Synthesis and Evaluation of The Thrombolytic Activity of Novel Condensed Pyrimidine Sulfonamide Derivatives

Mazin M. Mohsin[1] Mahmood J. Jawad[2], Saif M. Hassan[2], Samir M. Awad[3], Yassmine Ali Hussain[4], Najah R Hadi[5*]

ABSTRACT

Pyrimidine-5-sulfonamides are new organic compounds of wide spectrum activity. A new trend is to incorporate a salicylate moiety in an attempt to enhance a thrombolytic activity. We started this strategy using 2-thiouracil 1 as a blocking unit by its ability to be chlorosulfonated at 5th position by refluxing with chlorosulfonic acid giving sulfonyl derivative 2 which was condensed with three common aromatic amines namingmethyl-4-aminosalicylate, methyl-3-aminobenzoate and methyl-4-aminobenzoate respectively yielding sulfonamide derivatives 3a-c. Moreover, 3a-c derivatives were reacted with chloroacetic acid-producing thiazolopyrimidines 4a-c,which in turn were reacted with p-nitrobenzaldehyde giving arylidine derivatives 5a-c. Also compounds 3a-c were cyclocondensed with anthranilic acid yielding pyrimidoquinazoline derivatives 6a-c. They also were condensed with ethanolamine forming imidazopyrmidine derivatives 7a-c. All the newly synthesized compounds were subjected for thrombolytic evaluation and some of them showed promising activity especially those bearing methyl salicylate moiety as compared to ticlopidine and clopidogrel. We performed different modifications in the thienopyridine chemical structure of ticlopidine and clopidogrel to conclude that the presence of second nitrogen atom in the pyridine ring (yielding pyrimidine moiety) and the presence of the other cycle instead of thienyl ring would lead to enhanced the thrombolytic effect which was maximized by incorporation of a methyl salicylate moiety. We concluded that 4a, 6a, 8a, 7a, 3a, compounds have more potent than both clopidogrel and ticlopidine respectively. They certainly deserve further studying in the future.

Key Words: Antiplatelet, condensed pyrimidine sulphonamides; synthesis and evaluation

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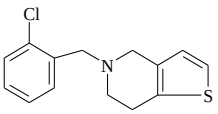
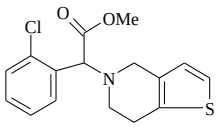
INTRODUCTION

Interest has increased in the recent period to discover and synthesize new drugs as thrombolytic agents, and except for aspirin, few have come into clinical application **(Joseph 2011)**. In 1978, Ticlopidine was firstly used as thrombolytic drug through blocking adenosine diphosphate (ADP) receptor **(Panak et al. 1983)** for treatment strokes and coronary stent occlusions **(Gent et al. 1989; Robless et al. 2001)**. This effect can't be observed in vitro and is detectable ex vivo only many hours after oral administration, this effect may be due to the formation of unstable metabolite. After that in 1996, it was observed that the ingestion of ticlopidine, at a dose of 500 mg by patients suffering from peripheral arterial diseases **(Gryglewski et al. 1996; Gryglewski et al. 1978)** was accompanied by an immediate fibrinolytic action shown by shortening of euglobulin clot lysis time. The rare side effects but it serious of aspirin such as neutropenia and thrombocytopenic purpura, the advent of newer and safer thrombolytic drugs such as clopidogrel and ticagrelor, its use remained limited **(Warner 2011)**. In 1988, Clopidogrel was available as an antiplatelet drug for treatment and the prevention of cardiovascular diseases associated with atherosclerosis such as MI and angina. In some recent studies, a series of compounds where pyridine ring was replaced by a pyrimidine or pyrimidinone moieties left active derivatives of comparable thrombolytic activities to that of thienopyridine drugs **(Committee 1996; Easton 1998)**. This was the aim of the present study where we describe the synthesis of a series of new compounds. Also, we replaced the thiophene ring with other isosteric rings to modify the thrombolytic activity. Also, methyl salicylate moiety was involved to give acceptable results.



