Journal of the Indian Chemical Society 98 (2021) 100033

Contents lists available at ScienceDirect

Journal of the Indian Chemical Society

journal homepage: www.editorialmanager.com/JINCS/default.aspx

One pot synthesis of some new N-allyl and N-benzyl quinazolinones and their anti-inflammatory activity

Sudharshan Reddy Sudula [a], Ranjith Jala [b], Kavitha Siddoju [a], Jagadeesh Kumar Ega [a,*]

[a] Department of Chemistry Chaitanya Deemed to be University Warangal Urban, Telangana, India
[b] Organic &Biomolecular Chemistry Division CSIR-Indian Institute of Chemical Technology, Hyderabad, T.S, India

ARTICLE INFO

Keywords:
Quinazolinones
One pot synthesis
Anti-inflammatory activity

ABSTRACT

The simple and more reliable one-pot synthesis of some novel compounds of allyl/Benzyl quinazolinone (4aa-4bd) with good yields from readily available derivatives of anthranilic acid and benzoyl chloride was also reported. Interestingly, as compared to Diclofenac sodium, compounds 4ac, 4ad, 4ba, 4bc and 4bd displayed remarkable anti-inflammatory activity (Scheme 1 & Table 2).

Introduction

A fair amount of analogue work has attended this area with the aim of manufacturing effective chemotherapeutic agents. In general, this effort has concerned the diamino heterocycle itself or the attached substituents. On the other hand, we were interested in examining the amino groups themselves to ascertain whether replacement of the amino group by more or less basic groups might alter the binding of the enzyme sufficiently to carry on profound changes in the compounds biological profile (see Fig. 1).

Natural products enclosing quinazolinone Luotonin A (II), Rutaecarpine (I), Chloroqualone (IV), Alloqualone (V), Tryptanthrin (III), etc.).Represent a class of compounds of medicinal and pharmaceutical relative importance [3,4]. Because of to their variety of biological behavior, such as anti-cancer, diuretic, anti-inflammatory, anticonvulsant and anti-hypertensive activities" [5–8]. Numerous natural products embedded for quinazolinone have been investigated in recent years [9–17]. Medically approved as anti-cancer agents" [18–26] are the cytotoxic alkaloid Luotonin A and its derivatives infused with quinazolinone moiety. Previous studies have clearly stated that Luo functions at position with DNA topoisomerase-I [27]. Considering the effectiveness of bioactivities of the compounds possessing Luo pharmacophore, we were interested to synthesize novel Luo analogues and evaluated their anti-cancer activities such as cytotoxicity, cell cycle regulation and mechanistic aspects. Consequently, many groups were inspired to develop new synthetic methods for the synthesis of quinazolinones by using oxidative synthesis [1] and metal catalyst [2]. Herewith described the targeted N-allyl and N-benzyl-quinazolinones 4aa-4bd **(**Scheme 1 & Table 2).

Chemistry

Initially, we treated 2-phenyl-4H-benzo [d] [1,3]oxazin-4-one**3a** (1.0 equiv) with allyl amine (1.0 equiv) and Cs_2CO_3 (2.0 equiv) in CH_3CN at 82 °C to afford the desired *N*-allyl quinazolinone (**4aa**) in good yield (91%) after 3 h (Table 1, entry 1). Further optimization using other organic solvents such as DMSO, toluene, 1,2- dichloroethane and THF resulted in no improvement (Table 1, entries 2–5). The applicability of other common bases such as K_2CO_3 and NaOAc were examined which resulted in lower yields (Table 1, entries 6 and 7). Having identified the effective conditions for synthesis of *N*-allyl quinazolinone**4aa** (Table 1, entry 1), the versatility of the reaction was tested.

