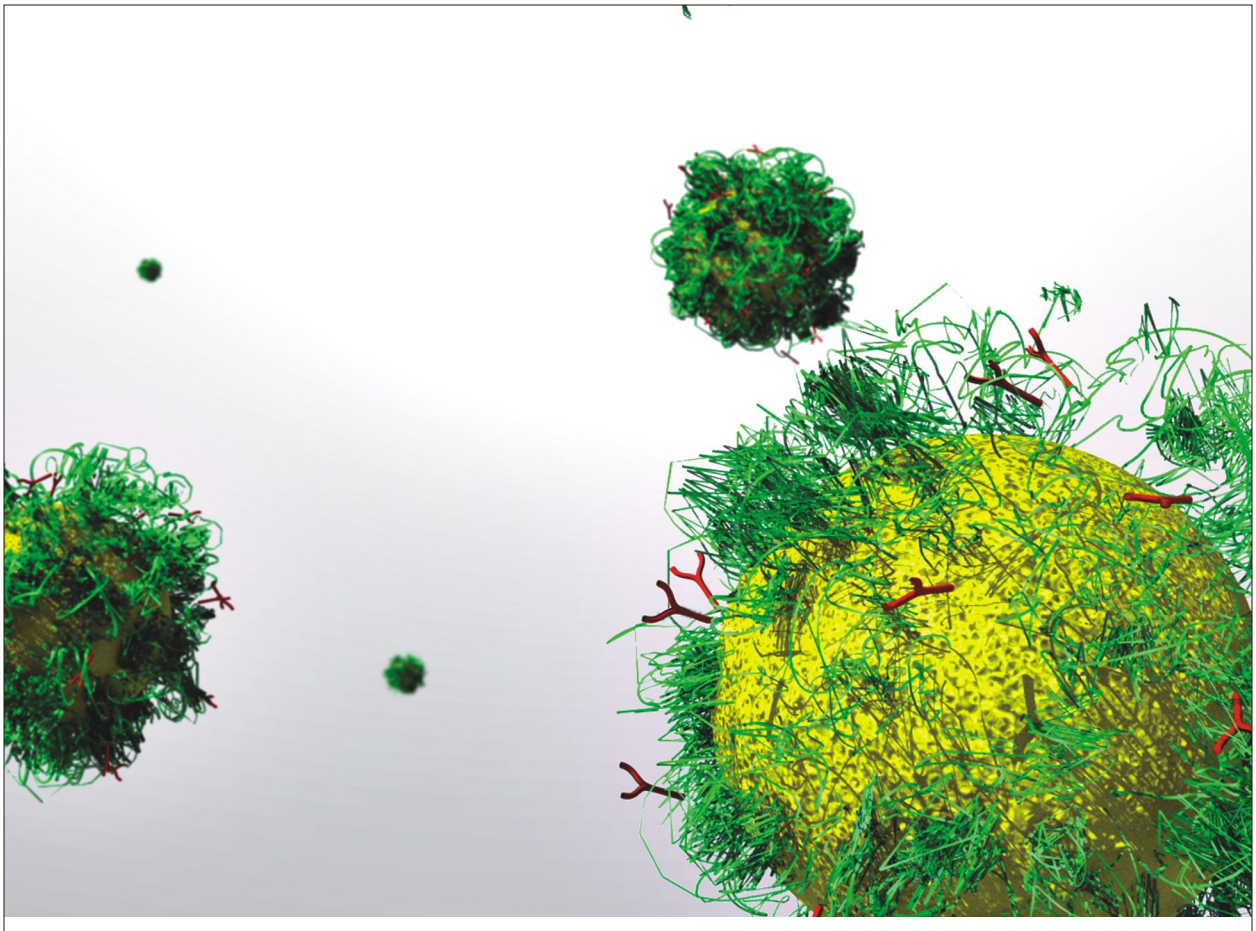


American Journal of
Drug Discovery and Development

ISSN 2150-427X

Academic
Journals Inc.

www.academicjournals.com

American Journal of Drug Discovery and Development 2 (1): 40-49, 2012
ISSN 2150-427x / DOI: 10.3923/ajdd.2012.40.49

Synthesis of Some Pyrrole Derivatives and their Anticoagulant Activity

[1]A. Idhayadhulla, [1]R. Surendra Kumar, [1]A. Jamal Abdul Nasser and [2]Aseer Manilal
[1]P.G and Research Department of Chemistry, Jamal Mohamed College, Tiruchirappalli-620020, Tamil Nadu, India
[2]Department of Microbiology, Bharathidasan University, Tiruchirappalli-620024, Tamil Nadu, India

Corresponding Author: A. Idhayadhulla, P.G and Research Department of Chemistry, Jamal Mohamed College, Tiruchirappalli-620020, Tamil Nadu, India

ABSTRACT

New pyrrole derivatives (2,3) were synthesized by condensation method and synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis. The novel pyrrole derivatives were screened for anticoagulant activity against Activated Partial Thromboplastin Time (APTT) and Prothrombin Time (PT) coagulation assays and compound (3) is highly response for anticoagulant activity compared with compounds (1) and (2) and standard Heparin at concentration (60 μg mL^{-1}) against APTT assay. The compound 3 showed highly significant anticoagulant effect and could be considered as leads for further investigations.

