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An efficient and convenient protocol for the synthesis of tetracyclic isoindolo[1,2-a]quinazoline derivatives

M. V. Madhubabu,[a] R. Shankar,[a] Satish.s.More,[a] Mandava V. Basaveswara Rao,[b] U. K. Syam Kumar,*[a] Ragunadh Akula*[a]

A convenient and one-pot synthesis of tetracylic isoindolo [1,2-a]quinazoline derivatives *via* a Lewis Acid mediated sequential C–N bond formation reactions is reported. This protocol provides a simple and rapid strategy for the synthesis of 12-benzylidene-10,12-dihydroisoindolo[1,2-b]quinazoline derivatives. However, a variety of tetracyclo indole fused quinazoline motifs were synthesized in good yields.

Isoindoloquinazolinones symbolize as the core structure in numerous biologically active molecules.[1] In addition, they are also important building blocks of potential drug molecules and natural products such as Camptothecin **1,** Belotecan (CKD-602) **2**,[2] Batracylin **3**,[3] Tryptanthrin **4**,[4] Ophiuroidine **5**,[5] (-)-Vasicine **6**,[6] Luotonin **7a, 7b & 7c**, [7]and Auranthine **8** (Fig 1).[8] Isoindolo quinazolinones have been reported with anti-cancer, anti-viral, anti-tubercular and anti-malarial activities. Recently Yang and co-workers [9] reported that substituted quinazolines have novel potent and selective FLT3 inhibitory and anti-acute myeloid leukaemia (AML) activities.

Because of varied biological properties of quinazolinone derivatives, it is necessary to develop efficient and convenient methods to prepare Isoindoloquinazolinone derivatives. Throughout the course of our literature survey we found minimum number of reports for the preparation of isoindoloquinazoline derivatives. Mitscher *et al.* have described intramolecular Aza-Wittig reaction using triethylamine, [10] Weaver *et al*. have reported oxidative radical cyclization for synthesis of quinazolines from quinazolin-4(3*H*)-one. [11]

The development of simple methodology for the preparation of Isoindoloquinazolinone derivatives is always in demand. In the past, our group described numerous protocols for the preparation of quinazolinone based natural products and their derivatives.[12]

[a]*Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Hyderabad 500049, India*
[b]*Department of Chemistry, Krishna university, Machilipatnam, Andhra Pradesh, India.*
E-mail:raghunadha@drreddys.com,
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In this communication, we wish to report simple and straight forward synthesis of poly-substituted Isoindoloquinazolinones derivatives.

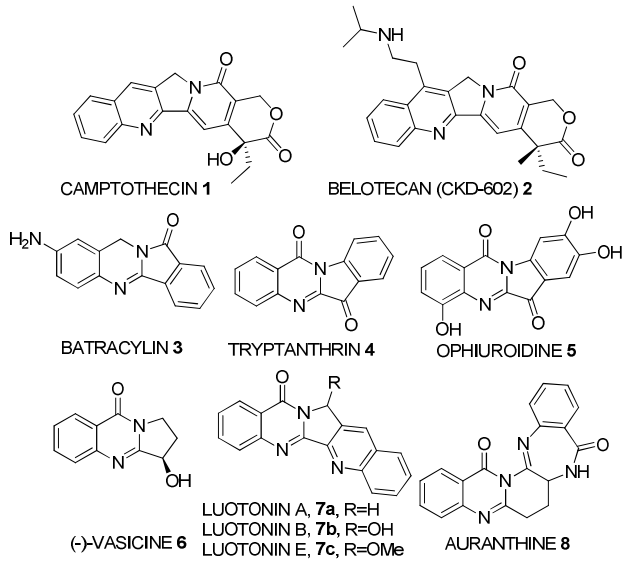
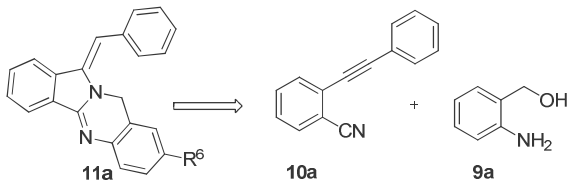


Fig. 1. Examples of natural products containing quinazolinone skeletons.

