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Synthesis of Some New Thieno[2,3-b]thiophene Derivatives and Prediction their Biological Activity by PASS INET

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Abstract: A series of thieno[2,3-*b*] thiophene moiety-containing *bis*-barbituric **2a,b** and *bis*-pyrazoles **3-4a**–**b** derivatives were synthesized and predict their biological activity using PASS INET. According to obtanied data the most frequently predicted, which they showed high biological activity predicted for a potential compound with the highest probability are oxidoreductase inhibitor, chemosensitizer, potassium channel large-conductance Ca-activated activator, Cystinyl aminopeptidase inhibitor and Neurotransmitter uptake inhibitor.

Keywords: Thieno[2,3-b]thiophene – Pass predicition – Azo dye – PASS INET.

1 Introduction

Thieno[2,3-*b*]thiophenes possess important biological activities, including antiinflammatory [**1, 2**], antimicrobial [**3**], analgesic [**4**] properties, antiproliferative activity [**5**], antagonism of α1 adrenoceptors [**6**] and prevention of cartilage destruction in articular diseases [**7**], In addition, they have shown useful reactivity as co-polymerization agents [**8**] and as semiconductors [**9**]. On the other hand, the synthesis of pyrazoles remains of great interest owing to their wide applications in the agrochemical and pharmaceutical industry due to their herbicidal, fungicidal, insecticidal, analgesic, antipyretic and anti-inflammatory properties [**10, 11**]. Pyridazine compounds are also commonly used as anticancer [**12**], antituberculosis [**13**], antihypertensive [**14**], antifungal [**15, 16**], or antimicrobial [**17, 18, 19**] agents, due to their intense biological activity.

We report in the present work an efficient and rapid method for the synthesis of a series of thieno[2,3-*b*]thiophene derivatives [**20**] and predict the biological activities.

2 Result and discussion

Active methylene compounds as barbituric acid, 3-methyl-1H-pyrazol-5(4H)-one and 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one were used as couplers with the diazonium salts of compounds **1a** and **1b** to yield; diethyl 3,4-bis(2,4,6-trioxohexahydropyrimidin-5-yl)diazenyl) thieno[2,3-b]thiophene-2,5-dicarboxylate **2a**, 3,4-bis(2,4,6-trioxohexahydropyrimidin-5-yl)diazenyl)thieno[2,3-b] thiophene-2,5-dicarbonitrile **2b**, diethyl 3,4-bis(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)thieno[2,3-b] thiophene-2,5-dicarboxylate **3a**, 3,4-bis(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)thieno[2,3-b] thiophene-2,5-dicarbonitrile **3b**, diethyl 3,4-bis(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)diazenyl) thieno[2,3-b]thiophene-2,5-dicarboxylate **4a** and 3,4-bis(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl) diazenyl)thieno[2,3-b]thiophene-2,5-dicarbonitrile **4b**, respectively (scheme 1). IR spectra of products showed disappearence of NH_2 group absorption bands and showed new bands of NH, C = O and N = N groups at 3418 - 3320, 1697 and 1598 Cm^{-1}, respectively. ^{1}H-NMR spectrum of compound **2a** showed new signals corresponding to exchangable NH groups and $CH_{pyrimidine}$ at δ 11.52, 11.27 and 3.59 ppm. Its ^{13}C-NMR spectrum shows signals for 3 $C = O$ and $CH_{pyrimidine}$ groups at δ 170.8, 162.3, 160.2 and 73.2 ppm, respetively.

3 Biological activity

Biological activity predicted by PASS

The biological activity spectra for all synthesized compounds **2a**,**b** – **4a**,**b** were obtained by PASS software [**21**]. The predictions of biological activity by using PASS

