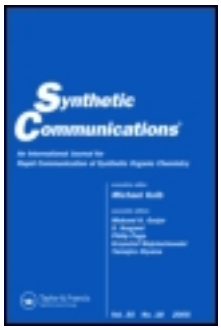

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Design, Synthesis and Antibacterial Evaluation of Same Novel 3'-(Phenylamino)-1'H-spiro[Indoline-3,2'-quinazoline] -2,4'(3'H)-dione Derivatives

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Accepted author version posted online: 27 Aug 2013.

To cite this article: Synthetic Communications (2013): Design, Synthesis and Antibacterial Evaluation of Same Novel 3'-(Phenylamino)-1'H-spiro[Indoline-3,2'-quinazoline] -2,4'(3'H)-dione Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI: 10.1080/00397911.2013.796992

To link to this article: http://dx.doi.org/10.1080/00397911.2013.796992

Design, synthesis and antibacterial evaluation of same novel 3'-(phenylamino)-1'*H*-spiro[indoline-3,2'-quinazoline] -2,4'(3'*H*)-dione derivatives

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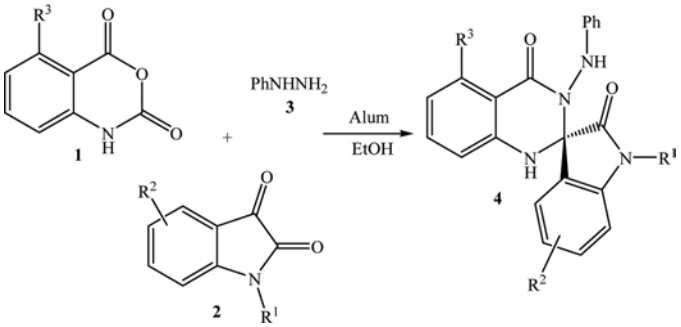
Abstract

A combinatorial synthesis and evaluated antibacterial activity against clinically isolated resistant strains of Gram-positive and Gram-negative bacteria of 3'-(phenylamino)-1'*H*-spiro[indoline-3,2'-quinazoline]-2,4'(3'*H*)-dione derivatives is described.



KEYWORDS: Isatoic anhydride, Spirooxindole , Quinazoline, Alum, Antibacterial activity

INTRODUCTION

Multicomponent[1-5] and domino reactions[6-9] are powerful tools in the creation of several bonds in a single operation as well as in modern drug discovery process in terms of lead finding and lead optimization.

2,3-Dihydroquinazoline-4(3*H*)-ones and spirooxindole derivatives are important in biologically active and heterocyclic compounds.

Quinazolinones derivatives are an important class of molecules with biological and pharmaceutical utility revealing antiinflammatory,[10] antihypertensive,[11] anticancer,[12] antiviral,[13] and antibacterial activity.[14] In addition, these compounds are present in several bioactive natural products.[15,16]

Spirooxindole are useful as antibacterial, antiinflammatory, anticancer and iaxatives.[17,18] Furthermore, this ring structures were recently isolated from plant and fungi; for example pteropodine or uncarine C (PT) was specifically isolated from *cat's claw*,[19] spirotryprostatin B, a natural alkaloid has been isolated from the fermentation broth of *aspergillusfumigatus* and identified as a novel inhibitor of microtubule assembly.[20,21] Also, horsfiline was isolated from the malaysian medicinal plant *horsfildea superba* warb,[22] whereas spiro[pyrrolidine-3,30-oxindole] alkaloid elacomine was derived from *E. commutate* (Figure 1).[23]

There are several methods reported in the literature for the preparation of spirooxindoles derivatives.[24-27]

