RJC

RASĀYAN *J. Chem.*
Vol. 14 | No. 3 |1534-1538| July - September | 2021
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESIS OF 2-(4-((1-PHENYL-1*H*-1,2,3-TRIAZOLE-4-YL) METHOXY) PHENYL)QUINAZOLINE-4(3*H*)-ONE

Thummala Rajamani[1] and K. Bhaskar[2,✉]
[1]Department of Chemistry, University Arts & Science College, Kakatiya University, Warangal – 506 001, Telangana, India
[2]Department of Chemistry, Osmania University, Hyderabad-500 007, Telangana, India
✉Corresponding Author: manithummala6@gmail.com

ABSTRACT
New chemical entities encompassing 1,2,3-triazole and quinazolinones (**7a-h)** have been synthesized starting from 4-hydroxy benzaldehyde (**1**) in three steps involving the addition of propoxyl bromide (**2**), iodine/dimethyl sulfoxide catalyzed condensation of anthranilamide (**4**) and finally 'Click' reaction with various phenylazides (**6a-h**). Several analogs have been synthesized in excellent yields and fully characterized by using ^{1}H NMR, IR and Mass spectroscopic methods and they were superior in accordance with the proposed structures.
Keywords: Anthranilamide, 4-hydroxy benzaldehyde, propoxyl bromide, and 1,2,3-triazole substituted quinazolinone.

RASĀYAN *J. Chem.*, Vol. 14, No.3, 2021

INTRODUCTION

The plethora of biological properties, such as anticancer[1], anti-HIV[2], antimicrobial[3] etc, exhibited in the quinazolinone core structure has attracted the immense interest of research groups across the globe. A much often employed strategy to bring about diversity in biologically important core moieties is through the structural modifications employing chemical means. This is especially true in the case of quinazolinones. The literature precedence indicates that the potency of the quinazolinone core structure can be manipulated through suitable structural changes.[4-7] The structural alterations of a lead compound are a frequently used strategy in drug discovery. Various naturally occurring molecules bearing quinazolinone core have been identified to have important biological properties. Camptothecin, Rutaecarpine, Luotonin etc are some of the examples (Fig.-1).[7-15]

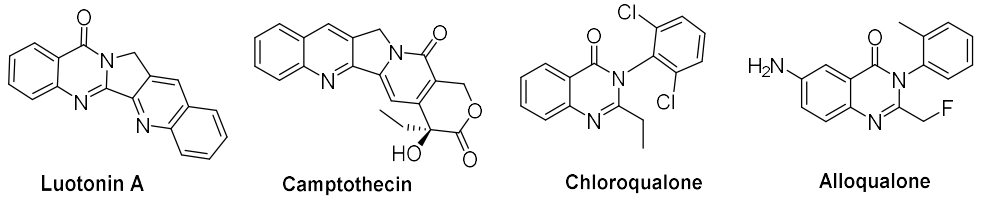


Fig.-1: Structures of Luotonin A, Camptothecin, Chloroqualone, Alloqualone

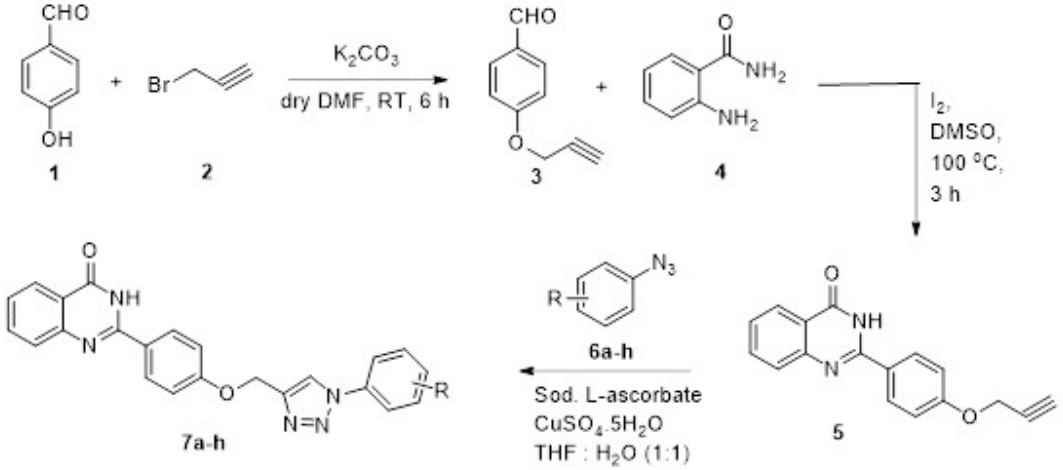
In continuation of our ongoing research in search of new biological active compounds, a series of novel analogs of 1,2,3-triazole substituted quinazolinones (7a-h) have been synthesized in the present investigation (Scheme-1).

