China Petroleum Processing and Petrochemical Technology

Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

POLYETHYLENE GLYCOL AS AN EFFICIENT AND RECYCLABLE REACTION MEDIUM FOR ONE-POT SYNTHESIS OF 2-AMINO-1,4-NAPTHOQUINONES UNDER CATALYST FREE CONDITIONS

Prasanthi Sarakula,[a]* , Pampayya thanthati[b] and Siddaiah Vidavalur [c]

[a] Assistant Professor,Department of chemistry, Adikavi Nannaya University, Tadepalligudem, India

[b] Research Scholar, Department of Botany, Srikrishna devaraya University, Anantapuramu, India

[c] Professor, Department of Organic chemistry & FDW, Andhra University Visakhapatnam, India

*Corresponding author: e-mail: prasanthis2011@gmail.com

Abstract

A mild, simple, efficient and eco-friendly convenient general method for the synthesis of 2-amino-1,4-napthoquinones from 1,4-naphthoquinones and anilines using PEG-400 as a solvent under mild conditions.

Keywords:2-amino-1,4-napthoquinones, PEG-400, Eco-friendly, Catalyst free conditions.

Introduction

Functionalized heterocyclic building blocks are of great importance in both medicinal and synthetic chemistry and development of new efficient synthetic methodologies for these scaffolds remains a great challenge in modern organic synthesis.[1] Quinones, including 1,4-naphthoquinones are ubiquitous in nature[2,3] and several well-known clinically important anticancer drugs used to treat solid tumours such as anthracyclines, mitoxantrones and saintopin (e.g. doxorubicin, idarubicin, mitomycin and mitoxantrone) shows excellent anticancer activity which possess a quinonoid structure.[4,5]

These anticancer agents are effective inhibitors of DNA topoisomerase, and it is generally known that the cytotoxicity of quinine analogues results from the inhibition of DNA topoisomerase II.[6-9] The DNA intercalative ability of quinonoid antitumor agents, such as daunorubicine, doxorubicine, mitoxantrone, and mitomycin C is due to their large and planar polycyclic structures, which facilitates the binding between the base pairs through hydrogen bonds and p-stacking interactions.[10,11]

Even simple 1,4-NQs bearing limited substituents generally possess a wide spectrum of biological activities. For example, alkylamino-substituted 1,4-NQ (I) showed dose-dependent antiangiogenic activity in rat aortic ring assay.[12] Phenylamino substituted 1,4-NQ (II) belongs to a class of antimycrob acterial agents.[13] 1,4-NQ (III) bearing a benzylamino substituent is an analogue of vitamin K possessing neuroprotective effects against neuronal oxidative stress.[14] **(Fig 1)** The presence of the nitrogen atom allows modulation of the substituent's effects on the

* Corresponding author. Tel.: +91 9989343423; e-mail: *prasanthis2011@gmail.com*

Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

electronic properties of the quinone system, as well as modification of the geometry of the neutral molecules and of their reduction intermediates.

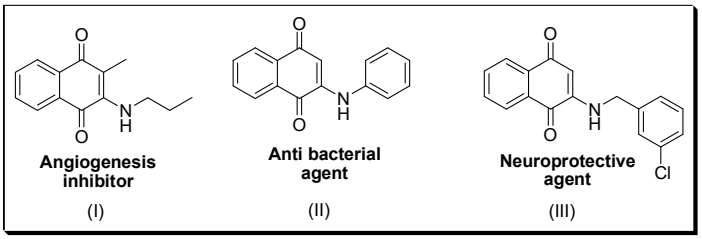


Fig 1. Structures of 1,4-NQ (I), (II) and (III).

Hence among the 1,4-naphthoquinones, synthetic and natural 2-amino-1,4-naphthoquinone derivatives are interesting molecules and many of them find use in a variety of medicinal and biological applications[15,16] for example as anti-tuberculars,[17] antimalarials,[18] antibacterials,[19,20] antitumor agents,[21-25] larvicides, herbicides, fungicides,[69-71] molluscicidal,[26] cytotoxic,[27] anti-tumor[28] and antibacterial[29] activities. And also they serve as photosystem I electron acceptors [30] and as potential anti-tumor agents. [31-33] In addition, due to their functional properties they have found wide industrial applications in color chemistry[34] and hair dying[35] as well as photostabilizers.[36]

The 1,4-naphthoquinone pharmacophore, has been shown to impart anticancer activity in a number of pharmaceutics, for example, shikonin**,** a natural product isolated from the Chinese medicinal herb zicao (purple gromwell, the dried root of *Lithospermum erythrorhizon*) has demonstrated excellent anti-tumour potential through the inhibition of Epidermal growth Factor Receptor (EGFR) signalling in human epidermoid carcinoma cells.[72,73] Another promising lead compound atovaquone, a hydroxy-1,4-naphthoquinone, is an anti-parasitic drug that selectively targets the mitochondrial respiratory chain of the malaria parasite.[74,75] The anti-cancer activity of 2-piperidinyl and 2-piperazinyl analogues was evaluated on a range of human cancer cell lines using doxorubicin as a positive control.[75] And 2-arizidinyl- and 2,3-bis-(arizidinyl)-1,4-naphthoquinonyl sulfonate and acylate derivatives that are irreversibly bound and capable of redox cycling in malaria-infested red blood cells.[76] The 2-Hydroxyjuglones isolated from the plant tissue of the black walnut (*Juglans nigra*), naturally occurring 2-methoxy-1,4-naphthoquinones, shikonin and arnebin include the naphthoquinone pharmacophore and exhibit pronounced anti-fungal properties against a number of fungal strains.[77]

Frequently used pharmaceuticals containing the naphthoquinone pharmacophore including; menadione (2-methyl-1,4-naphthoquinone), plumbagin (2-methyl-5-hydroxy-1,4-naphthoquinone) and lapachol [2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthoquinone] exhibit trypanocidal activities against varied parasitic flagellate protozoa and *Leishmania* that are responsible for several human diseases such as African sleeping sickness (*Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*), Kala-azar (*Leishmania donovani*) and Chagas disease (*Trypanosoma cruzi*).[78] And all the above mentioned compounds are displayed in the (**Fig. 2)**.

Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

The 2-amino-1,4-naphthoquinone moiety can be even found in natural products, such as echinamines A and B [37] from the sea urchin Scaphechinus mirabilis and hygrocins A and B[38] from Streptomyces hygroscopicus. **(Fig 3).** Furthermore, the aminonaphthoquinone moiety is a component of the molecular framework of several natural products (e.g. rifamycins,[39] kinamycins,[40] rifampicins,[41] streptovaricins,[42] etc.) and has been used as a synthetic key intermediate for benzo[b]acridine-6,11-diones,[43-45] benzo[f]indole-4,9- diones,[43-46]1H-1-azaanthracene-9,10-diones[47] and 1,2,3,4-tetrahydrobenzo[quinazoline-5,10-diones.[48]

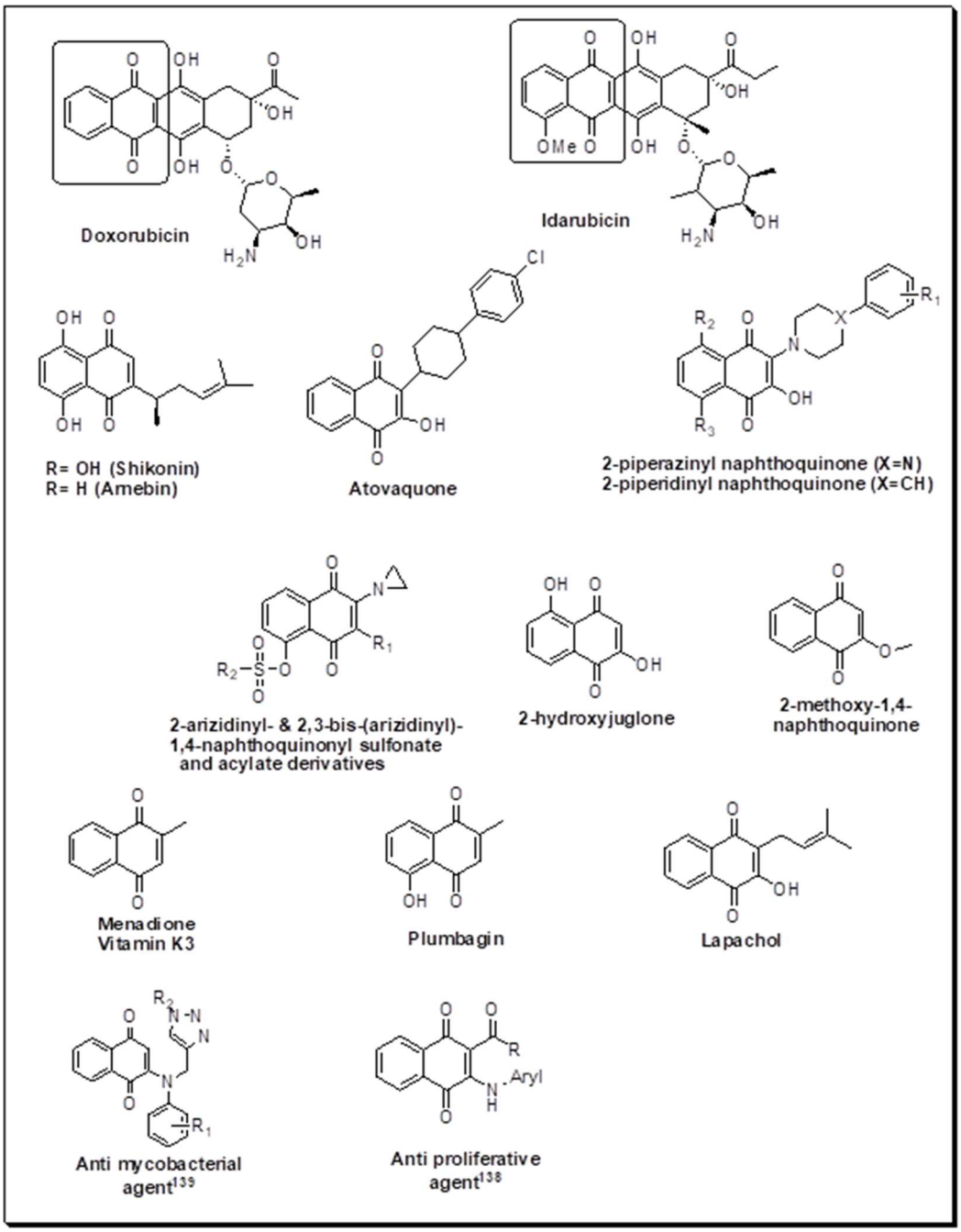


Fig 2. Selected examples of bio-active and naturally occurring 1,4-napthoquinones

Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

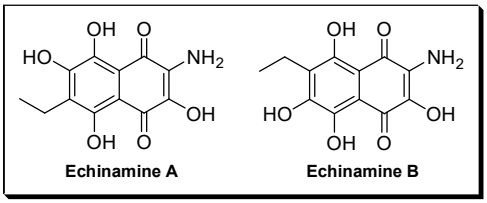
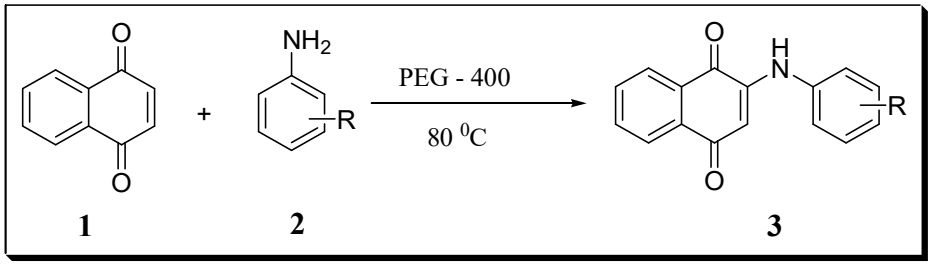


Fig 3. Structure of Echinamines A & B

In general, there are two main synthetic strategies for the synthesis of 2-amino-1,4-naphthoquinones: one approach involves the nucleophilic displacement of a halogenated 1,4-naphthoquinone.[49-56] The second approach is typically performed via a Michael addition of an amine with 1,4 naphthoquinone.[57-64] However, both methods are unpractical and tedious and usually give very low yields and many side products, especially with primary amines. The mixture of compounds obtained in these reactions are a consequence of the physicochemical properties of 1,4-naphthoquinone: the presence of several electrophilic centers of comparable reactivity leads to the formation of 1,4- and 1,2-addition adducts and the redox properties of the naphthoquinone favour the formation of an inert 1,4-naphthodiol. These drawbacks, in conjunction with the difficulties encountered during their chromatographic purification[65] makes these methods synthetically unattractive. Therefore, developing a benign, eco-friendly, mild and easy general procedure to access 2-amino-1,4-napthoquinones with simple substrates remains a continued strong demand.

In view of the environmental aspects, designing of novel, catalyst-free methods to synthesize a variety of pharmacological agents has acquired immense importance in recent years.[66] Replacement of hazardous solvents with environmentally benign solvents[67] is one of the major focus areas of green chemistry. Also, catalyst-free synthetic methods not only for laboratory synthesis but also in the chemical industry have acquired immense interest because of reduced pollution, lower cost, mild conditions, and ease of purification.[68]

Based on the above facts, in continuation of our studies in developing inexpensive and environmentally benign methodologies for the synthesis of bioactive molecules, herein, the author has reported a new methodology for 2-amino-1,4-napthoquinones from 1,4-naphthoquinones and anilines using PEG as a solvent (**Scheme 1**).