RESULTS AND DISCUSSION

We have concentrated most of our recent studies on the synthesis of heterocycles compounds,[28] alum,[29,30] and MCRs[31,32] for the synthesis of 2,3-dihydroquinazolin-4(3*H*)-one,[33] spiro[indoline-3,2-quinazoline]-2,4(3*H*)-dione,[34] oxindole,[35] and spirooxindole.[36] In the course of our investigations, we envisioned the one-pot three-component synthesis of 3'-(phenylamino)-1'*H*-spiro[indoline-3,2'-quinazoline]-2,4'(3'*H*)-dione **4a**-m from isatoic anhydride **1**, isatins **2** and phenyl hydrazine **3** in the presence of alum as a non-toxic, easily available and heterogeneous catalyst.(Scheme 1)

The results of optimization experiments for the preparation of 3'-(phenylamino)-1'*H*-spiro[indoline-3,2'-quinazoline]-2,4'(3'*H*)-dione by a straightforward one-pot three-component condensation involving isatoic anhydrides **1**, isatins **2**, and phenyl hydrazine **3** in ethanol was stirred and refluxed with alum as catalysts are presented in Table 1.

It is noticeable that when the isatoic anhydride **1a-b**, isatin **2a–m**, and phenyl hydrazine **3** in the presence of alum were stirred at reflux for within 1 h, in all cases the reaction led to the formation of the intermediates **8** that could be isolated and characterized by spectroscopic methods. Furthermore, the continuation of reaction for 3 h led to a mixture of **4a–m** and intermediates **8** (monitored by TLC and spectroscopic methods), meanwhile after the times indicated in Table 1, just **4a–m** were obtained and the intermediates **8** was

not detected in the final mixture.

According to the results, the reaction can be mechanistically considered to proceed via the initial formation of the intermediates **8** by the nucleophilic addition of phenyl hydrazine to isatoic anhydride as a key intermediate. Then, the isatin attacks *N*-atom from **8** to form an intermediate **9**, leaving a water to afford **10**, which then transforms the final product via nucleophilic attack taking place by the nitrogen group. (Scheme 2)

The newly synthesized compounds were screened in vitro for their antibacterial activities against of bacteria *Escherichia coli ATCC 25922, Pseudomonas aeruginusa* ATCC 85327, *Klebsiella pneumonia*, ATCC 29655 (Gram-negative bacteria), *Enterococcus faecalis* ATCC 29737, *Bacillus subtilis* ATCC 465, *Bacillus pumilus* PTCC 1114, *Micrococcus luteus* PTCC 1110, *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Sterptococcus mutans* PTCC 1601 (Gram-positive bacteria) by the disk diffusion method (IZ),[37] and subsequently the minimum inhibitory concentration method (MIC).[38]

Activities of each compound were compared with Tetracycline and Gentamicin as standards. MIC and IZ results for bacterial strains are shown in Table 2.

The screening results indicate that some of the tested compounds exhibit significant antibacterial activities when compared with the reference drugs. It was observed that the compounds containing R^1=H and R^3=Cl substituted groups show better activity than the other test compounds and the reference, Tetracycline and Gentamicin, drugs.

Meanwhile, 3'-(phenylamino)-1'*H*-spiro[indoline-3,2'-quinazoline]-2,4'(3'*H*)-dione compounds **4e**, **4j**, **4k**, **4l** exhibited good activity, while the remaining compounds generally showed inferior activities against all the tested strains.

CONCLUSION

In summary, we have developed a new strategy that provides an efficient entry in to 1'*H*-spiro[isoindoline-1,2'-quinazoline]-3,4'(3'*H*)-dione derivatives via a one-pot three component reaction from isatoic anhydride, isatine, and phenyl hydrazine. Our designed process requires mild reaction conditions, have high yields of products, uses very simple accessible starting materials and solvents, as well as an inexpensive, non-toxic, and easily available heterogeneous catalyst, and easy experimental workup procedure.

EXERIMENTAL

General

Melting points were obtained in open capillary tubes and were measured on an electro-thermal 9200 apparatus. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. The IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz. Elemental analysis for C, H and N were performed using a Heraus CHN rapid analyzer.

