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An unexpected tandem cycloaddition reaction of α,β-unsaturated acid chloride with amines: Synthesis of dihydropyrancarboxamide derivatives and biological activity

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ABSTRACT

Tandem cycloaddition reaction of α,β-unsaturated acid chloride with amines afforded in *situ* *N*-acylated amines, which undergoes cycloaddition reaction with other molecule of acid chloride to give dihydropyran carboxamide derivatives as an unexpected product. 2-Amino benzimidazole, 2-aminobenzthiazole, 2-aminothiazole, anthranilic acid, *o*-pheneylenediamine, and 3-methyl-1*H*-pyrazol-5(4*H*)-one are reacted with methacryloyl chloride at 0 °C to give different derivatives of dihydropyran carboxamide. The latter compound was obtained through acylation of the organic amines followed by tandem cycloaddition reaction. In contrast acryloyl chloride afforded only *N*-acylated derivatives. Both products are characterized by single crystal X-ray diffraction method. Bioactivity of the newly synthesized products was studied against Gram-positive, Gram-negative bacteria and fungus.

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1. Introduction

There are several kinds of known organic reactions available to use in tandem cycloaddition reactions those are particularly attractive in organic synthesis [1-5]. Tandem reactions are referred to multistep one-pot reactions [6], these have many advantages over a series of individual reaction where it allow construction of complex structure in as few steps as possible, no need for a purification step, save on cost and amounts of reagents and reduce the amount of waste that is generated. On the other hand, cycloaddition reactions are considered as one of the most important synthetic processes, with both synthetic and mechanistic interest in organic chemistry. In the last decades the cycloaddition reactions of carbonyl compounds with conjugated dienes have been developed and mainly focused on reactions leading to optically active compounds.

The cycloaddition reaction of conjugated dienes with carbonyl compounds, known as the hetero-Diels-Alder reaction, has been, since its discovery, one of the cornerstone reactions in organic synthesis for the construction of six-membered rings containing an oxygen atom [7-11]. In this article, we are aimed to prepare *N*-acylated derivatives from the reaction of metacryloyl chloride and heterocyclic amines or organic amines then used in the synthesis of heterocyclic compounds.

2. Experimental

2.1. Instrumentation

All melting points are uncorrected. IR spectra were recorded in KBr with an IR spectrophotometer Shimadzu 408. ^{1}H and ^{13}C NMR spectra were recorded on Varian EM-390 MHz spectrometer using TMS as internal reference and chemical shifts are expressed as δ ppm. Mass spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass spectrometer. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University, Egypt.

2.2. General method for the preparation of compound 9 and 10a-f

Ice-cold solution (0 °C) of methacryloyl chloride (0.01 mole) in acetone or THF (20 mL) was added drop-wise to another ice-cold solution of 4-aminopyridine or 2-aminobenz-

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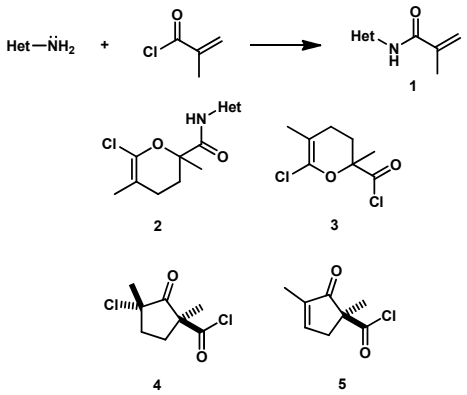
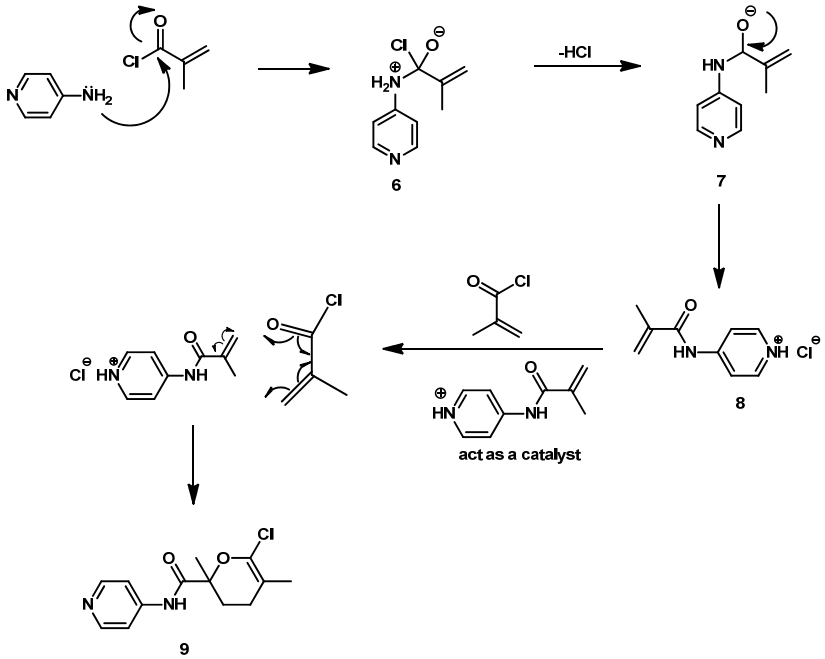