Scheme 1: Preparation of 2-amino-1,4-napthoquinones

Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

Results and Discussion

The author initially attempted her study with the reaction of 1,4-naphthoquinone **(1a)** and aniline **(2a**) at 80 ^{0}C without any solvent. The product was obtained in very low yield after prolonged time. Therefore her investigation was focused for the search of suitable solvent. At first she tested her reaction in THF solvent at 80 ^{0}C. As a result she observed long reaction times with poor yields (**Table 1, entry 6**). Then she moved the reaction with toulene and dioxane as solvents at 80 ^{0}C. Hopefully she observed the formation of the desired product **3a**, albeit in a low yield of 48 and 52 % respectively. (**Table 1, entries 1and 2**). Next she checked the reaction with isopropyl alcohol (IPA), acetonitrile and n-butyl alcohol (n-BuOH) as solvents at 80 ^{0}C, surprisingly the yields were noted to be increased 60, 62, 70% respectively (**Table 1, entries 3, 4 and 5**). To further explore the effect of solvent on the reaction medium we choose PEG as solvent at 80 ^{0}C and it was found that the yield was increased with wide variation when compared with previous solvents as 89 % (**Table 1, entries 8, 9 and 10**). For a change she conducted the same reaction at room temperature but comparatively the yields were low 40% (**Table 1, entries 7**). On observing different solvents reaction times and yields in (**Table 1**), she concluded that aprotic solvents like toluene, dioxane gave no positive effects, whereas protic solvents like isopropyl alcohol (IPA) or polyethylene glycol (PEG) improved the yield and declined the reaction time. However, PEG had superior solvent effects for this reaction and was therefore used for all subsequent reactions.

Table 1. Effect of various solvents in the synthesis of **3a**

	Solvent	Temp (°C)	Time (min)	Yield(%)[a]
1	Toluene	80	35	48
2	1,4-dioxane	80	40	52
3	IPA	80	25	60
4	Acetonitrile	80	35	62
5	n-BuOH	80	30	70
6	THF	80	100	35
7	PEG 400	rt	120	40
8	PEG 200	80	10	89
9	PEG 300	80	10	89
10	PEG 400	80	10	89

a-Isolated yield after column chromatography

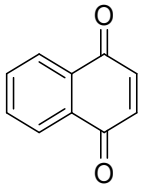
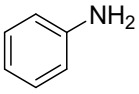
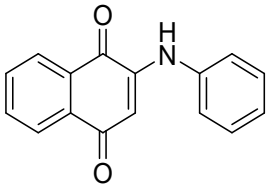
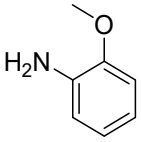
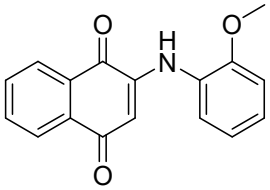
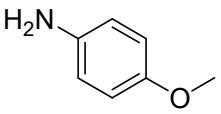
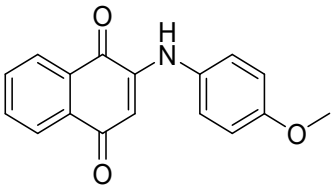
To explore the generality and scope of the method, the optimized reaction conditions 1,4-naphthoquinones (**1a**) (1.7 mmol), aniline (**2a**) (1.8 mmol) and PEG (0.5 mL), at 80 °C were applied to various structurally diverse 1,4-naphthoquinone and anilines (**Table 2**).

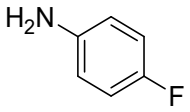
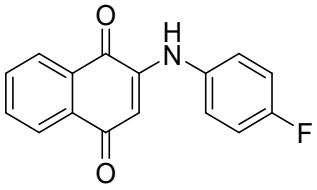
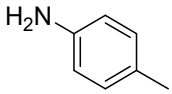
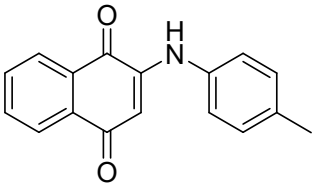
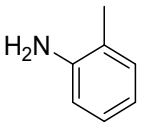
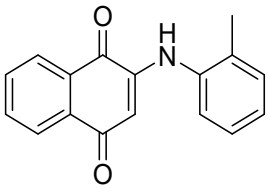
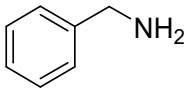
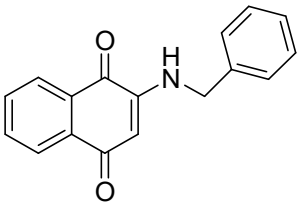
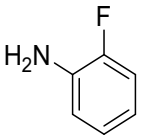
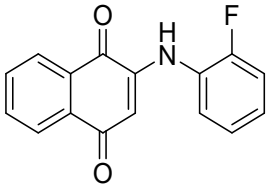
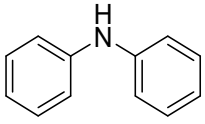
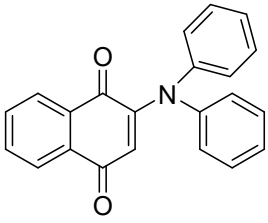
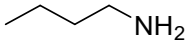
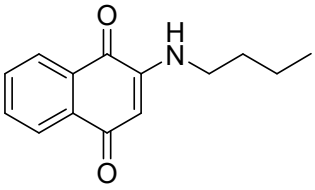
Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

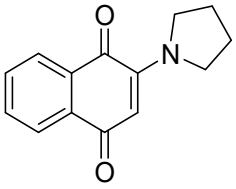
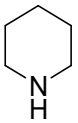
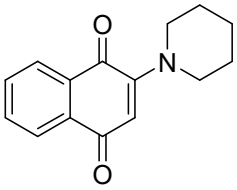
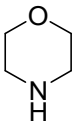
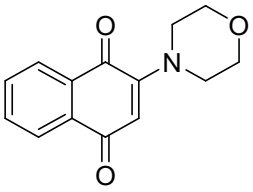
By prompting this success, the author extended the reaction of 1,4-naphthoquinone with a wide range of other amines under similar conditions at 80 °C **(Scheme 1)**, furnishing the 2-amino-1,4-naphthoquinone compounds in moderate to excellent yields (**Table 2**). She found the wide applicability and usefulness of this method. As shown in **Table 2**, she found that the reaction of aromatic amines bearing electron-donating groups with 1,4-naphthoquinone can proceed effectively to provide the desired products in excellent yields (80–86%, **Table 2, entries 2, 3, 5, 6 and 7**). Even primary and secondary aliphatic amines such as, butan-1-amine **2j**, pyrrolidine **2i,** piperidine **2l** and morpholine **2m** react with 1,4-naphthoquinone to afford the desired products in moderate to excellent yields (70–88%, **Table 2, entries 10-13**). However, the yield of diphenylamine **2i (Table 2, entrie 9**) is low, presumably because of steric hinderance when compared with other amines.

