Synthesis of 2, 3-Disubstituted-Quinazolin-4-(3*H*)-ones

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Abstract: The present review covers a concise account of the synthesis of bioactive 2, 3-disubstituted-quinazoline-4(3*H*)-ones and the recent developments in the area of versatile quinazolinones with a special emphasis on new synthetic routes and strategies.

Keywords: Benzoxazinones, microwave irradiation, quinazolinones, solid support synthesis.

INTRODUCTION

The quinazolinones are a class of fused heterocycles that are of considerable interest because of the diverse range of their biological properties, such as antimalarial [1], anticancer, anti-HIV [2], antiviral [3], antibacterial [4], anticonvulsant [5], antihypertensive [6], antidiabetic [7], antihistaminic [8] and anti-inflammatory activity [9].

The use of combinatorial synthesis, microwave-enhanced processes and new catalytic methodologies in the preparation of these heterocycles is a clear indication that significant advancement has been made in recent years. The syntheses of quinazolinones can be classified into the following five categories, based on the substitution patterns of the ring system:

1) 2-Substituted-4-(3H)-quinazolinones

2) 3-Substituted-4-(3H)-quinazolinones

3) 4-Substituted-quinazolinones

4) 2,3-Disubstituted-4-(3H)-quinazolinones

5) 2,4-Disubstituted-4-(3H)-quinazolinones

In this review, we have described new and improved methods for the construction of 4-(3H)-quinazolinone skeletons for the period of 2005-2009, with a particular emphasis on 2, 3-disubstituted-4-(3H)-quinazolinone analogues.

1. Benzoxazinones

Ji-Feng Liu reported the microwave promoted one-pot, two-step synthesis of 2,3-disubstituted-3H-quinazolin-4-ones **4**. The synthesis begins with the condensation of an anthranilic acid **1**, with either an acylchloride or a carboxylic acid followed by dehydration to form the intermediate benzoxazinones **2**. Subsequent addition of an amine initially provides the transient amidine salt species **3** which rapidly cyclizes to yield the desired 2,3-disubstituted-3H-quinazolin-4-ones **4** (Scheme **1**) [10].

Kostakis *et al.* reported an efficient methodology for the preparation of a series of 2,3-disubstituted-quinazolin-4-(3*H*)-ones *via* a three step reaction from anthranilic acid [11]. The synthesis of the desired quinazolin-4-(3*H*)-ones **9a–e** and **10a–e** was performed in three steps starting from anthranilic acid **1** (Scheme **2**). The first synthetic step involved the condensation of anthranilic acid **1** with acetic or propionic anhydride to afford the desired benzoxazinones (**5** and **6** respectively) in quantitative yields. These intermediates were then totally converted into diamides **7a-e** and **8a-e** through treatment with an excess of the appropriate aliphatic amines. Finally, the obtained diamides were subjected to microwave-assisted cyclocondensation to give the desired quinazolinones **9a-e** and **10a-e** in good yields (Table **2**).

Kashaw *et al*., reported the synthesis of several new 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-ureas **12**. 2-Ethylbenzoxazin-4-one or 2-phenylbenzoxazin-4-one **6** and substituted aryl semicarbazides (**11**a–l) were refluxed in the presence of glacial acetic acid to yield **12**a-l, (Yield 45-78 %) [12].

Nouira *et al*., reported the generation of ammonia *via* thermal decomposition of formamide under microwave conditions to provide an efficient tool for the synthesis of nitrogen-containing heterocycles as quinazolin-4-ones, which are known as building blocks for molecules with pharmaceutical interest. The 2,3-disubstituted quinazolin-4-(3*H*)-ones **13** in 74-84 % yield were obtained in three steps starting from anthranilic acid **1** and using 3,1-benzoxazinones as intermediates (Scheme **4**). In these compounds, an alkyl group was inserted into the quinazolinone ring in position 2 by nucleophilic attack of an appropriate aliphatic amine ($R\text{-}NH_2$) and a microwave-assisted cyclocondensation of the intermediate diamides [13].

