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Synthesis, reactions and applications of naphthofurans: A review

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REVIEW ARTICLE

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ABSTRACT

Considering the highly important biological and medicinal properties of naphthofurans, the synthesis of these heterocycles has attracted the interest of medicinal and organic chemists. This review aims to describe the different strategies developed so far for the synthesis of naphthofurans and their applications and the literature reports for the period of 2000 to early 2020. After a brief introduction of the types of naphthofurans and their biological activities, the different synthetic approaches such as chemical and photochemical, methods are described and organized on the basis of the catalysts and the other reagents employed in the syntheses. Some of the reactions have been applied successfully to the synthesis of biologically important compounds.

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1. Introduction

Naphthofuran is a bicyclic organic compound that results from the fusion of a naphthalene ring to a heterocyclic furan ring [1]. Naphthofuran nuclei are key structural moieties found in a large number of biologically important natural products [2,3]. Therefore, the synthesis of various derivatives of naphtho [2,1-b]furan was taken up in our laboratory [1-4] in search of new biologically and pharmacologically active heterocyclic compounds. Many of the natural naphthofurans, such as (±)-Laevigatin [5,6] (**1**), (+)-Heritol [7-9] (**2**) and Balsaminone A, [10] (**3**), (Figure 1) possess interesting pharmacological and cytotoxic properties. Several synthetic compounds containing this ring skeleton are associated with diverse biological activities such as antifungal, antibacterial [11,12], antiviral [13], antitumor [14], anthelmintic [15], anti-trypanosomal and cytotoxicity [16]. The nitro derivatives of naphtho[2,1-b]furans have been extensively studied for their mutagenic activities, for example, 7-methoxy-2-nitronaphtho[2,1-b]furan (**4**), the genotoxicity of (R7000) as well as that of other nitrofurans, is due to the presence of the nitro group, actively reduced in bacteria by endogenous nitroreductases, (R7000) is one of the strongest mutagens described for mammalians.

Naphthofuran derivatives have been isolated from various natural sources like *Fusarium Oxysporum* [16] and *Gossypium barbadense* [17]. The Maturin and maturing were isolated from the roots of *Cacalia* decomposition [18]. Later, another group of authors [19-21] isolated the natural analogs of the naphthofurans from the roots of *Senecio Canescens*, one was identified as naphtho[1,2-*b*]furan-4,5-dione (**5**), and the other two tentatively as 3-hydroxynaphtho[1,2-*b*]furan-4,5-dione (**6**) and 2-(2-hydroxypropan-2-yl)naphtho[1,2-*b*]furan-4,5-dione (**7**) (Figure 2).

Dehydrocacalohastine (**8a**) was isolated from wild-growing *Cacalia Hastata* in 1973 [22,23]. This compound is also found in young green leaves or roots of plants of the Senecio genus of the daisy family such as *Senecio Canescens* [24,25], *Senecio Macrospermus* [26], *Senecio Lydenburgensi* [27], and *Senecio Crispus* [28]. In addition to dehydrocacalohastine (**8a**), hydroxy- (**8b**) and acetoxydehydrocacalohastines (**8c**) [25], dehydrocacalohastinol (**8d**) [28], methoxydehydro-cacalohastine (**8e**) [26], and naphtho[2,3-b]furans **8f-9a**,**b** [27] were also isolated from these plants (Figure 3).

Recently, naphtho[2,3-b]furan (**10**) [29] was isolated from the roots of *Ligularia Veitchiana* found in China, and Avicenol B (**11**) was isolated from the bark of *Avicennia alba Blume* [30] (Figure 4).

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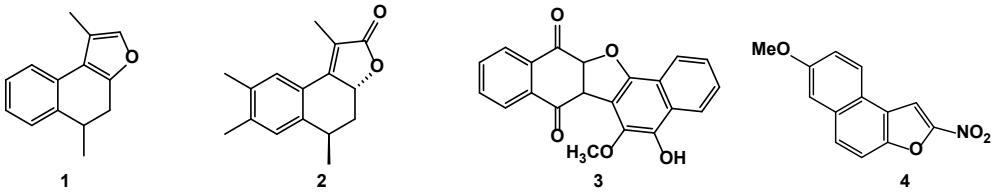


Figure 1. Examples of biological, pharmacological of naphthofurans.

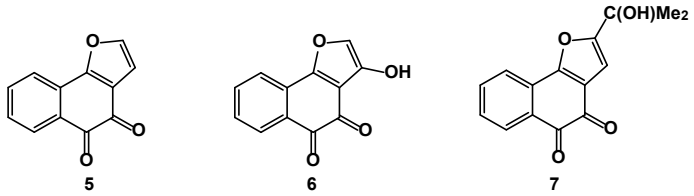
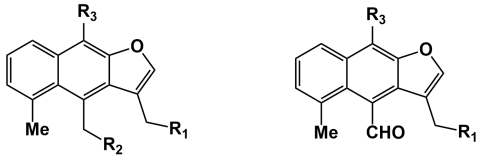


Figure 2. Naphtho[1,2-*b*]furan-4,5-dione derivatives.



8a-f

a) R_1 = H, R_2 = H, R_3 = OMe
b) R_1 = OH, R_2 = H, R_3 = OMe
c) R_1 = OAc, R_2 = H, R_3 = OMe
d) R_1 = H, R_2 = OH, R_3 = OMe
e) R_1 = H, R_2 = OMe, R_3 = OMe
f) R_1 = H, R_2 = OAc, R_3 = COOEt

9a-b

a) R_1 = OH
b) R_1 = OAc

Figure 3. Cacalohastine derivatives.

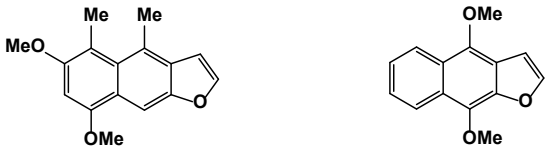


Figure 4. Naphtho[2,3-b]furan derivatives.

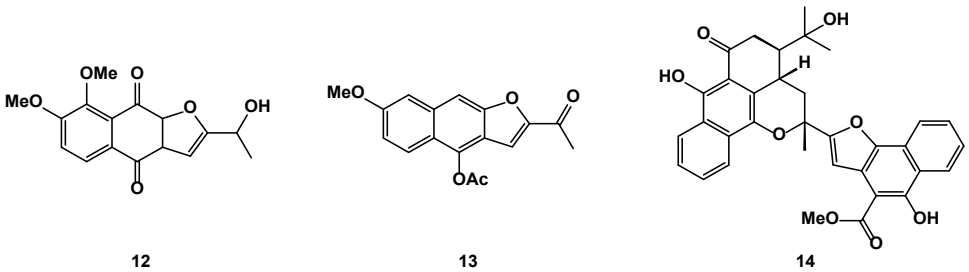


Figure 5. Structures of naphthofuroquinones **12**-**14**.

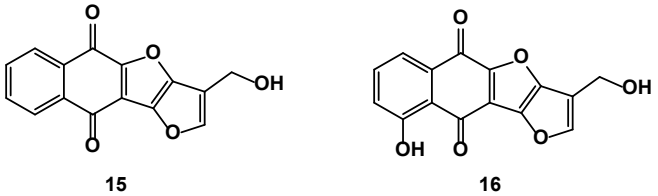
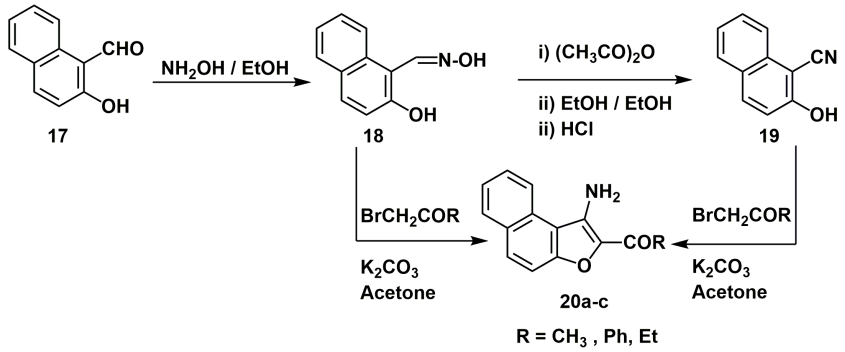
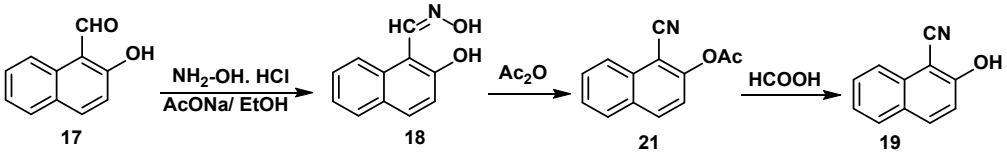


Figure 6. Structure of naphtho[2,3-*d*]furan-5,10-diones.

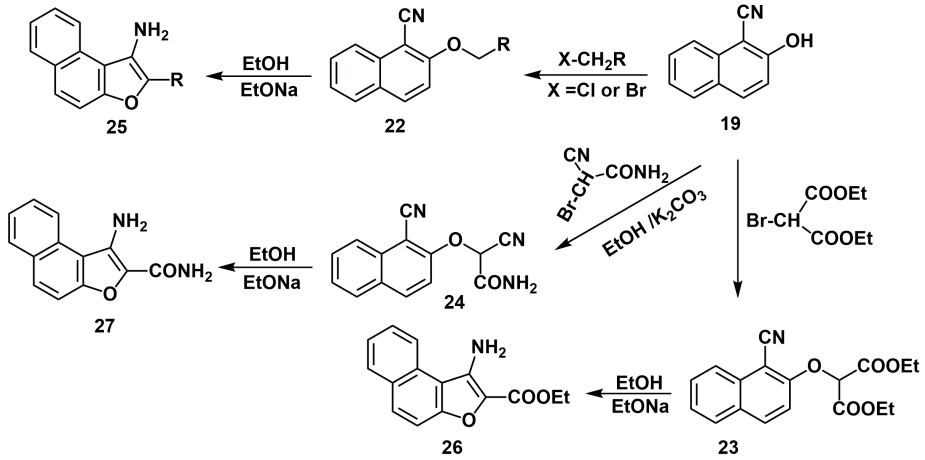
Various natural naphthofuroquinones are present in *Tabebuia Ochace* [31,32]. Derivatives of naphthofuroquinones (**12** and **13**) exhibit higher inhibitory activity [33,34] and compound **14**, which contains naphthofuran as one of the constituents [35,36] found in the Chinese medicinal plant *Rubiacordifolia* (Figure 5).



Scheme 1. Synthesis of aminonaphthofuran derivatives.



Scheme 2. Synthesis of 1-cyano-2-naphthol.



Scheme 3. Synthesis of 3-aminonaphthofurans.

During an investigation into potentially useful anticancer agents from the wood of *Crescentia Cujete*, Kingston and co-workers isolated a series of nine related furofuranonaphtho-quinone derivatives [37,38]. Of particular interest are two tetracyclic naphthoquinones, which were isolated as red pigments and assigned structures 3-hydroxy-methylfuro[3,2-*b*] naphtho[2,3-*d*]furan-5,10-dione (**15**) and 9-hydroxy-3-hyd roxymethylfuro[3,2-*b*]naphtho[2,3-*d*]furan-5,10-dione (**16**) on the basis of extensive spectroscopic analysis [39,40] (Figure 6).

2. Synthesis of naphthofurans

2.1. From 2-hydroxy-1- naphthaldehyde

Conversion of 2-hydroxy-1-naphthaldehyde (**17**) [41-43] into its oxime (**18**) [44] followed by dehydration using acetic anhydride, to obtain 2-hydroxy-1-naphthonitrile (**19**) [44]. The compounds **18** and **19** on reaction with bromoacetone/ phenacyl bromide or ethyl bromoacetate in presence of K_2CO_3 produced 1-(1-aminonaphtho[2,1-*b*]furan-2-yl)ethan-1-one (**20a**) or (1-aminonaphtho[2,1-*b*]furan-2-yl)(phenyl)metha-none (**20b**) and 1-(1-aminonaphtho[2,1-*b*]furan-2-yl)propan-1-one (**20c**) (Scheme 1).

