Journal of Pharmaceutical Research International

33(6): 20-27, 2021; Article no.JPRI.65952
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Synthesis, Characterization and Preliminary Biological Evaluation of New 3 and 4-nitro Isoindoline-1, 3-dione/phthalimide Analogues

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Authors' contributions

This work was carried out in collaboration between both authors. Author SS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author NC managed the literature searches, implemented the experiments, and managed the analyses of the study. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i631186
Editor(s):
(1) Dr. Rafik Karaman, Al-Quds University, Palestine.
Reviewers:
(1) Cyprian O. Onyeji, University of Nigeria, Nigeria.
(2) Hazem M. Shaheen, Damanhour University, Egypt.
Complete Peer review History: http://www.sdiarticle4.com/review-history/65952

Original Research Article

Received 14 December 2020
Accepted 18 February 2021
Published 01 March 2021

ABSTRACT

Aims: To synthesize new nitroisoindoline-1,3-diones analogues and evaluate their preliminary biological activities
Methodology: New isoindoline-1,3-diones analogues were synthesized by coupling phthalic anhydride derivatives with appropriate aromatic amines. Newly synthesized heterocyclic compounds were evaluated for their in vitro antibacterial activity against gram-positive bacterial strains and gram-negative bacterial strains. They were also tested for their in vitro antifungal activity against fungi strains. Determination of the preliminary antibacterial and antifungal activity were investigated using agar-dilution method. The structures of newly synthesized analogues were elucidated by ^{1}H and ^{13}C-NMR techniques.
Results: Bioassay indicated that some of the newly synthesized isoindoline-1,3-dione analogues shows moderate biological activities.
Conclusion: Newly synthesized analogues can be used as antibacterial or antifungal agents on modifications.

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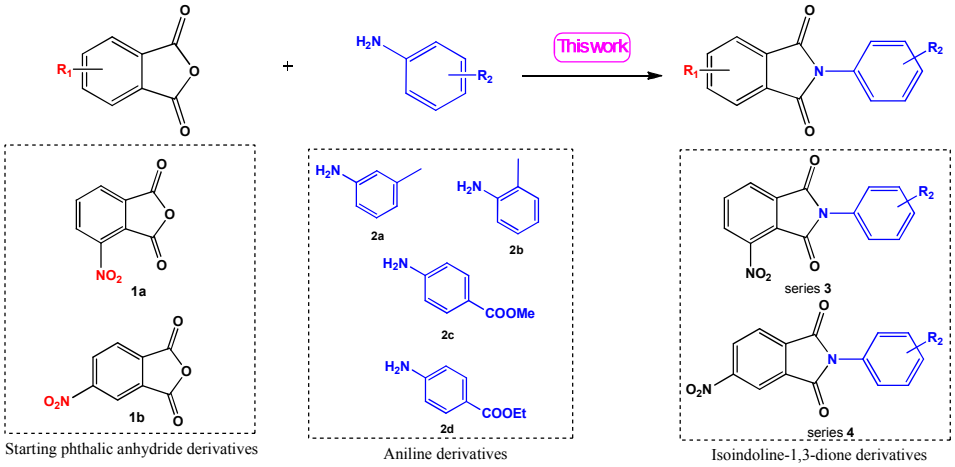
Graph 1. Graphical Abstract



Keywords: Biological activity; isoindoline-1,3-dione/phthalimide analogues; 3-nitro and 4-nitro phthalic anhydride; Primary aromatic amine.

1. INTRODUCTION

Phthalimides belong to community of cyclic imides which are obtained by various organic synthetic processes, generally using phthalic anhydride as the precursor. Phthalimide is an important drug structural unit. Norcantharimide 1, phthalimide 2, N-substituted norcantharimide 3 are some examples of isoindole derivatives containing imide (-CO-N(R)-CO-) functional group [1] (Fig. 1).