Earlier, the heterocyclic conversion of benzoxazin-4-ones to 2, 5-disubstituted Oxazolines preceded through the in situ *N*-allyl-2-benzamidobenzamide was established [27]. We then interested to expand this methodology to synthesize some new N-allyl and N-benzyl-quinazolinones directly in one-pot (Scheme 1). In this context, we started our synthesis from the commercially available starting materials. At the outset, the 2-amino benzoic acid derivatives **1** reacted with Benzoyl chloride **2** in the presence of Triethylamine in MeCN at reflux temperature (82 °C) for 2 h to give substituted Oxazolines [28]**3**. These Oxazolines further treated with allyl and benzyl amine under the same reaction conditions to yield in situ *N*-allyl and N-beznyl-2-benzamidobenzamide (as monitored by TLC), which then subsequently underwent

* Corresponding author.
E-mail address: jkjagadeeshkumare@gmail.com (J.K. Ega).

https://doi.org/10.1016/j.jics.2021.100033
Received 28 January 2021; Received in revised form 16 March 2021; Accepted 19 March 2021
0019-4522/© 2021 Indian Chemical Society. Published by Elsevier B.V. All rights reserved.

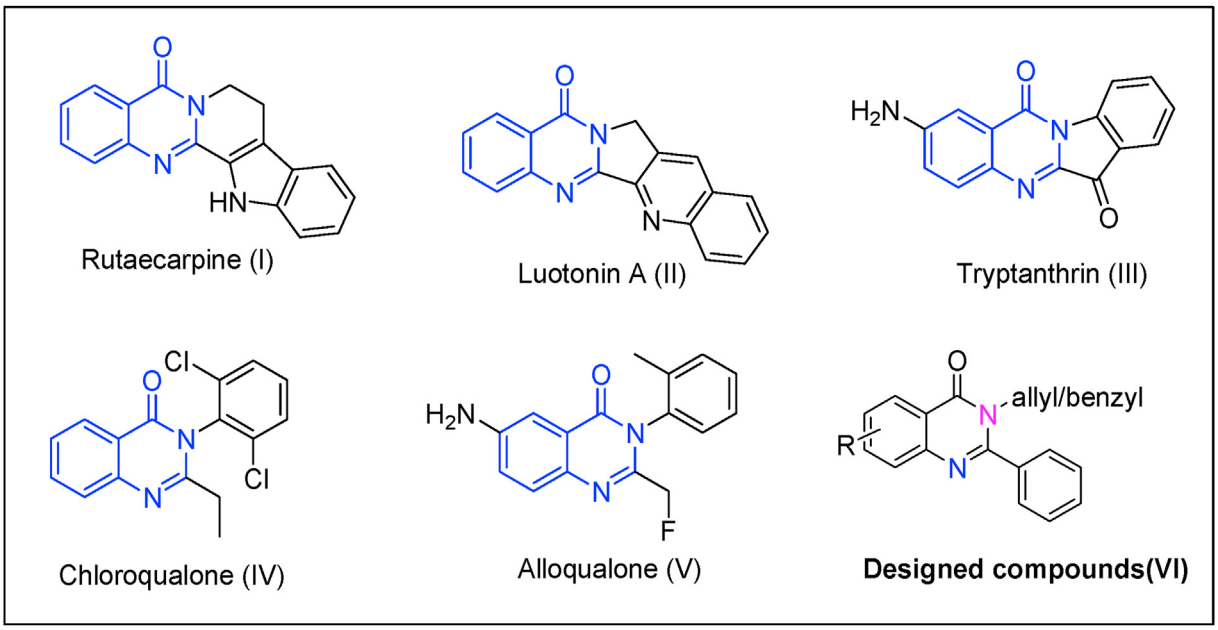
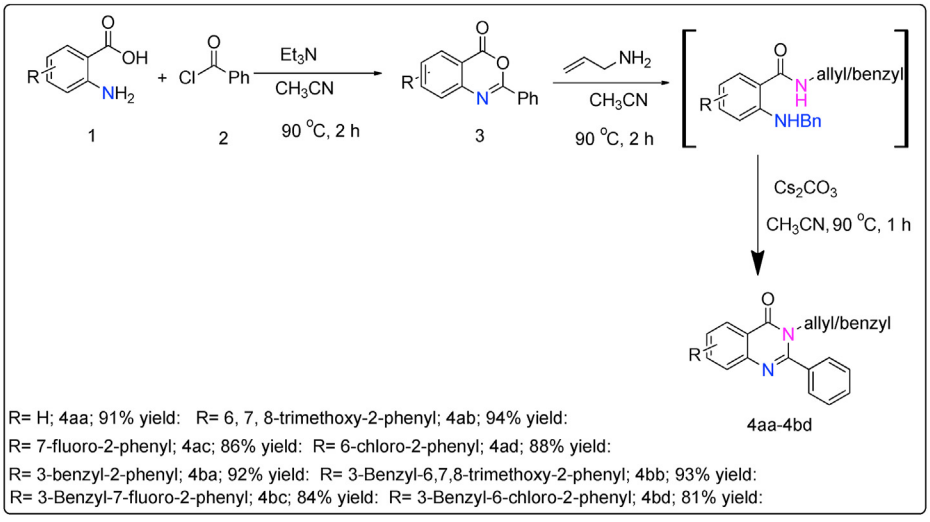