Ticlopidine



Clopidogrel

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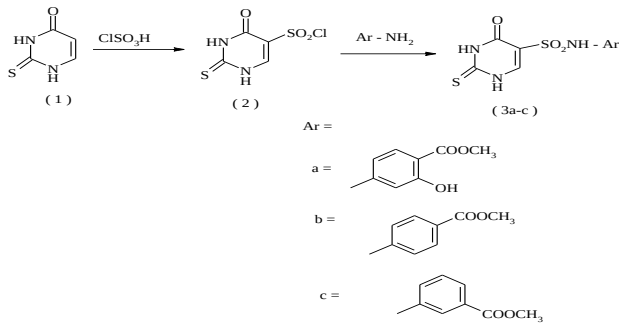
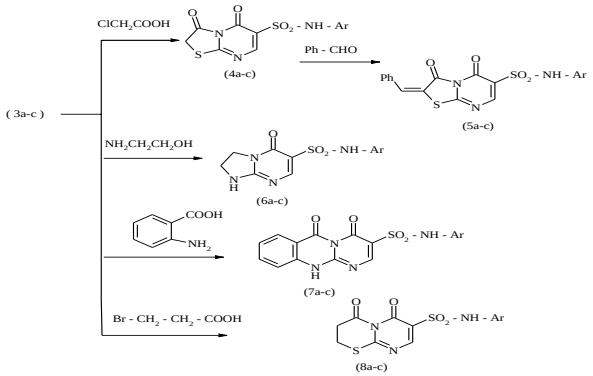
MATERIALS AND METHODS

All materials used in this study have been described previously **(Ahjel et al. 2020)**. The synthesis of new compounds was shown in the scheme I, and II.

Scheme I.



Scheme II.



