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Synthesis and Pharmacological Evaluation of Thiazolidinone Derivatives as Anticancer Agents

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ABSTRACT:
By cyclocondensing azomethines of type 2a–m with thioglycolic acid and thiolactic acid, respectively, 4-thiazolidinones of types 3a–m and 4a–m were created. The azomethines 2a–m are produced via the reaction of 2-chloro-6-methylquinoline-3-carboxaldehyde with arylamines. The products' ability to suppress the development of several microorganisms in vitro was assessed. 94.45% of the synthesized chemical had biological screening activity, and several of the compounds had strong antibacterial activity, including videlicet. Of the compounds, 36.12% were shown to be more effective against E. coli than the common medication Penicillin. It was shown that 44.45% of the synthesized compounds were more effective against A. niger than the common medication Greseofulvin. 8.34% of the substances were more effective against B. megaterium than the common medications, ampicilin, chloramphenicol, and penicillin.
KEYWORDS: 4-thiazolidinones, thiolactic acid, thioglycolic acid, quinolineazomethine, and antibacterial action.

INTRODUCTION

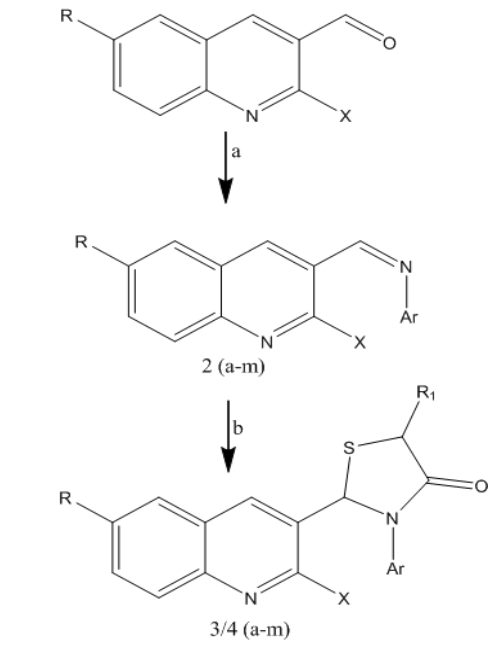
Antimicrobial and anti-tuberculosis medications [3], HIV-1 replication inhibitors [2], antihelmintic characteristics [4], and malaria [1] are all often treated using medications that include quinoline. In addition, since quinolines are often used as anti-inflammatory, anti-asthmatic, antibacterial, antihypertensive, antitumor [5, 6], antiproliferative [7], anticancer [8], and antiparasitic medicines [9], they play a special role in the design and synthesis of novel pharmacologically active molecules.

4. Display of Thizolidinones Antibacterial [15, 16], antifungal [17], anticonvulsant [11], anticancer [12], septicidal [13], antitubercular [14], strong antimicrobial agents [18], and allergy inhibitor [19], COX-1 inhibitors [24], antiviral [20], anti-HIV [21, 22, 23], and inhibits the activity of Aldose Reductase [25]. In order to further evaluate the pharmacological characteristics of this class of drugs, molecules with a quinoline moiety have been created.

The condensation of 2-chloro-6-methylquinolin-3-carboxaldehyde and aromatic amines yields the starting chemical 2–chloro–6–methylquinolin–3-ylazomethine (2). By reacting 2 with thioglycolic acid and thiolactic acid, 3–Aryl–2–(2'– chloro–6'–methylquinoline–3'–yl)–5H–methyl–4–thiazolidinones 3a–m & 4a–m have been created.

The constitution of all the products was established by elemental analyses, IR and PMR spectral study.

SCHEME-I



a = Ar - NH_2
b = thioglycolic acid / thiolactic acid
R = Alkyl
R_1 = H/-CH_3
X = Cl

