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Design, synthesis, characterization, quantum-chemical calculations and anti-inflammatory activity of novel series of thiophene derivatives

M.H. Helal [a,b], M.A. Salem [b], M.A. Gouda [c,d], N.S. Ahmed [a,e], A.A. El-Sherif [f,*]

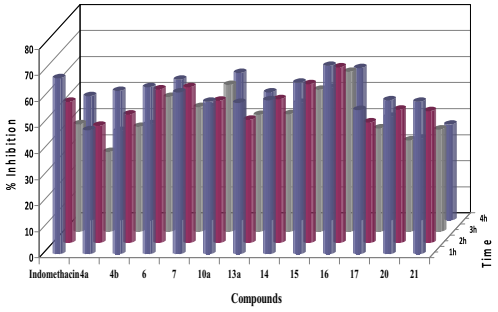
[a] Department of Chemistry, Faculty of Arts and Science, Northern Border University, Rafha, Saudi Arabia
[b] Department of Chemistry, Faculty of Science, Al-Azhar University, 11284 Nasr City, Cairo, Egypt
[c] Chemistry Department, Faculty of Science, Mansoura University, Mansoura 35516, Egypt
[d] Department of Chemistry, Faculty of Science and Arts, Taibah University, Ulla 41411, Saudi Arabia
[e] Department of Chemistry, National Institute of Oceanography and Fisheries, Alex, Egypt
[f] Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

HIGHLIGHTS

- Novel series of thiophene heterocyclic compounds were synthesized and characterized.
- Optimization of the geometric shape was carried out.
- Molecular parameters were calculated.
- The anti-inflammatory activities of the synthesized compounds were investigated.

GRAPHICAL ABSTRACT

Novel series of thiophene heterocyclic compounds have been synthesized and characterized by elemental analyses and spectral like IR, ^{1}H NMR, ^{13}C NMR and MS studies. The molecular modeling of the synthesized compounds has been drawn and their molecular parameters were calculated. The anti-inflammatory activity was investigated.



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ABSTRACT

Interaction of 1-(4-morpholinophenyl)ethanone **1** with either malononitrile or ethyl cyanoacetate **2** afforded Knoevenagel–Cope product **3**. In subsequent treatment of **3** with sulfur, the 2-aminothiophene derivatives (**4a**, **4b**) are formed under basic conditions. The solvent-free reaction of thiophene derivative **4a** with ethyl cyanoacetate afforded thieno[2,3-d][1,3]oxazine derivative **6**. The base catalyzed condensation of 2-aminothiophene derivative (**4a**) with ethyl cyanoacetate afforded *N*-(thieno-2-yl) cyanoacetamide derivative **7**. The latter was used to synthesize different heterocyclic derivatives comprising, pyridine and coumarin rings. Also, several substituted thieno[2,3-d]pyrimidines have been prepared from reaction of 2-aminothiophene-3-carbonitrile **4b** with some electrophilic reagents. The structure of the newly compounds were confirmed on the basis of elemental analysis and spectral data. The molecular modeling of the synthesized compounds has been drawn and their molecular parameters were calculated. Also, valuable information is obtained from calculation of the molecular parameters including electronegativity, net dipole moment of the compounds, total energy, electronic energy, binding energy, HOMO and LUMO energy. Evaluation of anti-inflammatory activity of the tested compounds was performed in albino rats by producing carrageenan induced paw oedema and measuring the zone of inflammation at different time intervals i.e. 1, 2, 3 and 4 h after carrageenan injection. Results indicated

* Corresponding author. Mobile: +20 1060160168.
E-mail address: aelsherif72@yahoo.com (A.A. El-Sherif).

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that most of the tested compounds showed moderate to good activity comparable to indomethacin. Also, compound 16 with additional morpholine ring beside the thiophene ring inhibits carrageenan induced paw oedema more than the standard indomethacin drug at all the time scales studied. Thus, compound 16 is considered as a promising compound for further modification to obtain clinically useful anti-inflammatory agent.

Introduction

As it is known, the wide occurrence of the heterocycles in bioactive natural products and pharmaceuticals has made them as important synthetic targets and had attracted the attention of pharmaceutical chemists to synthesize a large number of novel chemotherapeutic agents of heterocyclic nature. Among these heterocyclic compounds, multisubstituted 2-aminothiophenes are privileged structures as they have attracted considerable attention in designing of bioactive molecules and found in several biologically active and natural compounds [1–4] due to their broad spectrum of biological activities, such as antioxidant [5], antibacterial [6], antifungal [7], antitumor [8], anti-inflammatory [9], antianxiety [10] and antitubercular activities. Additionally, *N*-functionalized morpholines have found to possess diverse pharmacological activities. They are reported to exert a number of important physiological activities such as antidiabetic [11], antihyperlipo-proteinemics [12], antiemetic [13], platelet aggregation inhibitors, bronchodilators and growth stimulates [14] and anti-inflammatory [15]. These were also used in treatment of inflammatory diseases, pain, migraine and asthma [16]. The experimental studies have been accompanied by computational studies, especially in recent years [17] due to their important role in understanding of the probably behavior of the compound during reactions and identification of the important information about the compounds under investigations, like total energy, binding energy, electronic energy, dipole moment, bond lengths, HOMO, LUMO [18]. The applicability of the semi-empirical methods PM3 for the calculation of novel synthesized compounds has been evaluated [19]. In a continuance of our research program directed towards synthesis of medicinally potent new chemical entities and their biological screening, the present study is aimed to study synthesis, characterization, molecular modeling and biological evaluation of various novel bioactive compounds heterocyclic compounds [20–25]. It seems therefore to be of considerable interest to synthesize newly heterocyclic compounds containing both the thiophene and morpholine moieties. Additionally, our objective is also to study the anti-inflammatory activities of the synthesized compounds.

