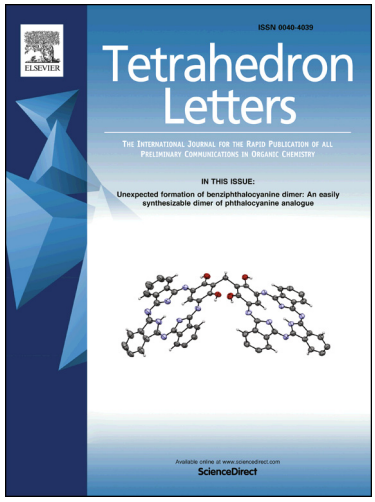


Novel One Pot Synthesis of substituted quinazolin-4(3*H*)-ones and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones using Copper iodide, Azides and Terminal Alkynes

V. Srishylam, N. Devanna, M.V. Basaveswara Rao, Naveen Mulakayala

PII: S0040-4039(17)30748-7
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.06.026
Reference: TETL 49018

To appear in: *Tetrahedron Letters*

Received Date: 24 April 2017
Revised Date: 8 June 2017
Accepted Date: 9 June 2017

Please cite this article as: Srishylam, V., Devanna, N., Basaveswara Rao, M.V., Mulakayala, N., Novel One Pot Synthesis of substituted quinazolin-4(3*H*)-ones and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones using Copper iodide, Azides and Terminal Alkynes, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.06.026

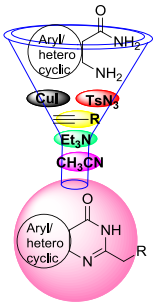
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Novel One Pot Synthesis of substituted quinazolin-4(3*H*)-ones and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones using Copper iodide, Azides and Terminal Alkynes

Leave this area blank for abstract info.

Srishylam.V, N. Devanna, MV Basaveswara Rao, Naveen Mulakayala



Tetrahedron Letters

journal homepage: www.elsevier.com

Novel One Pot Synthesis of substituted quinazolin-4(3*H*)-ones and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones using Copper iodide, Azides and Terminal Alkynes

Srishylam.V,[a] N. Devanna.[a] MV Basaveswara Rao,[b] Naveen Mulakayala[*c]

[a]Department of Chemistry, Jawaharlal Nehru Technological University Anantapur, Ananthapuramu, Andhra Pradesh, India.
[b] *Department of Chemistry, Krishna University, Machilipatnam – 521 00, India*
[c] *Clearsynth Labs Ltd, Plot no-177, IDA Mallapur, Nacharam, Hyderabad-500076, India*

E-mail:naveen071280@gmail.com

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
quinazolin-4(3*H*)-ones
pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones
Azides
Copper iodide
Terminal Alkynes

ABSTRACT

A simple and highly efficient copper iodide catalyzed one-pot synthesis of 2-substituted quinazolin-4(3*H*)-ones have been developed from anthranilamide, terminal alkynes and azides. A wide variety of alkynes were screened to understand the scope of this methodology. This method has been extended for the synthesis of 5-substituted pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones which are having potential applications in medicinal chemistry.

1. Introduction

4(3H)-Quinazolinones are an important class of fused heterocycles, which have drawn great importance due to their biological importance. Quinazolinone is an important scaffold found in about 200 naturally occurring alkaloids isolated till to day from a number of families of the plant kingdom, from animals and from microorganisms (Fig. 1). For example, 2-methyl-4(3*H*)-quinazolinone (1) was isolated from culture of the microorganism Bacillus cereus,[1] Pegamine (2), an alkaloid isolated from Peganum harmala, exhibits cytotoxic properties.[2] vasicinone (3) is a pyrrolo[2,1-*b*]quinazoline alkaloid, isolated from the aerial parts of adhatoda (Justica adhatoda), a plant used extensively in indigenous medicine for treating colds, coughs, bronchitis, and asthma.[3] Luotonine A (4) was isolated from a Chinese plant named Luo-Tuo-Hao (Peganum nigellastrum) is a human DNA topoisomerase I inhibitor and displays cytotoxicity toward the murine leukemia P388 cell line (IC50 = 1.8 μg/mL).[4] Rutaecarpine (5) is the major alkaloid component isolated from dried fruits of Evodia rutaecarpa, a Chinese herbal drug used extensively as a remedy for headache, cholera, dysentery and worm infections.[5] Bouchardatine (6) isolated from Bouchardatia neurococca[6] (Fig. 1).

