Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1458-1466 | ISSN:2251-6727

Synthesis, Biological Evaluation, And Kinetic Studies of Novel 3-Methoxynaphthalen-1-Amine Derivatives

Santosh R. Kshirsagar [1], Mahendra A. Gaikwad [1], Amarnath N. Jagdale [2], Achut S. Munde[1]*

[1]Department of Chemistry, Milind College of Science, Aurangabad-, 431001,(M.S.) India

[2]Department of chemistry, R.B. N. B. College, Shrirampur, Ahmednagar,-413709, (M.S.) India

Corresponding author: **Santosh R. Kshirsagar**

(Received: 11 June 2024 Revised: 16 July 2024 Accepted: 10 August 2024)

KEYWORDS

Synthesis, Kinetic study, 3-methoxynaphthalen-1-amine, antibacterial, Skraup reaction.

ABSTRACT:

The novel series of 3-methoxynaphthalen-1-amine derivatives has been synthesised. Skraup reaction method was used to synthesise the 6-methoxy-8-nitroquinoline. Further reduction and aldehyde substitutions, 10 novel compounds were synthesised. All the final compound structures were confirmed by the NMR and LCMS analysis. In the antibacterial studies, the compound (3a – 3j) was found to possess a good ZOI value than standard drugs against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Klebshella pneumonia respectively. The kinetic results of the enzyme by the Lineweaver-Burk plot of compound 3j showed that Vmax remains the same without significantly affecting the slopes. These compounds could be further modified to develop potential and safer antibacterial agents.

INTRODUCTION

Heterocyclic molecules are a class of organic compounds that contain a ring structure composed of at least one atom other than carbon, commonly nitrogen, oxygen, or sulfur. These heteroatoms introduce unique chemical properties and reactivities, distinguishing heterocycles from purely carbocyclic compounds [1]. Heterocyclic molecules are prevalent in various natural products, pharmaceuticals, and materials. Their structural diversity and functional versatility make them integral to the development of new drugs, agrochemicals, and advanced materials [2,3].

Studying the kinetics of heterocyclic molecules is crucial for understanding their reactivity and stability, which are essential for their practical applications. Kinetic studies involve measuring the rates of chemical reactions and examining how different factors, such as temperature, solvent, and concentration, influence these rates [4-6]. By analyzing reaction mechanisms and pathways, researchers can gain insights into the behavior of heterocyclic compounds under various conditions. This knowledge is pivotal in optimizing synthesis methods, improving yields, and minimizing side reactions [7].

One of the significant challenges in the kinetic studies of heterocyclic molecules is the complexity of their reaction mechanisms [8]. The presence of heteroatoms can lead to multiple reaction pathways, including nucleophilic or electrophilic substitutions, ring-opening reactions, and rearrangements [9]. Advanced analytical techniques, such as spectroscopy and chromatography, are often employed to monitor these reactions and identify intermediate species. Computational chemistry also plays a vital role in modeling reaction mechanisms and predicting the kinetics of heterocyclic compounds, providing a theoretical framework that complements experimental findings [10-13].

Kinetic studies are particularly important in the pharmaceutical industry, where the stability and reactivity of heterocyclic drugs can significantly impact their efficacy and safety [14-16]. Understanding the kinetic behavior of these molecules helps in designing drug formulations with improved stability and controlled release profiles. Moreover, kinetic data can inform the

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1458-1466 | ISSN:2251-6727

development of catalysts and reaction conditions that enhance the selectivity and efficiency of heterocyclic synthesis [17,18]. Overall, the integration of kinetic studies with heterocyclic chemistry fosters advancements in various scientific and industrial fields, driving innovation and improving the quality of life [19,20]. In this study, we synthesised some novel 3-methoxynaphthalen-1-amine derivatives and evaluated the antibacterial studies. Finally, kinetics studies were also performed.

METHODOLOGY

Synthesis of 6-methoxy-8-nitroquinoline (1a)

Skraup reaction from 4-methoxy-2-nitroaniline and glycerol (Equimolar (0.01M)) in the presence of sulfuric acid. The nitro group in this compound is reduced to make 6-methoxy-8-aminoquinoline. In this reaction, a mixture of aniline and glycerol is heated in the presence of sulphuric acid and a mild oxidizing agent, usually nitrobenzene or arsenic pentoxide. The reaction is exothermic and tends to become very violent. Ferrous sulphate or boric acid is generally added to make the reaction less violent.

Synthesis of 3-methoxy-1-nitronaphthalene (2a)

The 6-methoxy-8-nitroquinoline (0.01M) in AcOH (100 mL) and absolute EtOH (400 mL) was slowly added to iron powder (40 g). The reaction was cooled in an ice-H2O bath and treated with conc. HCl (1 mL). The addition was exothermic. The reaction was heated to reflux for 20 min, after which time it was allowed to cool to room temperature. The mixture was filtered through celite. The organic layer was separated and washed with sat aq NaHCO3, brine (100 mL), dried (Na2SO4), and concentrated to provide the product.

Synthesis of Schiff base intermediate molecules (3-a-j)

Equimolar (0.01M) amounts of 3-methoxy-1-nitronaphthalene (2a) and various aldehydes were dissolved in methanol (15 mL), then acetic acid (0.5 mL) was added and the mixture was refluxed for two hours. After the reaction was completed the reaction mixture was cooled and put into water, where the solid separated. To obtain equivalent Schiff bases intermediate compounds, the solid was filtered, washed with water, and crystallised from ethanol.

