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An efficient one pot synthesis of 2-amino quinazolin-4(3H)-one derivative *via* MCR strategy

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ABSTRACT

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A novel multi-component reaction strategy was developed for the construction of important building blocks, 2-amino 3- substituted quinazolinone derivatives from isatoic anhydride and amine with electrophilic cyanating compound, *N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide (NCTS). The quinazolinone synthesis proceeds *via* a sequential series of reactions such as nucleophilic attack of amine group on carbonyl group of isatoic anhydride followed ring opening and subsequent decarboxylation, nucleophilic attack of amine to nitrile, followed by heterocyclization.

Keywords: isatoicanhydride, *N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide, multi-component reaction

Quinazolinone and their derivatives exhibit a wide range of biological and pharmacological properties some of these activities include anti-cancer,[1] anti-inflammatory,[2] anti-fungal,[3] anti-microbial and anti-malarial properties.[4] Furthermore, the heterocyclic core constitutes more than 40 alkaloids and various natural products like luotonon A **1,** B **2**, and E **3**,[5] rutaecarpine **4**,[6] tryptanthrin **5**, [7] macckinazolinone **6**, [8] vasicinone **7**, [9] deoxy vasicinone **8** and evodiamine **9**, [10] (Fig 1).

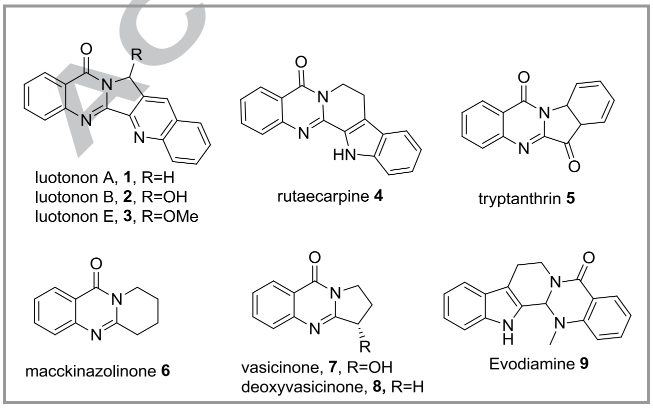
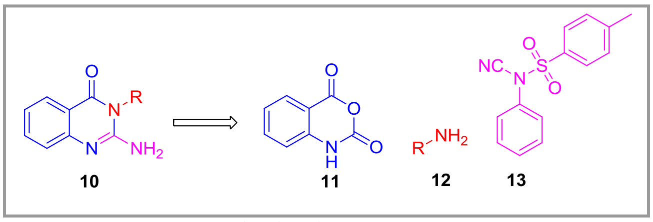


Fig. 1. Examples of natural products which contain quinazolinone skeleton

Because of varied biological properties of quinazolinone derivatives, a number of methodologies have been developed for their synthesis. However a limited number of synthetic strategy were reported in the literature for the synthesis of 2-amino 3- substituted quinazolinone with free amino group at 2nd position.[11] Zeghida and co-workers reported a novel synthetic method involving the Friedel-craft type substitution from aniline.[12] Kundu *et al.,* reported the synthesis of 2-amino quinazolinone *via* polymer-linked anthranilamide with isothiocyanates followed by coupling with secondary amines in the presence of DIC.[13] Yang and Kaplan reported solid-phase syntheses of quinazolin-4(3*H*)-ones *via* cyclocondensation of anthranilic acid with amino acids and aldehydes or by aza-wittig mediated annulation involving *o*-azidobenzoic acid.[14] Other methods reported recently involves cyclocondensation of 2-nitrobenzyl chloride with aryl amines and thioureas with isatoic anhydride.[15]

The development of simple methodology for the synthesis of 2-amino 3- substituted quinazolinone derivatives is always in demand due to its extensive biological activity. Multi-component reaction (MCRs) are highly desirable in any process as the target products are directly yielded by cascade or domino reaction sequences offer considerable advantages over conventional linear –step synthesis. Herein we wish to report a straight forward novel multi-component reaction for the synthesis of 2-amino 3- substituted quinazolinone derivatives.



Scheme 1: Retrosynthesis of **10**.

The retro synthetic strategy employed for the synthesis of 2-amino 3- substituted quinazolinone is depicted in **Scheme 1.** The 2-amino quinazolinone could be easily obtained by a reaction of isatoic anhydride **11** with amine **12** and NCTS (*N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide) **13.** NCTS could be synthesized using the reported methodology by Kurzer.[16] NCTS are quite stable, non toxic, crystalline solid, which is used as potential electrophilic cyanating agent on indoles and pyrroles.[17]

Table 1: Screening of solvents.