Scheme 1



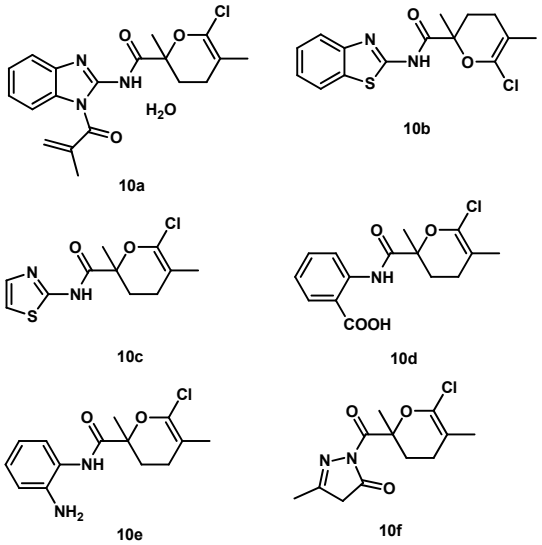
Scheme 2

thiazole or 1,3,4-thiadiazol-3(*2H*)-amine or anthranilic acid or o-phenylene diamine or 3-methyl-*1H*-pyrazol-5(*4H*)-one (0.01 mole) or 2-aminobenzimidazole (1:1 or 1:2 molar ratio) in acetone or THF (30 mL) (Scheme 1). The reaction mixture then treated with ammonium hydrogen carbonate or sodium hydrogen carbonate. The solid product, so formed, was collected by filtration and recrystallized from ethanol (Scheme 2 and 3).

6-Chloro-2, 5-dimethyl-N-(pyridin-4-yl)-3, 4-dihydro-2H-pyran-2-carboxamide (**9**): Color: White platelet crystals. Yield: 80%. M.p.: 133-134 °C. FT-IR (KBr, ν, cm^{-1}): 3223 (NH), 3063 (CH-aromatic), 2945 (CH-aliphatic), 1694 (CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.14 (br, 1H, NH, D_2O-exchange), 8.44 (d, 2H, *J* = 6.4 Hz, Pyridine-H), 7.70 (d, 2H, *J* = 6 Hz, pyridine-H), 2.34-1.72 (m, 4H, $2CH_2$, Pyran-H), 1.72 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6 δ, ppm): 172.25, 150.70, 145.74, 135.18, 114.50, 105.02, 82.71, 30.86, 25.18, 23.84, 18.42. MS (EI, *m/z* (%)): 266 (M^+, 100). HRMS (EI, *m/z*) calcd. for $C_{13}H_{15}ClN_2O_2$: 266.72; found 266.38. Anal. calcd. for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.59; H, 5.80; N, 10.41%.

6-Chloro-N-(1-methacryloyl-1H-benzo[d]imidazol-2-yl)-2, 5-dimethyl-3,4-dihydro-2H-pyran-2-carboxamide hydrate (**10a**): Color: Yellow crystals. Yield: 60%. M.p.: 143-144 °C. FT-IR (KBr, ν, cm^{-1}): 3428 (H_2O), 3326 (NH), 3057 (CH-aromatic), 2945 (CH-aliphatic), 1665 (CO). ^{1}H NMR (400 MHz, DMF-d_7, δ, ppm): 8.95 (br, 1H, NH, D_2O-exchange), 7.82-7.19 (m, 4H, C_6H_4), 7.98 (d, 1H, *J* = 12 Hz, $=CH_2$), 6.31 (d, 1H, *J* = 12 Hz, $=CH_2$), 4.69-4.30 (m, 4H, $2CH_2$), 3.50 (br., 2H, H_2O), 2.12 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.20 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMF-d_7, δ, ppm): 171.10, 170.30, 155.22, 141.39, 138.52, 134.50, 132.32, 130.01, 123.01, 119.08, 111.51, 103.30, 78.80, 30.51, 22.34, 21.50, 18.43. MS (EI, *m/z* (%)): 391.30 (M^+, 100). HRMS (EI, *m/z*) calcd. for $C_{19}H_{22}ClN_3O_4$: 391.85; found 391.30. Anal. calcd. for $C_{19}H_{22}ClN_3O_4$: C: 58.24; H: 5.66; N: 10.72. Found: C: 58.19; H: 5.76; N: 10.53%.