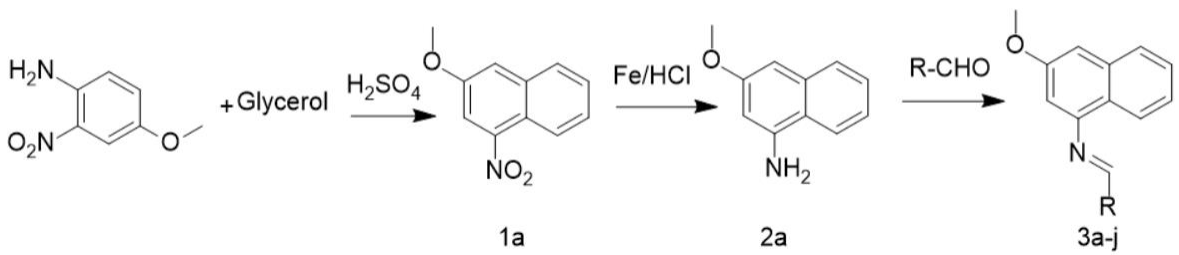
Antimicrobial activity

The antibacterial extracts were determined by the disc diffusion method on Muller Hinton agar (MHA) medium. Muller Hinton Agar (MHA) medium is poured into the Petri plate. After the medium was solidified, the inoculums were spread on the solid plates with sterile swabs moistened with the bacterial suspension. The disc was placed in MHA plates and 20 µl of sample (Concentration: 1000µg, 750µg and 500 µg) were placed in the disc. The plates were incubated at 37ºC for 24 hrs. Then the antimicrobial activity was determined by measuring the diameter of the zone of inhibition

RESULT AND DISCUSSION

Synthesis of 3-methoxynaphthalen derivatives

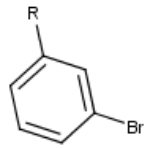
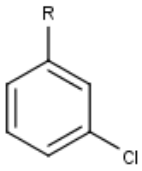
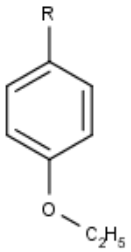
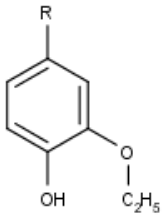
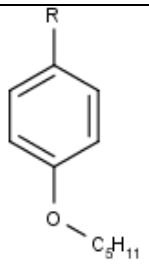
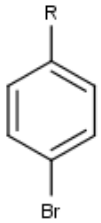
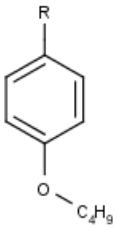
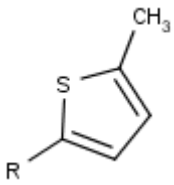
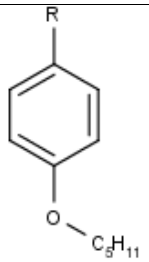
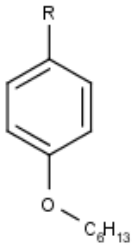
Scheme 1



Journal of Chemical Health Risks

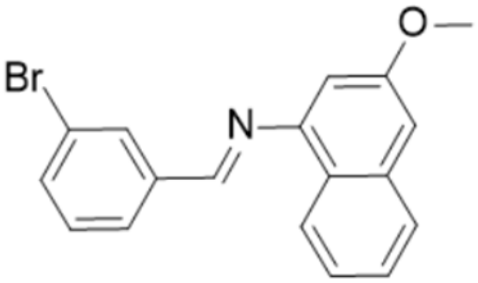
www.jchr.org

JCHR (2024) 14(5), 1458-1466 | ISSN:2251-6727

R=	**3a**	**3b**	**3c**	**3d**	**3e**
					
	3f	**3g**	**3h**	**3i**	**3j**
					

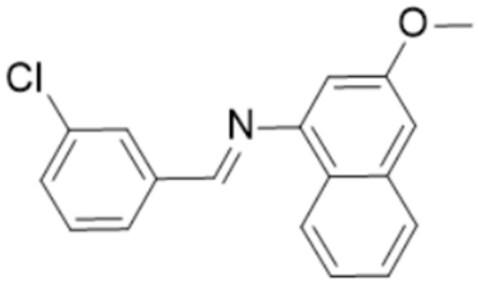
Characterization study of synthesized compounds

3a- (E)-N-(3-bromobenzylidene)-3-methoxynaphthalen-1-amine



IR (KBr, cm^{-1}) υ_{max} : 3377 (-NH), 2922 (O-CH_3) 1606 (C=O), 613 (C-Br): ^{1}H NMR: δ 1.17 (3H,d, *J* = 6.6 Hz), 1.67 (4H, t), 3.60-3.79 (7H, m), 4.3 (1H, t, *J* = 7.0Hz), 5.9 (1H, s), 6.90-6.91 (7H,m), 7.91 (1H, dt, *J* = 8.6 Hz), 8.72 (1H, dd, *J* = 4.7 Hz). ^{13}C NMR: δ 18.2 (1C, s), 22.1 (1C, s), 33.11 (1C, s), 34.3 (1C, s), 47.46 (1C, s), 50.1 (1C, s), 56.20 (1C, s), 65.2 (1C, s), 101.4 (1C, s), 106.5 (1C, s), 118.8 (1C, s), 122.8 (1C, s), 128.35 (1C, s), 128.3 (1C, s), 131.2 (3C), 135.2 (1C, s), 136.1 (1C, s), 136.1 (1C, s), 139.5 (1C, s), 149.7 (1C, s), 155.7 (1C, s), 169.8 (1C, s). LC-MS analysis for $C_{18}H_{14}BrNO$ calculated (EI, m/z (%): 339.03, found: 340.45 [M+1]. Melting point is 69-70ºC.