Entry	Solvents	Isolated Yield (%)
1	DMSO	45
2	DMF	48
3	1,4-Dioxane	70
4	Ethanol	0
5	Acetonitrile	48
6	THF	55
7	Toluene	40

Reaction and conditions: isatoic anhydride (1.0 eq), NCTS (1.0 eq), benzylamine (1.0 eq) and LiHMDS (3.0 eq) at reflux .

In an effort to develop an optimal conditions, various reaction parameters were studied for the preparation of **10** *via* condensation of isotoic anhydride **11** (1.0 mmol) with *N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide **13** (1.0 mmol) and benzylamine (1.0 mmol). The base and solvent had a pronounced effect on these reactions with respect to yield. The bases, namely K_2CO_3, DBU, DABCO, TEA, CS_2CO_3, and LiHMDS wree screened.The best result was obtained when the reaction was performed in the presence of LiHMDS in 1,4 dioxane solvent (Table 2, entries 1-8), solvents like DMSO, DMF, THF, Acetonitrile, Toluene and 1,4-Dioxane were screened in presence of LiHMDS. 1,4-Dioxane had proven to be the best solvent for this MCR (Table 1, entries 1–7).

Table 2: Screening of Bases.

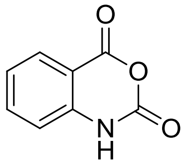
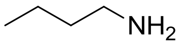
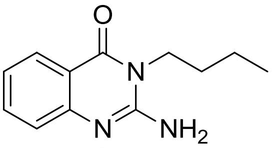
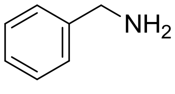
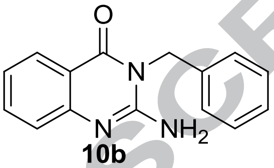
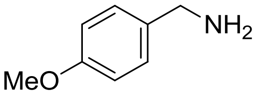
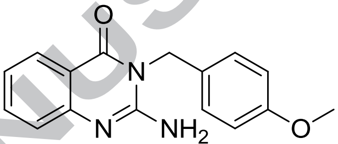
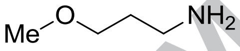
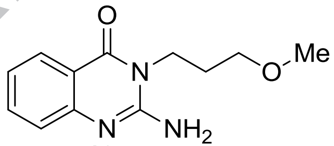
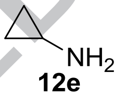
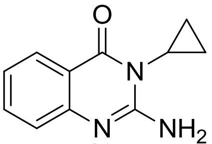
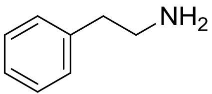
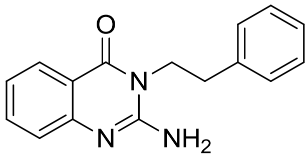
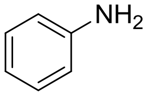
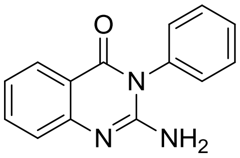
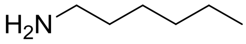
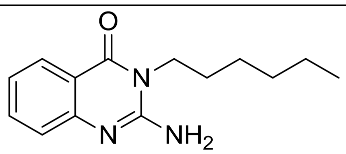
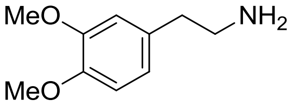
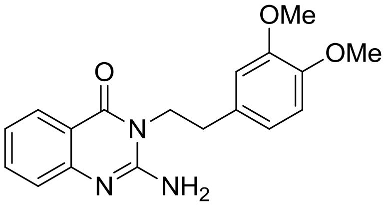
Entry	Base	Isolated Yield (%)
1	K_2CO_3	45
2	DBU	38
3	DABCO	35
4	TEA	0
5	CS_2CO_3	52
6	LiHMDS(3.0 eq)	72
7	LiHMDS (2.0 eq)	68
8	LiHMDS (1.0 eq)	62