EXPERIMENTAL

Material and Methods

To measure the melting points of the compounds Fischer-Johns melting point apparatus was used. Perkin Elmer-283B & Nicolet-740 was used to record IR spectra. Varian Gemini-200, Varian unit-500 and Avance 300 MHz, Avance 400 MHz, BrukerUx-NMR were used to record ^{1}H NMR spectra and VG

Micro mass 7070H (ESI was used to record Mass spectra).



Scheme-1

4-(Prop-2-yn-1-yloxy)benzaldehyde (3)

4-Hydroxy benzaldehyde (**1**, 1 equiv.), propoxyl bromide (**2**, 1.2 equiv.) was stirred at room temperature with K_2CO_3 in dry dimethyl formamide for 6.5 h. The mixture was poured onto crushed ice, formed solid was filtered and dried to get 4-(prop-2-yn-1-yloxy)benzaldehyde (**3**) as pale yellow. Yield: 90%, m. p. 64-66 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 2.59 (s, 1H, alkyne-H), 4.80 (s, 2H, -OCH_2-), 7.10 (d. 2H, aromatic-H), 7.90 (2H, aromatic-H), 9.95 (s, 1H, -aldehyde). ESI-MS: *m/z* = 161[M+H].

4-(Prop-2-yn-1-yloxy) phenyl) quinazolin-4(3*H*)-one (5)

A mixture of 4-(prop-2-yn-1-yloxy)benzaldehyde (**3,** 1.3equiv.) and anthranilamide (**4**, 1equiv.) were heated at 100 °C for 3 hr in presence of iodine and DMSO. Based on TLC reaction progress tested, the mixture was cooled to RT and hypo solution was used for quenching, then extracted with EtOAc (3x20 mL). Ethyl acetate layers were washed with H_2O (3x30 mL), dried and concentrated. The pure 4-(prop-2-yn-1-yloxy)phenyl) quinazoline-4(3*H*)-one (**5**) in excellent yield (92%) was obtained upon column chromatography with EtOAc : Hexane (2:8) as eluent; m. p. 166-168 ^{0}C.^{1}H NMR ($CDCl_3$): δ 3.64 (s, 1H, alkyne-H), 4.93 (s, 2H, -OCH_2-), 7.14-7.19 (m, 2H, aromatic-H), 7.48-7.52 (m, 1H, aromatic-H), 7.70-7.74 (m, 1H, aromatic-H), 7.80-7.85 (m, 1H, aromatic-H), 8.13-8.17 (m, 1H, aromatic-H), 8.19-8.22 (m, 2H, aromatic-H). ESI-MS: *m/z* = 277 [M+H].

Synthesis of 2-(4-((1-substituted phenyl-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)quinazolin-4(3*H*)-one derivatives (7a-h)

To the mixture of azido compound (**6a**, 1.4 equiv) and 2-(4-(prop-2-yn-1-yloxy)phenyl) quinazolin-4-(3*H*)-one (**5**, 1equiv) in THF:H_2O (1:1) was added $CuSO_4.5H_2O$ (3.2 eq) and sodium ascorbate (3.2 eq) at room temperature. The reaction mixture was stirred at RT for 3-4 h. Based on TLC, mixture was extracted with ethyl acetate (2x10 mL) and water (5 mL). The organic layer was separated, dried and concentrated to furnish following quinazolin tethered triazoles:

2-(4-((1-Phenyl-1*H*-1,2,3-triazol-4-yl) methoxy) phenyl)quinazolin-4(3*H*)-one (7a)

Yield: 85%, m. p. 232-234 ^{0}C. IR (KBr): υ 3444, 3058, 1658, 1606, 1564, 1482, 1444 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.39 (s, 2H, -OCH_2-), 7.15 (d, *J* = 3.5Hz, 2H, aromatic-H), 7.50-7.62 (m, 2H, aromatic-H), 7.70-7.81 (m, 5H, aromatic-H), 8.14-8.31 (m, 5H, aromatic-H). ESI-MS: *m/z* = 396 [M+H].