3b-(E)-N-(3-chlorobenzylidene)-3-methoxynaphthalen-1-amine



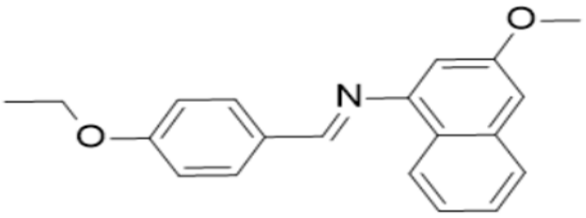
IR (KBr, cm^{-1}) υ_{max} : 3415 (-NH), 2981 (O-CH_3) 1797 (C=O), 875 (C-Cl), ^{1}H NMR: δ ^{1}H NMR: δ 1.18 (3H,d, *J* = 6.4 Hz), 1.60 (4H, t), 3.66-3.78 (7H, m), 4.3 (1H), 6.01 (1H, s), 6.91-6.92 (7H,m), 8.15 (1H, dt, *J* = 8.6 Hz), 8.81 (1H, dd, *J* = 4.7 Hz). ^{13}C NMR: δ 18.3 (1C, s), 22.7(1C, s), 33.1 (1C, s), 34.5 (1C, s), 47.3 (1C, s), 50.1 (1C, s), 56.2 (1C, s), 65.4 (1C, s), 101.9 (1C, s), 106.2 (1C, s), 122.8 (1C, s), 128.3 (2C, s), 131.2 (2C), 133.5 (1C, s), 136.1 (1C, s), 136.1 (1C, s), 139.4 (1C, s), 140.3 (1C, s), 149.2 (1C, s), 155.1 (1C, s), 169.1 (1C, s). LC-MS analysis for $C_{18}H_{14}ClNO$ calculated (EI, m/z (%): 295.08 Found: 296.08 [M+1]. Metling point is 72-73 ºC.

Journal of Chemical Health Risks

www.jchr.org

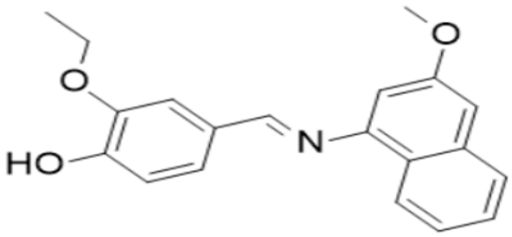
JCHR (2024) 14(5), 1458-1466 | ISSN:2251-6727

3c- (E)-N-(4-ethoxybenzylidene)-3-methoxynaphthalen-1-amine



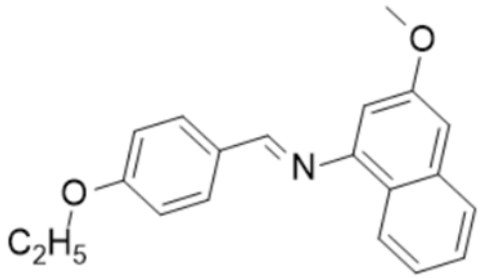
IR (KBr, cm^{-1}) υ_{max} : 3415 (-NH), 2981 (O-CH_3), 2669 (-SH) 1797 (C=O),1181 (C-O-C_2HH_5), ^{1}H NMR: δ ^{1}H NMR: δ 1.16-1.18 (10H,m), 1.60 (4H, t), 3.66-3.69 (7H, m), 4.1-4.2 (3H, m), 6.06 (1H, s), 6.91-6.92 (7H,m), 8.15 (1H, dt, *J* = 8.6 Hz), 8.79 (1H, dd, *J* = 4.7 Hz). ^{13}C NMR: δ 14.2 (1C, s), 18.8 (1C, s), 22.5 (1C, s), 33.4 (1C, s), 34.0 (1C, s), 47.6 (1C, s), 50.1 (1C, s), 56.0 (1C, s), 64.3 (1C, s), 65.2 (1C, s), 101.4 (1C, s), 106.4 (1C, s), 114.3 (2C, s), 122.4 (1C, s), 127.8 (2C, s), 129.6 (1C, s), 135.7 (1C, s), 136.3 (1C, s), 139.5 (1C, s), 140.2 (1C, s), 149.8 (1C, s), 155.8 (1C, s), 158.5 (1C, s), 169.8 (1C, s). LC-MS analysis for $C_{19}H_{17}NO_2S$ calculated (EI, m/z (%): 291.13 Found : 292.41 [M+1]. Metling point is 70-71ºC.

3d-(E)-2-ethoxy-4-(((3-methoxynaphthalen-1-yl)imino)methyl)phenol



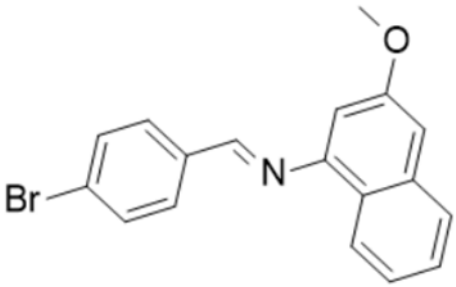
IR (KBr, cm^{-1}) υ_{max} : 3356 (-OH), 2918 (O-CH_3), 2851 (-SH) 1797 (C=O), 1171 (C-O-C_2HH_5): ^{1}H NMR: δ ^{1}H NMR: δ 1.17-1.18 (10H,m), 1.60 (4H, t), 3.66-3.69 (7H, m), 4.1-4.2 (3H, m), 6.06 (1H, s), 6.91-6.92 (7H,m), 8.15 (1H, dt, *J* = 8.6 Hz), 8.79 (1H, dd, *J* = 4.7 Hz), 8.72 (1H, dd, *J* = 4.7 Hz).^{13}C NMR: δ 14.2 (1C, s), 18.40 (1C, s), 22.7 (1C, s), 33.5 (1C, s), 34.6 (1C, s), 47.3 (1C, s), 50.7 (1C, s), 56.32 (1C, s), 64.47 (1C, s), 65.2 (1C, s), 101.9 (1C, s), 101.5 (1C, s), 110.5 (1C, s), 115.3 (1C, s), 122.8 (1C, s), 128.3 (1C, s), 128.39 (1C, s), 131.2 (2C, s), 136.2 (1C, s), 136.2 (1C, s), 137.15 (1C, s), 139.29 (1C, s) 146.2 (1C, s), 149.2 (1C, s), 155.2(1C, s), 169.11 (1C, s). LC-MS analysis for $C_{20}H_{19}NO_3$ calculated (EI, m/z (%): 321.14 and Found: 322.50 [M+1].Melting point is 87-88 ºC.