To check the reusability of polyethylene glycol, a mixture of 1,4-naphthoquinone (**1a**), aniline (**2a**) and polyethylene glycol was stirred at 80 °C for 10 min. After the completion of the reaction (monitored by TLC), the mixture was extracted with EtOAc (3 × 20 mL). The retained polyethylene glycol phase was reused three consecutive times with only a slight variation in the yields of the obtained products (89%, 85% and 82%).

Table 2. PEG catalyzed synthesis of 2-amino-1,4-napthoquinones derivatives.

S.No	1,4-Naphtho Quinone **(1)**	Aniline **(2)**	Product **(3)**	Time (min)	Yield %
1	 **1a**	 **2a**	 **3a**	10	86
2	**1a**	 **2b**	 **3b**	12	82
3	**1a**	 **2c**	 **3c**	10	84

4	**1a**	 **2d**	 **3d**	15	82
5	**1a**	 **2e**	 **3e**	12	85
6	**1a**	 **2f**	 **3f**	15	86
7	**1a**	 **2g**	 **3g**	10	80
8	**1a**	 **2h**	 **3h**	15	72
9	**1a**	 **2i**	 **3i**	20	82
10	**1a**	 **2j**		25	70

			3j		
11	**1a**	 **2k**	 **3k**	12	82
12	**1a**	 **2l**	 **3l**	10	86
13	**1a**	 **2m**	 **3m**	12	88

Conclusion

In conclusion, the author has developed a mild, simple, efficient and eco-friendly convenient general method for the synthesis of 2-amino-1,4-napthoquinones from 1,4-naphthoquinones and anilines using PEG-400 as a solvent under mild conditions. The advantages of this procedure is the use of an environmentally benign solvent, the wide scope of the reactants and satisfactory product yields. 2-Amino-1,4-napthoquinones derivatives are biologically and pharmaceutically active molecules, and therefore, the present protocol could be of wide application in medicinal chemistry and organic chemistry.

Acknowledgments

The author, Sarakula Prasanthi thank the University Grants Commision (UGC), New Delhi for financial assistance through the Rajiv Gandhi National Fellowship (RGNF). The author is also greatful to the Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam, Andhra Pradesh for providing the facilities to carry out research work.

Experimental section

Materials & Methods

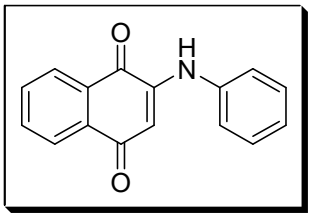
Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

Melting points were recorded on a Mel-Temp melting point apparatus and are uncorrected. Unless otherwise stated, all the materials were obtained from the commercial suppliers and are used without further purification. Chromatography was carried on silica gel (100-200 mesh). All the reactions were monitored by thin-layer chromatography and the spots were visualized under UV light. The ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer using TMS as internal standard and the values for chemical shifts (δ) being given in ppm and coupling constants (*J*) in Hertz (Hz). Mass spectra were recorded on an Agilent 1100 LC/MSD. All yields refer to isolated ones.

General experimental procedure for the synthesis of 2-amino-1,4-naphthoquinone derivatives (3a-3m):

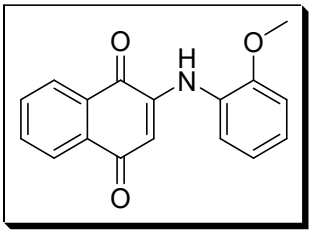
A mixture of 1,4-naphthoquinone **1** (1.8 mmol), aniline **2** (1.7 mmol) and PEG-400 (0.5 ml) was heated to 80 ^{0}C for 10 minutes. After completion of the reaction as monitored by TLC, reaction mixture was cooled to room temperature, aqueous Na_2CO_3 solution (10 ml) was added and extracted with ethyl acetate (2 × 15 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc : hexane as eluents to afford pure **3a-m**.

Characterization data of all synthesized compounds:



3a

2-(Phenylamino)-1,4-naphthoquinone (3a): Mp: 192-194 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 6.38 (s, 1H), 7.13 (d, j= 4 Hz, 1H), 7.21 (d, j= 4 Hz, 2H), 7.34-7.40 (m, 2H), 7.58(d, 1H), 7.77-7.79 (m, 2H), 8.12-8.14 (m, 1H), 8.19-8.21 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 103.41, 122.64, 125.64, 126.18, 126.54, 129.71, 132.36, 134.93, 137.46, 144.76, 182.07, 183.95; **LCMS:** *m/z* = 249 $[M]^+$; Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 81.15; H, 4.55; O, 14.41.

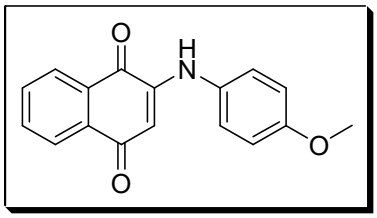


3b

2-(2-Methoxyanilino)-1,4-naphthoquinone (3b)[81]: Mp: 152-154 °C; **^{1}H NMR (400 MHz, DMSO-d6):** δ = 3.86 (s, 3H), 5.79 (s, 1H), 7.05 (td, *J = 7.6, 1.24 Hz,* 1H), 7.18 (dd, *J = 8.2 , 1.2*

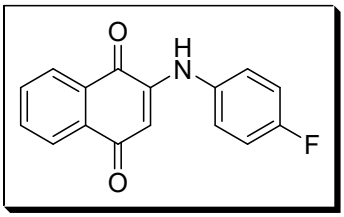
Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

Hz, 1H), 7.28 (td, *J = 8.0 , 1.4 Hz,* 1H), 7.38 (dd, *J = 8.2 , 1.2 Hz,* 1H), 7.80 (td, *J = 7.5 , 1.4 Hz,* 1H), 7.87 (td, *J = 7.4 , 1.6 Hz,* 1H), 7.96 (dd, *J = 7.4 , 1.2 Hz,* 1H), 8.07 (dd, *J = 7.6 ,1.4 Hz, 1H*), 8.66 (s, 1H); **^{13}C NMR (100 MHz, DMSO-d6):** δ = 55.75 , 102.52 , 112.14 , 120.83 , 124.22 , 125.33 , 126.09 , 126.11 ,126.89 , 130.24 ,132.62 , 132.65 , 134.97 ,145.49 ,152.31 , 181.49 , 182.29; **LCMS:** *m/z* = 279 [M]+, Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 81.15; H, 4.55; O, 14.41.



