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$FeCl_3$catalyzed an efficient protocol for synthesis of quinazolinones derivatives

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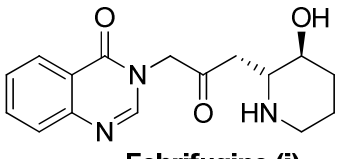
ABSTRACT

A highly efficient synthesis of 2-substituted 4(3H)-quinazolinones is elucidated using $FeCl_3$ catalyzed coupling of isatoic anhydride and benzamidine derivatives.

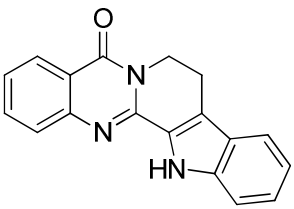
Key words: $FeCl_3$, Isatoic anhydride, benzamidine,quinazolinones.

INTRODUCTION

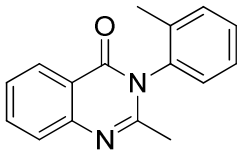
Quinazolinones are fused heterocyclic compounds that constitute the building block of numerous natural products and synthetic analogs possessing an extensive array of biological activities. Quinoxalinone andits derivatives have gained much attention in the recent past as an important pharmacore in the family of numerous biologically active heterocyclic compounds.Its derivatives have been used as synthetic precursors for many antihypertensive and analgesic drugs[1-9].



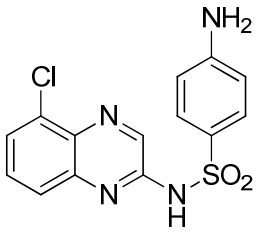
Febrifugine (i)



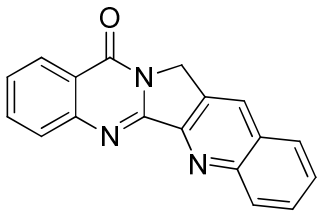
Rutaecarpine (ii)



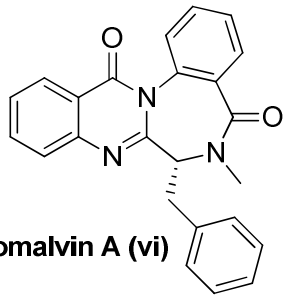
Methaqualone (iii)



CQS (iv)



Luotonine A (v)



Benzomalvin A (vi)

For example F*ebrifugine* (i) [10-13]is well known antimalarial drug possessing quinazolinone in their structural framework. Several quinoxaline derivatives like CQS (4) act as powerful chemotherapy agent and neurotransmitter antagonist , *Luotonine A* (**v**), commonly found in traditional Chinese plant named *Peganum nigellastrum* (Luo-Tuo-Hao) is a human DNA topoisomerase I inhibitor and displays cytotoxicity toward the murine leukemia P388 cell line (IC50 = 1.8 µg/mL) by stabilizing the topoisomerase I/DNA complex [14-15] Benzomalvin A (**vi**) is a human neurokinin NK1 inhibitor, isolated from a fungal culture of *Penicillium sp*[16]Rutaecarpine (**ii**) is the major alkaloid component of a Chinese herbal drug, Wu-Chu-Yu, used extensively as a remedy for headache, cholera, and dysentery[17-18].The diverse biological activities of quinazolinone-coupled with their applications in various active pharmaceutical ingredients demands the synthesis of highly substitutedquinazolinone derivatives by combinatorial drug discovery libraries.

MATERIALS AND METHODS

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reactions were stirred using Teflon-coated magnetic stirring bars. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O}. Chromatographic purification of products was carried out by flash column chromatography on silica gel (60-120mesh). Melting points were determined using an electro thermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier transform spectrometer. NMR spectra were measured in $CDCl_3$, acetone, DMSO-d_6 (all with TMS as internal standard) on a Varian Gemini 400 MHz FT NMR spectrometer magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t= triplet, q = quartet, m = multiplet. Mass spectra were recorded on an HP-5989A quadrapole mass spectrometer

General Procedure for the Synthesis of 2-substituted 4(3H)-quinozolinones (3): To a solution of isatoic anhydride (1 mmol) in 1,4-dioxane (10 vol) was added benzimidamide(1.1 mmol) followed by $FeCl_3$ (10 mol%). The reaction mixture was stirred at 80 °C for 2-9 h (TLC monitored). After completion of reaction, diluted with EtOAc (2×10 vol) and washed with water (2 × 5 vol). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Column chromatographic purification of crude on silica gel (30% EtOAc in hexanes) affords the product **3** in 79-93% yield.

All new compounds gave satisfactory analytical and spectroscopic data.

