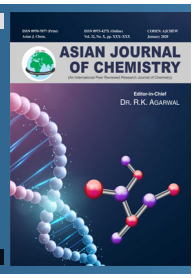
Asian Journal of Chemistry; Vol. 32, No. 3 (2020), 607-611

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22159



Synthesis and Anti-inflammatory Activity of 2-Methoxy-4-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)phenol) and Its Aminomethyl Derivatives

H. HAYUN*, R.N. FAUZAN, N.T. WIBOWO, A. ASRIANINGTIYAS, N. AFRILIANA and T. ANANDA

Laboratory of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, Universitas Indonesia, Depok 16424, West Java, Indonesia

*Corresponding author: Fax: +62 21 7863433; Tel: +62 21 7270031; E-mail: hayun@farmasi.ui.ac.id

Received: 28 April 2019; *Accepted*: 31 October 2019; *Published online*: 31 January 2019; AJC-19767

Using heat-induced protein denaturation technique, a series of novel synthesized 1,5-diarylpyrazole compounds, namely 2-methoxy-4-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)phenol (**1**) and its aminomethyl derivatives (**2a-e**) were evaluated for their anti-inflammatory potentiality. The structures of the synthesized compounds were elucidated using FTIR, NMR (^{1}H & ^{13}C) and mass spectral data. The study found that the activity of aminomethyl derivatives (**2a-e**) was higher than that of parent compound **1**. In this series, aminomethyl derivatives bearing dimethylamino-methyl, diethylaminomethyl and pyrrolidinomethyl moieties (**2a**, **2c** and **2e**, respectively) were more active than diclofenac sodium, which was used as a standard. A study on the structure-activity relationship (SAR) suggested that the activity of aminomethyl moiety of the compound was influenced by its pKa value. Thus, novel compounds act as potential anti-inflammatory agents.

Keywords: 1,5-Diarylpyrazole, Aminomethyl derivatives, Anti-inflammatory activity, Protein denaturation.

INTRODUCTION

In survey conducted by Arthritis Fountion of USA, more than 50 million peoples (approximately 22 %) of the US adult population have been diagnosed with arthritis and related diseases. Among the US adults, an estimated 12.4 million, 1.5 million and 3.0 million were diagnosed with osteoarthritis, rheumatoid arthritis and gout, respectively [1]. Globally, an estimated 23.7 million people have rheumatoid arthritis [2]. Adults usually develop these diseases in their productive years, between the age of 20 and 40 years [3]. For past 50 years, the mortality rates of patients with rheumatoid arthritis has been approximately 1.5 times higher than those of general population [4].

The most widely used drugs for arthritis medication are non-steroidal anti-inflammatory drugs (NSAIDs). The antipyretic, analgesic and anti-inflammatory properties of NSAIDs prove to be beneficial in reducing symptomatic and inflammatory conditions [5]. Approximately 30 million people worldwide use NSAIDs [6]. However, NSAIDs cause some serious side effects such as digestive tract irritation, cardiovascular disorders, hypersensitivity reactions and kidney disturbances [7]. Hence, research for discovering novel anti-inflammatory agents is of interest.

Pyrazole, a five-membered heterocyclic aromatic group, is present in several bioactive compounds. In some pyrazole derivative compounds, various biological activities have been identified, including anticancer, anticonvulsant, antimicrobial, anti-inflammatory and analgesics [8-10]. Pyrazole derivatives have been developed to afford anti-inflammatory drugs. They include 1,5-diarylpyrazole compounds such as celecoxib, rimonabant, and phenylbutazone [11]. However, to the best of our knowledge, no studies are available on the synthesis and anti-inflammatory activities of its aminomethyl derivatives. Introducing an aminomethyl group to aromatic moiety modifies biologically active compounds. Moreover, biological activity exhibited by some aminomethyl derivatives of anti-inflammatory agents, such as 2,5-disubstituted indoles, 6-substituted 2-aminobenzothiazole, dehydrosingerone (DHZ), chalcones, 5-methyl-2-benzoxazolinones, curcumin mono-carbonyl analogues and ibuprofen, are better than the respective parent analogues [12-18].