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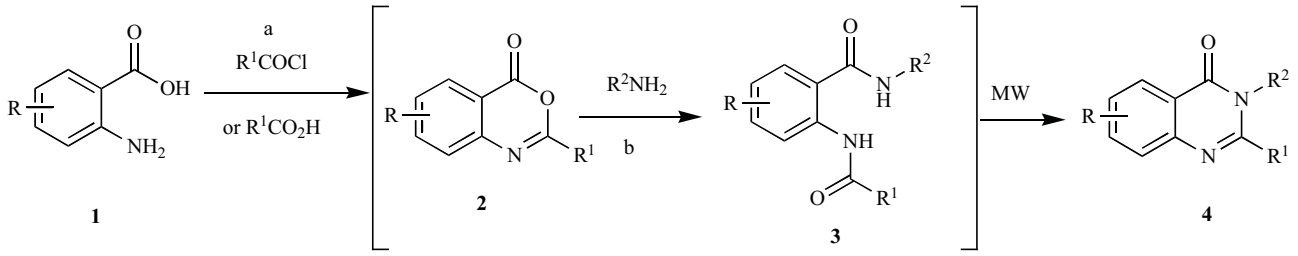
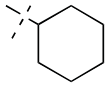
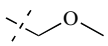
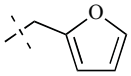
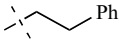
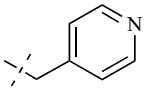
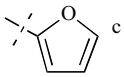
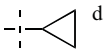
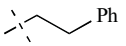
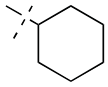
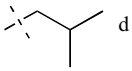
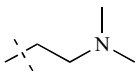
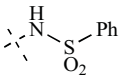
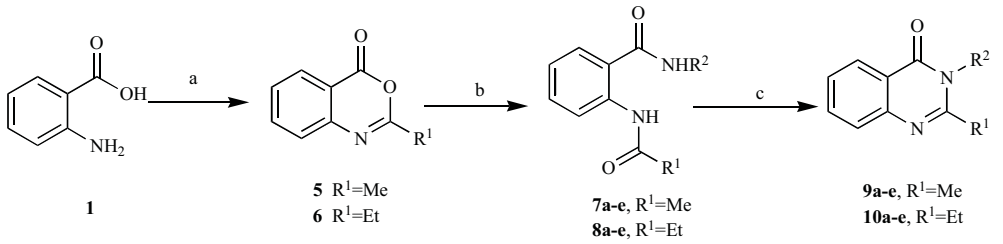


Scheme 1. "Optimized one-pot microwave promoted synthesis of 2,3-disubstituted-3H-quinazolin-4-ones" **4**, (Table **1**) optimized conditions: a) For R^1COCl (1.5 equi.), $P(PhO)_3$ (1.2 equi.), pyridine (2.0 mL), 250^0C, 60 min; or for R^1CO_2H (1.0 equiv), $P(PhO)_3$ (1.2 equiv), pyridine (1.0 mL), Microwave, 150^0C, 10 min; b) R^2NH_2 (1.5 equi.) when R^1COCl used, R^2NH_2 (1.0 equi.) when R^1CO_2H used, microwave, 250^0C, 3–10 min.

Table 1. Chemistry and Scope of Microwave Promoted Synthesis of 2,3-disubstituted-3*H*-quinazolin-4-ones 4