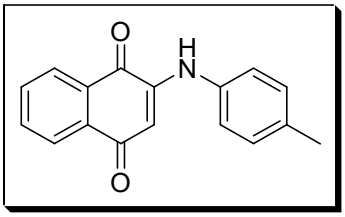
3c

2-(4-Methoxyphenylamino)-1,4-naphthoquinone (3c): Mp: 157-159 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 3.85 (s, 3H), 6.25 (s, 1H), 6.97 (d, *J = 8.0 Hz,* 2H), 7.21-7.28 (m, 2H), 7.46 (s, 1H), 7.66-7.70 (m, 1H), 7.75-7.79 (m, 1H), 8.11-8.14 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 55.57, 102.50, 114.49, 114.94, 124.86, 126.16, 126.46, 130.01, 130.43,132.22, 133.40, 134.89, 145.72, 157.71, 182.16, 183.73; **LCMS:** *m/z* = 279 [M]+, Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 81.15; H, 4.55; O, 14.41.



3d

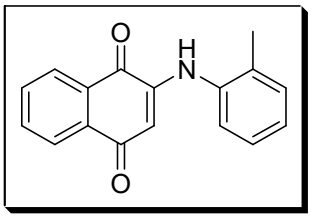
2-(4-Fluoroaniline)-1,4-naphthoquinone (3d)[81]: Mp: 162-164 °C; **^{1}H NMR (400 MHz, DMSO-d6):** δ = 6.00 (s, 1H), 7.24–7.33 (m, 2H), 7.37–7.45 (m, 2H), 7.78 (t, *J = 7.2 Hz,* 1H), 7.86 (t, *J = 7.4 Hz,* 1H), 7.95 (d, *J = 8.2 Hz,* 1H), 8.06 (d, *J = 7.8 Hz,* 1H), 9.24 (s, 1H); **^{13}C NMR (100 MHz, DMSO-d6):** δ = 101.74 , 116.06 , 125.25 , 126.00 ,126.09 , 130.40 , 132.56 , 132.61 , 134.33 , 134.88 , 146.56 , 159.36 ,181.48 , 182.4, **LCMS:** *m/z* = 267 [M]+, Anal. Calcd for $C_{16}H_{10}FNO_2$: C, 79.91; H, 3.77; N, 5.24, Found: C, 81.15; H, 4.55; O, 14.41.



3e

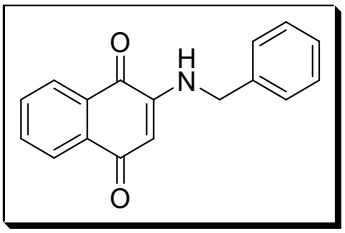
Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

2-(p-Tolylamino)-1,4-naphthoquinone (3e): Mp: 199-201 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.39 (s, 3H), 6.39 (s, 1H), 7.20-7.28 (m, 6H), 7.67-7.71 (t, J= 8.0 Hz, 1H), 7.76-7.80 (t, J= 8.0 Hz, 1H), 8.12-8.15 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 21.01, 103.03, 122.75, 126.17, 126.51, 130.26, 130.41, 132.29, 133.33, 134.74, 134.92, 135.68, 145.05, 182.17, 183.88; **LCMS:** *m*/*z* = 263 $[M]^+$; Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 81.15; H, 4.55; O, 14.41.



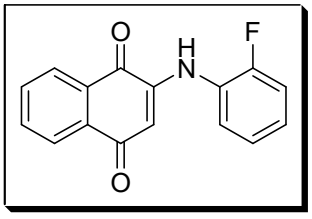
3f

2-(o-Tolylamino)naphthalene-1,4-naphthoquinone (3f)[82]: Mp: 149-151 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.30 (s, 3H), 5.98 (s, 1H), 7.19–7.33 (m, 5H), 7.67 (t, *J =7.2 Hz*, 1H), 7.76 (t, *J = 7.6 Hz*, 1H), 8.13 (t, *J = 5.6 Hz*, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 15.09, 103.10, 123.70, 126.20, 126.71, 130.32, 130.72, 132.40, 133.41, 134.69, 135.02, 135.86, 145.10, 182.19, 183.95; **LCMS:** *m*/*z* = 263 $[M]^+$; Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 81.15; H, 4.55; O, 14.41.



3g

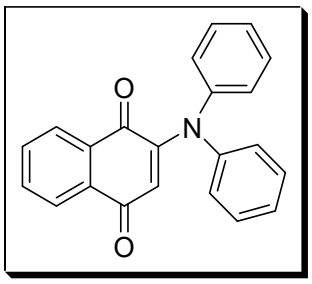
2-(Benzylamino)-1,4-naphthoquinone (3g): Mp: 159-161 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 4.40 (s, 2H), 5.86 (s, 1H), 6.29 (s, 1H), 7.28-7.43 (m, 5H), 7.63-7.67 (m, 1H), 7.73-7.77 (m, 1H), 8.07-8.13 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 46.88, 101.59, 126.29, 126.38, 127.69, 128.19, 129.05, 130.49, 132.15, 133.50, 134.84, 135. 81, 147.89, 181.76, 183.08; **LCMS:** *m*/*z* = 263 $[M]^+$; Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.78; N, 5.32. Found: C, 81.15; H, 4.55; O, 14.41.



3h

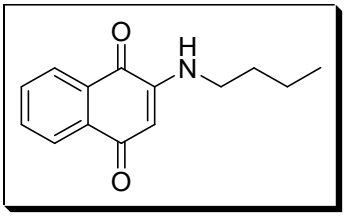
Catalyst Research Volume 23, Issue 2, November 2023 Pp. 3596-3612

2-(2-Fluorophenylamino)-1,4-naphthoquinone (3h)[81]**: Mp:** 159-161 °C; **^{1}H NMR (400 MHz, DMSO-d6):** δ = 5.56 (d, *J = 3.1 Hz*, 1H), 7.27–7.34 (m, 1H), 7.35–7.42 (m, 2H), 7.45 (td, *J = 7.4 , 1.2 Hz*, 1H), 7.80 (td, *J = 7.4, 1.6 Hz*, 1H), 7.87 (td, *J = 7.4,1.2 Hz*, 1H), 7.95 (dd, *J = 7.8, 1.2 Hz*, 1H), 8.07 (dd, *J = 7.4, 1.2 Hz*, 1H), 9.13 (s, 1H); **^{13}C NMR (100 MHz, DMSO-d6):** δ = 102.92, 116.56, 125.18, 125.23, 125.35, 126.11,127.78, 128.31, 130.33, 132.46, 132.74, 134.91, 146.79, 156.12, 181.15, 182.39; **LCMS:** *m/z* = 267 [M]+, Anal. Calcd for $C_{16}H_{10}FNO_2$: C, 79.91; H, 3.77; N, 5.24, Found: C, 81.15; H, 4.55; O, 14.41.