Herein, we described the synthesis and anti-inflammatory potential of a series of novel 1,5-diarylpyrazole compounds,

namely 2-methoxy-4-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)phenol (**1**) and its aminomethyl derivatives (**2a-e**).

EXPERIMENTAL

Chemicals were bought commercially from Sigma-Aldrich, USA, E. Merck, Germany and Mallinckrodt, USA. For the purification technique, TLC preparative on silica gel 60 F_{254} plates (Merck, Germany) were used. Using Fourier-transform infrared spectrophotometer (8400S, Shimadzu, Japan), nuclear magnetic resonance (NMR) spectrometer (Agilent, USA) and high-resolution mass spectrometer ESI-TOP LCT Premier XE (Waters Corp., USA), infrared, NMR and mass spectra, respectively, of the synthesized compounds were recorded.

Synthesis of 2-methoxy-4-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)phenol (1): An earlier reported method for the synthesis of 1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazoles was adopted with some modifications [19]. To a 100 mL of glacial acetic acid solution containing dehydrozingerone (47 mmol), phenylhydrazine hydrochloride (53 mmol) was added and heated under reflux for 7 days. After the reaction was completed based on TLC monitoring, a blackish green solution was formed. Crushed ice was added to this mixture with constant stirring, and then the substrate was extracted thrice into a hexane and ethyl acetate mixture (7:1). After the evaporation of organic solvent, oil residue was allowed to solidify at room temperature (**Scheme-I**). TLC preparative purification was done to afford pure 1,5-diarylpyrazole (**1**).

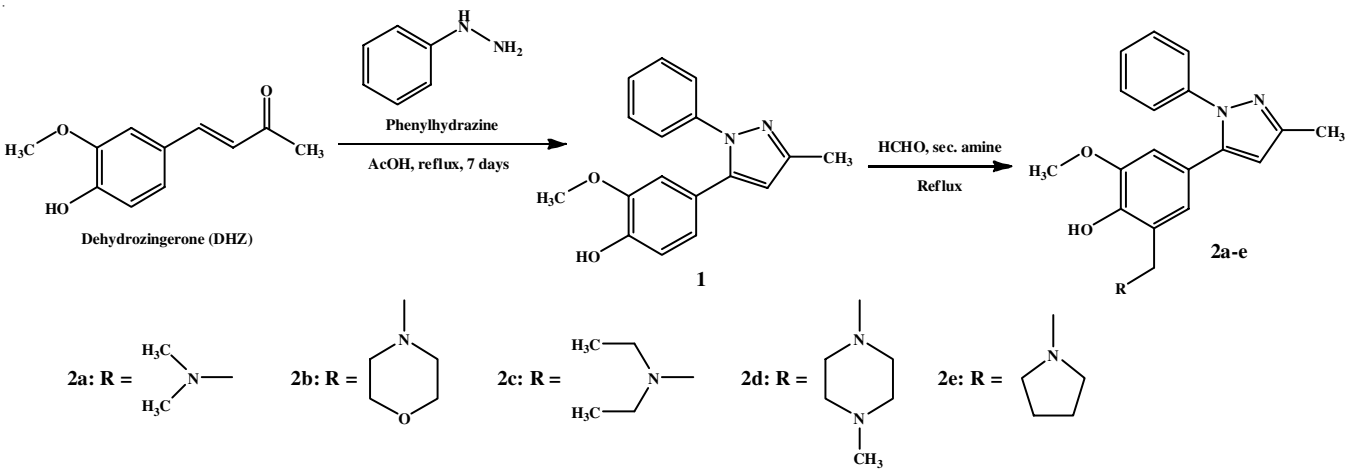
General synthesis of aminomethyl derivatives of 2-methoxy-4-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)phenol (2a-e): Mannich reaction of 1,5-diarylpyrazole (**1**) was used for synthesizing compounds by slightly modifying the method reported previously for the synthesis of hydroxybenzaldehyde derivatives [20]. Compound **1** (1.5 mmol) was added to a mixture of formaldehyde (37.5 %, 1.5 mmol) and corresponding 2º amines (1.5 mmol) in ethanol, and the solution was stirred for 30 min and refluxed for 3 h at 79 ºC, followed by constant stirring at 25 ºC until the reaction was complete based on TLC monitoring. Using a rotary vacuum evaporator, solvent was evaporated to obtain a crude product. TLC preparative purification of the crude product afforded pure **2a-e**.

