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Synthesis and pharmacological evaluation of a novel series of 3-aryl-2-(2-substituted-4-methylthiazole-5-yl)thiazolidin-4-one as possible anti-inflammatory and antimicrobial agents

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ABSTRACT

A new series of 3-aryl-2-(2-aryl/benzyl-4-methylthiazole-5-yl)thiazolidin-4-one was synthesized by condensation of 2-aryl/benzyl-4-methylthiazole-5-carbaldehyde, aromatic amines and thioglycolic acid in toluene. All the synthesized compounds are characterized by IR, NMR and elemental or mass analysis. Sixteen out of the newly synthesized compounds were screened for in vivo anti-inflammatory activity using carrageenan-induced rat paw edema method. Some of the synthesized compounds exhibited good anti-inflammatory activity compared with indomethacin. The synthesized compounds were also evaluated for their in vitro antimicrobial activity. Some of the compounds showed mild antibacterial activity while most of the compounds showed good antifungal activity.

The development of new synthetic methods leading to structures, which incorporates various biologically active moieties in a single molecule, has attracted much attention in organic chemistry. In particular, heterocyclic compounds hold a special place among pharmaceutically active products, and the development of simple and efficient synthesis of compounds incorporating multi heterocyclic rings has given a new dimension to the drug discovery.

Thiazole compounds have attracted continuing interest over the years because of their varied biological activities.[1–11] Thiazolidinones in particular have been investigated in great detail because of its biological importance.[12] Thiazolidinone nucleus containing compounds shows anti-inflammatory,[13–20] anticonvulsant,[21–24] hypnotic,[25–27] antitubercular,[25–27] antibacterial, antifungal and anticancer[28–35] activities.

Concurring with previous reports, thiazolyl/formazanyl indols,[36] admantane derivatives of thiazolyl-N-substituted amide,[37] 2-amino-5-thiazolyl motif,[38] 2-(2,4-disubstituted thiazol-5-yl)-3-aryl-3*H*quinazoline-4-one[39] and thiazolyl derivatives of 1-*H* pyrazole[40] have shown anti-inflammatory and antimicrobial activities. Literature also revealed that thiazolidinone nucleus at 2-position of thiazole showed good antifungal[41] and antiviral[42] activities. 3-hydroxy-2-(substituted thiazolyl)-4-thiazolidinones in which the thiazolidinone nucleus is at 5-position of thiazole ring showed antimicrobial activity.[43] Similarly, thiazolyl-thiazolidine-2,4-dione derivatives[44] and 2-thiazolylimino-5-arylidene-4-thiazolidinones[45] showed antimicrobial activity. In view of these observations, it was thought to synthesize some new thiazole based 1,3-thiazolidinone-4-one by the condensation of 2-aryl/substitutedbenzyl-4-methylthiazole-5-carbaldehyde with aromatic amine and thioglycolic acid.

The synthetic strategies adopted for the synthesis of title compounds **6a–r** are depicted in Schemes 1 and 2. The key starting material 2-aryl/benzyl-4-methylthiazole-5-carbaldehyde **3a–c** was prepared by oxidation of corresponding alcohols **2a–c** using IBX.[46–48] The alcohols in turn were obtained by reduction of esters **1a–c** by $LiAlH_4$. These esters **1a–c** were synthesized by reaction of aryl/benzyl thioamide with ethyl 2-chloro-3-oxobutanoate in dry ethanol in good yield.[49]

Thiazolidinone derivatives **6a–r** were obtained by one pot reaction of aldehydes **3a–c** with different substituted aromatic amines **4a–f** in toluene, with azeotropic separation of water, followed by cyclo-condensation with thioglycolic acid.