General Procedure For Preparation Of 3'-(Phenylamino)-1'*H*- Spiro[Indoline-3,2'-Quinazoline]-2,4'(3'*H*)-Dione (3a-M)

A mixture of isatoic anhydride **1** (1 mmol), isatin **2** (1 mmol), phenyl hydrazine **3** (1 mmol), 0.3 g (0.6 mmol) alum, and 10 ml EtOH in a 50 ml flask was stirred at reflux for time period as indicated in Table 1. After completion of the reaction (monitored by TLC, ethylacetate/n-hexane, 1:1), 25 ml EtOH was added to the reaction mixture, and recrystallized from ethanol to afford pure product.

3'-(Phenylamino)-1'*H*-Spiro[Indoline-3,2'-Quinazoline]-2,4'(3'*H*)-Dione (4a)

yellow powder (92%); mp: 174 -176 ºC. IR (KBr): ν_{max} = 3296, 3067, 1736, 1656, 1613 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 6.67-7.92 (15H, m, H-Ar, 2NH), 10.45 (1H, s, NH) ppm; ^{13}C NMR ($CDCl_3$) δ= 78.7, 110.5, 110.8, 113.5, 113.9, 114.4, 117.9, 119.7, 122.2, 125.6, 127.7, 127.9, 128.7, 131.1, 134.4, 143.3, 146.7, 148.9, 165.6, 175.8 ppm; MS: *m/z* (%)= 356(M^+). Anal. Calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72%. Found: C, 70.71; H, 4.48; N, 15.64%.

SUPPLEMENTARY INFORMATION

General experimenl procedures, IR, ^1H and ^{13}C NMR, and MS data, and experimental analysis for compounds **4a-m** are available online.

ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the Research Council of Iran National Science Foundation: INSF.

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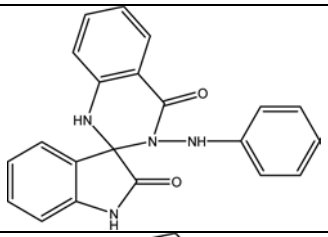
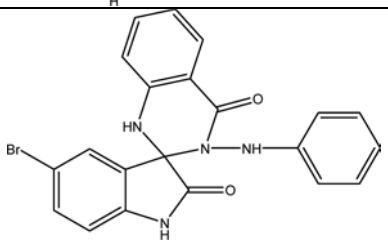
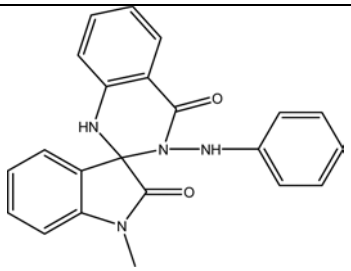
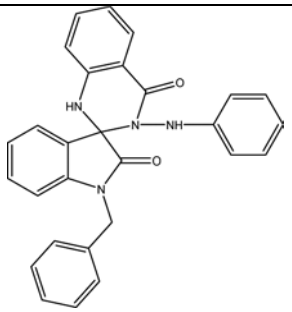
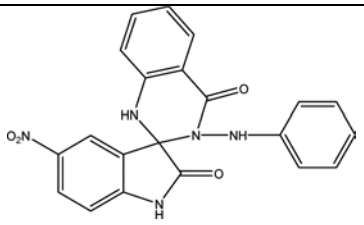
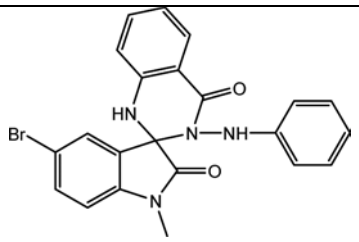
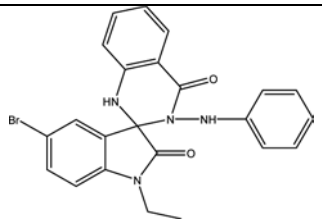
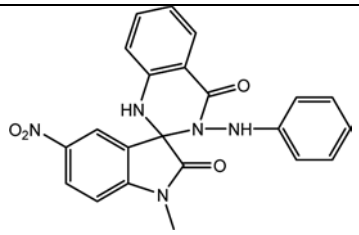
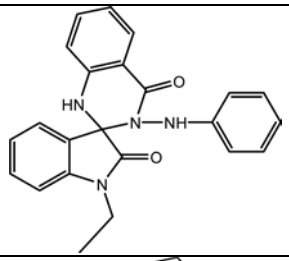
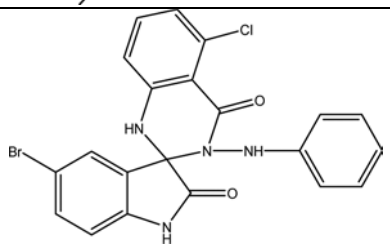
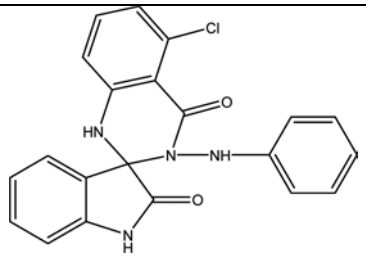
Table 1. The synthesis of 2-Aryl-3-(phenylamino)- 1'*H*-spiro[indoline-3,2'-quinazoline]-2,4'(3'*H*)-dione 4a–m

