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İÇİNDEKİLER / CONTENTS

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33 (2) 85-90, 2004

J. Fac. Pharm, Ankara
33(2) 85-90,2004

SYNTHESIS OF SOME NEW MANNICH BASES OF 6-ACYL-5-CHLORO-2-BENZOXAZOLINONES

BAZI YENİ MANNICH BAZI 6-AÇİL-5-KLORO-2-BENZOKSAZOLINONLARIN SENTEZLERİ

Fügen ÖZKANLI

Hacettepe University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 06100 Ankara-TURKEY

ABSTRACT

In this study, seven new 6-acyl-5-chloro-2-benzoxazolinone derivatives having a piperazinomethyl (or piperidinomethyl) group at the third position of the ring were synthesized by using appropriate benzoxazolinones and 4-substituted piperazines (or 4-substituted piperidines) via a Mannich reaction. The chemical structures of the compounds were elucidated by IR, 'H-NMR and elemental analysis.

Key Words: *2-Benzoxazolinones, synthesis, acylation, mannich bases*

ÖZET

Bu çalışmada, 3 numaralı konumda piperazinometil (veya piperidinometil) grubu taşıyan 6-açil-5-chloro-2-benzoksazolinon türevi yedi tane yeni bileşik, uygun benzoksazolinonlar ve 4-substitue piperazin (veya 4-substitue piperidin) kullanılarak Mannich reaksiyonuyla sentezlenmiştir. Bileşiklerin kimyasal yapıları IR, 'H-NMR ve elemental analizleriyle kanıtlanmıştır.

Anahtar kelimeler: *2-Benzoksazolinon, sentez, acilleme, mannich bazları*

INTRODUCTION

Benzoxazolinone and its biologically active derivatives are objects of numerous studies aiming to establish possibilities for their application as drugs and pesticides (1). It is known that halogen substituted 2-benzoxazolinones have well expressed for their antibacterial and fungicide properties (2,3). (2-Benzoxazolinone-3-yl)alkanoic acid (4) and aminomethyl derivatives (mannich bases) show some analgesic activity (5,6).

The 6-acylbenzoxazolinones in particular exhibit analgesic properties much more higher than those of the parent heterocycle and so this brings for the latest developments in the field of central nervous system drugs. Because of this, it is important to find a useful starting substance such as acyl derivatives of benzoxazolinone and it is clear that choosing such a compound is the key step for a medicinal chemist. In our laboratory, some derivatives of 2-benzoxazolinone

series have been designed, synthesized and evaluated in the search for new non-steroidal antiinflammatory agents (5-9). A considerable number of the prepared compounds have shown analgesic-antiinflammatory activity comparable to or higher than that of indomethacine.

In addition to introduction of aryl or heteroarylpiperazino groups on different pharmacophores has been of considerable interest for medicinal compounds, such as fluanisone, trazodone, buspirone and urapidil, with neuroleptic, antidepressant, anxiolytic and antihypertensive properties, respectively. Recently, many authors described benzoxazolinone, triazinone and pyridazinone derivatives including an arylpiperazino moiety with analgesic, antidepressant and tranquilizing activities, respectively (10-12).

For this reason the further investigation of the compounds containing 2-benzoxazolinone ring could result in the obtaining of new representatives of this class having valuable pharmacological properties

In view of these facts and as a continuation of the previous efforts carried out in our laboratory, it was thought worthwhile to synthesize a new series of 6-difluorobenzoyl-2-benzoxazolinones substituted at the 3rd position by various piperazinomethyl moieties.

MATERIALS AND METHODS

All chemicals used in this study were supplied from Aldrich (Steinheim, Germany). Melting points were determined with a Thomas-Hoover Capillary Melting Point Apparatus (Philadelphia, PA; USA) and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1720X (Beaconsfield, UK) FTIR . 'H-NMR spectra were acquired in DMSO-d_6 on a Bruker AC 80 MHz FT NMR Instrument (Karlsruhe, Germany). Tetramethylsilane was used as internal standart and all chemical shift values were recorded as 8 (ppm) values. The purity of the compounds was controlled by thin layer chromatography (Merck, silicagel, HF254+366. type 60, 0.25 mm, Darmstadt, Germany). The elemental analyses (C, H, N) were performed on Leco CHNS 932 (Leco Cooperation, St. Joseph, MI, USA) analyzer by the Scientific and Technical Research Council of Turkey Instrumental Analysis Laboratories (Ankara, Turkey) and were within ± 0.4 % of the theoretical values.