N-(benzo[d]thiazol-2-yl)-6-chloro-2,5-dimethyl-3,4-dihydro-2H-pyran-2-carboxamide (**10b**): Color: White crystals. Yield: 78%. M.p.: 179-180 °C. FT-IR (KBr, ν, cm^{-1}): 3294 (NH), 3049 (CH-aromatic), 2965 (CH-aliphatic), 1651 (CO).



Scheme 3

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.26 (br, 1H, NH, D_2O-exchange), 7.90 (d, 1H, *J* = 8 Hz, Aromatic-H), 7.57 (d, 1H, *J* = 8 Hz, Aromatic-H), 7.44 (d, 1H, *J* = 7.6 Hz, Aromatic-H), 7.30 (d, 1H, *J* = 7.6 Hz, Aromatic-H), 2.57-2.00 (m, 4H, $2CH_2$), 1.70 (s, 3H, CH_3), 1.60 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 177.88, 177.75, 138.44, 127.94, 126.71, 124.24, 124.12, 123.61, 122.22, 114.45, 73.60, 32.61, 26.36, 21.75, 17.35. MS (EI, *m/z* (%)): 322.28 [$M^{\bullet+}$, 100]. HRMS (EI, *m/z*) calcd. for $C_{15}H_{15}ClN_2O_2S$: 322.81; found 322.28. Anal. calcd. for $C_{15}H_{15}ClN_2O_2S$: C, 55.81; H, 4.68; N, 8.68. Found: C, 55.78; H, 4.66; N, 8.68%.

6-Chloro-2, 5-dimethyl-N-(thiazol-2-yl)-3,4 -dihydro-2H-pyran-2-carboxamide (**10c**): Color: White crystals. Yield: 68 %. M.p.: 145-146 °C. FT-IR (KBr, ν, cm^{-1}): 3115 (NH), 3088 (CH-aromatic), 2978 (CH-aliphatic), 1685 (CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.22 (br, 1H, NH, D_2O-exchange), 7.40 (s, 1H, thiazole-H), 6.45 (s, 1H, thiazole-H), 2.50-1.78 (m, 4H, $2CH_2$), 1.60 (s, 3H, CH_3), 1.54 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 171.03, 161.28, 141.83, 138.20, 110.92, 103.80, 81.75, 30.41, 24.61, 21.12, 14.94. MS (EI, *m/z* (%)): 272.05 (M^+, 100). HRMS (EI, *m/z*) calcd. For $C_{11}H_{13}ClN_2O_2S$: 272.04; found 272.05. Anal. calcd. for $C_{11}H_{13}ClN_2O_2S$: C, 48.44; H, 4.80; N, 10.27. Found: C, 48.66; H, 4.68; N, 10.33%.

2-(6-Chloro-2, 5-dimethyl-3, 4-dihydro-2H-pyran-2-carbox amido)benzoic acid (**10d**): Color: White crystals. Yield: 87 %. M.p.: 138-140 °C. FT-IR (KBr, ν, cm^{-1}): 3358 (NH), 3088 (CH-aromatic), 2978 (CH-aliphatic), 1684, 1656 (CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.50 (br, 1H, OH), 9.97 (br, 1H, NH, D_2O-exchange), 7.94-7.14 (m, 4H, aromatic-H), 2.28- 1.75 (m, 4H, $2CH_2$), 1.71 (s, 3H, CH_3), 1.60 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 177.81, 175.76, 143.63, 140.57, 135.21, 130.62, 125.84, 121.05, 119.78, 104.88, 75.18, 29.51, 23.93, 19.08, 17.32. MS (EI, *m/z* (%)): 309.22 (M^+, 100). HRMS (EI, *m/z*) calcd. for $C_{15}H_{16}ClNO_4$: 309.74; found 309.22. Anal. calcd. for $C_{15}H_{16}ClNO_4$: C, 58.16; H, 5.21; N, 4.52; Found: C, 58.09; H, 5.13; N, 4.35%.