These compounds and their N-substituted derivatives are interesting compounds due to their important biological properties in the field of synthetic organic chemistry and medicinal chemistry. For this reason, these molecules have been the object of several research centres studies worldwide. Isoindole and its N-substituted derivatives are of much important due to their optical [1], anti-HIV [2,3], antibacterial [3], antifungal [3], analgesic [3], vanxiolytic [3,4], anti-inflammatory [5], anticonvulsant [6], antitumor [3,7,8,9,10], antimicrobial activities [11,12] and their biological properties [13-17].

Cyclic imides such as phthalimides possess structural features which confer biologically potent and pharmaceutically very useful. Some marketed pharmaceutical products of isoindoline are reported in Table 1.

So, considering the efficacy of N-substituted derivatives of phthalimides, we decided to synthesize 8 new N-aryl phthalimides. All of them were tested for biological activities because the literature did not record such evaluation of these compounds against gram positive bacterial strains, gram negative bacterial strains and antifungal activity against fungi strains.

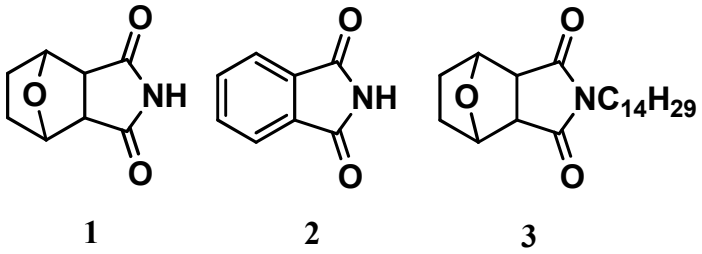
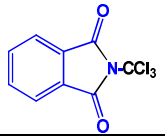
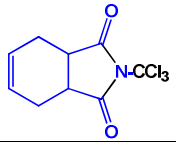
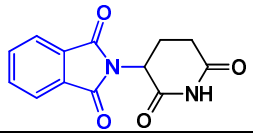
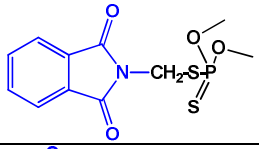
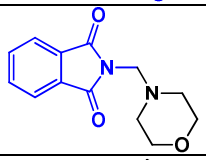
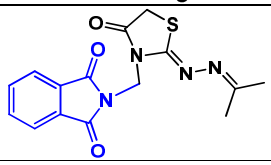


Fig. 1. The structure of norcantharimide 1, phthalimide 2 and N-substituted norcantharimide 3

Table 1. List for biological active some reported isoindoline analogues

S.N.	Structure	Use/s
1		Fungicide
2		Fungicide
3		Antineoplastic antileprotic
4		Pesticide, insecticide and acaricide.
5		A-glucosidase inhibitor
6		Anti-candida activity

2. MATERIALS AND METHODS

All chemicals required for the synthesis were purchased from commercial suppliers and were used without any further purification. Reactions were monitored by TLC analysis using silica gel plates (eluents petroleum ether – AcOEt in various proportions). Compounds were visualized by UV irradiation. ^{1}H and ^{13}C NMR spectra of all compounds were recorded on NMR spectrometer (600, 300 and 75 MHz). Chemical shifts are given in parts per million from TMS or deuterated solvent (DMSO-d_6, chloroform-d) as internal standard.

2.1 Isoindoline-1, 3-dione Analogues 3a-d and 4a-d; general procedure

The target compounds (3a-d and 4a-d) were synthesized by the condensation of an appropriate phthalic anhydride with an appropriate primary aromatic amine in refluxing glacial acetic acid for 2-3 hrs. The progress of the reaction was monitored using TLC. This reaction was then quenched in cold water. The crude product was filtered and washed several times with water and then dried.

