Efficient synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using heterogeneous solid acid catalysts: unexpected formation of 2,3-dihydro-2-(4-(tetrahydro-2*H*-pyran-2-yloxy)butyl)quinazolin-4(1*H*)-one

Sandip B. Bharate,* Nagaraju Mupparapu, Sudhakar Manda, Jaideep B. Bharate, Ramesh Mudududdla, Rammohan R. Yadav, and Ram A. Vishwakarma*

Medicinal Chemistry Division, Indian Institute of Integrative Medicine (Council of Scientific and Industrial Research), Canal Road, Jammu-180001, India

E-mail: sbharate@iiim.ac.in ; ram@iiim.ac.in

Abstract

The heterogeneous solid acid catalysts Amberlyst-15 and silica-HClO₄ displays efficient catalytic properties for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from anthranilamide and various aldehydes/ ketones under mild reaction conditions and in good yields. These catalysts also showed good catalytic activity for condensation of anthranilamide with a cyclic enol ether 3,4-dihydropyran and led to formation of new unexpected quinazolinone product **6** comprising two dihydropyran moieties. The new product **6** has been reported for the first time and is fully characterized using 2D-NMR data. Furthermore, both solid acid catalysts can be easily recycled without significant loss of activity.

Keywords: Aldehydes, Amberlyst-15, 2,3-dihydroquinazolin-4(1*H*)-ones, 3,4-dihydropyran, heterogeneous catalysis, ketones

Introduction

A large number of synthetic as well as natural 2,3-dihydroquinazolinone classes of fused heterocycles have been reported possessing a diverse range of biological activities.¹⁻³ Due to their promising biological potential and wide occurrence in nature, several efforts have been made to develop an elegant approach for their synthesis. These include condensation of anthranilamide with aldehydes in presence of acid catalysts^{4,5} reductive cyclization of *O*-nitrobenzamide or *O*-azido-benzamide with aldehydes and ketones using SmI₂,⁶ or using TiCl₄,⁷ ⁸ reductive desulfurization of 2-thioxo-3*H*-quinazolin-4-ones with nickel boride in dry methanol,⁹ one-pot conversion from 2-nitro-*N*-arylbenzamides using SnCl₂,¹⁰ one-pot synthesis using *p*TSA,¹¹ silica-SO₃H,¹² alum,¹³ montmorillonite K-10,¹⁴ ionic liquids,¹⁵ and gallium(III) triflate,¹⁶ and enantioselective synthesis using chiral auxiliary³ and Bronsted acid catalyst.¹⁷ Of these, the condensation of anthranilamide with aldehyde or ketone is one of the simplest and

direct approach for preparation of 2,3-dihydroquinazolin-4(*1H*)-ones. Several researchers reported this approach using various catalysts such as *p*TSA,^{4, 18} cellulose-SO₃H,⁵ TiCl₄,^{7, 8} CuCl₂,¹⁹ NH₄Cl,²⁰ ionic liquids,¹⁵ TFA,³ and chiral phosphonic acids.^{17, 21}

Limitations of the existing protocols realized in terms of longer reaction time, stringent conditions, homogeneous nature of catalysts (except cellulose-SO₃H) which makes the process very expensive, use of costly and water sensitive catalysts (*e.g.* TiCl₄,^{7, 8}) and special efforts required to prepare the catalyst (*e.g.* cellulose-SO₃H). A recently reported eco-friendly approach²² involving water as a reaction medium, requires refluxing conditions and is only faster and suitable for aromatic aldehydes. However, ketones and heterocyclic aldehydes require longer reaction times and producing lower yields. Inability of reaction for aromatic ketones is the major limitation of this strategy.

Heterogeneous catalysis⁵⁻²³ has gained tremendous importance in organic synthesis due to its recyclability which makes cost-effective synthesis. Amberlyst-15²⁴ is a strongly acidic ion-exchange resin developed particularly for heterogeneous acid catalysis of wide variety of organic reactions. It is also useful in non-aqueous ion-exchange systems for the removal of cationic impurities. Use of this catalyst has been reported for a variety of reactions such as Friedel-Craft reaction,²⁵ glycosylation,²⁶ deprotection of aromatic acetates,²⁷ and also in multi-component synthesis of dihydroquinoxalin-2-amines from *O*-phenylene diamine, ketones and isocyanides.²⁸ Similarly, silica-HClO₄ has also been used in various organic reactions like acylation of phenols, thiols etc.²⁹ However no report exist on use of these two solid acid catalysts for the preparation of 2,3-dihydroquinazolin-4(*1H*)-ones.