EXPERIMENTAL

2-Thiouracil-5-sulphonyl chloride (2)	Prepared as in literature (11)
4-Oxo-N-substituted phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-sulphonamide (3a-c)	A mixture of 2 (1.13 mol) and the proper aromatic amine namely, methyl-p-aminosalicylate, methyl-p-aminobenzoate, and methyl-m-aminobenzoate respectively and pyridine (0.016 mol) in absolute ethanol (50ml) was refluxed for 8 hours, then cooled, filtered, dried and recrystallized from DMF/water.
• **Methyl-2-hydroxy-4-([(4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl) sulphonyl] amino) benzoate: 3a.**	Yield: 75%: mp: 298-300ºC: IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1691, 1725 (2C=O), 1270 (C=S). 1HNMR (DMSO-d_6), δ:3.8 (3H,s, OCH_3), 7.1-7.4(3H,m,Ar-H),8.2(1H,s,pyrimidine), 3.5,9.5, 10.1,10.3(4H,s,OH,NH,exchangeable with D_2O),), MS: m/z (%), 357.36 (M^+,17.3%), Anal. Calcd., for $C_{12}H_{11}N_3O_6S_2$: C, 40.33; H, 3.10; N, 11.76. Found: C,40.12; H,3.27; N,11.66.
5-[(4-fluorophenyl)amino]methyl-2-thioxo-2,3-dihydropyrimidin-4-(1H)-one: 3b	Yield: 76%: mp: 276 ºC: IR (KBr cm-1): 3210 (NH), 3162 (CH,aromatic), 2981(CH,aliphatic),1688(C = O), 1270 (C = S). 1HNMR (DMSO-d_6), δ:3.3(2H,s, CH_2-NH), 7.1,7.3(4H,dd,Ar-H),8.1(1H,s,pyrimidine), 4.1,10.0,10.2(3H,s,NH,exchangeable with D_2O),), MS: m/z (%), 251.28 (M^+,21.7%), Anal. Calcd., for $C_{11}H_{10}FN_3OS$: C, 52.58; H, 4.01; N, 16.72. Found: C,52.52; H,4.27; N,16.83.
• **Methyl-4-([(4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl) sulphonyl] amino) benzoate: 3b.**	Yield: 76%: mp: 276-78 ºC IR (KBr/cm): 3226 (NH),3300 (OH), 3150 (aromatic-CH), 2986 (aliphatic-CH), 1689,1725(2C = O), 1271 (C = S). 1HNMR (DMSO-d_6), δ:3.9(3H,s, OCH_3), 7.2,7.4(4H,dd,Ar-H),8.1(1H,s,pyrimidine), 3.4,9.6, 10.0,10.2(4H,s,OH,NH,exchangeable with D_2O),), MS: m/z (%), 341.36 (M^+,11.1%), Anal. Calcd., for $C_{12}H_{11}N_3O_5S_2$: C, 42.22; H, 3.25; N, 12.31. Found: C,42.17; H,3.32; N,12.34.
• **Methyl-3-([(4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl) sulphonyl] amino) benzoate: 3c.**	Yield: 79%: mp: 285-87 ºC IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1686,1723(2C = O), 1270 (C = S). 1HNMR (DMSO-d_6), δ:3.8(3H,s, OCH_3), 7.1,7.3(4H,m,Ar-H),8.1(1H,s,pyrimidine), 3.4,9.6, 10.0,10.2(4H,s,OH, NH,exchangeable with D_2O),), MS: m/z (%), 341.36 (M^+,13.4%), Anal. Calcd., for $C_{12}H_{11}N_3O_5S_2$: C, 42.22; H, 3.25; N, 12.31. Found: C,42.26; H,3.26; N,12.35.
• **3,5-Dioxo-N-substituted phenyl-2,3-dihydro-5H-[1,3] thiazolo[3,2-a] pyrimidine-6-sulphonamide (4a-c):**	A mixture of **3a-c** (0.01 mole), chloroacetic acid (0.01 mole) and anhydrous sodium acetate (3 gm) in glacial acetic acid (30 ml) and acetic anhydride (10 ml) was refluxed for 4 hours, then allowed to cool and poured gradually with stirring onto cold water, the solid formed was filtered off and crystallized from DMF/water.