2.2 3-nitro-2-(m-tolyl) isoindoline-1,3-dione (3a)

3-Nitrophthalic anhydride 1a (0.10 g, 0.52 mmol) and m-toluidine 2a (0.36 g, 0.52 mmol) which were refluxed in glacial acetic acid. Product 3a was obtained in yield 0.090 g (62%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ-2.41 (s, 3H), δ-7.20-7.24 (m, 3H), δ-7.39 (t, *J* = 7.5 Hz, 1H), δ-7.97 (t, *J* = 8 Hz, 1H), δ-8.14 (d, *J* = 8 Hz, 1H), δ-8.21 (d, *J* = 7.5 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ-21.54 (CH), 123.58 (CH), 123.85 (CH), 127.37 (CH), 127.53 (C), 128.99 (CH), 129.23 (CH), 129.77 (CH), 130.93 (CH), 133.99 (C), 135.84 (C), 139.53 (C), 145.60 (C), 162.17 (C), 165.10 (C). Analysis for $C_{15}H_{10}N_2O_4$ (282.25): Calculated: C, 63.83; H, 3.57; N, 9.92; O, 22.67. Found: C, 64.09; H, 3.27; N, 9.65; O, 22.20.

2.3 3-nitro-2-(o-tolyl) isoindoline-1,3-dione (3b)

3-nitro Phthalic anhydride 1a (0.10 g, 0.52 mmol) and o-toluidine 2b (0.36 g, 0.52 mmol) which were refluxed in glacial acetic acid. Product 3b was obtained in yield 0.072 g (50%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ-2.20 (s, 3H), δ-7.18-7.41 (m, 4H), δ-7.98 (t, *J* = 7.5 Hz, 1H), δ-8.16 (d, *J* = 8 Hz, 1H), δ-8.21 (d, *J* = 7.5 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ-18.18 (CH), 123.81 (CH), 127.17 (CH), 127.63 (C), 128.73 (CH), 129.03 (CH), 130.05 (CH), 131.45 (CH), 134.13 (C), 135.87 (C), 136.55 (C), 145.59 (C), 162. (C), 165.01 (C). Analysis for $C_{15}H_{10}N_2O_4$ (282.25): Calculated: C, 63.83; H, 3.57; N, 9.92; O, 22.67. Found: C, 64.15; H, 3.85; N, 10.15; O, 23.10.

2.4 Methyl 4-(3-nitro-1,3-dioxoisoindolin-2-yl) (3c)

3-nitro phthalic anhydride 1a (0.50 g, 3.38 mmol) and 4-amino benzoate 2c (0.51 g, 3.38 mmol) which were refluxed in glacial acetic acid. Product 3c was obtained in yield 0.18 g (53%). ^{1}H-NMR (300 MHz, DMSO): δ-3.93 (s, 3H), δ-7.60 (d, *J* = 8.7 Hz, 1H), δ-8.10 (s, 1H), δ-8.17-8.10 (m, 4H), δ-8.26 (d, *J* = 7.8 Hz, 1H). ^{13}C-NMR (75 MHz, DMSO): δ-52.17 (CH), 126.44 (CH), 127.38 (C), 128.87 (CH), 129.56 (C), 130.03 (CH), 133.33 (CH), 135.22 (C), 136.33 (C), 145.07 (C), 161 (C), 163.21 (C), 164.10 (C). Analysis for $C_{16}H_{10}N_2O_6$ (326.26): Calculated: C, 58.90; H, 3.09; N, 8.59; O, 29.42. Found: C, 60; H, 3.45; N, 8.29; O, 29.12.

2.5 Ethyl 4-(3-nitro-1,3-dioxoisoindolin-2-yl) (3d)

3-nitro phthalic anhydride 1a (0.20 g, 1.04 mmol) and ethyl 4-amino benzoate 2d (0.172 g, 1.04 mmol) which were refluxed in glacial acetic acid. Product 3d was obtained in yield 0.13 g (55%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ-1.517 (t, *J* = 7.2 Hz, 3H), δ-4.513 (q, *J* = 7.2 Hz, 2H), δ-7.683-7.662 (m, 2H), δ-8.110 (d, *J* = 7.8 Hz, 1H), δ-8.306-8.275 (m, 2H), δ-8.334 (d, *J* = 1.2 Hz, 1H), δ-8.346 (d, *J* = 1.2 Hz, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ-14.30 (CH), 61.33 (CH), 119.33 (CH), 125.21 (CH), 125.79 (CH), 129.81 (C), 130.34 (CH), 130.55 (CH), 132.94 (C), 134.91 (C), 135.87 (C), 152.09 (C), 164.47 (C), 164.72 (C), 165.61 (C). Analysis for $C_{17}H_{12}N_2O_6$ (340.29): Calculated: C, 60; H, 3.55; N, 8.23; O, 28.21. Found: C, 60.25; H, 3.35; N, 8.49; O, 28.