Herein, we report the use of Amberlyst-15 and Silica-HClO₄ as efficient and reusable catalysts for synthesis of 2,3-dihydroquinazolin-4(*1H*)-ones **3** in shorter reaction time under mild reaction conditions (Figure 1). Furthermore, the ability of these catalysts for formation of anthranilamide – 2,3-dihydropyran condensation product has also been reported in the present paper. Developed protocol provides easy and economical access to biologically important dihydroquinazolin-4(*1H*)-one scaffold for a drug discovery program.

Figure 1. Condensation of anthranilamide (**1**) with aldehydes/ ketones **2**.

Results and Discussion

The model reaction between anthranilamide (**1**) and benzaldehyde was selected to investigate catalytic efficiency of different solid acid catalysts *viz.* Amberlyst-15 along with few other cation-exchange resins, silica gel and silica-HClO₄ (Table 1, entries 1-6). Based on the earlier

reports, acetonitrile⁵ and water²² were chosen for optimization study. No product was formed in the absence of catalyst either in acetonitrile or water up to 6 h of reaction time. No improvement was observed even after addition of molecular sieves (4 °A). Further, with the use of Amberlyst-15 or Amberlite-IRA-40 as catalysts and acetonitrile as a solvent resulted in complete conversion of starting materials to desired product with >85% isolated yield. Amberlyst-15 and silica-perchloric acid showed good catalytic ability compared with other catalysts. We performed further optimization for Amberlyst-15. Reaction when performed in presence of Amberlyst-15 in water resulted in formation of desired product in 60% yield. The amberlite-IRC-50 and silica gel were found to be inefficient in promoting the reaction rate. Amberlyst-15 in acetonitrile as a solvent was found to be more efficient and thus selected for further optimization studies.

Table 1. Reaction between anthranilamide (**1**) and benzaldehyde (**2c**) in presence of various catalysts^a

Entry	Catalyst (% w/w) ^b	Reaction conditions	Yield ^c (%)
1	Amberlite-IRC-50 (50)	ACN, rt, 1 h	0
2	Amberlite-IRA-400 (50)	ACN, rt, 1 h	60
3	Amberlite-IRA-40 (50)	ACN, rt, 6 h	85
4	Amberlyst-15 (50)	ACN, rt, 1 h	92
5	Amberlyst-15 (50)	H ₂ O, rt, 1h	60
6	Silica-HClO ₄ (50)	ACN, rt, 45 min	92
7	Amberlyst-15 (10)	ACN, rt, 45 min	30
8	Amberlyst-15 (20)	ACN, rt, 45 min	42
9	Amberlyst-15 (30)	ACN, rt, 45 min	65
10	Amberlyst-15 (40)	ACN, rt, 45 min	80
11	Amberlyst-15 (50)	ACN, rt, 45 min	90
12	Amberlyst-15 (10)	ACN, rt, 4 h	85
13	Amberlyst-15 (20)	ACN, rt, 3 h	85
14	Amberlyst-15 (30)	ACN, rt, 2.5 h	85
15	Amberlyst-15 (40)	ACN, rt, 2 h	90
16	Amberlyst-15 (10)	MS, ^d ACN, rt, 3.5 h	85
17	Amberlyst-15 (50)	MS, ^d ACN, rt, 0.5 h	90

^a 50 %w/w catalyst was used in this study.

^b Weight percentage of catalyst with respect to anthranilamide

^c the isolated yield after chromatography.

^d MS, molecular sieves (4 °A).

Next, we studied the effect of amount of catalyst on the efficient completion of the reaction. Different weight% of the catalyst was used and the percentage conversion after different time intervals was monitored (Table 1, entries 7-17). Results obtained here indicate that the efficiency

of the reaction (higher yield) increased when a higher amount of the catalyst is used. The percent yield of the reaction increases from 30 to 90% with increasing the amount of catalyst from 10 %w/w to 50%w/w at 45 min reaction time. However, the reaction went to complete conversion using 10%w/w of the catalyst after 4 h of reaction time and the isolated yield was also excellent. Among various amounts of catalysts used, the 50%w/w was found to be highly active and more efficient with respect to reaction time. The 50%w/w catalyst afforded complete conversion of reaction within 45 min time. Further with the addition of molecular sieves (4 °A) to promote the rate of reaction, there was not significant decrease in the reaction time.