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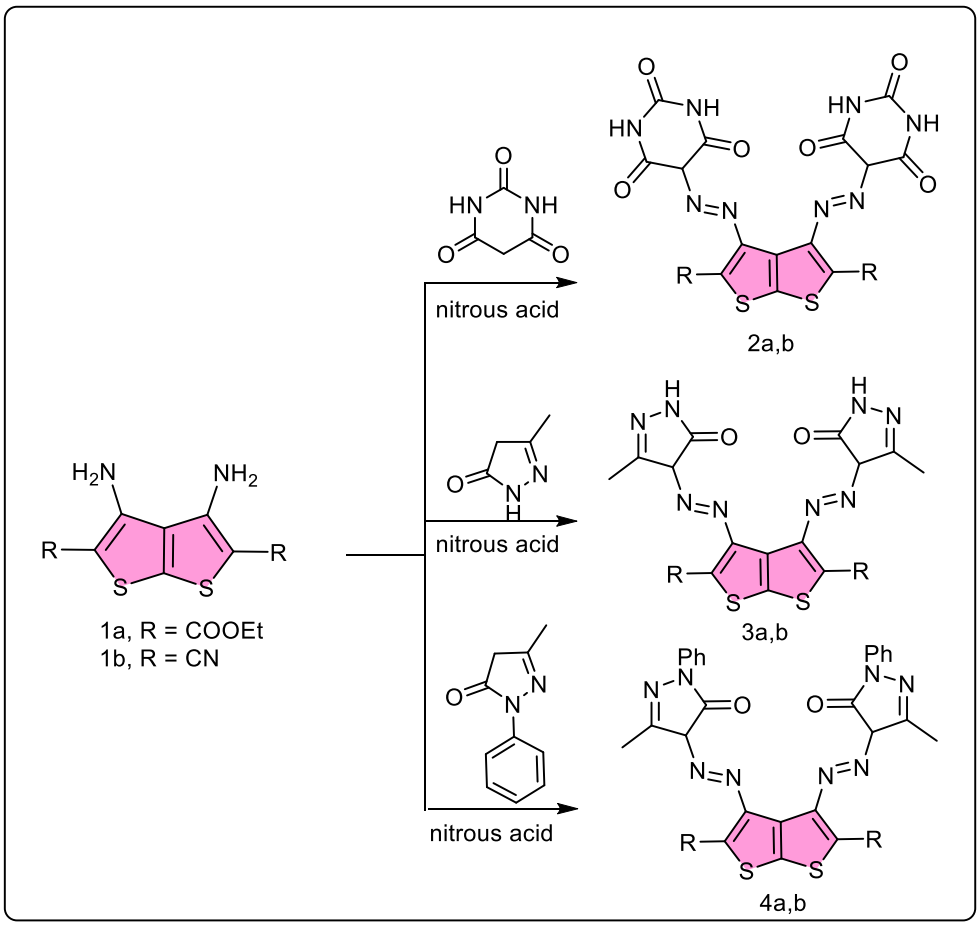
software were carried out via analysis of training set containing about 46,000 drugs and biologically active compounds as reference compounds for known chemical compounds with different biological activities. The percent activity (Pa) and inactivity (Pi) of our products are summarized in table 1. We have also selected the types of activities, which showed high biological activity predicted for a potential compound with the highest probability. According to obtanied data the most frequently predicted types of biological activities are Oxidoreductase inhibitor, Chemosensitizer, Potassium channel large-conductance Ca-activated activator, Cystinyl aminopeptidase inhibitor and Neurotransmitter uptake inhibitor. It showed that, compounds **2a**, **3a,b** and **4a**,**b** have activity as Oxidoreductase inhibitor predicted, as well as in compound such activity as Cystinyl aminopeptidase inhibitor and Potassium channel large-conductance Ca-activated activator, compound 3a such activity as Nicotinic acid receptor 1 agonist with percentage 89% has also been predicted.



Scheme 1

Table 1: Predicted activity of synthesized compounds

Compounds	Potassium channel large-conductance Ca-activated activator		Cystinyl aminopeptidase inhibitor		Oxidoreductase inhibitor		Chemosensitizer		Neurotransmitter uptake inhibitor	
	Pa	**Pi**	**Pa**	**Pi**	**Pa**	**Pi**	**Pa**	**Pi**	**Pa**	**Pi**
2a	0.799	0.003	0.811	0.005	0.943	0.003	0.812	0.005	0.811	0.118
2b	0.729	0.003	0.765	0.04	0.925	0.003	0.734	0.04	0.791	0.173
3a	0.673	0.003	0.553	0.004	0.498	0.003	0.691	0.004	0.891	0.019
3b	0.636	0.002	0.648	0.003	0.491	0.002	0.645	0.003	0.881	0.036
4a	0.612	0.002	0.713	0.003	0.721	0.002	0.738	0.003	0.797	0.036
4b	0.595	0.002	0.673	0.003	0.662	0.002	0.648	0.003	0.736	0.036

