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새로운 2-morpholino-*N*-(4,6-diarylpyrimidin-2-yl)acetamides의 합성과 분광학적 특성의 연구

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Design, Synthesis and Spectral Characterization of Novel 2-morpholino-*N*-(4,6-diarylpyrimidin-2-yl)acetamides

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요약. 무수탄산칼륨 존재 하에서 2-chloro-*N*-(4,6-diarylpyrimidin-2-yl)acetamides **25-33**를 모르포린과 축합 반응시켜서 2-morpholino-*N*-(4,6-diarylpyrimidin-2yl)acetamides **34-42** 화합물들을 합성하였다. 합성된 화합물들의 녹는점, 원소분석, MS, FT-IR, ^{1}H- & ^{13}C-NMR로 화학적인 구조를 규명되었다.

주제어: 2-Morpholino-*N*-(4,6-diarylpyrimidin-2-yl)acetamides, 2-Chloro-*N*-(4,6-diarylpyrimidin-2-yl)acetamides, 모르포린, 클로로아세틸화반응

ABSTRACT. A new series of novel 2-morpholino-*N*-(4,6-diarylpyrimidin-2-yl)acetamides **34-42** is synthesized by the condensation of 2-chloro-*N*-(4,6-diarylpyrimidin-2-yl)acetamides **25-33** with morpholine in the presence of anhydrous potassium carbonate. The synthesized compounds have been characterized by melting point, elemental analysis, MS, FT-IR, one-dimensional NMR (^{1}H & ^{13}C) spectroscopic data.

Keywords: 2-Morpholino-*N*-(4,6-diarylpyrimidin-2-yl)acetamides, 4,6-Diarylpyrimidin-2-amines, Chloroacetylation, Morpholine, Synthesis

INTRODUCTION

Pyrimidines being an integral part of nucleic acids and many chemotherapeutic agents display a wide range of pharmacological activities as bactericide,[1] fungicide,[2] phosphodiesterase inhibitor,[3] viricide,[4] and leishmancide.[5] Pyrimidines are the basic nucleus in nucleic acids and have been associated with a number of biological activities.[6] Substituted aminopyrimidine nuclei are common in marketed drugs such as anti-atherosclerotic aronixil, anti-histaminic thonzylamine, anti-anxielytic buspirone, anti-psoriatic enazadrem, and other medicinally relevant compounds.[7] Many pyrimidine derivatives have been found to be active against different forms of cancer.[8] Various method of synthesis and reactions of aminopyrimidines are reported.[9-11]

Amides are well known for their therapeutic values.[12] The chemistry of chloro acetyl group has received significant attention through the years resulting in substantial advances both in the synthetic and medicinal aspects. N-Benzyl-β-chloropropionamide is a well-proven anticonvulsant agent[13] and is marketed under the trade name Hibicon and Hydrane. Chloroacetyl derivatives of some amines were found to exert diverse biological properties such as antiepileptic,[14] antiplasmodic,[15] antitumour, anti-MDR,[16] antimicrobial,[17] herbicidal,[18] mild stimulant and depressant activities.[19] Antibiotics like penicillins and cephalosporins have amide group. Novel bioactive natural compounds[20] are synthesized by the conversion of ketones into amides, since amide group is an important pharmacophores.

Many N-fuctionalized morpholines have found to posses diverse pharmacological activites. They are reported to exert a number of important physiological activities such as antidiabetic,[21,22] antiemetic,[23,24] platelet aggregation inhibitors and antihyperlipo-proteinemics,[21] bronchodilators and growth stimulants[25] and antidepressants.[26] These were also used in the

treatment of inflammatory diseases, pain, migraine and asthma.[24]

