Synthesis and Spectral analysis of some novel 5-Amino-Salicylic Acid derivatives and their In-silico ADMET studies

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Abstract:

Aim and Objectives: Some novel 5-Amino-Salicylic Acid derivatives were synthesized by using 3-methyl-2-thiophenecarboxaldehyde as an starting material and followed by N,N-dicyclohexylcarbodiimide. **Methods:** In silico ADMET study has been applied for selection of ideal (according to Lipinski rule) novel drug moiety for synthesis. **Results:** The newly synthesized derivatives were confirmed by elemental analysis, mass, IR and NMR spectroscopy.

Key words: Lipinski rule, Schiff base, 5-ASA, N,N-dicyclohexylcarbodiimide.

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Introduction

Salicylic acid (SA) derivatives are widely used in the treatment of a wide range of diseases. Acetylsalicylic acid is the most commonly used drug in the world, 4-Aminosalicylic acid (4-ASA) was historically used as a systemic ant tuberculosis drug, and diflunisal is a powerful pain reliever and antipyretic. 5-Aminosalicylic acid (5-ASA), which was first synthesized at the end of the nineteenth century and used to make azo dyes, was later discovered to be a very valuable medicinal agent as well as a component of many biologically active agents. For pharmacological activity, 5-ASA is not metabolized to salicylic acid. It is not regarded as a true salicylate.. 5-ASA, unlike other salicylates, does not cause upper gastrointestinal (GI) side effects. Furthermore, it was discovered to be particularly beneficial in the treatment of inflammatory bowel disease (IBD). Since we are interested in this compound and its derivatives, it is unique among salicylates and has a wide range of biological activities including anti-inflammatory, analgesic, neuroprotective, and antitumor properties.

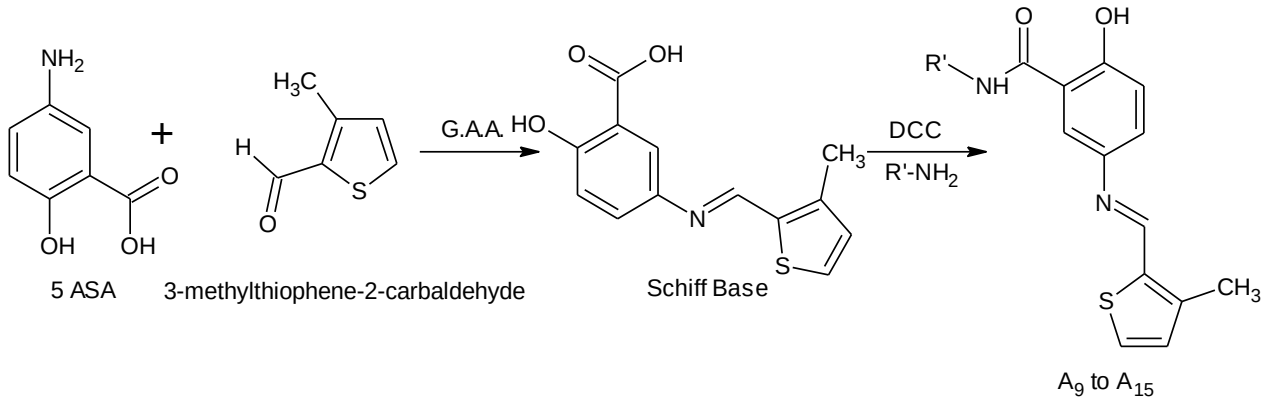
Results and Discussion

Chemistry

Scheme 1 depicts the synthetic route for novel derivatives. The formation of Schiff bases and the coupling reaction are two steps that result in novel derivatives. A Schiff base is a nitrogen analogue of an aldehyde or ketone that has the C=O group replaced by the C=N-R group. Condensation of an aldehyde or ketone with a primary amine produces it.

Because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates, direct conversion of a carboxylic acid to an amide is difficult. The carboxylic acid

reacts with the DCC molecule to form a good leaving group, which is then displaced by an amine during nucleophilic substitution. DCC induced coupling, resulting in the formation of an amide linkage is an important reaction in the synthesis of peptides.