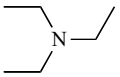
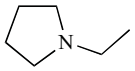
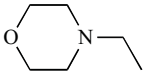
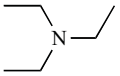
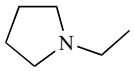
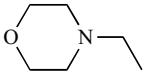
Entry	R	R^1	R^2	Yield[a] of 4[b] (%)
4a	H	Ph[c]	Ph	100 (88)
4b	H	Ph[c]		90 (60)
4c	H	Ph[c]	Bn	95 (80)
4d	H	Ph[c]		100 (85)
4e	H	Ph[c]		95 (66)
4f	H	Bn[d]		100 (62)
4g	H			94 (46)
4h	H		Bn	100 (53)
4i	H			95 (50)
4j	H	Et[d]	Bn	100 (64)
4k	5-CH_3	Me[d]		100 (59)
4l	4-Cl		Bn	100 (66)
4m	4,5-$(OCH_3)_2$	4-OMe-Bn[d]		100 (64)
4n	Note[e]	Ph[c]	Bn	95 (68)
4o	H	Me[d]		95 (65)

[a]The yields determined by HPLC (ELSD) from LC–MS results of the reaction mixture.
In bracket, isolated yields by preparative TLC or flash column chromatography.
[b]Characterized by ^1H NMR, ^{13}C NMR, and HRMS.
[c]R^1COCl used: 25^0C/60 min.
[d]R^1CO_2H used: Microwave 150^0C/10 min.
[e]2-Aminonicotinic acid used.

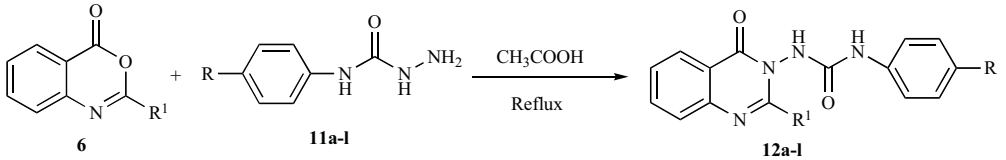


Scheme 2. "Reagents and conditions" (Table **2**), a) (R^1 = Me): acetic anhydride, MW (200 W), 130^{0}C, 10 min; (R^1 = Et): propionic anhydride, MW (200 W), 160^{0}C, 10 min; b) aliphatic amine (R^2–NH_2) (2 equiv), CH_2Cl_2, rt, 10–40 min; c) formamide, MW (200 W), 170^{0}C, 10 min.

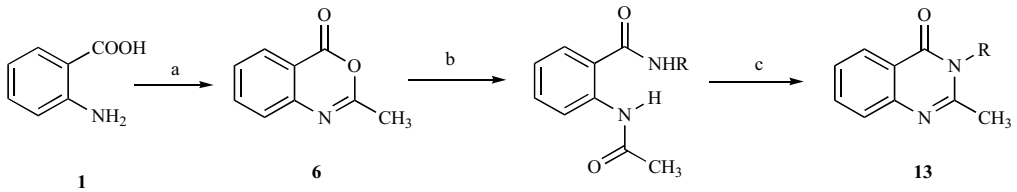
Table 2. Synthesis of 2,3-disubstituted-quinazolin-4-(3*H*)-ones, 9a-e and 10a-e from Anthranilic Acid

Entry	R^1	R^2	Yield[a] (%)
9a	Me	Me	84
9b	Me	*n*-Bu	75
9c	Me		77
9d	Me		83
9e	Me		77
10a	Et	Me	87
10b	Et	*n*-Bu	74
10c	Et		85
10d	Et		86
10e	Et		87

[a]Overall yield from anthranilic acid.



Scheme 3. "Synthesis of 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-ureas", **12**a-l, Optimized conditions: glacial acetic acid, 65^{0}C, 4h.



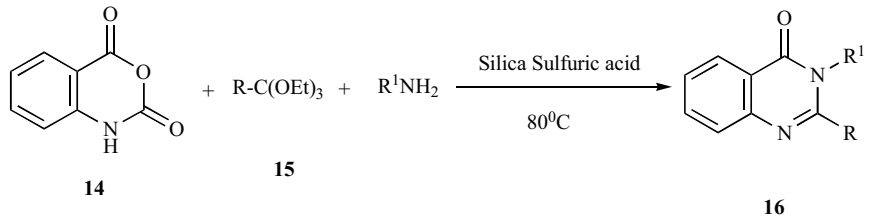
Scheme 4. "2,3-disubstituted quinazolin-4-(3*H*)-ones from anthranilic acid, optimized conditions: a) acetic anhydride, MW (200W), 130^{0}C, 10 min, b) aliphatic amines (2 equi.),CH_2Cl_2, rt, 10-40 min, c) Niementowski reaction, formamide, MW 200W, 10 min, 170^{0}C.