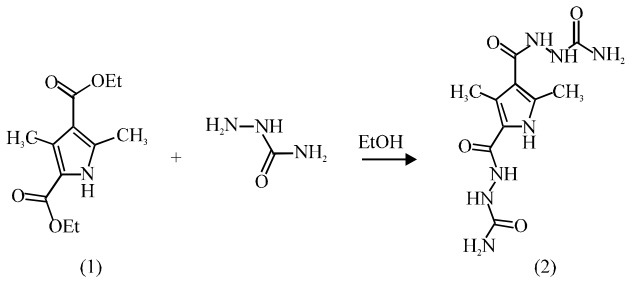
Key words: Pyrrole derivatives, thiosemicarbazide, semicarbazide, heparin, condensation method, structure conformation, anticoagulant screening, APTT assays, PT assays

INTRODUCTION

Pyrrole derivatives represent a class of compounds of great importance in heterocyclic chemistry and effective biological importance (Almerico *et al*., 1998). Pyrrole derivative have significant biological activity such as antitubulin activity (Tripathi *et al*., 2008), non-Competitive mGluR1 antagonists (Micheli *et al*., 2003), DNA-Binding applications (Krutzik and Chamberlin, 2002), Structure-based design of MEK inhibitors (Wallace *et al*., 2010), antitumor activity (Lv *et al*., 2011), antidepressant activity (Kang *et al*., 2010), A new class of mGluR1 antagonists (Micheli *et al*., 2006), DNA-intercalators as potential DNA ligands or topoisomerase inhibitors (David-Cordonnier *et al*., 2007), antitumour activity (Baraldi *et al*., 2002). Cytotoxicity (Dannhardt *et al*., 2000), *in vitro* cytotoxic activity against solid tumor models (Burnham *et al*., 1998; Gupton *et al*., 1999), treatment of hyperlipidemias (Holub *et al*., 2004), cytotoxicity (Almerico *et al*., 2000), antiviral (Dannhardt *et al*., 2000), antimicrobial (Ramazanzadeh and Nasiri, 2009).

Basically thiosemicarbazone connected heterocyclic compounds have significant of biological activity such as antifungal and antibacterial Agents (Ashalatha *et al*., 2006), other activity of thiosemicarbazone derivatives, such as antimicrobial (Surendra Kumar *et al*., 2010), anticonvulsant activity (Surendra Kumar *et al*., 2010), anticancer activities (Kumar *et al*., 2011a,b).

The heparin had been widely used for anticoagulant therapy for more than 50 years (Fan *et al*., 2011). Heparin from animal sources had the potential to induce disease affecting mammals, such as the avian influenza virus and bovine spongiform encephalopathy



Scheme 1: Synthetic route of the compound (2)

(Mendes *et al.*, 2009). These reasons strongly motivated the necessity to find new anticoagulants and antithrombotics to replace heparin.

Our previous investigations have shown that the 1,4-dihydropyridine connecting with thiosemicarbazide and their anticoagulant activity due to presenting of sulfur groups (Kumar *et al.*, 2011c). These references will serve as the main rationales for the synthesis of new pyrrole derivatives 3a-f (Schemes 1) and evaluate them for anticoagulant activity.

MATERIALS AND METHODS

All the chemicals used were of AR grade (Sigma-Aldric; Acros; Hi-media). This research article was a part of synthetic work carried out from department of chemistry Jamal Mohamed college, tamil nadu, india starting at June 2009 till November 2009 and another part of work conducted at Department of Microbiology, Bharathidasan University. Tiruchirappalli-620024, Tamil Nadu, India; starting at July 2010 till November 2010.

Chemistry: Melting points were recorded in open capillary tubes and were uncorrected. The IR spectra (KBr) were recorded on a Shimadzu 8201pc (4000-400 cm^{-1}). The ^{1}H NMR and ^{13}C NMR were recorded on Bruker DRX-400 MHZ. Mass spectra (EI) were recorded on a Jeol JMS D-300 spectrometer operating at 70eV. The Elemental analysis (C, H, N and S) were recorded using an Elementer analyzer model (Varian EL III). The purity of the compounds was checked by Thin Layer Chromatography (TLC).

Synthesis of diethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (1): A mixture of ethyl acetoacetate (0.1 mol) and glacial acetic acid, the mixture was cooled in freezing mixture to 5° and added sodium nitrite drop wise with vigorous stirring at such a rate that the temperature remains between 5 and 7°. Zinc dust was added in reaction mixture, the mixture was stirred at room temperature. The mixture was heated and refluxed for an additional 1 h which are poured into the water. After standing overnight, the crude product was obtained, the crude product was filtered and washed with water.

IR (KBr, cm^{-1}): v = 3325(NH), 1749(C = O in ester); ^{1}H NMR($CDCl_3$): δ = 11.80(s, 1H, NH of pyrrole ring), 4.32 (q, 4H, 2,4-OCH_2CH_3), 2.40(s, 2H, C3-CH_3), 2.16(s, 3H, C5-CH_3), 1.21 (t, 6H, 2,4-OCH_2CH_3).