N-(2-Aminophenyl)-6-chloro-2, 5-dimethyl-3,4-dihydro-2H-pyran-2-carboxamide (**10e**): Color: Pink crystals. Yield: 76 %. M.p.: 230-231 °C. FT-IR (KBr, ν, cm^{-1}): 3325, 3215 (NH_2 & NH), 3088 (CH-aromatic), 2978 (CH-aliphatic), 1661 (CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.80, 9.45, 9.30 (br, 3H, NH & NH_2, D_2O-exchange), 7.80-7.00 (m, 4H, aromatic-H), 2.50-1.94 (m, 4H, $2CH_2$), 1.63 (s, 3H, CH_3), 1.60 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 177.39, 149.91, 139.53, 125.98, 125.72, 123.86, 121.07, 118.79, 117.50, 70.44, 25.21, 22.89, 22.72, 16.66. MS (EI, *m/z* (%)): 280.27 (M^+, 100). HRMS (EI, *m/z*) calcd. for $C_{14}H_{17}ClN_2O_2$: 280.75; found 280.27. Anal. calcd. for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.98; Found: C, 60.01; H, 5.99; N, 10.01%.

1-(6-Chloro-2, 5-dimethyl-3, 4-dihydro-2H-pyran-2-carbon yl)-3-methyl-1H-pyrazol-5(4H)-one (**10f**): Color: White crystals. Yield: 70 %. M.p.: 186-188 °C. FT-IR (KBr, ν, cm^{-1}): 3088 (CH-aromatic), 2972 (CH-aliphatic), 1675, 1658 (CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.42-1.88 (m, 6H, $3CH_2$), 1.59 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 178.16, 177.00, 158.00 136.37, 121.84, 102.27, 85.86, 40.17, 31.14, 25.82, 19.27, 18.61. MS (EI, *m/z* (%)): 270.09 (M^+, 100). HRMS (EI, *m/z*) calcd. for $C_{12}H_{15}ClN_2O_3$: 270.71; found 270.09. Anal. calcd. for $C_{12}H_{15}ClN_2O_3$: C, 53.24; H, 5.58; N, 10.35; Found: C, 53.33; H, 5.47; N, 10.22%.

2.3. Biological activities

A solution or suspension of the tested compounds (prepared by dissolving 400 µg/mL (*w:v*) in sterile DMSO) was poured aseptically in a well of 6 mm diameter made by a borer in the seeded agar medium. After transferring *via* pipetting the same volume in wells of all tested microorganisms, bacteria test plates were incubated at 37 °C for 24 h and fungal test plates were incubated at 25 °C for 48 h. The activities were expressed as inhibition zones (mm, diameter, as clear areas). The least concentration, which showed the inhibitory effect on any specific microorganism, was considered as the minimum inhibitory concentration (MIC) which was determined using streptomycin and Mycostatin (50 µg/mL) as the references.

2.4. X-ray crystallography

Data collection of compound ***9*** (Deposit number CCDC 1027749-1027750): A colorless platelet crystal of $C_{13}H_{15}Cl$ N_2O_2 having approximate dimensions of 0.200×0.200×0.040 mm was mounted on a glass fiber. The crystal to detector distance was 127.40 mm.

Data collection of N,N′-1,2-phenylene-bis-2-propenamide (Deposit number CCDC 1030018-1030019): A colorless prism crystal of $C_{12}H_{12}N_2O_2$ having approximate dimensions of 0.300×0.100×0.040 mm was mounted on a glass fiber. All measurements were made on a Rigaku R-AXIS RAPID

diffractometer using filtered Mo-Kα radiation. The crystal to detector distance was 127.40 mm.

3. Results and discussion

3.1. Chemistry

In last few years, we are involved in a program aimed to prepare different monomers. While we are trying to prepare heterocyclic monomers **1**, (Scheme 1), from reaction of methacryloyl chloride (MAC) and different heterocyclic amine, we observe that the target monomers are not afforded but another reaction product **2** was obtained, where the mass spectrum referred to molar mass equal to the summation of two molecules of MAC and one molecule of amines with the elimination of HCl molecule.