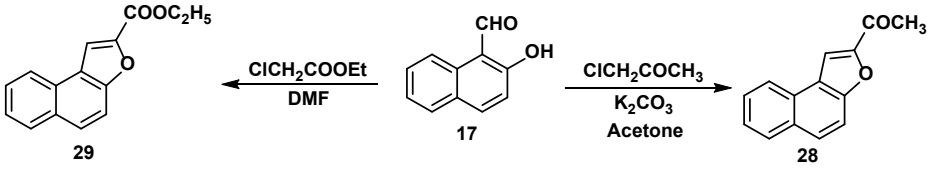
Also, 2-hydroxynaphthalene-1-carbaldehyde (**17**) when allowed to react with hydroxylamine hydrochloride in the presence of fused sodium acetate yielded the corresponding oxime (**18**) which was acetylated using acetic anhydride to give 2-acetyloxynaphthalene-1-carbonitrile (**21**) [45]. Treatment of compound **21** with formic acid yielded 1-cyano-2-naphthol (**19**), Scheme 2.

Alkylation of 1-cyano-2-naphthol (**19**) using different activated halogenated compounds, namely chloroacetonitrile, chloroacetone, phenacyl bromide and its derivatives in acetone and the presence of potassium carbonate, *o*-alkylated products (**22**-**24**) were produced, that underwent ring closure by sodium ethoxide to afford the corresponding naphthofurans **25**-**27** (Scheme 3).

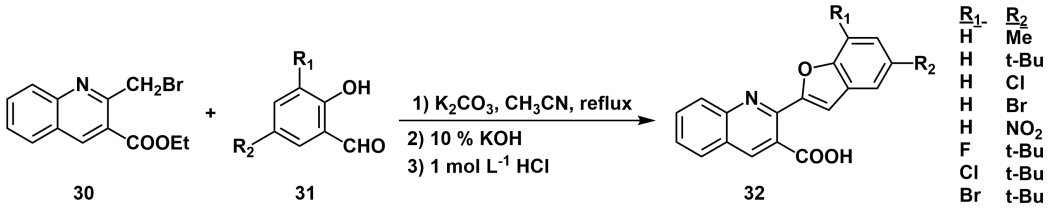
In addition, thus, treatment of 2-hydroxy-1-naph-thaldehyde (**17**) with chloroacetone in refluxing acetone in the presence of anhydrous potassium carbonate gave the 2-acetylnaphtho[2,1-b]furan (**28**) and ethyl naphtho-[2,1-*b*] furan-2-carboxylate (**29**) was prepared by treating 2-hydroxy-1-naphthaldehyde (**17**) with ethyl chloroacetate in presence of potassium carbonate in dimethylformamide (Scheme 4).

2.2. From various substituted salicylaldehyde

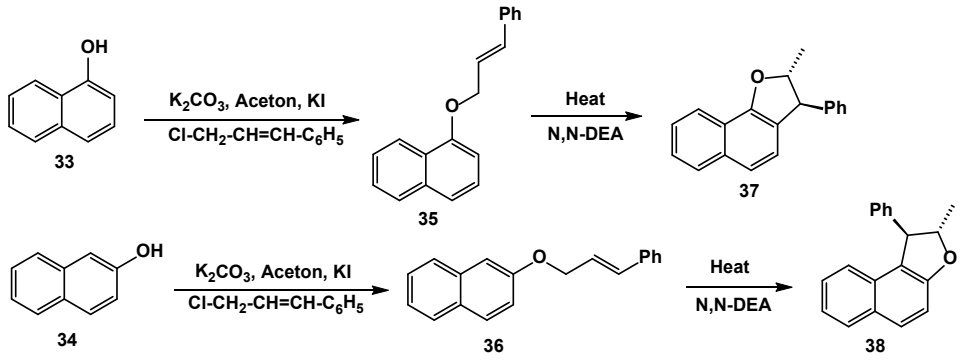
The preparation of novel 2-(1-benzofuran-2-yl)quinoline-3-carboxylic acid derivatives (**32**), involving the in situ formation of ether by Williamson reaction between ethyl 2-(bromomethyl)quinoline-3-carboxylate (**30**) and various substituted salicylaldehyde (**31**) followed by the hydrolysis and



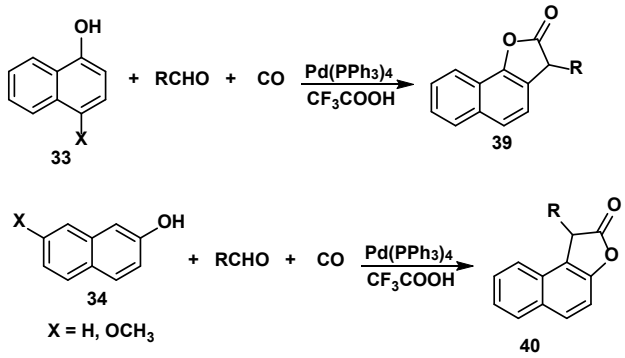
Scheme 4. Synthesis of 2-acetyl or ethyl carboxylate naphtho[2,1-*b*]furan.



Scheme 5. Synthesis of 2-(1-benzofuran-2-yl)quinoline-3-carboxylic acid derivatives.



Scheme 6. Synthesis of 3-phenyl naphthofurans.



Scheme 7. Synthesis of alkyl naphthofuran-2(3*H*)-one.

intramolecular cyclization reactions. This novel procedure provides quick and easy access to the incorporation of the benzo[b]furan core to the quinoline nucleus at 2-position (Scheme 5) [46].

2.3. From 1-naphthol or 2-naphthol

Treatment of 1-naphthol or 2-naphthol (**33** and **34**) with alkenyl or propargyl halide gave the corresponding naphthyl ether **35** and **36** by the known methods [47,48], heating in *N*,*N*-diethyl aniline afforded naphthofurans **37** and **38** (Scheme 6).

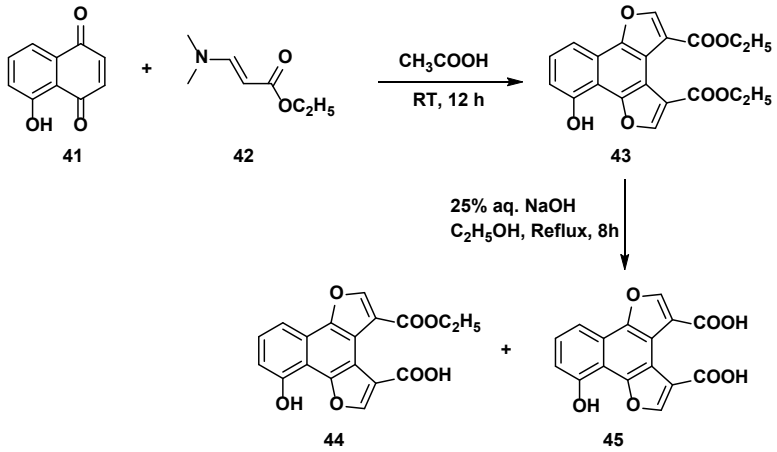
The present three-components reaction may involve the initial nucleophilic addition of naphthol (**33** and **34**) to aldehyde, which may be promoted by CF_3COOH in C_6H_6 (5 mL) under CO (5 atm) at 120 °C for 18 h to give naphthofuran-2(3*H*)-one (**39** and **40**) (Scheme 7) [49].

2.4. From 5-hydroxy-1,4-naphthoquinone

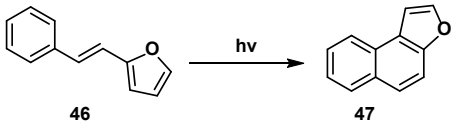
5-Hydroxy-1,4-naphthoquinone (**41**) was reacted with ethyl-*N*,*N*-dimethyaminocrylate (**42**), which afforded novel diethyl-7-hydroxynaphtho[1, 2-*b*:4, 3-*b*`]difuran-3,4-dicarboxy late (**43**). Hydrolysis of compound **43** of lead to formation of two novel derivatives *viz*. 4-ethoxycarbonyl-7-hydroxynaphtho[1, 2-*b*:4, 3-*b*`]difuran-3-carboxylic acid (**44**) and 7-hydroxy naphtho[1, 2-*b*:4, 3-*b*`]difuran-3,4-dicarboxylic (**45**) due to partial and complete hydrolysis of both the ester (Scheme 8) [50].

2.5. From 2-styrylfuran

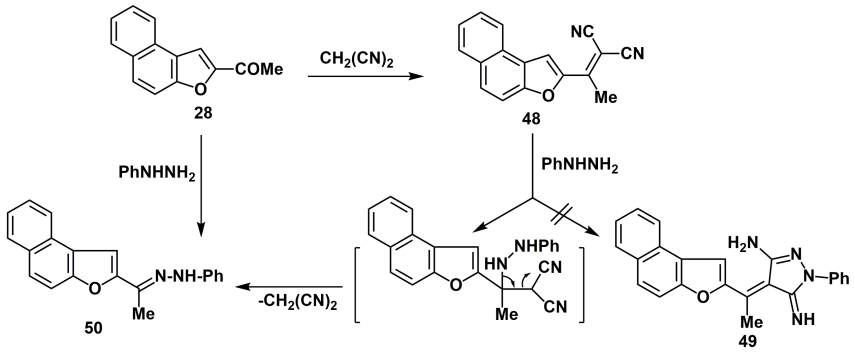
Loader and Timmons [51] synthesized naphtho[2,1-*b*]furan (**47**) by photo cyclodehydrogenation of 2-styrylfuran in pure form **46** (Scheme 9).



Scheme 8. Synthesis of naphtho[1,2-*b*:4,3-*b*`]difurans.



Scheme 9. Synthesis of naphtho[2,1-*b*]furan.



Scheme 10. Condensation of 2-acetylnaphtho[2,1-b]furan.

3. Reaction of naphtha[2,1-*b*]furan

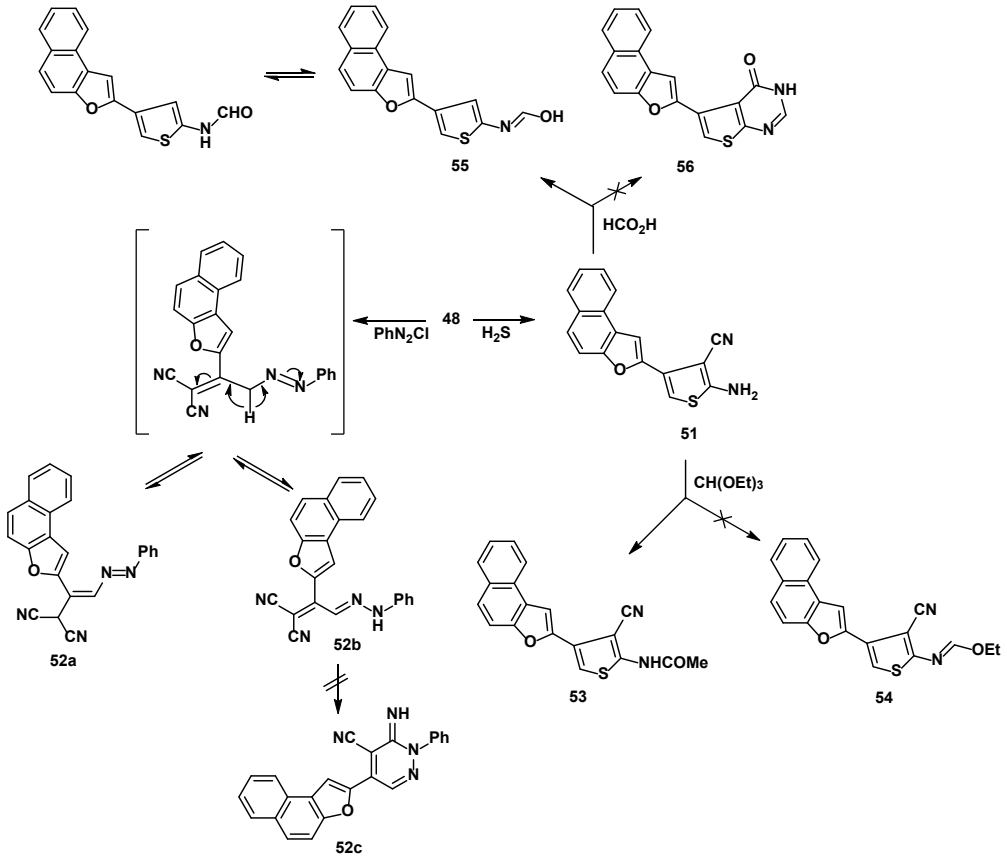
Condensation of 2-acetylnaphtho[2,1-*b*]furan (**28**) [52] with malononitrile in boiling benzene containing ammonium acetate and acetic acid afforded 2-(2,2-dicyano-1-methyl vinyl) naphtho[2,1-*b*]furan (**48**) In contrast to the anticipated formation of pyrazoline derivatives **49**, the reaction of compound **28** with phenyl hydrazine in boiling ethanol gave the imino compound **50** and is assumed to proceed via elimination of malononitrile (Scheme 10).