Scheme 1.-Synthesis of some novel 5-Amino-Salicylic Acid derivatives.

Where,

Table 1 : Novel 5-ASA derivatives containing amines

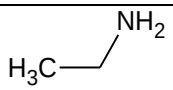
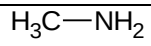
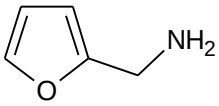
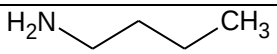
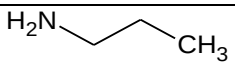
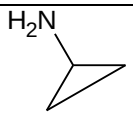
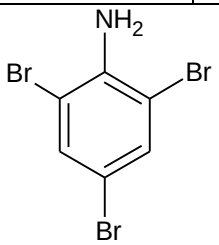
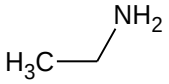
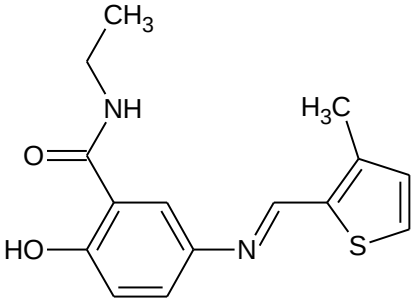
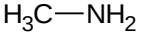
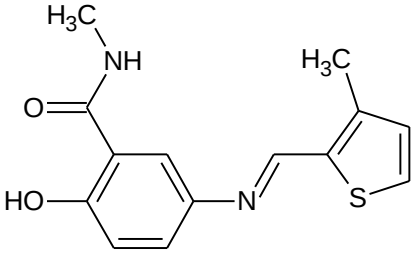
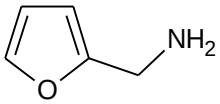
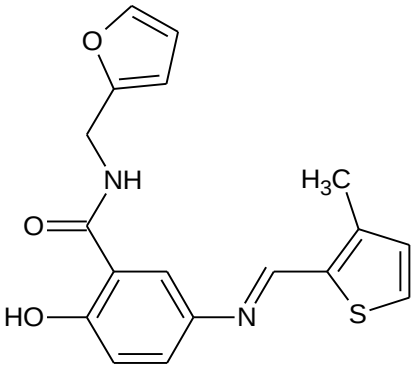
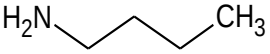
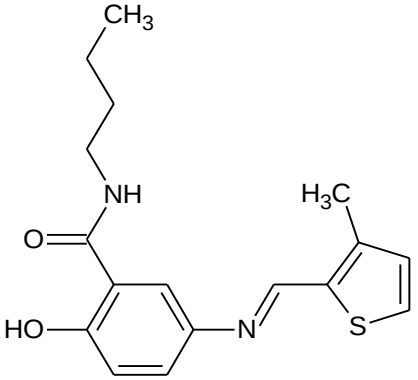
Compound	Amines	Compound	Amines
A9	 Ethylamine	**A10**	 Methylamine
A11	 Furfurylamine	**A12**	 Butylaminne
A13	 Propylamine	**A14**	 Cyclopropylamine
A15	 2,4,6-tribromoaniline		

Table 2 : List of compounds synthesized (A9 to A15)

Sr. No.	RNH2(AMINE)	Chemical name	Derivatives
A9	 Ethylamine	N-ethyl-2-hydroxy-5-{[(E)-(3-methylthiophen-2-yl)methylidene]amino}benzamide	
A10	 Methylamine	2-hydroxy-*N*-methyl-5-{[(*E*)-(3-methylthiophen-2-yl)methylidene]amino}benzamide	
A11	 Furfurylamine	N-(furan-2-ylmethyl)-2-hydroxy-5-{[(E)-(3-methylthiophen-2-yl)methylidene]amino}benzamide	
A12	 Butylaminne	*N*-butyl-2-hydroxy-5-{[(*E*)-(3-methylthiophen-2-yl)methylidene]amino}benzamide	