Spectral data

2-Methoxy-4-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)-phenol (1): Dark yellow powder, yield 15.8 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3500-2500 (broad, OH), 1724 (C=N), 1595 and 1512 (C=C), 1261 (C-O), 1124-1033 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm: 2.37 (s, 3H, CH_3), 3.64 (s, 3H, CH_3-O-Ar), 6.26 (s, 1H, CH=C), 6.61 (d, 1H, *J* = 1 Hz, HAr), 6.77 (d, 1H, *J* = 1 Hz, HAr), 6.82 (d, 1H, *J* = 1 Hz, HAr), 7.30 (m, 5H, HAr). ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm: 13.72 (1C), 55.86 (1C), 106.85 (1C), 107.17 (1C), 111.46 (1C), 111.67 (1C), 114.59 (1C), 125.41 (2C), 127.12 (1C), 128.82 (2C), 140.42 (1C), 143.89 (1C), 147.24 (1C), 147.66 (1C), 149.42 (1C). HR ESI-MS (*m/z*) found 281.1295 $(M+H)^+$, calcd. mass 281.1290 for $C_{17}H_{17}N_2O_2$ (error ~1.8 ppm).

2-[(Dimethylamino)methyl]-6-methoxy-4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)phenol (2a): Brownish yellow viscous liquid, yield 29.2 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3000-2850 (C-H aliphatic), 1579 (C=N), 1250 (C-O), 1502, 1460 (C=C), 1165, 1088 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm: 2.27 (s, 6H, N-$(CH_3)_2$), 2.34 (s, 3H, CH_3), 3.52 (s, 2H, Ar-CH_2-N-), 3.61 (s, 3H, CH_3-O-Ar), 6.23 (s, 1H, CH=C), 6.45 (s, 1H, HAr), 6.55 (s, 1H, HAr), 7.21-7.29 (m, 5H, HAr). ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm: 1 3.67 (1C), 44.5 (2C), 55.75 (1C), 62.54 (1C), 106.80 (1C), 111.67 (1C), 121.13 (1C), 122.02 (1C), 125.34 (2C), 125.43 (2C), 127.04 (1C), 127.19 (1C), 128.77 (2C), 140.40 (1C), 143.98 (1C), 147.60 (1C), 147.63 (1C), 149.37 (1C). HR ESI-MS (*m/z*) found 338.1862 $(M+H)^+$, calcd. mass 338.1869 for $C_{20}H_{24}N_3O_2$ (error ~2.1 ppm).

2-Methoxy-4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-6-[(morpholin-4-yl)methyl]phenol (2b): Brown viscous liquid, yield 15.6 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3000-2850 (C-H aliphatic), 1692 (C=N), 1597, 1500 (C=C), 1261 (C-O), 1094 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm: 2.36 (s, 3H, CH_3), 2.53 (t, 4H, -CH_2-CH_2-N-morpholine), 3.61 (s, 2H, Ar-CH_2-N-), 3.66 (s, 3H, CH_3-O-Ar), 3.73 (t, 4H, *J* = 10 Hz, -CH_2-CH_2-O-), 6.24 (s, 1H, CH=C), 6.50 (d, 1H, *J* = 1 Hz, HAr), 6.57 (d, 1H, *J* = 1 Hz, HAr), 7.23-7.32 (m, HAr). ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm: 13.71 (1C), 52.94 (2C), 55.80 (1C), 61.51 (1C), 66.88 (2C), 106.90 (1C), 111.80 (1C), 120.86 (1C), 121.35 (1C), 121.65 (1C), 125.43 (2C), 127.18 (1C), 128.85 (2C), 140.40 (1C), 143.82 (1C), 146.96 (1C), 147.69 (1C), 149.46 (1C).



