DESIGN, SYNTHESIS, AND ANTIBACTERIAL EVALUATION OF SOME NOVEL 3’-(PHENYLAMINO)-1’H-SPIRO[INDOLINE-3,2’-QUINAZOLINE]-2, 4’(3’H)-DIONE DERIVATIVES

Ali A. Mohammadi,1 Saber Askari,1 Hamed Rohi,2 and Ali Abolhasani Soorki3
1Chemistry and Chemical Engineering Research Center of Iran (CCERCI), Tehran, Iran
2Department of Chemistry, Faculty of Sciences, Shahid Beheshti University, Tehran, Iran
3Research Institute of Applied Sciences, Academic Center for Education, Culture, and Research, Tehran, Iran

GRAPHICAL ABSTRACT

Abstract A combinatorial synthesis and evaluation of 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 Alum; antibacterial activity; isatoic anhydride; spirooxindole; quinazoline

INTRODUCTION

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

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Address correspondence to Ali A. Mohammadi, Chemistry and Chemical Engineering Research Center of Iran (CCERCI), P. O. Box 14335-186, Tehran, Iran. E-mail: aliamohammadi@ccerci.ac.ir
2,3-Dihydroquinazoline-4(3H)-one and spirooxindole derivatives are important in biologically active and heterocyclic compounds.

Quinazolinone derivatives are an important class of molecules with biological and pharmaceutical utility such as anti-inflammatory,\textsuperscript{[10]} antihypertensive,\textsuperscript{[11]} anticancer,\textsuperscript{[12]} antiviral,\textsuperscript{[13]} and antibacterial activity.\textsuperscript{[14]} In addition, these compounds are present in several bioactive natural products.\textsuperscript{[15,16]}

Spirooxindoles are useful as anti-bacterial, anti-inflammatory, anticancer, and laxative\textsuperscript{[17,18]} agents. Furthermore, this ring structure was recently isolated from plants and fungi; for example, pteropodine or uncarine C (PT) was specifically isolated from cat’s claw;\textsuperscript{[19]} spirotryprostatin B, a natural alkaloid, has been isolated from the fermentation broth of \textit{Aspergillus fumigatus} and identified as a novel inhibitor of microtubule assembly.\textsuperscript{[20,21]} Also, horsfiline was isolated from the Malaysian

![Figure 1. Pteropoline, spirotryprostatin B, horsfiline, and elacomine.](image)

![Scheme 1. Synthesis of spirooxindoles 4a–m.](image)
### Table 1. Synthesis of 2-aryl-3-(phenylamino)-1'H-spiro[indoline-3,2':quinazoline]-2,4'(3'H)-dione 4a–m

| Entry | R<sub>1</sub> | R<sub>2</sub> | R<sub>3</sub> | Product 4 | Yield<sup>a</sup> (%) | Time (h) |
|-------|--------------|--------------|--------------|-----------|-----------------------|----------|
| A     | H            | H            | H            | ![Product A](image) | 92                    | 5.5      |
| B     | H            | Br           | H            | ![Product B](image) | 97                    | 5        |
| C     | CH<sub>3</sub>| H            | H            | ![Product C](image) | 90                    | 5        |
| D     | Bz           | H            | H            | ![Product D](image) | 83                    | 6        |
| E     | H            | NO<sub>2</sub>| H            | ![Product E](image) | 95                    | 4        |

(Continued)
Table 1. Continued

| Entry | R₁ | R₂ | R₃ | Product 4 | Yield (%) | Time (h) |
|-------|----|----|----|-----------|-----------|----------|
| F     | CH₃| Br | H  | ![Chemical Structure](image1.png) | 85        | 5        |
| G     | Et | Br | H  | ![Chemical Structure](image2.png) | 93        | 5        |
| H     | Me | NO₂| H  | ![Chemical Structure](image3.png) | 90        | 4        |
| I     | Et | H  | H  | ![Chemical Structure](image4.png) | 60        | 7        |
| J     | H  | Br | Cl | ![Chemical Structure](image5.png) | 87        | 6        |

(Continued)
medicinal plant *Horsfildea superba* warb,

There are several methods reported in the literature for the preparation of spirooxindole derivatives.