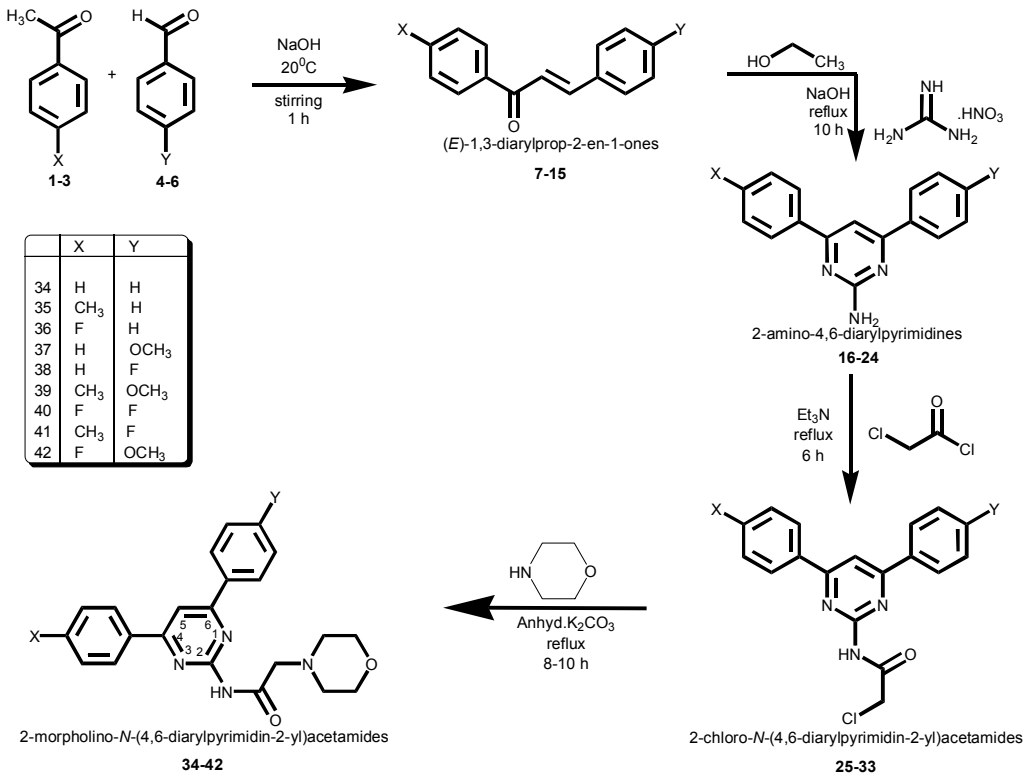
Recently, we exploited the synthesis of some novel structurally diverse heterocyclic compounds comprising pyrimidine nucleus such as 3,4-dihydropyrimidin-2(*1H*)-ones[27] and - thiones and 2-phenyl-3-(4,6-diarylpyrimidin-2-yl)thiazolidin-4-ones,[28] morpholine nucleus namely (E)-1-4-morpholinophenyl)-3-aryl-prop-2-en-1-ones[29] and amide moiety such as 2,7-diaryl-[1,4]-diazepan-5-ones.[30] In the interest of above, we planned to synthesize a target molecule, 2-morpholino-N-(4,6-diarylpyrimidin-2-yl)acetamides which unite biolabile 4,6-diarylpyrimidin-2-amines, chloroacetyl chloride and morpholine moieties together to furnish a new series of compounds.

RESULTS AND DUSCUSSION

A four-step synthetic route furnished the target compounds 2-morpholino-N-(4,6-diarylpyrimidin-2-yl)acetamides **34-42** in good yields. A general schematic representation is given in *Scheme* 1. The Claisen-Schmidt[31] condensation of equimolar quantities of appropriate acetophenone and appropriate benzaldehyde in the presence of sodium hydroxide gives *E*-1,3-diarylprop-2-en-1-ones **7-15**. When *E*-1,3-diarylprop-2-en-1-ones **7-15** are refluxed with guanidine nitrate in the presence of sodium hydroxide, 2-amino-4,6-diarylpyrimidines[32] **16-24** are formed. Various substituted 2-chloro-N-(4,6-diarylpyrimidin-2-yl)acetamides[33] **25-33** are synthesized by electrophilic substitution reaction of chloroacetyl chloride with the corresponding parent 2-amino-4,6-diarylpyrimidines **16-24** in the presence of triethyl amine as base and toluene as solvent. Then, condensation of 2-chloro-N-(4,6-diarylpyrimidin-2-yl)acetamides **25-33** with morpholine in the presence of anhydrous potassium carbonate furnished 2-morpholino-N-(4,6-diarylpyrimidin-2-yl)acetamides **34-42**. The physical and analytical data for compounds **34-42** is given in *Table* 1.