• **Methyl-4-([(3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidin-6-yl)sulphonyl]amino)-2-hydroxybenzoate:4a.**	Yield: 61%: mp: 263-65ºC: IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic),1681,1683,1722 (3C = O). 1HNMR (DMSO-d_6), δ:3.7(3H,s, OCH_3),4.1(2H,s,CH_2) 7.1-7.3(3H,m,Ar-H),8.2(1H,s,pyrimidine), 3.5, 10.1 (2H,s,OH,NH,exchangeable with D_2O),), MS: m/z (%), 397.38 (M^+,10.2%), Anal. Calcd., for $C_{14}H_{11}N_3O_7S_2$: C, 42.31; H, 2.79; N, 10.57. Found: C,42.47; H,2.72; N,10.56.
• **Methyl-4-([(3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidin-6-yl) sulphonyl] amino) benzoate:4b.**	Yield: 63%: mp: 270-72 ºC IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1680,1689,1725(3C = O), 1HNMR (DMSO-d_6), δ:3.7(3H,s, OCH_3), 4.0(2H,s,CH_2) 7.1,7.3(4H,dd,Ar-H),8.1(1H,s,pyrimidine), 10.0, (1H,s, NH,exchangeable with D_2O),), MS: m/z (%), 381.38 (M^+,9.6%), Anal. Calcd., for $C_{14}H_{11}N_3O_6S_2$: C, 44.09; H, 2.91; N, 11.02. Found: C,44.17; H,2.82; N,11.14.
• **Methyl-3-([(3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidin-6-yl) sulphonyl] amino) benzoate:4c.**	Yield: 61%: mp: 275-77 ºC IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1681,1683,1723(3C = O), 1HNMR (DMSO-d_6), δ:3.8(3H,s, OCH_3), 4.1(2H,s,CH_2) 7.1,7.3(4H,m,Ar-H),8.1(1H,s,pyrimidine), 10.1, (1H,s, NH,exchangeable with D_2O),), MS: m/z (%), 381.38 (M^+,8.7%), Anal. Calcd., for $C_{14}H_{11}N_3O_6S_2$: C, 44.09; H, 2.91; N, 11.02. Found: C,44.09; H,2.85; N,11.17.
• **(2Z)-2-Benzylidene-3,5-dioxo-N-substituted phenyl-2,3-dihydro-5H-[1,3] thiazolo[3,2-a] pyrimidine-6-sulphonamide (5a-c).**	A mixture of **4a-c** (0.01 mole) and benzaldehyde (0.01 mole) and anhydrous sodium acetate (2gm) in glacial acetic acid (20 ml) and acetic anhydride (10 ml) was heated under reflux for 6 h, allowed to cool, then poured onto cold water, the solid formed was collected by filtration and crystallized from DMF/water.
• **Methyl-4-(([(2Z)-2-benzylidene-3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a] pyrimidin-6-yl sulphonyl) amino)-2 hydroxybenzoate:5a.**	Yield: 63%: mp: 310-12ºC: IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1680,1682,1721 (3C = O). 1HNMR (DMSO-d_6), δ:3.7(3H,s, OCH_3), 7.2-7.8(8H,m,Ar-H + 1H benzylic proton),8.1(1H,s,pyrimidine), 3.5, 10.1 (2H,s,OH,NH,exchangeable with D_2O),), MS: m/z (%), 485.48 (M^+,8.8%), Anal. Calcd., for $C_{21}H_{15}N_3O_7S_2$: C, 51.95; H, 3.11; N, 8.66. Found: C,51.84; H,3.22; N,8.57.
Methyl-4-(([(2Z)-2-benzylidene-3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a] pyrimidin-6-yl] sulphonyl) amino benzoate:5b	Yield: 69%: mp: 315-17ºC: IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1682,1686,1725 (3C = O). 1HNMR (DMSO-d_6), δ: 7.1-7.7(9H,m,Ar-H + 1H benzylic proton),8.1(1H,s,pyrimidine), 10.1 (1H,s, ,NH,exchangeable with D_2O),), MS: m/z (%), 469.49 (M^+,12.8%), Anal. Calcd., for $C_{21}H_{15}N_3O_6S_2$: C, 53.72; H, 3.22; N, 8.95. Found: C,53.82; H,3.12; N,8.97.
• **Methyl-3-(([(2Z)-2-benzylidene-3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidin-6-yl] sulphonyl) amino) benzoate:5c**	Yield: 70%: mp: 320-22ºC: IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1681,1685,1720 (3C = O). 1HNMR (DMSO-d_6), δ: 7.1-7.7(9H,m,Ar-H + 1H benzylic proton),8.2(1H,s,pyrimidine), 10.2 (1H,s, ,NH,exchangeable with D_2O),), MS: m/z (%), 469.49 (