2. Synthesis of Quinazolin-4(3*H*)-one derivatives using silica sulfuric acid

Quinazolin-4-(3*H*)-one derivatives **16** were synthesized successfully *via* a one-pot, three component reaction of isatoic anhydride **14** and an orthoester **15** with ammonium acetate or a primary amine catalyzed by silica sulfuric acid under solvent-free conditions. This was the first report on the synthesis of 2-substituted quinazolin-4-(3*H*)-ones catalyzed by silica sulfuric acid. When isatoic anhydride, a primary amine, and an orthoester were mixed in the presence of catalytic amounts of silica sulfuric acid under solvent-free conditions, the products were obtained with satisfactory yields (Scheme **5**) [14]. The results are summarized in Table **3**.

3. Intramolecular Dehydrative Cyclization of Diamides

A simple and efficient general approach to various quinazolinone scaffolds, including peptidomimetic examples, has been demonstrated by employing hexamethyldisilazane (HMDS)/I_2 for the intramolecular dehydrative cyclization of diamides. Kshirsagar *et al.* had reported a new, facile

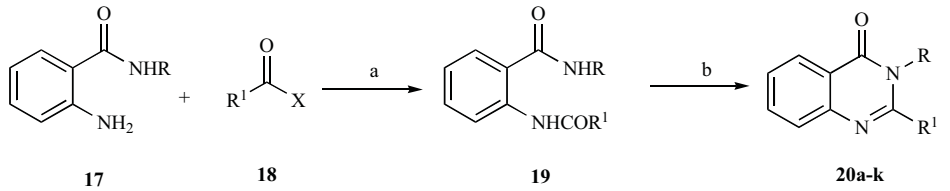


Scheme 5. "Synthesis of 2,3-disubstituted quinazolin-4(3H)-ones **16** in the presence of catalytic amounts of silica sulfuric acid under solvent-free conditions", (Table **3**).

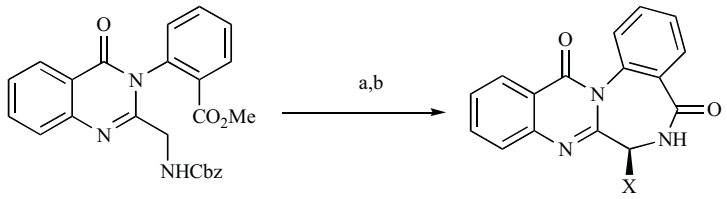
Table 3. Synthesis of 2,3-disubstituted Quinazolin-4-(3H)-ones 16 a-u by the Reaction of Isatoic Anhydride, Primary Amines and Different Orthoesters Under Solvent Free Conditions

Entry	R	R^1	% Yield[a]
a	CH_3	4-ClC_6H_4	78
b	CH_3	4-$CH_3C_6H_4$	80
c	CH_3	Ph	81
d	CH_3	4-$CH_3CH_2C_6H_4$	80
e	CH_3	$C_6H_5CH_2$	85
f	CH_3	$C_6H_5CH_2CH_2$	83
g	CH_3	CH_3CH_2	87
h	CH_3	2-$CH_3C_6H_4$	81
i	CH_3CH_2	CH_3CH_2	86
j	CH_3CH_2	4-$CH_3C_6H_4$	81
k	CH_3CH_2	4-BrC_6H_4	78
l	$CH_3CH_2CH_2$	4-$CH_3C_6H_4$	84
m	$CH_3CH_2CH_2$	$C_6H_5CH_2CH_2$	81
n	$CH_3CH_2CH_2$	4-BrC_6H_4	77
o	$CH_3CH_2CH_2$	Ph	80
p	$CH_3CH_2CH_2$	4-$CH_3C_6H_4$	79
q	$CH_3CH_2CH_2CH_2$	$C_6H_5CH_2CH_2$	79
r	Ph	Ph	79
s	Ph	4-$CH_3C_6H_4$	79
t	Ph	4-ClC_6H_4	75
u	Ph	$C_6H_5CH_2CH_2$	80

[a]Isolated yield.