MATERIALS AND METHODS

Every melting point is measured in an open capillary without correction. Using TMS as an internal standard and DMSO D6 as a solvent, 1H NMR spectra were recorded on a Bruker F-60 MHz and Infrared Spectra (KBr) were recorded on a Shimadzu-435-IR Spectrophotometer.
A combination of p-methylaniline (1.07 g, 0.01 mol) and 2-chloro 6-methyl quinoline carboxaldehyde (0.01 mol) was refluxed in ethanol for 6–7 hours to produce 2-chloro-6-methylquinolin-3-yl-azomethine (2a-m). After adding the ingredients to freezing water, a sodium bisulphite solution was used to triturate them. After being separated from dioxan, the product solidified. 1H NMR: 2.4 (s, 3H–CH3), 2.5 (s, 3H–CH3), 7.2 to 7.8 (m, 8H, Ar–H), IR (KBr): 2920 (C–H), 1601 (C=N), 1572 (C=C), and 797 (C–Cl) cm–1. Acetone:Benzene (1:9) is the TLC solvent system. [Discovery: C, 74.02, H, 5.09, N, 9.50% is needed for C, 70.00, H, 5.00, N, 9.45 of C18H15CIN2.
Others were also developed; Table 1 lists their physical constants.
3. 2-chloro-6'-methylquinoline-3'-yl, or aryl-2- A combination of N–4'–methyl phenyl 2-chloro–6–methyl quinolineazomethine (0.01 mol) and thioglycolic acid (0.01 mol) was heated to 120° for 12 hours to produce -5H-4-thiazolidinones (3a–m). After cooling, a 10% sodium bicarbonate solution was used to triturate the reaction mixture. After being separated from dioxan, the product solidified. IR (3i) KBr: 7.2 to 8.5 (m, 9H, Ar–H), 634 (C–S–C), 764 (C–Cl), 1581 (C=C), 2920 (C–H), 1656 (C=O), and 1H NMR 2.9 (s, 3H, –CH3). [Discovery: C, 65.02, H, 4.61, N, 7.59% is needed for C, 65.0, H, 4.60, N, 7.55 of C20H17CION2S], (Table 1).

3-Aryl-2-(2'-chloro-6'-methylquinolin-3'-yl)-5-methyl-4-thiazolidinones (4a-m):

A mixture of N–2–methoxyphenyl–2–chloro–6–methylquinolin–3–ylazomethine (3.10g, 0.01 mol) and thiolactic acid (1.06 ml, 0.01 mol) was heated at 120° for 12 hr. The reaction mixture was cooled, poured in ice and triturated with 10% sodium bicarbonate solution. The product was isolated and crystallized from dioxan. IR (**4h**) (KBr) 2924 (C–H), 1666 (C=O), 1599 (C=C), 754 (C–Cl), 620 (C–S–C), ^{1}H NMR 1.6 (d, 3H–CH–CH_3), 2.7 (s, 3H, Ar–CH_3), 3.9 (3H, Ar–OCH_3), 4.3 (1H,–CH–CH_3), 6.9 to 8.3 (m, 8H, Ar–H). [Found: C, 65.20, 4.70, N, 7.0 of $C_{21}H_{19}ClO_2N_2S$ requires C, 63.24, H, 4.76, N, 7.02%], (Table–1).