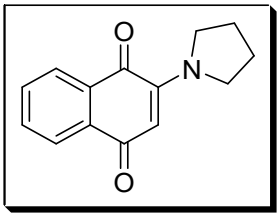
3i

2-(Diphenylamino)-1,4-naphthoquinone (3i): Mp: 160-162 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 6.83-6.92 (m, 1H), 7.07-7.13 (m, 2H), 7.15 (d, J= 8.0 Hz, 2H), 7.23 (d, J= 8.0 Hz, 2H), 7.34-7.38 (t, 2H), 7.59 (d, j= 8.0Hz, 2H), 7.78-7.80 (m, 2H), 8.12-8.14 (m, 1H), 8.19-8.21 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 116.01, 119.91, 122.84, 123.84, 125.85, 126.61, 127.01, 128.28, 129.54, 129.86, 131.10, 132.24, 132.51, 132.72, 133.64, 133.72, 135.03, 147.26, 185.06, 185.22; **LCMS:** *m/z* = 325 $[M]^+$; Anal. Calcd for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.30. Found: C, 81.15; H, 4.55; O, 14.41.



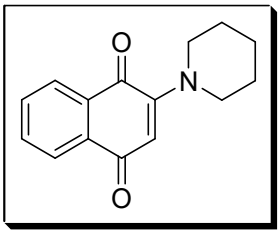
3j

2-(Butylamino)-1,4-naphthoquinone (3j)[82]**: Mp:** 120-122 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 0.96–1.00 (m, 3H), 1.42–1.49 (m, 2H), 1.66–1.72 (m, 2H), 3.17–3.21 (m, 2H), 5.74 (s, 1H), 5.90 (s, 1H), 7.62 (t, *J = 7.6 Hz*, 1H), 7.74 (t, *J = 7.4 Hz,* 1H), 8.04–8.12 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 14.2, 21.4, 33.6, 45.6, 61.3, 112.9, 127.10, 133.42, 133.90, 134.25, 156.22, 184.19, 185.53; **LCMS:** *m/z* = 229 $[M]^+$; Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 81.15; H, 4.55; O, 14.41.



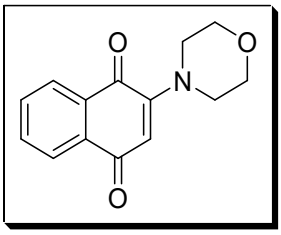
3k

2-(Pyrrolidin-1-yl)-1,4-naphthoquinone (3k)[82]**: Mp:** 160-162 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.02 (s, 4H), 3.23 (s, 2H), 3.99 (s, 2H), 5.75 (s, 1H), 7.59–7.72 (m, 2H), 8.01–8.08 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 26.0, 52.2, 65.3, 108.9, 125.44, 126.60, 132.22, 132.58, 132.97, 133.75, 154.14, 183.39, 183.53; **LCMS:** *m*/*z* = 227 $[M]^+$; Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 81.15; H, 4.55; O, 14.41.



3l

2-(Piperidin-1-yl)-1,4-naphthoquinone (3l): Mp: 82-84 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.73 (s, 6H), 3.51 (s, 4H), 6.03 (s, 1H), 7.61-7.65 (m, 1H), 7.67-7.71 (m, 1H), 7.99 (d, J= 8.0Hz, 1H), 8.04 (d, J= 8.0Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 24.32, 25.76, 50.44, 110.35, 125.44, 126.60, 132.22, 132.58, 132.97, 133.75, 154.14, 183.39, 183.53; **LCMS:** *m*/*z* = 241 $[M]^+$; Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 81.15; H, 4.55; O, 14.41.



3m

2-Morpholino-1,4-naphthoquinone (3m): Mp: 151-153°C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 3.52(s, 4H), 3.88 (s, 4H), 6.04 (s, 1H), 7.67–7.72 (m, 2H), 8.01-8.07 (m, 2 H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 43.33, 49.17, 63.83, 66.43, 111.97, 125.63, 126.73, 132.24, 133.73, 133.98, 153.65, 182.91, 183.77; **LCMS:** *m*/*z* = 243 $[M]^+$; Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 81.15; H, 4.55; O, 14.41.

References

1. Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449; (b) Teagues, S. J.; Davis, A. M.; Leeson, P. D.; Opera, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 3743.
2. Sunassee, S. N.; Davies-Coleman, M. T. *Nat. Prod. Rep.* **2012***, 29*, 513.
3. Asche, C.; Mini- *Rev. Med. Chem.* **2005**, *5* 449.
4. Kovacic, P.; Somanathan, R. *Anti-Cancer Agents Med. Chem.* **2011**, *11*, 658.
5. Salustiano, E.; Netto, C.; Fernandes, R.; da Silva, A.; Bacelar, T.; Castro, C.; Buarque, C.; Maia, R.; Rumjanek, V.; Costa, P. *Invest. New Drugs* **2009**, *28*, 139.
6. Foye, M. O. Cancer Chemotherapeutic Agents; *American Chemical Society*: Washington, D.C., **1995**, 203.
7. Liu, L. F.; Row, T. C.; Yang, L. *J. Biol. Chem.* **1984**, *259*, 9182.
8. Leopold, W. R.; Shillis, J. L.; Mertus, A. E.; Nelson, J. M.; Roberts, B. J.; Jackson, R. C. *Cancer Res.* **1984**, *44*, 1928.
9. Scheithauer, W.; Von Hoff, D. D.; Clark, G. M.; Shillis, J. L.; Elslager, E. F. *Eur. J. Cancer Clin. Oncol.* **1986***, 22*, 921.
10. Wakelin, L. P. G.; Waring, M. J. *DNA Intercalating Agents. In Comprehensive Medicinal Chemistry*; Sammes, P. G., Ed.; Vol. 2; Pergamon Press: Oxford, UK, **1990,** 703.
11. Chabner, B. A.; Allegra, C. J.; Curt, G. A.; Calabresi, P. Antineoplastic Agents. In Goodman and Gilman's The Pharmacological Basis of Therapeutics; Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon, R. W., Gilman, A. G., Eds., 9th ed.; McGraw-Hill: New York, NY, USA, **1996**, 1233.
12. Kayashima, T.; Mori, M.; Mizutani, R.; Nishio, K.; Kuramochi, K.; Tsubaki, K.; Yoshida, H.; Mizushina, Y.; Matsubara, K. *Bioorg. Med. Chem.* **2010***, 18*, 6305.
13. Mital, A.; Sonawane, M.; Bindal, S.; Mahlavat, S.; Negi, V. *Der. Pharm. Chem.* **2010***, 2,* 63.
14. Josey, B. J.; Inks, E. S.; Wen, X.; Chou, C. J. *J. Med. Chem.* **2013***, 56*, 1007.
15. López, Ll. I.; Leyva, E.; García de la Cruz, R. *Rev. Mexicana de Ciencias Farmacéuticas* **2011***, 42*, 6.
16. El-Najjar, N.; Gali-Muhtasib, H.; Ketola, R. A.; Vuorela, P.; Urtti, A.; Vuorela, H. *Phytochem. Rev.* **2011***, 10*, 353.
17. Tran, T.; Saheba, E.; Arcerio, A. V.; Chavez, V.; Li, Q. Y.; Martínez, L. E.; Primm, T. P. *Bioorg. Med. Chem.* **2004***, 12*, 4809.
18. Kapadia, G. J.; Azuine, M. A.; Balasubramanian, V.; Sridhar, R. *Pharmacol. Res.* **2001***, 43,* 363.
19. Ibis, C.; Tuyun, A. F.; Ozsoy-Gunes, Z.; Bahar, H.; Stasevych, M. V.; Musyanovych, R. Y.; Komarovska-Porokhnyavets, O.; Novikov, V. *Eur. J. Med. Chem.* **2011**, *46*, 5861.
20. Kitagawa, R. R.; Bonacorsi, C.; da Fonseca, L. M.; Vilegas, W.; Raddi, M. S. G. *Rev. Bras. Farmacogn.* **2012***, 22*, 53.