Scheme 6. "Synthesis of unnatural quinazolinones and precursors of natural quinazolinones" **20,** (Table **4**), a) Triethylamine (TEA), Dichloromethane (DCM) / N-ethyl-*N'*-(3-dimethylaminopropyl) carbodiimde (EDCI), Hydroxybenzotriazole (HOBT), rt., 8 h; b) HMDS (1.5equi.), I_2 (0.5equi.), DCM, rt, 30 min-3h.



Scheme 7. "Synthesis of natural quinazolinones" **21**a and b, optimized conditions: a) HBr in AcOH (33%), 60^0C, 1 h; b) SiO_2, TEA, AcOEt, rt, 12 h.

and general approach to natural (Scheme **6**) and unnatural quinazolinones (Scheme **7**). Anthranilamides **17** were prepared in very good yields from the reactions of isatoic anhydride/sulfinamide anhydride with a variety of primary amines. Intermediates **19** were prepared by condensing anthranilamides **17** with the appropriate acid chlorides/carboxylic acids **18** in 82–98% yields (Table **4**, entries **20** a–k) [15]. Treatment of **19** with HMDS/$ZnCl_2$ in benzene solution under reflux (Vorbruggen's protocol) has furnished the desired products **20** a-k in ~100 % yields [16]. The protecting groups like -Boc, -Fmoc and -Cbz had well tolerated the reaction conditions, with no racemization.

4. Fused Quinazolinones

Pandey *et al*., reported three series of novel and new fused heterocyclic systems, viz., triazolo[4,3-a]-quinazolin-7-ones **23**, [1,2,4,5]-tetrazino[4,3-a]-quinazolin-8-ones **24** and indolo[2,3-c][1,2,4]-triazino[4,3-a]-quinazolin-8-ones **25** from the key intermediate 3-(substituted-phenyl)-2-hydrazino-quinazolin-4-ones **22** Scheme **8** [17].

Chung Tseng *et al*., had reported the direct one-pot double cyclodehydration of linear tripeptides to the total synthesis of pyrazino[2,1-b]quinazoline-3,6-diones (**26** a–l) Scheme **9**, on solid support using zinc triflate with good overall yields in short reaction time. These syntheses of the pyrazino[2,1-b]quinazoline-3,6-diones were conveniently achieved in three steps, starting from the amino acid-bound Wang resin.

Using the standard Fmoc-chemistry of solid-phase peptide synthesis (SPPS), the resin-bound amino acid derivative was sequentially condensed with anthranilic acid and Fmoc-protected amino acid chloride to produce the corresponding tripeptide on solid support (Wang resin). Previously, this tripeptide precursor was intramolecularly dehydrated with Ph_3P/I_2/DIEA, subsequently deprotected and cyclized with concomitant detachment from the solid support to finally afford the desired product. The multi-step procedure, however, suffered from the use of a large excess of reagents (5–10 equiv) and very long reaction time, especially when two non-Gly amino acids were involved as parts of the tripeptide substrate [18].

