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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and characterization of new types of 2-(6-methoxy-2-naphthyl)propionamide derivatives as potential antibacterial and antifungal agents

Mohamed H. Helal · Samir Y. Abbas · Mohamed A. Salem · Awatef A. Farag · Yousry A. Ammar

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Abstract A series of novel 2-(6-methoxy-2-naphthyl)propionamide derivatives have been efficiently synthesized in excellent yields via the reaction of naproxenoyl chloride with different amino compounds. Most of the synthesized compounds were screened in vitro for their antibacterial and antifungal activities. Most of the compounds showed significant antibacterial and antifungal activities, reaching, in certain cases, the same level of antimicrobial activity as the standard antibacterial agent Ampicilline and antifungal agent Flucanazole. *N*-(4-(*N*-arylsulfamoyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (**4a–c**), 4-(4-fluorobenzylidene)-2-(1-(6-methoxynaphthalen-2-yl)ethyl)oxazol-5(4*H*)-one (**10b**), 2-(6-methoxynaphthalen-2-yl)-*N*-((5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl)propanamide (**12**), and *N*-((4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl)-2-(6-methoxynaphthalen-2-yl)propanamide (**13**) were found to be the most potent compounds against most of the tested strains. The antimicrobial activity was further supported by using MIC technique. Structure activity relationship studies revealed several matching pairs.

Keywords Propionamides · Naproxen · Carboxamides · Chiral carbon · Antibacterial · Antifungal activity

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Introduction

Despite many significant progresses in antimicrobial therapy, infectious diseases caused by bacteria and fungi remain a major worldwide health problem due to rapid development of resistance to the existing antimicrobial drugs (antibacterial and antifungal drugs). In other words, the increasing use and misuse of the existing antimicrobial drugs have resulted in the development of resistant pathogens (Berber *et al.*, 2003; Appelbaum, 2006). So, the medical community faces a serious problem against infections caused by the pathogen bacteria and needs an effective therapy and search for novel antimicrobial agents.

Staphylococcus aureus, as example, has been recognized as an important pathogen of humans. Infections caused by this bacteria species can lead to serious consequences, especially in hospitalized patients. The appearance of methicillin-resistant strains of *S. aureus* (MRSA) has been a concern all over the world. This situation becomes worse and more threatening regarding the ease of transmission of the pathogen among individuals, resulting in the dissemination of MRSA (Gomes *et al.*, 2006). The resistance to a great number of antibiotics presented by MRSA makes it difficult to control in hospital environments (Hiramatsu *et al.*, 2002).

Considering the antimicrobial agents more recently approved for clinical use, a series of carboxamides, showed excellent in vitro and in vivo antibacterial activity present activity against Gram +ve organisms, including MRSA (Strigacova *et al.*, 2000; Zanatta *et al.*, 2007; Zhuravel *et al.*, 2005). Carboxamides which contain -CONH- bridge connect the benzene or heterocyclic rings with antimycobacterial activity. This moiety can form centrosymmetric dimer pairs with the peptidic carboxamido group of some peptides, needed for binding to the receptor site, possibly by forming hydrogen bond (Matsuoka *et al.*, 1999; Doležal *et al.*, 2006).

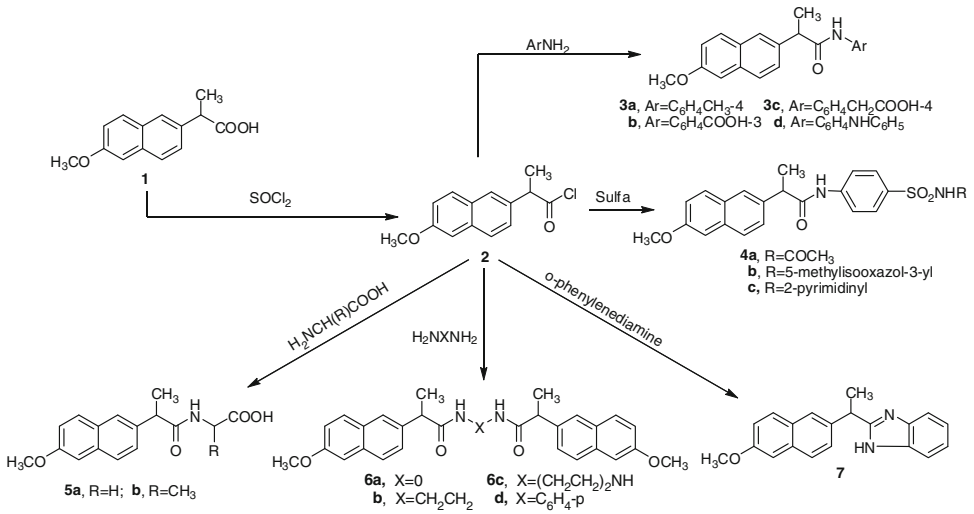
In view of the scenario presented above, the search for new and effective antimicrobial agents, resistant to the mechanisms of defense of these bacteria, is of paramount importance.

As a part of our extensive research program to rapidly assemble novel bioactive heterocycles under mild conditions (Khalifa *et al.*, 2013; Farag *et al.*, 2012; Ismail *et al.*, 2010; Ammar *et al.*, 2006; Aly *et al.*, 2010), we have employed naproxenoyl chloride (**2**) to prepare various new propionamide derivatives incorporating chiral carbon atom and also methoxy as lipophilic group to evaluate antimicrobial activity, hopefully, the new analogs with enhanced potency or of finding new applications. Various functional groups were introduced into the target compounds in order to investigate their preliminary structure activity relationships. The preceding functional groups have been suggested as being the pharmacophore responsible for the broad spectrum of biological activities shown by these moieties.

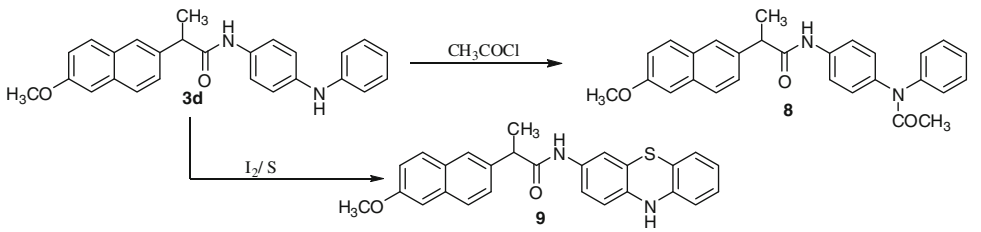
Results and discussion

Chemistry

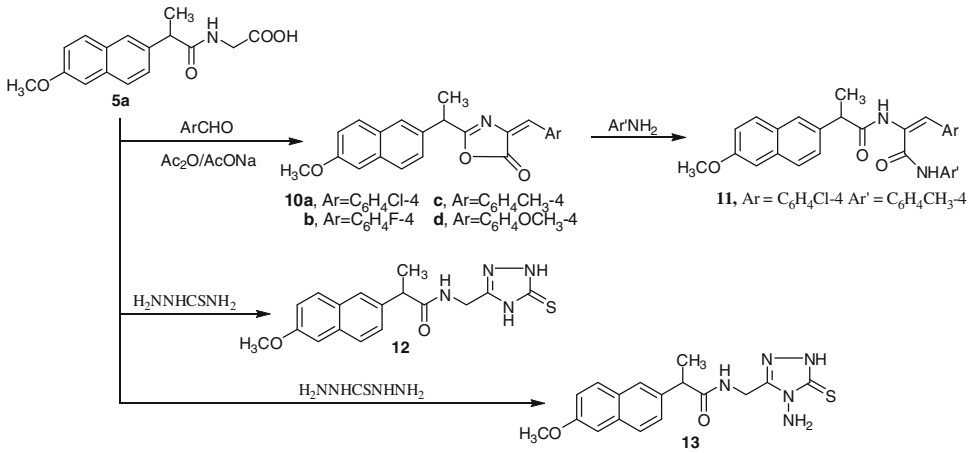
The synthesis of the target compounds is depicted in Schemes 1, 2, and 3. The starting material, naproxenoyl chloride **(2)**, was prepared through treatment of naproxen **(1)** with thionyl chloride (Al-Sehemi *et al.*, 2006). This compound was proven to be a good synthons for different highly biologically active compounds. Thus, propionamide derivatives **3a–d** were prepared via interaction of compound **2** with some aromatic amines. The structure of the products was characterized from their spectroscopic as well as elemental analytical data. For example, the IR spectrum of compound **3d** revealed the absorption bands at: 3,386, 3,301, 1,651 cm^{-1} corresponding to two 2NH and C=O functions, respectively. ^1H NMR spectrum of **3c** showed signals at: 1.47, 3.45 corresponding to CH_3 and CH_2 protons and showed a quartet signal at: 3.97 due to the CH proton and two D_2O exchangeable signals at 10.08 and 11.34 corresponding to NH and COOH protons. The sulfonamide functional group has a long and rich history in