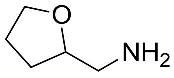
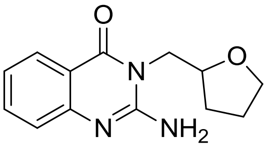
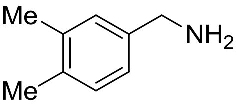
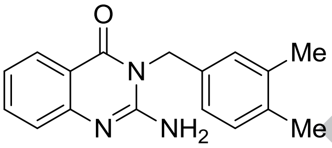
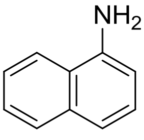
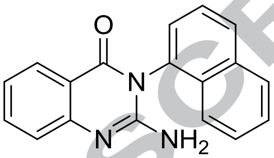
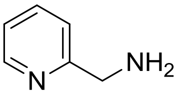
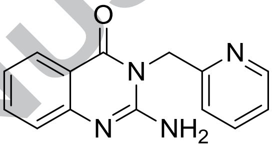
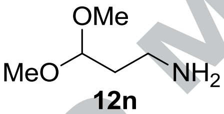
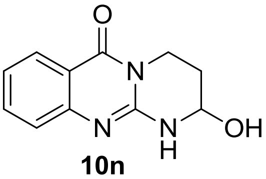
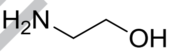
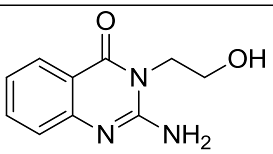
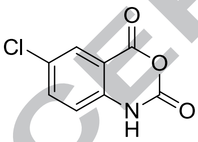
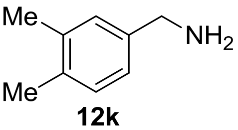
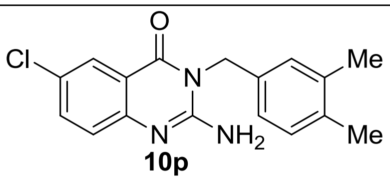
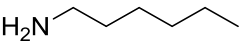
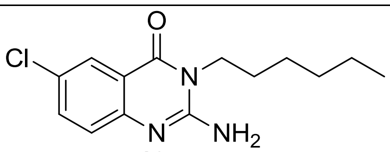
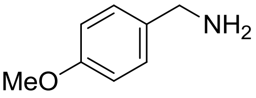
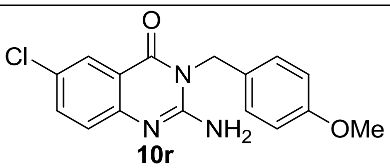
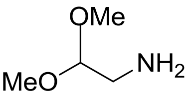
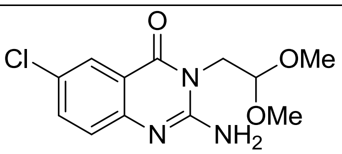
Reaction and conditions: isatoic anhydride (1.0 eq), NCTS (1.0 eq) and benzylamine (1.0 eq) at 100 °C.

We chose a variety of structurally diverse amines possessing a wide range of functional groups for our study to understand the scope and the generality of this MCR and the results are summarized in Table 3. The amines chosen for the study include aliphatic, aromatic, hetero aromatic amines

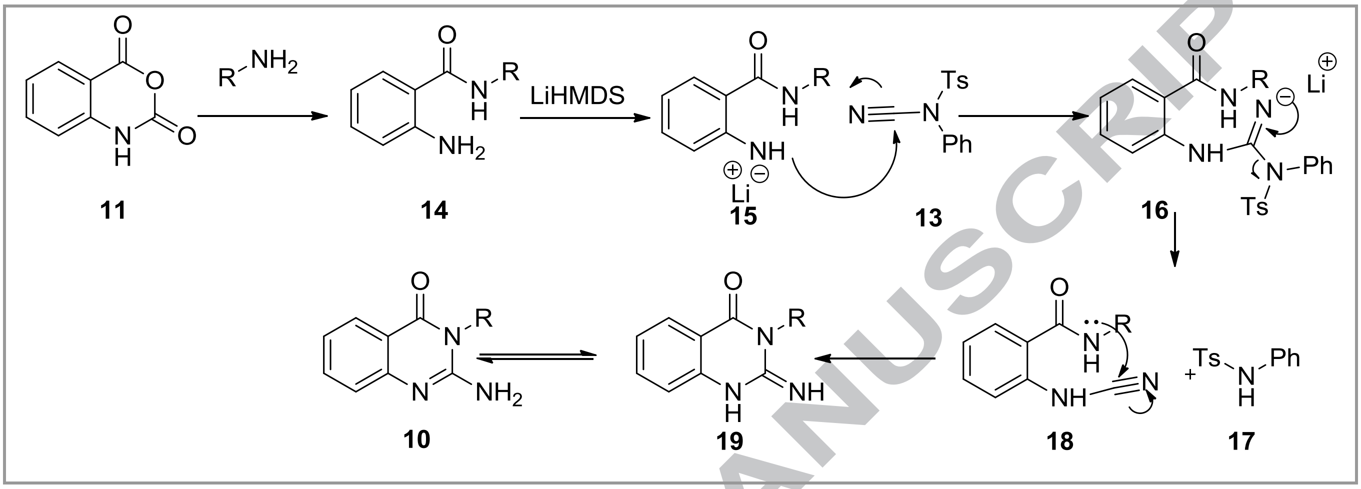
When the reaction was conducted with 3,3-dimethoxypropan-1-amine **12n** the cyclized product 2-hydroxy-3,4-dihydro-1H-pyrimido[2,1-b]quinazolin-6(2H)-one **10n** was obtained *via* the formation of the 2-amino 3-substituted quinazolinone followed by intramolecular cyclization. When the reaction was conducted with Aromatic amines afforded lower yields compared to aliphatic amines.