Quinazolinone derivatives have attracted the synthetic community due to their broad spectrum of biological and pharmaceutical activities such as anti-inflammatory,[7] anticancer,[8] anti-malarial,[9] anti-diabetic,[10] anti-tumor,[11] anti-microbial,[12] anti-convulsant,[13] anti-viral,[14] anti-hypertensive,[15]cholinesterase inhibition,[16] epidermal growth factor (EGFR) receptors of tyrosine kinase,[17] ligands for benzodiazepine and GABA receptors in central nervous system,[18] and several others.

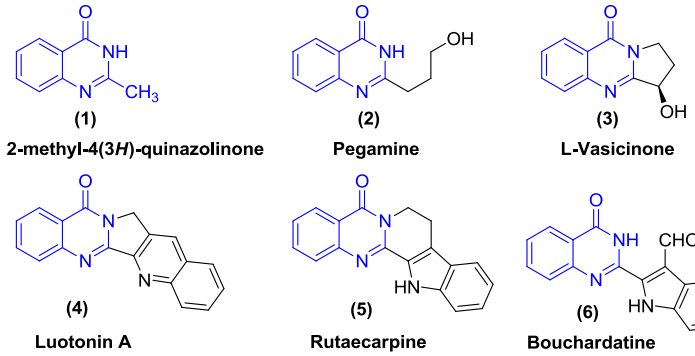
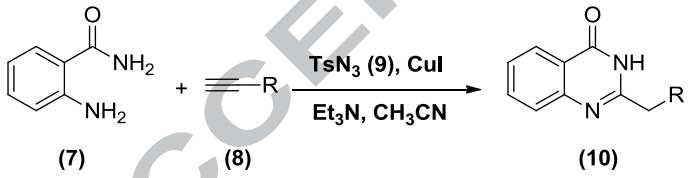


Figure 1: Naturally occurring 4(3H)-Quinazolinone alkaloids

Some synthetic quinazolinones such as raltitrexed (for the first-line palliative treatment of advanced colorectal cancer), afloqualone (as a muscle relaxant) ispinesib, and tempostatin are already in the market or are in clinical trials.[1]9

The most common synthetic methods to synthesize quinazolinone derivatives utilize 2-aminobenzoic acid or its derivatives, 2-halobenzoic acids (or) benzamides, 2-aminobenzamide, 2-aminobenzonitrile and isatoic anhydride as suitable precursors. While the reported methods are important in varying degree, some methods are still experience restrictions like poor or inconsistent yields, expensive and environmentally toxic catalysts, long reaction time, substrate tolerance and tedious work up procedures. Hence, a easier and high yielding method towards the synthesis of quinazolinones is much desirable.

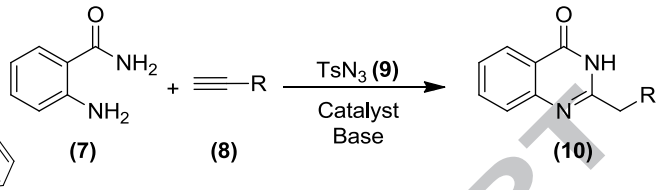
As a part of our ongoing research towards the development of new methodologies for the synthesis of biologically important heterocyclic compounds [20] we want to study the novel method for the synthesis of 2-substituted quinazolinones. Recently, Ketenimine, has attracted considerable attention due to its high reactivity, easiness to form, and wide scope of substrates tolerance. Herein we report a simple, scalable and straightforward copper catalyzed method for the synthesis of quinazolin-4(1*H*)-ones (10) (Scheme 1) by a one-pot three-component reaction of 2-aminobenzamide (7), Azides (9) and terminal alkynes (8).