Scheme-I: Synthetic route of 2-methoxy-4-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)phenol) (**1**) and its aminomethyl derivatives (**2a-e**)

HR ESI-MS (*m/z*) found 380.1976 $(M+H)^+$, calcd. mass 380.1974 for $C_{22}H_{26}N_3O_3$ (error ~0.5 ppm).

2-[(Diethylamino)methyl]-6-methoxy-4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)phenol (2c): Brown viscous liquid, yield 31.1 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3000-2850 (C-H aliphatic), 1597 (C=N), 1246 (C-O), 1499 and 1456 (C=C), 1300-1000 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm: 1.08 (t, 6H, CH_3), 2.05 (s, 2H, -CH_2-N-diethylamine), 2.36 (s, 3H, CH_3), 2.59 (q, 4H, *J* = 7 Hz, 7.2 Hz, CH_2-CH_3-diethylamine), 3.63 (s, 3H, CH_3-O-Ar), 3.67 (s, 2H, Ar-CH_2-N-), 6.24 (s, 1H, CH=C), 6.45 (d, 1H, *J* = 2 Hz, HAr), 6.57 (d, 1H, *J* = 2 Hz, HAr), 7.22-7.31 (m, 5H, HAr). ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm: 11.88 (2C), 11.23 (1C), 55.78 (1C), 46.44 (2C), 56.50 (1C), 106.82 (1C), 111.50 (1C), 120.96 (1C), 121.50 (1C), 121.95 (1C), 125.40 (2C), 127.08 (1C), 128.82 (2C), 140.41 (1C), 144.11 (1C), 147.78 (1C), 148.01 (1C), 149.42 (1C). HR ESI-MS (*m/z*) found 366.2183 $(M+H)^+$, calcd. mass 366.2182 for $C_{22}H_{28}N_3O_2$ (error ~0.3 ppm).

2-Methoxy-4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-6-[(4-methylpiperazin-1-yl)methyl]phenol (2d): Pale yellow powder, yield 32.4 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3000-2850 (C-H aliphatic), 1730 (C=N), 1597 and 1500 (C=CAr), 1247 (C-O), 1165-1082 (C-N). ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm: 2.28 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.50 (m, 8H, CH_2 piperazine), 3.61 (s, 3H and 2H, CH_3-O-Ar overlap with Ar-CH_2-N), 6.26 (s, 1H, CH=C), 6.50 (d, 1H, *J* = 1 Hz, HAr), 6.55 (d, 1H, *J* = 1 Hz, HAr), 7.25 (m, 5H, HAr). ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm: 13.71 (1C), 45.97 (1C), 52.50 (2C), 54.96 (2C), 55.77 (1C), 61.07 (1C), 111.67 (1C), 113.40 (1C), 121.20 (1C), 106.85 (1C), 125.41 (2C), 128.87 (2C), 128.91 (1C), 127.12 (1C), 140.42 (1C), 143.89 (1C), 147.24 (1C), 147.66 (1C), 149.42 (1C). HR ESI-MS (*m/z*) found 393.2295 $(M+H)^+$, calcd. mass 393.2291 for $C_{23}H_{29}N_4O_2$ (error ~1.0 ppm).