Recyclability of Amberlyst-15 was checked to prove the heterogeneous nature and its repeated use. The treatment of anthranilamide (**1**, 1 mmol) with benzaldehyde (**2c**, 1 mmol) in presence of Amberlyst-15 led to formation of desired 2-phenyl-2,3-dihydroxyquinazolin-4-one **3c** with complete consumption of starting materials in 45 min, 4 h, 8 h and 12 h over four cycles respectively. Similarly Silica-HClO₄ also showed excellent recyclability. Thus it is noteworthy to mention that these catalysts could be recycled several times, although there is increased reaction time after each cycle.²⁵

Next, we studied the scope of the reaction. As expected, this reaction proceeded smoothly and the desired products were obtained in excellent yields. A series of aldehydes with either electron-donating or electron-withdrawing groups attached to the aromatic ring were investigated (Table 2). The substitution groups on the aromatic ring had no obvious effect on the reaction yield. Aliphatic (Table 2, entries 'a' and 'b'), aromatic (Table 2, entries 'c-l') as well as heteroaromatic aldehydes (Table 2, entries 'm-o') produced desired products in good yields. Similarly several aliphatic (Table 2, entries 'p-r') as well as aromatic ketones (Table 2, entry 's') participated well in this reaction. Reaction of 3-formyl indole (**2n**) with anthranilamide (**3**) when performed under reflux conditions for 45 min using Amberlyst-15 and silica-HClO₄, it was observed that yield of the product **3n** was improved (75 and 85% respectively). Similarly, for quinoline substituted compound **3o**, higher yield was obtained using silica-HClO₄ catalyst under heating condition.

Aromatic ketones were found to be less reactive compared to aliphatic or alicyclic ketones.²² Reaction of **1** with acetophenone (entry 's') when performed at room temperature, desired product was obtained in only 35% yield; however under refluxing condition for 90 min, 70% yield of **3s** was obtained. For this reaction, silica-HClO₄ produced similar yield (78%). All synthesized compounds were stable and were fully characterized by NMR, MS and melting point analysis. Compounds **3j**, **3n** and **3o** are new compounds and have been synthesized for the first time. One of our synthesized compound **3l** (naphtha-1-yl analog) is reported to possess *in vivo* anti-leukemic activity as well as tubulin polymerization inhibitory activity (IC₅₀ 1.7 μM).^{30, 31}

Table 2. Amberlyst-15 catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones^a **3** *via* scheme shown in Figure 1

Entry	Aldehyde/ Ketone, 2		Product		Time (min)	Yield ^b (%)	mp (°C)	
	R	R'	Structure	Code			Found	Reported
a	-CH ₃	-H		3a	60	80	137-140	nr ^d
b	-CH ₂ CH ₂ CH ₃	-H		3b ^{5,20}	60	75	160-162	162-164 ²⁰
c		-H		3c ^{16,17,20,32}	60	85	213-215	218-219 ¹⁶
d		-H		3d ¹⁷	45	90	213-215	215.8 ¹⁷
e		-H		3e ^{5, 16, 32}	60	75	200-202	198-200 ²²
f		-H		3f ^{16, 17}	60	85	280-282	278-280 ¹⁶
g		-H		3g ¹⁷	45	80	182-184	184.8 ¹⁷
h		-H		3h ³³	60	85	222-225	nr ^d
i		-H		3i ^{5, 16, 32}	60	85	203-205	206-207 ^{16, 22}
j		-H		3j ^c	60	85	243-246	nr ^d

Table 2. Continued

Entry	Aldehyde/ Ketone, 2		Product		Time (min)	Yield ^b (%)	mp (°C)	
	R	R'	Structure	Code			Found	Reported
k		-H		3k ¹⁷	60	70	200-203	201 ¹⁷
l		-H		3l ³⁰	60	75	173-175	nr ^d
m		-H		3m ^{5, 16}	60	75	160-163	163-165 ^{1, 16, 22}
n		-H		3n ^c	90	65	227-230	nrd
o		-H		3o ^c	120	55	272-274	nr ^d
p	-CH ₃	- CH ₃		3p ³⁴	60	75	179-182	182-183 ³⁴
q	-CH ₂ CH ₃	- CH ₂ CH ₃		3q ^{8, 35}	60	75	197-200	nr ^d
r				3r ^{5, 20, 34}	60	70	215-217	217-219 ²⁰
s ^e		-CH ₃		3s ²²	120	70	218-221	222-224 ²²

^a All products were characterized by NMR and MS data.^b Yields refer to pure products after silica gel column chromatography.^c New compounds.^d Melting point not reported (nr) or not available in the literature^e Reaction was performed under reflux condition.