2.6 4-nitro-2-(m-tolyl) isoindoline-1,3-dione (4a)

4-nitro Phthalic anhydride 1b (0.50 g, 2.59 mmol) and m-toluidine 2a (0.28 g, 2.59 mmol) which were refluxed in glacial acetic acid. Product 4a was obtained in yield 0.48 g (73%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ-2.43 (s, 3H), δ-7.27-7.21 (m, 3H), δ-7.42 (t, *J* = 7.7 Hz, 1H), δ-8.15 (d, *J* = 8 Hz, 1H), δ-8.67 (d, *J* = 8.1 Hz, 1H), δ-8.77 (s, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ-21.37 (CH), 119.11 (CH), 123.48 (CH), 124.95 (CH), 126.98 (CH), 129.11 (CH), 129.54 (CH), 129.62 (CH), 130.80 (C), 133.13 (C), 136.12 (C), 139.42 (C), 151.94 (C), 164.98 (C), 165.24 (C). Analysis for $C_{15}H_{10}N_2O_4$ (282.25): Calculated: C, 63.83; H, 3.57; N, 9.92; O, 22.67. Found: C, 64.15; H, 3.65; N, 9.50; O, 22.25.

2.7 4-nitro-2-(o-tolyl) isoindoline-1,3-dione (4b)

4-nitro Phthalic anhydride 1b (0.50 g, 2.59 mmol) and o-toluidine 2b (0.28 g, 2.59 mmol) which were refluxed in glacial acetic acid. Product 4b was obtained in yield 0.48 g (73%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ-2.20 (s, 3H), δ-7.20 (d, *J* = 7.7 Hz, 1H), δ-7.43-7.34 (m, 3H), δ-8.16 (d, *J* = 8.2 Hz, 1H), δ-8.68 (d, *J* = 8.2 Hz, 1H), δ-8.77 (s, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ-17.97 (CH), 119.18 (CH), 125.02 (CH), 127.04 (CH), 128.39 (CH), 129.52 (CH), 129.85 (CH), 131.92 (C), 133.32 (C), 136.22 (C), 136.29 (C), 151.93 (C), 164.91 (C), 165.17 (C). Analysis for $C_{15}H_{10}N_2O_4$ (282.25): Calculated: C, 63.83; H, 3.57; N, 9.92; O, 22.67. Found: C, 63.50; H, 3.90; N, 9.55; O, 23.

2.8 Methyl 4-(4-nitro-1,3-dioxoisoindolin-2-yl) (4c)

4-nitro phthalic anhydride 1b (0.10 g, 0.518 mmol) and 4-amino benzoate 2c (0.078 g, 0.518 mmol) which were refluxed in glacial acetic acid. Product 4c was obtained in yield 0.060 g (34%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ-3.96, (s, 3H), δ-7.60 (dd, *J* = 8.8 Hz, 2H), δ-8.22-8.17 (m, 3H), δ-8.69 (d, *J* = 1.92 Hz, 1H), δ-8.79 (s, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ-52.39 (CH), 119.33(CH), 125.22 (CH), 125.80 (CH), 129.82 (CH), 129.97 (C), 130.58 (CH), 132.93 (C), 135.03 (C), 135.85 (C), 152.11 (C), 164.45 (C), 164.70 (C), 166.09 (C). Analysis for $C_{16}H_{10}N_2O_6$ (326.26): Calculated: C, 58.90; H, 3.09; N, 8.59; O, 29.42. Found: C, 59.20; H, 3.39; N, 8.29; O, 29.72.