2-(4-nitrobenzyl)quinazolin-4(3H)-one(3a): Light brown solid; Yield: 82.3%;**^{1}H NMR (DMSO-*d_6*, 400 *MHz*):**δ 4.11 (s, 2H, $PhCH_2$), 7.46-7.49 (t, J = 8.0Hz, 1H, ArH), 7.57-7.59 (d, J=8.4Hz, 1H, ArH), 7.64-7.66 (d, J = 8.4 Hz, 2H, ArH), 7.75-7.79 (m, 1H, ArH), 8.07-8.09 (d, J=6.8Hz, 1H, ArH), 8.19-8.21 (d, J = 8.8 Hz, 2H, ArH), 12.49 (s, br 1H, NH), **^{13}C NMR (, DMSO-*d_6*, 400*MHz*)**: 40.70 123.55, 125.70, 126.39, 126.92, 128.29, 128.64, 130.38, 134.42, 144.35, 154.88, 161.74 **HRMS(ESI)**:calcd for $C_{15}H_{12}N_3O_3$(M+H): 282.0879; found: 282.0877

2-phenylquinazolin-4(3H)-one (3b): White solid; Yield: 84.6 %;Mp: 236-238°C;**^{1}HNMR (DMSO-*d6*,400 *MHz*)**: δ7.53-7.58 (m,4H, ArH,)7.74-7.75 (d, J = 7.6 Hz, 1H, ArH),7.82-7.86 (dd, J = 1.2,1.2 Hz, 1H, ArH),8.15-8.19 (m, 3H, ArH), 12.54 (s, br, 1H, NH);**^{13}C NMR (DMSO-*d6*,400 *MHz*,):**δ120.9, 125.8, 126.9, 127.4, 127.7, 128.1, 128.6, 131.4, 132.4, 134.7, 152.4, 161.7; MS: m/z = 223.1 [M +H]; **HRMS(ESI):** calcd for $C_{14}H_{11}N_2O$ [M + H]: 223.0871, found: 223.0882.

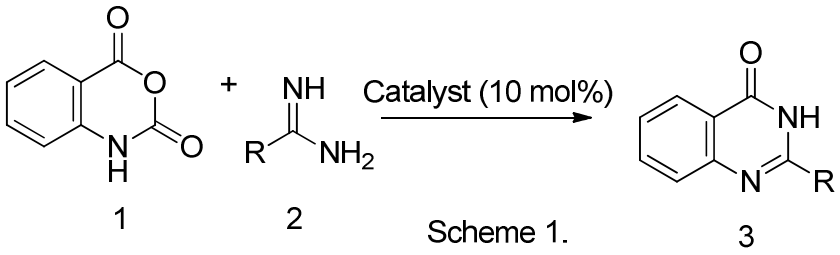
2-(tert-butyl)quinazolin-4(3H)-one(3e): White solid; Yield: 89.0%; **^{1}HNMR (DMSO-*d6*, 400 *MHz*,):** δ 1.35 (s, 9H, 3XCH_3), 7.44-7.48 (t, J= 7.6 Hz 1H, ArH), 7.59-7.62 (d, J=8.4 Hz, 1H, Ar H), 7.75-7.78 (t, J=7.2Hz.1H, ArH), 8.07-8.09 (dd, J=1.6, 2.0 1H, ArH), 11.79 (s, br, 1H, NH); **^{13}C NMR (DMSO-*d6*, 400 *MHz*,)**: 27.76, 27.79, 37.20, 120.62, 125.56, 126.20, 127.27, 134.26, 148.29, 162.27, 162.63; **HRMS(ESI):**calcd for $C_{12}H_{15}N_2O$(M+H): 203.1184; found: 203.1185.

2-(cyclopropylmethyl)quinazolin-4(3H)-one(3g): White Solid; Yield: 91.0 %; **^{1}HNMR (CDCl$_3$, 400 *MHz*,):***δ* 0.38-0.42 (m, 2H, CH_2), 0.70-0.73 (m, 2H, CH_2), 1.14-1.21 (m, 1H, CH), 2.69-2.76 (d, J=7.6, 2H CH_2), 7.45-7.48 (t, J=6.8 Hz, 1H, ArH), 7.74-7.79(m, 1H), 7.67-7.69 (d, J=7.6 Hz, 1H, ArH), 8.26-8.29 (dd, J=1.2, 1.2 Hz, 1H, ArH), 10.20 (s, br 1H, NH); **^{13}CNMR (DMSO-d_6, 400*MHz*,):***δ* 4.21, 9.20, 38.87, 120.79, 125.68,125.97, 126.83, 134.29, 149.01, 157.16, 161.85; **HRMS(ESI):** calcd for $C_{12}H_{13}N_2O$(M+H).: 201.1028; found: 201.1037