3e-(E)-N-(4-ethoxybenzylidene)-3-methoxynaphthalen-1-amine



IR (KBr, cm^{-1}) υ_{max} : 3472 (-NH), 2075 (O-CH_3), 1641 (C=O): ^{1}H NMR: δ 0.3 (3H, t, *J* = 7.0 Hz), 1.12-1.6 (7H, 1.17 m), 3.62-3.78 (2H, m), 3.51 (1H, d, *J* = 16.0 Hz), 3.66-3.86 (7H, m), 4.20 (3H, tq, *J* = 7.0, 6.6 Hz), 5.99 (1H, s), 6.9-7.95 (7H, m), 7.92 (1H, dt, *J* = 8.1 Hz), 8.73 (1H, dd, *J* = 4.8 Hz). ^{13}C NMR: δ 14.0 (1C, s), 18.2 (1C, s), 22.3 (1C, s), 22.3 (1C, s), 28.9 (1C, s), 29.0 (1C, s), 33.11 (1C, s), 34.3 (1C, s), 47.5 (1C, s), 50.1 (1C, s), 56.1 (1C, s), 65.1 (1C, s), 69.3 (1C, s), 101.4 (1C, s), 106.3 (1C, s), 118.3 (2C, s), 122.3 (1C, s), 128.38 (2C, s), 128.4 (1C, s), 131.2-131.36 (3C, s), 135.2-136.1 (3C, s), 139.5 (1C, s), 146.2 (1C, s), 155.6 (1C, s), 169.4 (1C, s). LC-MS analysis for $C_{20}H_{19}NO_2$ calculated (EI, m/z (%): 305.14 and Found: 306.18 [M+1]. Melting point is 81-82 ºC

3f-(E)-N-(4-bromobenzylidene)-3-methoxynaphthalen-1-amine



IR (KBr, cm^{-1}) υ_{max} : 3472 (-NH), 1641 (C=O), 502 (C-Br): ^{1}H NMR: δ 1.18 (3H, d, *J* = 6.2 Hz), 1.60-1.60 (4H, m), 3.67-3.69 (7H, m), 4.28 (1H, tq, *J* = 7.0, 6.2 Hz), 6.01 (1H, s), 6.91-7.0 (7H, m), 8.13 (1H, dt, *J* = 8.6 Hz), 8.84 (1H, dd, *J* = 4.1 Hz). ^{13}C NMR: δ 18.7 (1C, s), 22.8 (1C,

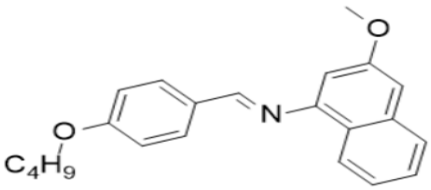
Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1458-1466 | ISSN:2251-6727

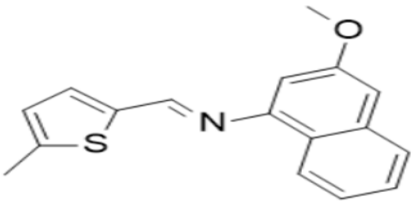
s), 33.2 (1C, s), 34.3 (1C, s), 47.0 (1C, s), 50.7 (1C, s), 56.3 (1C, s), 65.3 (1C, s), 101.82 (1C, s), 106.2 (1C, s), 118.8 (1C, s), 122.3 (1C, s), 128.3 (2C, s), 131.3 (2C, s), 133.69 (1C, s), 136.2 (1C, s), 139.25 (1C, s), 140.2 (1C, s), 149.1 (1C, s), 155.3 (1C, s), 169.2. (1C, s). LC-MS analysis for $C_{18}H_{14}BrNO$calculated (EI, m/z (%): 339.03 and Found: 340.16 [M+1]. Melting point is 59-60 ºC

3g-(E)-N-(4-butoxybenzylidene)-3-methoxynaphthalen-1-amine



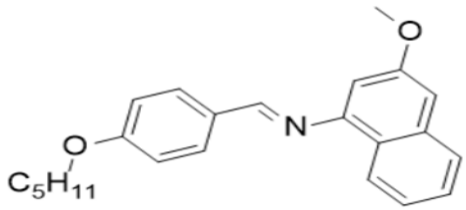
IR (KBr, cm^{-1}) υ_{max} : 3443 (-NH), 2992 (O-CH_3), 1613 (C=O), 819 (C-Cl) ^{1}H NMR: δ 0.36 (3H, t, *J* = 7.1 Hz), 1.12 (3H, d, *J* = 6.6 Hz), 1.60-1.61 (11H, m), 3.62-3.36 (4H, m), 3.77-3.78 (3H,m), 4.3 (H, m) 5.35 (1H, d, *J* = 8.1 Hz), 5.68 (1H, d, *J* = 8.1 Hz), 6.91-6.92 (7H, m) 7.91 (1H, dt, *J* = 8.2 Hz), 8.74 (1H, dd, *J* = 4.3 Hz). ^{13}C NMR: δ 14.5 (1C, s), 18.2 (1C, s), 22.2 (2C, s), 28.9(1C, s), 29.19 (1C, s), 34.3 (1C, s), 47.6 (1C, s), 50.3 (1C, s), 56.1 (1C, s), 58.3 (1C, s), 69.2 (1C, s), 101.4 (1C, s), 106.3 (1C, s), 118.2 (2C, s), 122.2 (1C, s), 128.4 (2C, s), 128.4 (1C, s), 131.6 (3C, s) 135.2 (1C, s), 136.2 (1C, s), 136.7 (1C, s) 139.4 (1C, s), 146.3 (1C, s), 155.3 (1C, s), 168.7 (1C, s). LC-MS analysis for $C_{22}H_{23}NO_2$ calculated (EI, m/z (%): 333.17 and Found: 334.25 [M+1]. Melting point is 67-68 ºC.