The anti-inflammatory screening of the selected synthesized compounds was carried out using carrageenan-induced paw edema method of inflammation in rats.[50] The results of anti-inflammatory analysis is reported in Table 1. From the anti-inflammatory

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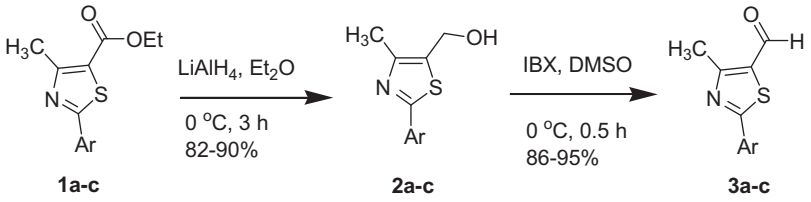
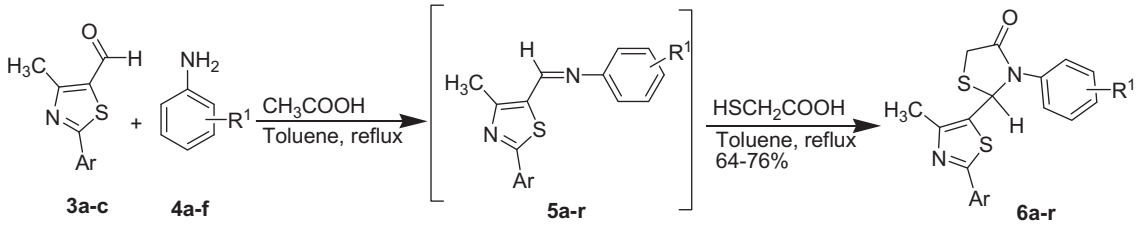


Scheme 1.



Compd.	Ar	R^1
6a	C_6H_5	H
6b	C_6H_5	4-Cl
6c	C_6H_5	3-Cl-4-F
6d	C_6H_5	4-F
6e	C_6H_5	4-OMe
6f	C_6H_5	4-Me

Compd.	Ar	R^1
6g	4-ClC_6H_4	H
6h	4-ClC_6H_4	4-Cl
6i	4-ClC_6H_4	3-Cl-4-F
6j	4-ClC_6H_4	4-F
6k	4-ClC_6H_4	4-OMe
6l	4-ClC_6H_4	4-Me

Compd.	Ar	R^1
6m	4-$ClC_6H_4CH_2$	H
6n	4-$ClC_6H_4CH_2$	4-Cl
6o	4-$ClC_6H_4CH_2$	3-Cl-4-F
6p	4-$ClC_6H_4CH_2$	4-F
6q	4-$ClC_6H_4CH_2$	4-OMe
6r	4-$ClC_6H_4CH_2$	4-Me

Scheme 2.

activity result analysis, it was observed that compounds **6b**, **6d**, **6f**, **6j**, **6k**, **6l** and **6r** showed good activity with 53.99% to 85.33% inhibition of edema. The data also revealed that maximum protection was shown in the tested compounds **6b**, **6d**, **6f**, having phenyl group at 2-position of thiazole nucleus (Ar = C_6H_5–) and phenyl group of thiazolidinone ring having 4-methyl, 4-chloro or 4-fluoro substituent (R^1 = 4-CH_3, 4-Cl, 4-F). The % inhibition is retained for compounds **6j** and **6l** in which phenyl group on thiazole nucleus is replaced by 4-chloro phenyl group (Ar = 4-Cl-C_6H_4–) and phenyl ring on thiazolidinone nucleus having 4-methyl or 4-fluoro substituent (R^1 = 4-CH_3, 4-F). It was also seen that when the 4-chlorophenyl group of thiazole ring was replaced by 4-chlorobenzyl group (Ar = 4-Cl-C_6H_4-CH_2–), only compound **6r** in which the phenyl group of thiazolidinone ring has 4-methyl substituent (R^1 = CH_3) showed anti-inflammatory activity. In general, it is concluded that 2-phenyl thiazole show better inhibition as compared to 2-(4-chlorophenyl)thiazole or 2-(4-chlorobenzyl)thiazole. The synthesized compounds **6a–r** were also evaluated for their antimicrobial activity against *Escherichia coli* (ATCC 25922) representing Gram-negative bacteria, *Staphylococcus aureus* (ATCC 25923) representing Gram-positive bacteria and *Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 9029) representing fungi. The in vitro minimal inhibitory concentrations (MIC) screening[51] results of tested compounds are listed in Table 2.