Interaction of compound **48** with sulfur via Gewald reaction [53] produced 2-(5-amino-4-cyano-3-thienyl)naphtho[2,1-*b*] furan (**51**) while with benzene diazonium chloride afforded the open-chain product **52a** instead of the closed product 2,3-dihydro-3-imino-5-(naphtho[2, 1-*b*]furan-2-yl)-2-phenylhydrazine-4-carbonitrile (**52c**). Treatment of compound **51** with triethyl orthoformate in acetic anhydride at reflux afforded the *N*-acetylamino derivative **53** instead of the 2-(5-ethoxy methyleneamino-4-cyano-3-thienyl)naphtho[2,1-*b*]furan (**54**) [52], while with formic acid gave the *N*-formyl amino derivative **55** instead of the pyrimidine derivative **56** (Scheme 11).

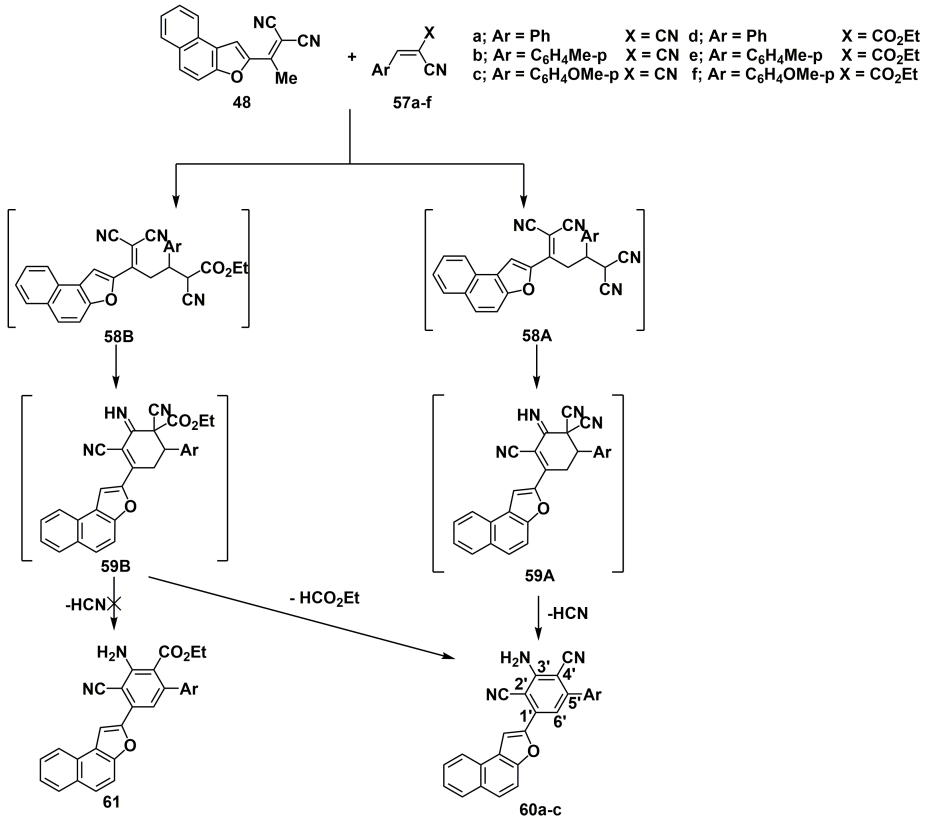
Interaction of compound **48** with various substituted α-cyanocinnamonitriles (**57a-f**) in boiling ethanol containing a few drops of piperidine, afforded 2-(3-amino-2,4-dicyano-5-arylphenyl)naphtho[2,1-*b*]furan (**60a-c**) (Scheme 12). The formation of compound **60** from the reaction of compounds **48** and **60a-c** is assumed to proceed via a Michael type addition of the methyl function in compound **28** to the activated double bond to yield a cyclic Michael adduct **58a** which then cyclizes into compound **59a**. The latter readily loses HCN to yield the final isolable thermodynamically stable compounds (**60a-c**) (Scheme 12). In contrast to the anticipated formation of the esters **61**, the reaction of compound **34** with various substituted ethyl α-cyanocinnamates (**59d-f**), afforded compounds **60a-c** and are assumed to proceed via elimination of ethyl formate from the intermediate (**60b**) [52] (Scheme 12).

Thus, chalcone **62** was prepared by condensation of compound **28** with *p*-anisaldehyde in the presence of dry HCl gas in ethanol, while bromination of compound **62** afforded 3-[(3-bromo-4-methoxyphenyl)naphtho[2, 1-*b*]furan-2-yl]prop-2-en-1-one (**63**) (Scheme 13). The bromine was introduced in the active aryl moiety rather than the α, β-unsaturated double bond.

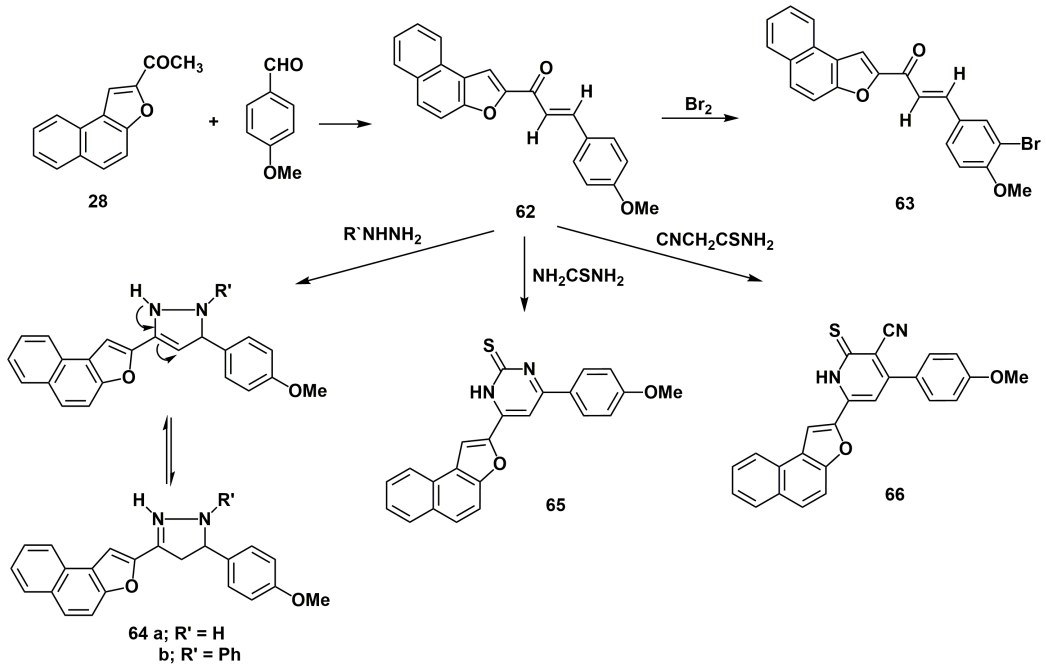
Treatment of the chalcone **63** with hydrazine hydrate and phenyl hydrazine in refluxing ethanol afforded 5-(4-methoxy phenyl)-3-(naphtho[2, 1-*b*]furan-2-yl)-4, 5-di-hydro-1*H*-pyrazole (**64a**) and 5-(4-methoxyphenyl)-3-(naphtho[2,1-*b*]furan-2-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazole (**64b**), respectively (Scheme 12), while with thiourea or cyanothioacetamide gave 4-(4-methoxyphenyl)-6-(naphtho[2, 1-*b*]furan-2-yl)pyramidine-2(1*H*)-thione (**65**) and 1,2-dihydro-4-(4-methoxyphenyl)-6-(naphtho[2, 1-*b*]furan-2-yl)-2-thioxopyridine-3-carbonitrile (**66**), respectively (Scheme 13) [52].



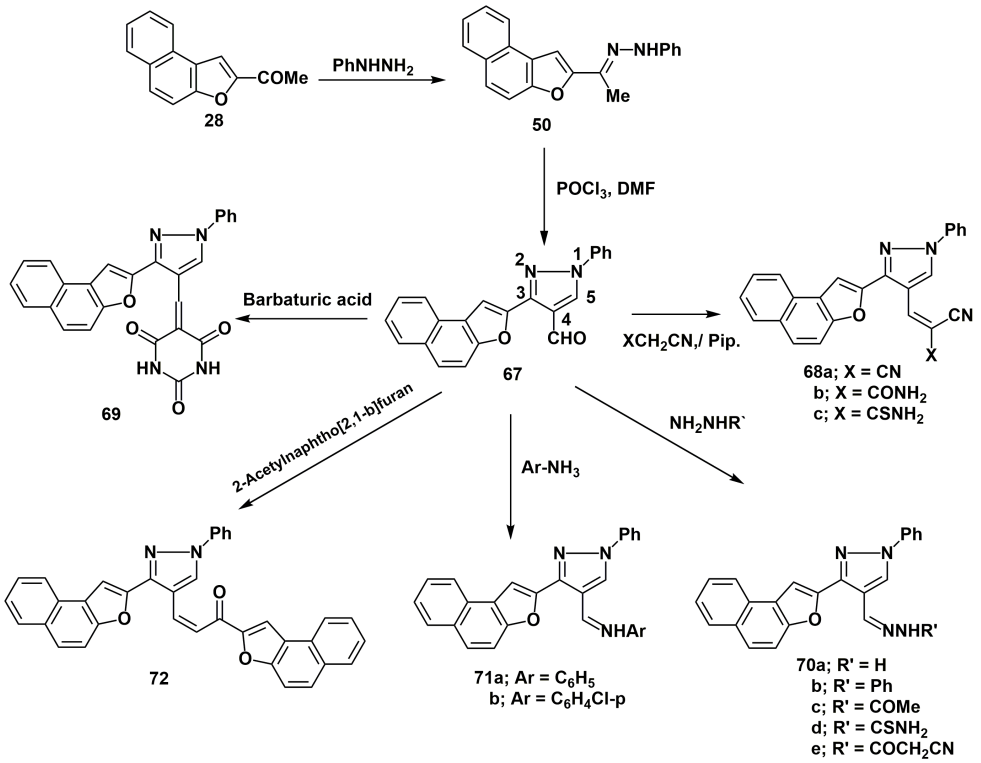
Scheme 11. Reaction of 2-acetylnaphtho[2,1-*b*]furan with sulfur via Gewald reaction, benzene diazonium chloride, and triethyl orthoformate.



Scheme 12. Reaction of 2-acetylnaphtho[2,1-*b*]furan with various substituted α-cyanocinnamonitriles.



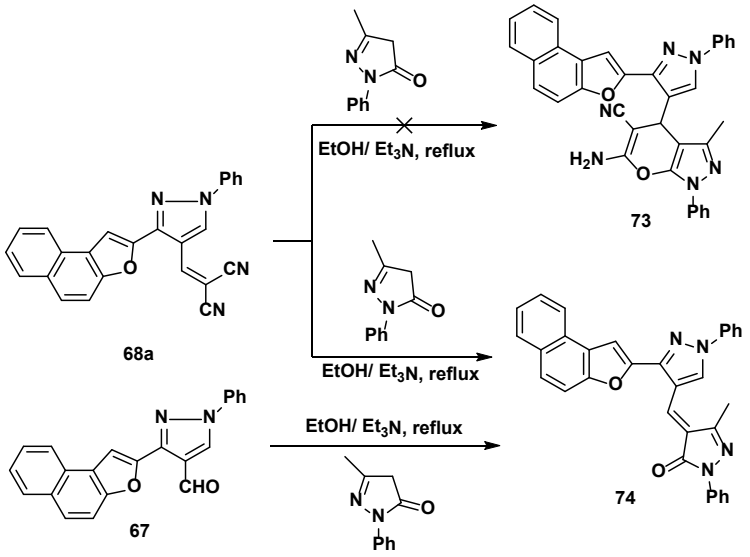
Scheme 13. Synthesis of naphtho[2,1-b]furan-2-yl)-pyrazole and naphtho[2,1-b]furan-2-yl)-thioxopyridine.