3h-(E)-3-methoxy-N-((5-methylthiophen-2-yl)methylene)naphthalen-1-amine



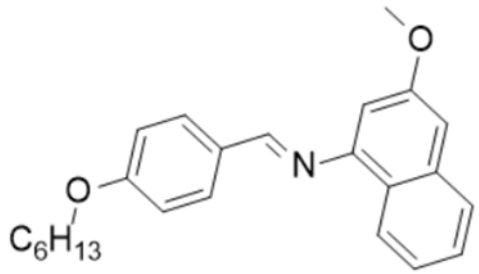
IR (KBr, cm^{-1}) υ_{max} : 3501 (-NH), 2992 (O-CH_3), ^{1}H NMR: δ 1.18 (3H, d, *J* = 6.6 Hz), 1.65 (4H, td, *J* = 7.4 Hz), 2.32 (3H, s), 3.51-3.68 (6H, m 4.20 (1H, tq, *J* = 7.0 Hz), 6.01 (1H, s), 6.92-7.01 (7H, m 6.95 (d, *J* = 2.3 Hz), 8.12 (1H, dt, *J* = 8.6 Hz), 8.75 (1H, dd, *J* = 4.4, Hz). ^{13}C NMR: δ 18.2 (1C, s), 22.4 (1C, s), 33.7 (1C, s), 34.0 (1C, s), 47.2 (1C, s), 50.7 (1C, s), 56.3 (1C, s), 65.1 (1C, s), 101.6 (1C, s), 106.6 (1C, s), 122.3 (1C, s), 128.3 (2C, s), 131.2 (2C, s), 135.1 (1C, s), 136.9 (1C, s), 137.1-139.2 (2C, s), 149.6 (1C, s), 155.9 (1C, s), 169.9 (1C, s). LC-MS analysis for $C_{17}H_{15}NOS$ calculated calculated (EI, m/z (%) : 281.09 and Found : 282.14. [M+1]. Melting point is 78-79 ºC

3i-(E)-3-methoxy-N-(4-(pentyloxy)benzylidene)naphthalen-1-amine



IR (KBr, cm^{-1}) υ_{max} : 3338 (-NH), 2886 (O-CH_3), 1509 (C=O): ^{1}H NMR: δ 0.36 (3H, t, *J* = 7.0 Hz), 1.12 (3H, d, *J* = 6.2 Hz), 1.69-1.72 (6H, m), 3.26-3.38 (2H, m), 4.32-4.31 (3H t, *J* = 7.4 Hz), 5.09 (1H, d, *J* = 7.8 Hz), 5.35 (1H, d, *J* = 8.3 Hz), 6.93-6.96 (7H, m), 7.93 (1H, dt, *J* = 8.2 Hz), 8.72 (1H, dd, *J* = 4.7 Hz). ^{13}C NMR: δ 14.0 (1C, s), 18.35 (1C, s), 22.6 (1C, s), 28.51 (1C, s), 29.0 (1C, s), 33.0 (1C, s), 47.9 (1C, s), 49.70 (1C, s), 56.18 (1C, s), 56.25 (1C, s), 58.34 (1C, s), 69.0 (1C, s), 101.3 (1C, s), 106.2 (1C, s), 118.8 (2C, s), 122.4 (1C, s), 128.4 (2C, s), 131.4 (1C, s), 135.3 (1C, s), 136.0 (1C, s), 138.4 (1C, s), 139.4 (1C, s), 146.3 (1C, s), 155.1 (1C, s), 158.5 (1C, s), 16931 (1C, s). LC-MS analysis for $C_{23}H_{25}NO_2$ calculated (EI, m/z (%): 347.19 and Found :348.36 [M+1]. Melting point is 55-56 ºC

3j- (E)-N-(4-(hexyloxy)benzylidene)-3-methoxynaphthalen-1-amine



Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1458-1466 | ISSN:2251-6727

IR (KBr, cm^{-1}) υ_{max} : 3440 (-NH), 1635 (C=O) :^{1}H NMR: δ 0.45 (3H, t, *J* = 8.0 Hz), 1.14-1.15 (9H, m), 1.68 (6H, m), 3.68-3.77 (2H, m), 4.31 (1H, tq, *J* = 7.0) 5.0-5.36 (2H, d, *J* = 8.1 Hz), 6.97-6.93 (3H, m), 7.91 (2H, ddd, *J* = 8.8), 8.72 (1H, dd, *J* = 4.1 Hz). ^{13}C NMR: δ 14.0 (1C, s), 18.0 (1C, s), 22.6 (1C, s), 22.7 (1C, s), 28.4 (1C, s), 29.1 (1C, s), 31.2 (1C, s), 34.2 (1C, s), 47.8 (1C, s), 49.6 (1C, s), 56.1 (1C, s), 56.2 (1C, s), 58.3 (1C, s), 69.1 (1C, s), 101.4 (1C, s), 106.3 (1C, s), 118.6 (2C, s), 122.3 (1C, s), 128.3 (2C, s), 128.3 (1C, s), 131.3-131.4 (3C, s), 136.1 (1C, s), 138.26 (1C, s), 139.4 (1C, s), 146.2 (1C, s), 155.2 (1C, s), 169.6 (1C, s). LC-MS analysis of $C_{24}H_{27}NO_2$ calculated (EI, m/z (%): 361.20 and Found : 362.15 [M+1]. The melting point is 58-59 ºC.