	M^+,11.3%), Anal. Calcd., for $C_{21}H_{15}N_3O_6S_2$: C, 53.72; H, 3.22; N, 8.95. Found: C,53.77; H,3.11; N,8.83.
• **Methyl-4-([(3,5-dioxo-1,2,3,5-tetrahtdroimidazo[1,2-a]pyrimidin-6-yl)sulphonyl]amino)-2-hydroxybenzoate:6a**	Yield: 70%: mp: 267-69ºC: IR (KBr cm-1): 3220 (NH),3290 (OH), 3173 (CH,aromatic), 2975(CH,aliphatic),1681,1683,1724 (3C = O). 1HNMR (DMSO-d_6), δ:3.7(3H,s, OCH_3),2.9(2H,s,CH_2) 7.2-7.4(3H,m,Ar-H),8.1(1H,s,pyrimidine),3.5, 8.5, 10.1 (3H,s,OH,NH,exchangeable with D_2O),), MS: m/z (%), 380.33 (M^+,10.7%), Anal. Calcd., for $C_{14}H_{12}N_4O_7S$: C, 44.21; H, 3.18; N, 14.73. Found: C,44.34; H,3.25; N,14.67.
• **Methyl-4-([(3,5-dioxo-1,2,3,5-tetrahtdroimidazo[1,2-a]pyrimidin-6-yl)sulphonyl]amino) benzoate:6b.**	Yield: 66%: mp: 271-73ºC: IR (KBr cm-1): 3225 (NH), 3182 (CH,aromatic), 2976(CH, aliphatic),1680,1687,1725 (3C = O). 1HNMR (DMSO-d_6), δ:3.8(3H,s, OCH_3),2.9(2H,s,CH_2) 7.1,7.3(4H,dd,Ar-H),8.1(1H,s,pyrimidine), 8.4, 10.0 (2H,s, ,NH, exchangeable with D_2O),), MS: m/z (%), 363.33 (M^+,17.5%), Anal. Calcd., for $C_{14}H_{12}N_4O_6S$: C, 46.15; H, 3.32; N, 15.38. Found: C,46.04; H,3.25; N,15.27.
• **Methyl-3-([(3,5-dioxo-1,2,3,5-tetrahtdroimidazo[1,2-a]pyrimidin-6-yl)sulphonyl]amino) benzoate:6c.**	Yield: 67%: mp: 281-83ºC: IR (KBr cm-1): 3227 (NH), 3187 (CH,aromatic), 2985(CH, aliphatic),1681,1686,1726 (3C = O). 1HNMR (DMSO-d_6), δ:3.8(3H,s, OCH_3),2.9(2H,s,CH_2) 7.1-7.4(4H,m,Ar-H),8.1(1H,s,pyrimidine),3.5, 8.3, 10.0 (2H,s, ,NH,exchangeable with D_2O),), MS: m/z (%), 363.33 (M^+,13.6%), Anal. Calcd., for $C_{14}H_{12}N_4O_6S$: C, 46.15; H, 3.32; N, 15.38. Found: C,46.14; H,3.37; N,15.42.
• **4,6-Dioxo-N-substituted phenyl-6,11-dihydro-4H-pyrimido [2,1-b]quinazoline-3-sulphonamide (7a-c).**	A mixture of equimolar amounts (0.01 mole) of 3a-c and anthranilic acid in sodium ethoxide/ethanol (20 ml) was heated under reflux for 8 hours. The reaction mixture was allowed to cool, poured onto ice-cold dilute HCl, and the separated solid was collected by filtration and crystallized from DMF/water.
• **Methyl-4-([(4,6-dioxo-6,11-dihydro-4H-pyrimido[2,1-b] quinazolin-3-yl) sulphonyl] amino)-2-hydroxybenzoate:7a.**	Yield: 65%: mp: 314-16ºC: IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1682,1685,1725 (3C = O). 1HNMR (DMSO-d_6), δ:3.8(3H,s, OCH_3), 7.1-7.5(7H,m,Ar-H),8.2(1H,s,pyrimidine),3.5, 8.5 10.1 (3H,s,OH,NH,exchangeable with D_2O),), MS: m/z (%), 442.40 (M^+,13.6%), Anal. Calcd., for $C_{19}H_{14}N_4O_7S$: C, 51.58; H, 3.19; N, 12.66. Found: C,51.44; H,3.20; N,12.67.
• **Methyl-4-([(4,6-dioxo-6,11-dihydro-4H-pyrimido[2,1-b]quinazolin-3-yl)sulphonyl] amino) benzoate:7b.**	Yield: 61%: mp: 317-19ºC: IR (KBr cm-1): 3227 (NH), 3163 (CH,aromatic), 2975(CH,aliphatic),1680,1687,1724 (3C = O). 1HNMR (DMSO-d_6), δ:3.8(3H,s, OCH_3), 7.1-7.5(8H,m,Ar-H),8.1(1H,s,pyrimidine), 8.5 10.1 (2H,s, NH,exchangeable with D_2O),), MS: m/z (%), 426.40 (M^+,12.7%), Anal. Calcd., for $C_{19}H_{14}N_4O_6S$: C, 53.52; H, 3.31; N, 13.14. Found: C,53.64; H,3.41; N,13.07.
• **Methyl-3-([(4,6-dioxo-6,11-dihydro-4H-pyrimido[2,1-b] quinazolin-3-yl)sulphonyl] amino) benzoate:7c.**	Yield: 63%: mp: 320-22ºC: IR (KBr cm-1): 3229 (NH), 3163 (CH,aromatic), 2975(CH,aliphatic),1680,1687,1724 (3C = O). 1HNMR (DMSO-d_6), δ:3.9(3H,s, OCH_3), 7.2-7.5(8H,m,Ar-H),8.1(1H,s,pyrimidine), 8.4 10.0 (2H,s, NH, exchangeable with D_2O),), MS: m/z (%), 426.40 (M^+,12.7%), Anal. Calcd., for $C_{19}H_{14}N_4O_6S$: C, 53.52; H, 3.31; N, 13.14. Found: C,53.56; H,3.44; N,13.27.
• **Methyl -4-([(4,6-dioxo-3,4-dihydro-2H,6H-pyrimido[2,1-b][1,3] thiazin-7-yl) sulphonyl] amino)-2-hydroxybenzoate: 8a.**	Yield: 72%: mp: 322-24ºC: IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1683,1684,1722 (3C = O). 1HNMR (DMSO-d_6), δ:3.8(3H,s, OCH_3), 2.9 (2H,t,CH_2), 3.2 (2H,s,CH_2), 7.2-7.4(3H,m,Ar-H), 8.1(1H,s,pyrimidine), 3.5, 10.1 (2H,s,OH,NH,exchangeable with D_2O),), MS: m/z (%), 411.40 (M^+,7.8%), Anal. Calcd., for $C_{15}H_{13}N_3O_7S_2$: C, 43.79; H, 3.18; N, 10.21. Found: C,43.80; H,3.21; N,10.17.
• **Methyl -4-([(4,6-dioxo-3,4-dihydro-2H,6H-pyrimido[2,1-b][1,3] thiazin-7-yl) sulphonyl] amino)-benzoate: 8b.**	Yield: 70%: mp: 316-18ºC: IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1680,1681,1723 (3C = O). 1HNMR (DMSO-d_6), δ:3.9(3H,s, OCH_3), 2.8 (2H,t,CH_2), 3.1 (2H,s,CH_2), 7.1,7.3(3H,dd,Ar-H), 8.1(1H,s,pyrimidine), 10.0 (1H,s, NH,exchangeable with D_2O),), MS: m/z (%), 395.41 (M^+,10.3%), Anal. Calcd., for $C_{15}H_{13}N_3O_6S_2$: C, 45.56; H, 3.31; N, 10.63. Found: C,45.43; H,3.41; N,10.77.
• **Methyl -3-([(4,6-dioxo-3,4-dihydro-2H,6H-pyrimido[2,1-b][1,3] thiazin-7-yl) sulphonyl] amino)-benzoate: 8c.**	Yield: 71%: mp: 310-12ºC: IR (KBr cm-1): 3226 (NH),3300 (OH), 3150 (CH,aromatic), 2986(CH,aliphatic), 1681,1682,1725 (3C = O). 1HNMR (DMSO-d_6), δ:3.8(3H,s, OCH_3), 2.9 (2H,t,CH_2), 3.2 (2H,s,CH_2), 7.1,7.4(3H,dd,Ar-H), 8.2(1H,s,pyrimidine), 10.0 (1H,s, NH,exchangeable with D_2O),), MS: m/z (%), 395.41 (M^+,11.7%), Anal. Calcd., for $C_{15}H_{13}N_3O_6S_2$: C, 45.56; H, 3.31; N, 10.63. Found: C,45.53; H,3.29; N,10.68.