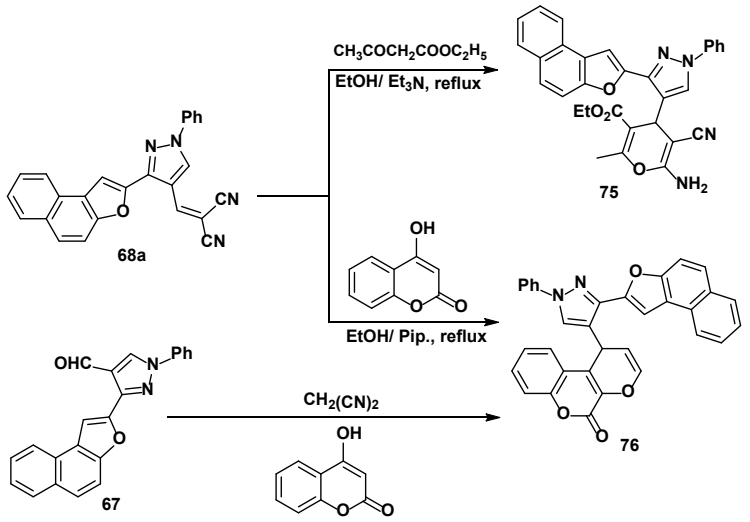
Scheme 14. Condensation reaction of 2-acetylnaphtho[2,1-b]furan.

Condensation of 2-acetylnaphtho[2,1-*b*]furan (**28**) [52] with phenylhydrazine afforded 2-(1-phenylhydrazonoethyl) naphtho[2,1-*b*]furan (**50**). Vilsmeier formylation of the latter afforded 3-(naphtho-[2,1-*b*]furan-2-yl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (**67**) [54]. Condensation of compound **67** with C-nucleophiles, namely, malononitrile, cyanoacetamide, cyanothioacetamide, barbaturic acid and 2-acetylnaphtho[2,1-*b*]furan (**28**) give the condensation products **68**, **69** and **70** while with *N*-nucleophiles namely; hydrazine derivatives or amines afforded the condensation products **71** and **72** (Scheme 14) [55].

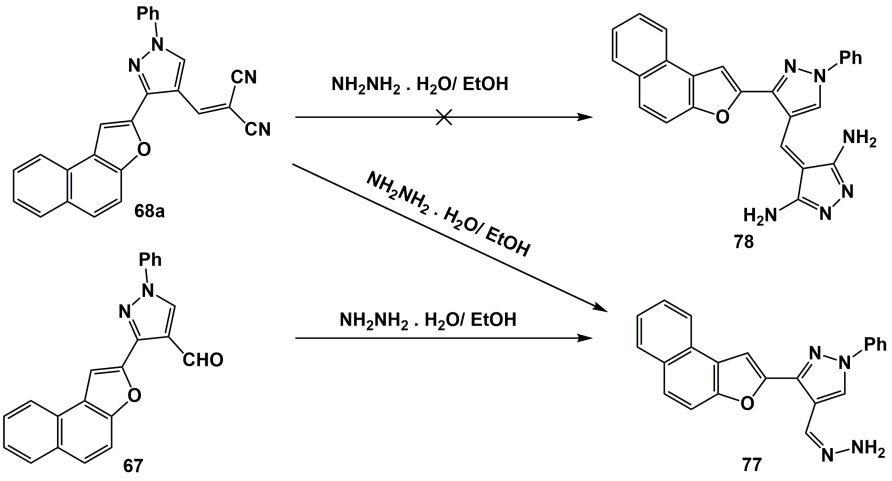
Compounds **68a** and **70d** were used as key intermediates in the synthesis of pyran, pyrazole, and thiazole derivatives via their interaction with different reagents. Thus, the reaction of compound **68a** with 3-methyl-1-phenyl-2-pyrazolin-5-one in the presence of triethylamine did not give the expected pyrazolopyran **73**. Instead, only one compound was isolated, which was identified as 4-[3-(naphtho[2,1-*b*]furan-2-yl)-1-phenyl-1*H*-pyrazol-4-yl]methylene-3-methyl-1-phenyl-2-pyra zoline-5-one (**74**). Condensation of compound **67** with methyl-1-phenyl-2-pyrazolin-5-one in the presence of triethylamine to give compound **74** (Scheme 15) [55].



Scheme 15. Synthesis of naphthofuranopyrazole derivatives.

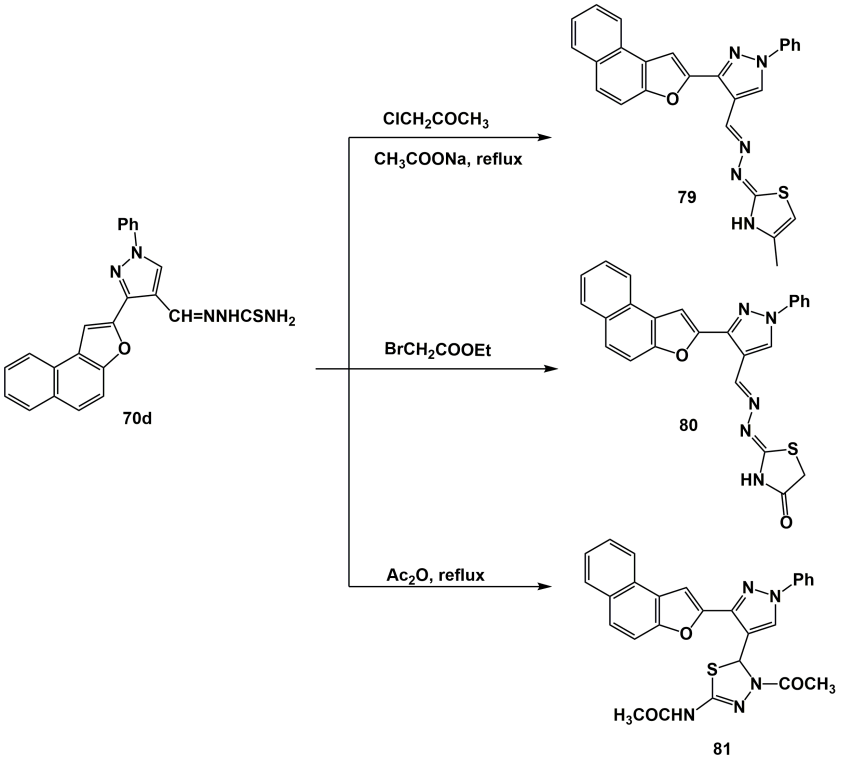


Scheme 16. Synthesis of pyrazolo pyran derivatives.

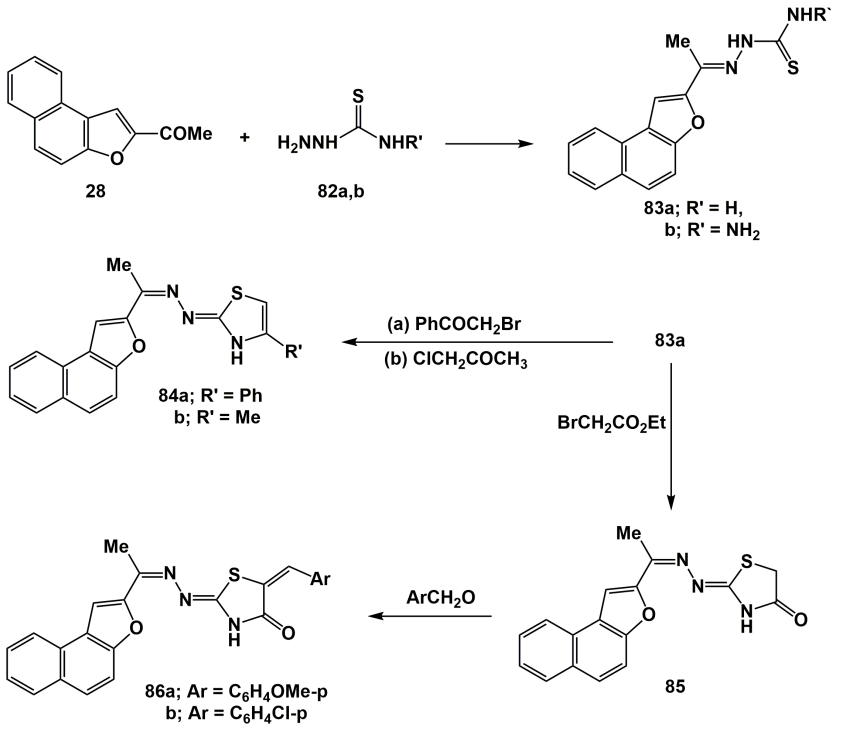


Scheme 17. Synthesis of 1-((3-(naphtho[2,1-*b*]furan-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazone.

The reaction of compound **68a** with ethyl acetoacetate in dry methylene chloride containing triethylamine gave the pyrazolopyran derivative **75**, while with 4-hydroxycoumarin under Michael reaction conditions afforded the 4*H*-pyran derivative **76**. Structure **76** was further confirmed by independent synthesis via direct condensation of compound **67**



Scheme 18. Synthesis of thiazolidinone, thiazoline, and thiadiazole derivatives.

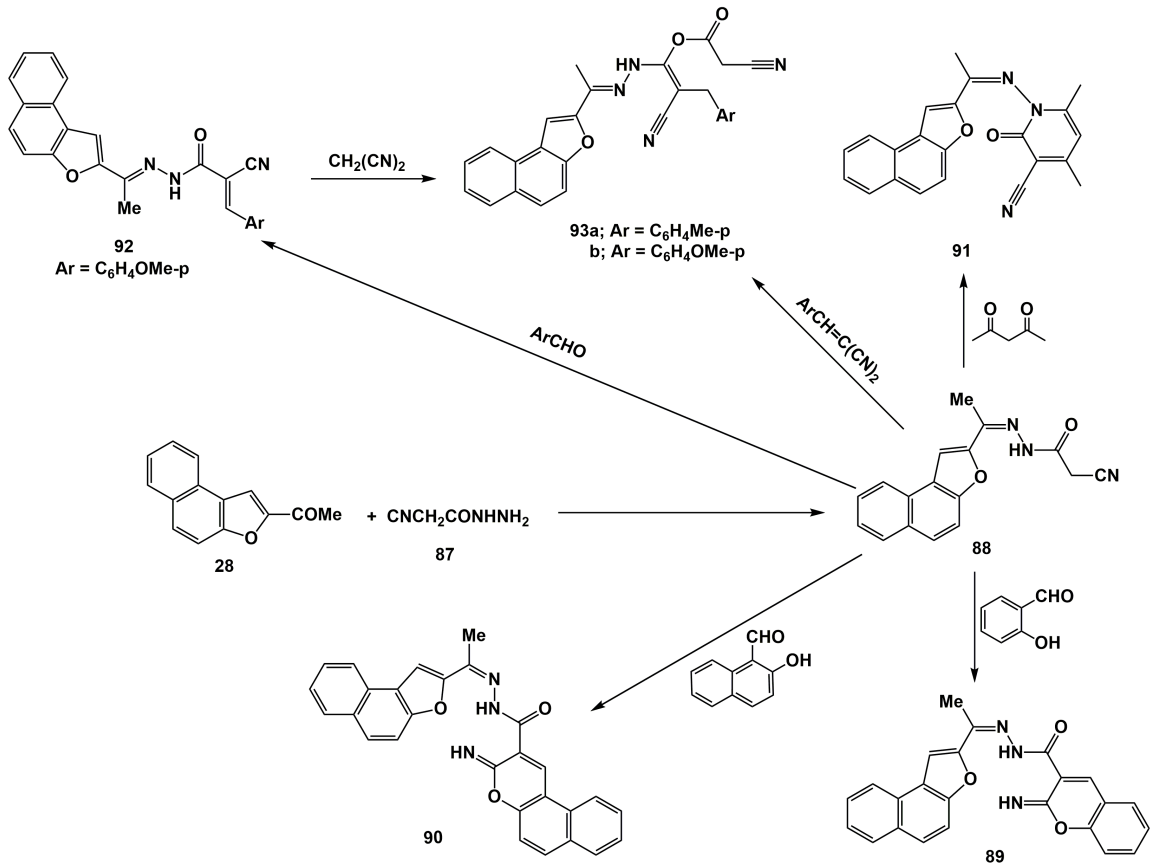


Scheme 19. Synthesis of thiosemicarbazone, thiazole and arylidene derivatives.