The following nine compounds **34-42** are synthesized from the corresponding 2-chloro-N-(4,6-diarylpyrimidin-2-yl)acetamides **25-33**:

- 2-morpholino-N-(4,6-diphenylpyrimidin-2-yl)acetamide **34**
- 2-morpholino-N-(4-(4-methylphenyl)-6-phenylpyrimidin-2-yl)acetamide **35**
- N-(4(4-fluorophenyl)-6-phenylpyrimidin-2-yl)2-morpholinoacetamide **36**
- N-(4-phenyl-6-(4-methoxyphenyl)-pyrimidin-2-yl)2-morpholinoacetamide **37**
- N-(4-phenyl-6-(4-fluorophenyl)-pyrimidin-2-yl)2-morpholinoacetamide **38**
- N-(4-(4-methoxyphenyl)-6-(4-methylphenyl)pyrimidin-2-yl)2-morpholinoacetamide **39**



	X	Y
34	H	H
35	CH_3	H
36	F	H
37	H	OCH_3
38	H	F
39	CH_3	OCH_3
40	F	F
41	CH_3	F
42	F	OCH_3

Scheme 1. Synthetic route for the formation of 2-morpholino-N-(4,6- diarylpyrimidin-2-yl)acetamides

Table 1. Physical and analytical data of compounds **34-42**

Compounds	X	Y	Yield (%)	m.p. (°C)	Elemental analysis (%)			*m/z* $(M+H)^{+\cdot}$ Molecular formula
					C Found (calculated)	H Found (calculated)	N Found (calculated)	
34	H	H	58	45	70.55 (70.57)	5.88 (5.92)	14.90 (14.96)	375 $C_{22}H_{22}N_4O_2$
35	CH_3	H	44	40	71.06 (71.11)	6.20 (6.23)	14.38 (14.42)	389 $C_{23}H_{24}N_4O_2$
36	F	H	45	50	67.30 (67.33)	5.35 (5.39)	14.25 (14.28)	393 $C_{22}H_{21}FN_4O_2$
37	H	OCH_3	88	40	68.28 (68.30)	5.95 (5.98)	13.82 (13.85)	405 $C_{23}H_{24}N_4O_3$
38	H	F	76	45	67.30 (67.33)	5.36 (5.39)	14.25 (14.28)	393 $C_{22}H_{21}FN_4O_2$
39	CH_3	OCH_3	54	50	68.87 (68.88)	6.22 (6.26)	13.36 (13.39)	419 $C_{24}H_{26}N_4O_3$
40	F	F	41	45	64.31 (64.38)	4.87 (4.91)	13.62 (13.65)	411 $C_{22}H_{20}F_2N_4O_2$
41	CH_3	F	48	55	67.95 (67.97)	5.66 (5.70)	13.76 (13.78)	407 $C_{23}H_{23}FN_4O_2$
42	F	OCH_3	50	50	65.36 (65.39)	5.46 (5.49)	13.21 (13.26)	423 $C_{23}H_{23}FN_4O_3$

Table 2. FT-IR absorption frequencies (cm^{-1}) for selected functional groups of compounds **34-42**

Compound	Amide NH stretching	Aromatic CH stretching	Aliphatic CH stretching	Amide C=O stretching	C=C stretching	C-N stretching	C-O-C ether linkage stretching	Aromatic ring stretching
34	3314	3193, 3058, 3030	2920, 2851	1682	1565	1360, 1236	1112	761, 693
35	3325	3196, 3058, 3032	2920, 2852	1683	1536	1360, 1233	1113	769, 694
36	3366	3207, 3056	2917, 2851	1670	1540	1361, 1229	1113	770, 694
37	3331	3199, 3060	2920, 2850	1687	1570	1362, 1245	1113	771, 693
38	3370	3203, 3061	2920, 2852	1682	1542	1360, 1225	1113	767, 694
39	3373	3199, 3054	2920, 2851	1676	1535	1362, 1300	1112	728, 668
40	3395	3215, 3068	2919, 2851	1674	1541	1363, 1228	1113	669, 566
41	3340	3200, 3062, 3032	2920, 2852	1680	1537	1361, 1226	1113	724, 689
42	3338	3207, 3080	2917, 2852	1676	1531	1364, 1294	1111	722, 677

- ❖ N-(4,6-bis(4-fluorophenyl)pyrimidin-2-yl)2-morpholinoacetamide **40**
- ❖ N-(4-(4-fluorophenyl)-6-(4-methylphenyl)pyrimidin-2-yl)2-morpholinoacetamide **41**
- ❖ N-(4-(4-methylphenyl)-6-(4-fluorophenyl)pyrimidin-2-yl)2-morpholinoacetamide **42**

The structures of all the newly synthesized compounds are characterized by m.p.'s, elemental analysis, FT-IR, MS, one-dimensional NMR (^1H and ^{13}C) spectra.