2,2'-[(3,5-dimethyl-1H-pyrrole-2,4-diyl)dicarbonyl]dihydrazinecarboxamide(2): A mixture of the compound 1 (0.1 mol) and semicarbazide (0.2 mol) in ethanol, the reaction mixture was refluxed for 7 h. The reaction mixture was poured in a crushed-ice. The precipitate was collected by filtration and recrystallised by absolute ethanol.

IR(KBr, cm^{-1}): v = 3343(NH), 3224(NH2), 1739(C = O), 1078(N-C-N); ^{1}H NMR(DMSO-d_6): δ = 11.91 (s,1H, NH of pyrrole ring), 10.38(d, 2H, 2,4-CONH), 6.34 (s, 4H, NH_2), 5.91(d, 2H, 2,4-$NHNHCONH_2$) , 2.39 (s, 3H, C3-CH_3), 2.06 (s, 3H, C5-CH_3); ^{13}C NMR (DMSO-d_6): δ = 168.46 (C2-CONH), 164.29(C4-CONH), 158.99(2,4-$CONH_2$), 144.74 (C3-CH_3), 141.69 (C5-CH_3), 128.69 (C2-CONH), 115.41(C4-CONH), 28.99(C3-CH_3), 15.04(C5-CH_3); MS(m/z): 297.26 [M^+, 25%], 254.24(5%), 211.22(100%), 151.16(12%), 96.07(21%).

2,2'-[(3,5-dimethyl-1H-pyrrole-2,4-diyl)dicarbonyl] dihydrazinecarbothioamide (3): A mixture of the compound (1) (0.1 mol) and thiosemicarbazide (0.2 mol) in ethanol and add few drop of DMSO, the reaction mixture was reflux for 7 h. The reaction mixture was poured in a crushed-ice. The predicated was collected by filtration and recrystallised by absolute ethanol.

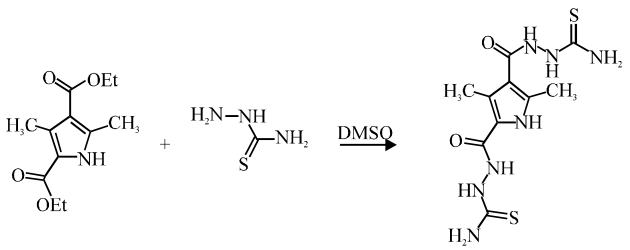
IR (KBr, cm^{-1}): v = 3354(NH), 3241(NH_2), 1747(C = O), 1265(C = S), 1084(N-C-N); ^{1}H NMR (DMSO-d_6): δ = 11.88 (s, 1H, NH of pyrrole ring), 10.41 (d, 2H, 2,4-CONH), 9.51 (s, 4H, NH_2), 2.32 (s, 3H, C3-CH_3), 2.10 (s, 3H, C5-CH_3), 1.71 (d, 2H, $NHNHCSNH_2$); ^{13}C NMR(DMSO-d_6): δ = 185.69 (2,4-$CSNH_2$), 165.76 (C4-CONH), 161.71(C2-CONH), 144.15(C3-CH_3), 141.16(C5-CH_3), 128.46(C2-CONH), 115.50(C4-CONH), 18.22 (C3-CH_3), 11.74(C5-CH_3). MS (m/z): 329.22 [M^+, 31%], 270.42(70%), 212.46 (100%), 151.16 (34.1%), 96.07(13%).

Human blood plasma preparation: Anticoagulant activity was evaluated by compounds(1-3). Human blood plasma presentation, Human blood was collected from healthy individual donors into conical tubes with 2.5% sodium citrate solution. The plasma was separated from blood cells by centrifuging at 5400 rpm at 4°C for 20 min. The blood plasma was stored at -70°C till use.

Anticoagulant activity experiment: The anticoagulant study was carried out by the method in the literature (De Zoysa *et al.*, 2008; Kumar *et al.*, 2011c), anticoagulant assay was determined by Activated Partial Thromboplastin Time (APTT) and Prothrombin Time (PT) coagulation assays (Fisher scientific company, USA). Briefly, citrated normal human plasma (90 µL) was mixed with 10 µL of synthesized compounds (1-3) and incubated for 1 min at 37°C. Then APTT assay reagent (100 µL) was added to the mixture and incubated for 5 min at 37°C. Thereafter, 0.05 mm $CaCl_2$ (100 µL) was added and clotting time(s) recorded using a coagulometer. Prothrombin Time (PT) was performed only for the purified synthesized compounds to determine the type of coagulation inhibition pathway. For the PT assay, citrated normal human plasma (90 µL) was mixed with 10 µL of solution of synthesized compound and incubated for 10 min at 37°C. Then pre-incubated PT assay reagent (200 µL) was added and clotting time was recorded. The activity was compared with Heparin, a commercial anticoagulant. The relative potencies were calculated as APTT index (Sample APTT/Control APTT ratio) or PT Index (Sample PT/Control PT ratio) using the following equation (Guerra-Rivas *et al.*, 2011).

$$\text{APTT index} = \text{APTTs} / \text{PTTc}$$
$$\text{PT index} = \text{PTs} / \text{PTc}$$

where, APTTs and PTs were APTT and PT at determined sample concentrations, respectively, while APTTc and PTc were those of the control assays.