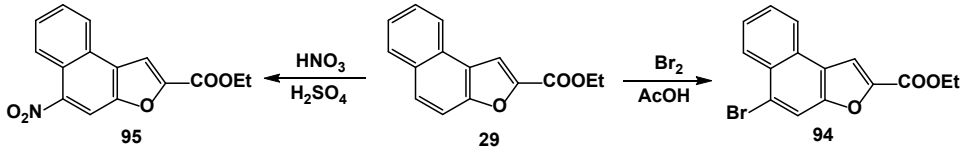
with 4-hydroxycoumarin in the presence of malononitrile and drops of piperidine as a base (one-pot reaction) (Scheme 16) [55].

The reaction of compound **68a** with hydrazine hydrate in refluxing ethanol afforded 1-((3-(naphtho[2,1-*b*]furan-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazone **77** instead of the pyrazole derivative **78**. The same product was prepared by condensation of compound **67** with hydrazine hydrate (Scheme 17).

When thiosemicarbazone derivative **70d** was allowed to react with ethyl bromoacetate or chloroacetone in the presence of fused sodium acetate, gave the corresponding thiazolidinone and thiazoline derivatives **79** and **80**, respectively, while with acetic anhydride by reflux afforded the thiadiazole derivative **81** (Scheme 18) [55].



Scheme 20. Synthesis of acetohydrazide, chromene, and pyridine derivatives.



Scheme 21. Bromination and nitration of naphthofuran.

Condensation of 2-acetylnaphtho[2,1-*b*]furan (**28**) with thiosemicarbazide or thiocarbohydrazide (**82a**,**b**) afforded the thiosemicarbazone or thiocarbohydrazone **83a**,**b**, respectively. The thiosemicarbazone **83a** was used as a key intermediate in the synthesis of the desired thiazoles via their interaction with different α-halo carbonyl derivatives. Thus, the reaction of compound **83a** with phenacyl bromide and/or chloroacetone in refluxing ethanol in the presence of sodium acetate afforded the thiazole derivatives (**84a**,**b**), respectively, while with ethyl bromoacetate afforded thiazolidin-4-one (**85**). Condensation of thiazolidin-4-one (**85**) with *p*-methoxybenzaldehyde and/or *p*-chlorobenzaldehyde in ethanol containing piperidine as a base gave arylidene derivatives (**86a**,**b**), respectively (Scheme 19) [55].

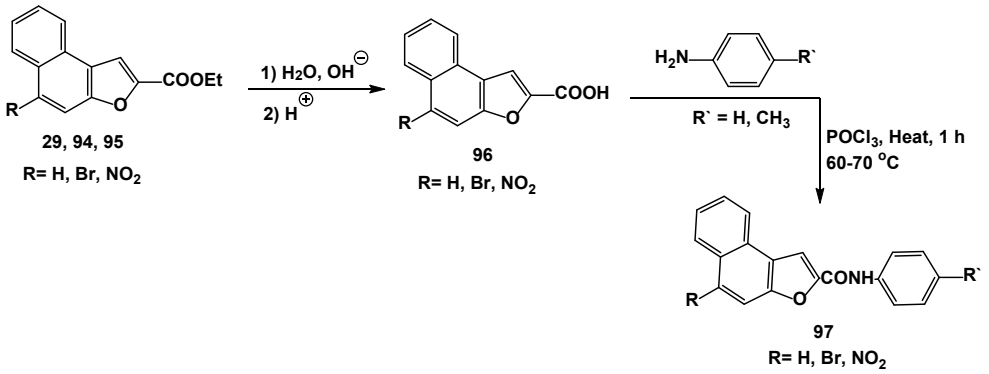
Condensation of compound **28** with cyanoacetohydrazide (**87**) afforded 2-cyano-*N*-[1-(naphtho[2,1-*b*]furan-2-yl)ethyli dene]acetohydrazide (**88**). Interaction of compound **88** with salicyaldehyde or 2-hydroxy-1-naphthaldehyde afforded the chromene derivatives **89** and **90**, while with acetylacetone gave the pyridine derivative **92**. Condensation of compound **89** with *p*-methoxy benzaldehyde afforded the arylidene derivatives **92**. Reaction of arylidene **92** with malononitrile afforded the pyranone derivative **93**. The structure **93** was further confirmed by independent synthesis via direct condensation of compound **88** with *p*-methoxy α-cyano-cinnamonitrile in refluxing ethanol/piperidine (Scheme 20) [56].

Bromination of compound **29** to give ethyl 5-bromonaphtho[2,1-*b*]furan-2-carboxylate (**94**) and nitration of compound **26** afforded 5-nitronaphtho[2,1-b]furan-2-carboxylate (**95**) (Scheme 21) [57].

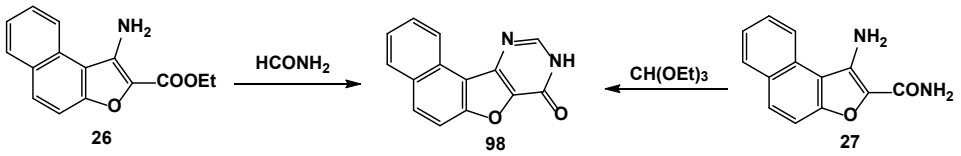
These esters (**29**, **94,** and **95**) were hydrolyzed in an alkaline medium to obtain their respective carboxylic acids (**96**). The resulting carboxylic acids were then warmed with 4-substituted aromatic amines, employing phosphorus oxychloride on a water bath maintained at 40-45 °C to yield 5-substituted-nahtho[2,1-*b*] furanoy1-4- substituted aromatic amines (**97**) (Scheme 22) [57].

Ethyl 3-aminonaphtho[2,1-*b*]furan-2-carboxylate **26** was reacted with formamide to afford naphtho[1',2':4,5]furo[3,2-*d*] pyrimidin-4(3*H*)-one (**98**) [58]. Later, the compound was obtained by an alternative route through the condensation of 3-aminonaphtho[2,1-*b*]furan-2-carboxamide (**27**) with triethyl orthoformate in the presence of catalytic amount of acetic acid (Scheme 23).

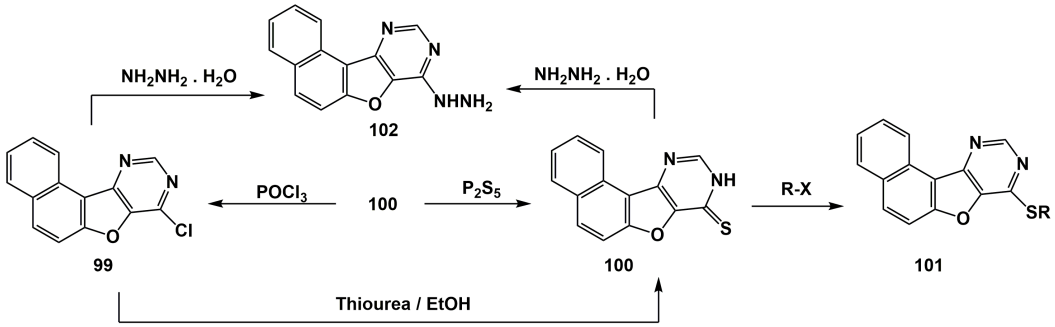
Compound **98** can be converted into 4-chloropyrimidine derivative (**99**) by refluxing with phosphorus oxychloride. Naphtho[1',2':4,5]furo[3,2-d]pyrimidin-4(3*H*)-thione (**100**) was prepared by two methods, either by thionation of compound **98** using phosphorus pentasulfide in pyridine or by the reaction of chloropyrimidine derivative **100** with thiourea in ethanol.



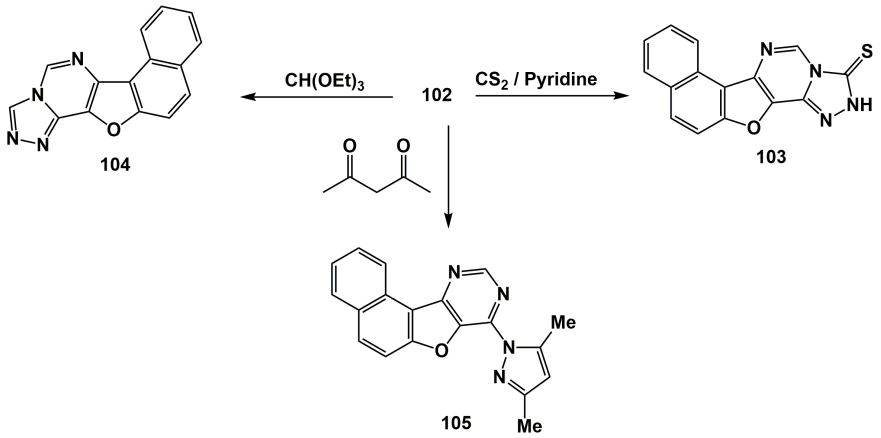
Scheme 22. Synthesis of nahtho[2,1-*b*] furanoy1-4-substituted aromatic amines.



Scheme 23. Synthesis of naphtho[1',2':4,5]furo[3,2-d] pyrimidin-4(3*H*)-one.



Scheme 24. Synthesis of naphtho[1',2':4,5]furo[3,2-d]pyrimidine derivatives.

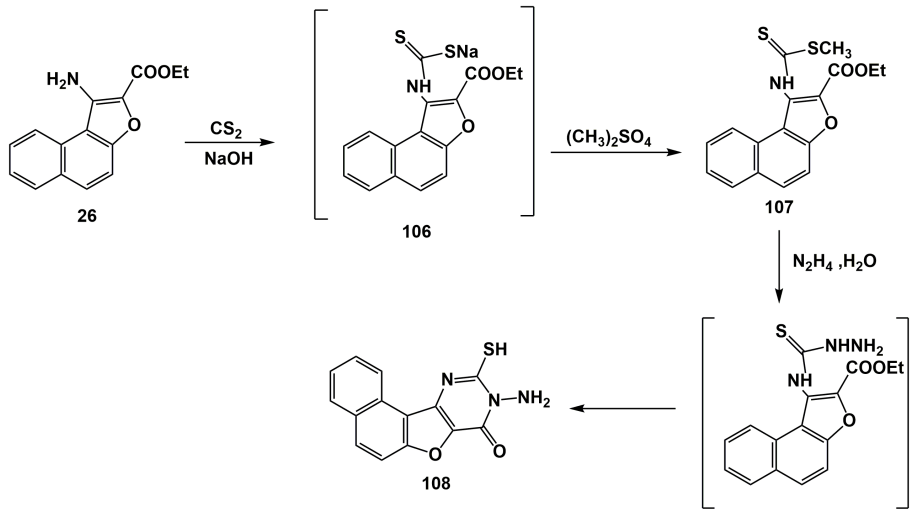


Scheme 25. Synthesis of naphthofuroriazolopyrimidine and pyrazolylnapthofuropyrimidine.

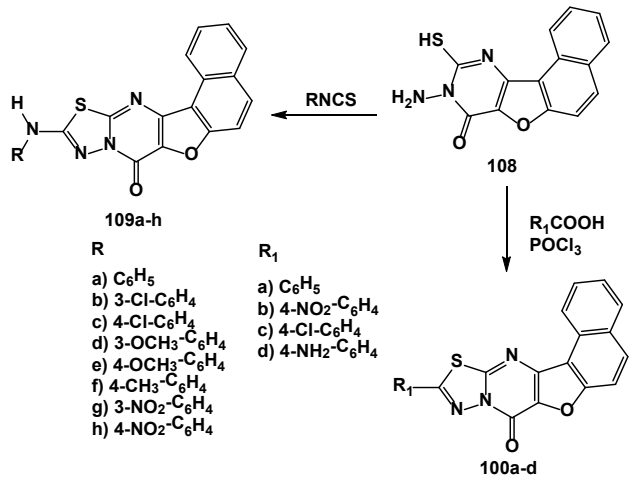
The produced naphthofuropyrimidinthione was S-alkylated using different halo compounds in ethanol in the presence of sodium acetate to afford S-alkylated derivative **101**. Reaction of compounds **99** and **100** with hydrazine hydrate to give 8-hydrazineylnaphtho[1', 2':4, 5]furo[3, 2-d]pyrimidine **102** (Scheme 24).