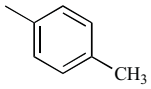
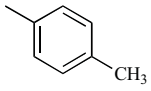
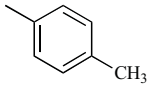
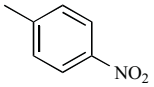
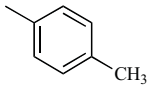
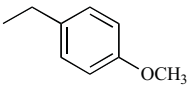
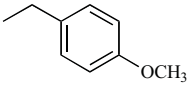
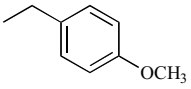
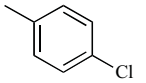
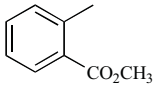
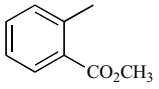
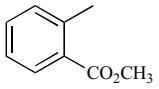
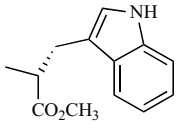
There are only two quinazolinone natural products isolated in the period of 1983-2005 [19], substituted both at the 2- and the 3-positions, they are tryptoquivaline analogs. 27-epi-Tryptoquivaline **27** and 27-epi-nortryptoquivaline **28** are the epimers of the previously known quinazolinone alkaloids, tryptoquivaline and nortryptoquivaline, respectively, which were isolated from *Aspergillus clavatus* (Scheme **10**). The first total synthesis of tryptoquivaline was achieved by Nakagawa *et al.,* [20] and this can be extended to the synthesis of the new tryptoquivalines by using an amino acid with the appropriate stereochemistry. Several efficient methods for the synthesis of a variety of 2,3-disubstituted quinazolinones are available in the literature [21,22].

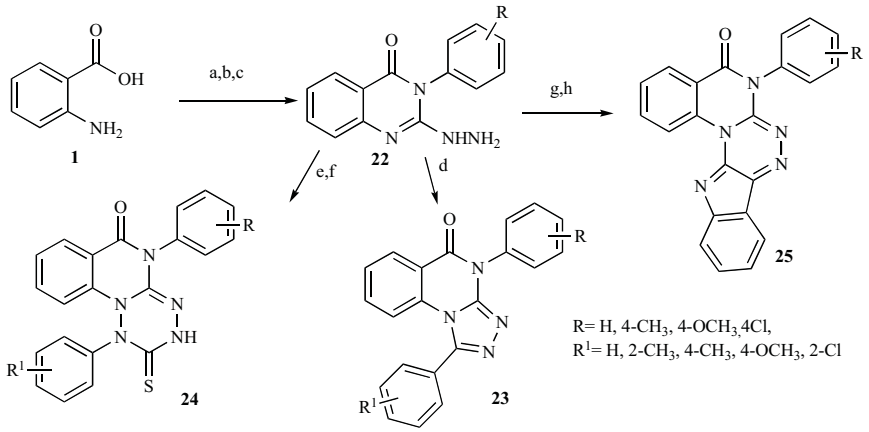
Heravi *et al*., reported a new synthesis of 4(3H)-quinazolinone from the reaction of 2-amino-benzamide and acylchlorides in the presence of catalytic amounts of silica-supported Preyssler nano particles as green, reusable and efficient catalyst under ultra sonic irradiation [23].

Alagarsamy *et al*., reported the 2-methyl-3-(substituted methylamino)-(3H)-quianzolin-4-ones **29** a-j by condensing the active hydrogen atom of the amino group of 3-amino-2-methyl-(3H)-quinazolin-4-one with formaldehyde and appropriate amines (Scheme **11**). The synthesis was achieved by adding a mixture of formalin (37-41%; 1 ml) and dimethylamine drop by drop with stirring to a slurry of 3-amino-2-methyl-(3H)-quinazolin-4-one in dimethylformamide [24].