Scheme 2: Synthetic route of the compound (3)

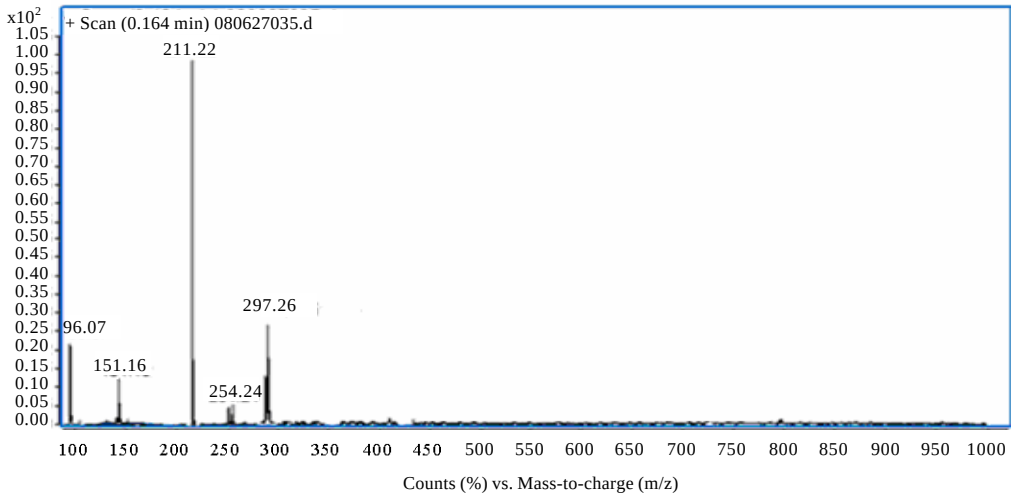


Fig. 1: Mass spectrum of the compound (2)

Table 1: Physiochemical properties of compounds (1-3)

					Elemental analysis calculated (found) (%)			
Comp. No	M.p	m .w	Yield (%)	M.f	C	H	N	S
1	127	239.27	71	$C_{12}H_{17}NO_4$	60.24 (60.28)	7.16 (7.13)	5.85 (5.81)	-
2	115	297.12	89	$C_{10}H_{15}N_7O_4$	40.40 (40.45)	5.09 (5.07)	32.98 (32.98)	-
3	95	329.40	85	$C_{10}H_{15}N_7O_2S_2$	36.46 (36.40)	4.59 (4.51)	29.77 (29.72)	19.47 (19.41)

RESULTS AND DISCUSSION

Chemistry: Diethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (1) was prepared by method descried in literature (Fischer, 1935). Compound 2,2'-[(3,5-dimethyl-1H-pyrrole-2,4-diyl)dicar bonyl]dihydra zinecarboxamide (2) (Scheme 1) were prepared by hydrazinolysis method (Ojha *et al.*, 2007). 2,2'-[(3,5-dimethyl-1H-pyrrole-2,4-diyl) dicarbonyl]dihydrazinecar bothioamide(3) (Scheme 2) were prepared by hydrazinolysis method (Ojha *et al.*, 2007). The chemical structures of these compounds were determined by the basis of spectral data analysis such as IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The physicochemical data are summarized in Table 1. IR spectra of compound (1) showed an absorption band at 3325 cm^{-1} corresponding to NH present in pyrrole ring, another absorption band at 1749 cm^{-1} corresponding to C = O containing in ester group. The ^{1}H NMR spectra of compound (1) showed as a quartet at δ 4.32 attributable to

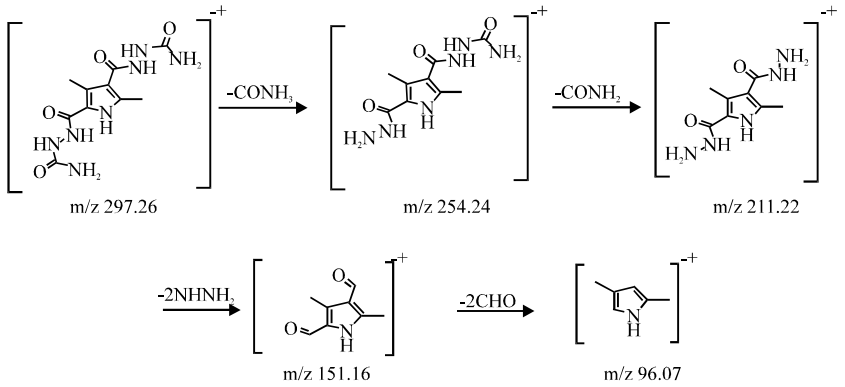


Fig. 2: Fragmentation pattern of compound (2)