21. Kayashima, T.; Mori, M.; Yoshida, H.; Mizushina, Y.; Matsubara, K. *Cancer Lett.* **2009***, 278*, 34.
22. Da Silva, E. N.; de Deus, C. F.; Cavalcanti, B. C.; Pessoa, C.; Costa-Lotufo, L. V.; Montenegro, R. C.; de Moraes, M. O.; Pinto, M. C. F. R.; de Simone, C. A.; Ferreira, V. F.; Goulart, M. O. F.; Andrade, C. K. Z.; Pinto, A. V. *J. Med. Chem.* **2010***, 53*, 504.
23. Zakharova, O. D.; Ovchinnikova, L. P.; Goryunov, L. I.; Troshkova, N. M.; Shteingarts, V. D.; Nevinsky, G. A. *Eur. J. Med. Chem.* **2010***, 45*, 2321.
24. Benites, J.; Valderrama, J. A.; Bettega, K.; Pedrosa, R. C.; Calderon, P. B.; Verrax, J. *Eur. J. Med. Chem.* **2010***, 45*, 6052.
25. Pradidphol, N.; Kongkathip, N.; Sittikul, P.; Boonyalai, N.; Kongkathip, B. *Eur. J. Med. Chem.* **2012***, 49*, 253.
26. Barbosa, T. C.; Camara, C. A.; Silva, T. M. S.; Martins, R. M.; Pinto, A. C.; Vargas, M. D. *Bioorg. Med. Chem.* **2005***, 13*, 6464.
27. Del Corral, J. M. M.; Castro, M. A.; Gordaliza, M.; Mart õn, M. L.; Gualberto, S. A.; Gamito, A. M.; Vuevas, C.; San Feliciano, A. *Bioorg. Med. Chem.* **2005***, 13*, 631.
28. (a) Moret, E. E.; de Boer, M.; Hilbers, H. W.; Tollenaere, J. P.; Janssen, L. H. M.; Holthuis, J. J. M.; Driebergen, R. J.; Verboom, W.; Reinhoudt, D. N. *J. Med. Chem.* **1996***, 39*, 720; (b) Bakare, O.; Ashendel, C. L.; Peng, H.; Zalkow, L. H.; Burgess, E. M. *Bioorg. Med. Chem.* **2003***, 11*, 3165.
29. Oliveira, C. G. T.; Miranda, F. F.; Ferreira, V. F.; Freitas, C. C.; Rabello, R.; Carballido, J. M.; Corre ˇ a, L. C. D. *J. Braz. Chem. Soc.* **2001***, 12*, 339.
30. King-Diaz, B.; Macias-Ruvalcaba, N.A.; Aguilar-Martinez, M.; Calaminci, P.; Koster, A. M.; Gomez-Sandoval, Z.; Reveles, J.U.; Lotina-Hennsen, B. *J. Photochem. Photobiol., B* **2006,** *83,* 105.
31. Cao, S.; Murphy, B. T.; Foster, C.; Lazo, J. S.; Kingston, D. G. I. *Bioorg. Med. Chem.* **2009,** *17,* 2276.
32. Francisco, A. I.; Casellato, A.; Neves, A. P.; Carneiro, J. W. M.; Vargas, M. D.; Visentin, L. D.; Magalhaes, A.; Camara, C. A.; Pessoa, C.; Costa-Lotufo, L.V.; Marinho Filho, J. D. B.; de Moraes, M. O. *J. Brazilian Chem. Soc.* **2010,** *21,*169.
33. Benites, J.; Valderrama, J. A.; Bettega, K.; Curi Pedrosa, R.; Buc Calderon, P.; Verrax, J. *Eur. J. Med. Chem.* **2010,** *45,* 6052.
34. (a) Takagi, K.; Matsuoka, M.; Hamano, K.; Kitao, T. *Dyes Pigments* **1984**, *5*, 241. (b) Matsuoka, M.; Takagi, K.; Obayashi, H.; Wakasugi, K.; Kitao, T. *J. Soc. Dyers Colour.* **1983**, *99*, 257.
35. (a) Kikuchi, M.; Komatsu, K.; Nakano, M. *Dyes Pigments* **1990***, 12,* 107. (b) Yoshida, M. Jpn Kokai Tokkyo Koho **1987**, JP 86-94307, 860423 (Chem. Abstr. **1988** *108*, 173357y). (c) Kikushi, M.; Nakano, M. *Sen'i Gakkaishi* **1987***, 43,* 602.
36. (a) Escolastico, C.; Santa Maria, M. D.; Claramunt, R. M.; Jimeno, M. L.; Alkorta, I.; Foces-Foces, C.; Cano, F. H.; Elguero, J. *Tetrahedron* **1994***, 50*, 12489. (b) Catalan, J.;

Febero, F.; Guijarro, M. S.; Claramunt, R. M.; Santa Maria, M. D.; Foces-Foces, M.; Cano, F. H.; Elguero, J.; Sastre, R. *J. Am. Chem. Soc.* **1990***, 112*, 747.