The synthetic strategy employed for the synthesis of (*Z*)-12-benzylidene-10,12-dihydroisoindolo[1,2-b]quinazoline derivatives is depicted in **Scheme 1.** The (*Z*)-12-benzylidene-10, 12-dihydroisoindolo[1,2-b]quinazolines derivatives **11a** could be easily obtained by a reaction of (2-aminophenyl)methanol **9a**[13] with 2-(phenylethynyl) benzonitrile **10a**.[14]



Scheme 1: Retrosynthesis of **11a**.

The compound **11** was characterized by ^{1}H NMR, ^{13}C NMR, HRMS and IR. Substituted (*Z*)-12-benzylidene-10,12-dihydroisoindolo [1,2-b]quinazoline derivatives were prepared from (2-aminophenyl)methanol **9** with 2-(phenylethynyl) benzonitrile **10**.

In an effort to develop an optimal conditions, various reaction parameters were studied for the preparation of **11** *via* condensation of 2-(phenylethynyl)benzonitrile **10** (1.0 eq) with (2-aminophenyl)methanol **9** (1.0 eq) and $BF_3.Et_2O$ (3.0 eq). The acids have a strong effect on these reactions with respect to yield.

Table 1: Screening of various acids.

Entry	Lewis acid (eq/vol)	Yield (%)[b]
1	$BF_3.Et_2O$[a](3.0eq)	62
2	$BF_3.Et_2O$[a](1.5 eq)	49
3	$BF_3.Et_2O$[a](2.0eq)	61
4	$BF_3.Et_2O$[c] (3.0eq)	49
5	$BF_3.Et_2O$[d] (3.0eq)	26
6	BF_3.2AcOOH (3.0eq)	
7	Acetic acid (5.0 eq)	8
8	TFA (5.0 eq)	16
9	H_2SO_4(2.0eq)	12
10	$AlCl_3$(3.0eq)	22
11	$AlBr_3$(3.0eq)	18
12	$Hg(OAc)_2$(3.0eq)	Traces
13	$TiCl_4$(3.0eq)	41

[a]48-50 % solution of reagent was used, [b]Isolated yields after column chromatography, [c] reaction at 45 °C,[d] reaction with Boron trifluoride acetic acid complex at 25 °C .
Reaction and conditions: (2-aminophenyl)methanol 9 (1.0 eq), 2-(phenylethynyl)benzonitrile 10 (1.0 eq) and $BF_3.Et_2O$ (3.0 eq) at 70 °C.

Among all the screened acids, optimum yields were obtained when the reaction was performed in the presence of $BF_3.Et_2O$ (3.0 eq) (Table 1). Solvents like DMSO, DMF, 1,4-Dioxane, THF, Acetonitrile and Toluene were screened in presence of $BF_3.Et_2O$. $BF_3.Et_2O$ alone had proven to be the best condition for this reaction instead of use of other solvents (Table 2).

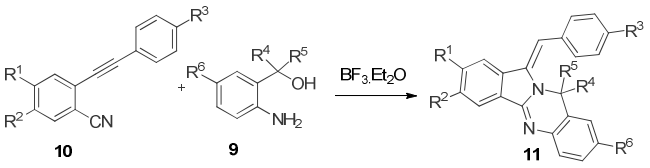
Table 2: Screening of solvents.

Entry	Solvents	Isolated Yield (%)
1	DMSO	30
2	DMF	26
3	1,4-Dioxane	62
4	$BF_3.Et_2O$	68
5	Acetonitrile	42
6	THF	15
7	Toluene	20

Reaction and conditions: (2-aminophenyl)methanol **9** (1.0 eq), 2-(phenylethynyl)benzonitrile **10** (1.0 eq) $BF_3.Et_2O$ (3.0 eq) at 70 °C.