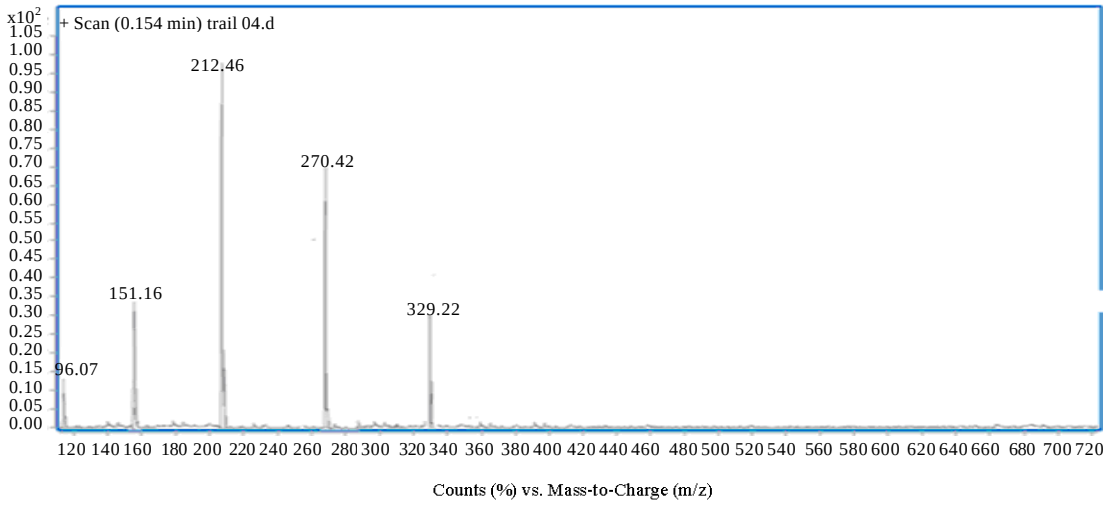


Fig. 3: Mass spectrum of the compound (3)

2,4-OCH_2CH_3 protons and triplet at δ 1.21 attributable to 2,4-OCH_2CH_3. The compound (2) shows an absorption bands for NH, NH_2, C = O and N-C-N a groups observed at 3343, 3224, 1739 and 1078 cm^{-1}, respectively. The ^1H NMR spectrum of compound (2) shows a singlet at δ 6.34, 11.91, 10.38 and 5.91 corresponding to NH_2, NH, 2,4-CONH and 2,4-$NHNHCONH_2$ protons, respectively. ^{13}C NMR spectra of compound (2) shows that peaks at δ 168.46 and 158.99 corresponding to 2,4- C2-CONH and 2,4-$CONH_2$ carbons, respectively. The mass spectrum of compound (2) showed (Fig. 1) that molecular ion peak at m/z 297.26 which is conformed the molecular mass of the compound (2). Fragmentation pattern of compound (2) is representing in Fig. 2.

The IR spectra of compound (3) shows an absorption band at 3354 cm^{-1} corresponding to NH group present in pyrrole ring another absorption bands at 1747, 1265, 3241 and 1084 cm^{-1} corresponding to C = O, C = S, NH_2 and N-C-N groups, respectively. The ^1H NMR spectra of compound (3) shows a signal at δ 9.51, 11.88, 10.41 and 1.71 attributable to NH_2, NH, 2,4-CONH and 2,4-$NHNHCSNH_2$ protons, respectively. ^{13}C NMR spectra of compound (3) shows that the peaks at δ 165.76, 161.71 and 185.69 corresponding to C4-CONH, C2-CONH and 2,4-$CSNH_2$ carbons, respectively. Mass spectrum (Fig. 3) of the compound (3) shows that molecular ion peak at m/z

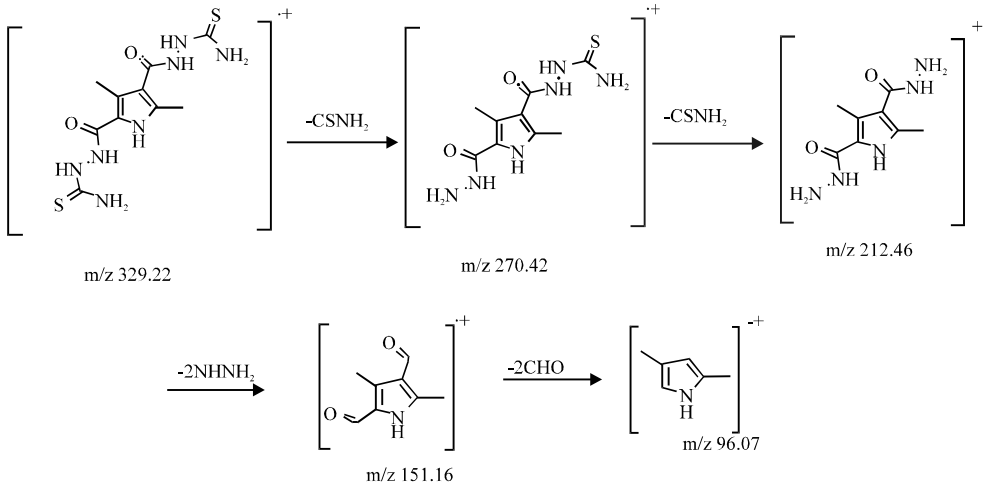


Fig. 4: Fragmentation pattern of compound (3)