2.9 Ethyl 4-(4-nitro-1,3-dioxoisoindolin-2-yl) (4d)

4-nitro phthalic anhydride 1b (0.20 g, 1.036 mmol) and ethyl 4-amino benzoate 2d (0.086 g, 1.036 mmol) which were refluxed in glacial acetic acid. Product 4d was obtained in yield 0.23 g (62%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ-1.42 (t, *J* = 7.2 Hz, 3H), δ-4.42 (q, *J* = 7.2 Hz, 2H), δ-8.59 (dd, *J* = 6.8, 2.1 Hz, 2H), δ-8.22-8.17 (m, 3H), δ-8.69 (d, *J* = 2 Hz, 1H), δ-8.79 (s, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ-14.30 (CH), 61.33 (CH), 119.33 (CH), 125.21 (CH), 125.79 (CH), 129.81 (C), 130.34 (CH), 130.55 (CH), 132.94 (C), 134.91 (C), 135.87 (C), 152.09 (C), 164.47 (C), 164.72 (C), 165.61 (C). Analysis for $C_{17}H_{12}N_2O_6$ (340.29): Calculated: C, 60; H, 3.55; N, 8.23; O, 28.21. Found: C, 59.75; H, 3.85; N, 8.47; O, 28.45.

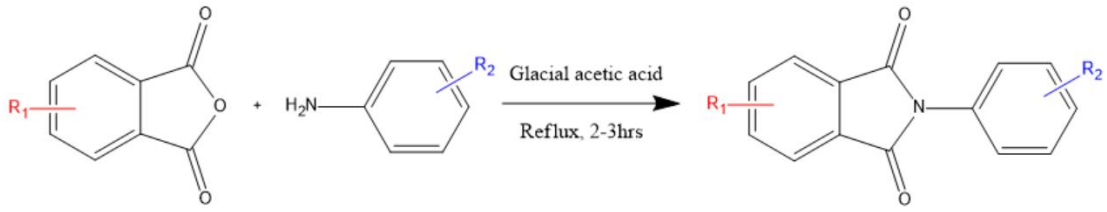
3. RESULTS AND DISCUSSION

The starting compound named 3-nitro phthalic anhydride (1a) was converted into 3-nitro-2-(m-tolyl) isoindoline-1,3-dione (3a) by the reaction with m-toluidine (2a) in glacial acetic acid for 2-3 hrs. The compounds (3b-d and 4a-d) were synthesized by using the same reaction conditions. The chemical structures of all newly synthesized compounds were confirmed by both elemental and spectral data.

3.1 Antibacterial and Antifungal Activity

All newly synthesized heterocyclic compounds were evaluated for their in *vitro* antibacterial activity against gram-positive bacterial strain (*S. aureus*) and gram-negative bacterial strain (*E. Coli*). They were also tested for their in vitro antifungal activity against fungi (*A. brasiliensis*) strain.

Determination of the preliminary antibacterial and antifungal activity were investigated using agar-dilution method. The results were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around discs in mm (Table 3). Results show that compounds 3a and 3b show antimicrobial activity against *E.Coli* whereas compounds 3b and 4a shows antimicrobial activity against A.Brasiliensis. Compounds 3c, 3d did not comply specification requirements and compound 4c did not show any antimicrobial activity upto 1 g/100 µl.



1a; R_1 = 3-NO_2
1b; R_1 = 4-NO_2

2a; R_2 = 3-Me
2b; R_2 = 2-Me
2c; R_2 = 4-COOMe
2d; R_2 = 4-COOEt

Series 3; 3a-3d
Series 4; 4a-4d
(see Table 2)

Scheme. Synthesis of new nitroisoindoline-1,3-dione analogues (3a-d and 4a-d)

Table 2. Nitroisoindoline-1,3-dione analogues prepared as per Scheme

Product Number	R_1	R_2	Yield (%)
3a	3-NO_2	3-Me	62
3b	3-NO_2	2-Me	50
3c	3-NO_2	4-COOMe	53
3d	3-NO_2	4-COOEt	55
4a	4-NO_2	3-Me	73
4b	4-NO_2	2-Me	73
4c	4-NO_2	4-COOMe	34
4d	4-NO_2	4-COOEt	62