Scheme 1: copper catalyzed one pot synthesis of 2-substituted quinazoline 4-(3H)-one

Initially, we examined one-pot, three-component condensation reaction of 2-aminobenzamide (7), phenyl acetylene (8a) and *p*-toluenesulfonyl azide (9) as the model substrates by using copper iodide (10 mol %) as catalyst in THF solvent (Table 1, entry 1) and triethylamine as a base. To our delight, the corresponding quinazolin-4(3*H*)-one (10a) derivative was obtained in 60 % yield after 24 h at room temperature. Encouraged by this result, we further carried out the optimization experiments with different solvents and different copper catalysts as shown in table-1.

Table 1: Optimization of catalyst and solvents for the preparation of quinazolin-4(3*H*)-one. [a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	CuI	CH_3CN	65
2	CuI	THF	41
3	CuI	1,4-Dioxane	49
4	CuI	CH_2Cl_2	10
5	CuI	DMF	58
6	CuBr	CH_3CN	37
7	CuCl	CH_3CN	31

[a] Reaction conditions: All the reaction were carried out 2-aminobenzamide (1 mmol.), phenylacetylene (1.1 mmol.), tosylazide (1.1 mmmol), triethylamine (1 mmol) and solvent (10 ml) at room temperatures. [b] Isolated yield.

As shown in the table-1, different solvents, including THF, 1, 4-dioxane, CH_2Cl_2 and DMF were screened but product formation was considerably lower than that obtained by using acetonitrile (entry 1). Further experiments were performed using copper bromide (entry 6) and copper chloride (entry 7) in acetonitrile gave lesser yields compared with copper iodide. Further we carried out optimization of bases and catalyst loading and the results are tabulated in table-2.

Table 2: Optimization of bases and catalyst loading for the synthesis of 2-substituted quinazoline 4-(3H)-one. [a]

Entry	Catalyst	Mol %	Base (eq.)	Time(h)	Yield (%)[b]
1	CuI	10	DIPEA (1.0)	24	29
2	CuI	10	K_2CO_3 (1.0)	24	10
3	CuI	10	Et_3N (1.0)	12	65
4	CuI	10	Et_3N (1.0)	24	81
5	CuI	10	Et_3N (2.0)	12	90
6	CuI	10	Et_3N (3.0)	12	91
7	CuI	10	Et_3N (4.0)	12	87
8	CuI	5	Et_3N (2.0)	12	68
9	CuI	20	Et_3N (2.0)	12	87
10	CuI	50	Et_3N (2.0)	12	74

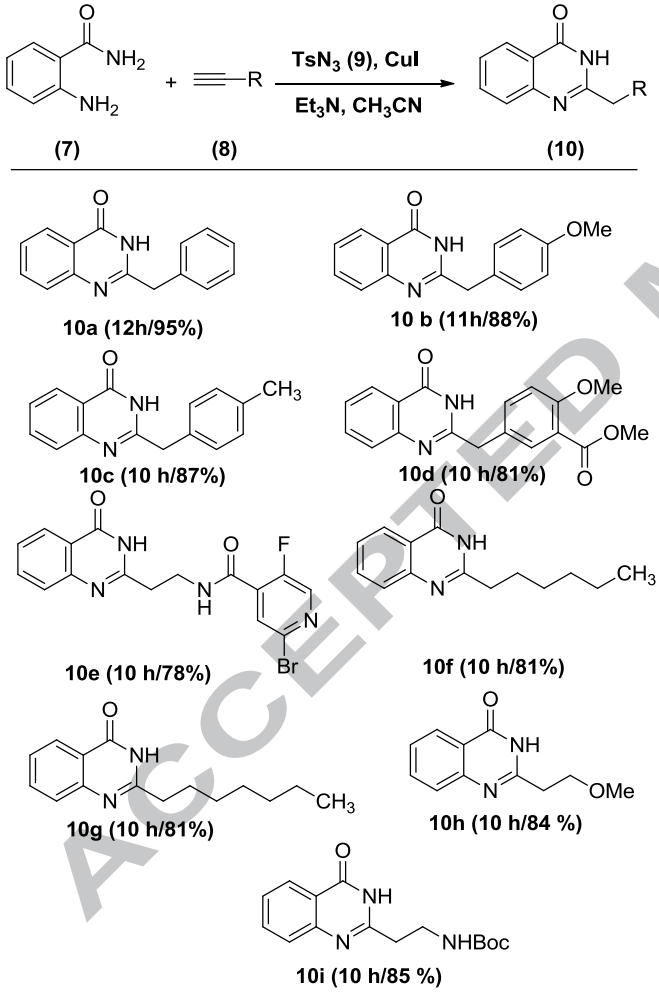
[a] Reaction conditions: All the reaction were carried out 2-aminobenzamide (1 mmol.), phenylacetylene (1.1 mmol.), tosylazide (1.1 mmmol) and acetonitrile (10 ml) at room temperatures. [b] Isolated yields.