2-Methoxy-4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-6-[(pyrrolidin-1-yl)methyl]phenol (2e): Brown viscous liquid, yield 52.5 %. FT-IR (KBr, ν_{max}, cm^{-1}): 3000-2850 (C-H aliphatic), 1724 (C=N), 1595, 1504 (C=CAr), 1246, 1167 (C–O), 1085, 1000 (C–N). ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm: 2.35 (s, 3H, -CH_3), 1.82 (p, 4H, -CH_2- pyrrolidine), 2.59 (t, 4H, *J* = 12.3 Hz -CH_2- pyrrolidine), 3.60 (s, 3H, CH_3-O-Ar), 3.72 (s, 2H, Ar-CH_2-N), 6.23 (s, 1H, CH=C), 6.48 (s, 1H, HAr), 6.54 (s, 1H, HAr), 7.22 (t, *J* = 1 Hz, 1H, HAr), 7.26 (t, *J* = 1 Hz, 2H, HAr), and 7.29 (d, *J* = 1 Hz, 2H, HAr). ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm: 13.70 (1C), 23.71 (2C), 53.48 (2C), 55.76 (1C), 58,34 (1C), 106,82 (1C), 111.52 (1C), 113.42 (1C), 120.69 (1C), 121.01 (1C), 122.42 (1C), 125.39 (2C), 127.06 (1C), 128.80 (2C), 140,45 (1C), 144.06 (1C), 147.61 (1C), and 149.4 (1C). HR ESI-MS (*m/z*) found 364.2028 $(M+H)^+$, calcd. mass 364.2025 for $C_{22}H_{26}N_3O_2$ (error ~0.8 ppm).

Anti-inflammatory activity: The inhibition of a heat induced protein denaturation technique [21-23] was used for evaluating the anti-inflammatory potential of synthesized compounds. Diclofenac sodium was used as a positive standard. The tested solution in methanol (0.5 mL) was mixed with bovine saline albumin (4.5 mL, 0.5 %, pH 6.3) solution prepared in tris-buffer saline and adjusted to the required pH using glacial acetic acid. After heating the mixture for 10 min in a water bath at 70 ± 2 ºC, it was cooled to room temperature and measured spectrophotometrically at 660 nm. For control, a similar mixture was used but without the test compound. Each experiment was performed in triplicate and the percentage of the inhibition of protein denaturation was calculated as follows:

$$\text{Inhibition (\%)} = \frac{A_c - A_t}{A_c} \times 100$$

where, A_c = absorbance of control solution; A_t = absorbance of test compound.

The percentage inhibition of the synthesized compounds was plotted *versus* final concentration of the compounds to determine the capacity of each test compound to inhibit denaturation (expressed as an IC_{50} value).

RESULTS AND DISCUSSION

The methods used for the synthesis of the title compounds (**1** and **2a-e**) are summarized in **Scheme-I**. Phenylhydrazine hydrochloride was used to condense dehydrozingerone in glacial acetic acid at reflux condition to provide a 1,5-diarylpyrazole (**1**). Treatment of compound **1** with formaldehyde and corresponding amines in ethanol under reflux conditions afforded its aminomethyl derivatives (**2a-e**). The infrared spectrum of compound **1** shows the peak of OH phenolic, C=N, C=C, aromatic C-O ether and C-N at 3650, 1724, 1595, 1512, 1261, and 1124-1033 cm^{-1}, respectively [24]. The ^{1}H NMR showed three singlet peaks of CH_3, OCH_3 and CH=C of the pyrazole ring at 2.37, 3.64 and 6.26 ppm, respectively. Three doublet peaks and one multiplet of the aromatic ring appearred at 6.61, 6.77, 6.82 and 7.30 ppm. The infrared spectra of compounds **2a-e** showed the peak disappearance of OH phenolic compared with that of compound **1**. The data indicated that aminomethyl substitution is at the *ortho*-position relative to the phenol group, and intramolecular hydrogen bonding OH-N was formed [19]. These were supported by their ^{1}H NMR spectra, where at the first aromatic ring, only two protons appeared as singlet peaks at δ 6.45-6.55 ppm (1H) and 6.55-6.57 ppm (1H) [25].

The structure of compounds **1** and **2a-e** were also elucidated through ^{13}C NMR spectral analysis, which confirmed the number and types of carbons of pyrazole, aromatic and aliphatic moieties of the synthesized compounds and also by mass data, which further confirmed the accurate molecular weight of the compounds.