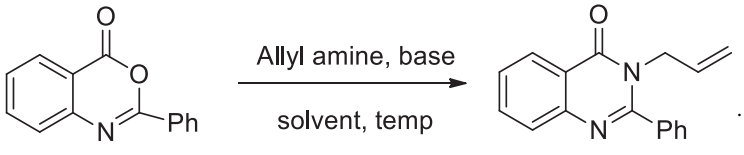
Fig. 1. Some known biologically potent quinazolinones (I–V) and designed strategy (VI).



Scheme 1. Synthesis of N-ally l and N-benzyl quinazolinones.

Table 1

Optimization of the quinazolinones reaction conditions.



3a **4aa**

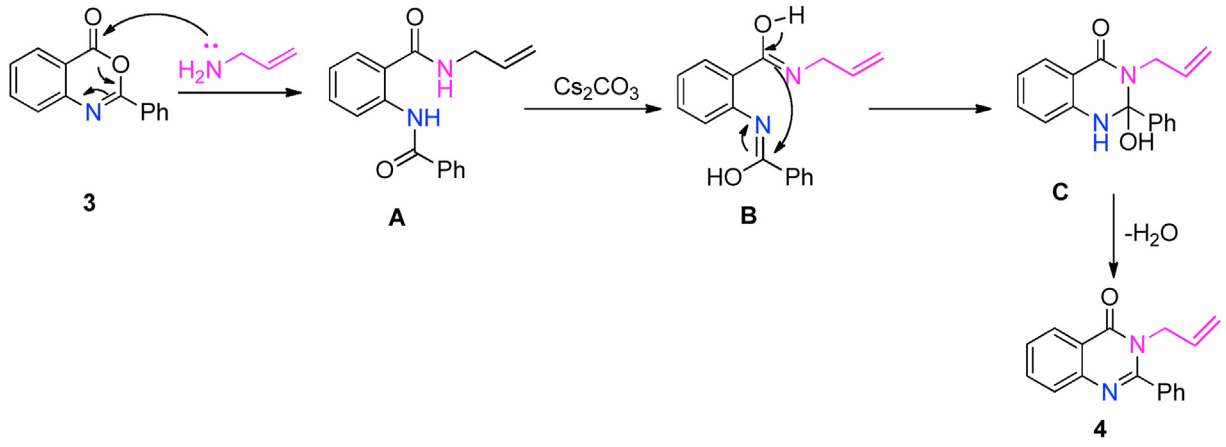
Entry	Base	Solvent	Yield (%)
1	Cs_2CO_3	CH_3CN	91
2	Cs_2CO_3	DMSO	83
3	Cs_2CO_3	Toluene	15
4	Cs_2CO_3	DCE	0
5	Cs_2CO_3	THF	0
6	K_2CO_3	CH_3CN	36
7	$Na(OAc)_2$	CH_3CN	23

[a] Reaction conditions: **3a** (0.35 mmol, 1 equiv), allyl amine (0.35 mmol, 1 equiv), Cs_2CO_3 (0.68 mmol, 2 equiv), solvent (2 mL) at 82 °C for 3 h.