Different bases were screened to optimize the reaction conditions mainly *N*, *N*-Diisopropylethylamine (DIPEA), potassium carbonate (K_2CO_3) and triethylamine(TEA). In all the above bases DIPEA and K_2CO_3 were produced less yields than triethylamine (Table-2). The influence of base equivalents were also studied further. When the reaction was performed with 2 eq. of triethylamine gave clean conversion after 12 h with 90 % isolated yield. Increasing the catalyst loading from 10 mol% to

20 mol % no significant yield improvement observed. However with increasing catalyst loading from 10 mol % to 50 mol %, also decreasing catalyst loading from 10 mol % to 5 mol % significant yield drop observed.

This observation encouraged us to extend the scope and generality of this methodology. A wide variety of terminal alkynes were evaluated using the optimized reaction conditions, and the results are tabulated in Table 3. The reactions were proceeded smoothly and all the alkynes participated well in the reaction. The aromatic alkynes participated well in the reaction affording the corresponding products in high yields (Table 3, entries 1–4). Hetero aromatic acetylenes (entry 5) and aliphatic acetylenes (entry 6-8) also readily participated giving desired products in good yields. More importantly, carbamate functional group (entry 9) also tolerated in the reaction conditions giving the corresponding quinazolinone in 85% yield.

Table 3: Synthesis of 2-substituted quinazoline 4-(3H)-one



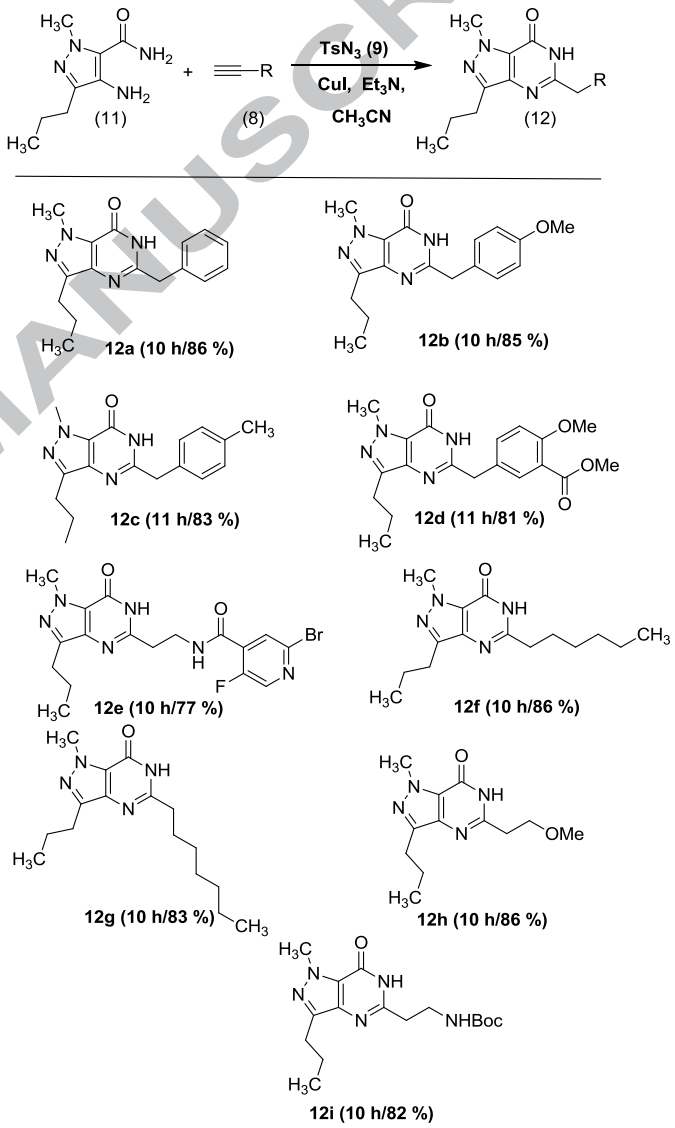
[a] Reaction conditions: 2-aminobenzamide (2.0 mmol), terminal alkyne (2.0 mmol), *p*-tolylsulfonyl azide (2.0 mmol), CuI (10 mol%), Et_3N (4.0 mmol), and CH_3CN (10 mL).

