d, 1H, H-7, *J*=7.7 Hz), 8.27 (d, 1H, H-6, *J*=7.4 Hz), 8.41 (s, 1H, H-9), 8.86 (s, 1H, H-5), 10.38 (s, 1H, CHO); MS: *m/z* 212 $[M]^+$.

Synthesis of 8-methyl-4-(substituted)-imino-methyltetrazolo[1,5-*a*]quinoline 3a-m. General procedure.

To a solution of **2** (0.01 mole) in dioxane (20 mL), substituted aromatic amine (0.01 mole) was added. The reaction mixture was heated under reflux for 4-12 hr, cooled and poured into cold water. The precipitate that separated out was filtered, washed with water, dried and recrystallized from ethanol.

IR, ^1H NMR and mass spectral data of compounds 3a-m are given below.

3a: (R^1 = H, R^2 = H, R^3 = H), IR (KBr): 1635 (C=N), 1556, (C=C), 1480 cm^{-1} (C-N); ^1H NMR (DMSO-d_6): δ 2.65 (s, 3H, CH_3), 7.39-7.52 (m, 5H, Ar-H), 7.6 (d, 1H, H-7, *J*=7.9 Hz), 8.3 (d, 1H, H-6, *J*=7.5Hz), 8.4 (s, 1H, H-9), 8.8 (s, 1H, H-5), 9.08 (s, 1H, CH=N); MS: *m/z* 287 $[M]^+$.

3b: (R^1 = H, R^2 = H, R^3 = CH_3), IR (KBr)**:** 1632 (C=N), 1586, (C=C), 1441 cm^{-1} (C-N);

^1H NMR (DMSO-d_6): δ 2.27 (s, 3H, Ar-CH_3), 2.58 (s, 3H, CH_3), 7. 7 (m, 4H, Ar-H), 7.6 (d, 1H, H-7, *J*=7.6 Hz), 8.2 (d, 1H, H-6, *J*=7.3Hz), 8.4 (s, 1H, H-9), 8.8 (s, 1H, H-5), 9.03 (s, 1H, CH=N); MS: *m/z* 301 $[M]^+$.

3c: (R^1 = H, R^2 = H, R^3 = F), IR (KBr): 1613 (C=N), 1548, (C=C), 1490 cm^{-1} (C-N); ^1H NMR (DMSO-d_6): δ 2.67 (s, 3H, CH_3), 7.34-7.48 (m, 4H, Ar-H), 7.7 (d, 1H, H-7, *J*=7.6 Hz), 8.3 (d, 1H, H-6, *J*=7.2Hz), 8.4 (s, 1H, H-9), 8.8 (s, 1H, H-5), 9.12 (s, 1H, CH=N); MS: *m/z* 305 $[M]^+$.

3d: (R^1 = H, R^2 = H, R^3 = Cl), IR (KBr): 1623 (C=N), 1529, (C=C), 1479 cm^{-1} (C-N); ^1H NMR (DMSO-d_6): δ 2.65 (s, 3H, CH_3), 7.39-7.52 (m, 4H, Ar-H), 7.67 (d, 1H, H-7, *J*=7.6 Hz), 8.26 (d, 1H, H-6, *J*=7.2Hz), 8.43 (s, 1H, H-9), 8.81 (s, 1H, H-5), 9.06 (s, 1H, CH=N); MS: *m/z* 321 $[M]^+$, 323 $[M+2]^+$.

3e: (R^1 = H, R^2 = H, R^3 = Br), IR (KBr): 1624 (C=N), 1512, (C=C), 1481 cm^{-1} (C-N); ^1H NMR (DMSO-d_6): δ 2.65 (s, 3H, CH_3), 7.39-7.52 (m, 5H, Ar-H), 7.6 (d, 1H, H-7, *J*=7. Hz), 8.22 (d, 1H, H-6, *J*=7.5Hz), 8.40 (s, 1H, H-9), 8.80 (s, 1H, H-5), 9.01 (s, 1H, CH=N); MS: *m/z* 366 $[M]^+$, 368 $[M+2]^+$.

3f: (R^1 = H, R^2 = H, R^3 = NO_2), IR (KBr): 1624 (C=N), 1512, (C=C), 1481 cm^{-1} (C-N); ^1H NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 7.54-7.69 (m, 4H, Ar-H), 7.74 (d, 1H, H-7, *J*=7. Hz), 8.34 (d, 1H, H-6, *J*=7.5Hz), 8.49 (s, 1H, H-9), 8.94 (s, 1H, H-5), 9.08 (s, 1H, CH=N); MS: *m/z* 332 $[M]^+$.