Table 2
In vivo Anti-inflammatory activity of newly synthesized compounds 4aa-4bd 100 mg/kg b.wt as mean ± SD (Carrageenan-induced paw edema test in rats).

Entry	Rat paw edema in mL[b] (Treatment in hours)			
	1h	2h	3h	4h
4aa	2.42 ± 0.295	2.08 ± 0.310**	1.42 ± 0.254**	1.02 ± 0.265**
	11.67	27.52	54.48	67.61
4 ab	2.24 ± 0.278	1.82 ± 0.297**	1.12 ± 0.309**	0.98 ± 0.284**
	18.24	36.58	64.10	68.88
4ac	2.26 ± .0267	1.91 ± 0.281***	1.21 ± 0.302***	0.85 ± 0.262***
	17.51	33.44	61.21	73.01
4ad	2.21 ± 0.285	1.88 ± 0.292***	1.18 ± 0.275***	0.82 ± 0.270***
	19.34	34.49	62.17	73.96
4ba	2.11 ± 0.264	1.68 ± 0.289***	1.06 ± 0.284***	0.72 ± 0.308***
	22.99	41.46	66.02	77.14
4bb	2.14 ± 0.289	1.96 ± 0.276***	1.09 ± 0.266***	0.81 ± 0.254***
	21.89	31.70	65.06	74.28
4bc	2.18 ± 0.308	1.72 ± 0.295***	1.11 ± 0.278***	0.75 ± 0.249***
	20.40	40.06	64.42	76.19
4bd	2.16 ± 0.310	1.69 ± 0.306***	1.10 ± 0.256***	0.78 ± 0.251***
	21.16	41.11	64.74	75.23
Control	2.74 ± 0.242	2.87 ± 0.254	3.12 ± 0.289	3.15 ± 0.291
	NA	NA	NA	NA
Diclofenac Sodium	1.84 ± 0.251***	1.32 ± 0.254***	0.91 ± 0.257***	0.52 ± 0.309***
	32.84	54.01	70.83	83.49

Statistically significant compared to respective control values, ***P < 0.001, **P < 0.01, *P < 0.05 (Dunnet's test).
[a]Dose level: test compounds (100 mg/kg b.wt), Diclofenac sodium(10 mg/kg b.wt).
[b]Values are expressed as mean ± SD (number of animals N = 6 rats).



Scheme 2. Plausible Mechanism.

intramolecular cyclization by means of cesium carbonate under the standard conditions and afforded our targeted N-allyl and N-benzyl--quinazolinones **4aa-4bd** in good yields after 1 h.

On the basis of these results, a plausible mechanism is proposed (Scheme 2). Firstly, the regioselective addition of amine nucleophile on benzoxazinone **3** affords a ring opened intermediate **A**. Further, **A** by Cs_2CO_3 gives corresponding diimine intermediate **B**. which after cyclization generates dihydroquinazolinone **C**. Intermediate **C** on aromatization affords **4** with generation of H_2o.

Anti-inflammatory activity: The anti-inflammatory activity of the synthesized compounds were tested by injecting means of carrageen an induced rat paw edema method [28], using Diclofenac sodium as reference drug for comparison. The results are presented in Table 2.

In conclusion, we have synthesized some novel substituted quinazolinones (**4aa-4bd**) in good yields via simple and more effective one-pot tandem approach. The anti-inflammatory screening data of all the synthesized compounds indicated that all the compounds exhibited interesting activity, however with a degree of variation. Among all, the compounds **4ac**, **4ad**, **4ba**, **4bc** and **4bd** exhibited significant anti-inflammatory activity. Besides, rest of the compounds showed moderate anti-inflammatory activity.

Declaration of competing interest

The authors declare no conflict of interest regarding the publication of the article.

Acknowledgement

The authors are thankful to the Director, IICT, Hyderabad for providing ^{1}H NMR and ^{13}C NMR spectra and department of Biotechnology as well as Microbiology, Kakatiya University, TS for providing necessary facilities for anti-inflammatory activity studies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jics.2021.100033.