4-Hydrazinonaphthofuropyrimidine (**102**) was used as a versatile precursor to synthesis other heterocyclic compounds. It reacts with CS_2/Pyridine or triethyl orthoformate in the presence of catalytic drops of acetic acid to afford naphtho [1', 2':4, 5]furo[2, 3-e][1, 2, 4]triazolo[4, 3-c]pyrimidine-3(2*H*)-thione (**103**) and naphthofurotriazolopyrimidine **104**. On the other hand, when compound **102** was allowed to react with acetylacetone in ethanol, pyrazolylnapthofuropyrimidine **105** was produced (Scheme 25).

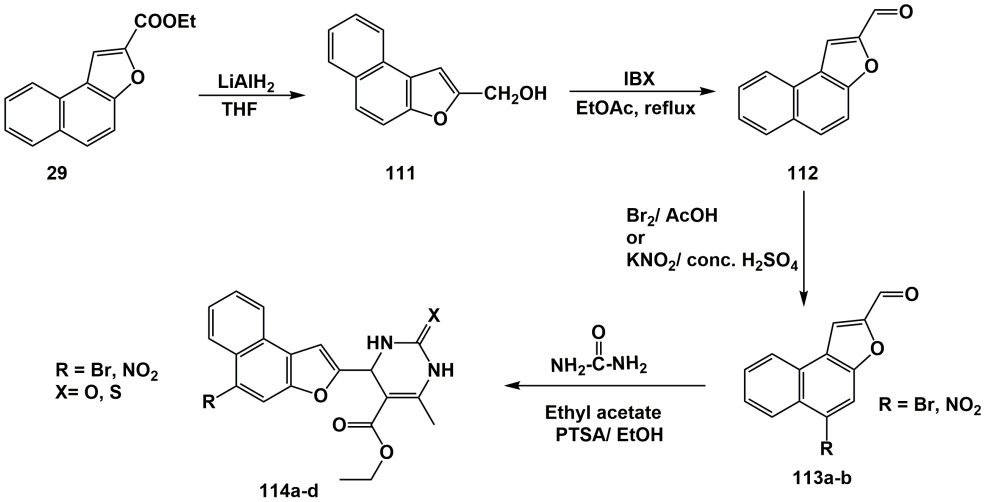
Thus, treatment of ethyl 3-aminonaphtho[2,1-b]furan-2-carboxylate (**26**) [59] with carbon disulphide and aqueous sodium hydroxide in dimethyl sulphoxide yielded a naphtho [2,1-b]furan-2-carboxylate (**106**) as a salt, which (without isolating) was then methylated with dimethyl sulphate to afford naphtho[2,1-b]furan-2-carboxylate (**107**). Compound **107** on reaction with hydrazine hydrate yielded the desired 3-amino-2-mercaptonaphthofuro[3,2-d]pyrimidin-4(3*H*)-one (**108**) [60-63] in excellent yield (Scheme 26).



Scheme 26. Synthesis of 3-amino-2-mercaptonaphthofuro[3,2-d]pyrimidin-4(3*H*)-one.



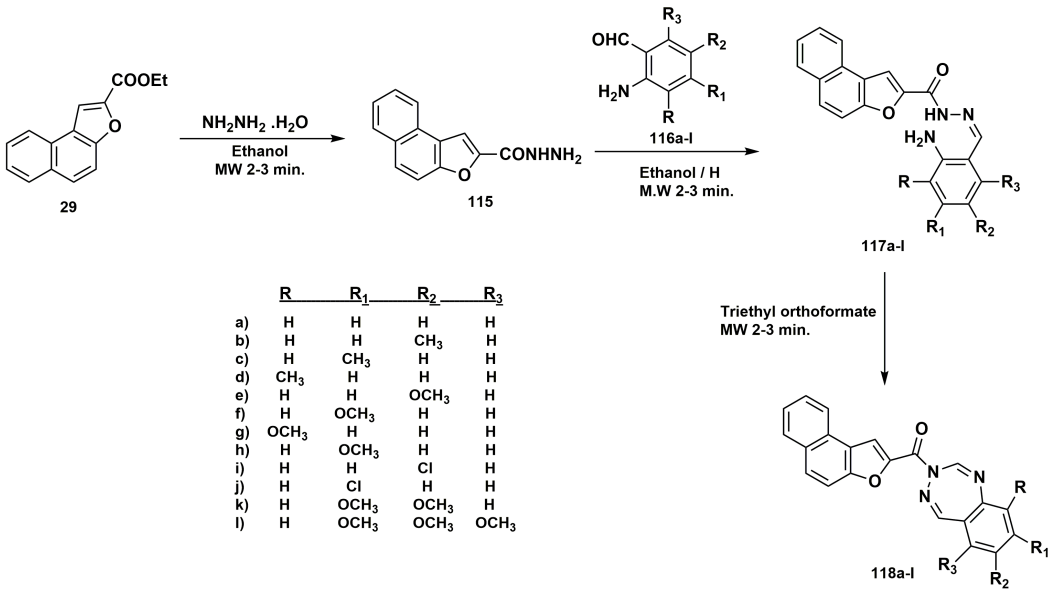
Scheme 27. Synthesis of 2-arylaminonaphthofurothiadiazolopyrimidin-5-ones.



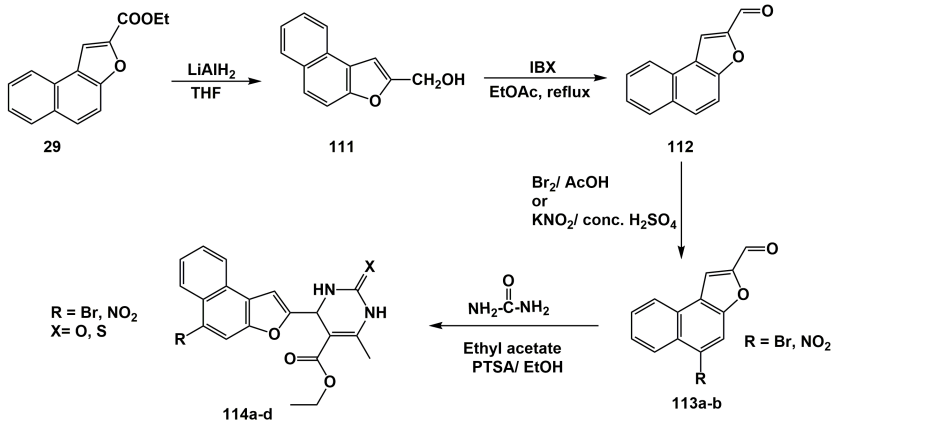
Scheme 28. Naphtho[2,1-*b*]furan-2-yl-pyrimidine-5-carboxylate.

Compound **108** on reaction with various aryl isothiocyanates yielded 2-arylaminonaphtho[2,1-b]furo-5*H*-[3, 2-d][1, 3, 4]thiadiazolo[3, 2-a]pyrimidin-5-ones (**109a-h**). Thus, reaction of compound **108**, having similar functionality, on treatment with different aromatic acids in phosphrusoxy chloride led to the formation of 2-aryl naphtho[2, 1-b]furo-5*H*-[3, 2-d][1, 3, 4]thiadiazolo[3,2-a]pyrimidin-5-ones (**100a-d**) (Scheme 27).

Reduction of compound **29** [64] with lithium aluminum hydride in tetrahydrofuran gave the corresponding reduction product alcohol (**111**) and, further the obtained compound **111** was oxidized with 2-iodoxybenzoic acid (IBX) in ethyl acetate



Scheme 29. Synthesis of naphthofurobenzotriazepine.



Scheme 30. Synthesis of azetidine-1-yl-naphth [2,1-*b*]furan-2-carboxamides.

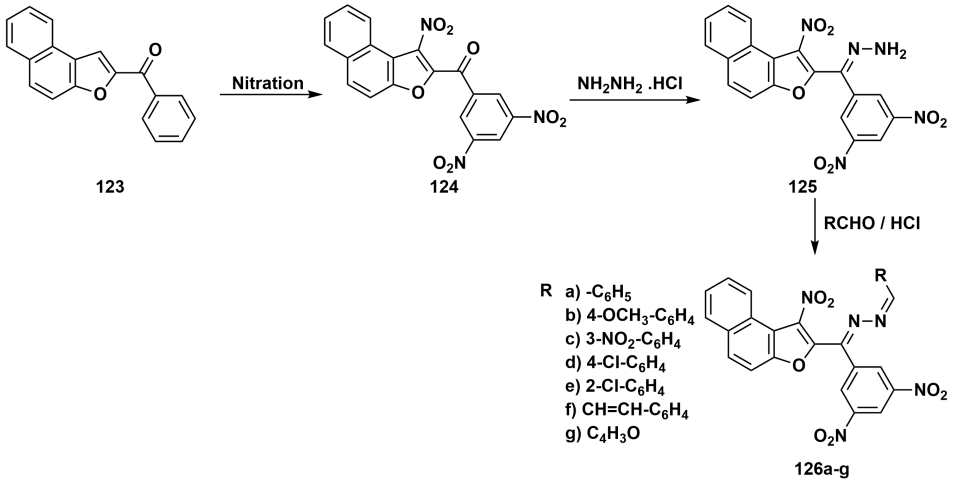
to get naphthofuran-2-carbaldehyde (**112**). Finally, compound **112** was subjected to bromination and nitration reaction to get compounds **113a-b**. Finally, compounds **112** and **113a-b** underwent acid catalyzed three-component condensation reaction with ethyl acetoacetate and urea/thiourea to give corresponding condensation products (**114a-d**) (Scheme 28).

The compound **29** was made to react with hydrazine hydrate at an acidic condition in ethanol under microwave produce naphtho[2,1-*b*]furan2-carbohydrazide (**115**) [62,65]. To prepare *N*'-(2-aminobenzylidene)naphtho[2,1-b]furan-2-carbohydrazides (**117a-l**), the compound **115** was treated with substituted 2-aminobenzaldehyde (**116a-l**) in presence of the catalytic amount of acetic acid in ethanol under microwave irradiation. Reaction of compound **117a-l** with triethyl ortho formate and was irradiated in a microwave oven afforded benzotriazepine (**118a-l**) (Scheme 29).

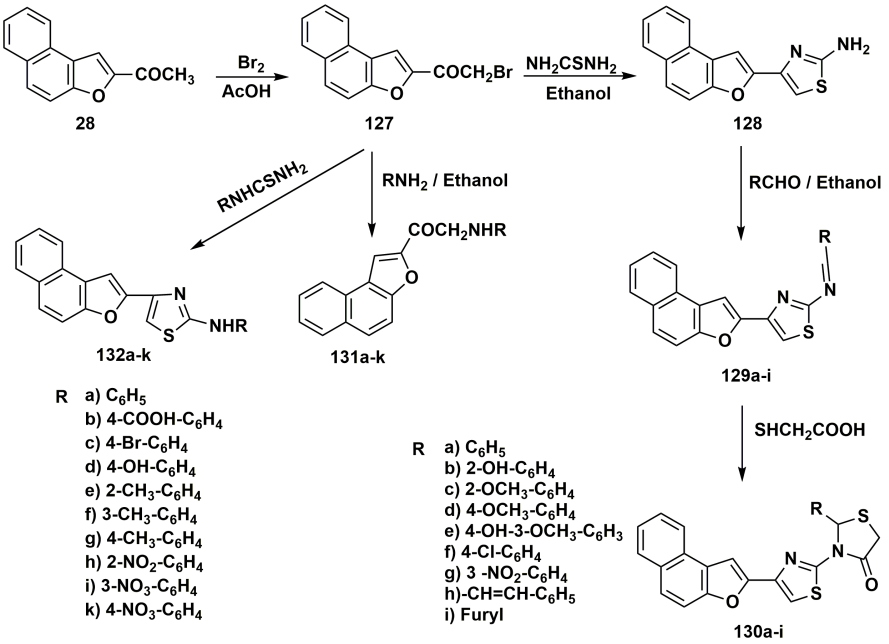
Nitration of compound **29** [66] afforded ethyl 3-nitro naphtho[2,1-*b*]furan-2-carboxylate (**119**) and reaction of compound **119**, with hydrazine hydrate to give 3-nitro-naphtho[2,1-b]furan-2-carbohydrazide (**120**). The carbohydrazide **120** was treated with various substituted aromatic aldehydes in refluxing ethanol to obtain the corresponding Schiff's base, 3-nitro-*N*'(aryl-methylene)-substituted-naphtho [2, 1-*b*]furan-2-carbohydrazides (**121a-g**) in good yield. Synthesis of 3-nitro-*N*-(3-chloro-2-oxo-substituted-phenyl-azetidine-1-yl)naphtho[2,1-*b*]furan-2-carboxamides (**122a-g**) was accomplished by the reaction between 3-nitro-*N´*(aryl-methylene)-substituted-naphtho[2,1-*b*]furan-2-carbohydrazides (**121a-g**) with chloroacetyl chloride in presence of triethyl amine in dioxane (Scheme 30).