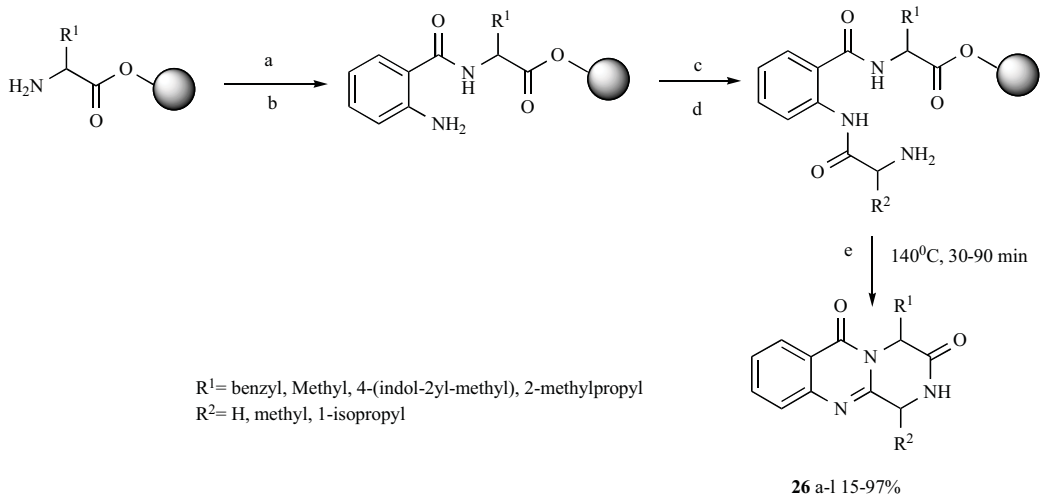
Sati *et al*., reported 2-phenyl-3-(substituted phenyl)-3H-quinazolin-4-ones **30**a-f from anthranillic acid **1** as described in Scheme **12** [25].

Table 4. Conversion of Anthranilamides 17 to Diamides 19 and Quinazolinones 21a-k

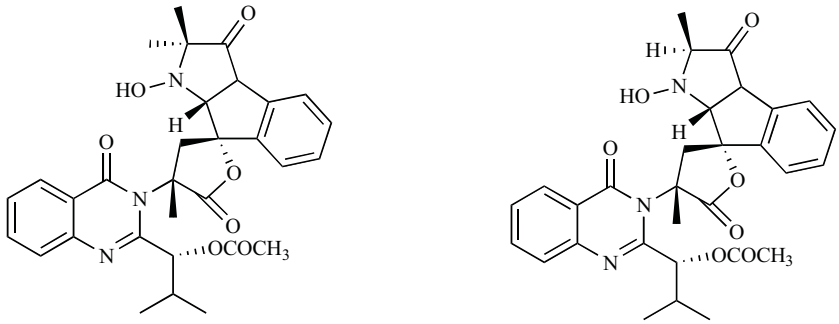
Entry	-R	-R^1	X	Yield %
20a		$-CH_2CH_3$	Cl	93
20b			Cl	95
20c			Cl	86
20d			OH	70
20e		$-CH_2CH_3$	Cl	97
20f			Cl	96
20g			Cl	90
20h		$-CH^2NHFmoc$	Cl	75
20i		$-CH_2NHCbz$	OH	65
20j			Cl	75
20k			Cl	65



Scheme 8. "Reagents and conditions": a) substituted phenylisothiocyanate, Me_2CO, reflux, 6h, b) Dioxane, CH_3COONa, CH_3I, 4h, c) $NH_2NH_2H_2O$, Dioxane, reflux, 6h, d) substituted benzoic acid, dicyclohexylcarbodiimide (DCC), CH_2Cl_2, 4h, e) substituted phenylisothiocyanate, MeOH, reflux, 4h, f) Br_2/CCl_4, 30 min, g) Isatin, MeOH, reflux, 3h, h) Conc. H_2SO_4, 5-10^0C, 2h.