3g: (R^1 = H, R^2 = H, R^3 = OCH_3), IR (KBr): 1625 (C=N),1530, (C=C), 1480 cm^{-1} (C-N); ^1H NMR (DMSO-d_6): δ 2.67 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3) 7.07-7.44 (m, 4H, Ar-H), 7.70 (d, 1H, H-7, *J*=7.9 Hz), 8.31 (d, 1H, H-6, *J*=7.5Hz), 8.48 (s, 1H, H-9), 8.84 (s, 1H, H-5), 9.14 (s, 1H, CH=N); MS: *m/z* 317 $[M]^+$.

3h: (R^1 = H, R^2 = CH_3, R^3 = H), IR (KBr): 1623 (C=N), 1529, (C=C), 1474 cm^{-1} (C-N). ^1H NMR (DMSO-d_6): δ 2.38 (s, 3H, Ar-CH_3) 2.64 (s, 3H, CH_3), 7.13-7.38 (m, 4H, Ar-H), 7.68 (d, 1H, H-7, *J*=7.9 Hz), 8.25 (d, 1H, H-6, *J*=7.5Hz), 8.44 (s, 1H, H-9), 8.84 (s,1H, H-5), 9.06 (s, 1H, CH=N). MS: *m/z* 301 $[M]^+$.

3i: (R^1 = CH_3, R^2 = H, R^3 = CH_3), IR (KBr): 1627 (C=N), 1541, (C=C), 1471 cm^{-1}(C-N); ^1H NMR (DMSO-d_6): δ 2.50 (s, 6H, Ar-CH_3) 2.67 (s, 3H, CH_3), 7.12-7.28 (m, 3H, Ar-H), 7.72 (d, 1H, H-7, *J*=7.9 Hz), 8.33 (d, 1H, H-6, *J*=7.5Hz), 8.50 (s, 1H, H-9), 8.88 (s, 1H, H-5), 9.01 (s, 1H, CH=N); MS: *m/z* 315 $[M]^+$.

3j: (R^1 = CH_3, R^2 = H, R^3 = H), IR (KBr): 1627 (C=N), 1585, (C=C), 1477 cm^{-1} (C-N); ^1H NMR (DMSO-d_6): δ 2.41 (s, 3H, Ar-CH_3) 2.66 (s, 3H, CH_3), 7.16-7.29 (m, 4H, Ar-H), 7.69 (d, 1H, H-7, *J*=7.9 Hz), 8.26 (d, 1H, H-6, *J*=7.5Hz), 8.45 (s, 1H, H-9), 8.84 (s, 1H, H-5), 8.98 (s, 1H, CH=N); MS: *m/z* 301 $[M]^+$.

3k: (R^1 = Cl, R^2 = H, R^3 = H), IR (KBr): 1627 (C=N), 1530, (C=C), 1469 cm^{-1} (C-N); ^1H NMR (DMSO-d_6): δ 2.67 (s, 3H, CH_3), 7.33-7.69 (m, 4H, Ar-H), 7.72 (d, 1H, H-7, *J*=7.9 Hz), 8.35 (d, 1H, H-6, *J*=7.5Hz), 8.50 (s, 1H, H-9), 8.92 (s, 1H, H-5), 9.05 (s, 1H, CH=N); MS: *m/z* 321 $[M]^+$, 323 $[M+2]^+$.

3l: (R^1 = H, R^2 = Cl, R^3 = H), IR (KBr): 1621 (C=N), 1529 cm^{-1}(C=C); ^1H NMR (DMSO-d_6): δ 2.63 (s, 3H, CH_3), 7.32-7.52 (m, 4H, Ar-H), 7.66 (d, 1H, H-7, *J*=7.9 Hz), 8.25 (d, 1H, H-6, *J*=7.5Hz), 8.80 (s, 1H, H-9), 8.90 (s, 1H, H-5), 9.03 (s, 1H,CH=N); MS: *m/z* 321 $[M]^+$, 323 $[M+2]^+$.

3m: (R^1 = H, R^2 = Cl, R^3 = F), IR (KBr): 1621 (C=N), 1561 cm^{-1} (C=C); ^1H NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 7.45-7.55 (m, 3H, Ar-H), 7.69 (d,1H, H-7, *J*=7.9 Hz), 8.31 (d, 1H, H-6, *J*=7.5Hz), 8.49 (s,1H, H-9), 8.86 (s,1H, H-5), 9.10 (s,1H, CH=N); MS: *m/z* 339 $[M]^+$, 341 $[M+2]^+$.

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