This result prompted us to look in literature to see what is about dimerization of MAC. Searches in literature provided very limited information about dimer of MAC. The literature has been described as impurities in samples of commercial methacryloyl chloride. To our knowledge, only four publications describe a study on structure elucidation of MAC dimmers [12-15]. In addition, compound **3** was found to be present in PubChem [16] without any details about preparation, purification, and no spectral characterization is available.

Therein, a mixture of three different dimers was proposed by Fisher *et al.* [12] as a common MAC impurity. However, only the formation of dimers **4** and **5** was proved on the basis of ^{1}H NMR spectra, while the existence of compound **3** could not been directly verified and no investigations on the mechanism of their formation have been reported. However, Azov *et al.* [13,14] isolate 6-chloro-3,4-dihydro-2,5-dimethyl-*2H*-pyran-2-carbonyl chloride (**3**) from commercial methacryloyl chloride samples after keeping a sample of MAC at 40 °C for two months. Earlier Fisher *et al.* [12] mentioned that the same product isolated after storing a commercial sample in the dark at room temperature for several years. The formation of compound **3** formally explained by a hetero-Diels-Alder reaction between two methacryloyl chloride molecules, which is similar to the dimerization reactions of many compounds [17-24]. Single crystal structure of compound **5** was reported [14].

In this article, we report the reaction of methacryloyl chloride with aromatic or heterocyclic amines to give the *N*-acylated product which undergoes tandem cycloaddition reaction in *situ* with another molecule of methacryloyl chloride to give dihydropyrancarboxamide derivatives in one-pot reaction.

One can postulate that the dimer of MAC first formed followed by reaction with amine to give the final isolated product. This postulation may be ruled out based on the previous publications which refer to the formation of the dimer in many weeks. While here MAC reacted with heterocyclic amines at 0 °C to give compound **2** as a final product. Thus, one can assume that the formation of quatranry ammonium salt **8**, (Scheme 2) first formed followed by oxo-Diels-Alder cycloaddition to give the final isolated product, **9**. The fast of the reaction may be due to the formation of pyridinium salt which may be acts as a catalyst for cycloaddition step and as a reactant in the same time, which accelerate, the cycloaddition step. For example, 4-amino pyridine reacted with MAC to give 6-chloro-2,5-dimethyl-*N*-(pyridin-4-yl)-3, 4-dihydro-*2H*-pyran-2-carboxamide, **9**. This reaction was believed to processed via addition of amino group in aminopyridine to the electrophilic carbonyl carbon to give the intermediate **6** which followed by loss of one molecule of HCl to give *N*-(pyridin-4-yl)methacrylamide **8** through compound **7**. The latter compound **8** undergoes oxo-Diel Alder [4+2] cycloaddition with another molecule of methacryloyl chloride to give the final isolated product 6-chloro-2, 5-dimethyl-*N*-(pyridin-4-yl)-3, 4-dihydro-*2H*-pyran-2-carboxamide (**9**) as a colorless crystals. In continuation to understand this unexpected product, as it known in Diels Alder reaction electron rich diene component is preferable and electron poor dienophiles due to electron withdrawing substituents are the best. The initial bonding interaction reflects this electron imbalance, with the two new sigma-bonds being formed simultaneously, but not necessarily at equal rates. Thus, in our case the formation of amine salt result from interaction between HCl, generated in *situ* as a by-product from the first step, acts as a catalyst in addition the quaternary ammonium salt can acts as electron withdrawing group which increase the dienophile activity, while presence of methyl group in the diene, methacryloyl chloride, make it more electron rich which increase its activity as a diene (Scheme 2).

The structure of colorless crystals of compound **9** obtained by slowly evaporating a solution in ethanol (Deposit number CCDC 1027749-1027750) was solved by X-ray single crystal diffraction technique. Figure 1, Table 1 and 2 shows the crystal structure, crystal and structure refinement data and selected bond lengths and angles of 6-chloro-2,5-dimethyl-*N*-(pyridin-4-yl)-3,4-dihydro-*2H*-pyran-2-carboxamide, **9**, respectively.

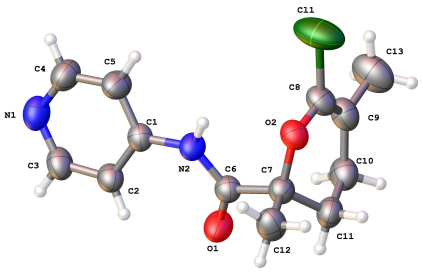


Figure 1. Crystal structure of 2H-pyran-2-carboxamide derivative **9**.