4 Experimental: Materials and methods

All melting points were recorded on the Melt-Temp II melting point apparatus and uncorrected. IR spectra were measured by using Brucker Alpha Fourier transforms (FT-IR). 1H-NMR and ^{13}C-NMR spectra were recorded on a Bruker at 400 / 100 MHz using TMS as an internal reference and DMSO-d6 as a solvent. Chemical shift (δ) values are expressed in parts per million (ppm). The elemental analyses were carried out by a Perkin-Elmer 240C Microanalyzer. Reaction progress was monitored by thin-layer chromatography, 0.25 mm thick pre-coated silica plates (Merck Fertigplatten Kieselgel 60 F254), and spots were visualized under UV light. The microwave irradiation was carried out using Microwave chemistry reaction platform of SINEO Microwave Chemistry Technology Co., Ltd, MAS-II Plus microwave synthesis/extraction reaction workstation (where the place).

Synthesis of compounds 1a and 1b

General procedure

To a mixture of (41.5 g, 0.3 mol) oven dried potassium carbonate in 30 to 40 mL DMF and (6.6g, 0.1 mol) malononitrile dissolved in 20 mL DMF, 9.0 mL, (0.15 mol) carbon disulfide was added dropwise under vigorous stirring. After 30 minutes, the mixture was cooled to 0 °C and of ethyl bromoacetate or chloroacetonitrile (0.2 mol) in 10 mL DMF was added in 20 minutes. The reaction mixture was heated in microwave for 3 min. at power 900 W then, the reaction mixture was poured into 200 mL of cold water. The precipitate was collected, washed 3 times with 100 mL water, dried and crystallized from ethanol.

Diethyl 3,4-diaminothieno[2,3-b]thiophene-2,5-dicarboxylate (1a)

Yield 60 %, yellow powder, mp 208 ºC; FT-IR (KBr, Cm^{-1}): 3439, 3349 (2NH_2), 2979 (aliphatic), 1694 (CO_{ester}); ^{1}H-NMR (DMSO-d_6): δ 7.06 (s, 4H, 2NH_2), 4.26-4.21 (q, J = 3.5 Hz, 4H, 2CH_2 ester), 1.29-1.26 (t, J = 3.5 Hz, 6H, 2CH_3 ester); ^{13}C-NMR: δ 161.3, 134.2, 130.7, 123.1, 118.5, 60.8, 14.3; for Chemical Formula: $C_{12}H_{14}N_2O_4S_2$ (314); Elemental Analysis: C, 45.85; H, 4.49; N, 8.91; S, 20.40. Found: C, 45.87; H, 4.48; N, 8.89; S, 20.38.

3,4-Diaminothieno[2,3-b]thiophene-2,5-dicarbonitrile (1b)

Yield 85%, brown powder, mp >350 ºC; FT-IR (KBr, Cm^{-1}): 3424, 3348, 3296, 3239 (2NH_2), 2194 (2CN); ^{1}H-NMR: δ 6.77 (s, 4H, 2NH_2); ^{13}C-NMR: δ 146.2, 134.09, 121.6, 114.8, 85.7; for Chemical Formula: $C_{28}H_{14}N_6O_2S_2$ (219); Elemental Analysis: C, 43.62; H, 1.83; N, 25.44; S, 29.11. found: C, 43.63; H, 1.85; N, 25.42; S, 29.10.

Synthesis of compounds (2a,b – 4a,b)

General procedure

Diethyl 3,4-diaminothieno[2,3-b]thiophene-2,5-dicarboxylate (**1a**) (1 mmol, 0.314 g), or 3,4- d iaminothieno[2,3-b] thiophene-2,5-dicarbonitrile (**1b**) (1 mmol, 0.219 g) was added in portions during 1 h to a cold mixture of nitrosyl sulphuric acid [sodium nitrite (2 mmol, 0.6 g) and concentrated sulphuric acid (10 cm^3)] at 0°C. The mixture was stirred for an additional 1 h at 0°C.