**RESULTS AND DISCUSSION**

We have concentrated most of our recent studies on the synthesis of heterocycles compounds,\textsuperscript{[28]} alum,\textsuperscript{[29,30]} and MCRs\textsuperscript{[31,32]} for the synthesis of 2,3-dihydroquinazolin-4(3\textit{H})-one,\textsuperscript{[33]} spiro[indoline-3,2-quinazoline]-2,4(3\textit{H})-dione,\textsuperscript{[34]} oxindole,\textsuperscript{[35]} and spirooxindole.\textsuperscript{[36]} In the course of our investigations, we envisioned the one-pot, three-component synthesis of 3’-(phenylamino)-1’\textit{H}-spiro[indoline-3, 2’-quinazoline]-2,4’(3’\textit{H})-dione \textit{4a–m} from isatoic anhydride \textit{1}, isatins \textit{2}, and phenyl hydrazine \textit{3} in the presence of alum as a nontoxic, 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 catalyst are presented in Table 1.

It is noticeable that when the isatoic anhydride 1a and b, isatin 2a–m, and phenyl hydrazine 3 in the presence of alum were stirred at reflux for 1 h, in all cases the reaction led to the formation of the intermediate 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 thin-layer chromatography, 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 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 aeruginosa ATCC 85327, and Klebsiella pneumonia ATCC 29655 (Gram-negative bacteria) and Enterococcus faecalis ATCC 29737, Bacillus subtilis ATCC 465, Bacillus pumilus PTCC 1114, Micrococcus luteus PTCC 1110, Staphylococcus aureus ATCC 25923, Staphylococcus epidermidis ATCC 12228, and Streptococcus mutans PTCC 1601 (Gram-positive bacteria) by the disk diffusion method (IZ) and subsequently the minimum inhibitory concentration method (MIC).

Scheme 2. Reasonable mechanism for the formation of 3′-(phenylamino)-1′H-spiro[indoline-3, 2′-quinazoline]-2,4′(3′H)-dione derivatives 4a–m.
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