Compounds preparation and administration

Stander's drugs (donated by Sanofi Recherche)were prepared by dissolving them in distilled water at room temperature, while the new compounds were dissolved in 0.1% DMSO plus enough distilled water. The standard and new compounds were administration IV at 3-30 mg/kg.

Thrombolysis evaluation

Eighty-five Wistar rats weighting 350-450g were divided into seven groups, the first two groups for standers and the others five were subdivided into three subgroups each group and subgroup contain 5 rats. The rats were subjected to general anesthesia with thiopental (800U/kg IP). The right carotid artery was cannulated to delivering blood into a collagen strip then returned to the left femoral vein. After 20-30 minutes and during this circulation, a clot was weighting by using an auxotonic 386 Harvard transducer. The compounds were injected at a lower dose of 1 µg/kg then increased gradually until 30 µg/kg after one hour of injection, the thrombolytic effect of the compounds was recorded and ED50was 30% of maximal thrombolysis (ED50) obtained from the equation of regression lines.

RESULTS

The antiplatelet activity of newly synthesized compounds was measured and compared with ticlopidine and clopidogrel as standard reference drugs. We found that the newly synthesized compounds showed a vary thrombolytic effect as compared with standers. However, 3a, 4a, 6a, 7a, and 8a have been lower ED30 than other new compounds as well as the standers. 4a and 6a (14.37 ± 0.94 and 22.89 ± 1.00 respectively) have been shown lowered ED30 than others. There is an insignificant difference ($p>0.05$) between 3a and 7a, 4a and 6a, and between 7a and 8a. There is a significant difference ($p<0.05$) between them and standers as well as other compounds. Table (1), figure (1), figure (2), and figure (3).