Table 1. Crystal data and structure refinement for compound **9**.

Crystal data	
Chemical formula	$C_{13}H_{15}ClN_2O_2$
M_r	266.73
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	293
a, *b*, *c* (Å)	13.2310 (9), 9.4915 (5), 11.0814 (8)
β (°)	103.477 (7)
V (Å^3)	1353.31 (16)
Z	4
Radiation type	Mo *Kα*
μ (mm^{-1})	0.28
Crystal size (mm)	0.20 × 0.20 × 0.04
Data collection	
Diffractometer	Rigaku R-AXIS RAPID diffractometer
Absorption correction	Multi-scan, *ABSCOR* (Rigaku, 1995)
T_{min}, T_{max}	0.618, 0.989
No. of measured, independent and observed [$F^2 > 2.0\sigma(F^2)$] reflections	8591, 2742, 1762
R_{int}	0.031
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.624
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.042, 0.124, 1.10
No. of reflections	2742
No. of parameters	165
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.21, −0.35

Furthermore, 2-aminobenzimidazole reacted with methacryloyl chloride (1:1 molar ratio) to give diacylated product which readily undergoes cycloaddition reaction to give 6-chloro-*N*-(1-methacryloyl-*1H*-benzo[*d*]imidazol-2-yl)-2, 5-dimethyl-3, 4-dihydro-*2H*-pyran-2-carboxamide (**10a**). It was observed in this case that the reaction yield with 1:2 molar ratios is better than that in case of 1:1 molar ratio; in addition, in latter case a mixture of mono- and diacylated products was obtained. Monoacylated product was obtained insignificant yield and was detected by GC-MS. Similarly, methacryloyl chloride reacted with 2-aminobezthiazole, 1,3,4-thiadiazol-2-

amine, anthranilic acid, *o*-phenylene diamine and 3-methyl-*1H*-pyrazol-5(*4H*)-one to give *N*-(benzo[*d*]thiazol-2-yl)-6-chloro-2, 5-dimethyl-3, 4-dihydro-*2H*-pyran-2-carboxamide (**10b**), (6-chloro-2,5-dimethyl-3,4-dihydro-*2H*-pyran-2-yl)(1, 3, 4-thiadiazol-3(*2H*)-yl)methanone (**10c**), 2-(6-chloro-2, 5-di methyl-3,4-dihydro-*2H*-pyran-2-carboxamido) benzoic acid (**10d**), *N*-(2-aminophenyl)-6-chloro-2,5-dimethyl-3,4-dihydro-*2H*-pyran-2-carboxamide (**10e**) and 1-(6-chloro-2,5-dimethyl-3, 4-dihydro-*2H*-pyran-2-carbonyl)-3-methyl-*1H*-pyrazol-5 (*4H*)-one (**10f**), respectively.

Table 2. Selected geometric parameters (Å, °) for compound **9**.

Cl1—C8	1.7270 (19)	C2—C3	1.376 (3)
O1—C6	1.217 (2)	C4—C5	1.378 (3)
O2—C7	1.447 (2)	C6—C7	1.535 (3)
O2—C8	1.368 (3)	C7—C11	1.518 (3)
N1—C3	1.331 (3)	C7—C12	1.514 (3)
N1—C4	1.332 (3)	C8—C9	1.320 (3)
N2—C1	1.411 (3)	C9—C10	1.495 (3)
N2—C6	1.357 (3)	C9—C13	1.495 (4)
C1—C2	1.383 (3)	C10—C11	1.514 (4)
C1—C5	1.383 (3)		
C7—O2—C8	115.48 (14)	O2—C7—C11	110.27 (14)
C3—N1—C4	115.23 (18)	O2—C7—C12	104.73 (15)
C1—N2—C6	126.49 (14)	C6—C7—C11	110.88 (16)
N2—C1—C2	123.80 (16)	C6—C7—C12	108.26 (15)
N2—C1—C5	118.43 (15)	C11—C7—C12	112.27 (17)
C2—C1—C5	117.76 (17)	Cl1—C8—O2	108.03 (14)
C1—C2—C3	118.20 (17)	Cl1—C8—C9	123.92 (17)
N1—C3—C2	125.37 (17)	O2—C8—C9	128.05 (17)
N1—C4—C5	124.4 (2)	C8—C9—C10	118.77 (19)
C1—C5—C4	119.05 (17)	C8—C9—C13	123.99 (19)
O1—C6—N2	124.44 (17)	C10—C9—C13	117.24 (18)
O1—C6—C7	119.77 (16)	C9—C10—C11	111.70 (17)
N2—C6—C7	115.71 (14)	C7—C11—C10	111.65 (17)
O2—C7—C6	110.25 (15)		