[b] Isolated yields.

After successful synthesis of 2-substitued quinazoline 4-(3H)-one **10** we want to use this methodology on 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide **11** which can be used as 2-aminocarboxamide source. When 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (**11**), reacted with a mixture of terminal alkynes (**8**) tosyl azide (**9**), TEA in acetonitrile using copper iodide as catalyst afforded corresponding pyrazolo[4,3-*d*] pyrimidin-7(6*H*)-ones (**12**) in good to excellent isolated yields.

Based on the results summarized in Table 4 it was evident that the cascade reaction was proceeded well to give the desired product **12** in good to excellent yields using terminal alkynes. All the synthesized compounds were well characterized by spectral data (NMR and MS).

Table-4: copper iodide-catalyzed synthesis of pyrazolo[4,3-*d*] pyrimidin-7(6*H*)-ones

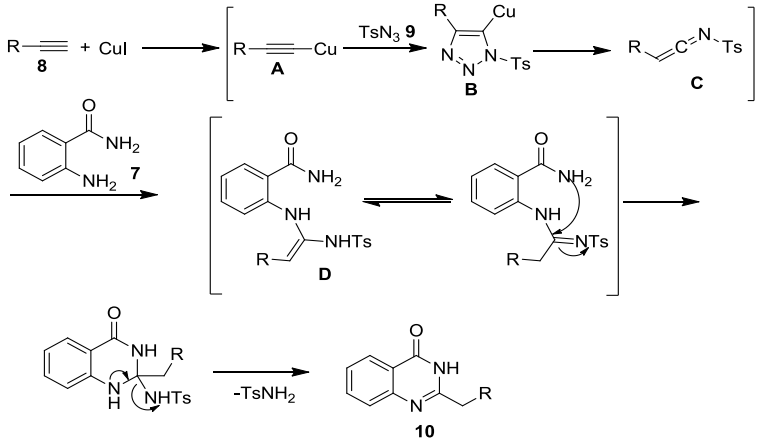


[a] Reaction conditions: 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide, **11** (2.0 mmol), terminal alkyne (2.0 mmol), *p*-tolylsulfonyl azide (2.0 mmol), CuI (10 mol %), Et_3N (4.0 mmol), CH_3CN (10 mL).

[b] Isolated yields.

A plausible mechanism for the formation of substituted quinazoline 4-(3H)-one is illustrated in Scheme 2. Based on previous reports, the copper acetylide **A**, formed from alkyne **8** and copper(I) iodide, undergoes a 1,3-dipolar cycloaddition with azide **9** to give triazole derivative **B**. This intermediate is

converted into ketenimide **C**, which is attacked by amine **7** to afford intermediate **D**. This intermediate upon intramolecular cyclization afforded the final product **10**.