2-(4-((1-(2-(Trifluomethyl)phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)quinazolin-4(3*H*)-one (7b)

Yield: 90%, m. p. 210-212^{0}C. IR (KBr): υ 3445, 3060, 1656, 1600, 1565, 1485, 1445 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 2H, -OCH_2-), 7.00 (d, 2H, aromatic-H), 7.50 (m, 2H, aromatic-H), 7.80 (m, 2H,

aromatic-H), 7.90 (d, 2H, aromatic-H), 8.00(d, 2H, aromatic-H),8.10 (s, 1H, aromatic-H), 8.30 (d, 1H, aromatic-H), 9.78 (s, 1H, -NH).ESI-MS: *m/z* = 464 [M+H].

2-(4-((1-(2-Fluorophenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)quinazolin-4(3*H*)-one (7c)
Yield: 87%, m. p. 263-265 ^{0}C. IR (KBr): υ 3417, 3063, 2924, 1677, 1599, 1561, 1247 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 2H, -OCH_2-), 7.08 (d, 2H, aromatic-H), 7.22-7.38 (m, 3H, aromatic-H), 7.40-7.47 (m, 2H, aromatic-H),7.76-7.80(m,3H,aromatic-H)8.15-8.20 (m, 3H, aromatic-H), 11.20 (brs, 1H, -NH). ESI-MS: *m/z* = 414 [M+H].

2-(4-((1-(4-chlorophenyl-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl) quinazolin-4(3*H*)-one (7d)
Yield: 92%, m. p. 263-265 ^{0}C. IR (KBr): υ 3440, 3055, 1650, 1605, 1560, 1482, 1442 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.80 (s, 2H, -OCH_2-), 7.00-7.05 (m, 2H, Ar-H), 7.60-7.62 (m, 3H, aromatic-H), 8.00-8.05 (m, 2H, aromatic-H), 8.10-8.21 (m, 6H, aromatic-H). ESI-MS: *m/z* = 430 [M+H], 432 [M+2].

2-(4-((1-(2,4-dichlorophenyl-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)quinazolin-4(3*H*)-one (7e)
Yield: 92%, m. p. 240-242 ^{0}C. IR (KBr): υ 3447, 3063, 2918, 2850, 1664, 1603, 1566, 1518, 1486 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 2H, -OCH_2-), 7.20 (d, 1H, aromatic-H), 7.50 (s, 1H, aromatic-H), 7.65-7.85 (m, 5H, aromatic-H), 8.00-8.05 (m, 2H, aromatic-H), 8.20-8.38 (m, 3H, aromatic-H). ESI-MS: *m/z* = 464 [M+H], 466 [M+2], 468 [M+4].

2-(4-((1-(2-Nitrophenyl-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)quinazolin-4(3*H*)-one (7f)
Yield: 82%, m. p. 226-228 ^{0}C. IR (KBr): υ 3444, 2925, 2859, 1671, 1462 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.41 (s, 2H, -OCH_2-), 7.15 (s, 1H, NH), 7.80 (m, 4H, aromatic-H), 8.00 (d, 1H, aromatic-H), 8.18 (m, 4H, aromatic-H), 8.38 (d, 2H, aromatic-H). ESI-MS: *m/z* = 441 [M+H].

2-(4-((1-(4-Nitrophenyl-1*H*-1,2,3-triazol-4-yl)methoxy) phenyl)quinazolin-4(3*H*)-one (7g)
Yield: 92%, m. p. 233-235 ^{0}C. IR (KBr): υ 3448, 3079, 1672, 1603, 1483 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.80 (s, 2H, -OCH_2-), 7.15 (d, 2H, aromatic-H), 7.20 (d, 2H, aromatic-H), 7.58 (d, 1H, aromatic-H), 8.00 (d, 2H, aromatic-H), 8.30 (d, 4H, aromatic-H), 8.48 (d, 2H, aromatic-H). ESI-MS: *m/z* = 441 [M+H].

2-(4-((1-(3-(Trifluomethyl)phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)quinazolin-4(3*H*)-one (7h)
Yield: 89%, m. p. 263-265 ^{0}C. IR (KBr): υ 3447, 2918, 1664, 1518, 1243, 765 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 2H, -OCH_2-), 7.20 (d, 1H, aromatic-H), 7.50 (m, 2H, aromatic-H), 7.80-7.85 (m, 4H, aromatic-H), 7.98 (d, 2H, aromatic-H), 8.08 (d, 2H, aromatic-H), 8.18 (s, 1H, aromatic-H), 8.30 (d, 1H, aromatic-H), 9.80 (brs, 1H, -NH). ESI-MS: *m/z* = 464 [M+H].