Nitration of 3',5'-dinitrobenzoyl-3-nitronaphtho[2,1-*b*] furan (**123**) [67]. The reaction of compound **124** with hydrazine hydrate in ethanol was straightforward and produced corresponding hydrazone (**125**), with excellent yield. However, in this case, the reaction of 2-(3',5'-dinitrobenzoyl)-3-nitro-naphtho[2,1-*b*]furanhydrazone (**125**) with various aldehydes at reflux temperature in ethanol, in the presence of acid to give Schiff's base (**126a-g**) (Scheme 31).

The compound **28** [68] was converted into 2- bromo-acetylnaphtho[2,1-*b*]furan (**127**) by bromination in the presence of acetic acid at 20 °C, which served as an excellent intermediate for the synthesis of various naphtho[2,1-*b*]furan derivatives. The compound **128** was refluxed with thiourea and the product obtained was identified as 2-(2-aminothiazol-4-yl)naphtho[2,1-b]furan (**129**), based on spectral studies. The compound **129** was made to undergo condensation with various aromatic aldehydes to obtain the corresponding Schiff bases, 2-(2-arylideneaminothiazol-4-yl)naphtho[2, 1-b]furans (**130a-j**). On refluxing Schiff bases (**130a-j**), with thioglycolic acid in dimethyl formamide in the presence of a catalytic amount of anhydrous zinc chloride, cyclo-condensation occurred very smoothly and resulted in the formation of new



Scheme 31. Synthesis of Schiff's base.



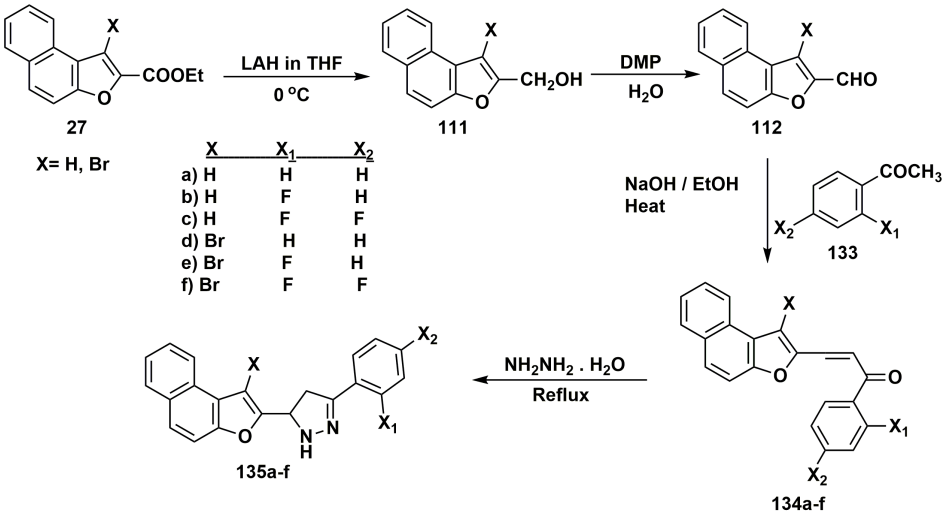
Scheme 32. Thiazol-4-ylnaphtho[2,1-*b*]furan derivatives.

tri-heterocyclic compounds, 2-[2-(2-aryl-4-thiazolidinono) thiazol-4-yl]naphtho[2,1-*b*]furans (**131a-i**). The compound **127** on reaction with various aromatic amines in ethanol produced 2-(*N*-aryl-2-amino)acetylnaphtho[2,1-*b*]furans (**131a-k**). Various substituted thiourea were prepared by the reaction between potassium thiocyanate and appropriate amines, these substituted thiourea on refluxing with compound (**127**), produced 2-(2-*N*-arylaminothiazol-4-yl)naphtho[2,1-*b*]furans (**132a-k**) in good yield (Scheme 32).

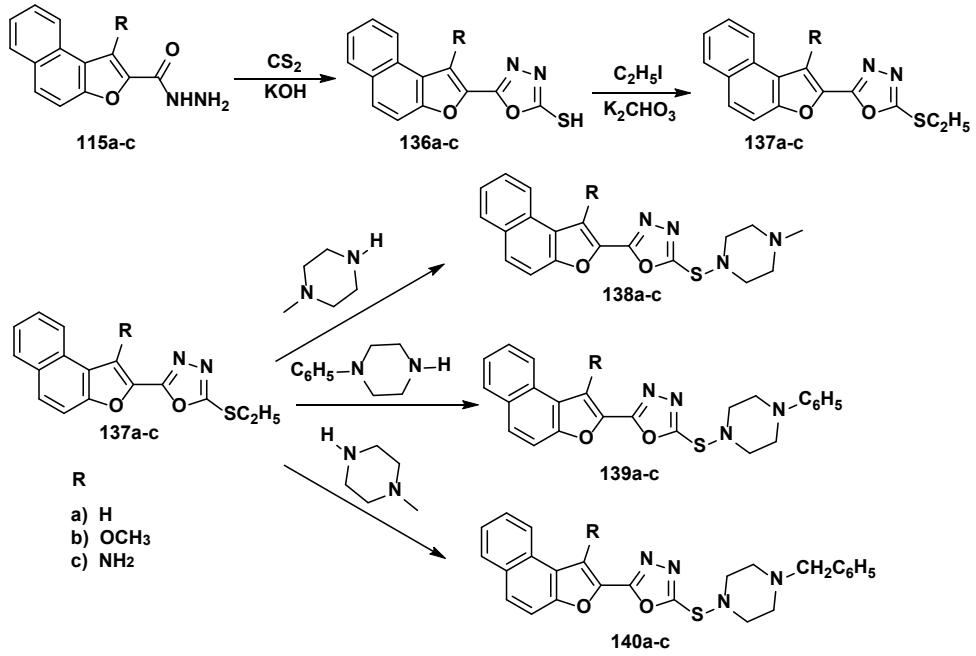
Reduction of compound **27** [69] by lithium aluminum hydride in THF was added slowly with continuous stirring at 0 °C. Stirring was continued for 2 hrs afforded naphtho[2,1-*b*]furan-2-ylmethanol (**111**), and the Dess-Martin oxidation of compound **111** to corresponding 3-substituted-naphthofuran-2-carboxaldehyde (**112**). condensation of compound **112** with substituted acetophenones (**133**) in the presence of sodium hydroxide afforded aryl-3-[(3-substituted)-2-naphthofuryl]-2-propen-1-ones (**134a-f**). Compounds **134a-f** were then treated with hydrazine hydrate to afford 3-substituted aryl-5-(3-substituted-2-naphthofuryl)-2-pyrazolines(**135a-f**) (Scheme 33).

1-Substituted-naphtho[2,1-b]furan-2-carbohydrazide [70] **115a-c** were cyclized with carbon disulfide in presence of potassium hydroxide to get mercaptoxadiazoles **136a-c** which were then stirred with ethyl iodide to obtain 2-(ethylsulfanyl)-5-(1-substitutednaphtho[2, 1-*b*]furan-2-yl)-1, 3, 4-oxadiazoles (**137a-c**). Compounds **137a-c** were refluxed with different substituted piperazines like *N*-methylpiperazine, *N*-benzyl-piperazine, and *N*-phenylpiperazine to afford 1-methyl-4-[5-(1-substituted-naphtho[2, 1-*b*]furan-2-yl)-1, 3, 4-oxadiazol-2-yl] piperazines (**138a-c**), 1-benzyl-4-(5-(1-substitutednaphtho [2,1-*b*]furan-2-yl)-1,3,4-oxadiazole-2-yl)piperazines (**139a-c**) and 1-(5-(1-substituted-naphtho[2,1-*b*]furan-2-yl)-1,3,4-oxa diazol-2-yl)-4-phenylpiperazines (**140a-c**), respectively (Scheme 34).

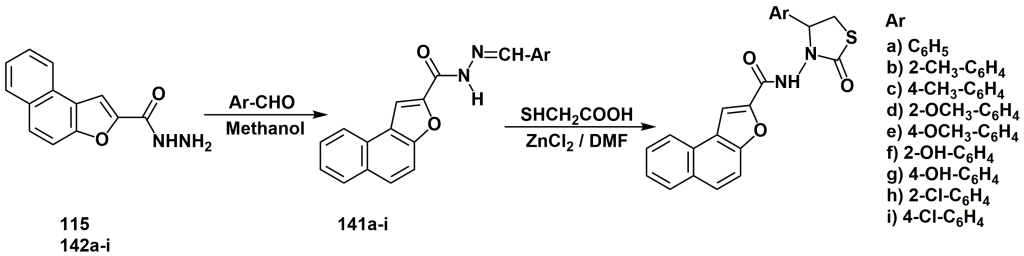
It was observed that naphtho[2,1-*b*]furan-2-carbohydrazide (**115**) [71], on condensation with aromatic aldehydes, yields *N*-arylidene-naphtho[2,1-*b*]furan-2-carbohydrazide (**141a-i**). *N*-arylidene-naphtho[2,1-*b*]furan-2-carbohydrazide (**141a-i**) in THF and thioglycolic acid with a pinch of anhydrous $ZnCl_2$ was refluxed for 11-12 hrs to give *N*-(4-oxo-2-arylthiazolidin-3-yl)naphtho[2,1-*b*]furan-2-carboxamide (**142a-i**) (Scheme 35).



Scheme 33. Synthesis of 2-naphthofuryl pyrazolines.



Scheme 34. Synthesis of naphtho[2,1-*b*]furan-2-yl-oxadiazol derivatives.

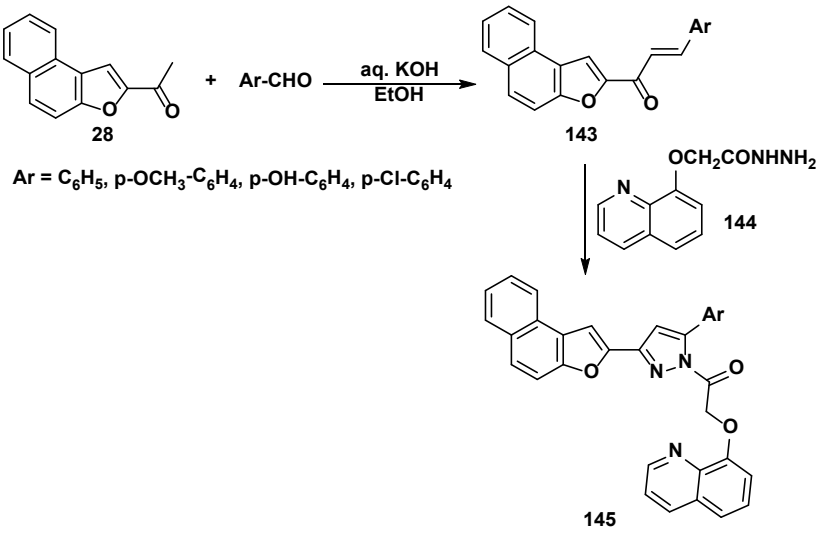


Scheme 35. Synthesis of naphtho[2,1-b]furan-2-carboxamide derivatives.