Scheme 1 Synthesis of propionamide, sulfonamide, acyl aminoacid, bispropionamide and benzoimidazole derivatives



Scheme 2 Synthesis of *N*-phenylacetamido and phenothiazine derivatives



Scheme 3 Synthesis of oxazolone, acrylamide and 1,2,4-triazole derivatives

organic chemistry and drug discovery. Beginning with the discovery of the 'sulfa' antibiotics in the 1930s that revolutionized the treatment of bacterial infections, and continuing into the present day with the development of potent antiretrovirals used to treat patients infected with HIV, sulfonamides remain a particularly important class of compounds for the treatment of infectious diseases. Thus, condensation of the acid chloride **2** with some derivatives of sulfa drugs afforded the corresponding carboxamide derivatives **4a–c**, Scheme 1. The analytical and spectral data were in agreement with the proposed structure. Thus, the ^{1}H NMR spectrum of **4a** showed a singlet at: $\delta = 1.88$ for the CH_3 of acetyl group and two singlets at: 9.85 and 10.56 singlet for two NH groups. Owing to the higher biological activity of amino acids, the authors planned to couple some of the amino acids with naproxene in one structure through an amide linkage. Hence, reaction of the naproxenoyl chloride with amino acids in the presence of pyridine furnished the amide derivatives **5a**,**b**, Scheme 1. The structure of the isolated products was evidenced by its spectroscopic and elemental analysis data. Thus, IR spectrum of **5a** exhibited absorption bands at: 3,380, 3,200–2,700, 1,740, 1,675 corresponding to NH, COOH, and two C=O groups. Moreover, its ^{1}H NMR spectrum revealed signals corresponding to CH_2 protons at: 3.72 and two D_2O-exchangeable signals at: 8.25 and 12.55 corresponding to one NH and COOH. Further, the molecular ion peak recorded in the mass spectrum is also in agreement with the molecular weight of the compound.

Bis-compounds were reported to possess a wide range of biological activities. Thus, bis-naproxamide derivatives **6a–d** were synthesized through interaction of two moles of the acid chloride derivative **2** with hydrazine hydrate, ethylenediamine, diethylenetriamine, and *p*-phenylenediamine, Scheme 1. Their structural assignment was secured via spectroscopic and microanalytical methods. Thus, the microanalyses were in satisfactory agreement with the calculated values (C, H, N fvalues were within ±0.4 %). The mass spectra produced the desired molecular ion peaks with the appropriate isotopic distributions where applicable. Thus, the mass spectrum of compound **6d** showed *m/z* at: 532 (M^+) which is the base peak. Structures of the prepared compounds were further elucidated by the use of NMR and IR techniques. Thus, IR spectrum of product **6a** revealed absorption bands at: 3,178 cm^{-1} due to NH group, a band near 1,651 cm^{-1} that was attributed to the carbonyl group. ^{1}H NMR spectrum of compound **6b** revealed, besides an aromatic multiplet in the region of $\delta = 7.12$–7.80 ppm, two singlet signals at: $\delta = 3.1$, 8.1 attributed to CH_2 and NH, respectively. The authors planned to couple naproxene moiety with biologically active heterocyclic compounds such as benzimidazole moiety. Thus, heating the acid chloride **2** with *o*-phenylenediamine in DMF under reflux affected cyclization to afford benzimidazole derivative **7**. Structure **7** was suggested for this product based on analytical and spectral data. Thus, the IR spectrum revealed absorption bands at 3,225 and 1,608 due to (NH) and (C=N), respectively, and the absence of a band in the region of C=O group absorption. The ^{1}H NMR spectrum revealed D_2O exchangeable proton at 10.80 due to NH besides the ten aromatic protons in the region signals at: $\delta = 7.20$–7.89; the mass spectrum of this product showed the molecular ion peak at *m/z* 302 (M^+, 85.0) and base peak at 151 (100).

Now, we have extended our synthetic program to the synthesis of otherwise inaccessible ring system utilizing compound **3d** as the key starting material. A mixture of **3d** and acetyl chloride were reacted in dioxane under reflux condition in the presence of catalytic amounts of pyridine to yield a product which may be formulated as the acetyl derivative **8**. The structure of acetyl derivative **8** was established from their IR, ^{1}H NMR, and mass spectra. Its IR spectrum showed the presence of peaks at 3,280 due to NH group, in addition, for two bands in the region of 1,680, 1,670 corresponding to two carbonyl groups. ^{1}H NMR spectrum showed two singlet signals at: 1.95, 10.2 due to CH_3 acetyl and NH, and a multiplet signal in the region of 6.8–7.94 due

to 15 aromatic protons. Mass spectrum showed molecular ion peak at: *m/z* 438 (M^+) (29.13 %) with a base peak *m/z* 184. Also, upon treatment of compound **3d** with sulfur and iodine in dichlorobenzene, the corresponding phenothiazine derivative **9** was obtained. Structure **9** was suggested for this product based on analytical and spectral data. The IR spectrum revealed absorption bands at: 3,312, 3,224 cm^{-1} (2NH), 1,650 cm^{-1} (C=O). ^1H NMR spectrum revealed signals at: $\delta = 7.18–7.85$ and 10.12, 12.13 ppm due to the aromatic and 2NH protons, respectively. (Scheme 2).

The authors planned to cover the coupling of naproxen moiety with different biologically active heterocyclic compounds such as oxazolone and triazole moieties.

Compound **5a** was also used as a precursor for the synthesis of heterocyclic compounds. Thus, treatment of **5a** with aromatic aldehydes in acetic anhydride containing catalytic amounts of sodium acetate under reflux afforded the oxazolone derivatives **10a–d**, (Scheme 3). The structure of the obtained products was confirmed by their IR, NMR, and mass spectrum. The IR spectrum of compound **10a** confirmed the formation of the lactone function through the presence of the carbonyl group at: 1,730. ^1H NMR spectrum of compound **10c** showed the presence of two singlet signals at: 2.32, 3.80 due to CH_3 and OCH_3, also the presence of doublet and quartet signals at: 1.48 and 3.9 corresponding to CH_3 and CH besides multiplet signals at: $\delta = 7.13–7.88$ ppm due to 11 aromatic protons. Mass spectrum of **10a** exhibited a molecular ion peak at *m/z* 391 (M^+: 8.4 %) with a base peak at: 197. The lactone function in the oxazolone ring was opened upon treatment of compound **10a** with *p*-toluidine in ethanol under reflux, where the acrylic acid amide derivative **11** was obtained from Scheme 3. The IR spectrum showed absorption bands at 3,300 cm^{-1} (NH) and 1,675 cm^{-1} (C=O amide); ^1HNMR showed two D_2O exchangeable protons at: $\delta = 8.87$ and 11.40 due to NH protons and a singlet signal at 2.23 due to CH_3 group. In addition, compound **5a** was allowed to react with either thiosemicarbazide or thio-carbohydrazide, where the triazole derivatives **12**, **13** were obtained, respectively. Structure **13** was proved by its IR spectrum which revealed stretching frequencies of NH_2 and NH at 3,400, 3,300 cm^{-1}, and 1,221 (C=S). The ^1H NMR for compound **13** showed three D_2O exchangeable at: 5.56, 8.51, and 13.5 due to NH_2, NH amide, and NH triazole, respectively, besides multiplet bands at $\delta = 7.13–7.82$ ppm due to six aromatic protons.