RESULTS AND DISCUSSION

Because of several synthetic, biological, and pharmacological applications of quinazolinone derivatives, the present work is aimed to synthesize new triazole containing quinazolinone derivatives. On the other hand, in the search for new drugs, if any structural modification on existing quinazolinone that leads to possess significant biological activities. Therefore, there is an urgent need to develop synthetic methods for the quinazolinone skeleton and its analogs. In this context, synthesized new analogs of 1,2,3-triazole substituted quinazolinone from 4-hydroxy benzaldehyde, propoxyl bromide and anthranilamide.

4-Hydroxy benzaldehyde (**1**) was treated with propoxyl bromide (**2**) in presence of K_2CO_3 in dry *N,N′*-dimethyl formamide at RT for 6 h to get *O*-alkylated intermediate of 4-(prop-2-yn-1-yloxy)benzaldehyde (**3**), which upon treated with anthranilamide (**4**) in presence of iodine in dimethyl sulfoxide at 100 °C for 3 h obtained an intermediate of 4-(prop-2-yn-1-yloxy)phenyl) quinazoline-4(3*H*)-one (**5**) in excellent yield (92%). Finally, the desired triazole products **7a-h** have been achieved by the reaction of the intermediate of 4-(prop-2-yn-1-yloxy)phenyl) quinazoline-4(3*H*)-one (**5**) with various phenylazides (**6a-h**) in presence of copper sulphate and Na+ ascorbate in 1:1 ratio of THF-water at RT for 3 h (Scheme-1).

Newly synthesized derivatives were confirmed by using ^{1}H NMR, IR and ESI-Mass spectral analysis and are in good agreement with the proposed derivative structures. In ^{1}H NMR the triazole characteristic

signal appeared in the range of δ 7.50-7.62 ppm of **7a** as a singlet and triazole attached of -OCH_2- protons detected as single at δ 5.39 ppm. The derivative structures were confirmed further by ESI-MS data which molecular ion peak was displayed at *m/z*=396 $[M+H]^+$ of $C_{22}H_{17}N_5O_2$ and IR spectra shown absorption bands at 1602-1664 cm^{-1} and 1520, 1482, 1444 cm^{-1} which corresponded to C=O ,-OCH2, N-N, N=N as characteristics.