Table 1
In vivo anti-inflammatory effect of the compounds against carrageenan-induced rat paw model

Test sample	1 h		2 h		4 h	
	Swelling	% Inhibition	Swelling	% Inhibition	Swelling	% Inhibition
Control	3.10 ± 0.09	—	3.88 ± 0.10	—	4.83 ± 0.11	—
6a	2.95 ± 0.09	44.40	4.00 ± 0.09	50.61	4.72 ± 0.08	63.68
6b	2.47 ± 0.05*	54.76	2.64 ± 0.06*	59.07	2.14 ± 0.05*	80.75
6c	3.16 ± 0.23	55.92	3.51 ± 0.08	20.87	3.75 ± 0.04	28.64
6d	2.68 ± 0.07*	63.90	2.71 ± 0.11*	63.36	2.13 ± 0.11*	85.33
6e	2.92 ± 0.04	52.30	3.72 ± 0.05	48.15	4.15 ± 0.08	67.14
6f	2.60 ± 0.06*	58.14	2.79 ± 0.06*	60.10	2.32 ± 0.07*	80.56
6h	3.87 ± 0.16	69.28	3.32 ± 0.08	45.70	2.87 ± 0.07	43.15
6i	2.93 ± 0.09	53.41	3.69 ± 0.06	45.15	4.29 ± 0.11	65.11
6j	2.71 ± 0.11*	63.36	2.71 ± 0.16*	63.87	2.41 ± 0.08*	67.61
6k	2.48 ± 0.04*	53.99	2.13 ± 0.04*	80.74	2.63 ± 0.06*	59.06
6l	2.59 ± 0.09*	38.30	2.40 ± 0.08*	37.60	2.72 ± 0.16*	63.86
6m	NA	NA	NA	NA	NA	NA
6n	2.30 ± 0.10*	48.90	3.09 ± 0.11	40.07	3.20 ± 0.29	53.89
6o	2.92 ± 0.10	40.74	3.15 ± 0.12	45.07	2.71 ± 0.07*	68.89
6q	3.51 ± 0.08	20.87	3.75 ± 0.04	28.64	3.16 ± 0.23	55.92
6r	2.61± 0.09*	59.90	2.69± 0.10*	61.39	2.19± 0.13*	81.32
Indomethacin	2.48 ± 0.18*	70.2	2.42 ± 0.15*	78.30	2.29 ± 0.15*	87.26

Values are expressed mean ± SEM in carrageenan-induced rat model of paw edema.
Indomethacin and test compounds were administered orally at the dose of 40 mg/kg. NA: non-active.
* $P < 0.05$ versus saline control; $n = 6$.