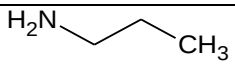
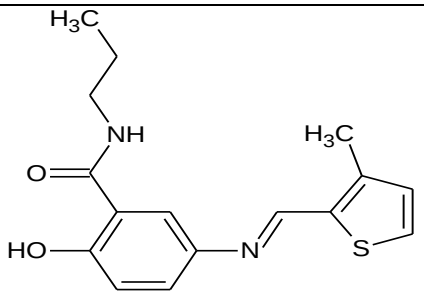
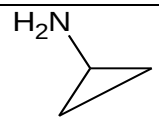
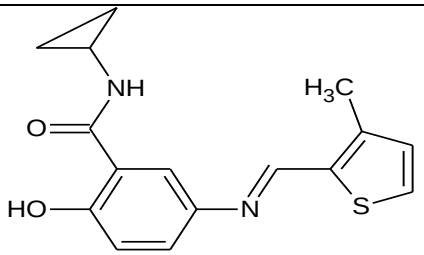
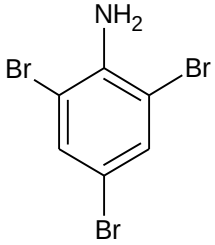
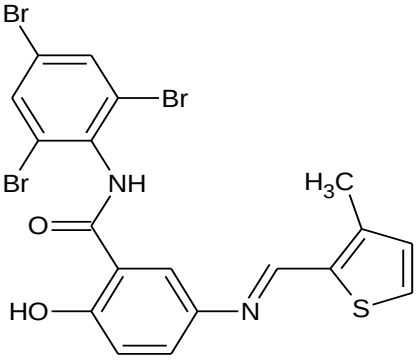
A13	 Propylamine	2-hydroxy-5-{[(*E*)-(3-methylthiophen-2-yl)methylidene]amino}-*N*-propylbenzamide	
A14	 Cyclopropylamine	*N*-cyclopropyl-2-hydroxy-5-{[(*E*)-(3-methylthiophen-2-yl)methylidene]amino}benzamide	
A15	 2,4,6-tribromoaniline	2-hydroxy-5-{[(*E*)-(3-methylthiophen-2-yl)methylidene]amino}-*N*-(2,4,6-tribromophenyl)benzamide	

Table 3: Physicochemical Data of Synthesized compounds (A9-A15)

Compound	Molecular formula	Molecular Weight g/mol	M.P. range (^{0}C)	Mobile phase	*R_F value
A9	$C_{15}H_{16}N_2O_2S$	288.36	238-240	Methanol:Ethyl acetate:Water:7:3:1	0.1 to 1.00
A10	$C_{14}H_{14}N_2O_2S$	274.34	240-242	Methanol:Ethyl acetate:Water:7:3:1	0.1 to 1.00
A11	$C_{18}H_{16}N_2O_3S$	340.40	240-242	Methanol:Ethyl acetate:Water:7:3:1	0.1 to 1.00
A12	$C_{17}H_{20}N_2O_2S$	316.42	238-240	Methanol:Ethyl acetate:Water:7:3:1	0.1 to 1.00
A13	$C_{16}H_{18}N_2O_2S$	302.39	240-242	Methanol:Ethyl acetate:Water:7:3:1	0.1 to 1.00
A14	$C_{16}H_{16}N_2O_2S$	300.38	244-246	Methanol:Ethyl acetate:Water:7:3:1	0.1 to 1.00
A15	$C_{19}H_{13}Br_3N_2O_2S$	573.045	238-240	Methanol:Ethyl acetate:Water:7:3:1	0.1 to 1.00

Predictions of pharmacokinetics (ADME)

Molsoft, Molinspiration, and Swiss ADME tools were used to predict ADME characteristics of bioactive molecules. This method computes pharmacokinetic and toxicological participants based on the compound's construction.