These promising results prompted us to study catalytic efficiency of Amberlyst-15 for condensation of anthranilamide with cyclic enol ether. The reaction of **1** with 3,4-dihydropyran (**4**) in ACN in presence of Amberlyst-15 (50% w/w) at 80 °C did not led to formation of expected product **5** (reported by Reddy *et al*);⁵ however an unexpected product **6** was formed (60% yield; Figure 2). The product **6** was also formed in room temperature reaction but only in 30% yield. The ¹H NMR data of sulphonamide analog of **5** provided in Reddy *et al.*'s paper⁵ contain a triplet at δ 4.69 ppm for terminal methylene protons (-CH₂-CH₂OH) of side chain. As per our knowledge, such a downfield chemical shift value for these type of protons have never been encountered in the literature.

Figure 2. Reaction between anthranilamide (**1**) and 2,3-dihydropyran (**4**).

The ¹H NMR spectrum of our 3,4-dihydropyran condensed product showed unexpected peaks at 4.92 (t, 1H), 4.56 (t, 1H), 3.58-3.42 (m, 2H) and extra 6 protons in δ 1-2 ppm region. ¹³C NMR also showed similar observation with a presence of several extra signals in aliphatic region. DEPT-135 spectrum showed total 8 CH₂'s, two of which are in the 60-70 ppm region and two CH in non-aromatic region (99.3 and 65.3 ppm). Aromatic region showed four Ar-CH (133.8, 128.6, 119.3, 114.7 ppm) and three quaternary carbons (165.3, 147.4, 116.1 ppm) (see supplementary material). NMR information pointed towards presence of additional pyran ring. Further MS data (m/z 327 [M+Na]⁺) supported NMR results. The location of attachment of a second pyran moiety, whether on NH or terminal OH, was confirmed by HMBC/HSQC correlations. In HMBC spectrum, the additional CH peak (¹H NMR: δ 4.56 ppm) have not shown any correlation with either carbonyl or any aromatic carbon, ruling out the possibility of second pyran moiety linked to NH. The key HMBC correlations of compound **6** are shown in supporting information (Figure S5). Furthermore, extreme downfield CH signal (δ 99.3 ppm) in ¹³C NMR confirmed O-CH-O pattern. The combined spectral information of ¹H, ¹³C, DEPT, MS, HMBC/HSQC NMR data led to structure **6**. Further, this type of protection of primary alcohols using tetrahydropyran has been reported earlier under acidic conditions.³⁶

Results clearly indicate the heterogeneous nature of the catalyst with good recycling capability. The macroreticular pore structure of Amberlyst-15 permits ready access of liquid or gaseous reactants to the hydrogen ion sites located throughout the bead, thus ensuring successful performance even in non-swelling organic media. Amberlyst-15 is an inexpensive and non-hazardous commercially available solid acid catalyst. It can be easily handled and separated from the reaction mixtures by simple filtration. The recovered catalyst can be reused over more than three cycles without significant loss of catalytic activity.

Conclusions

An efficient protocol for synthesis of 2,3-dihydroquinazolin-4(*1H*)-ones using solid acid catalysts Amberlyst-15 and silica-HClO₄ as recyclable catalysts in shorter reaction times and high yields under milder reaction conditions has been described. Furthermore, the catalytic efficiency of these catalysts was also studied for cyclic enol ether 3,4-dihydropyran and the formation of 2,3-dihydro-2-(4-(tetrahydro-2*H*-pyran-2-yloxy)butyl)quinazolin-4(*1H*)-one (**6**) product has been reported for the first time. Catalyst being inexpensive, non-hazardous and heterogeneous in nature makes the method economically viable for the synthesis of titled compounds.