2-(4-(methylthio)phenyl)quinazolin-4(3H)-one(3l): White solid; Yield: 93.2%;**^{1}HNMR (DMSO-*d6*, 400 *MHz*):**δ 2.55 (s, 3 H, SCH_3), 7.39-7.41 (d, *J*= 8.4Hz, 2H), 7.49-7.52 (t, *J*=7.2Hz 1H, ArH), 7.71-7.73 (d, J=7.6Hz, 1H, ArH), 7.81-7.85 (t, J=7.6 Hz, 1H)), 8.13-8.16 m, 3H, ArH), 12.48 (s, br 1H,NH); **^{13}C NMR (DMSO-*d6*, 400 *MHz*):***δ*14.06, 120.84, 125.08, 125.82, 126.36, 127.35, 128.04, 128.62, 134.56, 143.02, 148.74, 151.78, 162.23; **HRMS(ESI):**calcd for $C_{15}H_{13}N_2OS$(M+H): 269.07486; found: 269.07846.

RESULTS AND DISCUSSION

A number of synthetic strategies have been developed for the preparation of substituted quinoxalin-2-one. The most common synthetic method involved condensation of aryl-1,2-diamines with 1,2-dicarbonyl compounds[19]. Other noteworthy syntheses of quinoxaline and related compounds include multicomponent reaction (MCR) [20] etc.Despite these remarkable efforts, development of an efficient methodology for the synthesis of highly functionalized quinazolinone derivatives is still an important challenge for organic chemists.Herein we report $FeCl_3$ catalyzed simple and efficient method for the preparation of 2-substituted quinazolinones (**3**) from isatoic anhydride (**1**) andarylimidamides (**2**) in high yield (**Scheme 1**).



1 2 3

Scheme 1.

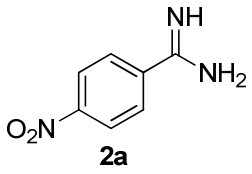
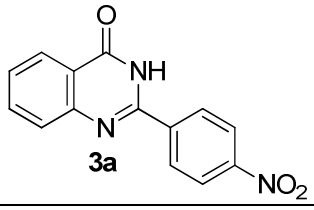
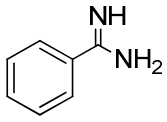
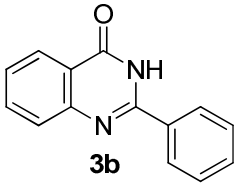
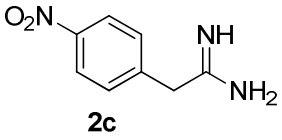
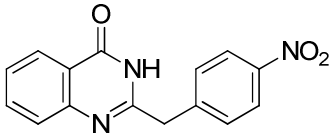
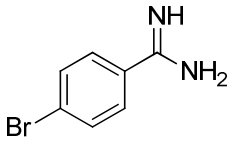
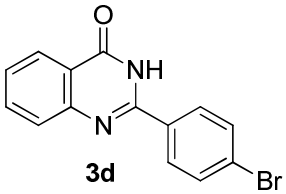
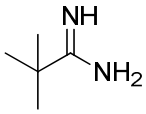
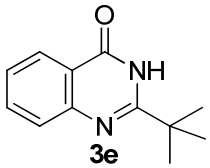
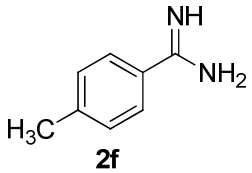
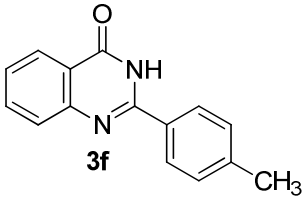
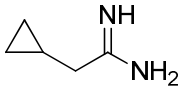
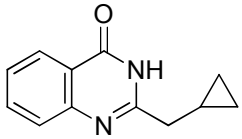
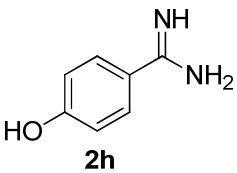
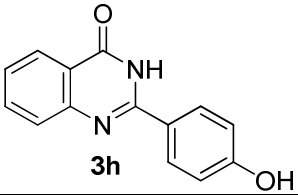
Table 1