Table 1: In silico ADMET screening for synthesized compound

Compound	M.F.	M.W.	nHBA	nHBD	logP	TPSA (A^0)	Rule of Five
Accepted values	----------	<500 g/mol	<5	<10	<5	<110	Max 4
A9	$C_{15}H_{16}N_2O_2S$	288.36	2	3	3.67	50.24	4
A10	$C_{14}H_{14}N_2O_2S$	274.34	2	3	3.16	50.77	4
A11	$C_{18}H_{16}N_2O_3S$	340.40	2	4	4.74	58.09	4
A12	$C_{17}H_{20}N_2O_2S$	316.42	2	3	4.79	50.46	4
A13	$C_{16}H_{18}N_2O_2S$	302.39	2	3	4.26	50.46	4
A14	$C_{16}H_{16}N_2O_2S$	300.38	2	3	3.86	50.40	4
A15	$C_{19}H_{13}Br_3N_2O_2S$	573.045	2	4	6.45	47.63	2
Schiff base	$C_{13}H_{11}NO_3S$	261.30	2	4	3.79	54.34	4

EXPERIMENTAL

The chemicals used in the present work were AR grade and LR grade, purchased from Sigma Aldrich, Loba Chemie and used as for preparation of novel derivatives. The list of chemicals used were 5-aminosalicylic acid, methanol, acetic acid, 3-methyl-2-thiophenecarboxaldehyde, N,N-dicyclohexylcarbodiimide, , Cyclopropylamine, ethanolamine, ethylamine, Furfurylamine, methylamine, n-butylamine, n-propylamine, etc. The water used was double distilled deionised water.

General procedure:

Step-1. Synthesis of Schiff base:-

5-ASA (9.7 mmol) was dissolved in 15ml methanol in a beaker. (9.7 mmol) of 3-methyl-2-thiophenecarboxaldehyde was dissolved in 15ml methanol. Mix both solution in round bottom flask and 3-4 drop of acetic acid was also added. Reflux it for about $2^1/_2$ hour. Reaction mixture was cooled to room temperature and placed in refrigerator for 24 hr. the precipitate solid was filtered and washed with methanol.

Step-2. Synthesis of 5ASA derivatives:-

To a magnetically stirred solution of carboxylic acid (1 mmol) in H_2O was added 1 mmol of N,N-dicyclohexylcarbodiimide and the reaction mixture was stirred at room temperature for 1 h after this period, the amine (1 mmol) was added and the reaction mixture was stirred at room temperature for the indicated time until the starting materials were totally consumed as checked by TLC. Then, the solvent was separated by filtration and the solid washed several times with water in order to remove the by-product diisopropyl urea (DIU).

Identification and characterization of synthesized products:

The synthesized compounds were scaled for yield and purified by recrystallization with suitable solvent system. The purified compounds were assigned for physical constant determination and further subjected for spectral analysis like Infrared spectroscopy, Nuclear magnetic resonance spectroscopy and Mass spectroscopy.

Spectral Data:

A9: N-ethyl-2-hydroxy-5-{[(E)-(3-methylthiophen-2-yl)methylidene]amino}benzamide

IR (cm^{-1}): 1570.74 (C=O), 3357.46(N-H), 2752.89 (Aromatic C-H), 3480.88 (O-H), 1098.26 (C-S)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.78 (s, 1H), 8.62 (s, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.14 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.99 – 6.93 (m, 2H), 3.36 (qd, *J* = 6.3, 4.3 Hz, 2H), 1.26 (t, *J* = 6.2 Hz, 3H).

Theoretical Mass : 288.36

Observed Mass : 290.0015

A10: 2-hydroxy-*N*-methyl-5-{[(*E*)-(3-methylthiophen-2-yl)methylidene]amino}benzamide

IR (cm^{-1}): 1701.87 (C=O), 3099.05(N-H), 2985.27 (Aromatic C-H), 3345.89 (O-H), 1026.91 (C-S)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.81 (s, 1H), 8.62 (s, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.14 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.99 – 6.93 (m, 2H), 6.75 (q, *J* = 4.9 Hz, 1H), 2.91 (s, 1H).