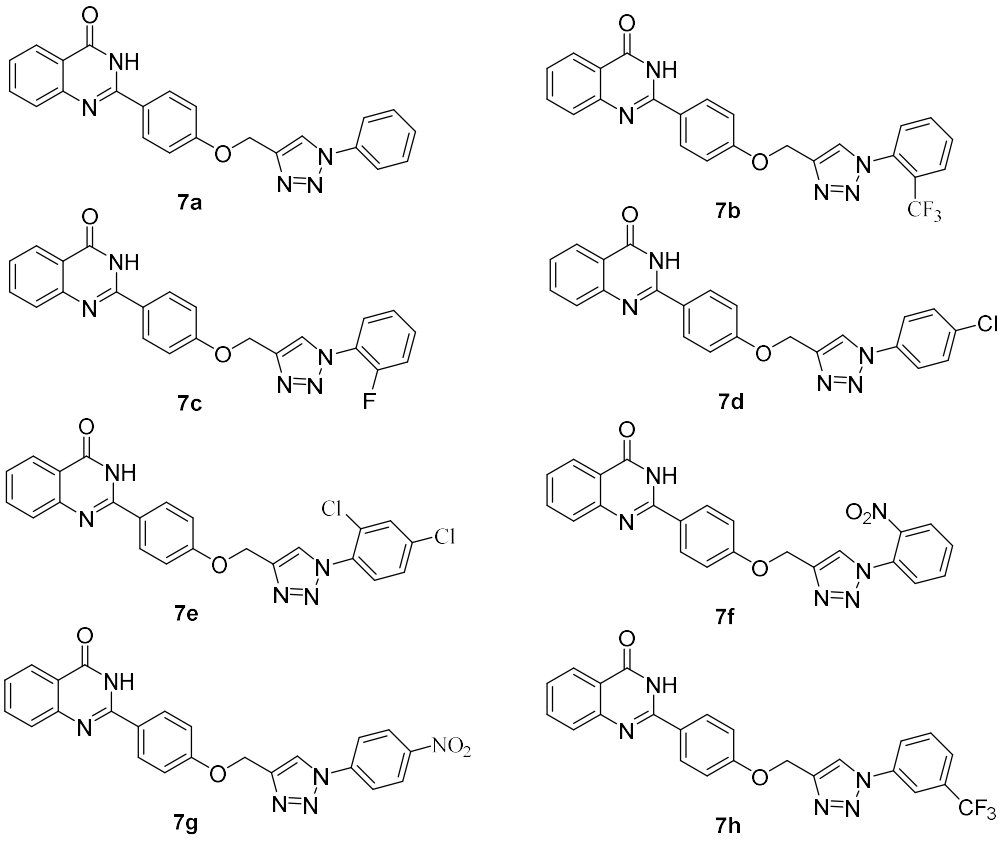


Fig.-1

CONCLUSION

In conclusion, we have designed and synthesized a new analog of 1,2,3-triazole substituted quinazolinone from 4-hydroxy benzaldehyde, propoxyl bromide and anthranilamide in good to excellent yields. Newly synthesized derivatives were confirmed by using ^1H NMR, IR and ESI-Mass spectral analysis and agreement with the proposed derivatives.

REFERENCES

1. L. A. Skelton, M. G. Ormerod, J. Titley, R. Kimbell, L. A. Brunton, A. L. Jackman, *British Journal of Cancer,* **79**, 1692(1999), https://doi.org/10.1038/sj.bjc.6690270 .
2. Yi Xia, Zheng-Yu Yang, Mann-Jen Hour, Sheng-Chu Kuo, Peng Xia, Kenneth F. Bastow, Yukuna Nakanishi, Priya Nampoothiri, Torben Hackl, Ernest Hamel, Kuo-Hsiung Lee, *Bioorganic Medicinal Chemistry Letters,* **11**, 1193(2001).
3. V. Alagarswamy, R. Revathi, S. Meena, K. V. Ramaseshu, S. Rajasekaran, E. De Clercq, *Indian Journal of Pharmaceutical Science,* **4**, 459(2004).
4. Maher F. El-Zohry, Abd El-Hamed N. Ahmed, Farghaly A. Omar, Mohamed A. Abd-Alla, *Journal of Chemical Technology & Biotechnology,* **53**, 329(1992), https://doi.org/10.1002/jctb.280530403
5. David J. Connolly, Declan Cusack, Timothy P. O'Sullivan, Patrick J. Guiry, *Tetrahedron,* **61**, 10153(2005), https://doi.org/0.1016/j.tet.2005.07.010
6. R. Rohini, K. Shanker, P. Muralidhar Reddy, V. Chandra Sekhar, V. Ravinder, *Arch Pharma Chemical Life Sciences,* **342**, 533(2009), https://doi.org/10.1002/ardp.200900068

7. Zhong-Ze Ma, Yoshio Hano, Taro Nomura, Ying-Jie Chen, *Heterocycles*, **46**, 541(1997), https://doi.org/10.3987/COM-97-S65
8. M. E. Wall, M. C. Qani, C. E. Cook, K. H. Palmer, A. T. Mcphail, G. A. Sim, *Journal of American Chemical Society*, **88**, 3888(1966), https://doi.org/10.1021/ja00968a057
9. C. H. Takimoto, J. Wright, S. G. Arbuck, *Biochimica Biophysica Acta*, **1400**, 107(1998), https://doi.org/10.1016/s0167-4781(98)00130-4
10. J. O'Leary, F. M. Muggia, *European Journal of Cancer*, **34**, 1500(1998), https://doi.org/10.1016/S0959-8049(98)00229-9
11. L. B. Saltz, J. V. Cox, C. Blanke, L. S. Rosen, L. Fechrenbacher, M. J. Moore, J. A. Maroun, S. P. Ackland, P. K. Locker, N. Pirotta, G. L. Elfring, L. L. Miller, *The New England Journal of Medicine*, **343**, 905(2000), https://doi.org/10.1056/NEJM200009283431302
12. R. T. Penson, K. Kronish, Z. Duan, A. J. Feller, P. Stark, S. E. Cook, L. R. Duska, A. F. Fuller, A. K. Goodman, N. Nikrui, K. M. MacNeill, U. A. Matulonis, F. I. Preffer, M. V. Seiden, *International Journal of Gynecological Cancer,* **10**, 33(2000), https://doi.org/10.1046/j.1525-1438.2000.00003.x
13. U. Vanhoefer, A. Harstrick, W. Achterrath, S. Cao, S. Seeber, Y. M. Rustum, *Journal of Clinical Oncology*, **19**, 1501(2001), https://doi.org/10.1200/jco.2002.20.5.1425
14. H. Ulukan, P. W. Swaan, *Drugs,* **62**, 2039(2002), https://doi.org/10.2165/00003495-200262140-00004
15. R. Garcia-Carbenero, J. G. Supko, *Clinical Cancer Research*, **8**, 641(2002), https://doi.org/10.1158/1078-0432.CCR-06-1347

[RJC-6259/2020]