Biological activity

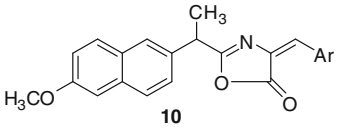
Antibacterial activity

The synthesized compounds **3a–d**, **4a–c**, **5a**, **b**, **6a**, **b**, **8**, **9**, **10a**, **b**, **11–13** (18 compounds) were tested in vitro for antibacterial activity against the following bacterial strains: Gram −ve bacteria, *S. aureus* RCMB 010027 and *Bacillus subtilis* RCMB 010063; and Gram-negative bacteria, *Escherichia coli* RCMB 000103 and *Pseudomonas aeruginosa* RCMB 010043. The results are summarized in Table 1. Antimicrobial tests were carried out by the agar well diffusion method (Scott, 1989) using 100 µl of tested compound solution prepared by dissolving 1 mg of the chemical compound in 1 ml of dimethyl sulfoxide (DMSO). The inoculated plates were then incubated for 24 h at 37 °C. The solution of Ampicilline (25 µg ml^{-1}) was prepared in sterilized water and used as standards for comparison of antibacterial activity. After incubation time, antimicrobial activity was evaluated by measuring the inhibition zone diameters against the test organisms and compared with standard zone size ranges that determine susceptibility, intermediate susceptibility, or resistance to the screened compounds. Visual bacterial growth is observed only in areas in which the drug concentrations are below those required for growth inhibition. The experiment was carried out in triplicate, and the average zone of inhibition was calculated.

To obtain a clear picture about the structure activity relationship for the synthesized compounds, the target compounds were represented in general formula in Table 1. The mean values of inhibition zone diameters show that all tested compounds in the antibacterial assay possess significant activity against the growth of most test organisms.

The tabulated antimicrobial screening results of the tested compounds revealed that: Structure **3**, Ar was aryl moiety (**3a**; 4-methylphenyl, **3b**; 4-carboxyphenyl, **3c**; 4-carboxymethylphenyl, **3d**; 4-phenylaminophenyl): the presence of 4-carboxyphenyl moiety showed the maximum potent activities against the most tested organisms, 4-carboxyphenyl moiety showed result near to the reference drug against the two gram-negative bacteria: *E. coli* and *P. aeruginosa*. Other moieties showed moderate activity against the most tested organisms. Structure **4** has sulfonamide side chain ending with alkyl or aryl moieties; these moieties were acetyl; **4a**, 5-methylisoxazol-3-yl; **4b**, and 2-pyrimidinyl; **4c**. The presence of pyrimidinyl moiety in **4c** exhibited the highest antibacterial activity against most of the test organisms; pyrimidinyl moiety showed results equipotent to the reference drug against the most tested organisms. Also, **4a**,**b** showed good activity against the most tested compounds. **4a**,**b** showed strong activity against *E. coli* near to reference drug. Structure **5**, Ar was CHRCOOH moiety (**5a**; R=H), **5b**; R=CH_3): all derivatives showed moderate activity against *Staphylococcus aureus* and *B. subtilis*, *E. coli* and no activities toward *P. aeruginosa*. Biscompounds **6a**, **b** with two naphthyl and two amide moieties showed moderate activity against *Staphylococcus aureus*, *B. subtilis* and no activities toward *P.*

Table 1 Antimicrobial activity of the synthesized compounds against the pathological organisms expressed as inhibition diameter zones in millimeters (mm) based on well diffusion assay



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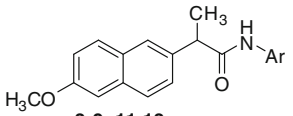


3-9, 11-13

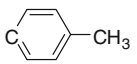
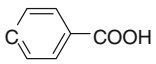
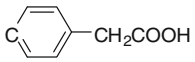
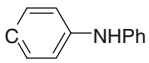
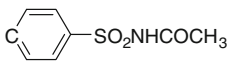
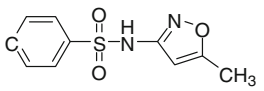
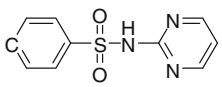
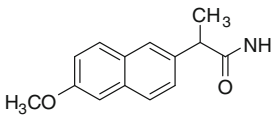
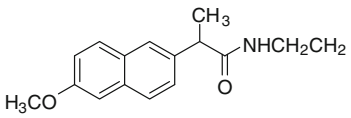
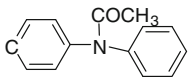
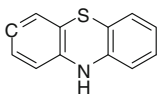
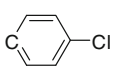
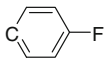
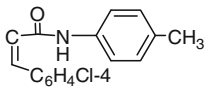
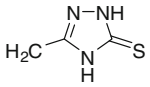
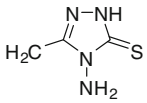
Compd. no.	Ar	Gram +ve		Gram −ve		Fungi	
		S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*Aspergill*	*Candida*
3a		16.1 ± 0.1	17.2 ± 0.3	15.6 ± 0.6	NA	14.7 ± 0.1	12.8 ± 0.6
3b		21.6 ± 0.5	23.7 ± 0.2	20.3 ± 0.8	15.9 ± 0.6	19.4 ± 0.3	15.6 ± 0.6
3c		17.3 ± 0.6	18.4 ± 0.4	16.6 ± 0.3	NA	13.9 ± 0.5	12.2 ± 0.4
3d		13.9 ± 0.2	15.4 ± 0.6	NA	NA	17.6 ± 0.2	NA
4a		23.3 ± 0.4	23.4 ± 0.6	21.3 ± 0.5	14.5 ± 0.4	18.6 ± 0.3	17.8 ± 0.3
4b		20.6 ± 0.6	21.7 ± 0.6	19.9 ± 0.3	13.0 ± 0.3	17.3 ± 0.4	16.5 ± 0.4
4c		25.3 ± 0.2	28.7 ± 0.2	21.6 ± 0.4	16.8 ± 0.3	11.7 ± 0.2	NA
5a	CH_2COOH	14.2 ± 0.3	16.4 ± 0.6	13.4 ± 0.6	NA	20.9 ± 0.3	20.6 ± 0.2
5b	$CH(CH_3)COOH$	15.1 ± 0.4	15.8 ± 0.7	14.3 ± 0.4	NA	12.7 ± 0.4	10.6 ± 0.6
6a		17.9 ± 0.5	19.4 ± 0.5	17.1 ± 0.7	NA	16.0 ± 0.3	13.5 ± 0.4
6b		13.1 ± 0.5	14.5 ± 0.3	NA	NA	12.6 ± 0.4	NA
8		16.2 ± 0.3	17.1 ± 0.2	14.6 ± 0.6	NA	12.4 ± 0.7	9.3 ± 0.2
9		21.4 ± 0.6	24.6 ± 0.4	20.2 ± 0.2	13.6 ± 0.7	17.6 ± 0.7	16.9 ± 0.4
10a		13.9 ± 0.3	15.0 ± 0.3	NA	NA	14.5 ± 0.3	NA