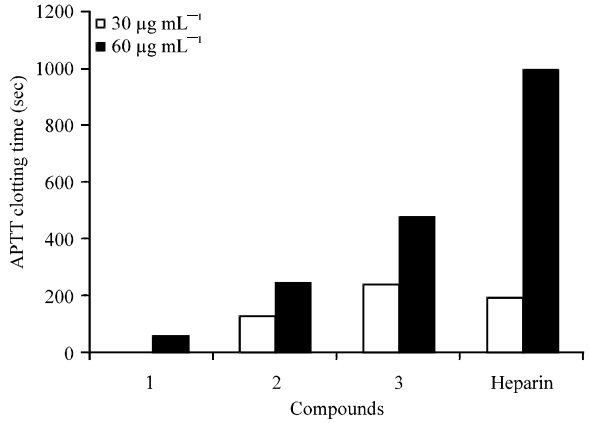


Fig. 5: Compounds (1-3) compared with clotting time (s) for APTT assay at concentration 30 and 60 µg mL^{-1}

329.22 which is conformed the molecular mass of compound (3). Fragmentation pattern of compound (3) is representing in Fig. 4.

Anticoagulant activity: Anticoagulant activity was screened for various sours like patients (Mard-Soltani *et al.*, 2011), Chinese Danshen Plant (Bisher, 2009), Effect of Decoction of *Satureja khuzestanica* Jamzad on Blood Coagulation Time (Nazari *et al.*, 2005), Anticoagulant Properties of *Phyllanthus fraternus* (Koffuor and Amoateng, 2011), clam *Katelysia opima* (Somasundaram and Vijayabaskar, 2007), medicinal Plant (Akram *et al.*, 2011). Our previous investigations have shown that the 1,4-dihydropyridine connecting with thiosemicarbazide and their anticoagulant activity (Kumar *et al.*, 2011c) compared with these results in present investigation, the compound (3) is highly active (241.21s) compared with compound (1) and (2) in APTT assay. The compound (3) has highly active compared with Heparin at concentration (30 µg mL^{-1}). Figure 5 shows that APTT assay for clotting time(s) variation in compounds (1-3). The compound (3) has highly active compared with other compounds (1 and 2) in PT assay coagulation time of (220.28s)

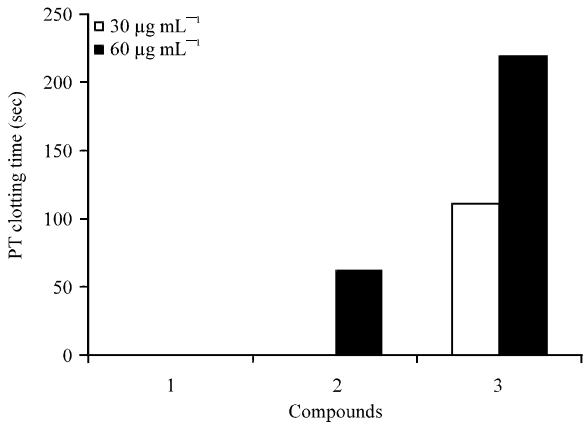


Fig. 6: Compounds (1-3) compared with clotting time (s) for PT assay at concentration 30 and 60 µg mL^{-1}

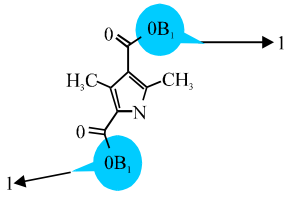
Table 2: Anticoagulant activity of compounds (1-3)

Comp. No	Concentration (µg mL^{-1})	Clotting time (s) APTT	APTT index	Clotting time (s) PT	PT index
1	30	0	0	0	0
	60	52.8	1.45	0	0
2	30	120.2	3.30	0	0
	60	240.51	6.59	62.2	3.23
3	30	241.21	6.62	110.24	5.56
	60	480.35	13.19[b]	220.28	11.22[b]
Heparin	30	185.0	5.08	-	-
	60	>1,000[a]	27.47		
Control	0	36.4	1.0	19.8	1.0

[a]Clotting time >1,000 sec considered as to calculate the relative clotting time values are expressed as mean of five trails; [b]Shows highly significant index

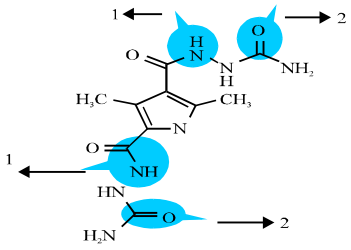
at concentration (60 µg mL^{-1}). Figure 6 shows that PT assay for clotting time(s) variation of the compounds (1-3). The values are summarized in Table 2.

Structural activity relationship of compound (1-3): From the results of anticoagulant activities of the synthesized pyrrole derivatives, the following structure activity relationships can be derived:



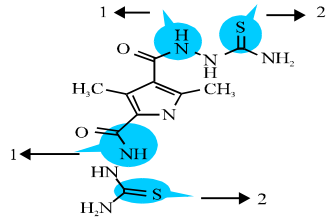
Compound (1)

The compound (1) have shows that -OEt group and pyrrole ring, which is give very less response an anticoagulant activity.



Compound (2)

The compound (2) exhibit -CONH and -CO-NH_2 groups containing pyrrole derivative very low response in anticoagulant activity.