Reaction of 2-acetylnaphtho[2,1-*b*]furan (**28**) with various substituted aromatic aldehydes in the presence of aq. KOH in ethanol to give substituted Chalcones (**143**). These chalcones on reaction with 2-[(quinoline-8-yl)oxy]acetohydrazide (**144**) [72] in presence of glacial acetic acid gave the naphtho[2,1-*b*]furo-2-y1)pyrazol-1-y1)-2-(quinolin-8-yloxy)ethanone derivatives (**145**) (Scheme 36).

4. Biologically active naphthofurans

Naphthofurans fused or coupled with oxygen and nitrogen heterocycles do not occur in nature. Even synthetic naphthofurans coupled or fused with oxygen and nitrogen heterocycle are not reported so far, except for some reports of such compounds from this literature method [73-78].



Scheme 36. Synthesis of chalcones and naphtho[2,1-*b*]furo-2y1pyrazol.

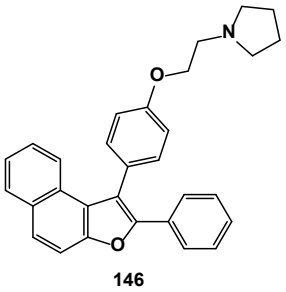


Figure 7. Structure 2-phenyl-3-*p*-(β-pyrrolidinoethoxy)-phenyl [2,1-b] naphthofuran.

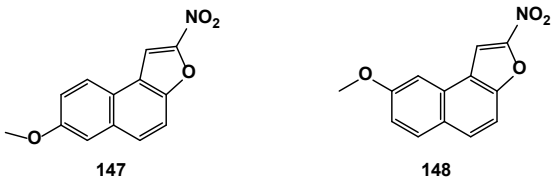


Figure 8. Structure of 2-nitronaphtho[2,1-b]furans.

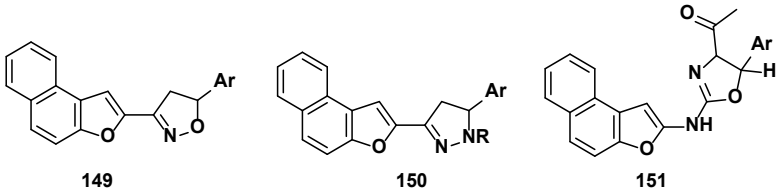


Figure 9. Naphtho[2,1-b]furans exhibit antimicrobial and fungi.

These observations prompted us to undertake the investigation of naphthofuran with oxadiazole and indole as second heterocyclic components. Some of the derivatives of naphthofurans which show biological and pharmacological activities are given below the biologic properties of a new oral antifertility agent, 2-phenyl-3-*p*-(β-pyrrolidinoethoxy)-phenyl [2,1-*b*]naphthofuran (**146**) (Figure 7) [79] have been investigated in detail on rodent species and rhesus monkeys the *rhesus macaque* (*Macaca mulatta*) is native throughout Asia and is considered to have the largest native range of any non-human primate by Kamboj *et al.* [80].

The influence of the uvr gene-dependent excision repair system on the lethal action, mutagenic specificity. The Save Our Souls (SOS) response inhibits septum formation until bacterial DNA can be repaired and is observable as filamentation when cells are examined by microscopy and DNA adducts formation of 7-methoxy-2-nitronaphtho[2,1-*b*]furan (**147**) and 2-nitro-8-methoxynaphtho[2, 1-b]furan (**148**) (R6998) (Figure 8), a potent genotoxic nitrofuran, were examined on *Escherichia coli* by Touati *et al.* [81].

Vagdevi *et al.* [82] and co-workers have reported that the derivatives of naphtho[2, 1-b] furan (**149**-**151**) (Figure 9) exhibit antimicrobial activity against *Staphylococcus aureus*, *Klebsiella pneumoniae* and *fungi Aspergillus niger.*

Lee *et al.* [83] and Bor-Ruey Huang, reported the tricyclic naphtho[2, 1-b]furan derivatives (**152**) and these compounds exhibit a unique cytotoxicity profile (Figure 10). They are highly cytostatic for leukemia cancer cells but are not cytocidal. However, they are both cytostatic and cytocidal for almost all the solid tumors tested.

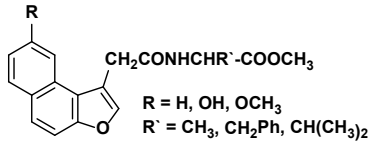


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Figure 10. Structure of naphtho[2,1-b]furan derivatives.

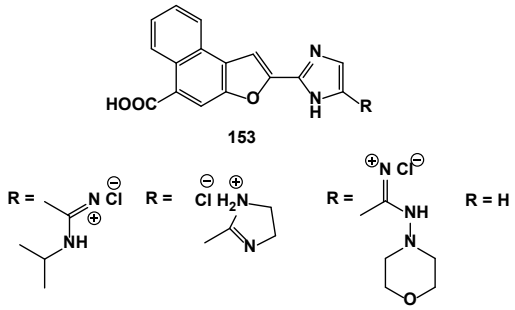


Figure 11. Naphtho[2,1-b]furan-carboxylates.

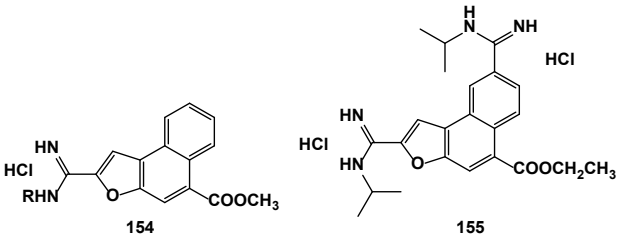


Figure 12. Naphthofurans are inhibition of tumor cell growth *in vitro*.

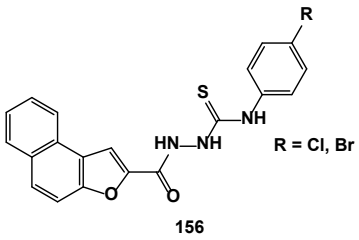


Figure 13. Structure of 2-(naphtho[2,1-b]furan-2-carbonyl)-*N*-phenylhydrazine-1-carbothioamide derivatives.

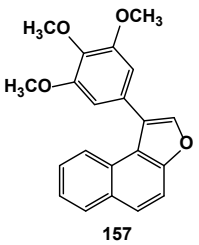


Figure 14. Structure of 1-(3',4',5'-trimethoxy)phenylnaphtho[2,1-b]furan.

Hranjec *et al.* [84], reported substituted naphtho[2,1-b]furan compounds (**153**) were tested for cytostatic activities against malignant cell lines like, pancreatic carcinoma (MiaPaCa2), breast carcinoma (MCF7), cervical carcinoma (HeLa), laryngeal carcinoma (Hep2), colon carcinoma (HT 29), melanoma (HBL), and human fibroblasts cell line (WI38). All compounds inhibited the proliferation of tumor cell lines (Figure 11).

Starcevic *et al.* [85], report details about their synthesis of naphthofurans (**154**,**155**) characterization in respect to their potential of photoinduced cyclization, interactions with DNA, and inhibition of tumor cell growth *in vitro* (Figure 12).

Naphtho[2,1-b]furans and their complexes (**156**) have been screened for their fungicidal and bactericidal activities [86]. Complex was derived from reaction between naphthofuran-2-carboxyhydrazide and *p*-chlorophenylisothiocynate (NCClPT)/ *p*-bromophenylisothiocynate (NCBrPT) (Figure 13).

Srivastava *et al.* [87] reported 1-(3',4',5'-trimethoxy)phenyl naphtho[2,1-b]furan (Figure 14) and other derivatives as a novel anticancer agent an anti-cancer agent. Base catalyzed intramolecular condensation of 3',4',5'-trimethoxybenzoyl-naphthalene 2-*o*-acetic acid yield exclusively 1-(3`,4',5'-trimethoxy)phenylnaphtho[2,l-b]furan (**157**) and reported the compounds (**157**) that showed significant anticancer activity

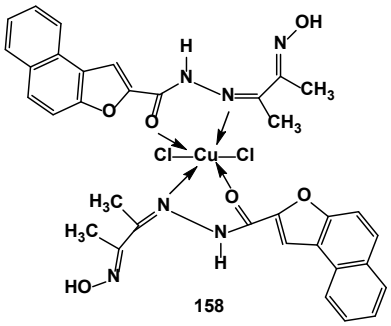


Figure 15. Naphthofuran-2-carbohydrazide

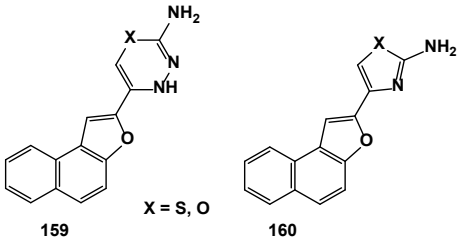


Figure 16. Naphthofurans are antimicrobial, and anthelmintic, analgesic and anti-inflammatory.

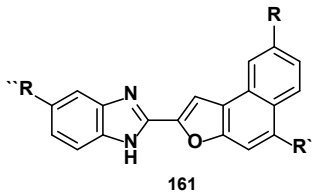


Figure 17. Structure of naphthofurans are antitumor activity.

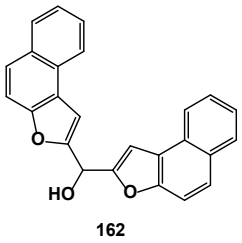


Figure 18. Structure *bis*(naphtho[2,1-b]furan-2-yl)methanol.

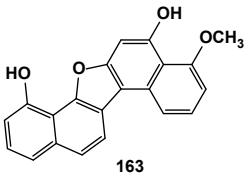


Figure 19. Structure of 4-methoxydinaphtho[1,2-b:1',2'-d]furan-5,8-diol.

against human cancer cell lines COLO320DM (colon), $CaCo_2$ (colon) and WRL68 (liver) in the *in-vitro* MTT assay.

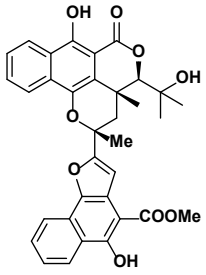
Sumathi *et al.* [88], reported the compounds (**158**) (Figure 15) screened for their antibacterial and antifungal activities against *Pseudomonas aeruginosa, Staphylococcus aureus and Candida albicans* exhibited significant activity.

Mahadevan *et al.* [89], reported the synthesized compounds (**159**, **160**) (Figure 16) which are screened for antimicrobial against *S. aureus, K. pneumoniae, A. niger,* and anthelmintic, analgesic and anti-inflammatory and exhibited significant activity.

Hranjec *et al.* [90], the tested synthesized compounds (**161**) (Figure 17) show very differential and strong antitumor activity without apparent difference depending on their structures.

Kirilmis *et al.* [86], tested synthesized compounds (**162**) (Figure 18) were tested for anti-microbial activity against *S. typhimurium*, *E. coli*, *B. subtilis*, *C. Globrata* and *C. Tropicalis.* All of the selected compounds showed weak antimicrobial activity against microorganisms.

Xylarianaphthol-1, a novel dinaphthofuran derivative (**163**) (Figure 19), was isolated from a marine sponge-derived fungus of order *Xylariales* on the guidance of a bioassay using transfected human osteosarcoma MG63 cells ($MG63^{luc}$+) [91].



164

Figure 20. Structure of rubicordifolin.

The biomimetic (**164**) synthesis and full structural elucidation of rubicordifolin (Figure 20), a cytotoxic natural product isolated from *Rubia cordifolia* [36], was described.

5. Conclusion

In this review, a wide range of synthetic strategies of naphthofurans as an important class of arene ring-fused furans has been discussed. We started with chemical and photochemical for the synthesis of naphthofurans, followed by presenting of their diverse biological and pharmacological activities. In general, of 2-hydroxy-1-naphthaldehyde plays an important role and works well in construction of naphthofurans. Moreover, different types of reactions of naphthols and various substituted salicylaldehyde and etc. were demonstrated for synthesis of naphthofurans. We explained in this report that naphthofurans are based on the construction of new heterocyclic compounds that are used in the medical field.

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