Anti-inflammatory activity: The anti-inflammatory potential of the synthesized compounds (**1** and **2a-e**) was also evaluated using a heat-induced protein denaturation technique. Decreased absorbance with the addition of test compounds compared with the control indicated the ability of the compound to inhibit protein denaturation [21-23]. The inhibition of heat-induced protein denaturation of the synthesized compounds indicates concentration-response relation (Fig. 1), with IC_{50} values in the range of 4.70-127.12 μM (Table-1). Their activities were 1.3-43 fold higher than those of the parent compound **1** and 0.06-1.7-fold higher than the standard diclofenac sodium and 1.6-106-fold higher than dehydrozingerone. Thus, aminomethyl group improves the anti-inflammatory property of the parent compound, as reported earlier [12-18]. It indicated that the aminomethyl moiety acts as a new pharmacophore in

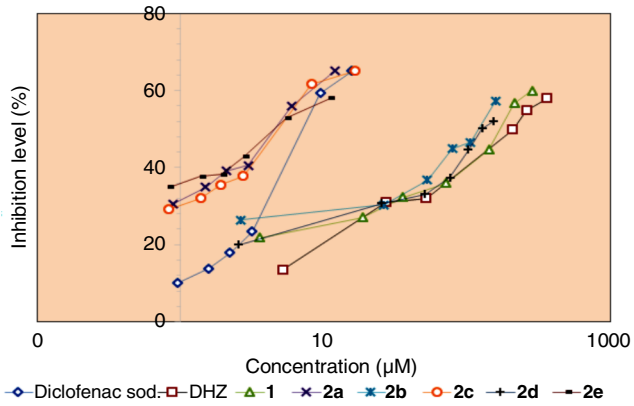


Fig. 1. Inhibitory activity against heat-induced protein denaturation of the synthesized compounds

TABLE-1
INHIBITORY ACTIVITY OF HEAT-INDUCED PROTEIN DENATURATION OF THE SYNTHESIZED COMPOUNDS

Compound	IC_{50} ± SD (μM)[a]	log 1/IC_{50} (μM)	Calculated pKa[b]
1	170.22 ± 2.97	-2.23100	–
2a	4.70 ± 0.12	-0.67210	8.90
2b	114.57 ± 4.09	-2.05910	6.90
2c	5.25 ± 0,20	-0.72020	9.46
2d	127.12 ± 2,58	-2.10420	7.67 & 7.55
2e	4.75 ± 0.34	-0.67670	9.18
Dehydrozingerone	201.94 ± 5.37	-2.30520	–
Diclofenac sodium	7.81 ± 0.04	-0.89265	–

[a]Mean of n = 3; [b]pKa of N atom of the Aminomethyl moiety, MarvinSketch 17.17.0 [Ref. 31]

the drug interaction, altering the binding interaction involved in the mechanism of protein denaturation [26,27].

Protecting endogenous proteins from denaturation is one of the action mechanisms of NSAIDs in rheumatoid arthritis. Moreover, anti-inflammatory activity has also been observed in agents showing protective effects against heat-induced protein denaturation [28-30]. In this series, aminomethyl derivatives of 2-methoxy-4-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)phenol bearing dimethylaminomethyl, diethylaminomethyl and pyrrolidinomethyl groups (**2a**, **2c** and **2e**, respectively) were more active than standard drug *viz*. diclofenac sodium. Studies on the structure-activity relationship have shown that the pKa value of aminomethyl moiety of the compound influences the inhibitory activity against protein denaturation (Fig. 2).