Table 1 continued

Compd. no.	Ar	Gram +ve		Gram −ve		Fungi	
		S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*Aspergill*	*Candida*
10b		20.3 ± 0.4	20.6 ± 0.4	19.3 ± 0.2	15.3 ± 0.4	18.3 ± 0.4	19.9 ± 0.6
11		19.9 ± 0.4	19.6 ± 0.4	14.3 ± 0.3	NA	14.8 ± 0.3	13.6 ± 0.6
12		21.9 ± 0.3	23.9 ± 0.4	20.9 ± 0.6	16.8 ± 0.4	20.2 ± 0.3	18.8 ± 0.4
13		21.6 ± 0.1	23.7 ± 0.2	20.3 ± 0.7	15.9 ± 0.6	19.4 ± 0.3	20.6 ± 0.6
Standard		28.9 ± 0.1	34.6 ± 0.4	21.4 ± 0.3	17.3 ± 0.1	21.9 ± 0.1	26.4 ± 0.2

aeruginosa. Structure **8** showed moderate activity against two Gram +ve bacteria, one Gram −ve bacteria (*E coli*) and showed no activity toward *P. aeruginosa*. Compound **9** with phenothiazine moiety showed strong activities against all of tested organisms. The activity was equipotent to the reference drug against the two Gram -ve bacteria. Structure **10** has oxazole side chain ending with chlorophenyl and fluorophenyl moieties. The presence of fluorophenyl moiety in case of **10b** showed activity more than chlorophenyl moiety in case of **10a**. Fluorophenyl moiety showed strong results against the most tested organisms. Compounds **12**, **13**, the aryl group have triazole moiety, showed good results against most of the test organisms. Compounds **12**, **13** showed activity equipotent to the reference drug against *E. coli* and *P. aeruginosa.* The comparison between the antibacterial activities of our potent synthesized compounds and ciprofloxacin as standard antibacterial reference drug against the used Gram +ve and Gram-negative bacteria was represented graphically in Fig. 1.

Antifungal activity

The search for newer antifungal agents continues due to the rapid development of the resistance among fungi to the existing antifungal agents. Even though novel broad spectrum antifungal agents were reported in recent years, the emergence of resistance has become an obstacle. Thus, more effective classes of such agents are desired. As such, propionamide derivatives may comprise a new class of antifungal agents. We chose *Aspergillus ochraceus* (RCMB 02593) and *Candida albicans* (RCMB 05035) in the antifungal susceptibility tests. Antifungal agents are evaluated against isolates of standard strains of fungi by the agar well diffusion method (Scott, 1989). The compounds

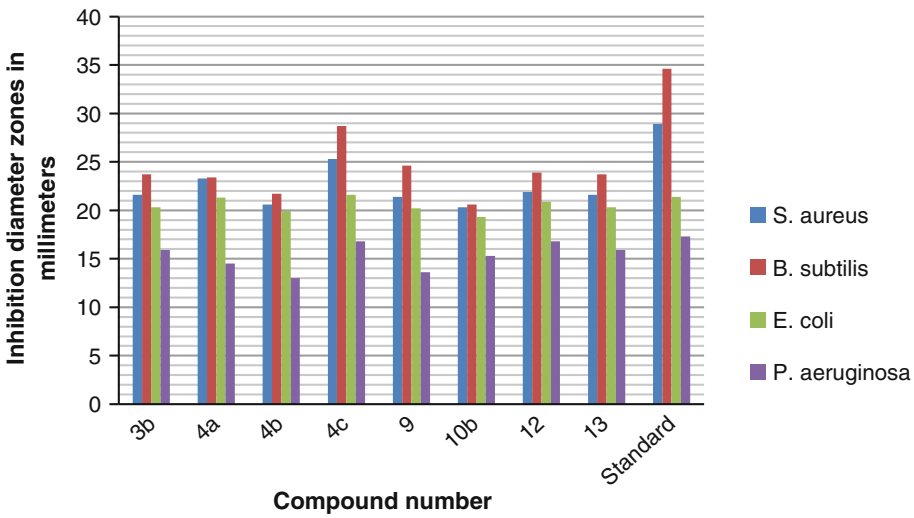


Fig. 1 The comparison between the antibacterial activities of our potent synthesized compounds and standard drug against the used Gram positive and Gram negative bacteria

were tested at a concentration of 1 mg ml^{-1} in DMSO solution. The solution of Flucanazole (25 μg ml^{-1}) was prepared in sterilized water and used as standards for comparison of antifungal activity. The inoculated plates were then incubated for 72 h at 25 °C. After incubation time, antifungal activity was evaluated by measuring the inhibition zone against the test organisms and compared with that of the standard. Antifungal activities were expressed as inhibition zone diameter in millimeters (mm). The experiment was carried out in triplicate, and the average zone of inhibition was calculated. The results are tabulated in Table 1.

In general, some compounds were very effective antifungal agents and in several cases achieved similar or greater levels of activity as the standard antifungal agent Flucanazole (22 and 26 mm). It is noted, though, that some fluctuation in antibacterial activity for individual tested compounds was observed across the two strains of tested fungi. As anticipated, a clear difference in antifungal activity is noted between compounds within and between each series, pointing to the reinforcing and opposing effects of the Ar groups. The presence of 4-carboxyphenyl moiety in structure **3** showed the maximum potent activities against the test organism, 4-carboxyphenyl moiety showed result near to the reference drug against *A. ochraceus.* Other moieties showed moderate activity against the test organisms. For instance, compound **5a** (Ar=CH_2COOH) showed good activities against *A. ochraceus* (21 mm) and *C. albicans* (21 mm) related to the standard antifungal agent (21 and 26 mm). **10b**, which has oxazole side chain ending with fluorophenyl moieties, showed good activity against the test fungi. Compounds **12**, **13**, the aryl group have triazole moiety and showed strong results near to the reference drug against *A. ochraceus*. Thus, these compounds comprise a promising new class of promising and potential broad spectrum antifungal agents. The comparison between the antifungal activities of our potent synthesized compounds and Flucanazole as standard antifungal drug against the used fungi is represented graphically in Fig. 2.

Minimum inhibitory concentrations against various tested strains

The minimum inhibitory concentration (MIC) is a standard technique used to measure the lowest concentration of a compound required to inhibit visible growth of a microorganism being investigated after approximately 24 h of incubation in the appropriate growth medium. MIC technique is a reliable means to determine the susceptibilities of microorganisms to drugs and also to monitor the activity of new ones. This technique provides a quantitative assessment of in vitro antimicrobial activity. Hence, further to the preceding tests of the potential antimicrobial and antifungal activities of synthesized compounds, we conducted a more quantitative assessment of the antimicrobial and antifungal activity of a narrow selection of potential leads by evaluating their minimum inhibitory. MIC values of the highest eight active synthesized compounds were measured by the procedure outlined in the Manual of Clinical Microbiology (Jones *et al.*, 1984) against the same strains used earlier, and the results were reported in Table 2. As shown in Table 2, all compounds tested showed inhibitory effect, ranging from as low as 0.24 μg ml^{-1} to as high as 62.5 μg ml^{-1}. In certain cases, such values are low enough to render such agents as potential candidates for further studies. Most of the tested compounds revealed MIC values lower than the standard against *P. aeruginosa,*, whereas compound **4c** was consistently the most effective against all bacterial strains, producing the lowest MIC against test organisms. In relation to structure activity trends, the effect of the aryl moiety