References

[1] Han B, Wang C, Han R-F, Yu W, Duan X-Y, Fang R, Yang X-L. Chem. Commun. 2011; 47:7818.(b) Fujita S-i, Tanaka M, Arai M. Catal. Sci. Technol. 2014;4:1563.(c) Sarma R, Prajapati D. Green Chem. 2011;13:718.

[2] (a) Zhan D, Li T, Wei H, Weng W, Ghandi K, Zeng Q. RSC Adv. 2013;3:9325.(b) Xu L, Jiang Y, Ma D. Org. Lett. 2012;14:1150.(c) Pulakhandam SK, Katari NK, Jonnalagadda SB. Mol. Divers. 2019;23:351.

[3] Bonola G, Da Re P, Magistretti MJ, Massarani E, Setnikar I. J. Med. Chem. 1968;11: 1136.

[4] Okumura K, Oine T, Yamada Y, Hayashi G, Nakama M. J. Med. Chem. 1968;11:348.

[5] Chan JH, Hong JS, Kuyper LF, Jones ML, Baccanari DP, Tansik RL, Boytos CM, Rudolph SK, Brown AD. J. Heterocycl. Chem. 1997;34:145.

[6] Gackenheimer SL, Schaus JM, Gehlert DR. J. Pharmacol. Exp. Therapeut. 1996;732: 113.

[7] Dempcy RO, Skibo EB. Biochemistry 1991;30:8480.

[8] Nordisk-Droge NA. 18113, patent. In: Nordisk Drogeand Kemi-Kalieforretning AIS: Luchthaven Schiphol; 1965. The Netherlands.

[9] Michael JP. Nat. Prod. Rep. 2005;22:627.

[10] Michael JP. Nat. Prod. Rep. 2004;21:650.

[11] Michael JP. Nat. Prod. Rep. 2003;20:476.

[12] Michael JP. Nat. Prod. Rep. 2002;19:742.

[13] Michael JP. Nat. Prod. Rep. 2001;18:543.

[14] Michael JP. Nat. Prod. Rep. 2000;17:603.

[15] Zhang Ying, Huang Yin-Jiu, Xiang Hong-Mei, Wang Pei-Yi, De-Yu Hu, Xue Wei, Song Bao-An, Yang Song. Eur. *J. Med. Chem.* 2014;78:23.

[16] Barbosa MLC, Lima LM, Tesch R, Mauricio C, Sant'Anna R, Totzke F, Kubbutat MHG, Schachtele C, Laufer SA, Barreirot EJ. Eur. J. Med. Chem. 2014;71: 1.

[17] Khan Imtiaz, Ibrar Aliya, Abbas Naeem, Saeed Aamer. Eur. J. Med. Chem. 2014;76: 193.

[18] Ma ZZ, Hano Y, Nomura T, Chen Y. J. Heterocycles. 1997;46:541.

[19] Wall ME, Wani MC, Cook CE, Palmer KH, Mcphail AT, Sim GA. *J. Am. Chem.* Soc. 1966;88:3888.

[20] Takimoto CH, Wright J, Arbuck SG. Biochim. Biophys. Acta 1998;1400:107.

[21] Leary OJ, Muggia FM. Eur. J. Canc. 1998;34:1500.

[22] Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LLN. Eng. J. Med. 2000;343: 905.

[23] Ozols RF. Int. J. Gynecol. Canc. 2000;10:33.

[24] Vanhoefer U, Harstrick A, Achterrath W, Cao S, Seeber S, Rustum YM. J. Clin. Oncol. 2001;19:1501.

[25] Ulukan H, Swaan PW. Drugs 2002;62:2039.

[26] Garcia-Carbonero R, Supko JG. Clin. Canc. Res. 2002;8:641.

[27] Cagir A, Jones SH, Gao R, Eisenhauer BM, Hecht SM. J. Am. Chem. Soc. 2003;125: 13628.

[28] Winter CA, Risely EA, Nuss GW. Proc Soc Exp Biol Med 1962;111:544.