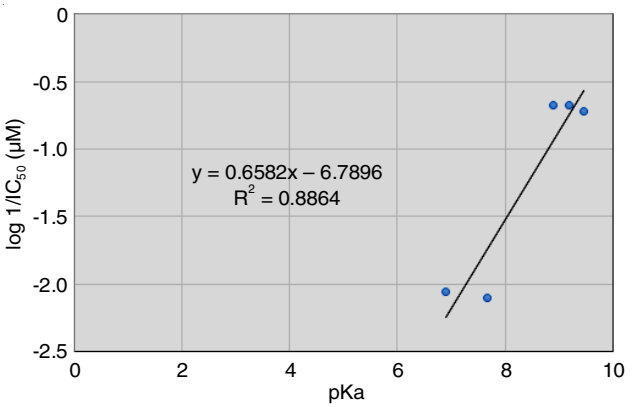


Fig. 2. Calculated pKa - activity relationship as heat-induced protein denaturation inhibitor of the synthesized compounds

Conclusion

A series of novel 1,5-diarylpyrazoles, consisting of 2-methoxy-4-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)phenol and its aminomethyl derivatives, were synthesized and screened for their anti-inflammatory activity by using the inhibitory heat-induced protein denaturation technique. Compounds **2a**, **2c** and **2e**, containing dimethylamine, diethylamine and pyrrolidine moieties, respectively, were more active than standard diclofenac sodium. Thus, 1,5-diarylpyrazole compounds act as a potential anti-inflammatory agents. Further studies are necessary to evaluate their *in vivo* activity, toxicity and action mechanism.

ACKNOWLEDGEMENTS

The authors thank The Directorate of Research and Community Services, Universitas Indonesia, Depok, Indonesia for providing the financial support *via* PITTA Grant 2018. Thanks are also due to Department of Chemistry, Institut Teknologi Bandung (ITB), Bandung, Indonesia for recording NMR and mass spectra.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. Arthritis Foundation, Arthritis Foundation Scientific Strategy 2015-2020 (2015). http://www.arthritis.org/Documents/arthritis-foundation-scientific-strategy.pdf
2. R. Seah, Terapi rheumatoid arthritis (RA) baru–Terapi sel mesoblast (2018). https://today.mims.com/terapi-ra-dengan-sel-mesoblast
3. World Health Organization, Chronic rheumatic conditions (2018). http://www.who.int/chp/topics/rheumatic/en/
4. J. van den Hoek, H.C. Boshuizen, L.D. Roorda, G.J. Tijhuis, M.T. Nurmohamed, G.A.M. van den Bos and J. Dekker, *Rheumatol. Int.*, **37**, 487 (2017); https://doi.org/10.1007/s00296-016-3638-5
5. B.G. Wells, J.T. DiPiro, T.L. Schwinghammer and C.V. DiPiro, Pharmacotherapy Handbook, The McGraw-Hills Co. Inc., N.Y., USA, edn 7 (2009).
6. P.G. Conaghan, *Rheumatol. Int.*, **32**, 1491 (2012); https://doi.org/10.1007/s00296-011-2263-6
7. S. Wongrakpanich, A. Wongrakpanich, K. Melhado and J. Rangaswami, *Aging Dis.*, **9**, 143 (2018); https://doi.org/10.14336/AD.2017.0306.
8. M. Khan, M. Alam, G. Verma, W. Akhtar, M. Shaquiquzzaman and M. Akhter, *Eur. J. Med. Chem.*, **120**, 170 (2016); https://doi.org/10.1016/j.ejmech.2016.04.077
9. K. Karrouchi, S. Radi, Y. Ramli, J. Taoufik, Y.N. Mabkhot, F.A. Al-aizari and M. Ansar, *Molecules*, **23**, 134 (2018); https://doi.org/10.3390/molecules23010134
10. A. Jamwal, A. Javed and V. Bhardwaj, *J. Pharm. Biomed. Sci.*, **3**, 114 (2013).
11. R.S. Kumar, I.A. Arif, A. Ahamed and A. Idhayadhulla, *Saudi J. Biol. Sci.*, **23**, 614 (2016); https://doi.org/10.1016/j.sjbs.2015.07.005
12. A. Kaur and A. Kapoor, *Der Pharm. Lett.*, **8**, 157 (2016)
13. D.S. Bele and I. Singhvi, *Int. J. Res. Pharm. Chem.*, **1**, 1058 (2011).
14. H. Hayun, A. Arrahman, E.M. Purwati, A. Yanuar, F. Fortunata, F. Suhargo, D.W. Syafiqah, C. Ignacia and A.R. Novalia, *J. Young Pharm.*, **10**, s6 (2018); https://doi.org/10.5530/jyp.2018.2s.2
15. B.P. Bandgar, S.A. Patil, R.N. Gacche, B.L. Korbad, B.S. Hote, S.N. Kinkar and S.S. Jalde, *Bioorg. Med. Chem. Lett.*, **20**, 730 (2010); https://doi.org/10.1016/j.bmcl.2009.11.068