Table 2
Antimicrobial antifungal activity of compounds **6a–r**

Compound	MW	MIC μg/mL (μM)			
		E. coli	*S. aureus*	*C. albicans*	*A. Niger*
		ATCC 25922	ATCC 25923	ATCC 10231	ATCC 9029
6a	352.47	25(70.92)	25(70.92)	50(141.85)	50(141.85)
6b	386.92	25(64.61)	50(129.23)	50(129.23)	50(129.23)
6c	404.91	25(61.74)	25(61.74)	50(123.48)	50(123.48)
6d	370.46	12.5(33.74)	25(67.48)	12.5(33.74)	12.5(33.74)
6e	381.49	25(65.53)	25(65.53)	12.5(32.76)	12.5(32.76)
6f	365.49	25(60.40)	50(120.80)	12.5(30.20)	12.5(30.20)
6g	386.92	12.5(32.30)	12.5(32.30)	50(129.22)	50(129.22)
6h	421.36	12.5(29.66)	25(59.33)	50(118.66)	50(118.66)
6i	439.35	25(56.90)	25(56.90)	50(113.80)	50(113.80)
6j	404.91	6.25(15.43)	12.5(30.87)	12.5(30.87)	25(61.74)
6k	416.94	12.5(29.98)	12.5(29.98)	12.5(29.98)	12.5(29.98)
6l	400.94	12.5(31.17)	12.5(31.17)	6.25(15.58)	12.5(31.17)
6m	368.88	25(67.77)	25(67.77)	12.5(33.88)	12.5(33.88)
6n	435.39	25(57.42)	12.5(28.71)	12.5(28.71)	12.5(28.71)
6o	453.38	25(55.14)	25(55.14)	12.5(27.57)	12.5(27.57)
6p	418.94	25(59.67)	25(59.67)	6.25(14.91)	6.25(14.91)
6q	430.97	25(58.00)	25(58.00)	6.25(14.50)	6.25(14.50)
6r	414.97	25(60.24)	25(60.24)	12.5(30.12)	6.25(15.06)
Ciprofloxacin	331.4	0.78(2.35)	1.56(4.70)	—	—
Fluconazole	306.27	—	—	0.78(2.55)	1.56 (5.09)

Out of all the compounds **6j**, **6k**, **6l** showed good activities for all the tested species at MICs 6.25–12.5 μg/mL (15.43–33.74 μM). Compound **6g** showed good antibacterial activities against both species, where as compounds **6d**, **6h** and **6n** showed good antibacterial activities against *E. coli* and *S. aureus* respectively. It was observed that compounds with 4-chlorophenyl group at 2-position of thiazole show enhanced antibacterial activity as compared to phenyl or 4-chloro benzyl group at 2-position of thiazole ring.

The result of antifungal activity revealed that compounds **6d**, **6e**, **6f**, **6j**, **6k**, **6l**, **6m**, **6n**, **6o**, **6p**, **6q**, **6r** showed good antifungal activities against both tested species with MIC values 6.25–12.5 μg/mL (14.50–33.38 μM). It is noteworthy that 4-F, 4-OMe, 4-Me attached to phenyl ring of thiazolidinone group (**6p**, **6q**, **6r**) show enhanced antifungal activity. It was also observed that when the phenyl group at 2-position of thiazole is replaced by 4-chlorophenyl group, no significant change in antifungal activity was observed. However, when 4-chlorobenzyl group is introduced at 2-position of thiazole, significant enhancement in antifungal activity is observed against both fungi species.

In summary, the biological screening result showed that compounds **6b**, **6d**, **6f**, **6j**, **6k**, **6l** and **6r** displayed good anti-inflammatory activity, however none of them was found superior than the reference drug indomethacin. On the other hand, some of the synthesized compounds showed good antifungal activity. It is also evident that the 4-chlorobenzyl group of the thiazole nucleus is more effective for antifungal activity while 4-chlorophenyl group of thiazole ring is effective for antibacterial activity. Finally compounds **6d** and **6r** were identified as good biologically active member within this study with an interesting dual anti-inflammatory and antimicrobial profile.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.08.073.