Table 1: Physical data of 2a–m, 3a–m, 4a–m

Compd. 1.	R 2.	M.W. 3.	M.P. (°C) 4.	Yield (%) 5.	Rf value 6.	N% Calcd.[Found] 7.
2a	C_6H_5–	280.5	150	75	0.29	9.98[9.95]
2b	4–$AsO(OH)_2$–C_6H_4–	404.5	210	70	0.48	6.92[6.90]
2c	4–$COOC_2H_5$–C_6H_4	352.5	180	73	0.45	7.94[7.91]
2d	3–Cl–C_6H_4–	315.0	>320	68	0.45	8.87[8.82]
2e	2,6–$(Cl)_2$–C_6H_3–	349.5	165	65	0.66	8.01[8.00]
2f	4–F–C_6H_4–	298.5	240	70	0.49	9.38 [9.34]
2g	4–F,3–Cl–C_6H_3–	333.5	260	72	0.50	8.39 [8.30]
2h	2–OCH_3–C_6H_4–	310.5	220	75	0.53	9.03[9.01]
2i	4–CH_3–C_6H_4–	294.5	190	62	0.61	9.50[9.45]
2j	2–NO_2–C_6H_4–	325.5	210	65	0.49	12.90[12.88]
2k	C_5H_4N–	281.5	150	60	0.57	14.92[14.90]
2l	$C_4H_3N_2$–	282.5	140	62	0.45	19.82[19.80]
2m	C_3H_2NS–	287.5	210	65	0.48	14.60[14.55]
3a	C_6H_5–	354.5	155	65	0.48	7.89 [7.85]
3b	4–$AsO(OH)_2$–C_6H_4–	478.5	175	60	Nil	5.85[5.80]
3c	4–$COOC_2H_5$–C_6H_4	426.5	170	59	Nil	6.56 [6.55]
3d	3–Cl–C_6H_4–	389.0	200	58	0.54	7.19[7.15]
3e	4–F,3–Cl–C_6H_3–	407.0	170	62	0.49	6.87 [6.85]
3f	2,6–$(Cl)_2$–C_6H_3–	323.5	180	55	0.50	6.61 [6.60]
3g	4–F–C_6H_4–	372.5	150	52	0.55	7.51 [7.48]
3h	2–OCH_3–C_6H_4–	384.5	178	62	Nil	7.28 [7.25]
3i	4–CH_3–C_6H_4–	368.5	152	68	0.52	7.59 [7.55]
3j	2–NO_2–C_6H_4–	399.5	210	65	0.57	10.51[10.54]
3k	C_5H_4N–	355.5	190	70	0.48	11.81[11.75]
3l	CH_3N_2–	356.5	220	65	Nil	15.70 [15.65]
3m	C_3H_2NS–	361.5	170	68	0.58	11.61[11.60]
4a	C_6H_5–	368.5	245	65	0.48	7.59[7.54]
4b	4–$AsO(OH)_2$–C_6H_4–	492.5	130	62	0.47	5.68[5.64]
4c	4–$COOC_2H_5$–C_6H_4	440.5	210	58	0.50	6.35[6.30]
4d	3–Cl–C_6H_4–	403.0	165	70	0.54	6.94[6.92]
4e	4–F,3–Cl–C_6H_3–	421.0	135	65	0.52	6.65[6.60]
4f	2,6–$(Cl)_2$–C_6H_3–	437.5	240	72	0.58	6.40[6.35]
4g	4–F–C_6H_4–	385.5	230	62	0.51	7.26[7.21]

Table 1: Continued

1.	2.	3.	4.	5.	6.	7.
4h	2–OCH_3–C_6H_4–	398.5	200	58	0.52	7.02[7.00]
4i	4–CH_3–C_6H_4–	382.5	145	59	0.50	7.32[7.27]
4j	2–NO_2–C_6H_4–	413.5	200	68	0.48	10.15[10.00]
4k	$C5H_4N$–	369.5	110	59	0.59	11.36[11.31]
4l	$C_4H_3N_2$	370.5	100	60	0.58	3.77[3.71]
4m	C_3H_2NS–	375.5	260(d)	72	Nil	11.18[11.13]

All compounds gave correct elemental data.

Table 2: Antimicrobial Screening Data

Compd. 1.	R 2.	*B. megaterium* 3.	*S. aureus* 4.	*E. coli* 5.	*S. typhosa* 6.	Antifungal activity Zone of inhibition in m. m. 24 hours	48hours
2a	C_6H_5–	11	13	14	12	18	18
2b	4–$ASO(OH)_2$–C_6H_4–	13	14	20	14	12	15
2c	4-$COOC_2H_5$-C_6H_4	12	13	15	12	18	17
2d	3–Cl–C_6H_4–	12	22	13	12	22	19
2e	2,6–$(Cl)_2$–C_6H_3–	13	17	10	15	23	19
2f	4–F–C_6H_4–	14	16	22	12	21	18
2g	4–F,3–Cl–C_6H_3–	12	12	18	12	18	15
2h	2–OCH_3–C_6H_4–	12	11	16	14	20	19
2i	4–CH_3–C_6H_4–	13	12	10	13	27	15
2j	2–NO_2–C_6H_4–	15	14	12	12	24	18
2k	C_5H_4N–	15	13	18	12	30	24
2l	$C_4H_3N_2$–	12	12	18	12	15	12
2m	C_3H_2NS–	15	13	20	15	15	10
3a	C_6H_5–	12	11	18	10	22	12
3b	4–$ASO(OH)_2$–C_6H_4–	11	12	12	18	27	25
3c	4–$COOC_2H_5$–C_6H_4	13	-	13	15	29	27
3d	3–Cl–C_6H_4–	13	13	18	14	18	17
3e	4–F,3–Cl–C_6H_3–	10	14	8	-	24	16
3f	2,6–$(Cl)_2$–C_6H_3–	12	10	12	14	30	24
3g	4–F–C_6H_4–	12	8	12	-	28	18
3h	2–OCH_3–C_6H_4–	13	9	14	12	32	18
3i	4–CH_3–C_6H_4–	10	10	11	10	25	12
3j	2–NO_2–C_6H_4–	12	13	12	11	25	15
3k	C_5H_4N–	14	12	13	12	24	12
3l	$C_4H_3N_2$	11	11	13	-	25	13
3m	C_3H_2NS–	12	14	15	12	25	21
4a	C_6H_5–	12	13	8	10	30	12
4b	4–$ASO(OH)_2$–C_6H_4–	15	15	14	12	28	22
4c	4–$COOC_2H_5$–C_6H_4	13	14	16	11	22	12
4d	3–Cl–C_6H_4–	14	17	18	13	27	20
4e	4–F ,3–Cl–C_6H_3–	14	15	12	11	20	12
4f	2,6–$(Cl)_2$–C_6H_3–	12	15	16	15	28	18
4g	4–F–C_6H_4–	15	14	26	12	30	22