Chemistry

The FT-IR spectrum of 3a- (E)-N-(3-bromobenzylidene)-3-methoxynaphthalen-1-amine compound showed the characteristic IR band at 3377 cm^{-1}, 2922 cm^{-1}, 1606 cm^{-1}, 613 cm^{-1}which indicated the presence of -NH, O-CH_3 -C=O, C-Br. Similarly, 3415cm^{-1}, 2981cm^{-1}, 1797cm^{-1}, 875cm^{-1}in 3b-(E)-N-(3-chlorobenzylidene)-3-methoxynaphthalen-1-amine confirm the NH, O-CH_3 -C=O, C-Br functional group. The range of 3338-3501 cm^{-1}confirm the presence of -NH group in all the molecules.

The ^{1}H spectra of the synthesised compounds 3a-j were recorded and their chemical shift values are presented. The doublet and triplet signals at δ 1.17 and 1.67 ppm indicate the presence of -CH_2 and -CH_3 group in the 3a molecule. Further, the multiplet signal at δ 3.60-3.79 ppm shows the presence of -CH_2 of 1,3 triazolinone and O-CH_3 group of in 3a. The aromatic H-atoms were confirmed by signal from δ 6.90-6.91ppm in NMR. Similarly, the NMR data for molecule 3c also found in same signal range. The signals at δ 1.17-1.18 ppm, δ 4.1-4.2 ppm and singlet peak at δ 6.06 ppm indicated the presence of -3-ethoxy-4-hydroxyphenyl in molecule 3d. Moreover, the pentyloxy group was confirmed by multiplet signal at δ 1.12-1.6 pmm in 3e NMR analysis. Additionally, the doublet peaks at δ 5.35 ppm and 5.68 ppm confirm the formation of Schiff bases in the molecule 3f and 3g. The doublet peaks at δ 1.18 ppm and singlet peak δ 6.01 ppm appeared in 3h NMR and confirmed the 5-methylthiophen-2-yl.

In the ^{13}C NMR spectrum, all the data confirm the number of carbon atomspresent in the synthesised molecules and its related to the ^{1}H NMR data. The ESI mass spectra were recorded at 70 eV and maintained at 150^{0}C. The molecular weight (m/z) of all the synthesised compounds was confirmed by MS. Finally, the structure of the synthesised new 3a-j were confirmed by the analysis of IR, ^{1}H ,^{13}C NMR and MS spectral data.Figure 1-4 shows the IR, ^{1}HNMR, and ^{13}CNMR analysis of the 3a- (E)-N-(3-bromobenzylidene)-3-methoxynaphthalen-1-amine molecules.

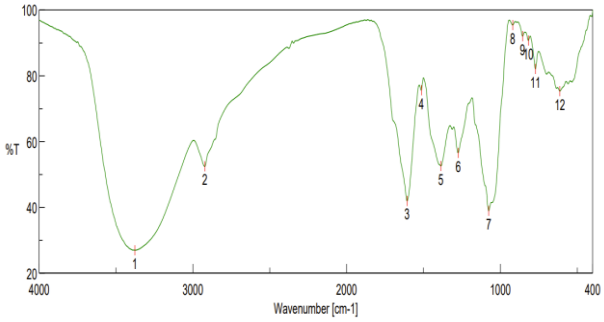


Figure 1. IR spectrum of the 3a- (E)-N-(3-bromobenzylidene)-3-methoxynaphthalen-1-amine.

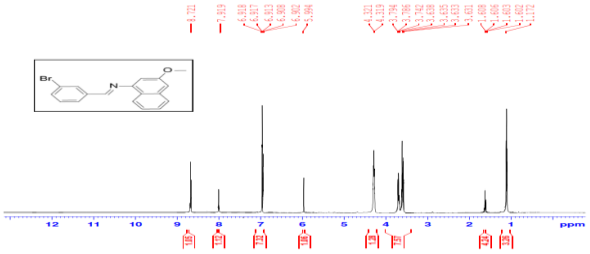


Figure 2. 1H NMR spectrum of the 3a- (E)-N-(3-bromobenzylidene)-3-methoxynaphthalen-1-amine.

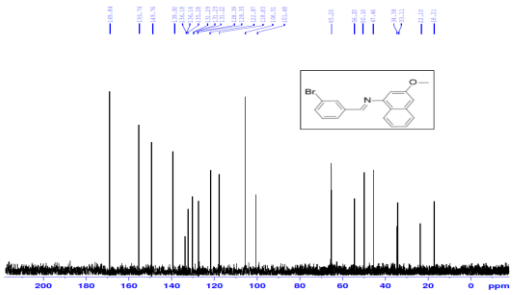


Figure 3. 13C NMR spectrum of the 3a- (E)-N-(3-bromobenzylidene)-3-methoxynaphthalen-1-amine.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1458-1466 | ISSN:2251-6727

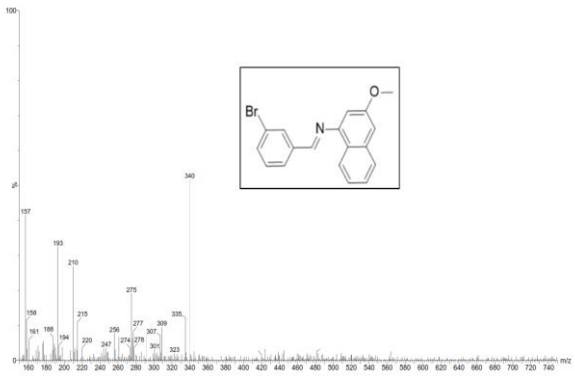


Figure 4. Mass spectrum of the 3a- (E)-N-(3-bromobenzylidene)-3-methoxynaphthalen-1-amine.

Anti-bacterial activities

This section deals with the anti-bacterial properties of synthesised methoxynaphthalen-1-amine Schiff bases derivatives. Table 1 depicts anti-bacterial activities of synthesized compounds. All synthesized compounds were screened for their in-vitro antibacterial activity against four different pathogenic strain, including two gram-positive bacteria, Staphylococcus aureus, Bacillus subtilis and two gram-negative namely, *Escherichia coli, and Klebshella pneumonia* using against standard drug Ciprofloxacin and Ampicillin (10µg/disc) respectively.