Figure 1: ED30 value of newly synthesized compounds and standers

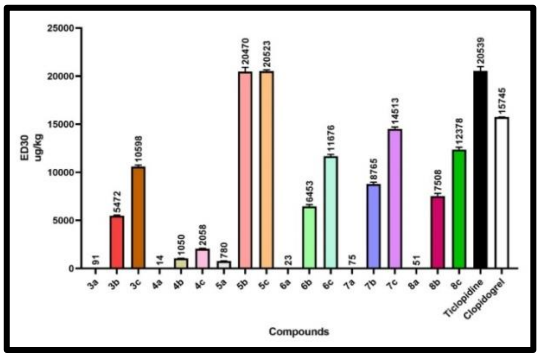


Figure 2: ED30 value of most potent compounds

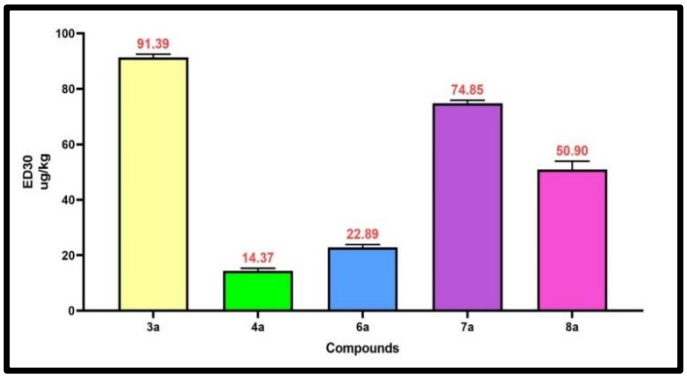
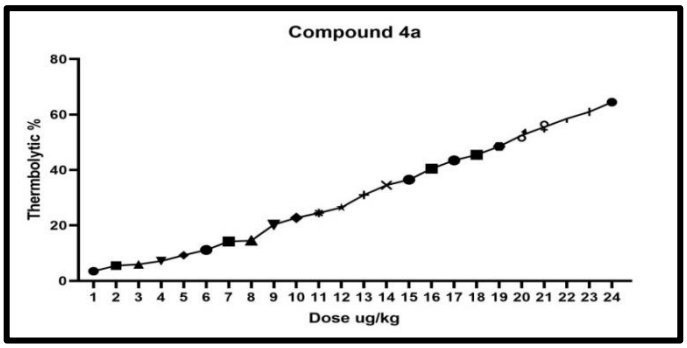


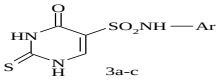
Figure 3: Thrombolytic percent of 4a that's used to calculate ED30. No. of the dose was 24 doses

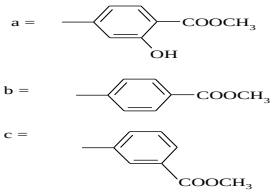


DISCUSSION

Pyrimidine nucleus is a poor ring relative to most common electrophilic substitution reactions such as nitration, sulphonation, halogenation etc. The relative inertness is attributed to the –I and –M effects of the two nitrogen atoms. These reactions could be augmented by the introduction of electron releasing groups, thus for example in 2-thiouracil, the presence of –OH and SH groups counteract the deactivation caused by the two nitrogen atoms, consequently, 2-thiouracil undergoes most of these reactions. Chlorosulphonation is one of these reactions specially to prepare important pharmaceutical precursors or biologically active intermediates **(Ahjel 2020; Awad 2018)**. Chlorosulphonation of thiouracil was one of the difficult interactions that embraced the scholars, and each time the result was not clear until it was prepared in the year 2002 by Fathalla OA **(Fathalla 2005)**, who showed that the reaction is subjected to temperature gradient technique and the optimum temperature to obtain good yields was 120oC. In 2020 the yield was increased by the synergistic effect of thionyl chloride when added with chlorosulphonic acid in this chlorosulphonation reaction. Thus 2-thiouracil-2-sulphonyl chloride was efficiently prepared and was used as a starting material to prepare a huge number of biologically active 2-thiouracil-5-sulphonamides by its reaction with series of aromatic amines in a SN2 reaction in presence of pyridine as an acid binder. Three aromatic amines were selected in this research namely, methyl-4-aminosalicylate, methyl-3-aminobenzoate, and methyl-3-aminobenzoate in an attempt to increase the thrombolytic effects. Also, to mimic thienopyridines of common thrombolytic effects, 2-thiouracil-sulphonamides 3a-c were cyclo-condensed with chloroacetic acid in acetic acid /acetic anhydride mixture yielding thiazolopyrimidinesulphonamides4a-c which were condensed with benzaldehyde due to the presence of active methylene group giving benzylidene derivatives 5a-c. Furthermore, 3a-c were cyclocondensed with ethanol amine, anthranilic acid, and 3-bromopropanoic acd to give imidazopyrimidines, pyrimidoquinazolines and pyrimidothiazines6a-c, 7a-c, and 8a-c respectively.

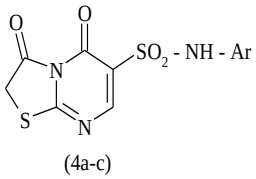
Series 1. 3a-c

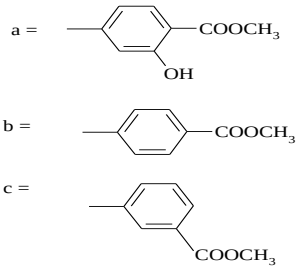




The optimum activity was obtained when the aryl group is methyl salicylate, the activity is decreased by removing the OH group (aryl group is methyl benzoate), the activity is dramatically decreased when m-substituted methyl benzoate is used (3c). Thus, salicylate augments the thrombolytic effect through inhibition of platelet prostaglandin synthesis a recently reported to stimulate nitric oxide synthesis in platelets that produce fibrinogen/ fibrinolytic effect.