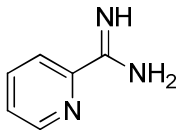
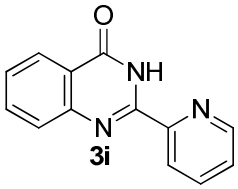
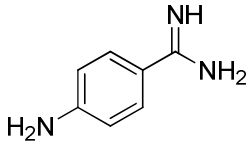
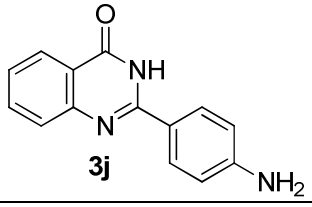
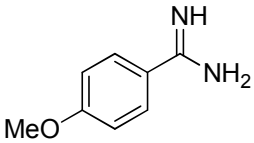
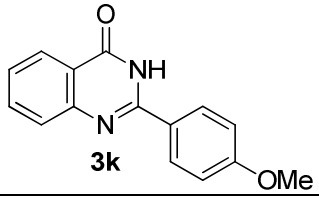
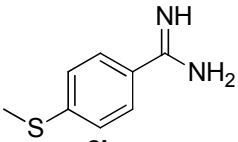
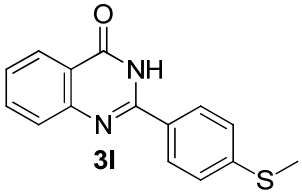
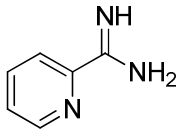
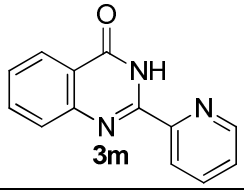
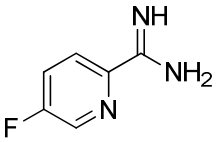
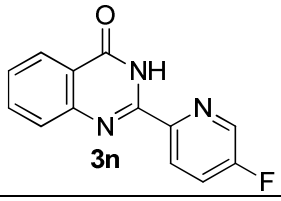
Entry	solvent	Temp	Time(h)	% of Yield
1	Water	100 °C	14 Hrs	0
2	Toluene	110 °C	14 Hrs	0
3	NMP	150 °C	6 Hrs	35.0
4	MeOH	65 °C	30 Hrs	38.0
5	EtOH	80 °C	26 Hrs	60.5
6	1,4-Dioxane	80 °C	4 Hrs	86

We intended to couple isatoic anhydride (**1**) and arylimidamides (**2**) to build the quinazolinone moiety under mild Lewis acid conditions in different solvents such as, water, NMP, MeOH, EtOH and 1,4-Dioxane were examined. To our delight reaction in 1,4-dioxane showed clean conversion in ~4 hrs and isolated yield was improved to 86% (entry 6). No product formation was observed in reactions with toluene and water as they showed poor solubility for isatoic anhydride (1) and benzimidamide(2). From these optimization studies right conditions were identified for the selective formation of 2-aryl quinazolinone using isatoic anhydride (1) and benzimidamide (2).

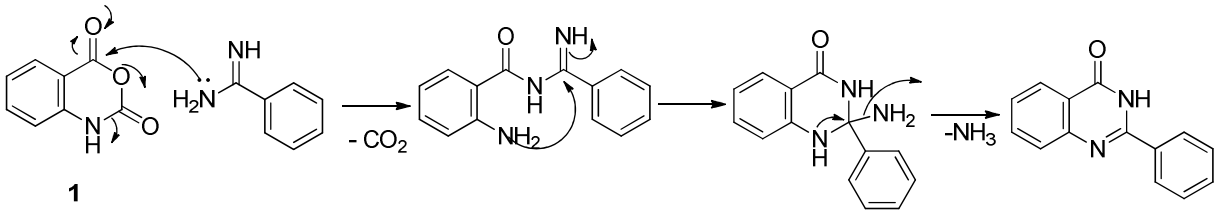
Further, the scope of this methodology was evaluated using a variety of substituted aryl arylimidamidesfollowing optimized conditions and the results were shown in **Table 2**.

Table 2.

Entry	Benzimidamide	Quinazolinones	Yield (%)
1	 **2a**	 **3a**	84.0
2	 **2b**	 **3b**	84.6
3	 **2c**	 **3c**	89.0
4	 2d	 **3d**	80.4
5	 **2e**	 **3e**	89
6	 **2f**	 **3f**	83.2
7	 **2g**	 **3g**	**91.0**
8	 **2h**	 **3h**	80.0

9	 **2i**	 **3i**	79.2
10	 **2j**	 **3j**	78.2
11	 **2k**	 **3k**	90.1
12	 **2l**	 **3l**	93.2
13	 **2m**	 **3m**	79.2
14	 **2n**	 **3n**	80.2

Proposed mechanism for formation of 2-substituted 4(3H)-quinazolinones



CONCLUSION

In conclusion, we have developed an efficient $FeCl_3$ catalyzed synthesis of 2-substituted quinazolinones using isatoic anhydride (1) and benzimidamide(2). The reaction proceeds under mild conditions with good to excellent yields.

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