Table 1. In vitro Anti-microbial Properties of methoxynaphthalen-1-amine Schiff bases derivatives

Molecules	**Zone of Inhibition (mm) (1000 µg/mL)**			
	Gram Positive		**Gram Negative**	
	S. aereus	***B. subtilis***	***E. coli***	***K. pneumonia***
3a	10	9	8	10
3b	11	12	14	11
3c	8	14	21	11
3d	16	10	12	10
3e	14	11	15	9
3f	9	8	20	13
3g	10	12	18	15
3h	12	14	11	13
3i	8	9	10	12
3j	7	9	11	14
Ciprofloxacin	18	14	25	22
Ampicillin	19	16	20	19

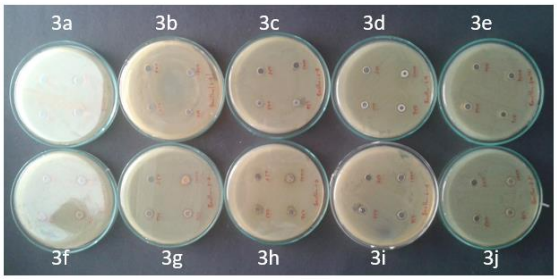


Figure 5. Zone of inhibition of the synthesised compounds in E. coli

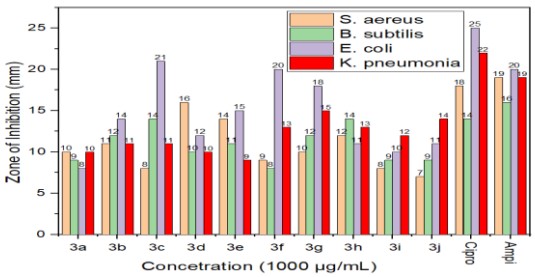


Figure 5. Zone of inhibition of the synthesised compounds in S. aureus, B. Subtilis, E. coli and K. poneumonia.

In vitro Anti-microbial Properties of methoxynaphthalen-1-amine Schiff bases derivatives have been subjected to summarised (Figure5 and 6), the [ZOI (millimeter), (1000 µg/ml)] value against the pathogenic organism. According to this, all the compound found to possess the good ZOI value than standard drug against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Klebshella pneumonia respectively. In Staphylococcus aureus the 3c, 3f, 3i and 3j shows 10 mm, 8mm, 8mm and 7 mm respectively. In Bacillus subtilis 3a, 3f, 3i and 3j shows 9mm, 8mm, 9mm and 9mm respectively. The molecules 3a, 3h, 3i, 3j shows 8mm, 11mm, 10mm, and 11mm on Escherichia

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1458-1466 | ISSN:2251-6727

coli. Similarly, in Klebshella pneumonia, 3a, 3b,3c, 3d and 3e shows 10mm, 11mm, 11mm, 10mm and 9mm respectively. The standard drug Ciprofloxacin and Ampicillin (10µg/disc) less activity than synthesised compounds. Figure. represented a bar diagram of the in-vitro antibacterial activities of methoxynaphthalen-1-amine Schiff bases derivatives. All target compounds are investigated, but the ZOI value has been found that all the compounds having good inhibition activity against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Klebshella pneumonia using against standard drug Ampicillin respectively.

Kinetic Analysis

To understand the inhibitory mechanism of synthetic methoxynaphthalen-1-amine Schiff bases derivatives, a kinetic study was performed. Based on our In vitro Anti-microbial results, we selected the most potent compound 3j to determine their inhibition type and inhibition constant. The kinetic results of the enzyme by the Lineweaver-Burk plot of 1/V versus 1/[S] in the presence of different inhibitor concentrations gave a series of straight lines, the result of Lineweaver-Burk plot of compound 3j showed that Vmax remains the same without significantly affecting the slopes. Km increases with increasing concentration, while Vmax remains the same with an insignificant difference. This behavior indicated that 3j competitively inhibited the enzyme tyrosinase (Figure. 7). The slope against the concentration of 3j showed EI dissociation constant. Ki was calculated from the inhibitor concentration of 3j versus the slope and Ki was found to be 0.0027 µM.

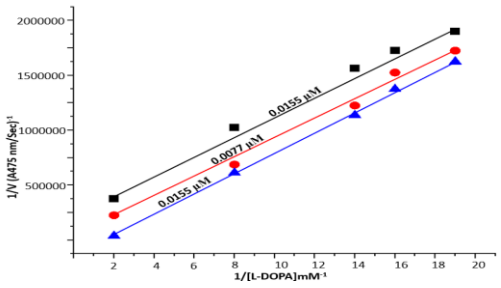


Figure 7. Lineweaver–Burk plots for inhibition of tyrosinase in the presence of compound 3j. Concentrations of 3j were 0.00, 0.0077, and 0.0155 µM, respectively.

CONCLUSION

In this study, ten novel 3-methoxynaphthalen-1-amine derivatives were synthesised using the Skraup reaction. All the compounds exhibited promising antimicrobial activity. The kinetics study was evaluated for compound 3j by Lineweaver–Burk plots for inhibition of tyrosinase. These compounds could be further modified to develop potential and safer antibacterial agents.

Acknowledgement

The authors are deeply acknowledged the Central Instrumental Facility, Savitribai Phule, Pune University, Pune, India and DST - FIST sponsored Central Instrumentation Laboratory, Dada Patil Mahavidyalaya, Karjat, Dist.- Ahmednagar, Maharashtra India for the spectral analysis. The author thanks to the Principal of Milind College of Science, Aurangabad for providing research facility.