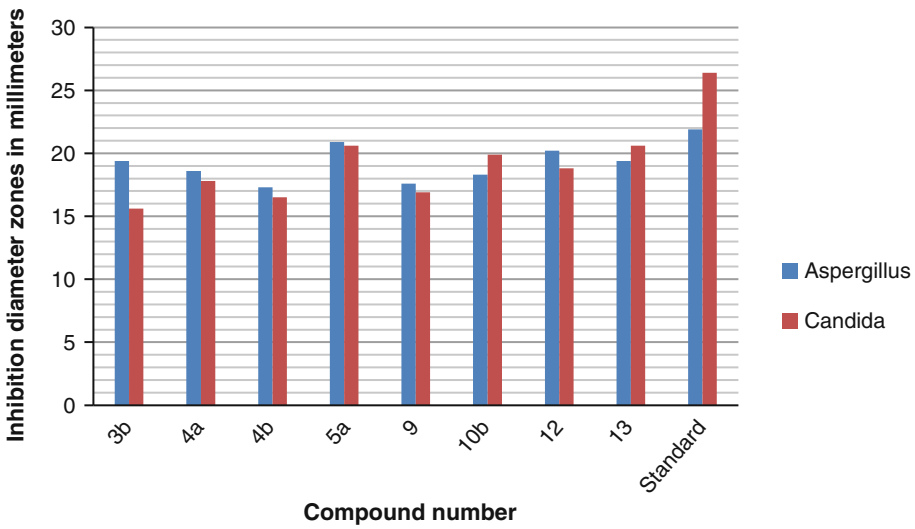


Fig. 2 The comparison between the antifungal activities of our potent synthesized compounds and standard drug

Table 2 Minimum inhibitory concentration (μg ml^{-1}) of the most potent synthesized compounds against the pathological organisms

Compd. No.	Gram +ve		Gram −ve		Fungi	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*Aspergillus*	*Candida*
3b	0.24	3.9	1.95	15.63	7.81	62.5
4a	0.97	0.97	3.9	125	15.63	31.25
4b	31.25	62.5	3.9	1.95	7.81	250
4c	0.24	7.81	3.9	3.9	3.9	NA
9	3.9	0.97	7.81	7.81	15.63	31.25
10b	7.81	3.9	15.63	62.5	15.63	125
12	3.9	0.97	7.81	31.25	7.81	31.25
10	3.9	0.97	7.81	62.5	15.63	62.50
Standard	0.06	0.007	1.95	31.25	1.95	0.24

is much more discernible and dominant as clearly reflected in the significant disparity of MIC values obtained against a given strain for compound with a different aryl moiety.

Conclusion

In conclusion, sulfonamide and triazoles containing (6-methoxy-naphthalen-2-yl)-propionamide which were easily prepared revealed promising antibacterial and antifungal activities. Thus, these compounds could be used as lead structure in pharmaceutical chemistry.

Experimental section

Melting points were determined on a digital Gallen-Kamp MFB-595 instrument and are uncorrected. IR spectra (KBr) were measured on a Shimadzu 440 spectrometer. ^{1}HNMR and ^{13}C spectra were recorded in deuterated dimethylsulfoxide (DMSO-d_6) on a Varian Gemini 300 (500 MHz) spectrometer using TMS as an internal standard; chemical shifts are reported as δ units. Mass spectra were performed on a Shimadzu GSMS-QP 1000 Ex mass spectrometer at 70 eV. The elemental analyses were carried out at the Microanalytical Center, Cairo University, Cairo (Egypt).

Synthesis of naproxenoyl chloride (**2**)

Naproxenoyl chloride was synthesized according to our reported procedure (Al-Sehemi *et al.*, 2006) as follows: To a solution of naproxen (**1**) (0.01 mol) in *m*-xylene (30 ml), $POCl_3$ (5 ml) was added. The reaction mixture was heated under reflux for 3 h, left to cool, the resulting precipitate was filtered off, washed with ether, and dried to give **2** as colorless crystals; mp 80–82 °C; Yield 75 %; ^{1}H NMR: δ/ppm = 1.62 (d, 3H, J = 6.5 Hz, CH_3), 3.84 (q, 1H, J = 6.5 Mz, CH), 3.94 (s, 3H, OCH_3), 7.13–7.73 (m, 6H, Ar–H). ^{13}C NMR: 18.24 (CH_3), 45.21(CH), 55.32 (OCH_3), 105.59 (C-5), 119.01 (C-7), 126.12 (C-4), 126.26 (C-8a), 127.21, 128.91, 129.31, 133.79, 135.16, 157.68, 179.27.

Synthesis of propionamides **3a–d**

Equimolar amounts of naproxenoyl chloride (**2**) (0.01 mol) and the requisite amine (namely *p*-toluidine, 4-aminobenzoic acid, 2-(4-aminophenyl)acetic acid, and *N1*-phenylbenzene-1,4-diamine) (0.01 mol) in dioxane (20 ml) were treated with pyridine (0.5 ml). The reaction mixture was heated under reflux for 3 h. The solution was concentrated under vacuum, left to cool. The resulting solid was filtered off and recrystallized from ethanol.

*2-(6-Methoxynaphthalen-2-yl)-N-(4-methylphenyl)-propionamide (**3a**)*

Yield 70 %; mp 130–131 °C; IR: υ/cm^{-1} = 3,250 (NH), 3,039(CH–Ar), 2,979–2,932 (CH-sp3), 1,653(C=O); ^{1}H NMR: δ/ppm = 1.56 (d, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.90 (q, 1H, CH), 7.25–8.89 (m, 10H, Ar–H), 10.0 (s, 1H, NH); ^{13}C NMR; 18.24 (CH_3), 20.25 (CH_3), 45.31(CH), 55.38 (OCH_3), 105.76 (C-5), 119.21 (C-7), 120.42, 120.43, 126.25 (C-4), 126.27 (C-8a), 127.23, 128.94, 129.32, 129.53, 129.54, 133.24, 133.82, 135.16, 138.2, 157.67, 179.65; Anal. Calc. for $C_{21}H_{21}NO_2$ (319.40): C, 78.97; H, 6.63; N, 4.39. Found: C, 78.80; H, 6.40; N, 4.20.

*4-(2-(6-Methoxynaphthalen-2-yl)propanamido)benzoic acid (**3b**)*

Yield 73 %; mp 235–236 °C; IR: υ/cm^{-1} = 3,278 (NH), 3,230–2,750 (broad COOH), 3,073(CH–Ar), 2,985–2,919 (CH-sp3), 1,700, 1,658(2C=O); ^{1}H NMR: δ/ppm = 1.53 (d, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.86 (q, 1H, CH), 7.13–7.88 (m, 10H, Ar–H), 9.54, 11.25 (2s, 2H, NH + COOH); ^{13}C-NMR: 18.35 (CH_3), 45.23(CH), 55.38 (OCH_3), 105.63 (C-5), 119.22 (C-7), 121.23, 121.25, 126.23 (C-4), 126.28 (C-8a), 126.89, 127.27, 128.87, 129.39, 130.12, 130.14, 133.87, 135.34, 137.23, 157.65, 173.32, 179.46; Anal. Calc. for $C_{21}H_{19}NO_4$ (349.38): C, 72.19; H, 5.48; N, 4.01. Found: C, 72.30; H, 5.20; N, 4.20.

*2-(4-(2-(6-Methoxynaphthalen-2-yl)propanamido)-phenyl)acetic acid (**3c**)*

Yield 68 %; mp 245–246 °C; IR: υ/cm^{-1} = 3,330, (NH), 3,250–2,750 (broad COOH), 3,070(CH–Ar), 2,970 (CH-sp3), 1,720, 1,660 (2C=O); ^{1}H NMR: δ/ppm = 1.47 (d, 3H, CH_3), 3.45 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.97 (q,1H, CH), 7.10–7.80 (m, 10H, Ar–H), 10.08, 11.34 (2s,

2H, NH + COOH); ^{13}C-NMR: 18.26 (CH_3), 41.43 (CH_2), 45.28(CH), 55.38 (OCH_3), 105.46 (C-5), 119.21 (C-7), 120.86, 120.89, 126.23 (C-4), 126.36 (C-8a), 127.25, 128.87, 129.45, 130.12, 130.14, 131.34, 133.65, 135.34, 138.21, 157.76, 177.23, 179.34; Anal. Calc. for $C_{22}H_{21}NO_4$ (363.41): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.60; H, 5.50; N, 3.60.