4h	2–OCH_3–C_6H_4–	18	17	12	10	20	15
4i	4–CH_3–C_6H_4–	12	14	10	12	22	12
4j	2–NO_2–C_6H_4–	19	15	8	11	20	10
4k	C_5H_4N–	12	13	12	13	30	21
4l	$C_4H_3N_2$	11	13	16	13	25	18
4m	C_3H_2NS–	13	12	15	12	28	17

RESULTS AND DISCUSSION

Biological Evaluation of the Compounds Exhibiting Highest Activity Against the Microbes Investigated:

Table 3:

Antibacterial activity*				**Antifungal activity***
B.megaterium	***S.typhosa***	***E.coli***	***S.aureus***	***A.niger***
2b(13)	2b(14)	2b(20)	2d(22)	2d(22)
2e (13)	2e (15)	2f (22)	4b(15)	2e(23)
2f (14)	2h (14)	2g (18)	4d(17)	2f(21)
2i (13)	2k (17)	2l (18)	4e(15)	2i(27)
2j (15)	2m (15)	2m (18)	4f(15)	2j(24)
3d(13)	3b(18)	3a(18)	4h(17)	2l(30)
3c(13)	3c(15)	3d(18)	4j(15)	3b(27)
3h(13)	3d(14)	3k(30)		3c(29)
3k(13)	3f(14)	4c(18)		3f(30)
3l(14)	4d(13)	4d(18)		3g(28)
4i(18)	4f(15)	4e(16)		3h(32)
4k(19)	4k(13)	4g(26)		4a(30)
4l(16)	4l(13)	4m(16)		4b(28)
				4f(28)
				4g(30)
				4l(30)
*Bracket shows the zone of inhibition in mm				
Ampicillin(14) Penicillin(14) Chloramphenicol(15)	Ampicillin(20) Penicillin(22)	Ampicillin(18) Penicillin(15) Chloramphenicol(18)	Ampicillin(22) Penicillin(23)	Greseofulvin(20)

Biological Screening:

- 34 compounds have exhibited the activity out of 36 synthesised compounds.
- 16 compounds have shown more activity against *A. niger* than the Standard Drug Greseofulvin.
- 3 compounds 4i, 4k and 4l have shown more activity than Standard Drugs Ampicilin, Penicillin and Chloramphenicol against *B. megaterium*.
- 13 compounds have shown more activity than Standard DrugPenicillin against *E. coli*
- Remaining compounds have shown comparable activity with standard drugs against *S. typhosa* and *S. aureus*

CONCLUSION

Spectral analysis and elemental studies were used to determine the composition of each product. 94.45% of the compounds that were synthesized had antimicrobial activity. It was shown that 44.45% of the synthesized compounds were more effective against A. niger than the common medication Greseofulvin. 8.34% of the substances were more effective against B. megaterium than the common medications, ampicilin, chloramphenicol, and penicillin. Of the substances, 36.12% were more effective against E. coli than the common medication Penicillin. As a result, the produced compounds have been shown to be effective antimicrobials.

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