6-Acyl-5-chloro-2-benzoxazolinone (2a,2b)

To a suspension of 5-chloro-2-benzoxazolinone (0.01 mol) in polyphosphoric acid was added to difluorobenzoic acid (0.015 mol) slowly. The reaction mixture was heated at 140-160 °C for 6-8 h. The hot reaction mixture was poured into ice-water and upon stirring a white precipitate was obtained. Recrystallization from different solvents produced the acyl derivatives (13).

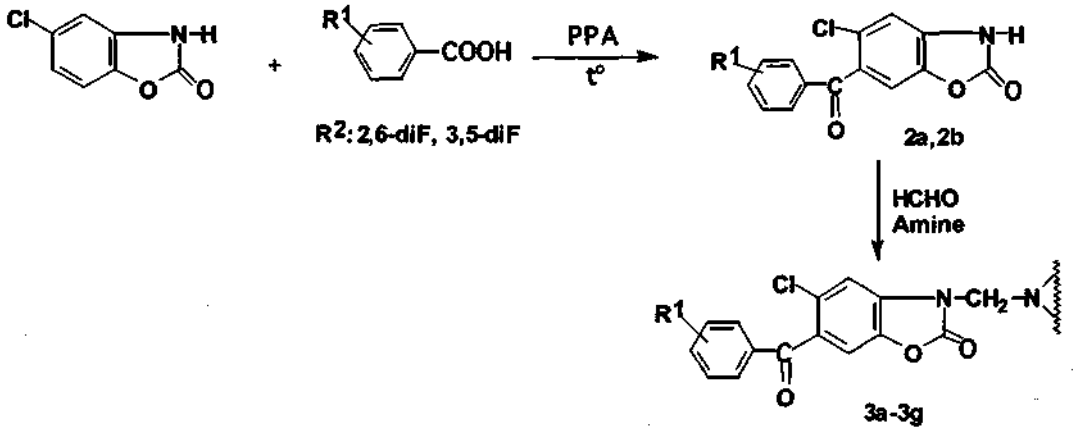
6-Acyl-5-chloro-3-piperazinomethyl and/or piperidinomethyl -2-benzoxazolinones (3a-3g)

A solution of 6-acyl-5-chloro-2-benzoxazolinone (0.0015) in 50 ml methanol was refluxed with 0.0015 mol piperazine (or piperidine) derivatives and 0.33 mL of 35 % (w/w)

formaldehyde for 30 min. Crude products were filtered and purified by crystallization with appropriate solvents.

RESULTS AND DISCUSSION

6-Acyl-3-aminomethyl-2-benzoxazolinones listed in Table I were prepared by the methods shown in Scheme 1. Reaction of formaldehyde and arylpiperazine with 6-acyl-2-benzoxazolinone *2a,2b* afforded derivatives *3a-3g* via Mannich condensation. The compounds *2a,2b* were prepared by reacting 2-benzoxazolinone with difluorobenzoic acids in the presence of polyphosphoric acid at 140-160 °C. Formulas, melting points and % yields of the compounds are shown in Table 1. The structures of derivatives *3a-3g* were supported by elemental analysis (Table 1) and spectral data (Table 2).



Scheme 1: The synthesis pathway of the compounds 3a-3g

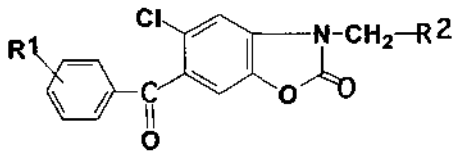
Electrophilic substitution, such as chlorination, sulfonation and nitration was achieved using classical reagents but acylation yielding 6-acyl derivatives was found to require particular conditions such as polyphosphoric acid as the solvent and catalyst with free acids serving as the acylating agents (14). But these conditions presented some limitations for the preparation of a number of 6-acylbenzoxazolinones. For example, they were not applicable to dicarboxylic acids, or carboxylic acids containing a halogenoalkyl or heterocyclic moiety (15). In the light of this knowledge we prefer the first method. Because we had free acids containig difluoro substituents and managed to synthesize them in excellent yields using PPA .

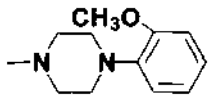
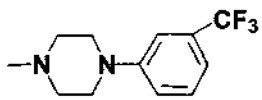
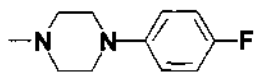
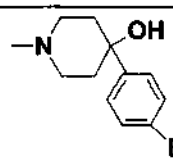
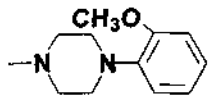
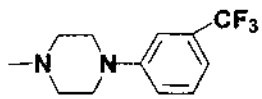
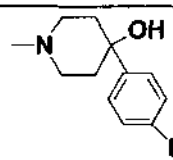
In the IR spectra of the compounds, no absorption bands were detected at about 3100-3400 cm'" indicating the absence of N-H group which is evidence for the addition reaction. The lactam and ketone C=0 stretching bands were seen at about 1791-1760 and 1610-1604 cm^{-1} and aliphatic stretching bands belonging to piperazine/piperidine ring were appeared at about 2840 cm^{-1}. Other stretching bands seen at spectra confirmed the structures.