Entry	R_1	R_2	R_3	Product 4	Yield[a] (%)	Time(h)
A	H	H	H		92	5.5
B	H	Br	H		97	5
C	CH_3	H	H		90	5
D	Bz	H	H		83	6
E	H	NO_2	H		95	4

F	CH_3	Br	H		85	5
G	Et	Br	H		93	5
H	Me	NO_2	H		90	4
I	Et	H	H		60	7
J	H	Br	Cl		87	6
K	H	H	Cl		90	6

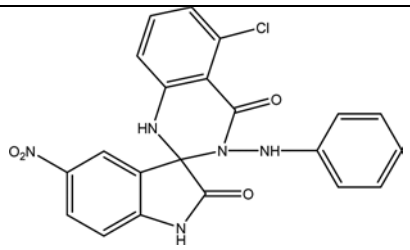
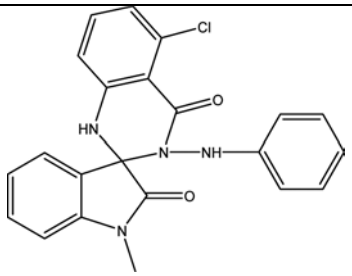
L	H	NO_2	Cl		94	5
M	Me	H	Cl		88	6

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Table 2. Antibiotic activity of the synthesized compounds and standard antibiotics against some gram positive and gram negative bacteria, as determined by disc diffusion test (IZ) and Minimum Inhibitory Concentration (MIC) methods.

Microorganisms	Tetracycline (30 (ig/disc)		Gentamicin (10 iig/disc)		4a		4b		4c		4d		4e		4f	
	IZ[a]	MIC[b]	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
***Bacillus subtilis* (ATCC 465)**	21	4	0	NT[c]	14	128	13	256	0	NT	0	NT	16	4	12	512
***Bacilluspumilus* (PTCC 1114)**	17	8	0	NT	18	16	14	128	0	NT	0	NT	18	4	0	NT
***Micrococcus luteus* (PTCC 1110)**	19	4	0	NT	14	64	12	256	0	NT	0	NT	16	8	0	NT
***Staphylococcus aureus* (ATCC 25923)**	20	4	0	NT	16	32	14	256	0	NT	0	NT	18	4	14	128
***Staphylococcus epidermidis* (ATCC**	34	<2	0	NT	14	32	15	256	0	NT	0	NT	16	4	8	512

12228)																
Sterptococcus mutans **(PTCC 1601)**	24	2	0	NT	16	32	16	64	0	NT	0	NT	18	<2	15	32
Escherichia coli **(ATCC 25922)**	0	NT	23	4	14	64	0	NT	0	NT	0	NT	16	4	14	32
Enterococcus faecalis **(ATCC 29737)**	9	8	0	NT	8	256	0	NT	0	NT	0	NT	14	16	0	NT
Pseudomonas aeruginosa **(ATCC 85327)**	0	NT	12	8	10	256	0	NT	0	NT	0	NT	15	32	0	NT
Klebsiella pneumonia **(ATCC 29655)**	8	16	0	NT	10	256	0	NT	0	NT	0	NT	14	8	13	256