*2-(6-Methoxynaphthalen-2-yl)-N-(4-(phenylamino)-phenyl)propanamide (**3d**)*

Yield 70 %; mp 135–137 °C; IR: υ/cm^{-1} = 3,386, 3,301 (2NH), 3,062 (CH–Ar), 2,936 (CH-sp3), 1,651(C=O); ^{1}H NMR: δ/ppm = 1.45 (d, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.95 (q, 1H, CH), 7.13–7.87 (m, 15H, Ar–H), 9.65, 10.45 (2s, 2H, 2NH); Anal. Calc. for $C_{26}H_{24}N_2O_2$ (396.48): C, 78.76; H, 6.10; N, 7.07. Found: C, 78.60; H, 6.30; N, 7.20.

Synthesis of sulfonamide derivatives **4a–c**

A mixture of **2** (0.01 mol) and the appropriate sulfa drugs (namely sulfacetanilide, Sulfamethoxazole, and sulfadiazine) (0.01 mol) in dioxane (30 ml) was treated with pyridine (0.5 ml). The reaction mixture was heated under reflux for 3 h. The solution was concentrated under vacuum, left to cool. The resulting solid was filtered off and recrystallized from a mixture of ethanol/diaxone.

*N-(4-(N-acetylsulfamoyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (**4a**)*

Yield 75 %; mp 230–231 °C; IR: υ/cm^{-1} = 3,325, 3,116 (2NH), 3,052(CH–Ar), 2,977 (CH-sp3), 1,710, 1,681(2C=O); ^{1}H NMR: δ/ppm = 1.50 (d, 3H, CH_3), 1.88 (s, 3H, $COCH_3$), 3.87 (s, 3H, OCH_3), 4.01(q, 1H, CH), 7.14–7.85(m, 10H, Ar–H), 9.85, 10.56 (2s, 2H, 2NH); ^{13}C NMR: 16.56 (CH_3), 18.34 (CH_3), 45.43(CH), 55.42 (OCH_3), 105.23 (C-5), 119.25 (C-7), 120.87, 120.88, 125.34, 125.35, 126.34 (C-4), 126.65 (C-8a), 127.35, 128.87, 129.24, 133.67, 135.12, 135.24, 142.54, 157.62, 174.54, 179.45; Anal. Calc. for $C_{22}H_{22}N_2O_5S$ (426.49): C, 61.96; H, 5.20; N, 6.57. Found: C, 61.60; H, 5.30; N, 6.20.

*2-(6-Methoxynaphthalen-2-yl)-N-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)propanamide (**4b**)*

Yield 80 %; mp 130–131 °C; IR: υ/cm^{-1} = 3,365, 3,254 (2NH), 3,087(CH–Ar), 2,937 (CH-sp3), 1,664 (C=O); ^{1}H NMR: δ/ppm = 1.49(d, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.94 (q, 1H, CH), 4.87 (s, 1H, CH-isoxazole), 7.15–7.77(m, 10H, Ar–H), 9.45, 10.32 (2s, 2H, 2NH); Anal. Calc. for $C_{24}H_{23}N_3O_5S$ (465.52): C, 61.92; H, 4.98; N, 9.03. Found: C, 61.60; H, 4.70; N, 9.20.

*2-(6-Methoxynaphthalen-2-yl)-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)propanamide (**4c**)*

Yield 74 %; mp 175–176 °C; IR: υ/cm^{-1} = 3,350, 3,234 (2NH), 3,085(CH–Ar), 2,970 (CH-sp3), 1,680(C=O); ^{1}H NMR: δ/ppm = 1.48(d, 3H, CH_3), 3.87 (s, 3H, OCH_3), 3.91 (q, 1H, CH), 7.23–8.32 (m, 13H, Ar–H), 9.32, 10.21 (2s, 2H, 2NH); Anal. Calc. for $C_{24}H_{22}N_4O_4S$ (462.52): C, 62.32; H, 4.79; N, 12.11. Found: C, 62.40; H, 4.50; N, 12.20.

Synthesis of acyl aminoacid derivatives **5a**, **b**

Equimolar amounts of naproxenoyl chloride **(2)** (0.01 mol) and the requisite aminoacids (namely glycine and alanine) (0.01 mol) in dioxane (20 ml) were treated with pyridine (0.5 ml). The reaction mixture was heated under reflux for 3 h. The solution was concentrated under vacuum, left to cool. The resulting solid was filtered off and recrystallized from ethanol.

*2-(2-(6-Methoxynaphthalen-2-yl)propanamido)-acetic acid (**5a**)*

Yield 80 %; mp 125–126 °C; IR: υ/cm^{-1} = 3,380 (NH), 3,200–2,700 (COOH), 3,075(CH–Ar), 2,945 (CH-sp3), 1,740, 1,675(2C=O); ^{1}H NMR: δ/ppm = 1.41 (d, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.86 (q, 1H, CH), 3.95 (d, 2H, CH_2), 7.09–7.74 (m, 6H, Ar–H), 8.25 (s, 1H, NH), 12.5 (hump, 1H, NH); ^{13}C NMR: 18.35 (CH_3), 45.28(CH), 48.21 (CH_2), 55.43 (OCH_3), 105.63 (C-5), 119.28 (C-7), 126.39 (C-4), 126.48 (C-8a), 127.34, 128.89, 129.87, 133.84, 135.68, 157.69, 176.34, 179.64; MS, *m/z* (%): 287 (M^+; 1.2), 257 (4.77), 243 (3.82), 213 (4.98), 199 (3.78), 185 (100), 154 (13.43), and 126 (7.76); Anal. Calc. for $C_{16}H_{17}NO_4$ (287.31): C, 66.89; H, 5.96; N, 4.88. Found: C, 66.60; H, 5.70; N, 4.70.

*2-(2-(6-Methoxynaphthalen-2-yl)propanamido) propanoic acid (**5b**)*

Yield 65 %; mp 108–109 °C; IR: υ/cm^{-1} = 3,312 (NH), 3,200–2,750 (COOH), 3,076(CH–Ar), 2,954 (CH-sp3), 1,732, 1,665(2C=O); ^{1}H NMR: δ/ppm = 1.42, 1.49 (2d, 6H, $2CH_3$), 3.87 (s, 3H, OCH_3), 3.91, 4.23 (2q, 2H, 2CH), 7.13–7.67 (m, 6H, Ar–H), 8.92, 11.87 (2s, 2H, NH,COOH); ^{13}C-NMR: 16.32 (CH_3), 18.25 (CH_3), 45.28(CH), 52.21 (CH), 55.43 (OCH_3), 105.64 (C-5), 119.23 (C-7), 126.34 (C-4), 126.45 (C-8a), 127.24, 128.87, 129.54, 133.76, 135.61, 157.67, 176.34, 179.42; Anal. Calc. for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.36; N, 4.65. Found: C, 66.80; H, 6.60; N, 4.70.

Synthesis of bispropionamide derivatives **6a–d**

To a solution of the acid chloride **2** (0.01 mol) in dioxane (20 ml), hydrazine hydrate (0.012 mol) was added. In case of ethylenediamine, diethylenetriamine, or *p*-phenylenediamine (0.01 mol), pyridine (0.5 ml) was added. The reaction mixture was heated under reflux for 2 h. The solution was left to cool. The resulting solid was filtered off and recrystallized from dioxane.