Experimental Section

General. All chemicals were obtained from Sigma-Aldrich Company and used as received. NMR spectra were recorded on a Bruker-Avance DPX FT-NMR 400 MHz instrument. Mass spectra were recorded on an Agilent 1100 LC-Q-TOF. Elemental analyses were recorded on an Elementar Vario EL III and melting points were recorded on a digital melting point apparatus.

Synthesis of 2,3-dihydroquinazolin-4(*1H*)-ones **3 and **6**.** Amberlyst-15 (50%w/w with respect to **1**) was added to a solution of anthranilamide (**1**, 1 mmol) and aldehyde/ ketone/3,4-dihydropyran (**2** or **4**, 1.0 mmol) in acetonitrile (5 mL). The mixture was stirred at room temperature / 80 °C for the specified period of time. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was then allowed to cool to room temperature and filtered. Filtrate was concentrated and purified by silica-gel column chromatography to get products **3a-s** and **6**. Characterization data for new compounds is provided below:

2,3-Dihydro-2-(4-hydroxy-3-nitrophenyl)-quinazolin-4(*1H*)-one (3j**).** Yellow solid; yield: 85%; mp 243-246 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ(ppm) 8.31 (s, 1H), 7.99 (s, 1H), 7.68 (d, *J* 6.8 Hz, 1H), 7.62 (d, *J* 6.4 Hz, 1H), 7.28 (t, *J* 7.2 Hz, 1H), 7.14 (m, 2H), 6.76 (d, *J* 8.0 Hz, 1H), 6.72 (t, *J* 7.2 Hz, 1H), 5.78 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ(ppm) 163.4, 152.1, 147.5, 136.2, 133.6, 133.4, 132.7, 127.3, 123.5, 119.1, 117.3, 114.8, 114.4, 65.2; MS (Q-TOF):

m/z 286 $[M+1]^+$, 308 $[M+Na]^+$. analysis for $C_{14}H_{11}N_3O_4$ (285.07), calcd, C, 58.95; H, 3.89; N, 14.73; found, C, 59.13; H, 3.98; N, 14.82.

2,3-Dihydro-2-(naphthalene-1-yl)quinazolin-4(1H)-one (3l). White solid; Yield: 85%; mp 173-175 °C. 1H NMR (400 MHz, DMSO- d_6): δ (ppm) 8.56 (d, J 6.8 Hz, 1H), 8.27 (s, 1H), 7.98 (t, J 8.4 Hz, 2H), 7.70 (t, J 6.4 Hz, 2H), 7.57 (m, 3H), 7.26 (t, J 7.6 Hz, 1H), 7.08 (s, 1H), 6.74 (dd, J 8.0, 12.8 Hz, 2H), 6.49 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6): δ (ppm) 163.9, 148.3, 135.1, 133.7, 133.2, 130.4, 129.2, 128.5, 127.4, 126.0, 125.7, 125.1, 124.4, 117.2, 114.9, 114.4, 65.8; MS (Q-TOF): m/z 275 $[M+1]^+$, 297 $[M+Na]^+$. analysis for $C_{18}H_{14}N_2O$ (274.11), calcd, C, 78.81; H, 5.14; N, 10.21; found, C, 78.62; H, 5.27; N, 10.03.

2,3-Dihydro-2-(1H-indol-3-yl)quinazolin-4(1H)-one (3n). Light yellow crystalline solid; yield: 75%; mp 227-230 °C. 1H NMR (400 MHz, DMSO- d_6): δ (ppm) 8.08 (s, 1H), 7.77 (d, J 8.0 Hz, 1H), 7.67 (d, J 7.8 Hz, 1H), 7.40 (m, 2H), 7.22 (t, J 7.6 Hz, 1H), 7.09 (t, J 7.6 Hz, 1H), 7.02 (t, J 6.8 Hz, 1H), 6.92 (s, 1H), 6.76 (d, J 8.0 Hz, 1H), 6.69 (t, J 7.2 Hz, 1H), 6.03 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6): δ (ppm) 164.7, 149.2, 137.1, 133.5, 127.9, 125.8, 125.1, 121.9, 120.4, 119.2, 117.4, 115.7, 114.9, 112.1, 62.1; MS (Q-TOF): m/z 264 $[M+1]^+$, 286 $[M+Na]^+$. analysis for $C_{16}H_{13}N_3O$ (263.11), calcd, C, 72.99; H, 4.98; N, 15.96; found, C, 73.07; H, 5.02; N, 15.71.