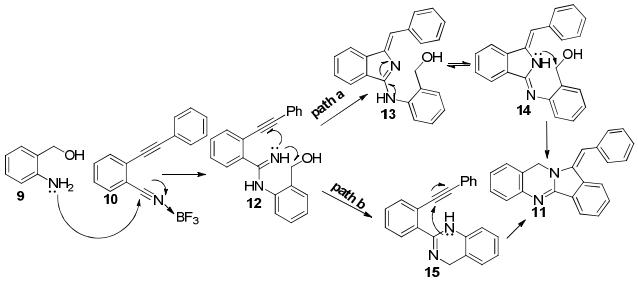
With the optimized reaction conditions in hand, we explored the applicability of our reaction. We employed a variety of substituted alcohols and substituted benzonitriles & the results were summarized in **Table 3.** Good yields were observed when the reaction was conducted with (2-aminophenyl)propan-2-ol and (2-aminophenyl)ethanol when compared to (2-aminophenyl)methanol due to the stability of the carbocation.

Table 3: Synthesis of various Isoindoloquinazolinones derivatives.



Entry	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield
1	H	H	H	H	H	H	**11a**	68
2	H	H	H	CH_3	H	H	**11b**	72
3	H	H	H	H	H	Cl	**11c**	65
4	H	H	CH_3	CH_3	H	H	**11d**	71
5	H	H	CH_3	H	H	H	**11e**	69
6	H	H	CH_3	CH_3	CH_3	H	**11f**	74
7	H	H	H	CH_3	CH_3	H	**11g**	75
8	H	H	H	CH_3	CH_3	OCH_3	**11h**	69
9	OCH_3	OCH_3	H	H	H	H	**11i**	67
10	OCH_3	OCH_3	H	CH_3	H	H	**11j**	64

The **Scheme 2** represents a plausible mechanism for the three component reaction leading to the compound **11**. The nucleophilic attack of primary amine on nitrile group of **10** yield imidamide intermediate **12**, imidamide can attack on alkyne or alcohol leads to the formation of cyclized intermediate either **13** or **15** which on subsequent cyclization will yield the **11.**



Scheme 2. Proposed reaction mechanism

In conclusion, we have established a short and efficient methodology for the synthesis of Isoindoloquinazolinone derivatives. The novel synthetic approach involves construction of two new rings *via* sequential C–N bond formation under Lewis Acid condition. This methodology is operationally simple and amenable for scale-up.