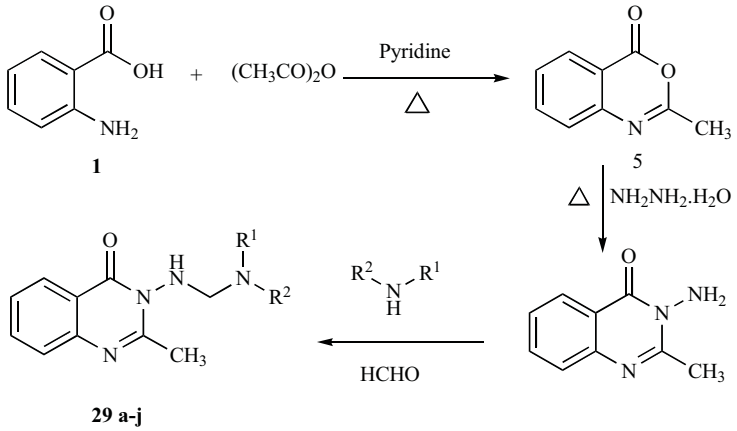
Scheme 9. "Solid-phase synthesis of pyrazino[2,1-b]quinazoline-3,6-diones", **26**; Optimized conditions: a) Anthranilic acid, DMF, HOBT/ HBTU, DIEA, 2h, b) 20% piperidine, 20 min, c) Fmco-amino acid chloride, DIEA, $CHCl_3$,2h, d) $Zn(oTf)_2$, DMF, 140^{0}C, 30-90 min.



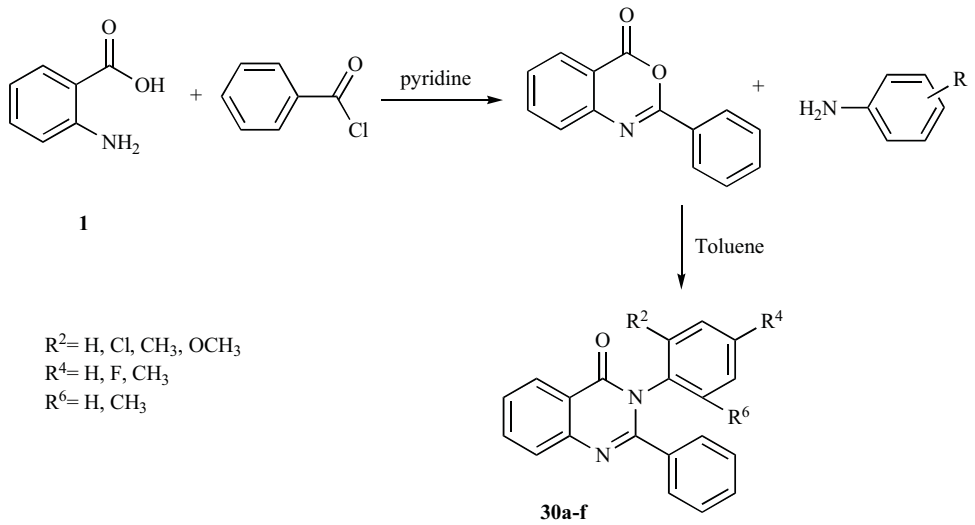
27
27-epi-tryptoquivaline
($C_{29}H_{30}N_4O_7$)

28
27-epi-nor-tryptoquivaline
($C_{28}H_{28}N_4O_7$)

Scheme 10. "Tryptoquivaline analogs".



Scheme 11. "Synthesis of 2-methyl-3-(substituted methylamino)-(3H)-quianzolin-4-ones", **29**a-j**,** Optimzed conditions: a) Acetic anhydride,pyridine, reflux, 4h, b) $NH_2NH_2.H_2O$, reflux, c) R^1NHR^2, HCHO, reflux, 4h: R^1= dimethyl, diethyl, pyrrolidinyl, morpholinyl, piperazinyl, phenyl, 4-carboxyphenyl, 4-sulphonamido phenyl, pyridi-2-yl, benzimidazole-1-yl, R^2= H, Methyl.



Scheme 12. "Synthesis 2-phenyl-3-(substituted phenyl)-3H-quinazolin-4-ones", **30**, optimized conditions: a) benzoyl chloride, pyridine, reflux, 3h, b) aromatic amines, toluene, reflux, :R^2 = H, Cl, CH_3, OCH_3; R^4= H, F, CH_3; R^6= H, CH_3.

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