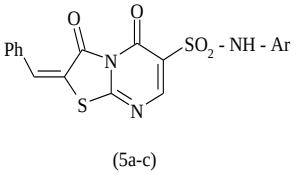
Series II.4a-c

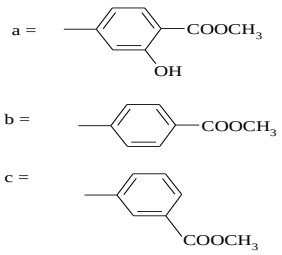




Thiazolopyrimidine 4a represents the most potent compound of our research (aryl group is methyl salicylate; activity is decreased by the removal of OH group (aryl group is p-methylbenzoate) and by m-substitution.

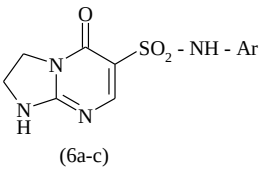
Series III.5a-c

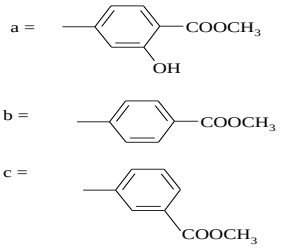




Benzylidene formation (reaction of 3a-c with benzaldehyde) dramatically decrease or abolish the thrombolytic activity in a relative manner according to the aryl group.

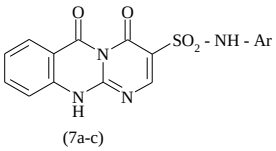
Series IV.6a-c





Analogous to 4a-c, maximum activity of imidazopyrimidines was obtained when the aryl group is methyl salicylate.

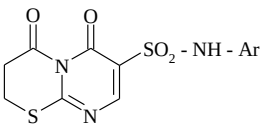
Series V.7a-c:



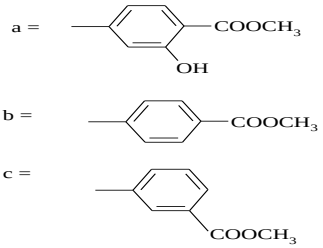
(7a-c)

In imidazoquinazoline derivatives promising thrombolytic activity was obtained when the aryl group is methyl salicylate, the activity is gradually decreased by the removal of OH group and by m-substitution.

Series VI.8a-c



(8a-c)



In pyrimidothiazines, maximum activity was obtained when the aryl group is methyl salicylate.

Table 1: ED30 value of newly synthesized compounds and standers

Compounds	Mean ± Std. Error	Std. Deviation	95% Confidence Interval for Mean	
			Lower Bound	Upper Bound
3a	91.39 ± 1.16	1.63	76.7093	106.0607
3b	5472.00 ± 85.00	120.21	4391.9726	6552.0274
3c	10598.00 ± 160.00	226.27	8565.0072	12630.9928
4a	14.37 ± 0.94	1.32	2.4847	26.2453
4b	1050.15 ± 20.05	28.35	795.3906	1304.9094
4c	2057.60 ± 49.70	70.29	1426.1016	2689.0984
5a	780.35 ± 10.05	14.21	652.6526	908.0474
5b	20470.00 ± 450.00	636.40	14752.2079	26187.7921
5c	20523.00 ± 130.00	183.85	18871.1934	22174.8066
6a	22.89 ± 1.00	1.41	10.2423	35.5277
6b	6453.00 ± 200.00	282.84	3911.7591	8994.2409
6c	11675.75 ± 200.15	283.05	9132.6031	14218.8969
7a	74.85 ± 1.05	1.48	61.5085	88.1915
7b	8765.00 ± 200.00	282.84	6223.7591	11306.2409
7c	14513.00 ± 195.00	275.77	12035.2901	16990.7099
8a	50.90 ± 3.00	4.24	12.7814	89.0186
8b	7508.00 ± 295.00	417.19	3759.6696	11256.3304
8c	12378.00 ± 225.00	318.20	9519.1039	15236.8961
Ticlopidine	20539.00 ± 455.00	643.47	14757.6768	26320.3232
Clopidogrel	15745.00 ± 10.00	14.14	15617.9380	15872.0620

CONCLUSION

Condensed pyrimidine sulphonamides as newly synthesized hetercyclic compounds were prepared in an attempt to mimic the thrombolytic activity of thienopyridines such as ticlopidine and clopidogrel, they showed higher promising activity especially when incorporated with methyl salicylate nucleus in an attempt to augment the thrombolytic activity.

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