*2-(6-Methoxynaphthalen-2-yl)-N′-(2-(6-methoxynaphthalen-2-yl)propanoyl)propanehydrazide (**6a**)*

Yield 72 %; mp 230–232 °C; IR: υ/cm^{-1} = 3,178 (NH), 3,066 (CH–Ar), 2,943 (CH-sp3), 1,654(C=O); ^{1}H NMR: δ/ppm = 1.45 (d, 6H, $2CH_3$), 3.75 (s, 6H, $2OCH_3$), 3.88 (q, 2H, 2CH), 6.98–7.81 (m, 12H, Ar–H), 8.2 (s, 2H, 2NH); MS, *m*/*z* (%): 456 (M^+; 2.32), 242 (0.32), 228 (1.12), 212 (100), 184 (13.75), 170 (22.8),128 (2.2); Anal. Calcd for $C_{28}H_{28}N_2O_4$ (456.53): C, 73.66; H, 6.18; N, 6.14. Found: C, 73.80; H, 6.30; N, 6.20.

*N,N′-(ethane-1,2-diyl)bis(2-(6-methoxynaphthalen-2-yl)propanamide) (**6b**)*

Yield 76 %; mp 200–202 °C; IR: υ/cm^{-1} = 3,294 (NH), 3,076 (CH–Ar), 2,939 (CH-sp3), 1,651(C=O); ^{1}H NMR: δ/ppm = 1.37 (d, 6H, $2CH_3$), 3.1 (m, 4H, $2CH_2$), 3.67 (s, 6H, $2OCH_3$), 3.87 (q, 2H, 2CH), 7.12–7.80 (m, 12H, Ar–H), 8.1 (s, 2H, 2NH); MS, *m*/*z* (%): 484 (M^+; 6.41), 300 (10.71), 255 (14.53), 242 (2.52), 228 (33.97), 212 (94.95), 184 (13.3), 171 (100), 100 (3.21); Anal. Calcd for $C_{30}H_{32}N_2O_4$ (484.59): C, 74.36; H, 6.66; N, 5.78. Found: C, 74.60; H, 6.40; N, 5.80.

*N,N′-(2,2′-azanediylbis(ethane-2,1-diyl))bis(2-(6-methoxynaphthalen-2-yl)propanamide) (**6c**)*

Yield 68 %; mp 220–222 °C; IR: υ/cm^{-1} = 3,317 (NH), 3,075 (CH–Ar), 2,939 (CH-sp3), 1,651(C=O); ^{1}H NMR: δ/ppm = 1.29 (d, 6H, $2CH_3$), 3.0–3.14 (m, 8H, $4CH_2$), 3.76 (s, 6H, $2OCH_3$), 3.87 (q, 2H, 2CH), 7.12–7.81(m, 12H, Ar–H), 8.14, 9.18 (2 br, 3H, 3NH); Anal. Calcd for $C_{32}H_{37}N_3O_4$ (527.65): C, 72.84; H, 7.07; N, 7.96. Found: C, 72.50; H, 7.20; N, 7.80.

*N,N′-(1,4-phenylene)bis(2-(6-methoxynaphthalen-2-yl)propanamide) (**6d**)*

Yield 74 %; mp 260–262 °C; IR: υ/cm^{-1} = 3,302 (NH), 3,065 (CH–Ar), 2,943 (CH-sp3), 1,666(C=O); ^{1}H NMR: δ/ppm = 1.48 (d, 6H, $2CH_3$), 3.87 (s, 6H, $2OCH_3$), 3.96 (q, 2H, 2CH), 7.13–7.83 (m, 16H, Ar–H), 10.06 (s, 2H, 2NH); MS, *m*/*z* (%): 532 (M^+; 100), 347 (35.2), 333 (14.35), 199 (27.22), 182 (1.48),171 (13.71); Anal. Calcd for $C_{34}H_{32}N_2O_4$ (532.63): C, 76.67; H, 6.06; N, 5.26. Found: C, 77.50; H, 6.20; N, 5.40.

Synthesis of 2-(1-(6-methoxynaphthalen-2-yl)ethyl)-1*H*-benzo[*d*]imidazole (**7**)

A mixture of **2** (0.01 mol) and *o*-phenylenediamine (0.01 mol) in DMF (20 ml) was heated under reflux for 4 h. The solution was poured into ice-contained HCl, the obtained product was filtered and crystallized from ethanol: yield 67 %; mp 211-212 °C; IR: υ/cm^{-1} = 3,225 (NH), 3,065 (CH–Ar), 2,950 (CH-sp3), 1,608 (C=N); ^{1}H NMR: δ/ppm = 1.56 (d, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.8 (q, 1H, CH), 7.20–7.89 (m, 10H, Ar–H), 10.80 (s, 1H, NH); MS, *m*/*z* (%): 302 (M^+; 85), 256 (25), 227 (65), 184(71), 151 (100), 133 (78), 94 (82); Anal. Calcd for $C_{20}H_{18}N_2O$ (302.37): C, 79.44; H, 6.00; N, 9.26. Found: C, 79.50; H, 6.30; N, 9.40.

Synthesis of 2-(6-methoxynaphthalen-2-yl)-*N*-(4-(*N*-phenylacetamido)phenyl)propanamide (**8**)

A mixture of **3d** (0.01 mol), acetyl chloride (0.02 mol), and pyridine (0.5 ml) in dioxane (20 ml) was heated under reflux for 4 h. The obtained product was filtered and crystallized from ethanol: yield 75 %; mp 180–182 °C; IR: υ/cm^{-1} = 3,280 (NH), 3,085 (CH–Ar), 2,950 (CH-sp3), 1,680, 1,670 (2C=O); ^{1}H NMR: δ/ppm=1.59 (d, 3H, CH_3), 1.95 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 4.00 (q, 1H, CH), 6.80–7.94 (m, 15H, Ar–H), 10.20 (s, 1H, NH); MS, *m*/*z* (%): 438 (M^+; 29.13), 396 (51.46), 227 (61.49), 214 (61.34), 185(97.09), 184 (100), 154 (17.6),128 (7.12); Anal. Calcd for $C_{28}H_{26}N_2O_3$ (438.52): C, 76.69; H, 5.98; N, 6.39. Found: C, 76.50; H, 5.70; N, 6.40.

Synthesis of 2-(6-methoxynaphthalen-2-yl)-*N*-(4aH-phenothiazin-7-yl)propanamide (**9**)

A mixture of **3d** (0.01 mol), sulfur metal and iodine (0.01 mol) in dichlorobenzene (20 ml) was heated under reflux for 6 h. The obtained product was filtered and crystallized from ethanol: yield 65 %; mp 305–306 °C; IR: υ/cm^{-1} = 3,312, 3,224 (2NH), 3,079 (CH–Ar), 2,940 (CH-sp3), 1,650 (C=O); ^{1}H NMR: δ/ppm = 1.48 (d, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.92 (q, 1H, CH), 7.18–7.85 (m, 13H, Ar–H), 10.12, 12.13 (2s, 2H, 2NH); Anal. Calcd for $C_{26}H_{22}N_2O_2S$ (426.53): C, 73.21; H, 5.20; N, 6.57. Found: C, 73.44; H, 5.45; N, 6.80.