It is of value to mention here that the behavior of amines with MAC is different than that with acryloyl chloride (AC), as reported by our group [25-28]. Thus, acryloyl chloride reacted with amines under similar condition to give the *N*-acylated product without further cycloaddtion reaction. For example, o-phenylene diamine reacted with AC at 0 °C to give *N,N'*-1,2-phenylene-*bis*-2-propenamide. The structure of the latter compound was established based on X-ray single crystal analysis (Deposit number CCDC 1030018-1030019). Figure 2, Table 3 and 4 shows the crystal structure, crystal and structure refinement data and selected bond lengths and angles of *N,N'*-1,2-phenylene-*bis*-2-propenamide.

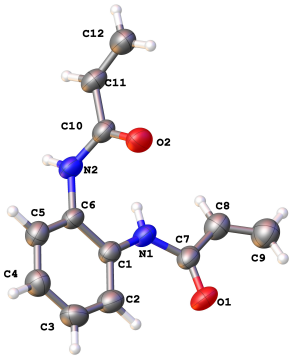


Figure 2. Crystal structure of *N,N'*-1,2-phenylene-*bis*-2-propenamide.

3.2. Biological activities

The various biological activities of tetrahydropyran [29-32], thiazole [33-36], benzthiazole [37-39] and benzimidazole derivatives [40,41] and other hetertocyclic compounds [42,43] prompted us to study the antimicrobial activities of our newly synthesized products. The *in vitro* antibacterial activities of compounds **9** and **10a**-**10f** were evaluated against Gram positive and Gram negative bacteria (*S. aureus, B. subtilis, E. coli* and *B. cereus*) and fungus (*Candida albicans*) are reported in Table 5.

Table 3. Crystal data and structure refinement for *N,N'*-1,2-phenylene-*bis*-2-propenamide.

Crystal data	
Chemical formula	$C_{12}H_{12}N_2O_2$
M_r	216.24
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	293
a, b, c (Å)	4.1556 (18), 14.759 (6), 17.497 (8)
β (°)	91.707 (7)
V (Å^3)	1072.6 (8)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.09
Crystal size (mm)	0.30 × 0.10 × 0.04
Data collection	
Diffractometer	Rigaku R-AXIS RAPID diffractometer
Absorption correction	Multi-scan *ABSCOR* (Rigaku, 1995)
T_{min}, T_{max}	0.453, 0.996
No. of measured, independent and observed [$F^2 > 2.0\sigma(F^2)$] reflections	5641, 1921, 1010
R_{int}	0.064
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.603
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.061, 0.196, 1.03
No. of reflections	1921
No. of parameters	145
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.29, −0.28

Table 4. Selected geometric parameters (Å, °) for *N,N'*-1,2-phenylene-*bis*-2-propenamide.

O1—C7	1.233 (4)	C2—C3	1.383 (5)
O2—C10	1.230 (4)	C3—C4	1.366 (6)
N1—C1	1.407 (4)	C4—C5	1.383 (5)
N1—C7	1.354 (4)	C5—C6	1.382 (5)
N2—C6	1.434 (4)	C7—C8	1.476 (5)
N2—C10	1.351 (4)	C8—C9	1.303 (6)
C1—C2	1.397 (5)	C10—C11	1.473 (5)
C1—C6	1.399 (5)	C11—C12	1.305 (5)
C1—N1—C7	129.1 (3)	N2—C6—C5	119.3 (3)
C6—N2—C10	122.4 (3)	C1—C6—C5	120.3 (3)
N1—C1—C2	123.0 (3)	O1—C7—N1	123.7 (3)
N1—C1—C6	118.7 (3)	O1—C7—C8	122.6 (3)
C2—C1—C6	118.3 (3)	N1—C7—C8	113.6 (3)
C1—C2—C3	120.1 (3)	C7—C8—C9	122.3 (4)
C2—C3—C4	121.4 (4)	O2—C10—N2	122.3 (3)
C3—C4—C5	119.1 (4)	O2—C10—C11	122.8 (3)
C4—C5—C6	120.8 (3)	N2—C10—C11	114.9 (3)
N2—C6—C1	120.4 (3)	C10—C11—C12	121.8 (4)