References and notes

1. Nicolaou, K. C.; Roschanger, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2014.
2. Hofle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem.* **1996**, *108*, 1671.
3. Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S. *J. Antibiot.* **1998**, *51*, 275.
4. Suzuki, Y.; Ojika, M.; Sakagami, Y.; Fudou, R.; Yamanaka, S. *Tetrahedron* **1998**, *54*, 11399.
5. El-Subbagh, H. I.; Al-Obaid, A. M. *Eur. J. Med. Chem.* **1996**, *31*, 1017.
6. Zhang, C.; Zink, D. L.; Ushio, M.; Burgess, B.; Onishi, R.; Masurekar, P.; Barrett, J. F.; Singh, S. B. *Bioorg. Med. Chem.* **2008**, *16*, 8818.
7. Kalkhambkar, R. G.; Kulkarni, G. M.; Shivkumar, H.; Rao, N. R. *Eur. J. Med. Chem.* **2007**, *42*, 1272.
8. Franklin, P. X.; Pillai, A. D.; Rathod, P. D.; Yerande, S.; Nivsarka, M.; Padh, H.; Vasu, K. K.; Sudarsanam, V. *Eur. J. Med. Chem.* **2008**, *43*, 129.
9. Zitouni, G. T.; Ozdemir, A.; Kaplancikli, Z. A.; Benkli, K.; Chevallet, P.; Akalin, G. *Eur. J. Med. Chem.* **2008**, *43*, 981.
10. Bekhit, A. A.; Ashour, H. M. A.; Abdel Ghany, Y. S.; Bekhit, A. E.-D. A; Baraka, A. *Eur. J. Med. Chem.* **2008**, *43*, 456.
11. Karegoudar, P.; Karthikeyan, M. S.; Prasad, D. J.; Mahalinga, M.; Holla, B. S.; Kumari, N. S. *Eur. J. Med. Chem.* **2008**, *43*, 261.
12. Verma, A.; Saraf, S. K. *Eur. J. Med. Chem.* **2008**, *43*, 897.
13. Kumar, A.; Rajput, C. S. *Eur. J. Med. Chem.* **2009**, *44*, 83.
14. Fu, J. Y.; Masferrer, J. L.; Seibert, K.; Raz, A.; Needleman, P. *J. Biol. Chem* **1990**, *265*, 16737.
15. Dubois, R. N.; Abramson, S. B.; Crofford, L.; Gupta, R. A.; Simon, L. S.; Van De Putte, L. B.; Lipsky, P. E. *FASEB J.* **1998**, *12*, 1063.
16. Previtera, T.; Vigorita, M. G.; Basile, M.; Fenech, G.; Trovato, A.; Occhiuto, F.; Monforte, M. T.; Barbera, R. *Eur. J. Med. Chem.* **1990**, *25*, 569.
17. Vigorita, M. G.; Previtera, T.; Basile, M.; Fenech, G.; Costa De Pasquale, R.; Occhiuto, F.; Circosta 11, C. *Farmaco Educ. Sci.* **1988**, *43*, 373.
18. Vigorita, M. G.; Previtera, T.; Ottana, R.; Grillone, I.; Monforte, F.; Monforte, M. T.; Trovato, A.; Rossitto, A. *Farmaco* **1997**, *52*, 43.
19. Vigorita, M. G.; Ottana, R.; Monforte, F.; Maccari, R.; Monforte, M. T.; Trovato, A.; Taviano, M. F.; Miceli, N.; De Luca, G.; Alcaro, S.; Ortuso, F. *Bioorg. Med. Chem.* **2003**, *11*, 999.
20. Ottana, R.; Mazzon, E.; Dugo, L.; Monforte, F.; Maccari, R.; Sautebin, L.; De Luca, G.; Vigorita, M. G.; Alcaro, S.; Ortuso, F.; Caputi, A. P.; Cuzzocrea, S. *Eur. J. Pharmacol.* **2002**, *448*, 71.
21. Dwivedi, C.; Gupta, S. S.; Parmar, S. S. *J. Med. Chem.* **1972**, *15*, 553.
22. Parmar, S. S.; Dwivedi, C.; Chaudhari, A.; Gupta, T. K. *J. Med. Chem.* **1972**, *15*, 99.
23. Chaudhary, S. K.; Verma, M.; Chaturvedi, A. K.; Parmar, S. S. *J. Pharm. Sci.* **1974**, *64*, 614.
24. Chaudhary, M.; Parmar, S. S.; Chaudhary, S. K.; Chaturvedi, A. K.; Ramasastry, B. V. *J. Pharm. Sci.* **1976**, *65*, 443.