Compound (3)

The compound (3) have -CONH and -CS-NH_2 groups, it is shows that higher anticoagulant activity than Heparin at concentration 30 μg mL^{-1} in APTT assay.

CONCLUSION

In summary three pyrrole derivatives(1-3) were synthesized and screening for anticoagulant activity, among the compound (3) is exert potent anticoagulant activity compared with compounds (1) and (2) and standard Heparin at concentration (60 μg mL^{-1}) against APTT assay, Therefore, we have found some anticoagulant properties of these pyrrole derivatives (1-3) but the majority of activity in compound (3) can be used as lead compound for developing new anticoagulant agent.

ACKNOWLEDGMENT

We wish to thank, Department of Microbiology Bharathidasan University, for their help in anticoagulant activities and we sincerely thank to management committee of Jamal Mohamed College, for providing Laboratory facilities.

REFERENCES

Akram, M., M.I. Shah, K. Usmanghan, E. Mohiuddin and A. Sami *et al.*, 2011. *Zingiber officinale* roscoe (A medicinal plant). Pak. J. Nutr., 10: 399-400.

Almerico, A.E., A. Lauria, P. Diana, P. Barraja, G. Cirrincione and G. Dattolo, 2000. Glycosidopyrroles. Part 4. 1-β-D-ribofuranosyl-pyrroles and indoles as potential antiviral agents. Arkivok, 1: 486-496.

Almerico, A.M., P. Diana, P. Barraja, G. Dattolo and F. Mingoia *et al.*, 1998. Glycosidopyrroles Part 1. Acyclic derivatives: 1-(2-hydroxyethoxy) methylpyrroles as potential anti-viral agents. II Farmaco, 53: 33-40.

Ashalatha, B.V., B. Narayana, K.K.V. Raj and N.S. Kumari, 2006. Synthesis of some new 5-fluoro/chloro/bromo-*N*`-(4-aryl-1, 3-thiazol-2-yl)- *1H*-indole-2-carbohydrazide derivatives as possible antifungal and antibacterial agents. J. Pharmacol. Toxicol., 1: 552-558.

Baraldi, P.G., R. Romagnoli, M.G. Pavani, M.D.C. Nunez, J.P. Bingham and J.A. Hartley, 2002. Benzoyl and cinnamoyl nitrogen mustard derivatives of benzoheterocyclic analogues of the tallimustine: Synthesis and antitumour activity. Bioorg. Med. Chem., 10: 1611-1618.

Bisher, A.S.A.B., 2009. The physiological changes in blood coagulation parameters induced by the therapeutic doses of the Chinese danshen plant (*Salvia miltiorrhiza*) in male guinea pigs (*Cavia porcellus*). J. Biol. Sci., 9: 73-77.

Burnham, B.S., J.T. Gupton, K. Krumpe, T. Webb and J. Shuford *et al.*, 1998. Cytotoxicity of substituted alkyl-3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylates in L1210 lymphoid leukemia cells. Arch. Pharm. Pharm. Med. Chem., 331: 337-341.

Dannhardt, G., W. Kiefer, G. Kramer, S. Maehrlein, U. Nowe and B. Fiebich, 2000. The pyrrole moiety as a template for COX-1/COX-2 inhibitors. Eur. J. Med. Chem., 35: 499-510.

David-Cordonnier, M.H., M.P. Hildebrand, B. Baldeyrou, A. Lansiaux and C. Keuser *et al.*, 2007. Design, synthesis and biological evaluation of new oligopyrrole carboxamides linked with tricyclic DNA-intercalators as potential DNA ligands or topoisomerase inhibitors. Eur. J. Med. Chem., 42: 752-771.

De Zoysa, M., C. Nikapitiya, Y.J. Jeon, Y. Jee and J. Lee, 2008. Anticoagulant activity of sulfated polysaccharide isolated from fermented brown seaweed *Sargassum fulvellum*. J. Applied Phycol., 20: 67-74.

Fan, L., L. Jiang, Y. Xu, Y. Zhou and Y. Shen *et al.*, 2011. Synthesis and anticoagulant activity of sodium alginate sulfates. Carbohydrate Polymers, 83: 1797-1803.

Fischer, H., 1935. 2,4-Dimethyl-3,5-Dicarbethoxypyrrole. Org. Synth., 15: 17-17.

Guerra-Rivas, G., C.M. Gomez-Gutierrez, G. Alarcon-Arteaga, I.E. Soria-Mercado and N.E. Ayala-Sanchez, 2011. Screening for anticoagulant activity in marine algae from the Northwest Mexican Pacific coast. J. Applied Phycol., 23: 495-503.

Gupton, J.T., B.S. Burnham, B.D. Byrd, K.E. Krumpe and C. Stokes *et al.*, 1999. The cytotoxicity and mode of action of 2,3,4-trisubstituted pyrroles and related derivatives in human tmolt4 leukemia cells. Pharmazie, 54: 691-697.

Holub, J.M., K. O'Toole-Colin, A. Getzel, A. Argenti and M.A. Evans *et al.*, 2004. Lipid-lowering effects of ethyl 2-phenacyl-3-aryl-1H-pyrrole-4-carboxylates in rodents. Molecules, 9: 134-157.