37. (a) Mischenko, N. P.; Fedoreyev, S. A.; Pokhilo, N. D.; Anufriev, V. Ph.; Denisenko, V. A.; Glazunov, V. P. *J. Nat. Prod.* **2005***, 68*, 1390; (b) Pokhilo, N. D.; Shuvalova, M. I.; Lebedko, M. V.; Sopelnyak, G. I.; Yakubovskaya, A. Ya.; Mischenko, N. P.; Fedoreyev, S. A.; Anufriev, V. Ph. *J. Nat. Prod.* **2005***, 69*, 1125.
38. Cai, P.; Kong, F.; Ruppen, M. E.; Glasier, G.; Carter, G. T. *J. Nat. Prod.* **2005***, 68*, 1736.
39. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981***, 37*, 3873 and references therein.
40. Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1973***, 21*, 931 and references therein.
41. Lancini, G.; Zanichelli, W. Antibiotics; Perlman, D., Ed.; Academic Press: New York, **1977**; 531-600.
42. Lanz, T.; Tropf, S.;Marner, F-J.; Schroder, J.; Schroder, G. *J. Biol. Chem.* **1991***, 266*, 9971.
43. Jiang, M. -C.; Chuang, C. -P. *J. Org. Chem.* **2000***, 65*, 5409.
44. Chuang, C. -P.; Wu, Y. -L.; Jiang, M. -C. *Tetrahedron* **1999***, 55*, 11229.
45. Chuang, C. -P.; Wang, S. -F. *Heterocycles* **1999***, 50*, 489.
46. (a) Wu, Y. -L.; Chuang, C. -P.; Lin, P. -Y. *Tetrahedron* **2001***, 57*, 5543; (b) Chuang, C. -P.; Wang, S.- F. *Tetrahedron* **1998***, 54*, 10043.
47. Marcos, A.; Pedregal, C.; Avendano, C. *Tetrahedron* **1994***, 50*, 12941.
48. Mohrle, H.; Herbr € uggen, G. S. € *Arch. Pharm.* **1991***, 324*, 165.
49. Kutyrev, A. A. *Tetrahedron* **1991***, 47*, 8043.
50. Thomson, R. H. *J. Org. Chem.* **1948***, 13*, 377.
51. Chu, K. Y.; Griffiths, J. *J. Chem. Soc., Perkin Trans.* **1979,** *1*, 696.
52. Agarwal, N. L.; Schaefer, W. *J. Org. Chem.* **1980***, 45*, 5139.
53. Agarwal, N. L.; Schaefer, W. *J. Org. Chem.* **1980***, 45*, 5144.
54. Agarwal, N. L.; Schaefer, W. *J. Org. Chem.* **1980***, 45*, 2155.
55. Couladouros, E. A.; Plyta, Z. F.; Papageorgiou, V. P. *J. Org. Chem.* **1996***, 61*, 3031.
56. Blackburn, C. *Tetrahedron Lett.* **2005***, 46*, 1405.
57. Matsuoka, M.; Takei, T.; Kitao, T. *Chem. Lett.* **1979***, 8*, 627.
58. Macleod, J. W.; Thomson, R. H. *J. Org. Chem.* **1960***, 25*, 36.
59. Panetta, C. A.; Fan, P.; Fattah, R.; Greever, J. C.; He, Z.; Hussey, C. L.; Sha, D.; Wescott, L. D., Jr. *J. Org. Chem.* **1999***, 64*, 2919.
60. Machocho, A. K.; Win, T.; Grinberg, S.; Bittner, S. *Tetrahedron Lett.* **2003***, 44*, 5531.
61. Aguilar-Martínez, M.; Cuevas, G.; Jiménez-Estrada, M.; González, I.; Lotina- Hennsen, B.; Macías-Ruvalcaba, N. *J. Org. Chem.* **1999***, 64*, 3684.
62. Lisboa, C.; Santos, V. G.; Vaz, B. G.; de Lucas, N. C.; Eberlin, M. N.; Garden, S. J. *J. Org. Chem.* **2011***, 76*, 5264.
63. Falling, S.; Rapoport, H. *J. Org. Chem.* **1980***, 45*, 1260
64. Charati, F. R.; Hossaini, Z. *Synlett.* **2012**, 2397; (b) Gu, Y.; De Sousa, R.; Frapper, G.; Bachmann, C.; Barrault, J.; Jerome, F. *Green Chem.* **2009***, 11*, 1968.

65. (a) McNulty, J.; Das, P. *Eur. J. Org. Chem.* **2009***, 24*, 4031; (b) McNulty, J.; Das, P. *Tetrahedron Lett.* **2009***, 50*, 5737; (c) McNulty, J.; Das, P.; McLeod, D. *Chem. Eur. J.* **2010***, 16*, 6756; (d) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005***, 21*, 3157; (e) Das, P.; McLeod, D.; McNulty, J. *Tetrahedron Lett.* **2011***, 52*, 199; (f) Andrade, C. K. Z.; Alves, L. M. Curr. *Org. Chem.* **2005***, 9*, 195.
66. (a) Choudhary, G.; Peddinti, R. K. *Green Chem.* **2011***, 13*, 276; (b) Liu, J.; Lei, M.; Hu, L. *Green Chem.* **2012***, 14,* 2534; (c) Kumaravel, K.; Vasuki, G. *Green Chem.* **1945***, 2009*, 11.
67. Lourenco, A. L.; Abreu, P. A.; Leal, B.; da Silva, E. N., Jr.; Pinto, A. V.; Pinto, M. C. F. R.; Souza, A. M. T.; Novais, J. S.; Paiva, M. B.; Cabral, L. M.; Rodrigues, C. R.; Ferreira, V. F.; Castro, H. C. *Curr. Microbiol.* **2011***, 62*, 684.
68. Tandon, V. K.; Maurya, H. K.; Verma, M. K.; Kumar, R.; Shukla, P. K. *Eur. J. Med. Chem.* **2010***, 45*, 2418.
69. Tandon, V. K.; Maurya, H. K.; Mishra, N. N.; Shukla, P. K. *Bioorg. Med. Chem. Lett.* **2011***, 21*, 6398.
70. Calonghi, N.; Pagnotta, E.; Parolin, C.; Mangano, C.; Bolognesi, M. L.; Melchiorre, C.; Masotti, L. *Biochem. Biophys. Res. Commun.* **2007**, *342*, 409.
71. Chen, Z.; Yang, Y.; Zhang, N.; Turpin, J.; Buckheit, A. R. W.; Osterling, C. Oppenheim, J. J.; Howard, O. M. Z. *Antimicrob. Agents Chemother.* **2003**, *47*, 2810.
72. Baggish, A. L.; Hill, D. R. *Antimicrob. Agents Chemother.* **2002**, *46*, 1163.
73. Zhou, J.; Duan, L.; Chen, H.; Ren, X.; Zhang, Z.; Zhou, F.; Liu, J.; Pei, D.; Ding, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5091.
74. Lin, T. -S.; Zhu, L. -Y.; Xu, S. -P.; Divo, A. A.; Sartorelli, A. C. *J. Med. Chem.* **1991**, *34*, 1634.
75. Tandon, V. K.; Rakeshwar, B. C.; Singh, R. V.; Rai, S.; Yadav, D. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1079.
76. Verma, R. P. *Anti-Cancer Agents Med. Chem.*, **2006**, *6*, 489.
77. Rios, D.; Benites, J.; Torrejon, F.; Theoduloz, C.; Valderrama, J. A. Med. Chem. Res. 2014, 23, 4149.
78. Bala, B. D.; Muthusaravanan, S.; Choon, T. S.; Ali, M. A.; Perumal, S. *Eur. J. Med.Chem.* **2014**, *85*, 737.
79. Leyva, E.; Baines, K. M.; Espinosa-Gonza´ lez, C. G.; Magaldi-Lara, D. A.; Loredo-Carrillo, S. E.; De Luna-Me´ndez, T. A.; Lo´ pez, L. I. *J. Fluorine Chem.* **2015,** *180,* 152.
80. Bing, L.; Ji, S. -J. *Synth. Commun.* **2008,** *38*, 1201.