2,3-Dihydro-2-(quinolin-3-yl)quinazolin-4(1H)-one (3o). Yellow solid; yield: 80%. mp 272-274 °C. 1H NMR (400 MHz, DMSO- d_6): δ (ppm) 9.06 (s, 1H), 8.47 (s, 1H), 8.40 (s, 1H), 8.04 (t, J 8.0 Hz, 2H), 7.82 (m, 1H), 7.79 (m, 2H), 7.29 (dd, J 7.2, 14.0 Hz, 1H), 6.79 (d, J 8.4 Hz, 2H), 6.75 (t, J 7.2 Hz, 1H), 6.06 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6): δ (ppm) 163.5, 149.9, 147.6, 147.4, 133.9, 133.8, 133.4, 129.8, 128.5, 128.2, 127.4, 127.0, 117.5, 115.0, 114.5, 64.9; MS (Q-TOF): m/z 276 $[M+1]^+$, 298 $[M+Na]^+$; analysis for $C_{17}H_{13}N_3O$ (275.11), calcd, C, 74.17; H, 4.76; N, 15.26; found, C, 73.68; H, 4.91; N, 15.18.

2,3-Dihydro-2-(4-(tetrahydro-2H-pyran-2-yloxy)butyl) quinazolin-4(1H)-one (6). Yellow oil; yield: 60%. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.87 (d, J 6.4 Hz, 1H), 7.32 (t, J 6.8 Hz, 1H), 6.87 (t, J 7.2 Hz, 1H), 6.67 (d, J 8.0 Hz, 1H), 6.31 (brs, D_2O exchangeable, NH), 4.92 (t, J 5.6 Hz, 1H), 4.56 (t, J 4.4 Hz, 1H), 3.89-3.74 (m, 2H), 3.58-3.42 (m, 2H), 1.89-1.62 (m, 6H), 1.60-1.45 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.3 (C), 147.4 (C), 133.8 (CH), 128.6 (CH), 119.3 (CH), 116.1 (C), 114.7 (CH), 99.3 (CH), 67.2 (CH_2), 65.3 (CH), 62.8 (CH_2), 33.3 (CH_2), 30.9 (CH_2), 29.3 (CH_2), 25.5 (CH_2), 21.0 (CH_2), 19.9 (CH_2); MS (Q-TOF): m/z 327 $[M+Na]^+$. analysis for $C_{17}H_{24}N_2O_3$ (304.18), calcd, C, 67.08; H, 7.95; N, 9.20; found, C, 67.18; H, 8.03; N, 9.10.

Supplementary material available

Supporting information for this article is available online at <http://www.arkat-usa.org>. Included are 1H NMR, ^{13}C NMR, DEPT and MS spectra of compound **6**.

