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One-pot multicomponent synthesis of medicinally important purine quinazolinone derivatives

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ABSTRACT

Herein, a protocol that involves microwave-assisted, multicomponent one-pot synthetic strategy for the construction of the medicinally important purine quinazolinone scaffold is reported. A series of compounds are prepared by cyclization and condensation reactions using this approach. The compounds are structural analogs of anticancer agents IC-87114 and CAL-101, which are highly isoform-selective PI3K-δ inhibitors and are presently under clinical investigation for chronic lymphocytic leukemia.

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Multicomponent reactions have been successfully adopted by the chemists for the synthesis of a library of biologically active molecules. These reactions have the potential to build complex molecular scaffolds in a straightforward way compared to classical organic synthesis. Since the last decade there has been an enormous interest for the discovery of novel reactions of this type.[1–3] The MCR strategy has several advantages and according to the current synthetic requirements, environmentally benign multicomponent reactions, particularly employing microwave approaches, are highly desirable.[4,5]

The usefulness of the multicomponent reactions becomes important when these strategies are employed and utilized for the generation of privileged scaffolds for medicinal chemistry. Our interest in microwave-assisted synthesis of medicinally important scaffolds[6] encouraged us to establish an efficient synthesis of purine quinazolinone based derivatives. Recently we initiated a program on the synthesis of isoform-selective PI3K inhibitors for targeting cancer utilizing the quinazolinone scaffold. Quinazolinones are a class of heteroaromatic compounds that have drawn more attention because of their biological and pharmacological attributes including anticancer, anti-HIV, antimicrobial activity, etc.[7] The structure of quinazolinone has been extensively utilized as a valuable scaffold for drug discovery in medicinal chemistry. Some synthetic quinazolinones, such as raltitrexed, ispinesib, tempostatin, halofuginone etc. (Fig. 2) have been in the market or are currently in clinical trials for various cancer treatments. Many natural products containing quinazolinone core structures viz. asperlicin C, benzomalvin A, circumdatin F, sclerotigenin, and many others (Fig. 3) have been reported as biologically important molecules.[8] The quinazolinone molecules are reported as PI3K inhibitors as anticancer agents. The first isoform-selective PI3K-δ inhibitor reported was based on purine quinazolinone scaffold, that is, IC87114 molecule patented by ICOS in 2001.[9] This is one of the most remarkable isoform-selective inhibitors described in the first generation PI3K inhibitors list. This compound exhibited nanomolar inhibition of PI3K-δ and a 100- to 1000-fold selectivity against the other class I PI3K's.[9] In subsequent years several molecules based on quinazolinone scaffold entered into preclinical and clinical investigation stages and one of the most promising PI3K-δ

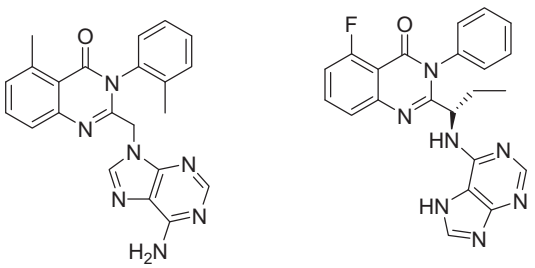

Figure 1. Structures of quinazolinone scaffold based anticancer molecules as isoform-selective PI3K-δ inhibitors.