REFERENCES

1. Abasolo, M. I., Gaozza, C. H., & Fernández, B. M. (1987). Kinetic study on the anelation of heterocycles. 1. Quinoxalinone derivatives synthesized by hinsberg reaction. *Journal of heterocyclic chemistry*, *24*(6), 1771-1775.
2. Bekerman, D. G., Abasolo, M. I., & Fernández, B. M. (1992). Comparative kinetic studies on the synthesis of quinoxalinone derivatives and pyrido [2, 3-b] pyrazinone derivatives by the hinsberg reaction. Journal of heterocyclic chemistry, 29(1), 129-133.
3. Rodrigo, G. A., Renou, S. G., Bekerman, D. G., Abasolo, M. I., & Fernández, B. M. (1997). Kinetic study on the synthesis of some benzo [g] quinoxalin-2 (1H)-one derivatives. *Journal of heterocyclic chemistry*, *34*(2), 505-508.
4. Cabañas, B., Baeza, M. T., Salgado, S., Martín, P., Taccone, R., & Martínez, E. (2004). Oxidation of heterocycles in the atmosphere: Kinetic study of their reactions with NO3 radical. *The Journal of Physical Chemistry A*, *108*(49), 10818-10823.
5. Liu, M., Liu, B., Zhong, S., Shi, L., Liang, L., & Sun, J. (2015). Kinetics and mechanistic insight into efficient fixation of CO2 to epoxides over N-heterocyclic compound/ZnBr2

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1458-1466 | ISSN:2251-6727

catalysts. *Industrial & Engineering Chemistry Research*, *54*(2), 633-640.

6. Grom, M., Stavber, G., Drnovšek, P., & Likozar, B. (2016). Modelling chemical kinetics of a complex reaction network of active pharmaceutical ingredient (API) synthesis with process optimization for benzazepine heterocyclic compound. *Chemical Engineering Journal*, *283*, 703-716.
7. Khan, F. M., Abbasi, M. A., Siddiqui, S. Z., Sadiq Butt, A. R., Raza, H., Zafar, A., ... & Seo, S. Y. (2021). Convergent synthesis of carbonic anhydrase inhibiting bi-heterocyclic benzamides: Structure–activity relationship and mechanistic explorations through enzyme inhibition, kinetics, and computational studies. *Journal of Heterocyclic Chemistry*, *58*(5), 1089-1103.
8. Campanati, M., Vaccari, A., & Piccolo, O. (2000). Environment-friendly synthesis of nitrogen-containing heterocyclic compounds. *Catalysis today*, *60*(3-4), 289-295.
9. Halimehjani, A. Z., Namboothiri, I. N., & Hooshmand, S. E. (2014). Part II: nitroalkenes in the synthesis of heterocyclic compounds. *RSC Advances*, *4*(93), 51794-51829.
10. Abasolo, M. I., Fernández, B. M., & Magrini, E. (1992). Kinetic study on the anelation of heterocycles. 3. Pyrazino [2, 3-d] pyrimidine derivatives synthesized by the hinsberg reaction. *Journal of heterocyclic chemistry*, *29*(5), 1279-1283.
11. Mukai, K., Kageyama, Y., Ishida, T., & Fukuda, K. (1989). Synthesis and kinetic study of antioxidant activity of new tocopherol (vitamin E) compounds. *The Journal of Organic Chemistry*, *54*(3), 552-556.
12. Halimehjani, A. Z., Namboothiri, I. N., & Hooshmand, S. E. (2014). Part I: Nitroalkenes in the synthesis of heterocyclic compounds. *RSC Advances*, *4*(89), 48022-48084.
13. Johnston, V. K., Maley, D., Gagnon, R. C., Grassmann, C. W., Behrens, S. E., & Sarisky, R. T. (2003). Kinetic profile of a heterocyclic HCV replicon RNA synthesis inhibitor. *Biochemical and biophysical research communications*, *311*(3), 672-677.
14. McAteer, C. H., Murugan, R., & Rao, Y. V. S. (2017). Heterogeneously catalyzed synthesis of heterocyclic compounds. In *Advances in heterocyclic chemistry* (Vol. 121, pp. 173-205). Academic Press.
15. Grigor'eva, N. G., Agliullin, M. R., Kostyleva, S. A., Bubennov, S. V., Bikbaeva, V. R., Gataulin, A. R., ... & Narender, N. (2019). Mesoporous Aluminosilicates in the Synthesis of N-Heterocyclic Compounds. *Kinetics and Catalysis*, *60*, 733-743.
16. Mustafa, Y. F. (2018). Synthesis, characterization and antibacterial activity of novel heterocycle, coumacine, and two of its derivatives. *Saudi pharmaceutical journal*, *26*(6), 870-875.
17. Butt, A. R. S., Abbasi, M. A., Siddiqui, S. Z., Raza, H., Hassan, M., Shah, S. A. A., ... & Seo, S. Y. (2019). Synthesis and structure-activity relationship of tyrosinase inhibiting novel bi-heterocyclic acetamides: Mechanistic insights through enzyme inhibition, kinetics and computational studies. *Bioorganic Chemistry*, *86*, 459-472.
18. Phan, H. B., Luong, C. M., Nguyen, L. P., Bui, B. T., Nguyen, H. T., Mai, B. V., ... & Tran, P. H. (2022). Eco-friendly synthesis of 5-hydroxymethylfurfural and its applications as a starting material to synthesize valuable heterocyclic compounds. *ACS Sustainable Chemistry & Engineering*, *10*(27), 8673-8684.
19. El-Hashash, M. A., Rizk, S. A., & Atta-Allah, S. R. (2015). Synthesis and regioselective reaction of some unsymmetrical heterocyclic chalcone derivatives and spiro heterocyclic compounds as antibacterial agents. *Molecules*, *20*(12), 22069-22083.
20. El-Saghier, A. M., Abd El-Halim, H. F., Abdel-Rahman, L. H., & Kadry, A. (2019). Green synthesis of new trizole based heterocyclic amino acids ligands and their transition metal complexes. Characterization, kinetics, antimicrobial and docking studies. *Applied Organometallic Chemistry*, *33*(1), e4641.