25. Litvinchuk, M. D. *Farmakol. Toksikol.* **1963**, *26*, 725. *Chem. Abstr.* **1964**, *60*, 13761.
26. Danila, G.; Radu, C. *Rev. Med.-Chir.* **1978**, *82*, 127. *Chem. Abstr.* **1979**, *90*, 33767.
27. Mousseron, M. J. U.S. Patent **1972**, 3678041; *Chem. Abstr.* **1972**, *77*, 114388c.
28. Gouveia, F. L.; de Oliveira, R. M. B.; de Oliveira, T. B.; da Silva, I. M.; Do Nascimento, S. C.; de Sena, K. X. F. R.; de Albuquerque, J. F. C *Eur. J. Med. Chem.* **2009**, *44*, 2038.
29. Gududuru, V.; Hurh, E.; Dalton, J. T.; Miller, D. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5289.
30. Khan, S. A.; Yusuf, M. *Eur. J. Med. Chem.* **2009**, *44*, 2597.
31. Balzarini, J.; Orzeszko-Krzesinska, B.; Orzeszko, A.; Maurin, J. K. *Eur. J. Med. Chem.* **2009**, *44*, 303.
32. Rawal, R. K.; Tripathi, R.; Christophe Pannecouque; Katti, S. B.; De Clercq, E. *Eur. J. Med. Chem.* **2008**, *43*, 2800.
33. Chen, H.; Bai, J.; Jiao, L.; Guo, Z.; Yin, Q.; Li, X. *Bioorg. Med. Chem.* **2009**, *17*, 3980.
34. El-Gaby, M. S. A.; El-Hag Ali, G. A. M; El-Maghraby, A. A.; Abd El-Rahman, M. T.; Helal, M. H. M *Eur. J. Med. Chem* **2009**, *44*, 4148.
35. Aridoss, G.; Amirthaganesan, S.; Kima, M. S.; Kim, J. T.; Jeong, Y. T. *Eur. J. Med. Chem.* **2009**, *44*, 4199.
36. Singh, N.; Bhati, S. K.; Kumar, A. *Eur. J. Med. Chem.* **2008**, *43*, 2597.
37. Kouatly, O.; Geronikaki, A.; Kamoutsis, C.; Hadjipavlou-Litina, D.; Eleftheriou, P. *Eur. J. Med. Chem.* **2009**, *44*, 1198.
38. Franklin, P. X.; Pillai, A. D.; Rathod, P. D.; Yerande, S.; Nivsarkar, M.; Padh, H.; Vasu, K. K.; Sudarsanam, V. *Eur. J. Med. Chem.* **2008**, *43*, 129.
39. Giri, R. S.; Thaker, H. M.; Giordano, T.; Williams, J.; Rogers, D.; Sudersanam, V.; Vasu, K. K. *Eur. J. Med. Chem.* **2009**, *44*, 2184.
40. Bekhit, A. A.; Ashour, H. M. A.; Abdel Ghany, Y. S.; Bekhit, A. A.; Baraka, A. *Eur. J. Med. Chem.* **2008**, *43*, 456.
41. Sharma, S. C. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2422.
42. Rawal, R. K.; Tripathi, R.; Christophe Pannecouque; Katti, S. B.; De Clercq, E. *Bioorg. Med. Chem.* **2007**, *15*, 1725.
43. Mane, R. A.; Ingle, D. B.; Indian, J. *Chem.* **1983**, *22B*, 690.
44. Bozdagdundar, O.; Ozgen, O.; Mentese, A.; Altanlar, N.; Atli, O.; Kendi, E.; Ertan, R. *Bioorg. Med. Chem.* **2007**, *15*, 6012.

45. Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zani, F. *Bioorg. Med. Chem.* **2006**, *14*, 3859.
46. Mhaske, P. C.; Vadgaonkar, K. S.; Jadhav, R. P.; Bobade, V. D. *J. Korean Chem. Soc.* **2011**, *55*, 882.
47. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
48. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.
49. Van Arman, Scott. A. *Tetrahedron Lett.* **2009**, *50*, 4693.
50. Winter, C. A.; Risley, E. A.; Nuss, G. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
51. Sarker, S. D.; Nahar, L.; Kumarasamy, Y. *Methods* **2007**, *42*, 321.