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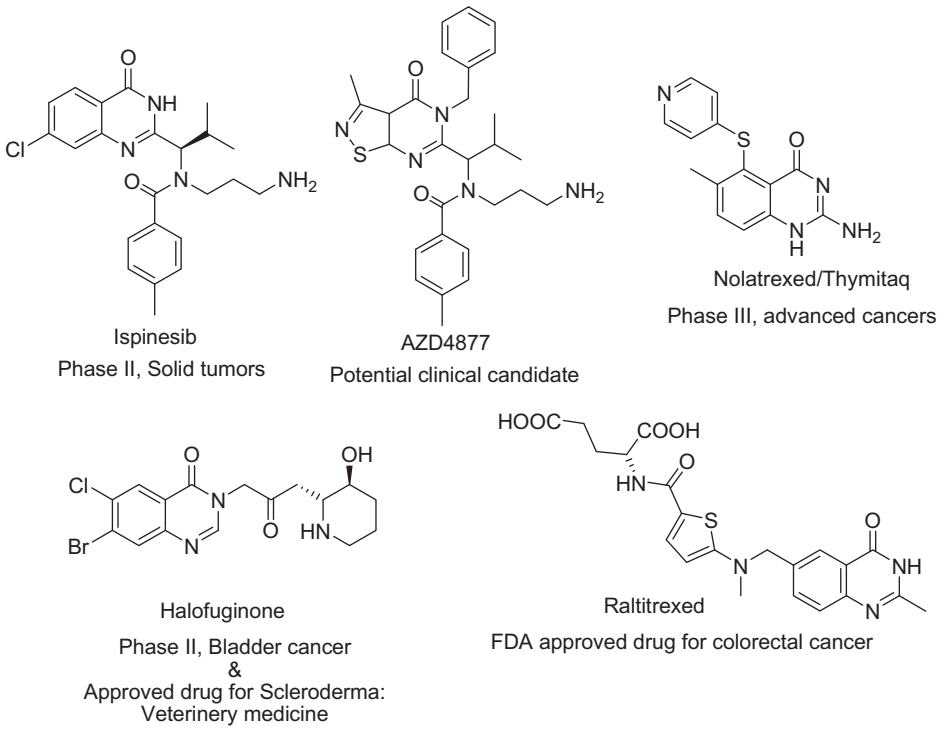


Figure 2. Quinazolinone based compounds as drugs or clinical candidates.

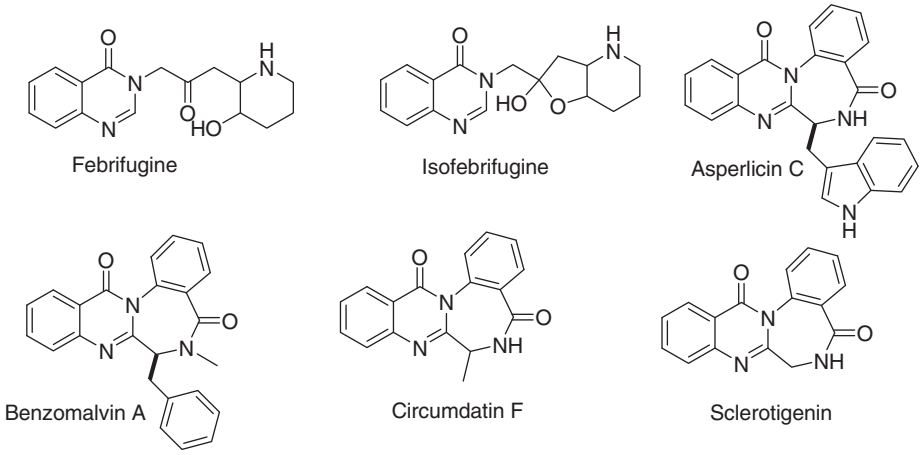
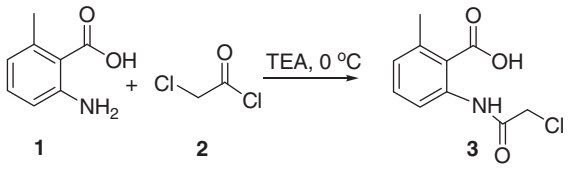


Figure 3. Quinazolinone based natural products as biologically important molecules.