Experimental

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer, ^{1}H NMR and ^{13}C NMR spectra were obtained in DMSO on a Varian Gemini 600 MHz spectrometer using TMS as internal standard; chemical shifts are reported as (ppm). Mass spectra were obtained on GCMS/QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Department of Chemistry, Faculty of Science, Cairo University, Egypt. Microbiology screening was carried out in Microbiology department, National Research Center, Cairo, Egypt.

Chemistry

*Preparation of compounds (**3a** and **3b**): General procedure*

A mixture of acetophenone **1** (0.05 mol), malononitrile (or ethyl cyanoacetate) (0.051 mol), acetic acid (2 mol) and ammonium acetate (0.05 mol) was added to 50 ml benzene with a Dean–Stark trap. The reaction mixture was stirred under reflux for 3 h for malononitrile (5 h for ethyl cyanoacetate) with removal of the condensed water. The excess benzene was evaporated and the resulting product was cooled to room temperature. The separated solid was then filtered, washed with water, and subjected to air drier and recrystallized from ethanol to give intermediate ethylidene **3**.

*Ethyl 2-cyano-3-(4-morpholinophenyl)but-2-enoate(**3a**).* Yield (70%); m.p. 57–58 °C; IR (KBr, $\bar{\nu}$, cm^{-1}):3010 (arom. CH), 2910 (aliph. CH), 2235 (C≡N) and 1660 (C=O). ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.27 (t, 3H, CH$_3$), 2.49 (s, 3H, CH$_3$), 3.26, 3.79 (2t, 8H, morphonyl-H), 4.27 (q, 2H, CH$_2$) and 7.03–7.53 (2d, 4H, Ar-H) ppm; ^{13}C NMR (600 MHz, CDCl$_3$): δ = 13.93 (CH$_3$), 22.53 (CH$_3$), 47.21 (C3, C5 of morpholine), 61.35 (CH$_2$), 65.86 (C2, C6 of morpholine), 113.33, 117.26, 128.70, 129.46 (phenyl-C), 100.22, 152.56 (C=C) ppm. Elemental analysis for $C_{17}H_{20}N_2O_3$. Calcd. C, 67.98; H, 6.71; N, 9.33; Found: C, 67.80; H, 6.20; N, 9.40.

*2-(1-(4-morpholinophenyl)ethylidene)malononitrile(**3b**).* Yield (70%); m.p. 98–90 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3001 (arom. CH), 2871 (aliph. CH), 2215 (C≡N) and 1609 (C=N). ^{1}H NMR (600 MHz, DMSO-d$_6$): δ = 2.49 (s, 3H, CH$_3$), 3.27, 3.74 (2t, 8H, morphonyl-H), and 6.96–7.83 (2d, 4H, Ar-H) ppm; Elemental analysis for $C_{15}H_{15}N_3O$. Calcd. C, 71.13; H, 5.97; N, 16.59; Found: C, 70.90; H, 5.60; N, 16.10.

*Preparation of compounds (**4a** and **4b**): General procedure*

In reaction flask both ethylidene **3** (0.05 mol) and sulphur (0.05 mol) were mixed in 50 ml ethanol. After the mixture was cooled to 15 °C, a solution of diethylamine (0.05 mol) was added dropwise at 15 °C, and stirred for 3 h at 65 °C. Left to cool, the separated solid was filtered, dried and recrystallized from ethanol to give **4**.

*Ethyl 2-amino-4-(4-morpholinophenyl)thiophene-3-carboxylate(**4a**).* Yield (70%); m.p. 209–210 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3404, 3300, 3165 (NH$_2$), 3090 (arom. CH), 2869 (aliph. C≡H) and 1666 (C=O). MS: 332 (M^{+1}, 55.0%), 286 (38.8%), 228 (100.0%), 172 (30.2%), 114 (25.5%), 77 (14.5%). ^{1}H NMR (600 MHz, DMSO-d$_6$): δ = 0.98 (t, 3H, CH$_3$), 3.10, 3.76 (2t, 8H, morphonyl-H), 4.01 (q, 2H, CH$_2$), 6.06 (s, 1H, thiophene-H5), and 6.89–7.29 (m, 6H, Ar–H + NH$_2$) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ = 13.84 (CH$_3$), 48.59 (C3, C5 of morpholine), 58.53 (CH$_2$), 66.05 (C2, C6 of morpholine), 103.01, 103.95 (thiophene-C5, C3),113.86, 129.16, 129.21 (phenyl-C), 140.47, 149.78 (thiophene-C4, C2), 164.92 (C=O) ppm. Elemental analysis for $C_{17}H_{20}N_2O_3S$. Calcd. C, 61.42; H, 6.06; N, 8.43; Found: C, 61.30; H, 5.80; N, 8.10.

*2-amino-4-(4-morpholinophenyl)thiophene-3-carbonitrile(**4b**).* Yield (70%); m.p. 185–186 °C; IR (KBr, $\bar{\nu}$, cm^{-1}): 3382, 3315, 3205 (NH$_2$), 2825 (aliph. CH), 2197 (C≡N) and 1613 (C=N). MS: 385 (M^{+1},60.4%), 217 (100.0%). 199 (15.5%), 172 (12.5%), 113 (32.0%), 99 (12.5%), 77 (10.0%). ^{1}H NMR (600 MHz, DMSO-d$_6$): δ = 3.13, 3.73 (2t, 8H, morphonyl-H), 6.37 (s, 1H, thiophene-H5), and 6.96–7.49 (m, 6H, Ar–H + NH$_2$) ppm; ^{13}C NMR (600 MHz, CDCl$_3$):