To a solution of barbituric acid (2 mmol, 0.256 g), 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one, (2 mmol, 0.348 g) or 3-methyl-1H-pyrazol-5(4H)-one (2 mmol, 0.196 g), respectively in diluted sodium hydroxide (10 % 20 ml) was kept at 0-5°C. The prepared diazonium salt was added slowly through 1 h to reaction mixture and the temperature did not rise above 5°C. (The pH of the reaction mixture was maintained alkaline throughout the coupling period (1h) by addition of solid sodium hydroxide in portions. The reaction mixture was stirred for 4 h, at r.t, the separated dye was filtered off, washed with water and dilutes hydrochloric acid, dried and crystallized from ethanol.

Diethyl 3,4-bis(2,4,6-trioxohexahydro-pyrimidin-5-yl) diazenylthieno[2,3-b] thiophene-2,5-dicarboxylate (2a)

Yield 76 %, orange powder, mp >330 ºC; FT-IR (KBr, Cm^{-1}): 3438, 3349 (4NH), 3167 (aromatic), 2980 (aliphatic), 1708 (2CO_{ester}), 1673 (4CO), 1588 (2$N = N$); ^{1}H-NMR (DMSO-d_6): δ 11.52 (s, 2H, 2NH), 11.27 (s, 2H, 2NH), 4.36-4.32 (q, J = 7.1 Hz, 4H, 2CH_2 ester), 3.59 (s, 2H barbituric ring), 1.26-1.23 (t, J = 7.1 Hz, 6H, 2CH_3 ester); ^{13}C-NMR: δ 170.8, 162.3, 160.2, 144.1, 133.5, 127.6, 115.4, 73.2, 59.6, 13.7; for Chemical Formula: $C_{20}H_{16}N_8O_{10}S_2$ (592); Elemental Analysis: C, 40.54; H, 2.72; N, 18.91; S, 10.82. Found: C, 40.53; H, 2.74; N, 18.90; S, 10.81.

3,4-bis(2,4,6-trioxohexahydropyrimidin-5-yldiazenyl) thieno[2,3-b]thiophene-2,5-dicarbonitrile (2b)

Yield 77 %, orange powder, mp >350 ºC; FT-IR (KBr, Cm^{-1}): 3418, 3394 (4NH), 3067 (aromatic), 2210 (2CN), 1669 (4CO), 1598 (2$N = N$); ^{1}H-NMR (DMSO-d_6): δ 12.34 (s, 2H, 2NH), 11.26 (s, 2H, NH), 3.72 (s, 2H barbituric ring); ^{13}C-NMR: δ 169.6, 150.3, 147.2, 133.9, 122.6, 113.7, 99.4, 79.3; Anal.calc. for Chemical Formula: $C_{16}H_6N_{10}O_6S_2$ (498); Elemental Analysis: C, 38.56; H, 1.21; N, 28.10; S, 12.86. Found: C, 38.55; H, 1.23; N, 28.12; S, 12.83.

Diethyl 3,4-bis(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)diazenylthieno[2,3-b]thiophene-2,5-dicarboxylate (3a)

Yield 75 %, orange powder, mp = 350 ºC; FT-IR (KBr, Cm^{-1}): 3325 (2NH), 3065 (aromatic), 2930 (aromatic), 1719 (2CO_{ester}), 1673 (2CO), 1598 (2$N = N$); ^{1}H-NMR (DMSO-d_6): δ 8.08 (s, 2H, 2NH), 4.35-4.31 (q, J = 7.1 Hz, 4H, 2CH_2 ester), 2.22 (s, 2H pyrazole ring), 1.51 (s, 6H, 2CH_3 pyrazole ring), 1.26-1.23 (t, J = 7.1 Hz, 6H, 2CH_3 ester); ^{13}C-NMR: δ 172.8, 162.3, 157.2, 146.3, 134.6, 130.2, 126.7, 69.7, 58.2, 18.2,

13.7; for Chemical Formula: $C_{20}H_{20}N_8O_6S_2$ (532); Elemental Analysis: C, 45.11; H, 3.79; N, 21.04; S, 12.04. Found: C, 45.10; H, 3.77; N, 21.07; S, 12.02.