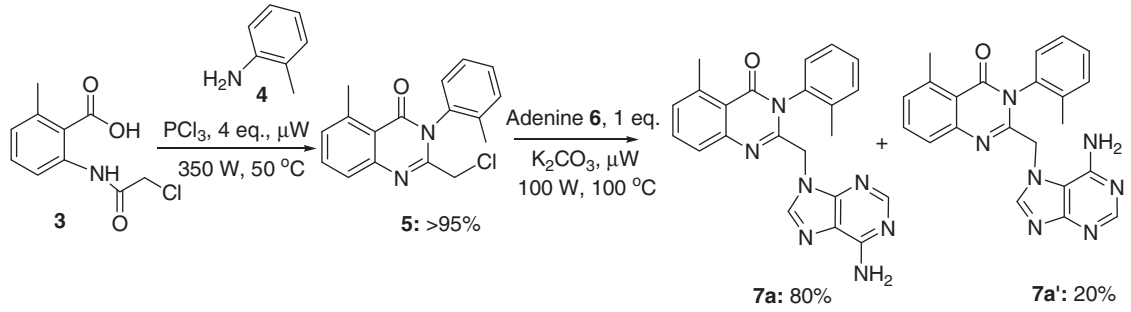
isoform-selective inhibitors to date is CAL-101/GS1104 by Gilead (initially developed by Calistoga) with IC_{50} of 2.5 nM (Fig. 1).[10]

In most of the cases, the quinazolinone structural scaffold is built in multiple steps using conventional synthesis approach.[9,11] To investigate the potential of the present strategy, we first examined the possibility of forming a cyclic intermediate containing quinazolinone ring and thereafter subsequent conjugation reaction of this intermediate with the adenine moiety in the same pot. In the preliminary experiments, we were pleased to observe the formation of quinazolinone scaffold as desired in a single step. The reactions were carried out under microwave irradiation in one pot giving purine quinazolinone compounds in good to excellent yields (Table 3).

Subsequently, we initiated the optimization of reaction conditions for all the steps using one-pot approach. The conversion in the first step gives quantitative yields of **3** (Scheme 1), prepared by a known method.[12] The starting materials viz. 6-methyl-2-amino benzoic acid **1** and 2-chloroacetyl chloride **2** were reacted in the presence of triethylamine at 0 °C to give 2-(2-chloroacetamido)-6-methylbenzoic acid as crystalline product **3**. The next step gave more than 95% conversion to form **5** with all the substrates used for reactions to form the cyclized quinazolinone intermediate by multicomponent strategy. Intermediate **3** was reacted with 2-methyl aniline **4** using PCl_3 as cyclizing agent under microwave



Scheme 1. Synthesis of intermediate **3**.



Scheme 2. One-pot multicomponent synthesis of IC87114 using microwave irradiation.

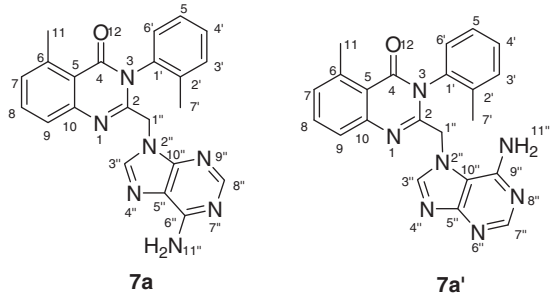


Figure 4. Regioisomers **7a** and **7a′**.

Table 1
Optimization of reaction conditions for synthesis of **5**

Entry	Substrate	MW (Watt)	Reaction time (min)	Product yields[a] (%): **5**
1	3	100	3	45
		250	3	78
		350	3	>95
		450	3	Decomposed product

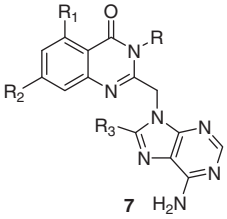
[a] Isolated yields.

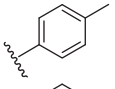
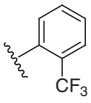
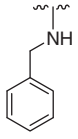
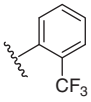
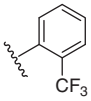
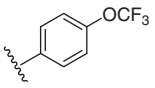
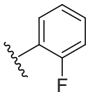
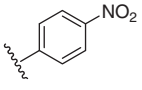
Table 2
Optimization of the reaction conditions for the synthesis of **7** using intermediate compound **5**