Scheme 2: Plausible reaction mechanism for the formation of 2-substituted quinazoline 4-(3H)-one

In conclusion, we have developed an efficient copper iodide catalyzed one-pot method for the synthesis of 2-substituted 4(3*H*)-quinazolinones from 2-aminobenzamide, azide and various alkynes using copper iodide.[21] The reaction proceeds under mild conditions, a wide range of substrates fit for the process to afford the corresponding 2-substituted 4(3*H*)-quinazolinones in moderate to good yields. This method was used for the synthesis of 5-substituted pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones which can be used as important cores in medicinal chemistry.

References:

1. Yoshida, S.; Aoyagi, T.; Harada, S.; Matsuda, N.; Ikeda, T.; Naganawa, H.; Hamada, M.; Takeuchi, T.. *J. Antibiot*. **1991**, *44*,111.
2. Khashimov, K. N.; Telezhenetskaya, M. V.; Rashkes, Y. V.; Yunusov, S. Y.; *Khimia. Prirodnykh soedinenii*, **1970**, 6, 453.
3. Poi, R.; Adityachaudhury, N. *J. Indian Chem. Soc.* **1988**, 65, 814.
4. (a) Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, Y. J. *Heterocycles* **1997**, *46*, 541. (b) Cagir, A.; Jones, S. H.; Gao,R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**,*125*, 13628.
5. (a) Chen, A. L.; Chen, K. K. *J. Am. Pharm. Assoc.* **1933**, *22*, 716. (b) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66. (c) Deng, P.-Y.; Ye, F.; Cai, W.-J.; Tan, G.-S.; Hu, C.-P.; Deng, H.-W.; Li, Y.-J. *J. Hypertens.* **2004**, *22*, 1819.
6. Wattanapiromsakul, C.; Forsterand, P. I.; Waterman, P. G. *Phytochemistry* **2003**, *64*, 609.
7. (a) Kenichi, O.; Yoshihisa, Y.; Toyonari, O.; Toru, I.; Yoshio, I. *J. Med. Chem.* **1985**, *28*, 568.; (b) Chao, Q.; Deng, L.; Shih, H.; Leoni, L. M.; Genini, D.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **1999**, *42*, 3860; (c) Daidone, G.; Maggio, B.; Raffa, D.; Plescia, S.; Bajardi, M. L.; Caruso, A.; Cutuli, V. M. C.; Roxas, M. A. *Eur. J. Med. Chem.* **1994**, *29*, 707.
8. (a) Xia, Y.; Yang, Z. Y.; Hour, M. J.; Kuo, S. C.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoothiri, P.; Hackl, T.; Hamel, E.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1193; (b) Mulakayala, N.; Kandagatla, B.; Ismail; Rapolu, R. K.; Rao, P.; Mulakayala, C.; Kumar, C. S.; Iqbal, J.; Oruganti, S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5063.
9. Verhaeghe, P.; Azas, N.; Gasquet, M.; Hutter, S.; Ducros, C.; Laget, M.; Rault, S.; Rathelot, P.; Vanelle, P. *Bioorg. Med. Chem. Lett.* **2008**, 18, 396.
10. Malamas, M.S.; Millen, J. *J. Med. Chem.* **1991**, 34, 1492.
11. Abdel Gawad, N.M.; Georgey, H.H.; Youssef, R.M.; El-Sayed, N.A. *Eur. J. Med. Chem.* 2010, *45*, 6058.
12. Kuyper, L.F.; Baccanari, D.P.; Jones, M.L.; Hunter, R.N.; Tansik, R.L. ; Joyner, S.S.; Boytos, C.; Rudolph, S.K.; Knick, V.; Wilson, H.R.; Caddell, J.M.; Friedman, H.S.; Comley, J.C.W.; Stables, J.N. *J. Med. Chem. 1996*, *39*, 892.
13. (a) Georgey, H.; Abdel-Gawad, N.; Abbas, S. *Molecules* 2008, 13, 2557; (b) Archana Srivastava, V.K.; Kumar, A. *Eur. J. Med. Chem.* 2002, 37, 873.