FT-IR spectrum of 2-morpholino-N-(4,6-diphenylpyrimidin-2-yl)acetamide **34** shows characteristic absorption frequency (*Table* 2) observed at 3314cm^{-1} is due to N-H stretching vibrations of the amide group. The absorption frequency at 3193 ~ 3030 cm^{-1} is assigned to aromatic stretching vibration. The absorption frequency at 2920 ~ 2851 cm^{-1} is assigned to aliphatic stretching vibration. The band at 1682 cm^{-1} is due to the presence of amide C=O stretching frequency. The absorption band at 1360 ~ 1236 cm^{-1} is consistent with C-N stretching vibration. The absorption band at 1565 cm^{-1} is due to C=C stretching vibration. In addition, compound **34** displayed characteristic absorption bands (cm^{-1}) in the regions 761 ~ 693 (aromatic ring stretching) and 1112 (C-O-C ether linkage in the morpholine ring); this gives positive evidence for the formation of compound **34**.

In the ^1H NMR spectrum of **34**, a singlet observed at 3.91 ppm for two protons is assigned to methylene protons. The singlet for H-5 proton is observed at 6.69 ppm. The amide proton resonates at 10.25 ppm. Two triplets are observed and they are due to the methylene protons $O(CH_2)_2$ and $N(CH_2)_2$ of morpholine ring. Among the triplets, one triplet observed in the region of 2.65 ~ 2.63 ppm corresponding to two protons and this signal

Table 3. Proton NMR chemical shifts (δ, ppm) of compounds **34-42**

Compounds	Morpholine ring		Acetamide moiety		Pyrimidine ring		
	$N(CH_2)$ (*triplet*)	$O(CH_2)$ (*triplet*)	CH_2 (*singlet*)	NH (*broad singlet*)	H-5 (*singlet*)	Ar-protons (*multiplet*)	Others (*singlet*)
34	2.65-2.63 J = 4.5 Hz	3.49-3.47 J = 4.8 Hz	3.91	10.25	6.69	8.20-7.30	-
35	2.68-2.66 J = 4.3 Hz	3.51-3.49 J = 4.6 Hz	3.88	10.24	6.65	8.37-7.06	3.85 OCH_3
36	2.66-2.64 J = 4.4 Hz	3.49-3.47 J = 4.6 Hz	3.93	10.30	6.72	7.97-7.04	-
37	2.65-2.63 J = 4.5 Hz	3.49-3.46 J = 4.7 Hz	3.98	10.30	6.72	8.45-7.02	-
38	2.68-2.66 J = 4.8 Hz	3.51-3.49 J = 4.6 Hz	3.87	10.25	6.66	8.46-7.05	3.84 OCH_3
39	2.656-2.64 J = 4.9 Hz	3.49-3.47 J = 4.6 Hz	3.97	10.30	6.62	8.45-6.74	-
40	2.68-2.66 J = 4.8 Hz	3.48-3.46 J = 4.4 Hz	3.89	10.26	6.67	8.35-7.25	2.37 CH_3
41	2.65-2.63 J = 4.5 Hz	3.49-3.46 J = 4.7 Hz	3.85	10.18	6.58	8.19-7.02	3.82, OCH_3 2.35, CH_3
42	2.66-2.64 J = 4.3 Hz	3.49-3.47 J = 4.6 Hz	3.95	10.26	6.68	8.28-7.27	2.36 OCH_3

is due to methylene protons $N(CH_2)_2$ of morpholine ring. Another triplet appeared in the region of 3.49 ~ 3.47 ppm, corresponding to two protons, which can be conveniently assigned to methylene protons $O(CH_2)_2$ of morpholine ring. The aromatic protons resonate in the region 8.20 ~ 7.30 ppm.

The ^{13}C resonance at 163.91 ppm is assigned to the amide group bearing carbon C-2 of pyrimidine moiety. The amide carbonyl carbon resonances at 169.40 ppm. The ^{13}C resonances observed at 164.72 and 101.27 ppm are due to the C-4 and C-5 carbons respectively. The ^{13}C resonances observed at 164.72 ppm is conveniently assigned to C-6 carbon. There are two ^{13}C resonances observed at 45.89 and 67.25 ppm. Among the two resonances, one ^{13}C resonance at 45.89 ppm is due to methylene carbon $N(CH_2)_2$ of morpholine ring and ^{13}C resonances at 67.25 ppm is unambiguously assigned to methylene carbon $O(CH_2)_2$ of morpholine ring. The methylene carbon attached to amide carbonyl carbon resonances at 66.23 ppm. The remaining ^{13}C signal at 137.38 ppm and 134.55 ppm are due to *ipso* carbons. The aromatic carbons are observed in the region of 130.30 ~ 126.87 ppm.