Kang, S.Y., E.J. Park, W.K. Park, H.J. Kim and D. Jeong *et al.*, 2010. Arylpiperazine-containing pyrrole 3-carboxamide derivatives targeting serotonin 5-HT2A, 5-HT2C and the serotonin transporter as a potential antidepressant. Bioorganic Med. Chem. Lett., 20: 1705-1711.

Koffuor, G.A and P. Amoateng, 2011. Antioxidant and anticoagulant properties of *Phyllanthus fraternus* GL Webster (Family: Euphorbiaceae). J. Pharmacol. Toxicol., 6: 624-636.

Krutzik, P.O. and A.R. Chamberlin, 2002. Rapid solid-phase synthesis of DNA-binding pyrrole-imidazole polyamides. Bioorg. Med. Chem. Lett., 12: 2129-2132.

Kumar, R.S., A. Idhayadhulla, A. Jamal Abdul Nasser and J. Selvin, 2011a. Synthesis and antimicrobial activity of a new series of 1,4-dihydropyridine derivatives. J. Serb. Chem. Soc., 76: 1-11.

Kumar, R.S., A. Idhayadhulla, A. Jamal Abdul Nasser and K. Murali, 2011b. Synthesis and anticancer activity of some new series of 1,4-dihydropyridine derivatives. Ind. J. Chem., 50B: 1140-1144.

Kumar, R.S., A. Idhayadhulla, A.J. Abdul-Nasser and J. Selvin, 2011c. Synthesis and anticoagulant activity of a new series of 1,4-dihydro pyridine derivatives. Eur. J. Med. Chem., 46: 804-810.

Lv, K., L.L. Wang, M.L. Liu, X.B. Zhou and S.Y. Fan *et al.*, 2011. Synthesis and antitumor activity of 5-[1-(3-(dimethylamino)propyl)-5-halogenated-2-oxoindolin-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxamides. Bioorg. Med. Chem. Lett., 21: 3062-3065.

Mard-Soltani, M., M.R. Dayer, G. Ataie, A.A. Moazedi, M.S. Dayer and S.M.R. Alavi, 2011. Coagulation factors evaluation in NIDDM patients. Am. J. Biochem. Mol. Biol., 1: 244-254.

Mendes, S.F., O. dos Santos Jr., A.M. Barbosa, A.F. Vasconcelos and G. Aranda-Selverio *et al.*, 2009. Sulfonation and anticoagulant activity of botryosphaeran from Botryosphaeria rhodinaMAMB-05 grown on fructose. Int. J. Biol. Macromol., 45: 305-309.

Micheli, F., P. Cavanni, R. di Fabio, C. Marchioro and D. Donati *et al.*, 2006. From pyrroles to pyrrolo[1,2-a]pyrazinones: A new class of mGluR1 antagonists. Bioorg. Med. Chem. Lett., 16: 1342-1345.

Micheli, F., R. di Fabio, P. Cavanni, J.M. Rimland and A.M. Capelli *et al.*, 2003. Synthesis and pharmacological characterisation of 2,4-dicarboxy-pyrroles as selective non-competitive mGluR1 antagonists. Bioorg. Med. Chem., 11: 171-183.

Nazari, A., B. Delfan, Y. Shirkhani, A.A. Kiyanei and A. Mandegary, 2005. Effect of decoction of *Satureja khuzestanica* Jamzad on blood coagulation time, triglyceride and glucose levels in rats. Pak. J. Biol. Sci., 8: 790-792.

Ojha, S., U. Ameta, N. Dhakar and G.L. Talesara, 2007. Synthesis and characterization of some alkoxyphthalimide derivatives of benzotriazolylthiadiazoles and benzotriazolylthiazolidinones. Indian J. Chem. B: Org. Chem., 46: 860-865.

Ramazanzadeh, R. and F. Nasiri, 2009. Dimethyl 2-hydroxy-1-methyl-3-[2-Oxo-2-Phenylethylidene]-2-Phenyl-1,2-Dihydro-3H-Pyrrole 4,5-dicarboxylate: A potential lead compound as anti-gram-positive and anti-gram-negative agent. J. Applied Sci., 9: 2198-2200.

Somasundaram, S.T. and P. Vijayabaskar, 2007. Histological and analytical evaluation of glycosaminoglycan from the clam *Katelysia opima*. Trends Med. Res., 2: 167-175.

Surendra Kumar, R., A. Idhayadhulla, A. Jamal Abdul Nasser, S. Kavimani and S. Indumathy, 2010. Synthesis and anticonvulsant activity of a new series of 1,4- dihydropyridine derivatives. Ind. J. Pharm. Sci., 72: 719-725.

Tripathi, A., M. Fornabaio, G.E. Kellogg, J.T. Gupton and D.A. Gewirtz *et al.*, 2008. Docking and hydropathic scoring of polysubstituted pyrrole compounds with antitubulin activity. Bioorg. Med. Chem., 16: 2235-2242.

Wallace, M.B., M.E. Adams, T. Kanouni, C.D. Mol and D.R. Dougan, *et al.*, 2010. Structure-based design and synthesis of pyrrole derivatives as MEK inhibitors. Bioorg. Med. Chem. Lett., 20: 4156-4158.