14. (a) Chien, T.-C.; Chen, C.-S.; Yu, F.-H.; Chern, J.-W. *Chem.Pharm. Bull.*, **2004**, *52*, 1422; (b) Herget, T.; Freitag, M.; Morbitzer, M.; Kupfer, R.; Stamminger, T.; Marschall, M. *Antimicrob. Agents Chemother.*, **2004**, *48*, 4154.
15. Ismail, M.A.H.; Barker, S.; Abau El Ella, D.A.; Abouzid, K.A.M.; Toubar, R.A.; Todd, M.H. *J. Med. Chem.* **2006**, *49*, 1526.
16. Decker, M. *Eur. J. Med. Chem.* **2005**, *40*, 305.
17. (a) Levitzky, A. *Acc.Chem. Res.* **2003**, *36*, 462; (b) Garofalo, A.; Goossens, L.; Lemoine, A.; Ravez, S.; Six, P.; Howsam, M. ; Farce, A.; Depreux, P. *Med. Chem. Commun.* **2011**, *2*, 65.
18. Lewerenz, A.; Hentschel, S.; Vissiennon, Z.; Michael, S.; Nieber, K. *Drug Dev. Res.* **2003**, *58*, 420.
19. (a) Hart, D.J. *ARKIVOC*, **2010**, 32; (b) Michael, J.P. *Nat.Prod. Rep.*, **2008**, *25*, 166; (c) Michael, J. P. *Nat. Prod. Rep.*,**2007**, *24*, 223.
20. (a). Shafi, S.; Alam , M.M.; Mulakayala, N.; Mulakayala, C.; Vanaja, G.; Kalle, A.M.; Pallu, R.; Alam, M.S. *Eur. J. Med. Chem.* **2012**, *49*, 324.; (b). Mulakayala, N.; Rao, P.; Iqbal, J.; Bandichhor, R.; Oruganti, S. *Eur. J. Med. Chem.* **2013**, *60*, 170.; (c). Sudhakar, H.; Pavana Kumari, G.; Mulakayala. N. Indian Journal of Advances in Chemical Science 2013, 2, 57. (d) Sudhakar, H.; Pavana Kumari, G.; Venkata Nadh, R. ; Mulakayala. N. Indian Journal of Advances in Chemical Science 2014, 2, 294; (b) Ismail; Kuthati, B.; Thalari, G.; Bommarapu, V.; Mulakayala, C.; Chita, S.K.; Mulakayala, N. *Bioorg. Med. Chem. Lett.* **2016**, *27*, 1446.
21. **General procedure for synthesis of 2-aryl Quinazolinones and 5- Substituted Pyrazolo[4,3-*d*]pyrimidine-7-one:** To a solution of 2-aminobenzamide (1.470 mmol, 1.0 eq.) was added to a solution of Terminal Alkyne (1.470 mmol, 1.0 eq.), Tosyl Azide, (1.470 mmol, 1.0eq.), CuI (0.147 mmol, 0.1 eq.), triethylamine (2.941 mmol, 2.0 eq.), in acetonitrile (10 ml) under N_2 atmosphere. The mixture was stirred at room temperature for 12 h. After completion of the reaction (as indicated by TLC) the reaction mixture was poured into water (25 mL) and extracted with ethyl acetate (2X25 mL), dried over Na_2SO_4, concentrated under vacuum to get crude compound which was purified by column chromatography using a mixture of petroleum ether: ethyl acetate to give the desired product as white solid.

Highlights:

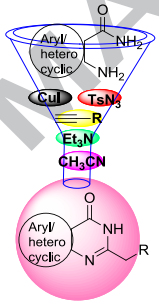
- Novel Method for the synthesis of substituted quinazolinones
- Novel Method for the synthesis of substituted pyrazolo pyrimidinones
- High Yielding reactions
- No inert atmosphere needed
- Important core for medicinal chemists

Graphical Abstract

To create your abstract, type over the instructions in the template box below.

Novel One Pot Synthesis of substituted quinazolin-4(3***H***)-ones and pyrazolo[4,3-***d***]pyrimidin-7(6***H***)-ones using Copper iodide, Azides and Terminal Alkynes **Srishylam.V, N. Devanna, MV Basaveswara Rao, Naveen Mulakayala**

Leave this area blank for abstract info.



Fonts or abstract dimensions should not be changed or altered.