The ^1H and ^{13}C NMR chemical shifts of all the newly synthesized compounds are furnished in *Table* 3 and 4 respectively.

CONCLUSION

In conclusion, we have synthesized a series of 2-morpholino-N-(4,6-diarylpyrimidin-2-yl)acetamides **34-42** by a four step synthetic route in good yields and characterized by their physical and analytical data. The target molecules **34-42** have pharmacophoric group such as amide besides the presence of biologically active morpholine and pyrimidine nuclei. The biological screening studies are under progress to evaluate the antibacterial, antifungal, antioxidant and anticancer potencies of the newly synthesized of 2-morpholino-N-(4,6-diarylpyrimidin-2-yl)acetamides **34-42**.

EXPERIMENTAL

Thin layer chromatography (TLC) was carried out to monitor the course of the reaction and purity of the product. All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Thermo Nicolet-Avatar-330 FT-IR spectrophotometer and important absorption values (cm^{-1}) alone are listed. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker Avance II 400 NMR spectrometer using DMSO-*d* as solvent. The ESI +ve MS spectra were recorded on a Bruker Daltonics LC-MS spectrometer. Satisfactory microanalysis was obtained on Carlo Erba 1106 CHN analyzer.

By adopting the literature precedent 1,3-diaryl-prop-2-en-1-ones[31] **7-15**, 2-amino-4,6-diarylpyrimidines[32] **16-24** and 2-chloro-N-(4,6-diarylpyrimidin-2-yl)acetamides[33] **25-33** were synthesized.

General method for the synthesis of 2-morpholino-N-(4,6-diarylpyrimidin-2-yl)acetamides 34-42

A mixture of 2-chloro-N-(4,6-diarylpyrimidin-2-yl)acetamides **25-33** (0.005 mol), anhydrous potassium carbonate (0.01

Table 4. Carbon NMR chemical shifts (δ, ppm) of compounds **34-42**

Compound	Morpholine ring		Acetamide moiety		Pyrimidine ring						
	$N(CH_2)$	$O(CH_2)$	CH_2	C=O	C-2	C-4	C-5	C-6	Aromatic Carbons	Ipso carbons	Others
34	45.89	67.25	66.23	169.40	163.91	164.72	101.27	164.72	130.30-126.87	137.38, 134.55	-
35	46.02	67.29	66.24	171.01	163.85	164.48	101.01	164.75	128.49-113.89	137.76, 136.87, 129.05	55.27 OCH_3
36	45.87	67.13	66.07	171.22	161.84	163.73	101.59	163.97	131.22-114.71	137.28, 136.55, 133.07	-
37	45.99	67.28	66.24	168.30	162.37	163.94	101.59	163.72	131.21-115.33	137.27, 136.14, 133.79	-
38	46.01	67.31	66.25	168.55	161.25	163.65	100.82	162.31	129.07-113.89	133.93, 129.79, 129.56, 129.27	55.27 OCH_3
39	45.93	67.20	66.07	170.37	162.42	163.80	101.37	163.80	130.20-114.29	133.73, 131.43	-
40	45.99	67.27	66.23	169.45	163.95	164.70	101.45	164.70	130.30-126.88	140.17, 137.39, 134.52, 131.11	20.89 CH_3
41	46.02	67.30	66.32	171.27	161.15	163.84	100.66	164.24	129.11-113.87	140.02, 134.66, 129.67	55.26, OCH_3 20.82, CH_3
42	45.93	67.21	66.08	170.21	161.38	163.89	101.24	164.83	127.98-115.31	140.23, 134.47, 129.15	20.90 CH_3

mol) and morpholine (0.005 mol) in dry toluene was refluxed for about 8 ~ 10 h. After completion of the reaction, potassium carbonate was removed by filtration and excess of solvent was removed under reduced pressure. The obtained residues were purified by column chromatography using benzene and ethyl-acetate (1:1) mixture as eluent which afforded 2-morpholino-N-(4,6-diarylpyrimidin-2-yl)acetamides **34-42** in good yields.

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