Microorganisms	4g		4h		4i		4j		4k		41		4m	
	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
Bacillus subtilis (ATCC 465)	14	64	0	NT	0	NT	20	4	16	8	23	<2	0	NT

Bacillus pumilus (PTCC 1114)	13	128	0	NT	0	NT	22	<2	19	4	28	<2	0	NT
Micrococcus luteus (PTCC 1110)	0	NT	0	NT	0	NT	18	4	16	8	20	2	0	NT
Staphylococcus aureus (ATCC 25923)	12	512	0	NT	0	NT	25	2	18	2	20	2	0	NT
Staphylococcus epidermidis (ATCC 12228)	0	NT	0	NT	0	NT	23	2	15	4	19	2	0	NT
Sterptococcus mutans (PTCC 1601)	0	NT	0	NT	0	NT	28	<2	17	8	16	8	0	NT
Escherichia coli (ATCC 25922)	0	NT	0	NT	0	NT	22	<2	14	32	19	<2	0	NT
Enterococcus faecalis (ATCC	0	NT	0	NT	0	NT	19	<2	10	128	16	8	0	NT

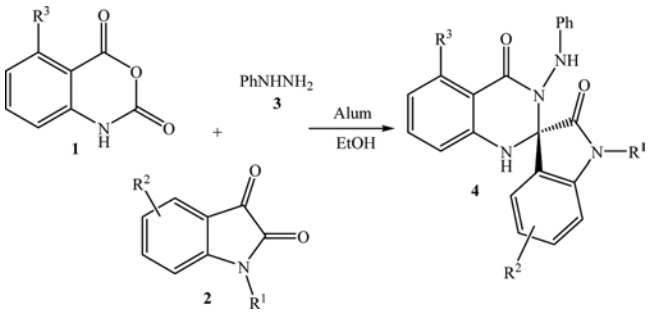
29737)														
Pseudomonas aeruginosa (ATCC 85327)	0	NT	0	NT	0	NT	17	8	0	NT	15	16	0	NT
Klebsiella pneumonia (ATCC 29655)	0	NT	0	NT	0	NT	15	4	0	NT	12	16	0	NT

[a]Inhibition Zone (mm)

[b]Minimum Inhibitory Concentration (ng/ml)

[c]Not Tested

Scheme 1. synthesis of pyrroles **3a-h**



Scheme 2.

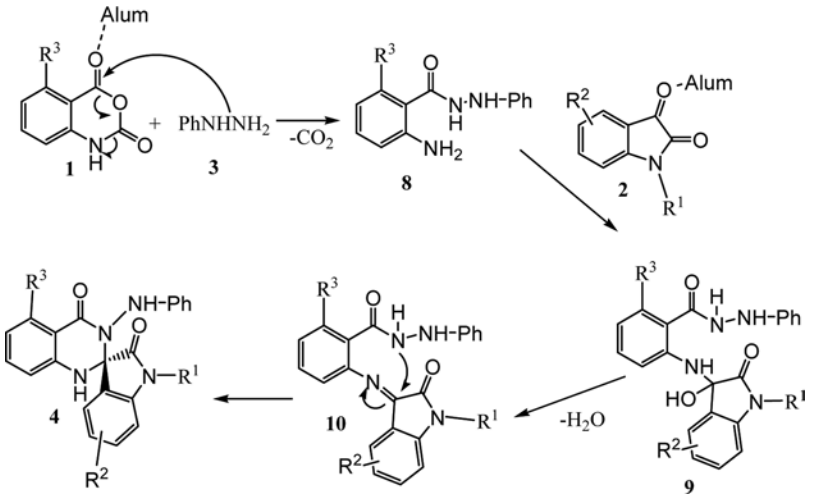


Figure 1.