Synthesis of oxazolone derivatives **10a–d**

A solution of **5a** (0.01 mol) in acetic anhydride (20 ml) was treated with the requisite aldehyde (0.01 ml) and fused sodium acetate (0.5 g). The reaction mixture was heated under reflux for 2 h. The obtained product was filtered and crystallized from ethanol:

*4-(4-Chlorobenzylidene)-2-(1-(6-methoxynaphthalen-2-yl)ethyl)oxazol-5(4H)-one (**10a**)*

Yield 72 %; mp 240–242 °C; IR: υ/cm^{-1} = 3,075 (CH–Ar), 2,950 (CH-sp3), 1,730 (C=O); ^{1}H NMR: δ/ppm = 1.47 (d, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.90 (q, 1H, CH), 7.08–7.89 (m, 11H, Ar–H + CH=); MS, *m/z* (%): 391 (M^+; 8.40), 227 (5.76), 197 (100), 181 (5.4), 154 (4.92), 127 (13.57); Anal. Calcd for $C_{23}H_{18}ClNO_3$ (391.85): C, 70.50; H, 4.63; N, 3.57. Found: C, 70.40; H, 4.60; N, 3.70.

*4-(4-Fluorobenzylidene)-2-(1-(6-methoxynaphthalen-2-yl) ethyl)oxazol-5(4H)-one (**10b**)*

Yield 72 %; mp 190–192 °C; IR: υ/cm^{-1} = 3,072 (CH–Ar), 2,954 (CH-sp3), 1,727 (C=O); ^{1}H NMR: δ/ppm = 1.46 (d, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.95 (q, 1H, CH), 7.1–7.84 (m, 11H, Ar–H + CH=); Anal. Calcd for $C_{23}H_{18}FNO_3$ (375.39): C, 73.59; H, 4.83; N, 3.73. Found: C, 73.40; H, 4.60; N, 3.80.

*2-(1-(6-Methoxynaphthalen-2-yl)ethyl)-4-(4-methylbenzylidene)oxazol-5(4H)-one (**10c**)*

Yield 63 %; mp 180–182 °C; IR: υ/cm^{-1} = 3,071 (CH–Ar), 2,958 (CH-sp3), 1,732 (C=O); ^{1}H NMR: δ/ppm = 1.48 (d, 3H, CH_3), 2,32 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.90 (q, 1H, CH), 7.13–7.88 (m, 11H, Ar–H + CH=); Anal. Calcd for $C_{24}H_{21}NO_3$ (371.43): C, 77.61; H, 5.70; N, 3.77. Found: C, 77.80; H, 5.50; N, 3.80.

*4-(4-Methoxybenzylidene)-2-(1-(6-methoxynaphthalen-2-yl)ethyl)oxazol-5(4H)-one (**10d**)*

Yield 64 %; mp 175–176 °C; IR: υ/cm^{-1} = 3,070 (CH–Ar), 2,958 (CH-sp3), 1,731 (C=O); ^{1}H NMR: δ/ppm = 1.47 (d, 3H, CH_3), 3.79, 3.82 (s, 6H, $2OCH_3$), 3.98 (q, 1H, CH), 7.14–7.88 (m, 11H, Ar–H + CH=); Anal. Calcd for $C_{24}H_{21}NO_4$ (387.43): C, 74.4; H, 5.46; N, 3.62. Found: C, 74.50; H, 5.50; N, 3.80.

Synthesis of 3-(4-chlorophenyl)-2-(2-(6-methoxynaphthalen-2-yl)propanamido)-*N*-p-tolylacrylamide (**11**)

A solution of **10a** (0.01 mol) in ethanol (30 ml) was treated with *p*-toluidine (0.01 ml). The reaction mixture was heated under reflux for 2 h. The obtained product was filtered and crystallized from ethanol: yield 64 %; mp 140–142 °C; IR: υ/cm^{-1} = 3,300 (NH), 3,069 (CH-Ar), 2,970 (CH-sp3), 1,675 (C=O); ^{1}H NMR: δ/ppm = 1.49 (d, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.93 (q, 1H, CH), 7.18–7.89 (m, 15H, Ar–H + CH=), 8.87 (s, 1H, 1NH); 11.4 (s, 1H, 1NH); Anal. Calcd for $C_{30}H_{27}ClN_2O_3$ (499.0): C, 72.21; H, 5.45; N, 5.61. Found: C, 72.40; H, 5.60; N, 5.70.

Synthesis of 1,2,4-triazoles **12** and **13**

A mixture of **5a** (0.01 mol) and thiosemicarbazide or thiocarbohydrazide (0.012 mol) was fused at 180 °C for 0.5 h. Left to cool, the solid product that remained was triturated with ethanol (20 ml), then filtered and crystallized from ethanol/dioxane.

*2-(6-Methoxynaphthalen-2-yl)-N-((5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)propanamide (**12**)*

Yield 62 %; mp 235–236 °C; IR: υ/cm^{-1} = 3,370, 3,300 (3NH), 3,071 (CH–Ar), 2,980 (CH-sp3), 1,650 (C=O), 1,223 C=S; Anal. Calcd for $C_{17}H_{18}N_4O_2S$ (342.42): C, 59.63; H, 5.30; N, 16.36. Found: C, 59.40; H, 5.40; N, 16.50.

*N-((4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-2-(6-methoxynaphthalen-2-yl)propanamide (**13**)*

Yield 63 %; mp 190–192 °C; IR: υ/cm^{-1} = 3,400, 3,300 (NH_2, NH), 3,069 (CH–Ar), 2,970 (CH-sp3), 1,656 (C=O), 1,221 C=S; ^{1}H NMR: δ/ppm = 1.45 (d, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.90 (q, 1H, CH), 4.29–4.36 (m, 2H, CH_2), 5.56 (s, 2H, NH_2), 7.13–7.82 (m, 6H, Ar–H), 8.51 (s, 1H, NH), 13.5 (s, 2H, NH-triazole); ^{13}C-NMR: 18.34 (CH_3), 45.43 (CH), 46.21 (CH_2), 55.54 (OCH_3), 105.23 (C-5), 119.34 (C-7), 126.23 (C-4), 126.54 (C-8a), 127.234, 128.86, 129.45, 133.65, 135.23, 156.21, 158.20, 174.34, 187.23 (C=S); Anal. Calcd for $C_{17}H_{19}N_5O_2S$ (357.43): C, 57.12; H, 5.36; N, 19.59. Found: C, 57.40; H, 5.60; N, 19.70.

Antimicrobial activity

Chemical compounds were individually tested against a panel of Gram +ve and gram-negative bacterial pathogens and fungi. Antimicrobial tests were carried out by the agar well diffusion method using 100 µl of suspension containing 1×10^8 CFU/ml of pathological tested bacteria and 1×10^6 CFU/ml of yeast spread on nutrient agar (NA) and Sabouraud dextrose agar (SDA) media, respectively. After the media had cooled and solidified, wells (10 mm in

diameter) were made in the solidified agar and loaded with 100 µl of tested compound solution prepared by dissolving 1 mg of the chemical compound in 1 ml of dimethyl sulfoxide (DMSO). The inoculated plates were then incubated for 24 h at 37 °C. Negative controls were prepared using DMSO employed for dissolving the tested compound. After incubation time, antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms and compared with that of the standard. The observed zone of inhibition is presented in Table 1. Antimicrobial activities were expressed as inhibition diameter zones in millimeters (mm). The experiment was carried out in triplicate, and the average zone of inhibition was calculated.

Minimal inhibitory concentration (MIC) measurement

The bacteriostatic activity of the active compounds was then evaluated using the twofold serial dilution technique. Twofold serial dilutions of the tested compounds solutions were prepared using the proper nutrient broth. The final concentration of the solutions were 100, 50, 25, 12.5, and 6.25 µg ml^{-1}. The tubes were then inoculated with the test organisms, grown in their suitable broth at 37 °C for 24 h for tested microorganisms (1×10^8 CFU/ml for bacteria and 1×10^6 CFU/ml of yeast), each 5 ml received 0.1 ml of the above inoculum and incubated at 37 °C for 24 h. The lowest concentration showing no growth was taken as the minimum inhibitory concentration (MIC).

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