The growth of *S. aureus* is severe inhibited mainly by compounds **10a**, **10b** and **10c** showing inhibition zones varying between 25.00 and 40.00 mm. The nature of the azole ring fused with benzene ring or alone could be the origin of the noted activity in these compounds. A moderate effect was observed with compounds **9**, **10d**, **10e** (500 μg/mL concentration) and **10f** (250 & 500 μg/mL concentration). On the other hand, a slight inhibition was observed with compound **10e** (100 & 250 μg/mL concentration) and compound **10f** (100 μg/mL concentration).

A severe effect against *B. subtilis* with compounds **10b** and **10c** may due to the presence of thiazole ring. On the other hand, moderate effect was observed with compounds **9**, **10a**, **10d** (250 and 500 μg/mL concentration), **10e** (500 μg/mL concentration). A slight effect was observed with **10d** (100 μg/mL concentration), **10e** (100 and 250 μg/mL concentration), and **10f**.

E. coli was very sensitive to compound **9** (250 and 500 μg/mL concentration), **10a** (250 and 500 μg/mL concentration), **10b** and **10c**, which gave inhibition zones varying from 30.00 to 40.00 mm. A moderate effect was observed with compound **9** and **10a** (100 μg/mL concentration) and**10d**-**10e** (250 and 500 μg/mL concentration) other concentration showed slight effect.

Table 5. Biological activities of some newly synthesized compounds *.

Compound	Concentration (µg/mL)	*S. aureus*	*B. subtilis*	*E. coli*	*Salmonella*	*Candida albicans*
9	100	21.00	22.50	29.00	17.00	-
	250	23.50	26.50	35.50	20.50	5.00
	500	28.00	29.50	37.00	25.00	7.50
10a	100	25.00	21.00	28.50	-	12.00
	250	31.50	24.50	32.50	-	16.50
	500	36.50	28.00	35.00	8.50	20.00
10b	100	31.00	30.00	32.00	20.25	21.00
	250	34.50	36.50	37.50	25.00	26.50
	500	39.00	38.50	40.00	29.50	29.50
10c	100	32.00	30.00	30.00	-	30.25
	250	36.50	32.50	34.25	10.50	35.50
	500	40.50	35.25	37.00	15.00	37.00
10d	100	21.00	19.00	17.50	10.00	-
	250	24.50	21.50	20.00	15.25	9.00
	500	29.50	23.00	22.50	17.50	13.00
10e	100	17.50	15.00	19.00	-	-
	250	19.00	17.50	21.50	5.00	6.50
	500	22.00	21.25	24.50	8.50	10.00
10f	100	18.00	10.00	17.00	10.50	8.50
	250	21.50	13.50	20.25	13.00	13.00
	500	25.00	17.50	23.50	17.25	17.50

* Diameter of inhibition zone expressed in mm, Severe effect (>30 mm); Moderate effect (20-29 mm); Slight effect (< 20 mm); - Not active.

Salmonella shows a moderate to slight effect with different tested compounds. Data shown that the fungus *Candida albicans* was very sensitive to compound **10c** may be due to the presence of the thiazole ring and tetra hydropyan. Generally, the effect became visible since the concentration of 250 µg/mL and the highest inhibition was recorded at 500 µg/mL.

Finally, the data reported in Table 5 indicates that the antibacterial activity of the tested compounds varied upon the concentrations used. The inhibition zones were more evident since the concentration of 250 µg/mL and the severe inhibitory effect was recorded at the concentration of 500 µg/mL with all tested compounds. Our results were concordance with that cited in the literature [27-39].

4. Conclusion

Methacryloyl chloride reacted with different amines to give the *N*-acylated product, which undergoes tandem cycloaddition reaction in *situ* to give dihydropyran carboxamide derivatives. The AC reacted with amines under similar reaction condition to afford *N*-acylate amines without further cycloaddition reaction. Rationalization of this different behavior was discussed. A comparison between the product in case of acryloyl chloride and methacryloyl chloride was studied and established by X-ray crystallography. A series of tandem reactions with different amine, six examples, was also studied. Bioactivity of the synthesized compounds against Gram positive, Gram negative and fungus showed a severe to low activities.

Supplementary materials

CCDC 1027749, 1027750, 1030018 and 1030019 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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