16. N. Gokhan, M. Koksal, E. Kupeli, E. Yesilada and H. Erdogan, *Turk. J. Chem.*, **29**, 445 (2005).
17. T.N. Putri, A. Bachtiar and H. Hayun, *J. Appl. Pharm. Sci*., **8,** 019 (2018); https://doi.org/10.7324/JAPS.2018.8503
18. K.V. Sujith, J.N. Rao, P. Shetty and B. Kalluraya, *Eur. J. Med. Chem.*, **44**, 3697 (2009); https://doi.org/10.1016/j.ejmech.2009.03.044
19. Z. Ratkovic, J. Muškinja, A. Burmudzija, B. Rankovic, M. Kosanic, G. Bogdanovic, B. Markovic, A. Nikolic, N. Arsenijevic, S. Dorgevic and R. Vukicevic, *J. Mol. Struct.*, **1109**, 82 (2016); https://doi.org/10.1016/j.molstruc.2015.12.079
20. A.K. Sinhababu and R.T. Borchardt, *Int. J. Rapid Com. Synth. Org. Chem.*, **13**, 677 (1983).
21. N.S. Acharya and J.J. Patel, *Int. J. Pharm. Pharm. Sci.*, **8**, 158 (2016).
22. V. Jayashree, S. Bagyalakshmi, D.K. Manjula and D.D. Richard, *Asian J. Pharm. Clin. Res.,* **9**, 108 (2016); https://doi.org/10.22159/ajpcr.2016.v9s2.12623
23. H. Hayun, B.P. Maggadani, A. Kurnia, A. Hanifah, M. Yuliandi, I. Fitriyani and S.P. Hadrianti, *Int. J. Appl. Pharm.*, **11**, 246 (2019); https://doi.org/10.22159/ijap.2019.v11s1.19448
24. R.M. Silverstein, F.X. Webster and D.J. Kiemle, Spectrometric Identification of Organic Compounds, John Wiley & Sons, Inc.: New Jersey, USA, edn 7 (2005).
25. C. Dank, B. Kirchknopf, M. Mastalir, H. Kählig, S. Felsinger, A. Roller, V. Arion and H. Gstach, *Molecules*, **20**, 1686 (2015); https://doi.org/10.3390/molecules20011686
26. S. Bala, N. Sharma, A. Kajal, S. Kamboj and V. Saini, *Int. J. Med. Chem.*, 2014, Article ID 191072 (2014); https://doi.org/10.1155/2014/191072
27. L.V. Nargund, G.R. Redd and V. Hariprasad, *Indian J. Exp. Biol.*, **31**, 395 (1993).
28. L. Saso, G. Valentini, M.L. Casini, E. Grippa, M.T. Gatto, M.G. Leone and B. Silvestrini, *Arch. Pharm. Res.*, **24**, 150 (2001); https://doi.org/10.1007/BF02976483
29. N.H. Grant, H.E. Alburn and C. Kryzanauskas, *Biochem. Pharmacol.*, **19**, 715 (1970); https://doi.org/10.1016/0006-2952(70)90234-0
30. G. Mahendran, M. Manoj, K.J.R. Prasad and V.N. Bai, *Food Sci. Hum. Wellness*, **4**, 169 (2015); https://doi.org/10.1016/j.fshw.2015.08.003
31. Chemaxon Ltd, http://www.chemaxon.com