In the 'H-NMR spectra, the CH_2 protons of compounds 3a-3g were seen at about 4.70-4.80 ppm as a singlet. The H_2 and H_6 protons of the piperazine ring were seen at about 2.40-3.00 ppm and the H_3 and H_5 protons were observed at 3.10-3.60 ppm. The H_3 and H_5 protons of the piperidine ring were seen at about 1.40-1.90 ppm and the H_2 and H_6 protons were observed at

2.40-3.10 ppm (Table 2). The protons belonging to substituents attached to piperazine/piperidine were appeared 3.80 ppm *(-OCH_3)* and 3.30-3.40 ppm (-0//), respectively. Aromatic ring protons were observed at the expected values.

Table 1: Some physical properties of the compounds 3a-3g



Comp No	R^1	R^2	M.p. (°C)	Yield (%)	Formula
3a	2,6-Difluoro		152-153[a]	55	$C_{26}H_{22}C1F_2N_30_4$
3b	2,6-Difluoro		130-132[b]	51	$C_{26}H_{19}ClF_5N_30_3$
3c	2,6-Difluoro		171-172[c]	45	$C_{25}H_{19}ClF_3N_3O_3$
3d	2,6-Difluoro		168-169[c]	43	$C_{26}H_{,0}ClBrF_2N_2$ **O_4**
3e	3,5-Difluoro		153-154*	60	$C_{26}H_{22}C1F_2N_3O_4$
3f	3,5-Difluoro		133-135*	48	$C_{26}H_{19}ClF_5N_3O_3$
3g	3,5-Difluoro		169(dec)[c]	40	$C_{26}H_{20}ClBrF_2N_2$ **O_4**

a: acetone/water, b: methanol, c:acetone,

Table 2: IR and 'H-NMR spectroscopic data of the compounds 3a-3g

Compound No	IR (KBr) _ (cm^{-1})	^{1}H-NMR (DMSO-D_6) _ (ppm)
3a	1605 (arom. ketone) 1786 (lactam C=0) 2820 (alip. C-H)	2.70-3.00 (4H; t; pip. H_2, H_6), 3.25-3.45 (4H; t; pip. H_3, H_5), 3.80 (3H; s; -OCH_3), 4.75 (2H; s; N-CH_2-N), 6.70-7.70 (9H; m; arom. H)
3b	1609 (arom. ketone) 1774 (lactam C=0) 2852 (alip. C-H)	2.50-2.95 (4H; t; pip. H_2, H„), 3.10-3.50 (4H; t; pip. H_3, H_5), 4.75 (2H; s; N-CH,-N), 6.95-7.75 (9H; m; arom. H)
3c	1605 (arom. ketone) 1791 (lactam C=0) 2830 (alip. C-H)	2.40-2.90 (4H; t; pip. H_2, H_6), 3.10-3.40 (4H; t; pip. H_3 H_5), 4.75 (2H; s; N-CH_2-N), 6.70-7.75 (9H; m; arom. H)
3d	1606 (arom. ketone) 1760 (lactam C=0) 2840 (alip. C-H)	1.40-1.90 (4H; t; pip. H_3, H_5), 2.40-3.00 (4H; t; pip. H_2, H_6), 3.30 (1H; s; -OH), 4.75 (2H; s; N-CH_2-N), 6.95-7.80 (9H; m; arom. H)
3e	1604 (arom. ketone) 1786 (lactam C=0) 2820 (alip. C-H)	2.50-3.00 (4H; t; pip. H_2, H_6), 3.20-3.60 (4H; t; pip. H_3, H_5), 3.80 (3H; s; -OCH_3),4.70 (2H; s; N-CH_2-N), 6.70-7.70 (9H; m; arom. H)
3f	1610 (arom. ketone) 1771 (lactam C=0) 2853 (alip. C-H)	2.50-3.00 (4H; t; pip. H_2, H_6), 3.15-3.55 (4H; t; pip. H_3, H_5), 4.80 (2H; s; N-CH_2-N), 7.00-7.75 (9H; m; arom. H)
3g	1607 (arom. ketone) 1761 (lactam C=0) 2840 (alip. C-H)	1.40-1.80 (4H; t; pip. H_3, H_5), 2.60-3.10 (4H; t; pip. H_2, H_6), 3.40 (1H; s; -OH), 4.80 (2H; s; N-CH_2-N), 7.00-7.80 (9H; m; arom. H)

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