| Microorganism          | Tetracycline (30 µg/disc) | Gentamicin (10 µg/disc) | 4a | 4b | 4c | 4d | 4e | 4f | 4g | 4h | 4i | 4j | 4k | 4l | 4m |
|------------------------|---------------------------|--------------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|
|                        | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC | IZ | MIC|
| Bacillus subtilis       | 21 | 4   | 0  | NT | 14 | 128 | 13 | 256 | 0  | NT | 0  | NT | 16 | 4  | 12 | 512 | 14 | 64 | 0  | NT | 0  | NT | 20 | 4   | 16 | 8  | 23 | <2 | 0  | NT |
| (ATCC 465)             |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Bacillus pumilus        | 17 | 8   | 0  | NT | 18 | 16  | 14 | 128 | 0  | NT | 0  | NT | 18 | 4  | 0  | NT | 13 | 128 | 0  | NT | 0  | NT | 22 | <2 | 19 | 4   | 28 | <2 | 0  | NT |
| (PTCC 1114)            |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Micrococcus luteus      | 19 | 4   | 0  | NT | 14 | 64  | 12 | 256 | 0  | NT | 0  | NT | 16 | 8  | 0  | NT | 0  | NT | 0  | NT | 0  | NT | 18 | 4   | 16 | 8  | 20 | 2   | 0  | NT |
| (PTCC 1110)            |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Staphylococcus aureus   | 20 | 4   | 0  | NT | 16 | 32  | 14 | 256 | 0  | NT | 0  | NT | 18 | 4  | 12 | 512 | 12 | 512 | 0  | NT | 0  | NT | 25 | 2   | 18 | 2   | 20 | 2   | 0  | NT |
| (ATCC 25923)           |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Staphylococcus epidermidis | 34 | <2 | 0  | NT | 14 | 32  | 15 | 256 | 0  | NT | 0  | NT | 16 | 4  | 8  | 512 | 0  | NT | 0  | NT | 0  | NT | 23 | 2   | 15 | 4   | 19 | 2   | 0  | NT |
| (ATCC 12228)           |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sterptococcus mutans   | 24 | 2   | 0  | NT | 16 | 32  | 16 | 64  | 0  | NT | 0  | NT | 18 | <2 | 15 | 32  | 0  | NT | 0  | NT | 0  | NT | 28 | <2 | 17 | 8   | 16 | 8   | 0  | NT |
| (PTCC 1601)            |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Escherichia coli        | 0  | NT  | 23 | 4  | 14 | 64  | 0  | NT | 0  | NT | 0  | NT | 16 | 4  | 14 | 32  | 0  | NT | 0  | NT | 0  | NT | 22 | <2 | 14 | 32  | 19 | <2 | 0  | NT |
| (ATCC 25922)           |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Enterococcus faecalis  | 9  | 8   | 0  | NT | 8  | 256 | 0  | NT | 0  | NT | 0  | NT | 14 | 16 | 0  | NT | 0  | NT | 0  | NT | 0  | NT | 19 | <2 | 10 | 128 | 16 | 8   | 0  | NT |
| (ATCC 29737)           |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Pseudomonas aeruginosa  | 0  | NT  | 12 | 8  | 10 | 256 | 0  | NT | 0  | NT | 0  | NT | 15 | 32 | 0  | NT | 0  | NT | 0  | NT | 0  | NT | 17 | 8   | 0  | NT | 15 | 16 | 0  | NT |
| (ATCC 85327)           |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Klebsiella pneumonia    | 8  | 16  | 0  | NT | 10 | 256 | 0  | NT | 0  | NT | 14 | 8  | 13 | 256 | 0  | NT | 0  | NT | 0  | NT | 15 | 4   | 0  | NT | 12 | 16 | 0  | NT |
| (ATCC 29655)           |    |     |    |    |    |     |    |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

*a* Inhibition zone (mm).

*b* Minimum inhibitory concentration (µg/ml).

*c* Not tested.
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 $R^1 = \text{H}$ and $R^3 = \text{Cl}$ substituted groups show better activity than the other test compounds and the reference (tetracycline and gentamicin), drugs.

Meanwhile, $3'(\text{phenylamino})-1'H$-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione compounds $4e$, $4j$, $4k$, and $4l$ exhibited good activity, whereas 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 to $1'H$-spiro[isoindoline-1,2'-quinazoline]-3,4'(3'H)-dione derivatives via a one-pot, three-component reaction from isatoic anhydride, isatin, and phenyl hydrazine. Our designed process requires mild reaction conditions, has good yields of products, uses very simple accessible starting materials and solvents as well as an inexpensive, nontoxic, and easily available heterogeneous catalyst, and has an easy experimental workup procedure.

Melting points were obtained in open capillary tubes and were measured on an Electrothermal 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. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz. Elemental analyses for C, H, and N were performed using a Heraus CHN rapid analyzer.

**General Procedure for Preparation of 3'(\text{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 the 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 it was recrystallized from ethanol to afford the pure product.

**3'(\text{phenylamino})-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (4a)**

Yellow powder (92%); mp 174–176°C. IR (KBr): $\nu_{\text{max}} = 3296, 3067, 1736, 1656, 1613$ cm$^{-1}$; $^1\text{H}$ NMR (CDCl$_3$) $\delta = 6.67$–7.92 (15H, m, H-Ar, 2NH), 10.45 (1H, s, NH) ppm; $^{13}\text{C}$ NMR (CDCl$_3$) $\delta = 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$_4$O$_2$: C, 70.77; H, 4.53; N, 15.72%. Found: C, 70.71; H, 4.48; N, 15.64%.
SUPPLEMENTARY INFORMATION

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

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