3,4-bis(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)thieno[2,3-b]thiophene-2,5-dicarbonitrile (3b)

Yield 75 %, orange powder, mp >350 ºC; FT-IR (KBr, Cm^{-1}): 3346, 3310 (2NH), 3120 (aromatic), 2930 (aromatic), 2191 (2CN), 1685 (2CO), 1594 ($2N=N$); ^{1}H-NMR (DMSO-d_6): δ 14.18 (s, 2H, 2NH), 2.11 (s, 2H $_{\text{pyrazole ring}}$), 1.33 (s, 6H, $2CH_{3\ \text{pyrazole ring}}$); ^{13}C-NMR: δ 173.2, 154.7, 150.3, 134.3, 122.1, 113.6, 99.4, 73.3, 19.2; for Chemical Formula: $C_{16}H_{10}N_{10}O_2S_2$ (438); Elemental Analysis: C, 43.83; H, 2.30; N, 31.95; S, 14.62. Found: C, 43.86; H, 2.31; N, 31.94; S, 14.61.

Diethyl 3,4-bis(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (4a)

Yield 78 %, orange powder, mp >350 ºC; FT-IR (KBr, Cm^{-1}): 3178 (aromatic), 2928 (aliphatic), 1710 ($2CO_{\text{ester}}$), 1631 (2CO), 1596 ($2N=N$); ^{1}H-NMR (DMSO-d_6): δ 7.90-7.85 (t, J = 8.4 Hz, 4H $_{\text{aromatic}}$), 7.49-7.45 (d, J = 8.4 Hz, 4H $_{\text{aromatic}}$), 7.24-7.21 (t, J = 8.4 Hz, 2H $_{\text{aromatic}}$), 4.25-4.21 (q, J = 7.1 Hz, 4H, $2CH_{2\ \text{ester}}$), 2.31 (s, 6H, $2CH_{3\ \text{pyrazole ring}}$), 1.89 (s, 2H $_{\text{pyrazole ring}}$), 1.26-1.23 (t, J = 7.1 Hz, 6H, $2CH_{3\ \text{ester}}$); ^{13}C-NMR: δ 170.1, 162.2, 156.4, 144.2, 137.2, 135.1, 129.2, 127.3, 123.5, 120.6, 114.8, 70.2, 59.7, 19.3, 14.4; for Chemical Formula: $C_{32}H_{28}N_8O_6S_2$ (684); Elemental Analysis: C, 56.13; H, 4.12; N, 16.36; S, 9.36. Found: C, 56.15; H, 4.11; N, 16.35; S, 9.38.

3,4-bis(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)thieno[2,3-b]thiophene-2,5-dicarbonitrile (4b)

Yield 76 %, orange powder, mp >350 ºC; FT-IR (KBr, Cm^{-1}): 3052 (aromatic), 2992 (aliphatic), 2212 (2CN), 1718 (2CO), 1585 ($2N=N$); ^{1}HNMR (DMSO-d_6): δ 7.90-7.75 (t, J = 8.4 Hz, 4H $_{\text{aromatic}}$), 7.49-7.41 (d, J = 8.4 Hz, 4H $_{\text{aromatic}}$), 7.28-7.20 (t, J = 8.4 Hz, 2H $_{\text{aromatic}}$), 2.22 (s, 2H, $_{\text{pyrazole ring}}$), 1.51 (s, 6H, $2CH_{3\ \text{pyrazole ring}}$); ^{13}CNMR: δ 172.1, 160.0, 146.5, 138.8, 129.7, 128.9, 128.6, 127.1, 124.4, 116.8, 114.3, 53.6, 16.2; Anal.calc. for Chemical Formula: $C_{28}H_{18}N_{10}O_2S_2$ (590); Elemental Analysis: C, 56.94; H, 3.07; N, 23.71; S, 10.86. Found: C, 56.97; H, 3.06; N, 23.70; S, 10.88.

5 Conclusions

A novel series of substituted thieno[2,3-b]thiophenes moieties were synthesized and predicit their biological activities using PASS INET. Most of the tested compounds was found to be equipotent or more potent than the standard drugs and showed high biological activity predicted for a potential compound with the highest probability Oxidoreductase inhibitor, Chemosensitizer, Potassium channel large-conductance Ca-activated activator, Cystinyl aminopeptidase inhibitor and Neurotransmitter uptake inhibitor.

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