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Notes and references

1. Bioactive Heterocyclic Compound Classes: Pharmaceuticals and Agrochemicals (Eds.: C. Lamberth, J. Dinges), Wiley-VCH, New York, 2012.
2. (a) Jew, S. S.; Kim, H. J.; Kim, M. G.; Roh, E.Y.; Cho, Y. S.; Kim, J. K.; Cha, K. H.; Lee, K. K.; Han, H. J.; Choi, J. Y.; Lee, H. *Bioorg. Med. Chem. Lett.* 1996, **6**, 845. (b) Lee, J. H.; Lee, J. M.; Kim, J. K.; Ahn, S. K.; Lee, S. J.; Kim, M. Y.; Jew, S. S.; Park, J. G.; Hong, C. *Arch. Pharm. Res*. 1998, **21**, 581.
3. (a) Dzierzbicka, K.; Trzonkowski, P.; Sewerynek, P. L.; Mysliwski, A. *J. Med. Chem*. 2003, **46**, 978; (b) Guillaumel, J.; Le´once, S.; Pierre, A.; Renard, P.; Pfeiffer, B.; Arimondo, P. B.; Monneret, C. *Eur. J. Med. Chem*. 2006, **41**, 379; (c) Yilin, R.; Yun Feng, C.; Ting, C.; Chen, A. Y.; Yu, C.; Liu, L. F.; Cheng, C. C. *Pharm. Res*. 1993, **10**, 918.
4. Friedländer, P.; Roschdestwensky, N. *Chem. Ber.* 1915, **48**, 1841.
5. Utkina, N. K.; Fedoreev, S. A.; *Tetrahedron Lett*. 2007, **48**, 4445-4447.
6. (a) Ziaee, V.; Jalalizadeh, H.; Iranshahi, M.; Shafiee, A. Iran. *J. Chem. Chem. Eng*. 2004, **23**, 33. (b) Kamal, A.; Ramana, V. K.; Rao, M. V. *J. Org. Chem*. 2001, **66**, 997.
7. (a) Harayama, T.; Morikami, Y.; Shigeta, Y.; Abe, H.; Takeuchi, Y. *Synlett,* 2003, 847-848; (b) Ma, Z.; Hano, Y.; Nomura, T.; Chen, Y. *Biorg. Med. Chem. Lett.* 2004, **14**, 1193-1196; (c) Tseng, M. C.; Chu, Y. W.; Tsai, H. P.; Lin, C. M. Hwang, J.; Chu, Y. H. *Org. Lett.* 2011, **13**, 920-923; (d) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* 2004, **69**, 4563-4566; (e) Chavan, S. P.; Sivappa, R. *Tetrahedron,* 2004, **60**, 9931-9935; (f) Wagh, M. B.; Shankar, R.; Kumar, U. K. S.; Gill, C. H. *Synlett,* 2011, 84-88; (g) Nagarapu, L.; Gaikwad, H. K.; Bantu R. *Synlett,* 2012, **23**, 1775–1778; (h) Tseng, M-C.; Lai, P-Y.; Shi, L.; Li, H-Y.; Tseng, M-J.; Chu, Y-H. *Tetrahydron* , 2014, **70**, 2629; (i) Shankar, R.; Wagh, M. B.; Madhubabu, M. V.; Vembu, N.; Kumar, U. K. S. *Synlett* 2011, 844-848
8. Yeulet, S. E.; Mantle, P. G.; Bilton, J. N.; Rzepa, H.S.; Sheppard, R. N.; *J. Chem. Soc.* Perkin Trans. 1, 1986, 1891-1894
9. Li, W.W.; Wang, X.Y.; Zheng, R. L.; Yan, H. X.; Cao, Z. X.; Zhong, L.; Wang, Z. R.; Ji, P.; Yang, L. L.; Wang, L. J.; Xu, Y.; Liu, J. J.; Yang, J.; Zhang, C. H.; Ma, S.; Feng, S.; Sun, Q. Z.; Wei, Y. Q.; Yang, S. Y. *J. Med. Chem***.** 2012, **55**, 3852
10. Mitscher, L. A.; Wong, W. C.; De Meulenere, T.; Sulko, J.; Drake, S.; *Heterocycles*, 1981, **15**, 1017–1019.
11. Bowman, W. R.; Elsegood, M. R. J.; Stein, T. Weaver, G. W. *Org. Bomol. Chem.* 2007, **5**, 103–113.
12. (a) Raghavendra R, K.; Ramamohan, M.; Raghunadh, A.; Suresh Babu, M.; Prav*een Kumar, S.*; Kalita*,* D.; Laxminarayana, E.; Prasad, B.; Pal. M. *RSC Advances* , 2015, **5**, 61575. (b) Murthy, N, V.; Nikumbh, S, P.; Praveen Kumar, S.; Vaikunta Rao, L.; Raghunadh, A. *Tetrahedron Lett*. 2015, **56**, 5767-5770
13. (a) MinQiang, J; Shu, Li, Y.; *ACS Catalysis*, 2013, **3**, 622.
14. (a) Yan, H.; Xinying, Z.; Xuesen, F.; *Chem. Comm*. 2014, **50**, 5641.(b) Pu, X.; Li,H.; Colacot, T. J. *J.Org. Chem*. 2013, **78**, 568.

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