Entry	Substrate	MW (Watt)	Temperature (°C)	Reaction time (min)	Product yields[a] (%)	
					7a	**7a′**
a	5	50	50	3	35	8
				5	38	8
				7	40	7
			100	3	50	10
				5	52	9
				7	52	10
			150	3	56	12
				5	58	12
				7	59	13
b	**5**	**100**	50	3	62	13
				5	64	14
				7	64	13
			100	3	70	17
				5	**80**	**20**
				7	74	17
			150	3	67	15
				5	69	15
				7	65	14
c	5	150	50	3	10	2
				5	15	2
				7	10	2
			100	3	5	—
				5	3	—
				7	2	—
			150	3	—	—
				5	—	—
				7	—	—

[a] Isolated yields.

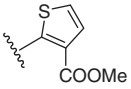
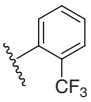
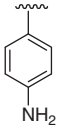
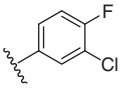
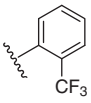
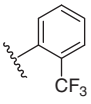
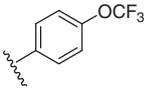
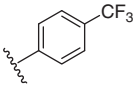
Table 3
Synthesis of purine quinazolinone derivatives at optimized conditions



Entry	R	R_1	R_2	R_3	Yield[a] **7**
a		$-CH_3$	–H	–H	80
b		–F	–H	–H	75
c		–F	–H	–H	73
d		$-CH_3$	–H		72
e		–H	–H	–H	76
f		–H	–H	–H	75
g		–F	–H	–H	76
h		–F	–H	–H	71
i		–F	–H	–H	79
j		–F	–H	–H	71

(*continued on next page*)

Table 3 (*continued*)

Entry	R	R_1	R_2	R_3	Yield[a] **7**
k		$-CH_3$	–H	–H	76
l		$-CH_3$	–H		73
m		$-CH_3$	–H		76
n		$-CH_3$	–H		77
o		$-CH_3$	–H	–H	80
p		$-CH_3$	–H		71
q		$-CH_3$	–H	–H	73
r		–H	$-CH_3$	–H	77
s		$-CH_3$	–H	–H	75
t		$-CH_3$	–H	–H	72

[a] Isolated yields.

irradiation for 3 min at 350 W to give the intermediate **5**, that is, 2-(chloromethyl)-5-methyl-3-*o*-tolylquinazolin-4(3*H*)-one. This intermediate without purification was used for coupling reaction with adenine **6**,[13] in the presence of K_2CO_3 (100 W microwave power, 5 min, 100 °C) to give the desired purine quinazolinone derivative **7a** and **7a′** as regioisomers in the ratio of 80:20 (Scheme 2).

The structures of these two regioisomers have been confirmed by comparison of ^{1}H NMR data with that of the reported compounds.[9d] In ^{1}H NMR of **7a**, the methylene group at 1″ position (Fig. 4) shows double doublet at δ 4.79 and 5.11 with J = 17.2 and 17.2 Hz. However, the same methylene group at 1″ position in case of **7a′** shows quartet at δ 5.23 with J = 17.6 and 17.2 Hz (^{1}H NMR of both regioisomers is given in Supplementary data). While optimization of the reaction, it was observed that change in reaction conditions like change in microwave power or temperature and time gave different results, which are summarized in Tables 1 and 2. The percentage conversion in the formation of intermediate **5** at 100, 250, and 350 W, was 45, 78, and >95 while at 450 W the product decomposed (Table 1). However, the conversion of **5** to **7** required several experiments for optimization of the reaction conditions. The best condition for the conversion of **5** to **7a**/**a′** was found to be irradiation with 100 W microwave power for 5 min at 100 °C. Therefore, all the reactions were performed under the optimized conditions (Table 2, entry b at 100 W for 5 min MW irradiation), and the examples are given in Table 3.

In conclusion, we have developed an environmentally friendly and efficient microwave-assisted one-pot multicomponent method for the synthesis of biologically important purine quinazolinone derivatives in good yields. The biological potential of these compounds is being studied and will be published in due course.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H/^{13}C NMR, DEPT at 135°, mass for some compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.137.

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