Table 3. Antimicrobial activity[m] of the newly synthesized selected compounds against G+, G- and fungal strains expressed as IZ (mm)

Compound	Code	GRAM +VE S.aureus (ATCC 6538)			GRAM –VE E.Coli (ATCC 8739)			FUNGI A.brasiliensis (ATCC 16404)		
		1 g	0.5 g	DMSO	1 g	0.5 g	DMSO	1 g	0.5 g	DMSO
		(Per 100µl)			(Per 100µl)			(Per 100µl)		
3a	NC-26	0	0	0	12	14	0	0	0	0
3b	NC-27	0	0	0	9	11	0	8	10	0
3c	NC-08	0	0	0	9	11	0	0	8	0
3d	NC-17	0	0	0	8	10	0	0	0	0
4a	NC-25	0	0	0	0	0	0	8	9	8
4c	NC-24	0	0	0	0	0	0	0	0	0

[m]*Analysis results by NSRT lab*

Table 4. Antimicrobial activity[n] of the newly synthesized compounds against G+, G- and fungal strains

Compound	Code	Antibacterial activity				Antifungal activity		
		Minimum inhibition concentration				Minimum fungicidal concentration		
		microgram/mL				microgram/mL		
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
		MTCC 443	MTCC 441	MTCC 96	MTCC 442	MTCC 227	MTCC 282	MTCC 1323
4b	NR-11	100	62.5	100	100	250	500	1000
4d	NR-13	25	50	500	250	500	>1000	>1000
Gentamycin		0.05	1	0.25	0.5	-	-	-
Ampicilin		100	-	250	100	-	-	-
Chloramphenicol		50	50	50	50	-	-	-
Ciprofloxacin		25	25	50	50	-	-	-
Norfloxacin		10	10	10	10	-	-	-
Nystatin		-	-	-	-	100	100	100
Greseofulvin		-	-	-	-	500	100	100

[n]*Analysis results by microcare lab*

Two newly synthesized heterocyclic compounds were evaluated for their in vitro antibacterial activity against gram positive bacterial strains (*S.Aureus* & *S.Pyogenus*) and gram negative bacterial strains (*E.Coli* & *P.Aeruginosa*). They were also tested for their in vitro antifungal activity against fungi (*C.Albicans*, *A.Niger* & *A.Clavatus*) strain.

Determination of the preliminary antibacterial and antifungal activity were investigated using agar-diffusion method (Broth Dilution Method). It is one of the non-automated in vitro bacterial susceptibility tests. This classic method yields a quantitative result for the number of antimicrobial agents that is needed to inhibit growth of specific microorganisms. It is carried out in tubes. The main advantage of the 'Broth Dilution Method' for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

Both the zones of inhibition (mm) and minimum inhibitory/fungicidal concentration (MIC) (µg/ml) of the investigated compounds were recorded and compared with Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin as antibacterial and Nystatin, Greseofulvin as antifungal reference medications. DMSO was used as vehicle to get desired concentration of drugs to test upon Standard bacterial strains.

The investigation of antibacterial screening data is summarized in Table 4. Results show that MIC value less than that of standard drug were considered promising, results reveal that compound 4b exhibited higher activity (100 µg/mL) against S. Aureus while compound

compound 4d possessed pronounced activity against *E. coli*.

4. CONCLUSION

It is concluded that new isoindoline-1,3-diones analogues were synthesized by coupling phthalic anhydride derivatives with appropriate aromatic amines. Newly synthesized heterocyclic compounds were evaluated for their in vitro antibacterial activity against gram-positive bacterial strain and gram-negative bacterial strain. Newly Synthesized compounds show moderate antibacterial and antifungal activities.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

ACKNOWLEDGEMENT

The authors are thankful to Prof. INN Namboothiri, Dr. Suyog Marathe, Dr. Rajesh Kenny, SAIF IIT Mumbai, NSRT lab Gujarat, Microcare Lab Surat, University of Mumbai, Patkar College and A. P. Shah Institute of Technology, for support.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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