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References

1. Yale, H. L.; Kalkstein, M. *J. Med. Chem.* **1967**, *10*, 334.
2. (a) Levin, J. I.; Chan, P. S.; Bailey, T.; Katocs, A. S.; Venkatesan, A. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1141. (b) Okumura, K.; Oine, T.; Yamada, Y.; Hayashi, G.; Nakama, M. *J. Med. Chem.* **1968**, *11*, 348. (c) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650; (d) Maskey, R. P.; Shaaban, M.; Grun-Wollny, I.; Laatsch, H. *J. Nat. Prod.* **2004**, *67*, 1131. (e) Somanadhan, B.; Leong, C.; Whitton, S. R.; Ng, S.; Buss, A. D.; Butler, M. S. *J. Nat. Prod.* **2011**, *74*, 1500.
3. Chinigo, G. M.; Paige, M.; Grindrod, S.; Hamel, E.; Dakshanamurthy, S.; Chruszcz, M.; Minor, W.; Brown, M. L. *J. Med. Chem.* **2008**, *51*, 4620.
4. (a) Moore, J. A.; Sutherland, G. J.; Sowerby, R.; Kelly, E. G.; Palermo, S.; Webdter, W. *J. Org. Chem.* **1969**, 887. (b) Sharma, S. D.; Kaur, V. *Synthesis* **1989**, 677.
5. Reddy, B. V. S.; Venkateswarlu, A.; Madan, C.; Vinu, A. *Tetrahedron Lett.* **2011**, *52*, 1891.
6. Su, W. K.; Yang, B. B. *Aust. J. Chem.* **2002**, *55*, 695.
7. (a) Shi, D. Q.; Rong, L. C.; Wang, J. X.; Zhuang, Q. Y.; Wang, X. S.; Hu, H. W. *Tetrahedron Lett.* **2003**, *44*, 3199. (b) Shi, D.; Wang, J.; Rong, L.; Zhuang, Q.; Tu, S.; Hu, H. *J. Chem. Res.* **2003**, *10*, 671.
8. Shi, D.-Q.; Rong, L.-C.; Wang, J.-X.; Zhuang, Q.-Y.; Tu, S.-J. *Chin. J. Chem.* **2004**, *22*, 743.
9. Khurana, J. M.; Kukreja, G. *J. Heterocycl. Chem.* **2003**, *40*, 677.
10. Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. *J. Org. Chem.* **2005**, *70*, 6941.
11. Baghbanzadeh, M.; Salehi, P.; Dabiri, M.; Kozehgarya, G. *Synthesis* **2006**, 344.
12. Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Baghbanzadeh, M. *Synlett* **2005**, 1155.
13. Dabiri, M.; Salehi, P.; Otokesh, S.; Baghbanzadeh, M.; Kozehgarya, G.; Mohammadi, A. A. *Tetrahedron Lett.* **2005**, *46*, 6123.
14. Salehi, P.; Dabiri, M.; Baghbanzadeh, M.; Bahramnejad, M. *Synth. Commun.* **2006**, *36*, 2287.
15. Chen, J. X.; Su, W. K.; Wu, H. Y.; Liu, M. C.; Jin, C. *Green Chem.* **2007**, *9*, 972.
16. Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 3814.
17. Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 908.
18. Hour, M. J.; Huang, L. J.; Kuo, S. C.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K. H. *J. Med. Chem.* **2000**, *43*, 4479.

19. Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. *Tetrahedron Lett.* **2004**, *45*, 3475.
20. Shaabani, A.; Ali Maleki, A.; Mofakham, H. *Synth. Commun.* **2008**, *38*, 3751.
21. Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786.
22. Wang, M.; Zhang, T. T.; Song, Z. G. *Chin. Chem. Lett.* **2011**, *22*, 427.
23. Chari, M. A.; Karthikeyan, G.; Pandurangan, A.; Naidu, T. S.; Sathyaseelan, B.; Javaid Zaidi, S. M.; Vinu, A. *Tetrahedron Lett.* **2010**, *51*, 2629.
24. (a) Santosh, T. K.; Thirupathi, P.; Kim, S. S. *Tetrahedron* **2009**, *65*, 10383. (b) Shiva Kumar, K.; Iqbal, J.; Pal, M. *Tetrahedron Lett.* **2009**, *50*, 6244.
25. Kadam, S. T.; Thirupathi, P.; Kim, S. S. *Tetrahedron* **2009**, *65*, 10383.
26. Tian, Q.; Zhang, S.; Yu, Q.; He, M.-B.; Yang, J.-S. *Tetrahedron* **2007**, *63*, 2142.
27. Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* **2003**, *44*, 5465.
28. Chari, M. A. *Tetrahedron Lett.* **2011**, *52*, 6108.
29. Chakraborti, A. K.; Gulhane, R. *Chem. Commun.* **2003**, 1896.
30. Hamel, E.; Lin, C. M.; Plowman, J.; Wang, H.-K.; Lee, K.-H.; Paull, K. D. *Biochem. Pharmacol.* **1996**, *51*, 53.
31. Meil, G. L.; Li, L. H.; Buskirk, H. H.; Moxley, T. E. *Cancer Chemother. Rep. Part 1* **1972**, *56*, 163.
32. Zeng, L.-Y.; Cai, C. *J. Heterocycl. Chem.* **2010**, *47*, 1035.
33. Strakovsk, A.; Avotins, F.; Petrova, M. *Rigas Tehniskas Universitates Zinatniskie Raksti, Serija 1: Materialzinatne un Lietiska Kimija* **2003**, *6*, 122.
34. Wang, X.-S.; Ke Yang, J. Z.; Tu, S.-J. *J. Comb. Chem.* **2010**, *12*, 417.
35. Shi, D.; Shi, C.; Wang, J.; Rong, L.; Zhuang, Q.; Wang, X. *J. Heterocycl. Chem.* **2005**, *42*, 173.
36. Bongini, A.; Cardillo, G.; orena, M.; Sandri, S. *Synthesis* **1979**, *8*, 618.