Table 3: Synthesis of various 2-amino 3- substituted quinazolinone derivatives.

Entry	Isatoic anhydride	Amine	Product	Isolated Yield (%)
1	 **11a**	 **12a**	 **10a**	71
2	**11a**	 **12b**	 **10b**	72
3	**11a**	 **12c**	 **10c**	67
4	**11a**	 **12d**	 **10d**	78
5	**11a**	 **12e**	 **10e**	77
6	**11a**	 **12f**	 **10f**	52
7	**11a**	 **12g**	 **10g**	47
8	**11a**	 **12h**	 **10h**	70
9	**11a**	 **12i**	 **10i**	72

10	**11a**	 **12j**	 **10j**	60
11	**11a**	 **12k**	 **10k**	57
12	**11a**	 **12l**	 **10l**	36
13	**11a**	 **12m**	 **10m**	52
14	**11a**	 **12n**	 **10n**	68
15	**11a**	 **12o**	 **10o**	50
16	 **11b**	 **12k**	 **10p**	56
17	**11b**	 **12h**	 **10q**	59
18	**11b**	 **12c**	 **10r**	62
19	**11b**	 **12p**	 **10s**	69

The **Scheme 2** represents a plausible mechanism for the three component reaction leading to the compound **10**. The nucleophilic attack of primary amine on carbonyl group of isatoic anhydride followed by ring opening and subsequent decarboxylation will yield to compound **14.** Deprotonation of aromatic amine **15** in the presence of base followed by nucleophilic attack to the nitrile group, **13** will yield imine **16**; subsequent cyclization followed by elimination of N-phenyl tosyl group will yield intermediate **17**. Cyclization of compound **18** will yield compound **19**. The intermediate **19** will undergo tautomerization leading to the formation of **10.**



Scheme 2: The proposed reaction mechanism for the formation of **10**.

Conclusion:

In conclusion, we have developed a novel multi-component reaction strategy for the synthesis of 2-amino 3- substituted quinazolinone in good yields from isatoic anhydride, amine and electrophilic cyanating agent, *N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide in a one pot process. The synthesis of 2-amino 3- substituted quinazolinone proceeded *via* a series of reactions such as ring opening, decarboxylation, dehydration, elimination and heterocycloannulation.

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General procedure for synthesis of 2-amino 3-substituted quinazolinone derivatives (10a – 10s): To the solution of isatoic anhydride (1.0 eq) in 1,4 dioxane (4.0 ml), Amine (1.0 eq) was added and then reaction mass temperature was raised to 90-100°C and maintained for 3-4 hrs, LiHMDS solution (3.0 eq) followed by N-cyano -4-methyl –N-phenyl benzene sulfonamide (NCTS) (1.0 eq) was added and reaction mass was further maintained for 10-12hrs at same temperature, reaction progress was monitored by TLC. After completion of the reaction, 20% aqueous ammonium chloride solution (5.0 ml) was added and reaction mass was diluted with ethyl acetate (10.0 ml). Ogranic layer was separated and aqueous layer extracted with ethyl acetate (4.0 ml). Combined organic layer was washed with water (4.0 ml) followed by 10% sodium chloride solution (4.0 ml). Solvent was evaporated under vacuum and crude material was purified by column chromatography in Ethyl acetate / hexane (3:7).

Graphical Abstract:

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An efficient one pot synthesis of 2-amino quinazolin-4(3H)-one derivative *Via* MCR strategy

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