Theoretical Mass : 274.34

Observed Mass :282.1025

A11: N-(furan-2-ylmethyl)-2-hydroxy-5-{[(E)-(3-methylthiophen-2-yl)methylidene]amino}benzamide

IR (cm^{-1}): 1678.73 (C=O), 3374.82(N-H), 2923.56 (Aromatic C-H), 3461.6 (O-H), 1148.4 (C-S)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.78 (s, 1H), 8.62 (s, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.62 (t, *J* = 4.8 Hz, 1H), 7.30 (t, *J* = 1.6 Hz, 1H), 7.14 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.99 – 6.93 (m, 2H), 6.31 – 6.23 (m, 2H), 4.69 – 4.65 (m, 2H).

Theoretical Mass : 340.40

Observed Mass :331.08

A12: *N*-butyl-2-hydroxy-5-{[(*E*)-(3-methylthiophen-2-yl)methylidene]amino}benzamide

IR (cm^{-1}): 1634.38 (C=O), 3366.14(N-H), 2767.35 (Aromatic C-H), 3481.85 (O-H), 1048.12 (C-S)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.78 (s, 1H), 8.62 (s, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.60 (t, *J* = 4.9 Hz, 1H), 7.14 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.99 – 6.93 (m, 2H), 3.32 (td, *J* = 5.8, 4.8 Hz, 2H), 1.57 (p, *J* = 6.0 Hz, 2H), 1.36 (h, *J* = 6.5 Hz, 2H), 0.92 (t, *J* = 6.7 Hz, 3H).

Theoretical Mass : 316.42

Observed Mass : 316.1208

A13: 2-hydroxy-5-{[(*E*)-(3-methylthiophen-2-yl)methylidene]amino}-*N*-propylbenzamide

IR (cm^{-1}): 1650.77 (C=O), 3246.57(N-H), 2979.48 (Aromatic C-H), 3648.66 (O-H), 1099.23 (C-S)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.78 (s, 1H), 8.62 (s, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.63 (t, *J* = 4.9 Hz, 1H), 7.14 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.99 – 6.93 (m, 2H), 3.29 (q, *J* = 5.3 Hz, 2H), 1.55 (qt, *J* = 7.3, 5.3 Hz, 2H), 0.83 (t, *J* = 7.1 Hz, 3H).

Theoretical Mass :302.39

Observed Mass : 302.1125

A14: *N*-cyclopropyl-2-hydroxy-5-{[(*E*)-(3-methylthiophen-2-yl)methylidene]amino}benzamide

IR (cm^{-1}): 1654.62 (C=O), 3235(N-H), 2954.41 (Aromatic C-H), 3580.31 (O-H), 1092.48 (C-S)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.78 (s, 1H), 8.62 (s, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.14 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.99 – 6.93 (m, 2H), 3.18 (dp, *J* = 7.2, 4.8 Hz, 1H), 0.93 (dd, *J* = 10.8, 4.7 Hz, 2H), 0.68 (dd, *J* = 10.7, 4.6 Hz, 2H).

Theoretical Mass : 300.38

Observed Mass : 300.0927

A15: *2*-**hydroxy-5-{[(E)-(3-methylthiophen-2-yl)methylidene]amino}-N-(2,4,6-tribromophenyl)benzamide**

IR (cm^{-1}): 1806.97 (C=O), 3227.29(N-H), 2959.23 (Aromatic C-H), 3838.61 (O-H), 1076.08 (C-S), 667.25 (C-Br)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.72 (s, 1H), 10.52 (s, 1H), 8.62 (s, 1H), 7.71 (d, *J* = 4.9 Hz, 3H), 7.14 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.99 – 6.93 (m, 2H).

Theoretical Mass : 569.82

Observed Mass : 571.0895

Conclusion

The current study reveals the synthesis of some novel 5-Amino-Salicylic Acid derivatives by using 3-methyl-2-thiophenecarboxaldehyde as an starting material and followed by N,N-dicyclohexylcarbodiimide. The newly synthesized derivatives were confirmed by elemental analysis, mass, IR and NMR spectroscopy.

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